國立交通大學

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碩士論文

Joined Use of Oxazolidinone and Desymmetic Amino Protection in Application of Oligosaccharide Synthesis

環胺基酸酯結合非對稱胺基保護在寡醣合成上的應用

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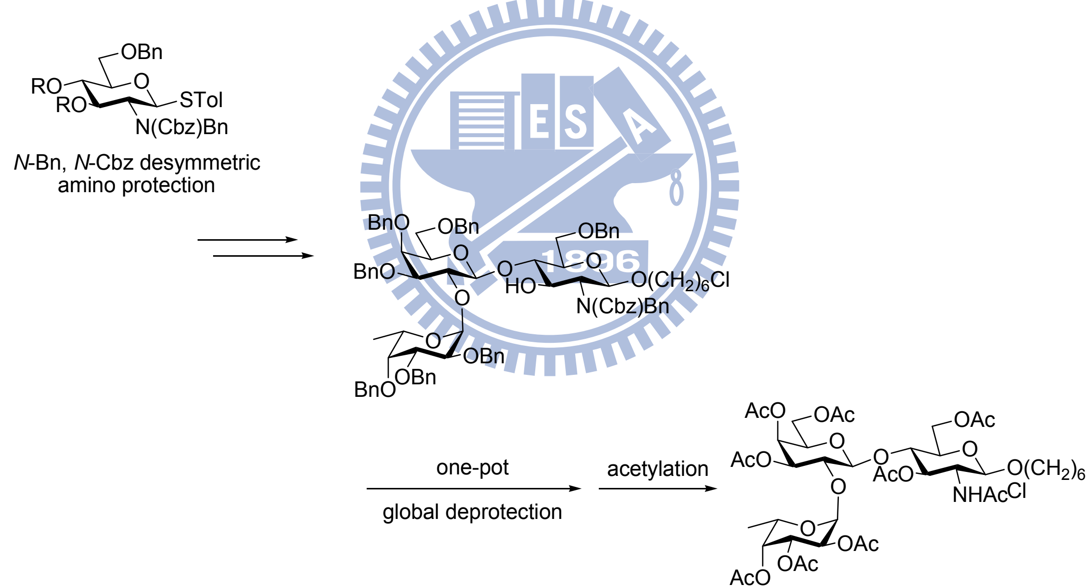
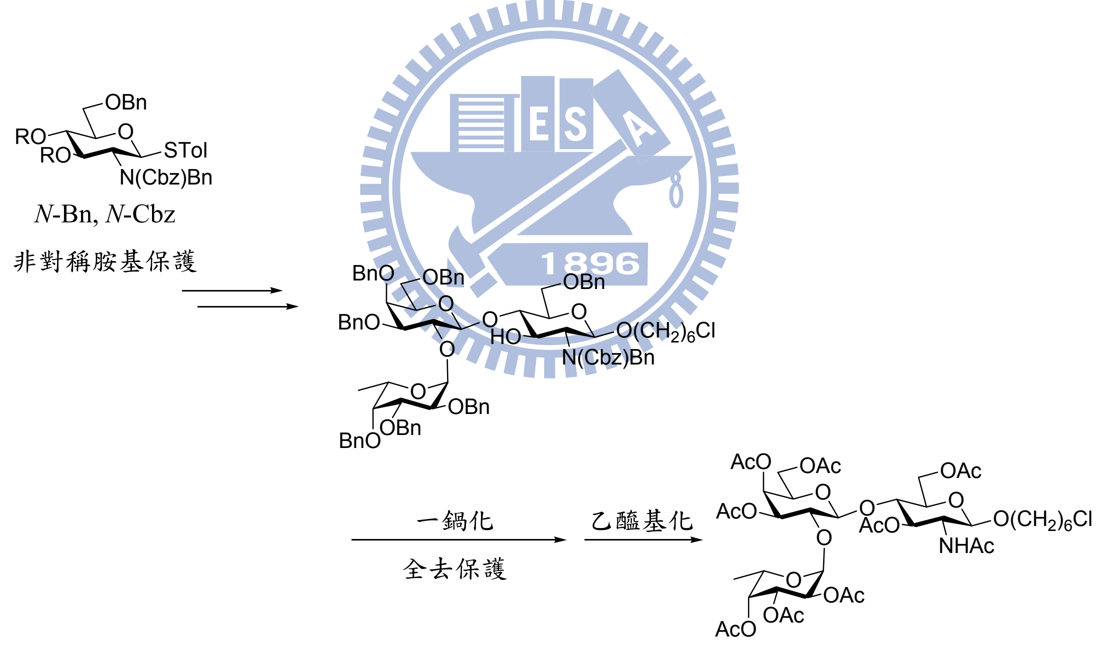
Abstract

Joined use of *N*-benzyl oxazolidinone and *N*-benzyl-*N*-benzyloxycarbonyl (*N*-BnCbz) desymmetric amino-protecting function is reported. The new synthetic approach enables the facile preparation of type 1 and type 2 LacNAc disaccharide in satisfactory yield. One-pot deprotection of *N*-BnCbz and *O*-benzyl ether is achieved by hydrogenolysis under mild conditions. Further application of this protection strategy realizes the synthesis of trisaccharide H blood group substrate.



摘要

本篇論文要報導苄基(benzyl group)取代的 oxazolidinone 和非對稱胺基保護(desymmetric amino protection)的應用性。我們應用此合成策略製備了一型和二型的乳糖胺，此方法不但容易操作而且有著極佳的產率。無論是在氮原子上面的苄氧羰基(benzyloxycarbonyl group)和苄基，或是在氧原子上的苄基，都可以在溫和條件下的氫解反應(hydrogenolysis)中一併去除。接著我們合成出 H 型血基質(H blood group substrate)中的部分三醣結構，再度證明此一策略的應用性。



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List of Abbreviations

AgOTf	silver triflate
$BF_3 \cdot OEt_2$	trifluoride etherate
BSM	benzenesulfinylmorpholine
BSP	benzenesulfinylpiperidine
Bu_4NBr	tetrabutyl ammonium bromide
t-BuOK	potassium *tert*-butoxide
Cbz	benzyloxycarbonyl
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
d	doublet
DMSO	dimethyl sulfoxide
DMTST	dimethyl(thiomethyl) sulfonium trifluoromethane sulfonate
DTBMP	2,6-di-*tert*-butyl-4-methyl pyridine
Et_3SiH	triethylsilane
Hz	hertz
m	multiplet
$NaBH_3CN$	cyanoborohydride
NIS	*N*-iodosuccinimide
$Na_2S_2O_3$	sodium thiosulphate
NEt_3	triethylamine
t	triplet

PhSOTf (PST)	phenylsulfenyltriflate
PTSA (TsOH)	*p*-toluenesulfonic acid
s	singlet
TFA	trifluoroacetic acid
Tf_2O	triflic anhydride
THF	tetrahydrofuran
TMSOTf	trifluoromethanesulfonate
TTBP	2,4,6-tri-*tert*-butylpyrimidine

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1 Introduction

1.1 Lewis blood group antigens

The involvement of carbohydrates and their conjugates in numerous biological processes are recognized.[1-4] An important calss is the series of Lewis blood group antigens which contain either Gal-β(1→3)-GlcNAc (type 1 LacNAc) or Gal-β(1→4)-GlcNAc (type 2 LacNAc) backbone.[5] The nomenclature of these Lewis blood group antigens is dependent on the linkages of fucose (Fuc), *N*-acetyl-neuraminic acid (Neu5Ac) or sulfate to the backbones (Figure 1).[6]

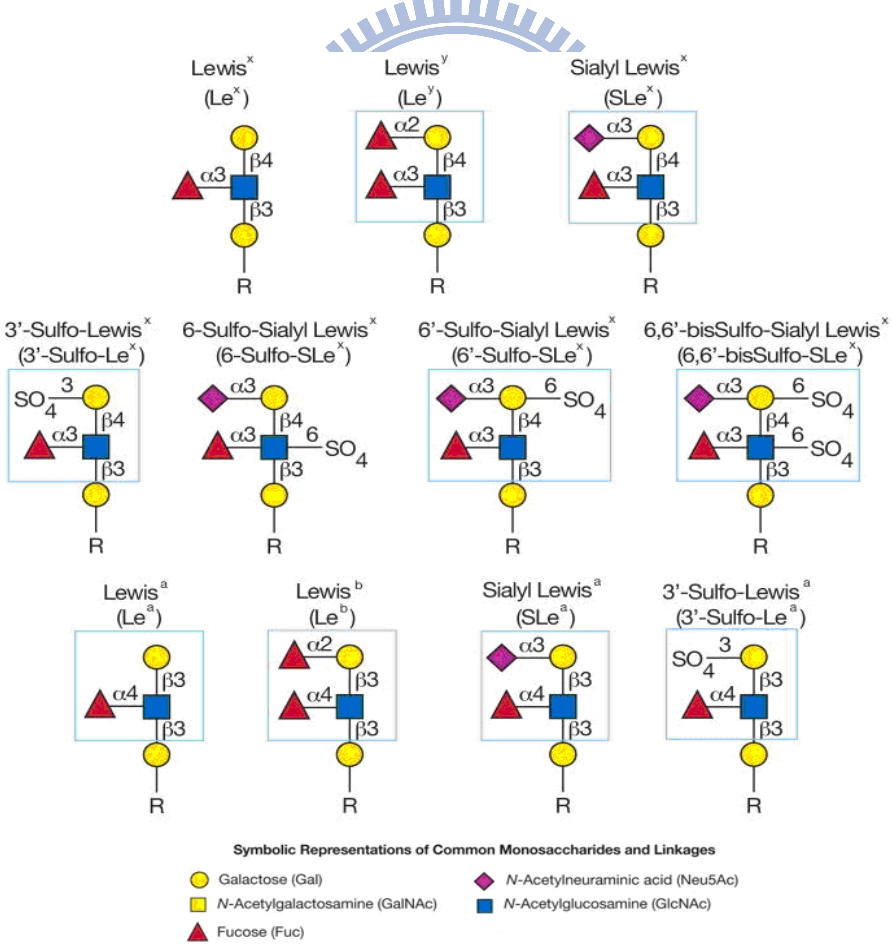
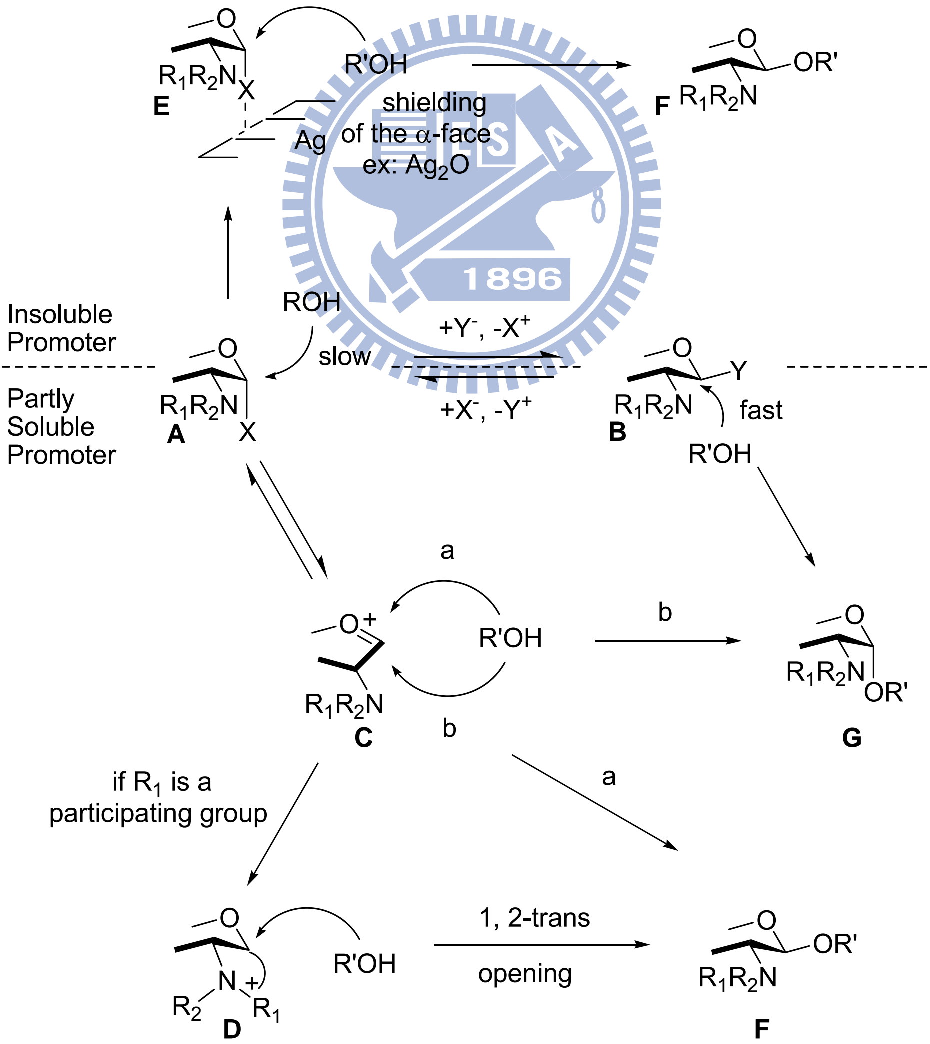


Figure 1. Type-1 and type-2 Lewis determinants

Some members of the Lewis blood group antigen family have been proven to be specific tumor makers for cancer diseases; thus, they are attractive targets for various biomedical investigations. For example, Lewis Y antigens have some relations with apoptosis in gastric and colorectal carcinomas.[7] Synthetic studies not only provide the evidence for chemical structures of the oligosaccharides but also supply sufficient amount of desired molecules or glycoconjugates for various study. Since nearly all Lewis blood group antigens contain the *N*-acetyl glucosamine which is connected to galactose in 1,2-*trans*-β-glycosidic linkage. To develop a facile method for the construction of this glycosidic linkage is necessary and desirable.

1.2 General mechanism for the 1,2-*trans*-glycosylation of 2-amino sugars

The so-called glycosylation involves the formation of a carbon-oxygen bond via a nucleophilic substitution reaction. This reaction involves the anomeric position (C-1) of a glycoside carrying a leaving group (X), namely the glycosyl donor **A** (Scheme 1). This glycosyl donor would react with the hydroxyl group of an alcohol (R^1OH, glycone or aglycone). The glycone acceptor can be a mono- or oligosaccharide (Scheme 1).[8] The glycosylation is promoted by an electrophilic activator, namely the promoter. The amount of promoter used can be varied from catalytic to stoichiometric



Scheme 1. General mechanism for the glycosylation of amino sugars

dependent on the types of leaving groups. The function of the promoter is to facilitate the departure of the anomeric leaving group (X), and then usually a mixtures of α and β-glycosides (path a and b respectively) are produced due to a lack of stereoselectivity.

In order to obtain 1,2-*trans*-β-glycosidic bond, two approaches are generally employed. The most widely used method is to protect the amino function with a neighboring group which results in a cyclic intermediate (**D**) shielding the "α-face" of the donor by participating effect.[9] In this way, the hydroxyl group of the acceptor can only access the "β-face" and afford the 1,2-*trans*-glycoside (**F**). Another method for the synthesis of 1,2-*trans*-β-glycoside (**F**) includes the use of 1,2-*cis*-2-azido-2-deoxy-α-D-glycopyranosyl halides (**A**) (having a nonparticipating amino–protecting group) and an insoluble promoter such that the "α-face" of the donor is shielded from reaction during the substitution with the acceptor alcohol (**E**). Similar to this concept is the use of 2-azido-2-deoxy-α-D-glycopyranosyl diphenyl phosphates or imidates in nitrile solvent, which promotes the formation of α-nitrilium intermediate with the oxocarbenium ion and shields the "α-face" of the donor.[10] The above non-participating methods used mainly with 2-azido-2-deoxy glycosyl donors, and the 1,2-*trans*-β-stereoselectivities obtained are often lower than those given by the use of donors containing the participating groups. As a result, to mask the amino function with a participating protecting group apparently is a better choice for the construction of the 1,2-*trans*-β-glycosidic linkage of 2-amino sugars.

1.3 Amino protecting groups for 1,2-*trans*-*β*-glycosylation of 2-amino sugars

2-Acetamido-2-deoxy-glucopyranose is an important constituent in all Lewis blood group antigens, and is present in 1,2-*trans*-glycosidic linkage. Apparently, a glycosylation strategy by using GlcNAc donors should give the simplest synthetic route in oligosaccharide synthesis. However, the reactions of these donors often suffer from the formation of relatively stable oxazoline intermediates (**D**) due to neighboring group participation. As a consequence, the glycosylation yield is moderate to the best.[8,11,12] Although the GlcNAc oxazoline derivatives can react with acceptor alcohols to afford 2-acetamido-2-deoxy-β-glycosides (**C**) via oxazolinium ion intermediates (**B** or **E**) in the presence of Brønsted or Lewis acids. The harsh reaction conditions required precluded their wide application (Scheme 2).[13-15] Therefore, a wide variety of amino-protecting groups for amino sugars have been developed. To be a suitable amino-protecting group, it should be stable to a wide range of reaction

Scmeme 2. Glycosylation of 2-acetamido-2-deoxy glycosyl donors

conditions. In addition, this amino protection provides desirable stereoselectivity and acceptable yield in glycosylations. Moreover, it should be removed under mild conditions after glycosylations. Based on literature search, the amino–protecting groups for 2-amino-2-deoxy sugars are briefly classified into three types according to the substituent patterns including (1) monosubstituted, (2) disubstituted, and (3) oxazolidinone amino-protecting group. The above three categories are described hereafter. This thesis mainly focuses on the discussion of oxazolidinone protecting group and its derived desymmetric protecting function.

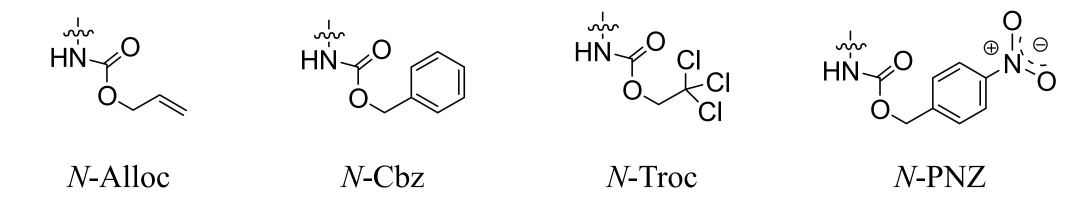
1.3.1 Monosubstituted amino–protecting groups

Monosubstituted protection is referred to those amino–protecting groups in GlcNAc that contains one acyl/alkoxycarbonyl function (Figure 2). Acyl derivatives include *N*-monochloroacetyl (*N*-$COCH_2Cl$),[16] *N*-dichloroacrtyl (*N*-$COCHCl_2$),[17] *N*-trichloroacetyl (*N*-$COCl_3$),[18] and *N*-trifluoroacetyl (*N*-$COCF_3$).[19] Carbamate derivatives include *N*-allyloxycarbonyl (*N*-Alloc),[20,21] *N*-benzyloxycarbonyl (*N*-Cbz),[22] *N*-2,2,2-trichloroethoxycarbonyl (*N*-Troc),[23,24] and *N*-*p*-nitrobenzyloxycarbon-yl (*N*-PNZ).[25] Recently, phosphoryl derivatives such as *N*-dimethylphosphoryl (*N*-DMP) and others were also repated.[26,27] Among of the monosubstituted amino–protecting groups mentioned above, the *N*-Troc group has wide application in oligosaccharide synthesis, and it is fairly stable to glycosylation conditions. However, the carbamate proton can be abstracted under standard basic conditions that leads to the formation of byproducts.

Acyl derivatives:

N-$COCH_2Cl$	*N*-$COCHCl_2$	*N*-$COCl_3$	*N*-$COCF_3$

Carbamate derivatives:



N-Alloc	*N*-Cbz	*N*-Troc	*N*-PNZ

Phosphoryl derivatives:

N-DMP

Figure 2. Monosubstituted amino–protecting groups

1.3.2 Disubstituted amino–protecting groups

Disubstituted amino protection is referred to those amino–protecting groups of GlcNAc that contains two acyl substitutions which are usually presented as cyclic or acyclic structure. In order to avoid the stable oxazoline intermediate **D** (Scheme 3), the abstractable amide proton may be substituted by a functional group that survives the glycosylation conditions.[28] This concept is manifested by installation of the bivalent group, or by blocking the amino group with two monovalent protecting groups. Electrophilic activation of the glycosyl donor **E** results an oxocarbenium ion **F** which can further form an oxazolinium ion **G**. The reactive intermediate **G** can only be attacked from the β-face by a nucleophile without forming a stable oxazoline.

(i) Monosubstituted amino protection:

AcO, AcO, OAc, O, L, N, H, O, R — Lewis acid → AcO, AcO, OAc, O, +, C⁻, N, H, O, R → AcO, AcO, OAc, O, H, N⊕, O, R, CH3⁻ — $-H^+$ → AcO, AcO, OAc, O, N, O, R

A **B** **C** **D**

(ii) Disubstituted amino protection:

AcO, AcO, OAc, O, L, O, N, O, X—X — Lewis acid → AcO, AcO, OAc, O, +, C⁻, O, N, O, X—X ⇌ AcO, AcO, OAc, O, O, N⊕, O, C⁻, X—X

E **F** **G**

R = Me (Ac), tBuO (Boc), AlO (Aloc), etc.
L = leaving group
C = counter ion
X–X = (Phth), S–S (Dts)

Scmeme 3. Intermediates in Lewis acid-activated glycosylation with D-glucosamine derivatives

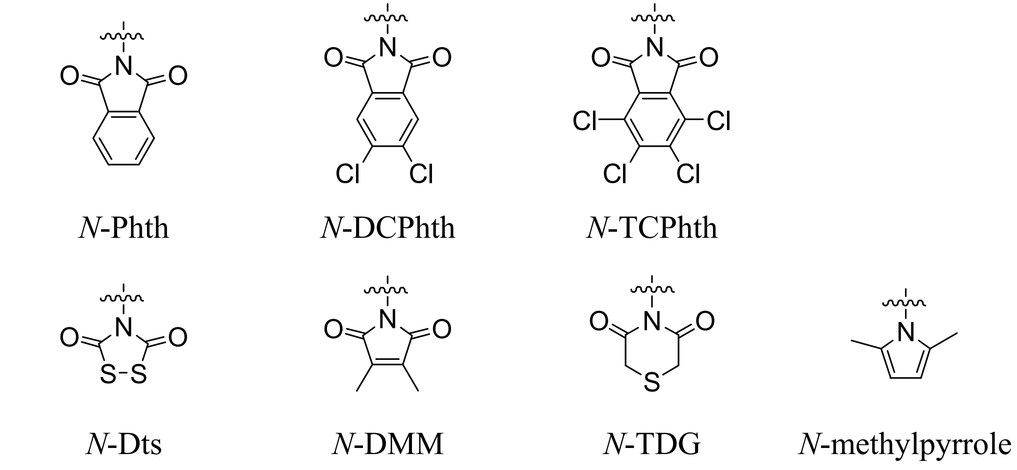
1.3.2.1 Symmetric disubstituted amino–protecting group

Most of the disubstituted symmetric amino–protecting groups are either by installation of the bivalent group or by protection of two symmetric monovalent protecting groups (Figure 3). Bivalent protecting groups include *N*-phthaloyl (*N*-Phth),[29,30] *N*-4,5-dichlorophthaloyl (*N*-DCPhth),[31] *N*-tetrachlorophthaloyl (*N*-TCPhth),[32] *N*-dithiasuccinoyl (*N*-Dts),[28,33,34] *N*-dimethylmaleoyl (*N*-DMM),[35] *N*-thiodiglycoloyl (*N*-TDG),[36] and *N*-methylpyrrole[37]. Protection of two symmetric monovalent protecting groups include *N*,*N*-diacetyl (N-Ac_2)[38] and *N*-dibenzyl (N-Bn_2).[39] Among of the disubstituted amino-protecting groups mentioned above, *N*-phthaloyl (*N*-Phth) thioglycosides are widely employed in oligosaccharide synthesis; however, the cleavage of *N*-phthaloyl moiety requires strongly basic conditions and high temperature that precludes its application to molecules with base-labile functions such as glycopeptides and glycolipids.[40]

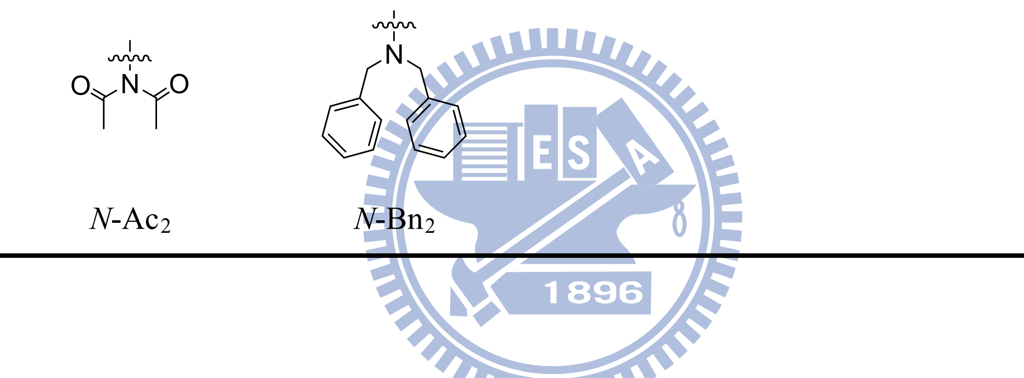
1.3.2.2 Desymmetric disubstituted amino–protecting group

Disubstituted desymmetric amino–protecting groups are rarely used in the glycosylations of oligosaccharide synthesis. Only *N*-acetyl-*N*-2,2,2-trichloroethoxy-carbonyl (*N*-AcTroc) thioglycoside has been exploited as a donor for oligosaccharide synthesis involving 1,2-*trans*-β-glycosylations (Figure 3).[41]

Bivalent protecting groups:



Symmetric monovalent protecting groups:



Desymmetric monovalent protecting groups:

N-AcTroc

Figure 3. Disubstituted amino–protecting groups

1.3.3 Oxazolidinone amino−protecting group

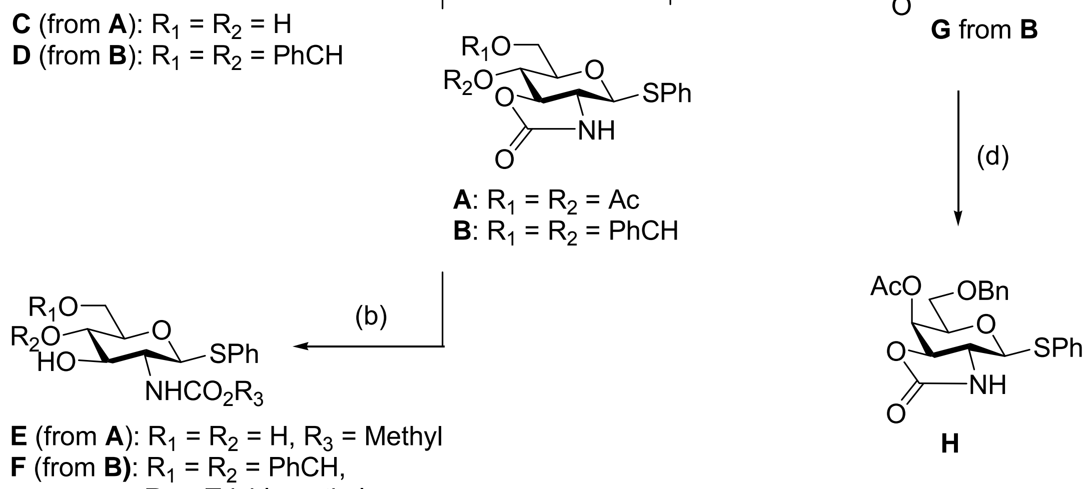
In 1969, Gross et al. first applied the cyclic carbamate (oxazolidinone) to the synthesis of the *trans*-2,3-*N*,*O*-carbamate protected glucosamine monosaccharide.[42] It was not noticed until Kerns *et al.* reported on the use of oxazolidinone protected glucosamine as donors in 2001.[43] This draws the attention of other chemists to exploit the use of the oxazolidinone protected glycosides in carbohydrate chemistry. The *N*-unsubstituted oxazolidinone protected glycosyl donors for 1,2-*cis*-α-glycosylations were further elaborated to *N*-acetyl and *N*-benzyl oxazolidinone derivatives. Both of them were applied to the oligosaccharide synthesis for either 1,2-*cis*-α-glycosylations or 1,2-*trans*-β-glycosylations.

1.3.3.1 *N*-Unsubstituted oxazolidinone

In 2001, Kerns *et al.* first applied the use of 2,3-*N*,*O*-carbamate protected glucosamine donors in glycosylations.[43] In their studies, using phenylsulfenyltriflate (PhSOTf) as the activating agent in dichloromethane at −78 °C, the *N*-unsubstituted oxazolidinone GlcNAc donor was condensed with an acceptor to afford α-linked glycosides in excellent yields (Table 1).[44] Another advantage of using *N*-unsubstituted oxazolidinone is that the mild condition for ring-opening deprotection of disaccharide **AF** (Table 1) did not promote β-elimination of the 4-linked uronic acid, a significant limitation of many base-labile protecting groups in glycosaminoglycan (GAG) synthesis. In addition to the stereoselective formation of α-linked glycosides, the ring-fused oxazolidinone provided a versatile protecting group for 2-amino sugar synthesis. Further elaborations of these oxazolidinone protected glycosyl donors to different glycosyl substrates were demonstrated (Scheme 4).

Table 1. Stereoselective formation of α-linked glycosides in high yields

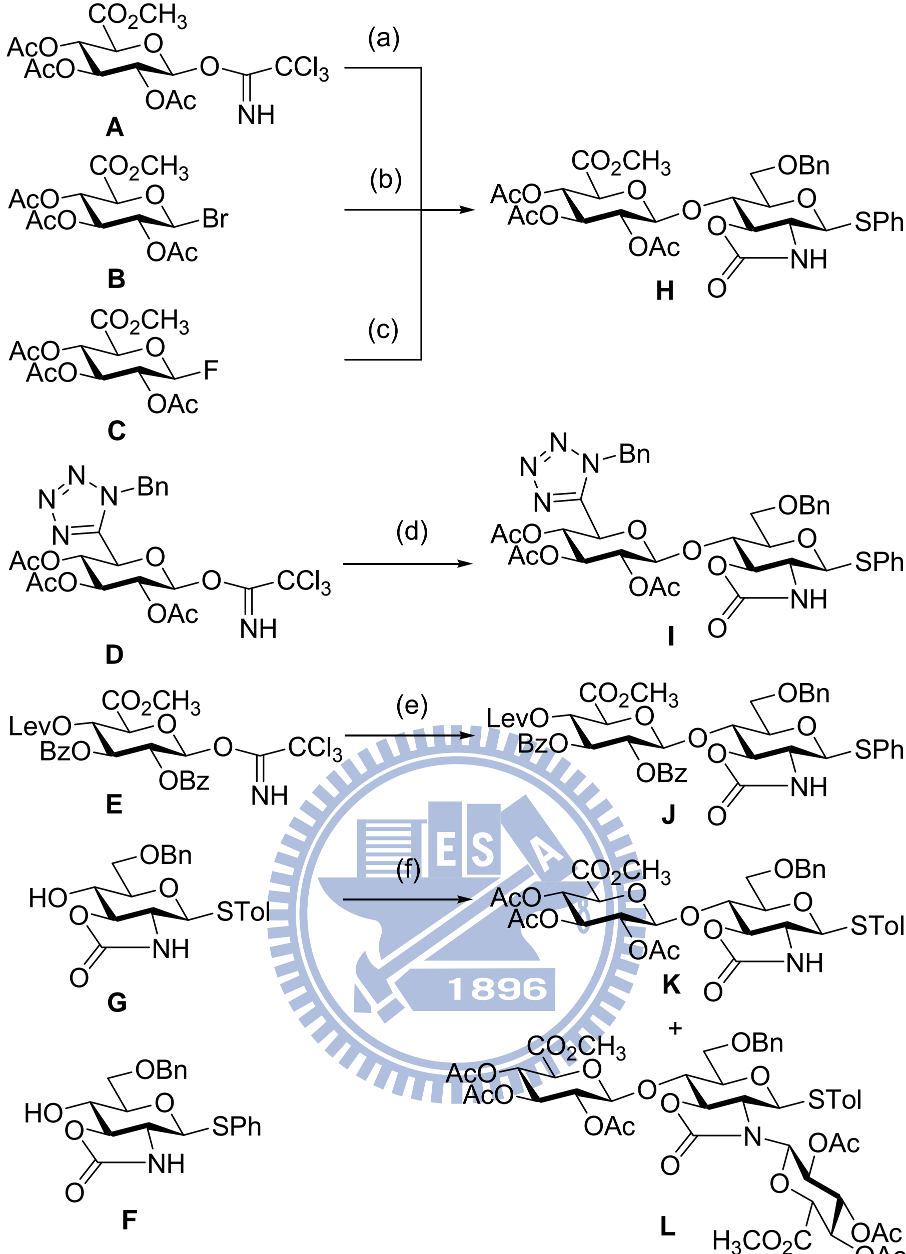
Entry	Glycosyl donor	Glycosyl acceptor	Disaccharides	Isolated yield (%)
1	**A**	**B**	**AB**	97
2	**A**	**C**	**AC**	75
3	**A**	**D**	**AD**	90
4	**A**	**E**	**AE**	95
5	**A**	**F**	**AF**	75



Scheme 4. Oxazolidinone donors as versatile intermediates

Reagents and conditions: (a) NaOH, H_2O/THF, 75–80%. (b) Cs_2CO_3, R-OH, 75–80%. (c) $NaCNBH_3$, HCl, Et_2O/THF, 98%. (d) (i) Tf_2O, pyridine; (ii) NaOAc, DMF; 86% (2 steps).

Further investigations of the same research focused on the utility of oxazolidinone protected thioglycosides as glycosyl acceptors. The accepter compatibility was demonstrated in different orthogonal glycosylation strategies (Scheme 5).[45] The yield was satisfactory; however, the following activation of the resulting disaccharides **H**-**J** using PST as previous procedure was not efficient at all. The activation was also unsuccessful at low temperatures despite the use of other promoter systems. Incompleteness of the reactions or loss of stereocontrol were observed at higher reaction temperatures (–20 °C to room temperature). This phenomenon is similar to that reported by Boons, *trans*-2,3-cyclic carbonate protected glycosyl donors have significantly lower anomeric reactivities than fully acylated and *N*-acyl protected donors.[46] When the phenyl thioglycoside was changed into *p*-methylphenyl thioglycoside which was anticipated more readily activated (Scheme 5), the yield was still moderate. What's even worse is that the oxazolidnone nitrogen was more readily glycosylated with the donor than an amide nitrogen, and this may complicate the iterative linking of sugar units. One way to avoid this off-target glycosylation was to protect the oxazolidinone nitrogen. Hence, to eliminate *N*-glycosylation and aim at improving the α-stereoselectivity, two types of *N*-protected oxazolidinone protected glycosides had been developed.

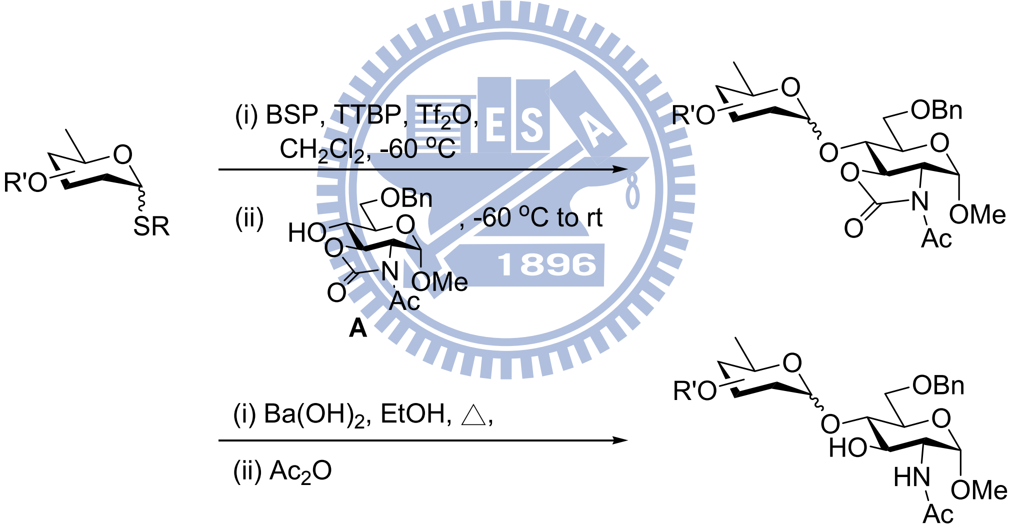


Scheme 5. Orthogonal glycosylation reactions of *N*-unsubstituted thioglycosides

Reagents and conditions: (a) **F**, $BF_3 \cdot OEt_2$, CH_2Cl_2, sieves, 0 °C to rt, 88%. (b) **F**, AgOTf, CH_2Cl_2, sieves, 0 °C to rt, 98%. (c) **F**, $AgClO_4$–$SnCl_2$, CH_2Cl_2, sieves, 0 °C to rt, 70%. (d) **F**, $BF_3 \cdot OEt_2$, CH_2Cl_2, sieves, 0 °C to rt, 91%. (e) **F**, $BF_3 \cdot OEt_2$, CH_2Cl_2, sieves, 0 °C to rt, 81%. (f) **A**, $BF_3 \cdot OEt_2$, CH_2Cl_2 or **B**, $BF_3 \cdot OEt_2$, CH_2Cl_2, 40–60% for **K**, 20–30% for **L**.

1.3.3.2 *N*-Acetyl oxazolidinone

In 2003, Crich *et al.* first reported that oxazolidinone protected *N*-acetyl glucosamine 4-OH derivative was a highly reactive glycosyl acceptor.[47] It is believed that the 4-hydroxyl group of *N*-acetyl glucosamine derivative is a poor glycosyl acceptor due to steric hindrance. This phenomenon is common to most pyranose 4-OH's.[48] In addition, the *N*-acetyl group is engaged in intermolecular hydrogen-bonded network that further decreases the nucleophilicity.[49] To overcome these situations, a suitable *N*-acetyl oxazolidinone **A** (Scheme 6) was prepared and subjected to couplings with a range of thioglycosides.



Scmeme 6. Glycosylation of *N*-acetyl oxazolidinone acceptors with thioglycosides

The donors were exposed to the combination of 1-benzenesulfinylpiperidine (BSP),[50] 2,4,6-tri-*tert*-butylpyrimidine (TTBP),[51] and triflic anhydride (Tf_2O) in CH_2Cl_2 at −60 °C before addition of the acceptor and followed by warming the reaction mixture to room temperature. Meanwhile, they tested the acceptor's generality by three other coupling methods such as Kahne's sulfoxide method,[52] Gin's dehydrative coupling sequence,[53] and Schmidt's trichloroacetimidate protocol (Table

2).[54] Even though the acceptor performed well in most cases, the selectivities and yields were varied with glycosyl donors and reaction conditions.

Table 2. Alternative coupling methods for the formation of disaccharide

B: X = β-SPh
C: X = β-S(O)Ph
D: X = α, β-OH
E: X = α-OC(=NH)CCl_3

A → (Promoters, CH_2Cl_2) → **F**

Donor	Promoters	Anomeric ratio (α/β)	Yield (%)
B	BSP; TTBP, Tf_2O; –60 °C	6.2:1	78
C	TTBP, Tf_2O; –60 °C	α only	63
D	Ph_2SO, Tf_2O, TTBP; –40 °C	α only	59
E	TMSOTf, –30 °C	3.5:1	82

Since there are reports on dependence of nucleophilicity of glycosyl acceptors on their anomeric configurations, Crich *et al.* wanted to synthesize both α- and β-methyl glycosides to compare their nucleophilicities in 2005.[55-57] At first, α-methyl glycosides were successfully obtained (Scheme 7). However, their attempt to prepare these glycosides met with some issues.[58] When the same reaction sequence was applied to β-thioglycosides, α-anomers were obtained instead of the expected β-anomers. β→α anomerization occurred during reductive ring opening of benzylidene. Repeated attempts at overcoming this epimerization by controlling the acidity of the medium were unsuccessful and consequently they turned to an alternative reaction sequence (Scheme 8). Because the typical reductive cleavage of benzylidine acetals to benzyl ethers under conditions using cyanoboro-

hydride–hydrogen chloride ($NaBH_3CN$–HCl) was suitable for numerous β-glycosides, this anomerization was unexpected.[59,60] They presumed that the strain imposed on the pyranose ring by the presence of the *trans*-fused oxazolidinone ring promoted the ring opening by endocyclic cleavage of the C1–O5 bond (detailed discussion in result & discussion P.32–33).

(a) 4-$O_2NC_6H_4OCOCl$
(b) Amberlyst IR 120, 76%

AcCl
EtN(*i*-Pr)$_2$, 92%

$NaCNBH_3$,
HCl, Et_2O, 80%

Scmeme 7. Preparation of the α-configured methyl oxazolidinone acceptor

(a) 4-$O_2NC_6H_4OCOCl$
(b) Amberlyst IR 120, 81%

AcCl
EtN(*i*-Pr)$_2$.89%

Pd/C, H_2
THF, 82%

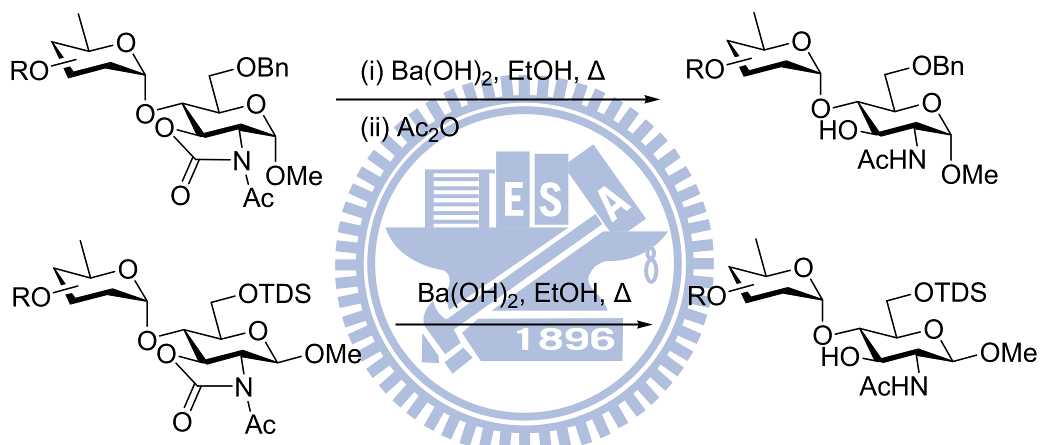
$NaCNBH_3$
HCl/Et_2O
53%

TDSCl, Imidazole
DMF, 92%

TDS = thexyldimethylsilyl

Scmeme 8. Preparation of the β-configured methyl oxazolidinone acceptor

With the α- and β-anomers in hand, a series of glycosylation couplings were examined with a variety of thioglycosides and they behaved analogously in glycosylation reactions. A major difference between these anomers was the deprotection of their resulting disaccharides (Scheme 9). The selective cleavage of oxazolidinone rings in the β-anomer was possible and led to *N*-acetyl-glucosamine-based disaccharide. While for the α-glycoside acceptor, complete removal of oxazolidinone and acetyl functions occurred, therefore reacetylation of amine was needed.



Scmeme 9. Removal of the oxazolidinone in α- and β-methyl oxazolidinone series

Shortly after Crich's report, Oscarson *et al.* used *N*-acetyl oxazolidinone protected thioglycosides as glycosyl donors to glycosylate with a steroid and glycosyl acceptors using *N*-iodosuccinimide (NIS) and catalytic amount of silver triflate (AgOTf) as promoters, high yields of β-linked glycosides were obtained. Surprisingly, when a larger quantity of AgOTf (0.4 equiv) was used in the coupling reactions, similar high yields of α-linked glycosides were obtained (Table 3).[61] This contrasting result may probably be related to *in situ* anomerization which was similar to Crich's

observation for reductive opening of the benzylidene ring in oxazolidinone protected *N*-acetyl glucopyranosides.

Table 3. Stereoselective coupling reactions between *N*-acetyl oxazolidinone donors and acceptors

Entry	Acceptor	Product	Yield (%)
1			91[a]
2			89[b]
3			90[a]
4			94[a]
5			91[b]

[a] 0.1 equiv AgOTf. [b] 0.4 equiv AgOTf.

Afterwards, also at the same year, Kerns *et al*. realized their hypothesis proposed in 2003 that substitution of the oxazolidinone nitrogen precluded *N*-glycosylation and prevented off-target reactions with activating reagents.[62] At first, they chose thioglycosides **B** (Figure 4) as glycosyl donors using PST as a promoter that previously employed. However, a complex reaction mixture was obtained and the yield of the disaccharide was low. After that, they tried BSP/TTBP/Tf_2O promoting system as previously reported by Crich *et al*. which enabled complete activation.

Figure 4. *N*-Unsubstituted and *N*-acetyl oxazolidinone protected thioglycoside donors

Encouraged by this observation, they estimated the coupling of **B** with a varirty of acceptors (Table 4). Since Crich and co-workers formerly reported α-glycosyl triflate intermediates during BSP/Tf_2O activation of thioglycosides. A dynamic system where α-glycosyl triflate is in equilibrium with its less stable but more reactive β-glycosyl triflate was proposed.[63,64] In addition, the molecular models of the α- and β-glycosyl triflate intermediates revealed that the *N*-acetyl moiety gave steric hindrance to β-face on the α-triflate which was attacked by hindered nucleophiles. As a result, they concluded that the stereoselectivity of glycosylation relied on the structure of the acceptors, *N*-substituent on the oxazolidinone ring, and promoters in glycosylations. These factors affect reaction rates and an equilibrium between α- and β-anomeric triflates, and finally induce the stereocontrol of the glycosidic bond.

Table 4. Glycosylation of oxazolidinone thioglycoside donor under BSP/Tf_2O activation conditions

Donor (SPhMe) + R-OH → (BSP, Tf_2O, TTBP; CH_2Cl_2, -60°C) → product (OR)

Entry	Acceptor (R-OH)	Product	t (h)	Ratio (α:β)	Yield (%)
1			1	β only	83
2			1	β only	95
3			4	β only	90
4			12	1:20	82
5			12	1:7	75
6			24	1:4.5	75
7			48	1.6:1	65
8			48	2.8:1	77
9			48	α only	90

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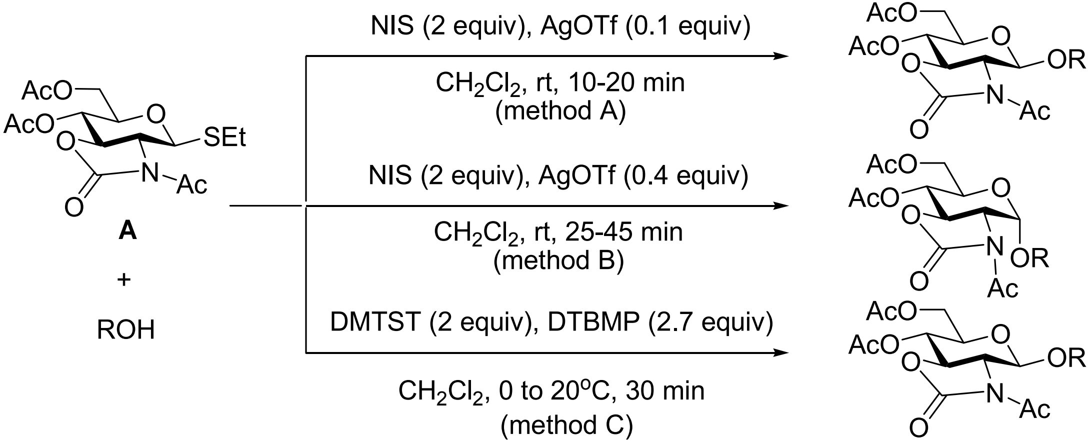
Later on, Kerns *et al*. reported another study for chemoselective manipulation of oxazolidinone derivatives of *N*-acetyl-D-glucosamine (Figure 5).[65] They presented specific methods that were useful for elaborating sugar glycosides of the glycoconjugates that containing variably substituted 2-amino-2-deoxy-D-hexopyranosides.

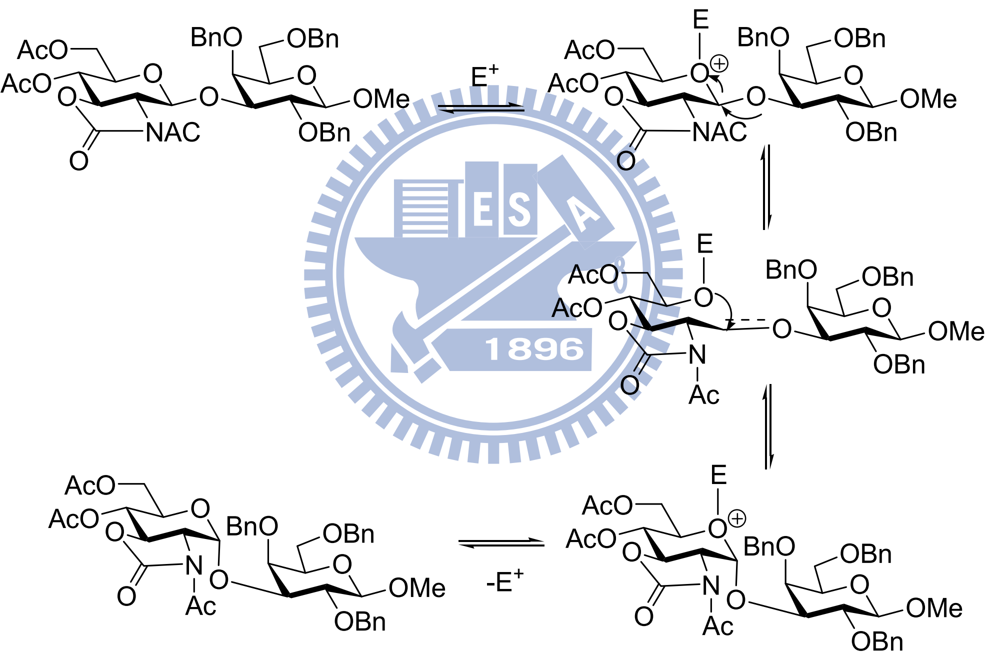
Figure 5. Chemoselective manipulation of *N*-acetyl protected oxazolidinone

Recently, Oscarson *et al*. extended their previous work and reported a more detailed investigation of their donor-promoter system and the reaction mechanism. Either β- or α-linked glucosamine-containing glycosides can be prepared by tuning the reaction conditions (Scheme 10).[66] The stereochemical outcome could be initially



Scmeme 10. Stereoselectivity-controllable glycosylation of the *N*-acetyl oxazolidinone donor

formed β-product in method **A**. To verify the assumption that the β-product which anomerized to α-glycoside in the presence of the oxazolidinone ring was most efficient under more acidic condition, the β-product was treated with a catalytic amount of AgOTf in the NMR tube. An efficient and high-yielded anomerization was observed giving the α-glycoside almost exclusively even an excess amount of methanol was added. Based on these results, they proposed that the mechanism is perhaps via an activation of the ring oxygen and consecutive endocyclic C–O bond cleavage in preference to exocyclic cleavage (Scheme 11).



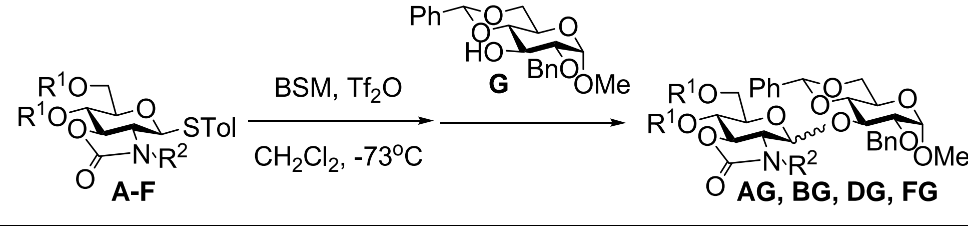
Scmeme 11. Proposed mechanism for the anomerization via endocyclic cleavage

To investigate the relationship between the stereochemistry outcomes of glycosylation and pre-activation protocol, Ye and *et al.* chose the known 2,3-oxazolidinone protected thioglycoside **A** (Scheme 12) as the glycosyl donor.[67] Donor **A** was preactivated at −73°C in anhydrous dichloromethane using benzenesulfinyl morpholine (BSM) and Tf_2O in the presence of TTBP.[68] After disappearance of donor

Scmeme 12. Stereoselectivity-controllable glycosylation of the *N*-acetyl oxazolidinone donor

A, the acceptor was added to the reaction mixture to furnish the glycosidic bond formation. The yields were high and the glycosylations proceeded with excellent β-selectivity. They attributed the β-selectivity to a S_N2-like process via the α-glycosyl triflate intermediate based on the preactivation protocol.[64] Since the use of hindered base (TTBP) is not necessary in their previous pre-activation protocol, they withdrew the base using BSM-Tf_2O promoter system in glycosylations.[68,69] Surprisingly, the yields are high and the glycosylations proceeded with excellent α-selectivity. The reversal of the stereoselectivity in the absence of TTBP probably resulted from *in situ* anomerization of the β-glycoside under acidic conditions. As a result, either β- or α-linked glucosamine-containing glycosides were prepared from the BSM-Tf_2O promoter system in the presence of TTBP or not. Next, they applied the protocol to a variety of oxazolidinone protected glucosamine thioglycosides (**A-F**) with the same acceptor **G** (Table 5).[70] The different stereoselectivities might arise from three major types of intermediates: oxocarbenium ion, α-triflate, β-triflate; the trend of the stereoselectivity remained inconsistent. In terms of the glycosylation results, the coupling between donor **B** and acceptor **G** showed the excellent β-stereoselectivity. Then they used this pair of donor and acceptor to investigate the influence on the stereoselectivity resulting from different glycosylation conditions such as solvent, te-

Table 5. Couplings of various oxazolidinone protected donors



Entry	Donor	T (°C)	Product	Yield (%)	Ratio (α:β)
1	**A**	−73	**AG**	87	1:2
2	**B**	−73	**BG**	85	β only
3	**C**	−73	no coupling	---	---
4	**D**	−60	**DG**	84	1:1
5	**E**	---	no activation	---	---
6	**F**	−50	**FG**	94	3:1

mperature, and promoter system (Table 6).[70] According to Ye's study, the stereochemistry outcomes of glycosylations are strongly influenced by the protecting groups in oxazolidinone protected glycosyl donors and the activation manner of donors; in addition, the properties of glycosyl acceptors also affect the stereoselectivity.

Table 6. The coupling of donor **B** and acceptor **G** (both in Table 5) under different conditions

Entry	Promoter system	Solvent	*T* (°C)	Yield (%)	Ratio (α:β)
1	BSM, TTBP, Tf_2O	CH_2Cl_2	–73	88	β only
2	BSP (or Ph_2SO), Tf_2O	CH_2Cl_2	–73	85–87	β only
3	*N*-(phenylthio)-ε-caprolactam, Tf_2O	CH_2Cl_2	15	86	1:1.5[a]
4	*N*-(phenylthio)-ε-caprolactam, Tf_2O	CH_2Cl_2	45	75	1:1[a]
5	*N*-(phenylthio)-ε-caprolactam, Tf_2O	toluene	15	87	1:1[a]
6	NIS, AgOTf	CH_2Cl_2	–10	86	1:2.5[a]

[a] Anomeric ratio was determined by the integration of ^1H NMR spectrum of the anomeric mixture.

1.3.3.3 *N*-Benzyl oxazolidinone

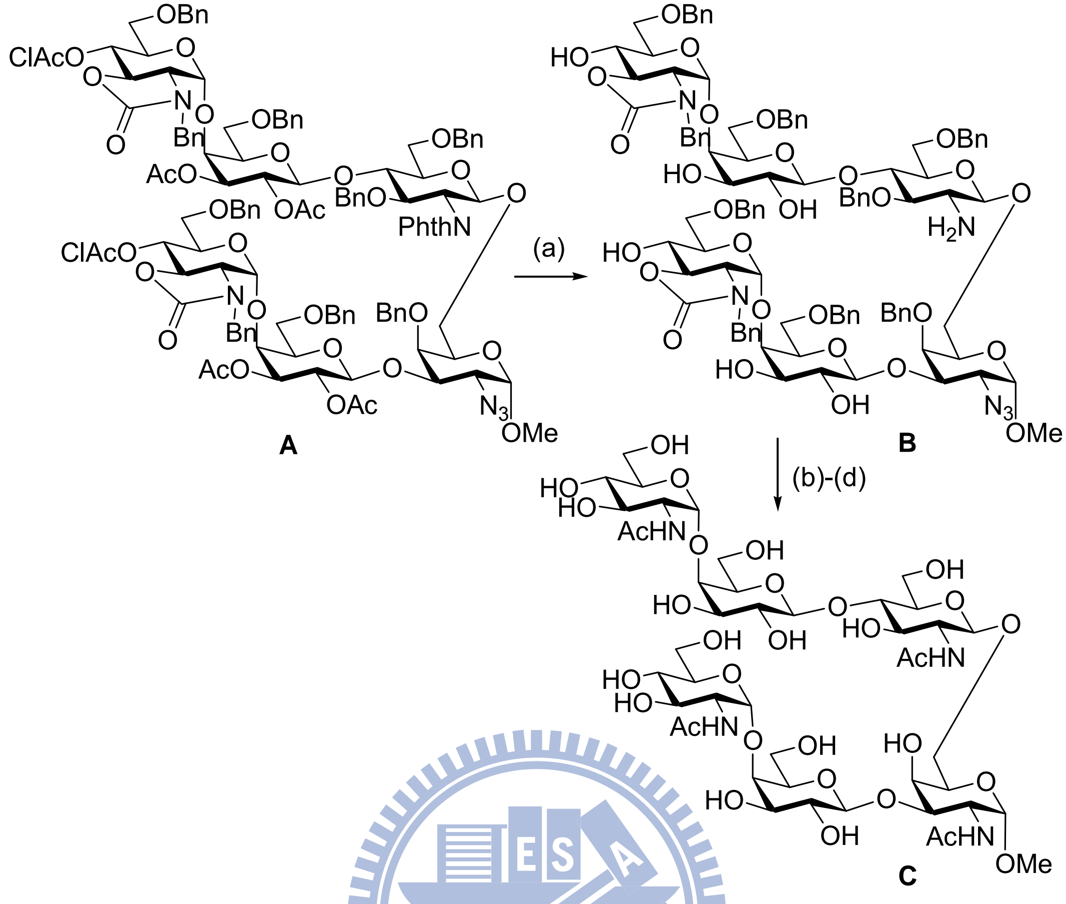
As mentioned before, although Kerns *et al.* made use of 2,3-*N*,*O*-carbamate protected glucosamine donor which gives high α-selectivity in glycosylation, this glycosyl donor has several disadvantages: (1) side reactions include *N*-sulfenylation and *N*-glycosylation, and (2) requirement of excess amount of promoter. To avoid these disadvantages, Kerns and Oscarson both protected the oxazolidinone nitrogen with acetyl group, but the α-selectivity depended on the activation conditions (e.g. lewis acid, reaction time, etc.) and the properties of donors and acceptors (e.g. reactivity, conformation, etc.). During this period, the *N*-substituent on the oxazolidinone ring except for acetyl group was not developed until Ito *et al*. reported the use of *N*-benzyl-2,3-*trans*-oxazolidinone novel glycosyl donors (**E** and **F**) for the 1,2-*cis*-α-glycosylation for 2-amino-2-deoxy sugars (Scheme 13).[71] The direct synthesis of **E** and **F** starts with the one-step conversion of trichloroethyl carbamate protected GlcNAc derivative **A** to oxazolidine derivative **B**. Reductive benzylidene acetal ring opening under typical conditions using $Et_3SiH–BF_3·OEt_2$ gave **C** (72%)

Scmeme 13. Synthesis of *N*-benzyl oxazolidinone protected donors and acceptors
Reagents and cinditions: (a) BnBr, NaH, DMF, 96%. (b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, **C**, 72%, **D**, 11% (c) chloroacetic anhydride, pyridine, CH_2Cl_2, 99%. (d) (i) Tf_2O (2 equiv), pyridine (4 equiv), CH_2Cl_2, -40 to -20 °C; (ii) NaOAc, DMF; 73% (2 steps).

and **D** (11%) with a free hydroxyl group at the 4-position.[72] The anomerization result was similar to previous reports proposed from Crich and Oscarson. Then **C** was converted to glucosamine donor **E** and galactosamine donor **F**. After a series of experiments, they selected PhSOTf/DTBMP promoting system in a solvent system of toluene/1,4-dioxane (3:1) as their optimized condition.[73] Then they used **E** and **F** in a one-pot operation to synthesize a trisaccharide which is a component of the immune system stimulating *O*-specific polysaccharide from *Proteus mirabilis* O48 (Scheme 14). The trisaccharide was obtained with complete α-selectivity, although Kerns reported the difficulty of activation of the disaccharide having 2,3-*trans*-oxazolidinone ring. The complete activation repated by Ito may be attributed to the protection of the *N* atom on oxazolidinone ring avoiding side reactions such as *N*-sulfenylation and *N*-glycosylation.

Scmeme 14. One-pot synthesis of trisaccharides via oxazolidinone glycosides
Reagents and conditions: (a) Br_2, CH_2Cl_2, 91%. (b) NaOMe, MeOH/1,4-dioxane, 99% (c) AgOTf, MS 4A, di-*tert*-butylmethylpyridine, toluene/1,4-dioxane (3:1). (d) AgOTf, PhSCl, 81% (2 steps)

Based on this successful result, the same group applied the *N*-benzyl-2,3-*trans*-oxazolidinone to the synthesis of anti-*Helicobacter pylori* oligosaccharides.[74,75] The hexasaccharide **C** was synthesized after a series of stereoselective glycosylations and deprotections (Scheme 15). This is the first total synthesis of an anti-*Helicobacter pylori* oligosaccharide which is completed with high overall efficacy by employing a *N*-benzyl-2,3-*trans*-oxazolidinone donor.



Scmeme 15. The deprotection sequence of an anti-*Helicobacter pyroli* oligosaccharides

Reagents and conditions: (a) *N*, *N*'-ethylenediamine, BuOH. (b) 1M NaOH, dioxane. (c) H_2, 20% $Pd(OH)_2/C$, AcOH, H_2O. (d) Ac_2O, MeOH, 57% (4 steps).

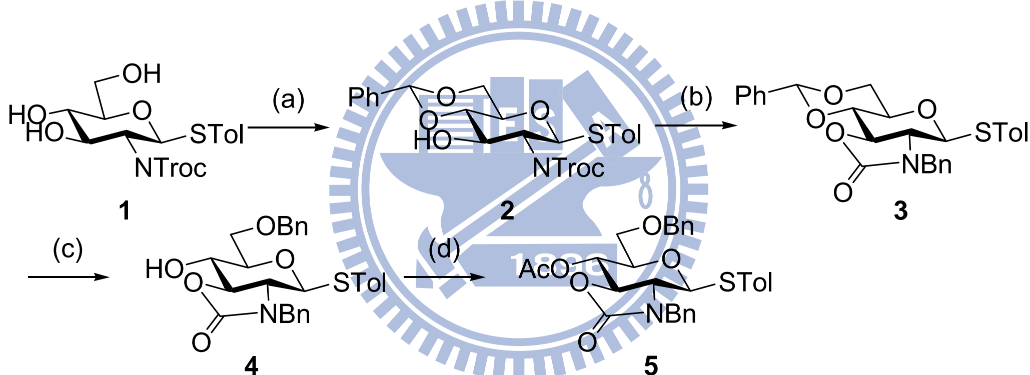
1.4 Motivation

Based on the literatures described before, we are attracted by the anomeric activity and its related stereoselectivity of *N*-benzyl oxazolidinone protected thioglycoside because these GlcNAc building blocks are relatively easy to prepare. Meanwhile, Kerns' study for chemoselective manipulation of *N*-acetyl oxazolidinone derivatives inspires us to consider the synthesis of novel donors via *N*-benzyl oxazolidinones for 1,2-*trans*-β-glycosylations (Figure 5). We herein report the investigations and findings based on our observations mentioned above.

2 Results and discussion

2.1 Anomerization phenomenon of oxazolidinone protected thioglycoside 4

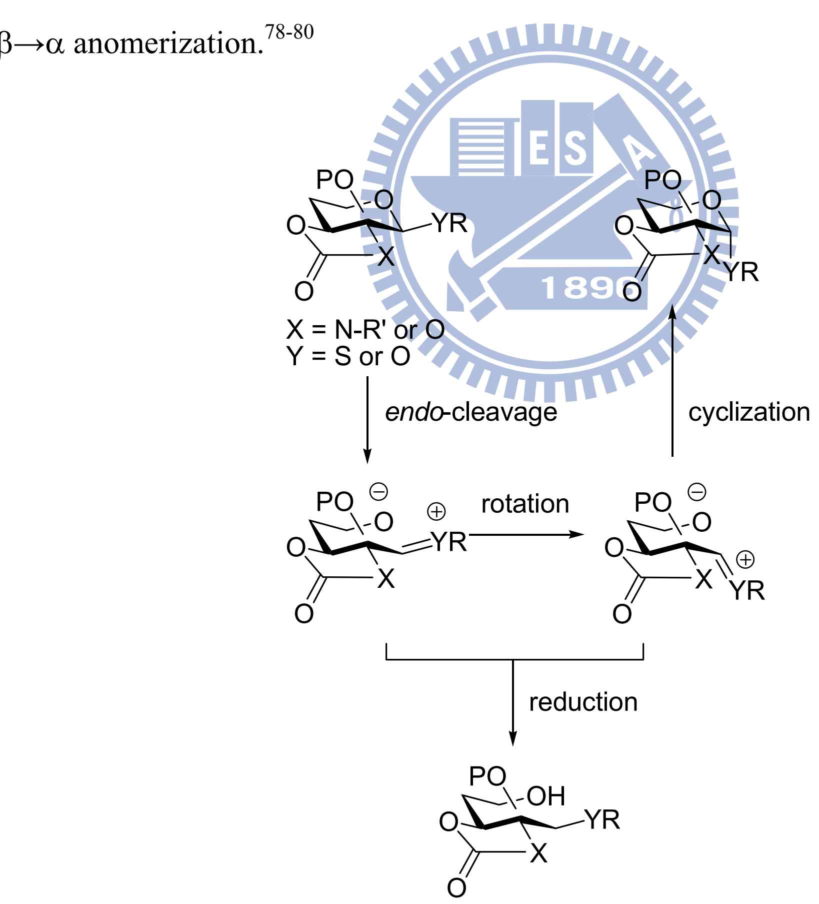
The amino protecting group that routinely used in our laboratory is the *N*-2,2,2-trichloroethoxycarbonyl group (*N*-Troc), and the transformation from the *N*-Troc to the *N*-benzyl oxazolidinone protecting group only needs one step. For an easier preparation, we seleted the *N*-benzyl oxazolidinone instead of the *N*-acetyl one. To investigate the chemical properties of the *N*-benzyl oxazolidinone derivative, the oxazolidinone glucosamine donor **5** was first prepared (Scheme 16).



Scmeme 16. Synthesis of *N*-benzyl oxazolidinone protected glucosamine donor **5**
Reagents and conditions: (a) $C_6H_5CH(OMe)_2$, cat. TsOH, CH_3CN, rt, 92%. (b) BnBr, NaH, DMF, 0 °C–rt, 80%. (c) Et_3SiH, CF_3CO_2H, 4A MS, CH_2Cl_2, -20 °C, 80%. (d) Ac_2O, pyridine, rt, 95%.

The *N*-Troc-protected thioglycoside **1** was converted to 4,6-*O*-benzylidene-2-*N*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy thioglucopyranoside **3** via benzylidene acetal intermediate **2**.[70,76] Reductive opening of the benzylidene acetal **3** afforded 4-hydroxy thioglycoside **4,** which was further acetylated to furnish the oxazolidinone glucosamine donor **5**.[77] In the selective opening of the benzylidene ring step, Crich reported that the β→α anomerization was observed when they reductively opened the benzylidene acetal using sodium cyanoborohydride–hydrogen chloride

($NaBH_3CN$–HCl)[59,60] and Ito also mentioned this phenomenon using triethylsilane–boron trifluoride etherate (Et_3SiH–$BF_3 \cdot OEt_2$)[72]. Both of them proposed the α/β mixture was from the β→α anomerization through *endo*-cleavage of C1–O5 bond under acidic conditions, while physical evidence for this phenomenon was given. This work was completed by Ito, who trapped the intermediate in the endo-cleavage process.[78] They obtained the reductive product of the pyranosides having 2,3-*trans*-carbamate and –carbonate during the reductive opening of the benzyldene ring and proposed the mechanism based on quantum mechanical computations and other related experimental data (Scheme 17). They found that acids, temperature, reaction time, solvents, and the conformation of fused ring of pyranosides affect the extent of β→α anomerization.[78-80]



Scmeme 17. Proposed mechanism for the anomerization of cyclic carbonate or -carbamate pyranosides

However, after some experimental efforts including changing reaction

temperature and addition of molecular sieves, the formation of α-anomer was ultimately eliminated when we used triethylsilane–trifluoroacetic acid (TES/TFA) combined with low reaction temperature (Table 7).[77]

Table 7. Optimizations of the reductive benzylidene ring opening of thioglycoside **3**

Ph O O O O NBn O STol

3

Et_3SiH, Acid, 4A MS,

CH_2Cl_2, *T* °C, yield%

OBn HO O O NBn O R^1 R^2

4: R^1 = STol, R^2 = H

6: R^1 = H, R^2 = STol

Entry	Acid (equiv)	Et_3SiH (equiv)	*T*	Yield (%)[a]	Ratio (α:β)
1	TFA (6)	5	25	35	1:1
2	TFA (6)	5	0	57	1:10
3	TFA (6)	5	–20	80	β only
4	$BF_3{\cdot}OEt_2$(2)	12	–20	65	1:6[b]

[a] Total yield of **4** and **6** after chromatography purification.
[b] The method was referred to ref 71.

To our delight, exclusive oxazolidinone protected β-thioglucopyranoside **4** was formed in high (80%) yield at –20 °C (Table 7, entry 3). The β-anomeric configuration of **4** was supported by the ^{13}C chemical shift at 86.7 ppm and $^1J_{CH}$ coupling constant of 161 Hz.[81] Nevertheless, the anomerization of β-anomer **4** to α-anomer **6** and trace amount of complete deacetalation product were observed at higher temperatures (Table 7, entries 1 and 2). Interestingly, the use of literature procedure resulted in a 1:6 α/β-amomeric mixture at –20 °C, which was consistent with literature finding (Table 7, entry 4).[71] We speculate that the weak coordinateon affinity of TFA with ring oxygen atom at low reaction temperature compared with $BF_3{\cdot}OEt_2$ may be the main reason for the reduction of anomerization.

2.2 Glycosylation studies of the thioglycoside donor 5

After the preparation of oxazolidinone thioglycoside **5**, we focused on the electrophilic activation of this donor and tried to use promoter systems which have not been reported. The activation of this donor was investigated using primary alcohol **7** as the acceptor, and the result was shown in Table 8. The thioglycoside **5** remained intact upon treatment with the *N*-iodosuccinimide/trimethylsilyl trifluoromethane-sulfonate combination (NIS/TMSOTf) at temperature range between −78 to −20 °C (Table 8, entry 1),[82] dimethyl(thiomethyl) sulfonium trifluoromethane sulfonate/ tetrabutyl ammonium bromide combination (DMTST/Bu_4NBr) at the temperature range of −78 to 0 °C (Table 8, entry 3)[83], *N*-iodosuccinimide/silver trifluoromethane-sulfonate combination (NIS/AgOTf) at temperature range between −78 to 0 °C (Table 8, entry 5), benzenesulfinyl piperidine/triflic anhydride/2,6-di-*tert*-butyl-4-methyl pyridine combination (BSP/Tf_2O/DTBMP) in CH_2Cl_2 at temperature range between −78 to 20 °C (Table 8, entry 7),[50] and BSP/Tf_2O/DTBMP in 1,4-dioxane/toluene (1:3) solvent mixtures at the temperature range of −78 to 25 °C (Table 8, entry 8).[50,73] When the temperature was raised, the thioglycoside **5** was activated but no glycosylation product was obtained (Table 8, entries 2, 4, and 6). From Table 8, we found that the activation temperature of the thioglycoside **5** was between −10 °C to room temperature among the promoter systems we selected.

Table 8. Glycosylation studies of *N*-benzyl oxazolidinone protected donor **5** and acceptor **7**

Entry	Promoters (equiv)	Solvent	*T* (°C)	Results
1	NIS (1.1), TMSOTf (0.3)	CH_2Cl_2	−78 to −20	no activation of **5**
2	NIS (1.1), TMSOTf (0.3)	CH_2Cl_2	−10	decomposition of **5**
3	Bu_4NBr (3), DMTST (3)	CH_2Cl_2	−78 to 0	no activation of **5**
4	Bu_4NBr (3), DMTST (3)	CH_2Cl_2	25	decomposition of **5**
5	NIS (1.5), AgOTf (0.3)	CH_2Cl_2	−78 to 0	no activation of **5**
6	NIS (1.5), AgOTf (0.3)	CH_2Cl_2	0 to 25	decomposition of **5**
7	BSP (1.3), Tf_2O (1.3), DTBMP (2.6)	CH_2Cl_2	−78 to −20	no activation of **5**
8	BSP (1.3), Tf_2O (1.3), DTBMP (2.6)	1,4-dioxane: toluene (1:3)	−78 to 25	no activation of **5**

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2.3 Reactivity based chemoselective glycosylations of thioglycoside 4

The reactivity of the thiotolyl leaving group in oxazolidinone protected donor **5** was poor in NIS/TMSOTf promoter system. Perhaps, we could use the oxazolidinone protected thioglycosides as glycosyl acceptors in reactivity-based chemoselective glycosylations.[46,84] To test our hypothesis, a series of glycosylations were studied using the NIS/TMSOTf promoter system and the results were shown in Table 9. In first instance, thiogalactopyranoside **8** [85] was selected as a donor to glycosylate with the thioglycoside acceptor **4**. As we expected, the Gal-α-(1→4)-GlcNAc disaccharide **13** was obtained in acceptable yield and complete α-selectivity was observed (Table 9, entry 1). This result encouraged us to further investigate the glycosylation with thiogalactopyranoside with an ester groups at C-2 position. Glycosylations of **9–11** [84] with **4** produced Gal-β-(1→4)-GlcNAc (type 2 LacNAc) disaccharides **14–16** with moderate to high (50–80%) yields (Table 9, entries 2–4). When the C-2 position of the thiogalactopyranoside was protected by the benzoyl group, the yield was high in comparison with the acetyl group which may induce side reactions such as acyl migrations to lower the yield of glycosylation. Intriguingly, the glycosylation of thiofucopyranoside **12** [86] with **4** furnished Fuc-α-(1→4)-GlcNAC disaccharide **17**, but the thiotolyl leaving group in the disaccharide underwent β→α anomerization forming an inseparable 1:3.5 α/β-anomeric mixture at temperature of -60 ^{o}C (Table 9, entry 5). This anomerization could be explained by C1–O5 endocyclic bond cleavage as described before. Due to the deactivation of the oxazolidinone, self-condensation of **4** was not observed under the present reaction conditions. The results implicates that the reactivity-based chemoselective glycosylation is feasible and oxazolidinone GlcNAc acceptor can be used as an acceptor with low donor reactivity.

Table 9. Glycosylation studies of *N*-benzyl oxazolidinone acceptor **4**

thioglycoside donor **8**, **9**, **10**, **11**, or **12** + glucosamine acceptor **4** → (NIS, cat. TMSOTf, 4A MS; CH_2Cl_2, *T*) disaccharide **13**, **14**, **15**,**16**, **or 17**

Entry	Thioglycoside donor	*T* (°C)	Disaccharide product	Yield (%)
1	**8**	−70	**13**	70
2	**9**	−65	**14**	50
3	**10**	−65	**15**	65
4	**11**	−70	**16**	80
5	**12**	−60	**17** (α:β = 1:3.5)	85

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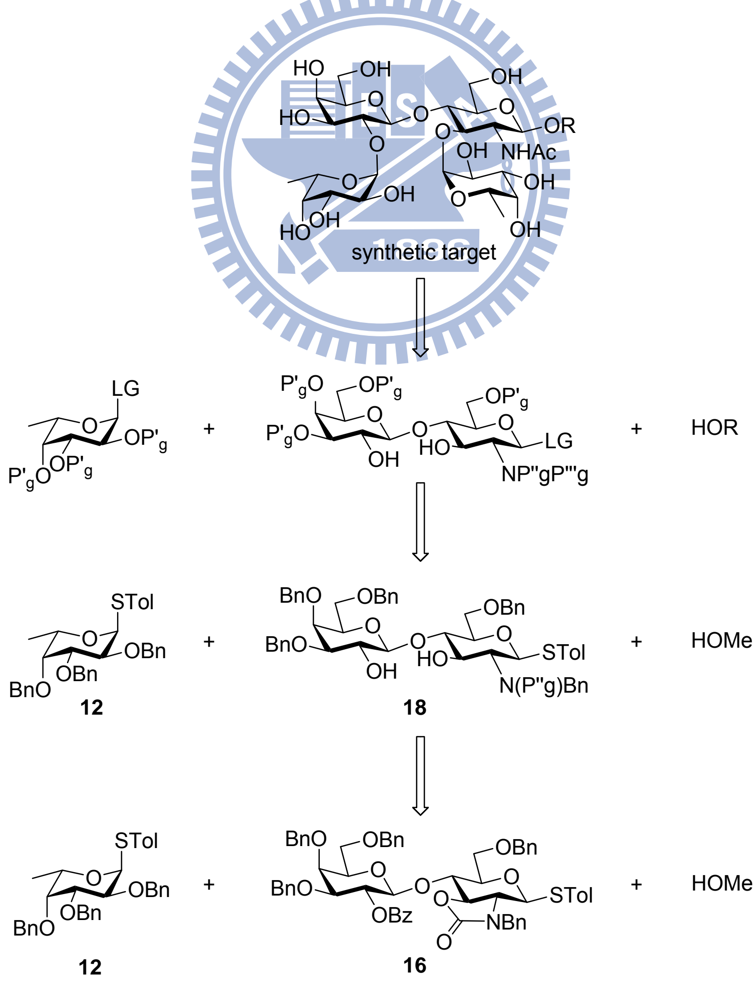
2.4 Retrosynthetic analysis of tetrasaccharide Lewis Y

On a close look at the structure of Lewis Y, empirically it could be synthesized from disaccharide **16** (Table 9, entry 4) which had the backbone structure of Gal-β-(1→4)-GlcNAc. If we can further elaborate disaccharide **16,** the synthetic route would be attainable to get tetrasaccharide which is part of Lewis Y oligosaccharide (Scheme 18). After removal of the oxazolidinone in **16**, the exposed secondary amine should be protected by a suitable protecting group to avoid *N*-glycosylation. This prompted us to design a desymmetry tertiary amino protecting function as illustrated by disaccharide **18**.



Scmeme 18. Retrosynthetic analysis of tetrasaccharide Le^{y}

2.5 Removal of oxazolidinone ring in monosaccharide

However, the reaction conditions for the removal of oxazolidinone ring should be carefully studied prior to the design of the tertiary amine. To start our study, glucosamine derivative **1** was transformed to oxazolidinone glucosamine **19** with only one step using the known literature procedure.[70] After preparation of thioglycoside **19**, it was used as a model and subjected to a range of reaction conditions to the suitable method for the removal of oxazolidinone rings (Table 10). Substrate **19** was remained when it was treating with *p*-toluenesulfonic acid (PTSA) in methanol,[87] and obtained in low yield with methyl magnesium chloride (CH_3MgCl) in THF (Table 10, entries 1 and 2).[88] In the event, the literature procedures were the suitable methods for the removal of the oxazolidinone ring. Substrate **19** under basic condition (1,4-dioxane/

Table 10. Removal studies of the *N*-benzyl oxazolidinone ring in monosaccharide **19**

OBn, BnO, O, STol, NBn, O — **19** —(Reagents / solvent, *T*, t)→ OBn, BnO, HO, O, STol, NHBn — **20**

Entry	Reagents (equiv)	Solvent	*T* (°C)	t	Yield (%)
1	CH_3MgCl (10)	THF	25	10 min	42
2	PTSA (1)	MeOH	−10	12h	no reaction
3	NaOH[a]	1,4-dioxane	25	12h	no reaction
4	NaOH[a]	1,4-dioxane	60	12h	73
5	*t*-BuOK (5)	DMSO	25	30 min	75

[a] 1 M aqueous NaOH solution

1M NaOH, v/v = 1:1) was deprotecd at 60 °C, but is was intact at room temperature (Table 10, entries 3 and 4).[71] Also, substrate **19** was deprotected under basic condition (*t*-BuOK/DMSO) at room temperature (Table 10, entry 5).[70] We finally selected the *t*-BuOK/DMSO basic condition (Table 10, entry 5) to remove the oxazolidinone ring because of the highest deprotection yield and shorter reaction time.

2.6 Synthesis and characterization of desymmetric amino–protecting groups

With glucosamine derivative **20** in hand, our attention was focused on the selection of a protecting group which can induce 1,2-*trans*-β-glycosylation and also can be removed under mild conditions. At first, acetyl group was our choice on account of the natural *N*-acetyl function, and it would simplify the subsequent deprotection. Although a number of conditions we had tried, the yield of glucosamine derivative **21** was not improved (Scheme 19). Hence, we changed to use *tert*-butoxyc-

Scmeme 19. Investigations of desymmetric glucosamine acceptors

Reagents and conditions: (a) Ac_2O, $NaHCO_3$, MeOH, rt, 30%. (b) Boc_2O, $NaHCO_3$, MeOH, rt, 76%. (c) $HO(CH_2)_6Cl$ **7**, NIS, cat. TMSOTf, 4A MS, -40 °C; (d) Ac_2O, pyr., rt; 50% (2 steps). (e) CbzCl, $NaHCO_3$, MeOH, rt, 82%. (f) $HO(CH_2)_6Cl$ **7**, NIS, cat. TMSOTf, 4A MS, -65 °C, 88%. (g) $PdCl_2$,

Et_3SiH, Et_3N, CH_2Cl_2, rt, 45%.

arbonyl group for its versatile deprotection methods. Treatment of **20** with $NaHCO_3$ in MeOH, followed by di-*tert*-butyl dicarbonate gave desymmetric *N*-benzyl-*N*-*tert*-butoxy protected glucosamine thioglycoside **22** in 76% yield.[89] Unfortunately, subsequent glycosylation of **22** with acceptor **7** was characterized by the cleavage of the *N*-substituent, and the main compound recovered was the amine **23**. The amine **23** was further acylated to **24** for characterizations. After searching literatures, we found that the experimental result was similar with Boullanger's work, and the formation of **23** could be due to removal of one of the carbamate protons from the intermediate **A** (Scheme 20) to form isobutylene together with **23**.[90] Boullanger *et al.* conducted a study on the glycosylation of simple acceptor alcohols with various *N*-alkoxycarbonyl derivatives of glucosamine. Their investigation inspired us to adopt the benzyloxycarbonyl group to protect the secondary amine in glucosamine derivative **20**. Again, treatment of **20** with $NaHCO_3$ in MeOH, followed by benzyloxycarbonyl chloroformate gave desymmetric *N*-benzyl-*N*-benzyloxycarbonyl (*N*-BnCbz) protected glucosamine thioglycoside **25** in high yield of 82%.[89] Subsequent glycosylation of **25** with primary alcohol **7** gave the β-glycoside **26** in 88% yield (Scheme 19). Although the yields of **25** and **26** were satisfactory and their preliminary

Scmeme 20. Plausible mechanism for the formation of compound **23**

identifications were evidenced by HRMS, the assignments of NMR spectra were difficult due to the peak broadening of the resonance signals. After searching literatures, we found that the peak broadening phenomenon was quite similar with Lafont's research.[91] The ^{1}H NMR spectrum of *N*-acetyl-*N*-allyloxycarbonyl protected glucosamine derivative **A** (Figure 6) revealed the presence of two conformers (45:55). They pointed that this observation could be due to the restricted rotations around the amide bond, and the coalescence of signals appeared when the temperature was increased. Compared to our study, the ^{1}H NMR spectrum was unclear at room temperature. When the temperature was raised, the broadened peaks became sharp at 100 ^{o}C as shown in Figure 7 (ca VT-NMR from 30 to 100 ^{o}C in deuterated DMSO solvent). This phenomenon could also be attributed to the restricted rotations around the amide bond based on our VT-NMR spectra and Lafont's research. Although we could get clear spectrum at elevated temperature of 100 ^{o}C, it was unpractical since the operation of NMR machine at such elevated temperature were quite time-spending and laborious. We predicted that the broadening of resonance signal was resulted from the presence of the carbamate function. In order to prove our predictions, the Cbz protecting group was removed under mild conditions (Scheme 19).[92] Consistent with our reasoning, the broadening phenomenon was disappeared, and the clear NMR spectrum of β-glycoside **27** (data were shown in experimental section) could be obtained at room temperature.

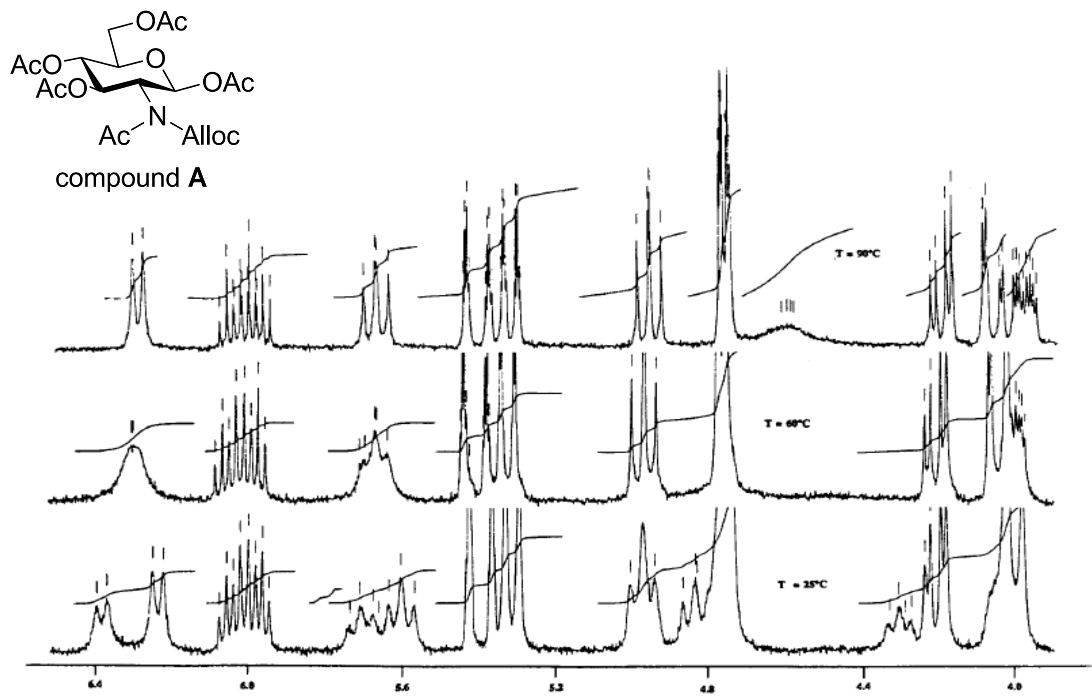


Figure 6. ^{1}H NMR spectra of compound A at different temperatures

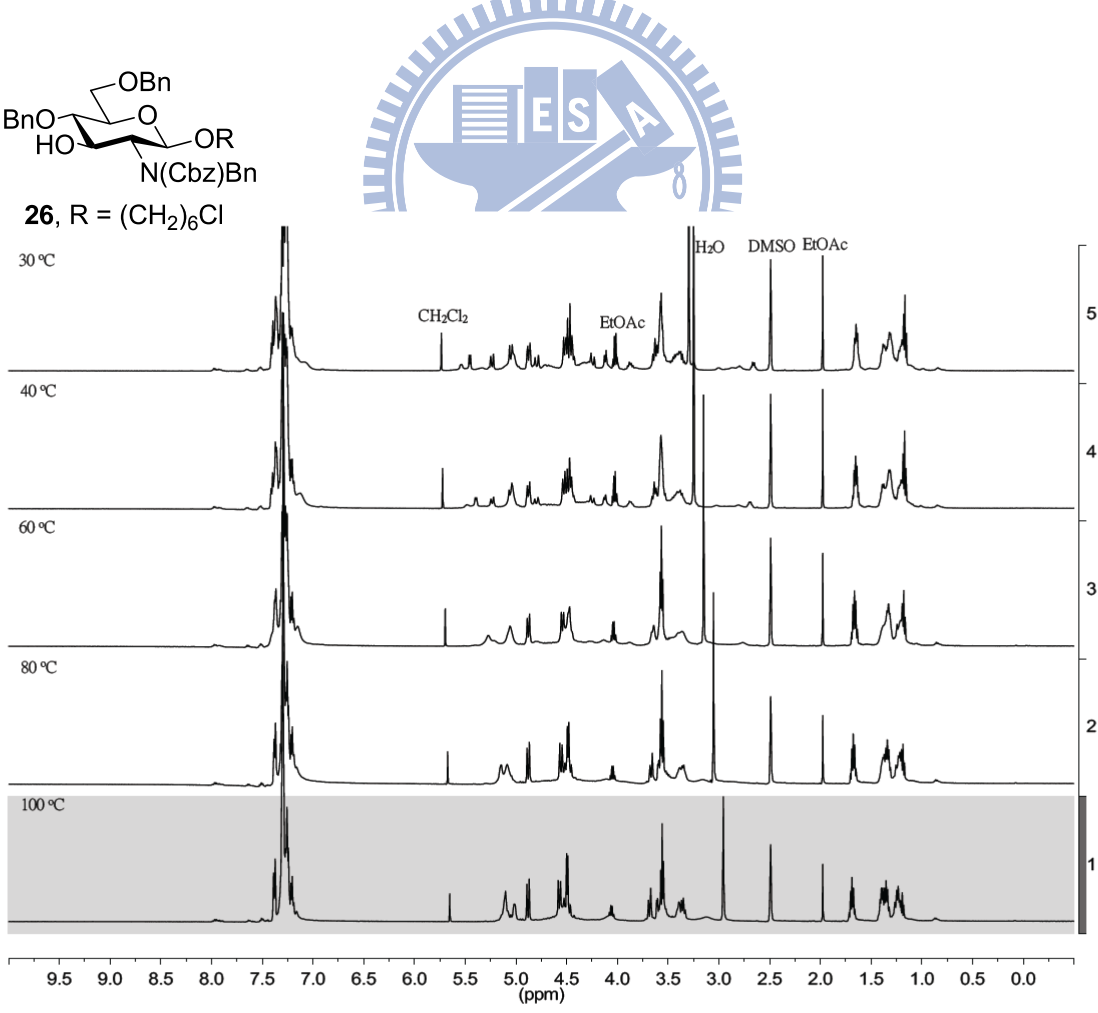


Figure 7. VT-NMR ^{1}H NMR spectrum stacked plot of compound **26**

2.7 Glycosylation studies of the glucosamine acceptor 25

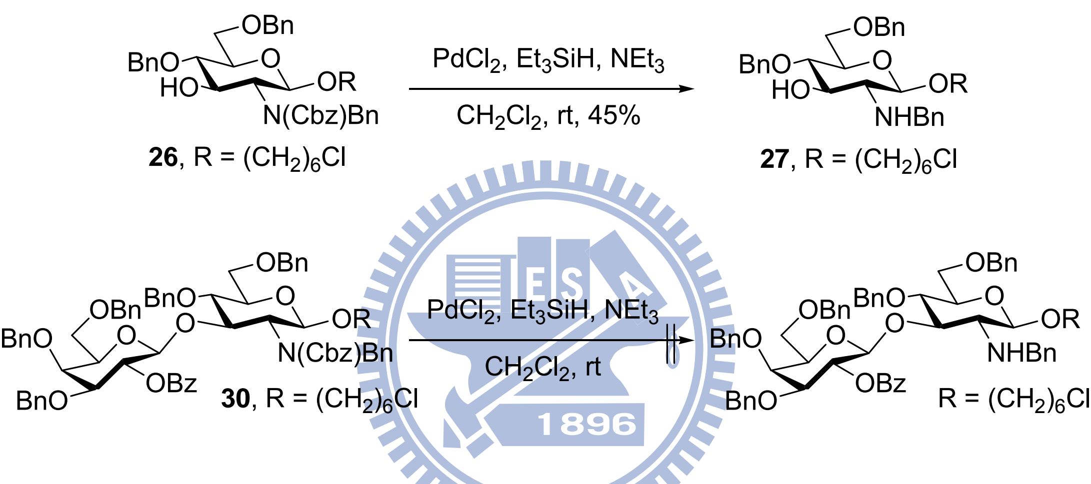
After characterizations of the desymmetric *N*-BnCbz protected glucosamine **25**, the next step was glycosylation studies of the acceptor **26** with thioglycosides **11**, **12**, **28**, and **29** (Table 11). Glycosylations of **26** with thioglactopyranosides **11**, **28**, and **29** furnished the expected Gal-β-(1→3)-GlcNAc (type 2 LacNAc) disaccharides **30–32** in high (73-80%) yields (Table 11, entries 1–3). The coupling of thiofucopyranoside

Table 11. Glycosylation studies of the desymmetric glucosamine acceptor **26**

thioglycoside donor **11**, **12**, **28**, or **29** + glucosamine acceptor **26** —NIS, cat. TMSOTf, 4A MS / CH_2Cl_2, *T*→ disaccharide **30**, **31**, **32**, **or 33**

Entry	Thioglycoside donor	*T* (°C)	Disaccharide product	Yield (%)
1	**11** (BnO, OBn, BnO, STol, OBz)	−65	**30**, R = $(CH_2)_6Cl$ (BnO, BnO, BnO, BnO, OBz, OBn, OR, N(Cbz)Bn)	80
2	**28** (BnO, OBn, AllO, STol, OBz)	−65	**31**, R = $(CH_2)_6Cl$ (BnO, BnO, AllO, BnO, OBz, OBn, OR, N(Cbz)Bn)	73
3	**29** (BnO, OBn, PMBO, STol, OBz)	−65	**32**, R = $(CH_2)_6Cl$ (BnO, BnO, PMBO, BnO, OBz, OBn, OR, N(Cbz)Bn)	70
4	**12** (STol, OBn, BnO, OBn)	−70	**33**, R = $(CH_2)_6Cl$ (BnO, OBn, OR, N(Cbz)Bn, OBn, BnO, OBn)	93

12 and acceptor **26** led to the Fuc-α-(1→3)-GlcNAc disaccharide **33** which is the backbone of type 1 Lewis antigens in high yield of 93% (Table 11, entry 4). All the glycosylations proceeded smoothly and the yields were satisfactory. The peak broadening was also occurred in the NMR spectroscopy of disaccharides **30–33**. We tried in vain to remove the Cbz protecting group in disaccharide **30** using the same condition which was feasible for monosaccharide **26** (Scheme 21). The reason is not clear at this stage.



Scmeme 21. Selective deprotection studies of the Cbz protecting group

2.8 Hydrogenolysis of oxazolidinone protected disaccharides

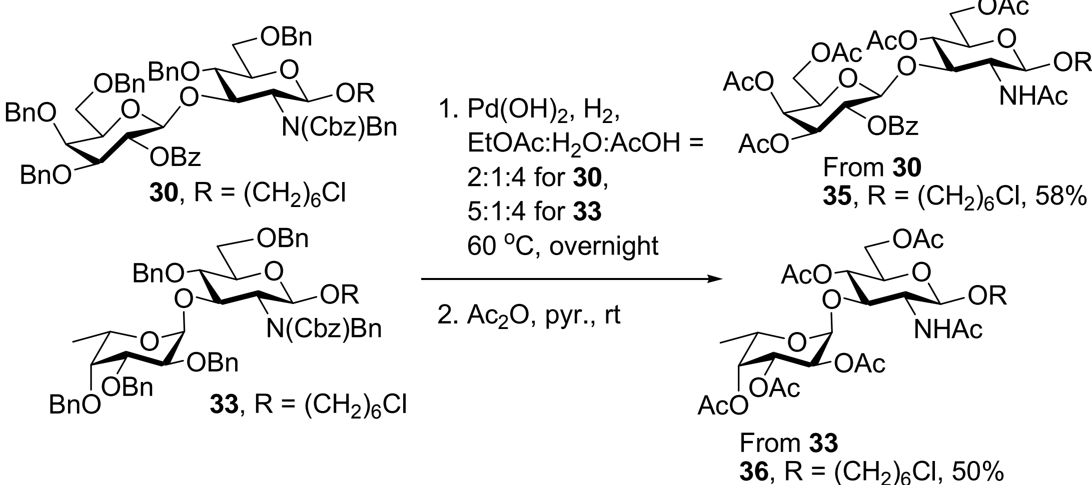
Hence, the Pd-catalyzed hydrogenolysis method may be another choice for the removal of Cbz protecting groups. At the same time, *O*-benzyl ethers and *N*-benzyl groups could be removed simultaneously during hydrogenolysis reaction. Consequently, the conditions for the total debenzylations in the presence of Cbz protecting groups were optimized. We used glucosamine derivative **26** as a model to study hydrogenolysis reactions and the results were shown in Table 12.

Table 12. Deprotection of desymmetric glucosamine acceptor **26**

Entry	Catalyst	Solvent	*T* (°C)	Results
1	Pd	MeOH:AcOH = 10:1	25	**26**[a]
2	Pd	MeOH:HCOOH = 10:1	25	not fully deprotected[a]
3	Pd	EtOH:HCOOH = 10:1	25	not fully deprotected[a]
4	Pd	THF:H_2O = 4:1	25	**26**[a]
5	Pd	THF:H_2O:AcOH = 8:2:1	25	**26**[a]
6	Pd	THF:H_2O:HCOOH = 8:2:1	25	not fully deprotected[a]
7	$Pd(OH)_2$	AcOH	25	**26**[a]
8	$Pd(OH)_2$	MeOH:AcOH = 2:1	25	**26**[a]
9	$Pd(OH)_2$	EtOAc:H_2O:AcOH = 2:1:4	25	**26**[a]
10	$Pd(OH)_2$	EtOAc:H_2O:AcOH = 2:1:4	60	**34** (70%)[b]

[a] Judged from TLC plates. [b] After acetylation, we got the low mass data.

At first, hydrogenolysis of monosaccharide **26** did not proceed over 10% Pd/C in solvent mixtures of MeOH/AcOH (10:1), THF/H_2O (4:1), and THF/H_2O/AcOH (8:2:1) at room temperature (Table 12, entries 1, 4 and 5).[70] Incomplete deprotections were observed and a series of spots were noted on the TLC plate, and changing the solvent mixture to MeOH/HCOOH (10:1), EtOH/HCOOH (10:1), and THF/H_2O/HCOOH (8:2:1) did not give the desired product either. After these failures, we took a step back to do a search hoping for finding the solutions to overcome this problem. We found that 20 % $Pd(OH)_2$ catalyst was used for the removal of *N*-benzyl groups, maybe it would fulfill all our requirements for total debenzylations along with the removal of Cbz protecting group. Hydrogenolysis reactions of monosaccharide **26** were not successful even over 20 % $Pd(OH)_2$ in solvent system of AcOH, MeOH/AcOH (10:1), EtOAc/H_2O/AcOH (2:1:4) at room temperature (Table 12, entries 7–9).[93,94] Eventually, the hydrogenolysis temperature was best performed at 60 ^{o}C.[74] After raising the temperature to 60 ^{o}C, the deprotection was achieved (Table 12, entry 10). To our delight, we applied the optimized condition to disaccharides **30** and **33**. As shown in Scheme 22, both of their hydrogenolysis reactions worked well in solvent mixture of EtOAc/H_2O/AcOH (the ratio was based on the solubility of disaccharide) over 20% $Pd(OH)_2$ under 1 atm H_2 at 60 ^{o}C. For NMR characterization, the resulting debenzylated products were further acetylated to produce the type 1 LacNAc glycoside **35** and the peracetyl Fuc-α-(1→3)-GlcNAc disaccharide **36** which was similar to part of Lewis Y structure.



Scmeme 22. Hydrogenolysis reactions of disaccharides **30** and **33**

2.9 Synthesis of disaccharides using desymmetric amino–protecting strategy

At present, we had developed the desymmetric amino–protecting strategy. The scope of investigation included the installation, deprotection, and application to glycosylations. At this stage, we focused on the removal of the oxazolidinone ring in disaccharide **16**. It seemed that basic condition (*t*-BuOK/DMSO) at room temperature would be practical (Table 10, entry 5), but it didn't proceed. The reaction outcome was not reproducible, and more intriguingly, the installation of Cbz protecting group failed when the residue was treated with $NaHCO_3$ in MeOH, followed by benzyloxycarbonyl chloroformate (Scheme 23). What we could do was using the other basic conditions (1,4-dioxane/1M NaOH, *v*/*v* = 1:1) which was also feasible for the monosaccharide **19** (Table 10, entry 4). Fortunately, the removal of the oxazolidinone ring was successful and further installation of Cbz protecting group furnished desymmetric protected disaccharide **38** in high yield.

Scmeme 23. Removal studies of the *N*-benzyl oxazolidinone ring in disaccharides **16**

2.10 Synthesis of trisaccharide 41 via one-pot glycosylation and deprotection

After some experimentation, the key component of disaccharide **38** was finally obtained. To investigate its chemical properties, **38** was coupled with primary alcohol **7** using NIS/Lewis acid promoter system (Table 13). At first, coupling of **38** and **7** gave desired product **39** in 86% yield (Table 13, entry 1). However, further glycosylation of **39** with fucosyl thioglycoside **12** gave undesired *N*-succinimide side product. Then we decided to change the Lewis acid to TfOH as the promoter, most disaccharides **38** were not activated at −60 °C, but we got the desired product **39** in 88% yield after raising the temperature to −50 °C (Table 13, entries 2 and 3). According to the experimental results in Table 13, the NIS/TfOH promoter system was employed in further glycosylation with fucosyl thioglycosides **12**. According to our retrosynthetic analysis, glycosylation of **39** with **12** should give the Lewis Y tetrasaccharide; however, we obtained the trisaccharide glycosylation product **40** even using 4 equiv of fucosyl thioglycoside and 1.2 equiv of TfOH.

Table 13. Glycosylation studies of donor **38** and acceptor **7**

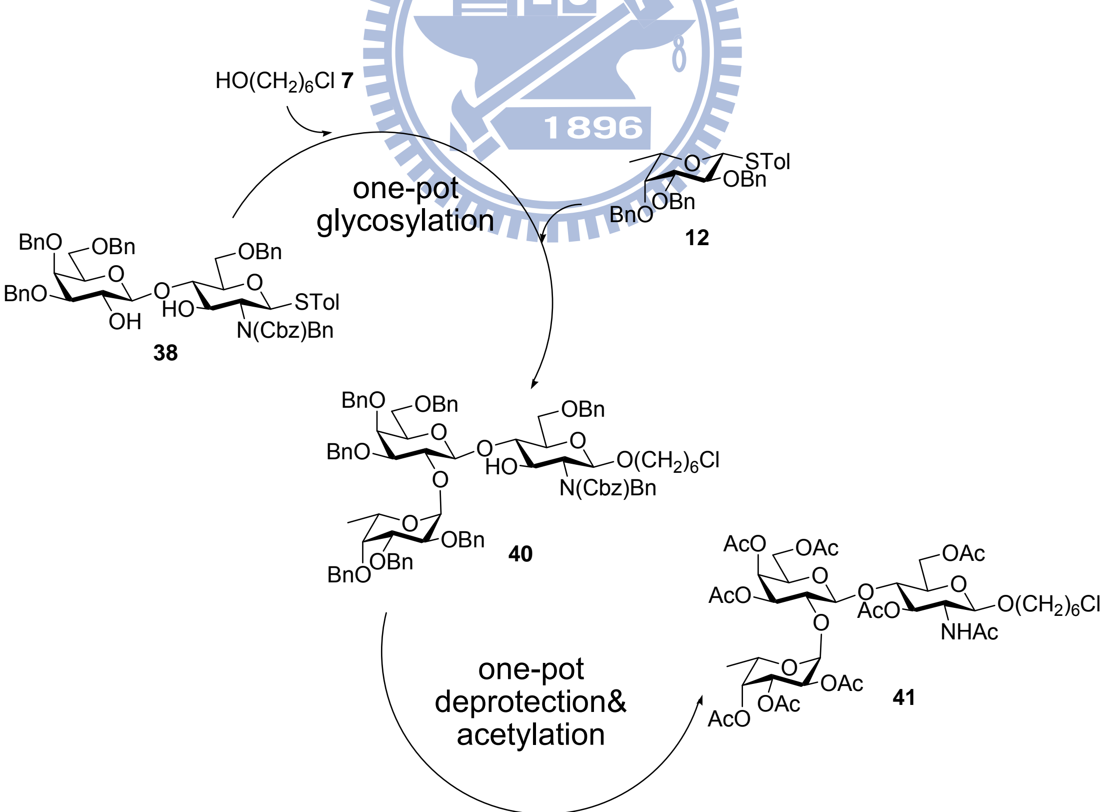
BnO OBn BnO O OH O HO OBn O STol N(Cbz)Bn
38

$HO(CH_2)_6Cl$ **7**, NIS, Lewis acid
DCM, *T*

BnO OBn BnO O OH O HO OBn O OR N(Cbz)Bn
39, R = $(CH_2)_6Cl$

Entry	Lewis acid promoter (equiv.)	*T* (°C)	Yield (%)
1	TMSOTf (0.3)	–65	**39** (86%)
2	TfOH (0.3)	–60	**38** (80%)
3	TfOH (0.3)	–50	**39** (88%)

Owing to the phenomenon of resonance peak broadening for **40**, its preliminary identification was evidenced by mass spectroscopy. In addition, the one-pot deprotection by hydrogenolysis reaction was useful for the trisaccharide **40** by using the $Pd(OH)_2$ catalyst (Degussa type) at room temperature instead of 60 ^{o}C. For further characterizations of the structure, the resulting debenzylated product was acetylated to produce the peracetyl Fuc-α-(1→3)-Gal-β-(1→4)-GlcNAc trisaccharide **41** which constitutes part of the H blood group substrate. In this stage, we have synthesized the trisaccharide glycosylation product **40** by stepwise glycosylation. Subsequently, synthesis of **40** from **38** was attempted. Fortunately, we obtained the trisaccharide **40** in 55% yield by one-pot glycosylation reaction (Scheme 24). It was a pity that the 3-OH group in the GlcNAc could not be glycosylated with the fucosyl thioglycoside to give Lewis Y oligosaccharide probably because of the steric hindrance.



Scmeme 24. Synthesis of trisaccharide **41** via one-pot glycosylation and deprotection strategy

3. Conclusion

In summary, the joined use of *N*-benzyl oxazolidinoe and *N*-BnCbz desymmetric amino protection is a versatile strategy for protection of 2-amino sugars. We have used oxazolidinone protected thioglucosamines which have lower anomeric reactivity as acceptors in reactivity-based chemoselective glycosylation. In addition, we have developed the desymmetric *N*-BnCbz protecting group including its installation, deprotection, and application in oligosaccharides synthesis. Disaccharides such as type 1 LacNAc, type 2 LacNAc, Fuc-a-(1→3)-GlcNAc, and Fuc-a-(1→4)-GlcNAc and trisaccharides H blood group substrate were synthesized based on this strategy. Moreover, one-pot global deprotection by hydrogenolysis reaction was also developed for both disaccharide and trisaccharide. Further application of this strategy such as Lewis Y tetrasaccharide synthesis is under investigations.

4. Experimental

4.1 General procedures

Chemicals were purchased as reagent grade from commercial venders and used without further purification. All of solvents were dried and distilled by standard techniques unless mentioned. Optical rotations were measured with the JASCO DIP-1000 polarimeter at 30˚C. Flash column chromatography was performed over silica gel 60 (70–230 mesh, E. Merck). NMR spectra were recorded with the Brüker console, Varian Unity-300 and Varian Unity-500. Chemical shifts are reported in ppm relative to internal tetramethylsilane (δ = 0.00 ppm) for ^{1}H and ^{13}C resonance signal of $CDCl_3$ (δ = 77.00 ppm) for ^{13}C NMR spectra. Coupling constant(s) in hertz (Hz) were derived from ^{1}H NMR spectra.

4.2 General procedure for glycosylations

Glycosyl donor (**8**, **9**, **10**, **11**, **12**, **27** or **28**), glycosyl acceptor (**4** or **26**), and activated 4 Å MS (100mg/1mL DCM, AW300) in CH_2Cl_2 were stirred at room temperature under nitrogen for 20 min. The mixture was then cooled in a cooling bath followed by addition of TMSOTf and NIS. After disappearance of acceptor detected by TLC, the mixture was diluted with CH_2Cl_2, quenched by Et_3N, and few droplets of sat. $NaHCO_3$ and excess of $Na_2S_2O_{3(s)}$ were added, removed from cooling bath, and then stirred at room temperature for 2h. The quenching mixture was then stirred at room temperature for 2h, filtered and finally concentrated. The residue was purified by column chromatography over silica gel to give **13**, **14**, **15**, **16**, **17**, **30**, **31**, **32** or **33**. The stoichiometric amounts of substrates and reagents were listed below (Table 13).

Table 14. The amounts of glycosyl donor, glycosyl acceptor, NIS, and TMSOTf used in glycosylation

Glycosyl donor (mg, mmol)	Glycosyl acceptor (mg, mmol)	NIS (mg, mmol)	TMSOTf (uL, mmol, mM)	DCM (mL)	Temp. (°C)	Product
8, 160, 0.244	**4**, 100, 0.204	55, 0.244	9, 0.049, 0.016	3	−70	**13**
9, 159, 0.265	**4**, 100, 0.204	60, 0.265	10, 0.053, 0.013	4	−60	**14**
10, 173, 0.265	**4**, 100, 0.204	60, 0.265	10, 0.053, 0.013	4	−65	**15**
11, 175, 0.265	**4**, 100, 0.204	60, 0.265	10, 0.053, 0.013	4	−70	**16**
12, 165, 0.306	**4**, 100, 0.204	69, 0.306	11, 0.061, 0.015	4	−60	**17**
11, 734, 1.112	**26**, 600, 0.856	252, 1.112	31, 0.171, 0.007	24	−70	**30**
28, 780, 1.275	**26**, 597, 0.850	289, 1.275	31, 0.170, 0.007	25	−65	**31**
29, 198, 0.293	**26**, 158, 0.225	67, 0.293	8, 0.045, 0.008	6	−65	**32**
12, 486, 0.899	**26**, 420, 0.599	204, 0.899	22, 0.120, 0.007	17	−70	**33**

4.3 Procedures and experimental data

***p*-Tolyl *N*-Benzyl-2-amino-4,6-*O*-benzylidene-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (3)**:

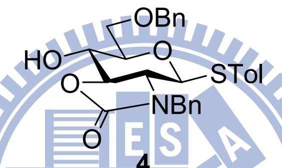
$C_6H_5CH(OMe)_2$, cat. TsOH, CH_3CN, rt

BnBr, NaH, DMF, 0°C–rt

To a solution of compound **1** (2.0 g, 4.36 mmol) and TsOH (67 mg, 0.35 mmol) in CH_3CN (15 mL) at room temperature, was added $C_6H_5CH(OMe)_2$ (0.78 mL, 5.23 mmol). After stirring for 4 h, the mixture was neutralized with NEt_3 and then concentrated under reduced pressure. The residue was crystallized from (EtOAc/hexane) to give compound **2** (2.2 g, 92%) as white solid. Counpound **2** (2.2 g, 4.02 mmol) was dissolved in dry DMF (20 mL) and stirred in an ice bath under nitrogen for 20 min. Then NaH (241 mg, 6.03 mmol, 60% in mineral oil) was added, followed by addition of benzyl bromide (0.58 mL, 4.82 mmol). After stirring for 30 min, the reaction mixture was warmed to room temperature and stirred for 2h. The reaction was concentrated under reduced pressure and purified by column chromatography over silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:3) to give **3** (1.57 g, 80%) as white solid. R_f = 0.45 (EtOAc/CH_2Cl_2/hexane, 1:1:3); $[\alpha]^{30}_D$ -66 (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.46–7.29 (m, 10H; Ar-*H*), 7.17–7.07 (m, 4H; Ar-*H*), 5.56 (s, 1H; benzylidene-*H*), 4.83 (d, *J* = 15.6 Hz, 1H; PhCH_2), 4.76 (d, *J* = 9.6 Hz, 1H; H-1),

4.75 (d, J = 15.9 Hz, 1H; PhCH_2), 4.31–4.24 (m, 2H; H-5, H-6), 3.99 (t, J = 9.3 Hz, 1H; H-4), 3.86 (t, J = 10.3 Hz, 1H; H-6), 3.54–3.45 (m, 2H; H-3, H-2), 2.33 (s, 3H, Ar-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.9 (C=O), 139.1, 136.4, 133.2, 129.9, 129.3, 128.7, 128.3, 128.0, 127.9, 127.6, and 126.1 (Ar-C), 101.4 (benzylidene-C), 88.0 (C-1), 78.9 (C-5), 78.4 (C-4), 72.7 (C-3), 68.3 (C-6), 61.5(C-2) , 47.7 (PhCH$_2$), 21.1 (Ar-CH$_3$).

***p*-Tolyl *N*-Benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (4)**



A solution of compound **3** (200 mg, 0.41 mmol), triethylsilane (322 μL, 2.05 mmol), and activated 4 Å MS (200 mg, AW300) in CH_2Cl_2 (2 mL) was stirred at room temperature under nitrogen atmosphere for 20 min. The mixture was then cooled to –20 °C in a cooling bath followed by addition of dry trifluoroacetic acid (177 μL, 2.5 mmol). After 1h, the mixture was diluted with CH_2Cl_2 (6 mL), and then quenched with Et_3N (0.4 mL, 3.3 mmol) at –20 °C. MS in the mixture was filtered off and the filtrate was concentrated. The residue was purified by column chromatogram-phy on silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:8→1:1:3) to give **4** (161 mg, 80%) as white solid. R_f = 0.09 (EtOAc/ CH_2Cl_2/hexane, 1:1:3); $[\alpha]^{30}_D$ -54 (c 2.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.21 (m, 12H; Ar-H), 7.03–7.01 (d, 2H; Ar-H), 4.73 (s, 1H; PhCH_2), 4.69 (d, J = 9.3 Hz, 1H; H-1), 4.57 (d, J = 12.3 Hz, 1H; PhCH_2), 4.53 (d, J = 12.0 Hz, 1H; PhCH_2), 4.04 (t, J = 10.3 Hz, 1H; H-3), 3.96 (t, J = 9.2 Hz, 1H; H-4), 3.76 (d, J = 4.5 Hz, 2H; H-6), 3.54–3.48 (m, 1H; H-5), 3.37 (dd, J = 10.7 Hz, J

= 9.6 Hz, 1H; H-2), 2.30 (s, 3H, Ar-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.5 (*C*=O), 138.6, 137.7, 136.3, 132.9, 129.8, 128.6, 128.4, 128.1, 127.74, 127.69, and 127.5 (Ar-*C*), 86.7 (C-1), 82.5 (C-3), 79.9 (C-5), 73.5 (Ph*C*H_2), 69.5 (C-6), 68.5 (C-4), 60.1(C-2) , 47.4 (Ph*C*H_2), 21.1 (Ar-*C*H_3); HRMS (ESI) calcd for $C_{28}H_{29}NO_5S$ $[M+Na]^+$: 514.1664, found: 514.1659.

***p*-Tolyl *N*-Benzyl-2-amino-4-acetyl-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (5)**

AcO OBn O STol O NBn O

5

To a solution of compound **4** (500 mg, 1.02 mmol) in pyridine (5 mL) at room temperature, was added acetic anhydride (145 μL, 1.53 mmol). After stirring for 2h, the mixture was directly concentrated under reduced pressure, and the residue was purified by column chromatography over silica gel (EtOAc/hexane, 1:7→1:4) to give **5** (516 mg, 95%) as colorless foam. R_f = 0.30 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33–7.17 (m, 12H; Ar-*H*), 6.94 (d, *J* = 7.8 Hz, 2H; Ar-*H*), 5.20 (dd, *J* = 10.4 Hz, *J* = 8.4 Hz, 1H), 4.67–4.64 (m, 3H; H-1, PhCH_2), 4.47 (d, *J* = 11.7 Hz, 1H), 4.40(d, *J* = 11.7 Hz, 1H), 4.09–4.02 (m, 1H), 3.63–3.51 (m, 3H), 3.44 (dd, *J* = 11.3 Hz, *J* = 9.3 Hz, 1H), 2.23 (s, 3H; Ar-CH_3), 1.93 (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.7, 137.6, 136.0, 132.9, 129.8, 128.6, 128.3, 128.12, 128.08, 127.7, 127.63, 127.56, 86.7 (C-1), 79.9, 78.7, 73.4, 68.6, 67.8, 60.1, 47.4, 21.0, 20.6.

***p*-Tolyl *N*-Benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-α-D-glucopyranoside (6)**

6

Based on literature stoichiometric amounts of reagents and the same experimental procedure as in the synthesis **4**, a mixture of **4** and **6** was obtained, and the ratio was determined by integration of the ^{1}H NMR spectrum (**4**:**6** = 1:6, 65%). We separated the α-glycoside **6** and obtained its characterization data. R_f = 0.15 (EtOAc/CH_2Cl_2/hexane, 1:1:3); $[\alpha]^{30}_{D}$ 168 (*c* 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36–7.23 (m, 12H; Ar-*H*), 7.09 (d, 2H; Ar-*H*), 5.32 (d, *J* = 4.5 Hz, 1H; H-1), 4.78 (d, *J* = 14.7 Hz, 1H; PhCH_2), 4.59 (d, *J* = 12.0 Hz, 1H; PhCH_2), 4.49 (d, *J* = 12.0 Hz, 1H; PhCH_2), 4.36 (dd, *J* = 11.9 Hz, *J* = 9.8 Hz, 1H; H-3), 4.19–4.11 (m, 2H; H-5, PhCH_2), 4.00 (td, *J* = 9.3 Hz, *J* = 3.0 Hz, 1H; H-4), 3.78 (dd, *J* = 10.5 Hz, *J* = 4.5 Hz, 1H; H-6), 3.71 (dd, *J* = 10.5 Hz, *J* = 4.5 Hz, 1H; H-6), 3.49 (dd, *J* = 12 Hz, *J* = 4.5 Hz, 1H; H-2), 2.99 (d, 1H, *J* = 3.3 Hz, 4-O*H*), 2.34 (s, 3H, Ar-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.6 (*C*=O), 138.3, 137.5, 134.4, 132.4, 129.94, 129.0, 128.9, 128.5, 128.4, 127.9, and 127.8 (Ar-*C*), 85.2 (C-1), 78.4 (C-3), 73.6 (Ph*C*H_2), 72.9 (C-5), 69.4 (C-4), 68.7 (C-6), 59.2(C-2) , 47.4 (Ph*C*H_2), 21.1 (Ar-*C*H_3).

***p*-Tolyl 2,3,4-Tri-*O*-benzyl-6-*O*-levulinoyl-α-D-galactopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (13)**

13

Compound **13** was prepared from **8** and **4**, and the stoichiometric amounts were referred to Table 13. The residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:7→1:1:3) to give **13** (146 mg, 70%) as amorphous white solid. R_f = 0.21 (EtOAc/CH_2Cl_2/hexane, 1:1:3); $[\alpha]^{30}_{D}$ +9 (*c* 2.67, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.42–7.22 (m, 27H, Ar-*H*), 6.99 (d, *J* = 11.1 Hz, 2H; Ar-*H*), 5.44 (d, *J* = 3.6 Hz, 1H; H-1), 4.94 (d, *J* = 11.1 Hz, 1H; PhCH_2), 4.87–4.64 (m, 7H), 4.62–4.55 (m, 2H), 4.47 (d, *J* = 12.0 Hz, 1H; PhCH_2), 4.21–4.06 (m, 4H), 3.94 (dd, *J* = 11.1 Hz *J* = 5.7 Hz, 1H), 3.76–3.65 (m, 6H), 3.45 (t, *J* = 10.1 Hz, 1H; H-2), 2.67–2.62 (m, 2H; CH_2), 2.45–2.40 (m, 2H; CH_2), 2.29 (s, 3H; Ar-CH_3), 2.12 (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.2 (*C*=O), 172.1 (*C*=O), 158.7 (*C*=O), 138.6, 138.5, 138.1, 138.0, 136.2, 132.8, 129.8, 128.6, 128.32, 128.26, 128.22, 128.14, 128.06, 127.7, 127.6, 127.5, and 127.3 (Ar-*C*), 96.3 (C'-1), 86.4 (C-1), 82.7, 79.1, 78.2, 75.8, 74.4 (Ph*C*H_2), 74.1, 73.34 (Ph*C*H_2), 73.29 (Ph*C*H_2), 73.1 (Ph*C*H_2), 71.0, 69.2, 69.0, 63.4, 60.0 (C-2), 47.4 (Ph*C*H_2), 37.7 (*C*H_2), 29.8 (*C*H_3), 27.6 (*C*H_2), 21.1 (Ar-*C*H_3). HRMS (ESI) calcd for $C_{60}H_{63}NO_{12}S$ $[M+Na]^+$: 1044.3969, found: 1044.3962.

***p*-Tolyl 3,4,6-Tri-*O*-benzyl-2-*O*-levulinoyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (15)**

Compound **15** was prepared from **10** and **4**, and the stoichiometric amounts were

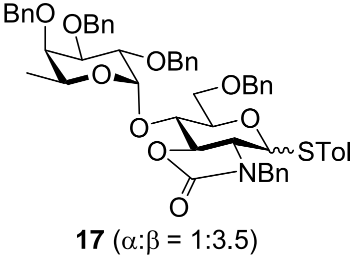
referred to Table 13. The residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:8→1:1:3) to give **15** (135 mg, 65%) as amorphous white solid. R_f = 0.19 (EtOAc/CH_2Cl_2/hexane, 1:1:3); $[\alpha]^{30}{}_{D}$ -21 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 7.42–7.26 (m, 27H; Ar-*H*), 7.05–7.02 (m, 2H, Ar-*H*), 5.37 (t, *J* = 9.0 Hz, 1H), 4.93 (dd, *J* = 11.5 Hz, *J* = 3.5 Hz, 1H), 4.79–4.74 (m, 2H), 4.69–4.60 (m, 4H), 4.57–4.46 (m, 5H), 4.21 (td, *J* = 10.5 Hz, *J* = 4.5 Hz, 1H), 4.10–4.06 (m, 1H), 4.00–3.97 (m, 1H), 3.82–3.71 (m, 4H), 3.66–3.63 (m, 1H), 3.61–3.59 (m, 1H), 3.49 (dd, *J* = 10.3 Hz, *J* = 2.75 Hz, 1H), 3.42–3.37 (m, 1H), 2.68–2.62 (m, 2H; CH_2), 2.53–2.46 (m, 2H; CH_2), 2.32 (s, 3H; Ar-CH_3), 2.11 (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 206.1 (*C*=O), 171.2 (*C*=O), 158.9 (*C*=O), 138.4, 138.2, 138.1, 137.9, 137.7, 136.3, 132.8, 129.7, 128.4, 128.24, 128.23, 128.14, 128.10, 128.05, 128.00, 127.95, 127.7, 127.60, 127.56, 127.48, 127.44, 127.37, and 127.33 (Ar-*C*), 100.3 (C'-1), 86.2 (C-1), 81.0, 80.0, 79.6, 74.31 (PhCH_2), 74.28, 73.5, 73.4 (PhCH_2), 73.3 (PhCH_2), 72.3, 71.8 (PhCH_2), 71.6, 68.2, 68.1, 60.2, 47.3 (PhCH_2), 37.5 (CH_2), 29.6 (CH_2), 27.7 (CH_2), 21.0 (Ar-CH_3); HRMS (ESI) calcd for $C_{60}H_{63}NO_{12}S$ $[M+Na]^+$: 1044.3969, found: 1044.4080.

***p*-Tolyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (16)**

Compound **16** was prepared from **11** and **4**, and the stoichiometric amounts were

referred to Table 13. The residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:7→1:1:4) to give **16** (167 mg, 80%) as amorphous white solid. R_f = 0.20 (EtOAc/CH_2Cl_2/hexane, 1:1:4); $[\alpha]^{30}_D$ -12 (*c* 2.19, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.4 Hz, 2H; Ar-*H*), 6.91 (t, *J* = 8.1 Hz, 1H; Ar-*H*), 7.41–7.07 (m, 29H; Ar-*H*), 6.91 (d, *J* = 8.1 Hz, 2H; Ar-*H*), 5.76 (dd, *J* = 10.1 Hz, *J* = 8.0 Hz, 1H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.69–4.52 (m, 7H), 4.47–4.35 (m, 3H), 4.18–3.94 (m, 4H), 3.75–3.66 (m, 3H), 3.46–3.39 (m, 3H), 3.40 (dd, *J* = 10.2 Hz, *J* = 2.7 Hz, 1H), 2.22 (s, 3H, Ar-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.6 (*C*=O), 158.9 (*C*=O), 138.4, 138.2, 138.0, 137.9, 137.6, 137.4, 136.2, 128.5, 128.3, 128.2, 128.18, 128.13, 128.06, 128.01, 127.8, 127.6, 127.3 (Ar-*C*), 100.8 (C'-1), 86.2 (C-1), 81.3, 79.4, 79.0, 74.7, 74.4, 73.6, 73.5, 72.7, 72.0, 71.9, 71.3, 68.1, 67.7, 60.0, 47.3 (Ph*C*H_2), 21.0 (Ar-*C*H_3); HRMS (ESI) calcd for $C_{62}H_{61}NO_{11}S$ $[M+Na]^+$: 1050.3863, found: 1050.3860.

_p_-Tolyl 2,3,4-Tri-_O_-benzyl-α-L-fucopyranosyl-(1→4)-_N_-benzyl-2-amino-6-_O_-benzyl-2,3-_N_,_O_-carbonyl-2-deoxy-1-thio-D-glucopyranoside (17)



17 (α:β = 1:3.5)

Compound **17** was prepared from **12** and **4**, and the stoichiometric amounts were referred to Table 13. The residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:9→1:1:5) to give **17** (157 mg, 85%) as an inseparable α-/β-anomeric mixture, and the ratio was determined by integration of the

Ar-CH_3 ^{1}H resonance signals at ca. 2.3–2.4 ppm of the reaction mixture. R_f = 0.28 (EtOAc/ CH_2Cl_2/hexane, 1:1:5); HRMS (ESI) calcd for $C_{55}H_{57}NO_9S$ $[M+Na]^+$: 930.3652, found: 930.3723.

_p_-Tolyl _N_-Benzyl-2-amino-4,6-di-_O_-benzyl-2,3-_N_,_O_-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (19)

OBn
BnO
O
STol
O
NBn
O
19

Counpound **1** (600 mg, 1.31 mmol) was dissolved in dry DMF (10 mL) and stirred at −15 °C under nitrogen for 20 min. Then NaH (314 mg, 7.84 mmol, 60% in mineral oil) was added, followed by addition of benzyl bromide (0.7 mL, 5.88 mmol). After stirring in a cooling bath for 30 min, the reaction mixture was warmed to room temperature and stirred for 2h. The reaction was quenched with crushed ice, stirred at room tempeture for 10 min, and the whole was extracted with EtOAc (30 mL × 3). The organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered, and finally concentrated. The residue was purified by column chromatography over silica gel (EtOAc/hexane, 1:3) and then crystallized from (EtOAc/hexane) to give **19** (608 mg, 80%) as white amorphous solid. R_f = 0.43 (EtOAc/hexane, 1:3); $[\alpha]^{30}_D$ -32 (*c* 0.87, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43–7.23 (m, 17H, Ar-*H*), 7.00 (d, *J* = 8.1 Hz, 2H; Ar-*H*), 4.88 (d, *J* = 11.1 Hz, 1H; PhCH_2), 4.86 (s, 2H; PhCH_2), 4.69 (d, *J* = 9.3 Hz, 1H; H-1), 4.56 (d, *J* = 12.0 Hz, 1H; PhCH_2), 4.54 (d, *J* = 11.4 Hz, 1H; PhCH_2), 4.48 (d, *J* = 12.0 Hz, 1H; PhCH_2), 4.16 (dd, *J* = 11.1 Hz, *J* = 9.9 Hz, 1H; H-3), 3.86 (dd, *J* = 9.6 Hz, *J* =8.7 Hz, 1H; H-4), 3.75 (dd, *J* = 10.8 Hz, *J* = 2.1 Hz, 1H; H-6), 3.67 (dd, *J* = 10.8 Hz, *J* = 4.5 Hz, 1H; H-6), 3.58–3.53 (m, 1H; H-5), 3.44 (dd, *J*

= 11.1 Hz, *J* = 9.6 Hz, 1H; H-2), 2.29 (s, 3H; Ar-C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 159.2 (*C*=O), 138.6, 138.0, 137.2, 136.3, 128.6, 128.4, 128.35, 128.29, 128.11, 127.96, 127.89, 127.81, 127.7, 127.6 and 127.5 (Ar-*C*), 86.6 (C-1), 83.4 (C-3), 79.8 (C-5), 73.6 (C-4), 73.3 and 73.1 (Ph*C*H$_2$), 68.4 (C-6), 60.2 (C-2), 47.4 (Ph*C*H$_2$), 21.1 (Ar-*C*H$_3$); HRMS (ESI) calcd for $C_{28}H_{29}NO_5S$ $[M+Na]^+$: 514.1664, found: 514.1659.

_p_-Tolyl *N*-Benzyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (20)

To a solution of compound **19** (190 mg, 0.33 mmol) in DMSO (5 mL) at room temperature, was added *t*-BuOK (183 mg, 1.64 mmol). After stirring for 1 h, the reaction mixture was diluted with EtOAC, and then washed with water. The aqueous layer was washed with EtOAc three times. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (EtOAc/hexane, 1:3) to give **20** **(**136 mg, 75%) as yellow oil. R_f = 0.18 (EtOAc/hexane, 1:3); $[\alpha]^{30}_{D}$ -9 (*c* 2.83, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.47 (d, *J* = 8.1 Hz, 2H; Ar-*H*), 7.33–7.20 (m, 15H; Ar-*H*), 7.01 (d, *J* = 8.1 Hz, 2H; Ar-*H*), 4.86 (d, *J* = 11.1 Hz, 1H; PhC*H*$_2$), 4.62 (d, *J* = 10.2 Hz, 1H; H-1), 4.59 (d, *J* = 11.1 Hz, 1H; PhC*H*$_2$), 4.58 (d, *J* = 11.1 Hz, 1H; PhC*H*$_2$), 4.51 (d, *J* = 12.0 Hz, 1H; PhC*H*$_2$), 3.94 (d, *J* = 12.3 Hz, 1H; PhC*H*$_2$), 3.84 (d, *J* = 12.3 Hz, 1H; PhC*H*$_2$), 3.81–3.62 (m, 3H; H-3, H-6), 3.52–3.43 (m, 2H; H-4, H-5), 2.63 (t, *J* = 9.9 Hz, 1H; H-2), 2.28 (s, 3H, Ar-C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 140.0, 138.3, 137.6, 132.2, 129.6, 129.4, 128.4, 128.3, 128.19, 128.18, 127.8, 127.6,

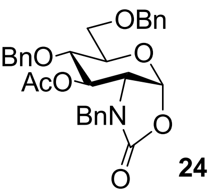
127.5, 127.4, and 127.1 (Ar-*C*), 87.3 (C-1), 78.8 (C-4), 77.9 (C-5), 76.0 (C-3), 74.2 and 73.2 (Ph*C*H_2), 69.2 (C-6), 61.7 (C-2), 49.7 (Ph*C*H_2), 21.0 (Ar-*C*H_3); HRMS (ESI) calcd for $C_{34}H_{37}NO_4S$ $[M+H]^+$: 556.2522, found: 556.2516.

_p_-Tolyl _N_-Benzyl-_N_-_tert_-butoxycarbonyl-2-amino-4,6-di-_O_-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (22)

22

To a solution of compound **20** (340 mg, 0.61 mmol) and $NaHCO_3$ (410 mg, 4.88 mmol) in non-dried MeOH (6 mL) at room temperature, was added $(Boc)_2O$ chloroformate (0.26 mL, 1.22 mmol). After stirring for 2h, MeOH was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (5 mL), poured into a two-layer mixture of CH_2Cl_2 (10 mL) and brine (10 mL), and the whole was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel ($EtOAc/CH_2Cl_2$/ hexane, 1:1:5) to give **22** (304 mg, 76%) as yellow oil. R_f = 0.49 ($EtOAc/CH_2Cl_2$/ hexane, 1:1:3); HRMS (ESI) calcd for $C_{39}H_{45}NO_6S$ $[M+Na]^+$: 678.2865, found: 678.2860. Standard ^1H and ^{13}C NMR spectra were obscured by peak broadening.

_N_-Benzyl-2-amino-3-_O_-acetyl-4,6-di-_O_-benzyl-1,2-_cis_-_O_,_N_-carbonyl-2-deoxy-D-glucopyranoside (24)



R_f = 0.47 (EtOAc/CH_2Cl_2/ hexane, 2:2:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30–7.15 (m, 15H; Ar-*H*), 5.76 (d, *J* = 7.2 Hz, 1H; H-1), 5.24–5.23 (m, 1H), 4.88 (d, *J* = 15.3 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.43 (dd, *J* = 11.7 Hz, *J* = 4.5 Hz, 2H), 4.27 (d, *J* = 11.7 Hz, 1H), 3.89 (d, *J* = 15.3 Hz 1H), 3.77–3.72 (m, 1H), 3.66 (d, *J* = 8.4 Hz, 1H), 3.61–3.56 (m, 1H) 3.52 (dd, *J* = 15.6 Hz, *J* = 2.4 Hz, 1H), 3.38 (dd, *J* = 11.0 Hz, *J* = 3.6 Hz, 1H), 1.92 (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.6, 156.9, 137.7, 137.1, 134.5, 129.0, 128.50, 128.46, 128.29, 128.27, 128.19, 127.8, 127.7, 93.7 (C-1), 73.3, 72.9, 72.0, 69.6, 68.7, 65.9, 52.7, 46.0, 20.8 (CH_3CO); HRMS (ESI) calcd for $C_{30}H_{31}NO_7$ $[M+H]^+$: 518.2179, found: 518.2180.

_p_-Tolyl _N_-Benzyl-_N_-benzyloxycarbonyl-2-amino-4,6-di-_O_-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (25)

To a solution of compound **20** (870 mg, 1.57 mmol) and $NaHCO_3$ (1.32g, 15.68 mmol) in non-dried MeOH (10 mL) at room temperature, was added benzyl chloroformate (0.8 mL, 2.36 mmol, 50 wt% solution in toluene). After stirring for 2h, MeOH was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (10 mL), poured into a two-layer mixture of CH_2Cl_2 (20 mL) and brine (20 mL), and the whole was extracted with CH_2Cl_2 (40 mL × 3). The combined organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The

residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:4) to give **25** (886 mg, 82%) as yellow oil. R_f = 0.31 (EtOAc/CH_2Cl_2/hexane, 1:1:4); $[\alpha]^{30}_D$ -6 (*c* 4, $CHCl_3$); HRMS (ESI) calcd for $C_{42}H_{43}NO_6S$ $[M+H]^+$: 690.2889, found: 690.2894. Standard ^1H and ^{13}C NMR spectra were obscured by peak broadening.

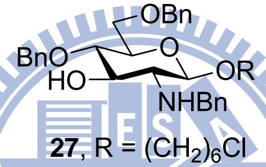
6-Chlorohexyl *N*-Benzyl-*N*-benzyloxycarbonyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (26)

26, R = $(CH_2)_6Cl$

Compound **25** (1.60 g, 2.32 mmol), 6-chlorohexanol **7** (0.46 mL, 3.48 mmol), and activated 4 Å MS (6.5 g, 100mg/1mL CH_2Cl_2, AW300) in CH_2Cl_2 (65 mL) were stirred at room temperature under nitrogen for 20 min. The mixture was then cooled in a cooling bath at –65 °C followed by addition of TMSOTf (84 μL, 7 mM) and NIS (526 mg, 2.32 mmol). After disappearance of acceptor detected by TLC, the mixture was diluted with CH_2Cl_2 (65 mL), quenched by Et_3N, and few droplets of sat. $NaHCO_3$ and pieces of $Na_2S_2O_{3(s)}$ were added. The quenching mixture was then stirred at room temperature for 2h, filtered and finally concentrated. The residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:8→1:1:3) to give **26** (1.43 g, 88%) as yellow oil. R_f = 0.42 (EtOAc/CH_2Cl_2/hexane, 1:1:3); $[\alpha]^{30}_D$ -12 (*c* 2.33, $CHCl_3$); ^1H NMR (500 MHz, $(CD_3)_2SO$, 100°C) δ: 7.44–7.21 (m, 20H; Ar-*H*), 5.21–5.10 (m, 2H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.66–4.45 (m, 6H), 3.73 (d, *J* = 10.0 Hz, 1H), 3.68–3.55 (m, 5H), 3.52–3.36 (m, 4H), 1.77–1.70 (m, 2H), 1.49–1.36 (m, 4H), 1.34–1.25 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$,

100°C) δ: 139.4, 139.0, 128.5, 128.43, 128.36, 128.13, 128.07, 127.95, 127.92, 127.7, 127.59, 127.56, 126.88, 100.0, 80.1, 74.8, 73.9, 73.0, 70.0, 68.7, 66.7, 45.5, 32.5, 29.3, 26.4, 25.1; HRMS (ESI) calcd for $C_{41}H_{48}ClNO_7$ $[M+Na]^+$: 724.3017, found: 724.3012. Standard ^1H and ^{13}C NMR spectra were obscured by peak broadening in $CDCl_3$, and the peaks became clear at 100°C in deuterated DMSO solvent based on the VT–NMR experiments.

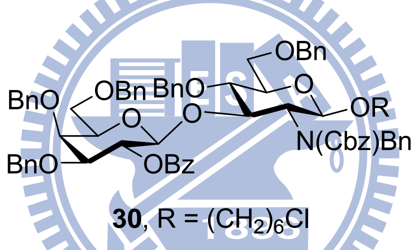
6-Chlorohexyl *N*-Benzyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (27)



To a solution of compound **26** (100 mg, 0.14 mmol), triethylsilane (90 μL, 0.56 mmol), and Et_3N (18 μL, 0.14 mmol) in CH_2Cl_2 (1 mL) at room temperature, was added $PdCl_2$ (31 mg, 0.17 mmol). After stirring for 1h, the reaction mixture was diluted with ether (2 mL), filtered, poured into a two-layer mixture of ether (5 mL) and sat. $NaHCO_3$ (5 mL), and the resulting mixture was extracted with ether (5 mL × 3). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel ($EtOAc/CH_2Cl_2$/hexane, 1:1:3→1:1:1) to give **27** (37 mg, 45%) as yellow oil. R_f = 0.38 ($EtOAc/CH_2Cl_2$/hexane,1:1:3); $[\alpha]^{30}_D$ +2 (*c* 0.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.20 (m, 15H; Ar-*H*), 4.79 (d, J = 11.1 Hz, 1H; PhCH_2), 4.63 (d, J = 12.3 Hz, 1H; PhCH_2), 4.58 (d, J = 11.1 Hz, 1H; PhCH_2), 4.55 (d, J = 12.0 Hz, 1H; PhCH_2), 4.31 (d, J = 8.1 Hz, 1H; H-1), 4.09 (d, J = 12.9 Hz, 1H; PhCH_2), 4.00–3.92 (m, 1H; O-CH_2), 3.87 (d, J = 12.9 Hz, 1H; PhCH_2), 3.78–3.66 (m, 2H;

H-6), 3.58– 3.44 (m, 6H, H-3, H-4, H-5; O-CH_2, CH_2Cl), 2.58 (t, J = 8.7 Hz, 1 H; H-2), 1.80–1.40 (m, 4H; CH_2), 1.54–1.35 (m, 4H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.0, 138.3, 138.2, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, and 127.0 (Ar-*C*), 104.0 (C-1), 78.4 (C-4), 75.4 (C-5), 74.9 (C-3), 74.4 and 73.5 (Ph*C*H_2), 69.5 (C-6), 69.1 (O-*C*H_2), 62.7 (C-2), 51.7 (Ph*C*H_2), 45.0 (*C*H_2Cl), 32.5, 29.6, 26.6, and 25.5 (*C*H_2); HRMS (ESI) calcd for $C_{33}H_{42}ClNO_5$ $[M+H]^+$: 568.2830, found: 568.2824.

6-Chlorohexyl 2-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→3)-*N*-benzyl-*N*-benzyloxycarbonyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (30)



Compound **30** was prepared from **11** and **26**, and the stoichiometric amounts were referred to Table 13. The residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:7→1:1:5) to give **30** (847 mg, 80%) as yellow oil. R_f = 0.31 (EtOAc/CH_2Cl_2/hexane, 1:1:5); $[\alpha]^{30}_D$ +20 (c 2.38, $CHCl_3$); HRMS (ESI) calcd for $C_{75}H_{80}ClNO_{13}$ $[M+Na]^+$: 1260.5216, found: 1260.5215. Standard ^{1}H and ^{13}C NMR spectra were obscured by peak broadening at room temperature.

6-Chlorohexyl 3-Allyl-2-benzoyl-4,6-di-*O*-benzyl-β-D-galactopyranosyl-(1→3)-*N*-benzyl-*N*-benzyloxycarbonyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (31)

31, R = $(CH_2)_6Cl$

Compound **31** was prepared from **28** and **26**, and the stoichiometric amounts were referred to Table 13. The residue was purified by column chromatography over silica gel ($EtOAc/CH_2Cl_2$/hexane, 1:1:8→1:1:6) to give **31** (738 mg, 73%) as yellow oil. R_f = 0.41 ($EtOAc/CH_2Cl_2$/hexane, 1:1:5); $[\alpha]^{30}_{D}$ 10 (*c* 1.29, $CHCl_3$); HRMS (ESI) calcd for $C_{71}H_{78}ClNO_{13}$ $[M+Na]^+$: 1210.5059, found: 1210.5054. Standard ^1H and ^{13}C NMR spectra were obscured by peak broadening.

6-Chlorohexyl 2-*O*-Benzoyl-4,6-di-*O*-benzyl-3-paramethoxybenzyl-β-D-galactopyranosyl-(1→3)-*N*-benzyl-*N*-benzyloxycarbonyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (32)

32, R = $(CH_2)_6Cl$

Compound **32** was prepared from **29** and **26**, and the stoichiometric amounts were referred to Table 13. The residue was purified by column chromatography over silica gel ($EtOAc/CH_2Cl_2$/hexane, 1:1:8) to give **32** (197 mg, 70%) as yellow oil. R_f = 0.23 ($EtOAc/CH_2Cl_2$/hexane, 1:1:5). Standard ^1H and ^{13}C NMR spectra were obscured by peak broadening.

6-Chlorohexyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1→3)-*N*-benzyl-*N*-benzyl-oxycarbonyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (33)

33, R = $(CH_2)_6Cl$

Compound **33** was prepared from **12** and **26**, and the stoichiometric amounts were referred to Table 13. The residue was purified by column chromatography over silica gel ($EtOAc/CH_2Cl_2$/hexane, 1:1:10→1:1:8) to give **33** (623 mg, 93%) as yellow oil. R_f = 0.44 ($EtOAc/CH_2Cl_2$/hexane, 1:1:5); $[\alpha]^{30}_{D}$ -43 (*c* 0.98, $CHCl_3$); HRMS (ESI) calcd for $C_{68}H_{76}ClNO_{11}$ $[M+Na]^+$: 1140.5005, found: 1140.5008. Standard ^1H and ^{13}C NMR spectra were obscured by peak broadening.

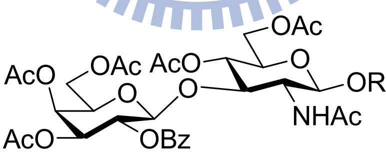
6-Chlorohexyl 2-acetamido-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (34)

34, R = $(CH_2)_6Cl$

A solution of compound **26** (200 mg, 0.29 mmol) and 20 % $Pd(OH)_2/C$ (100 mg) in $EtOAc/H_2O/AcOH$ (6 mL, 2:1:4) was stirred at 60 ^oC under hydrogen at 1 atm overnight. The catalyst was filtered off through celite and the filtrate was concentrated. To a solution of the reaction crude in pyridine (4 mL) at room temperature was added acetic anhydride (2 mL). After stirring for 4h, the mixture was directly concentrated under reduced pressure, and the residue was purified by column chromatography over

silica gel ($EtOAc/CH_2Cl_2$, 1:8→1:4) to give **34** (92 mg, 70%) as white solid. R_f = 0.19 ($EtOAc/CH_2Cl_2$, 1:4); $[\alpha]^{30}_{D}$ -11 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.11 (d, J = 8.7 Hz, 1H), 5.31 (dd, J = 10.5 Hz, J = 9.6 Hz, 1H), 5.06 (t, J = 9.6 Hz, 1H), 4.70 (d, J = 8.4 Hz, 1H; H-1), 4.27 (dd, J = 12.3 Hz, J = 4.8 Hz, 1H), 4.14 (dd, J = 12.0 Hz, J = 2.4 Hz, 1H), 3.91–3.81 (m, 2H), 3.76–3.70 (m, 1H), 3.54 (t, 6.6 Hz, 3H), 2.09 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 2.03 (s, 3H, CH_3CO), 1.95 (s, 3H, CH_3CO), 1.81–1.72 (m, 2H, CH_2), 1.64–1.54 (m, 2H, CH_2), 1.47–1.32 (m, 4H, *CH*2); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.7 (*C*=O), 170.6 (*C*=O), 170.2 (*C*=O), 169.3 (*C*=O), 100.6 (C-1), 72.3, 71.5, 69.4, 68.7, 62.1, 54.5, 44.9 (CH_2Cl), 32.3 (CH_2), 29.1 (CH_2), 26.3 (*C*H2), 25.0 (CH_2), 23.1 (CH_3CO), 20.63 (CH_3CO), 20.58 (CH_3CO), 20.50 (CH_3CO); LRMS (ESI) calcd for $C_{20}H_{32}ClNO_9$ $[M+H]^+$: 466.18, found: 466.15.

6-Chlorohexyl 3,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-β-D-galactopyranosyl-(1→3)-2-acetamido-4,6-di-*O*-acetyl-β-D-glucopyranoside (**35**)



35, R = $(CH_2)_6Cl$

A solution of compound **30** (175 mg, 0.14 mmol) and 20 % $Pd(OH)_2/C$ (100 mg) in $EtOAc/H_2O/AcOH$ (6 mL, 2:1:4) was stirred at 60 °C under hydrogen at 1 atm overnight. The catalyst was filtered off through celite and the filtrate was concentrated. To a solution of the reaction crude in pyridine (4 mL) at room temperature, was added acetic anhydride (2 mL). After stirring for 4h, the mixture was directly concentrated under reduced pressure, and the residue was purified by column chromatography over silica gel (CH_2Cl_2/MeOH, 80:1→40:1) to give **35** (67 mg, 58%) as colorless foam. R_f

= 0.37 (EtOAc/CH_2Cl_2, 1:1); $[\alpha]^{30}_{D}$ +2 (*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 8.00 (d, 2H; Ar-*H*), 7.64 (t, 1H; Ar-*H*), 7.50 (t, 2H; Ar-*H*), 5.40–5.32 (m, 3H), 5.25–5.20 (m, 1H), 5.05 (d, *J* = 8.1 Hz, 1H; H'-1), 4.95 (t, 1H), 4.69–4.63 (m, 2H), 4.30–4.00 (m, 4H), 3.99 (t, 1H), 3.79–3.73 (m, 1H), 3.69–3.60 (m, 1H), 3.50 (t, 2H), 3.44–3.38 (m, 1H), 2.85–2.70 (m, 1H), 2.20–1.85 (m, 18H; CH_3CO), 1.85–1.70 (m, 2H; CH_2), 1.60–1.10 (m, 6H; CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 170.9, 170.7, 170.3, 170.2, 170.0, 169.3 and 164.6 (*C*=O), 133.7, 129.5, 129.2, 128.7 (Ar-*C*), 100.9 (C'-1), 98.3 (C-1), 71.6, 70.6, 69.9, 69.8, 69.0, 66.9, 62.4, 61.0, 58.9, 44.8 (CH_2), 32.3 (CH_2), 29.1 (CH_2), 26.4 (CH_2), 25.0 (CH_2), 23.4 (CH_3CO), 20.71 (CH_3CO), 20.66 (CH_3CO), 20.6 (CH_3CO), 20.4 (CH_3CO); HRMS (ESI) calcd for $C_{37}H_{50}ClNO_{17}$ $[M+Na]^+$: 838.2665, found: 838.2659.

6-Chlorohexyl 2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)-2-acetamido-4,6-di-*O*-acetyl-β-D-glucopyranoside (36)

36, R = $(CH_2)_6Cl$

A solution of compound **33** (180 mg, 0.16 mmol) and 20 % $Pd(OH)_2/C$ (100 mg) in EtOAc/H_2O/AcOH (10 mL, 5:1:4), was stirred at 60 °C under hydrogen at 1 atm overnight. The catalyst was filtered off through celite and the filtrate was concentrated. To a solution of the reaction crude in pyridine (4 mL) at room temperature, was added acetic anhydride (2 mL). After stirring for 4h, the mixture was directly concentrated under reduced pressure, and the residue was purified by column chromatography over silica gel (CH_2Cl_2/MeOH, 80:1→40:1) to give **36** (56 mg, 50%) as colorless foam. R_f

= 0.15 (EtOAc/CH_2Cl_2, 1:4); $[\alpha]^{30}_{D}$ -36 (*c* 0.61, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.80 (d, *J* = 7.0 Hz, 1H), 5.31 (dd, *J* = 11.0 Hz, *J* = 3.0 Hz, 1H), 5.26–5.24 (m, 2H), 5.09 (dd, *J* = 11.0 Hz, *J* = 3.5 Hz, 1H), 4.99–4.92 (m, 2H), 4.42 (t, *J* = 9.5 Hz, 1H), 4.20–4.13 (m, 2H), 4.08 (dd, *J* = 12.0 Hz, *J* = 2.5 Hz, 1H), 3.87–3.82 (m, 1H), 3.64–3.58 (m, 1H), 3.54 (t, *J* = 6.8 Hz, 2H), 3.51–3.46 (m, 1H), 3.2 (m, 1H) 2.15 (s, 3H) 2.11 (s, 3H) 2.08 (s, 3H), 2.07 (s, 3H), 1.98 (s, 6H), 1.80–1.74 (m, 4H), 1.62–1.74 (m, 2H), 1.48–1.42 (m, 2H); 1.08 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.7, 170.6, 170.5, 169.9 and 169.7 (*C*=O), 99.0 (C-1), 96.8 (C'-1), 76.2, 71.8, 71.2, 71.0, 69.7 (Ph*C*H_2), 68.7, 67.3, 65.5, 62.6 (*C*H_2), 58.0, 45.0 (*C*H_2), 32.4 (*C*H_2), 29.2 (*C*H_2), 26.5 (*C*H_2), 25.2 (*C*H_2), 23.6 (*C*H_3CO), 21.0 (*C*H_3CO), 20.9 (*C*H_3CO), 20.8 (*C*H_3CO), 20.7 (*C*H_3CO), 20.6 (*C*H_3CO), 15.5 (*C*H_3CO); HRMS (ESI) calcd for $C_{30}H_{46}ClNO_{15}$ $[M+Na]^+$: 718.2454, found: 718.2448.

***p*-Tolyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside** (37)

BnO OBn
BnO O OH O
OBn O HO STol NHBn
37

A solution of compound **16** (300 mg, 0.29 mmol) in 1M NaOH (9 mL) and 1,4-dioxane (9 mL) was stirred at 80 °C for 12h. The mixture was cooled to room temperature, diluted with EtOAc, and then washed with water. The aqueous layer was washed with EtOAc three times. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (CH_2Cl_2/MeOH, 50:1) to give **37** (220 mg, 84%) as

yellow oil. R_f = 0.22 (CH_2Cl_2/MeOH, 50:1); $[\alpha]^{30}_{D}$ -25 (*c* 2.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43–7.16 (m, 27 H; Ar-*H*), 7.01 (d, *J* = 8.1 Hz, 2H; Ar-*H*), 4.86 (d, *J* = 11.7 Hz, 1H), 4.68 (s, 2H), 4.59–4.50 (m, 5H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.27 (d, *J* = 7.8 Hz, 1H), 3.98 (s, 2H), 3.95–3.33 (m, 11H), 2.68 (t, *J* = 9.6 Hz, 1H), 2.28 (s, 1H; Ar-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.4, 138.0, 137.9, 137.5, 137.3, 132.6, 129.4, 129.0, 128.3, 128.2, 128.15, 128.08, 128.06, 127.8, 127.7, 127.65, 127.61, 127.5, 127.44, 127.40, 127.15, 126.7, and 126.68 (Ar-*C*), 104.2 (C'-1), 88.0 (C-1), 82.5, 81.8, 75.5, 74.3, 73.8, 73.6, 73.4, 73.3, 73.2, 72.7, 72.5, 70.9, 69.5, 68.6, 66.8, 64.6, 61.4, 53.3, 52.4, 20.9 (Ar-CH_3); HRMS (ESI) calcd for $C_{54}H_{59}NO_9S$ $[M]^+$: 897.3911, found: 897.3920.

***p*-Tolyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-*N*-benzyloxy-carbonyl-2-amino-6-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (38)**

To a solution of compound **37** (430 mg, 0.48 mmol) and $NaHCO_3$ (323 mg, 3.84 mmol) in non-dried MeOH (5 mL) at room temperature, was added benzyl chloroformate (0.2 mL, 0.72 mmol, 50 wt% solution in toluene). After stirring for 2h, the residue was diluted with CH_2Cl_2 (10 mL), poured into a two-layer mixture of CH_2Cl_2 (20 mL) and brine (20 mL), and the whole was extracted with CH_2Cl_2 (40 mL × 3). The combined organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2/hexane, 1:1:4) to give **38** (405 mg,

82%) as colorless foam. R_f = 0.30 (EtOAc/CH_2Cl_2/hexane, 1:1:2); $[\alpha]^{30}_{D}$ -9 (*c* 1.68, $CHCl_3$). Standard ^1H and ^{13}C NMR spectra were obscured by peak broadening.

6-Chlorohexyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-*N*-benzyloxycarbonyl-2-amino-6-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (39)

39, R = $(CH_2)_6Cl$

Compound **38** (100 mg, 0.097 mmol), 6-chlorohexanol **7** (26 μL, 0.194 mmol), and activated 4 Å MS (400 mg, 100mg/1mL CH_2Cl_2, AW300) in CH_2Cl_2 (4 mL) were stirred at room temperature under nitrogen for 20 min. The mixture was then cooled in a cooling bath at –50 °C followed by addition of TfOH (58 μL, 7 mM) and NIS (26 mg, 0.116 mmol) and stirred for 2h. After disappearance of acceptor detected by TLC, the mixture was diluted with CH_2Cl_2 (12 mL), quenched by Et_3N, and few droplets of sat. $NaHCO_3$ and pieces of $Na_2S_2O_{3(s)}$ were added. The quenching mixture was then stirred at room temperature for 2h, filtered and finally concentrated. The residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2, 1:16→1:6) to give **39** (89 mg, 88%) as colorless foam. R_f = 0.33 (EtOAc/CH_2Cl_2, 1:16); $[\alpha]^{30}_{D}$ -4 (*c* 1.5, $CHCl_3$). Standard ^1H and ^{13}C NMR spectra were obscured by peak broadening.

6-Chlorohexyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-*N*-benzyloxycarbonyl-2-amino-6-*O*-benzyl

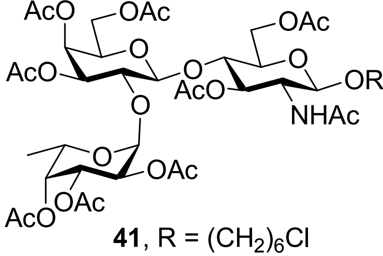
-2-deoxy-1-thio-β-D-glucopyranoside (40)

40, R = $(CH_2)_6Cl$

Compound **38** (290 mg, 2.32 mmol), 6-chlorohexanol **7** (56 μL, 0.42 mmol), and activated 4 Å MS (1.2 g, 100mg/1mL CH_2Cl_2, AW300) in CH_2Cl_2 (12 mL) were stirred at room temperature under nitrogen for 20 min. The mixture was then cooled in a cooling bath at −50 °C followed by addition of NIS (76 mg, 0.34 mmol) and TfOH (168 μL/0.5 M ether, 0.084 mmol) and stirred for 2h. After disappearance of donor **38** detected by TLC, the temperature was cooled to −70 °C followed by addition of fucosyl donor **12** (453 mg, 0.84 mmol), NIS (203 mg, 0.90 mmol) and TfOH (504 μL/0.5 M ether, 0.25 mmol) in sequential order. After 10 min, the temperature was raised to −60 °C and the reaction was stirred for 2h. After disappearance of donor **12** detected by TLC, the mixture was diluted with CH_2Cl_2 (24 mL), quenched by Et_3N, and few droplets of sat. $NaHCO_3$ and pieces of $Na_2S_2O_{3(s)}$ were added. The quenching mixture was then stirred at room temperature for 2h, filtered and finally concentrated. The residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2, 1:12→1:8) to give **40** (240 mg, 58%) as colorless syrup. R_f = 0.51 (EtOAc/CH_2Cl_2, 1:16). Standard ^{1}H and ^{13}C NMR spectra were obscured by peak broadening.

6-Chlorohexyl 2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2-acetamido-3,6-di-*O*-acetyl-β-D-glucopyranoside

(**41**)



A solution of compound **40** (240 mg, 0.16 mmol) and 20 % $Pd(OH)_2$/C (100 mg) in THF/MeOH/H_2O/AcOH (10 mL, 5:1:1:3) was stirred at room temperature under hydrogen at 1 atm for 2 days. The catalyst was filtered off through celite and the filtrate was concentrated. To a solution of the reaction crude in pyridine (4 mL) at room temperature, was added acetic anhydride (2 mL). After stirring for 4h, the mixture was directly concentrated under reduced pressure, and the residue was purified by column chromatography over silica gel (EtOAc/CH_2Cl_2, 1:4→1:1) to give **41** (72 mg, 45%) as white solid. R_f = 0.17 (EtOAc/CH_2Cl_2, 1:2); $[\alpha]^{30}_{D}$ -65 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.51 (d, *J* = 9.0 Hz, 1H), 5.37 (d, *J* = 4.0 Hz, 1H), 5.31 (d, *J* = 2.5 Hz, 1H), 5.28 (d, *J* = 3.0 Hz, 1H), 5.16–5.08 (m, 2H), 5.00–4.95 (m, 2H), 4.54–4.50 (m, 2H), 4.44–4.41 (m, 2H), 4.27 (dd, *J* = 12 Hz, *J* = 6 Hz, 1H), 4.14 (dd, *J* = 11 Hz, *J* = 6.5 Hz, 1H), 4.08 (dd, *J* = 11.3 Hz, J = 7.0 Hz, 1H), 3.93 (q, *J* = 5.0 Hz, 1H), 3.86–3.80 (m, 4H), 3.64–3.60 (m, 1H), 3.55–3.46 (m, 3H), 2.16 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.98−1.97 (m, 6H), 1.96 (s, 3H), 1.80−1.73 (m, 4H), 1.65−1.54 (m, 2H), 1.46−1.41 (m, 2H), 1.19 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.9, 170.64, 170.60, 170.3, 170.1, 170.0, 169.9, 169.7, 101.1, 100.2, 95.5, 74.4, 73.4, 73.0, 71.7, 71.5, 71.0, 70.7, 69.6, 68.0, 67.4, 67.0, 64.8, 62.4, 60.9, 54.0, 45.0, 32.4, 29.2, 26.4, 25.1, 23.3, 20.82, 20.76, 20.62, 20.62, 20.59, 20.58, 20.55, 20.53, 15.51.

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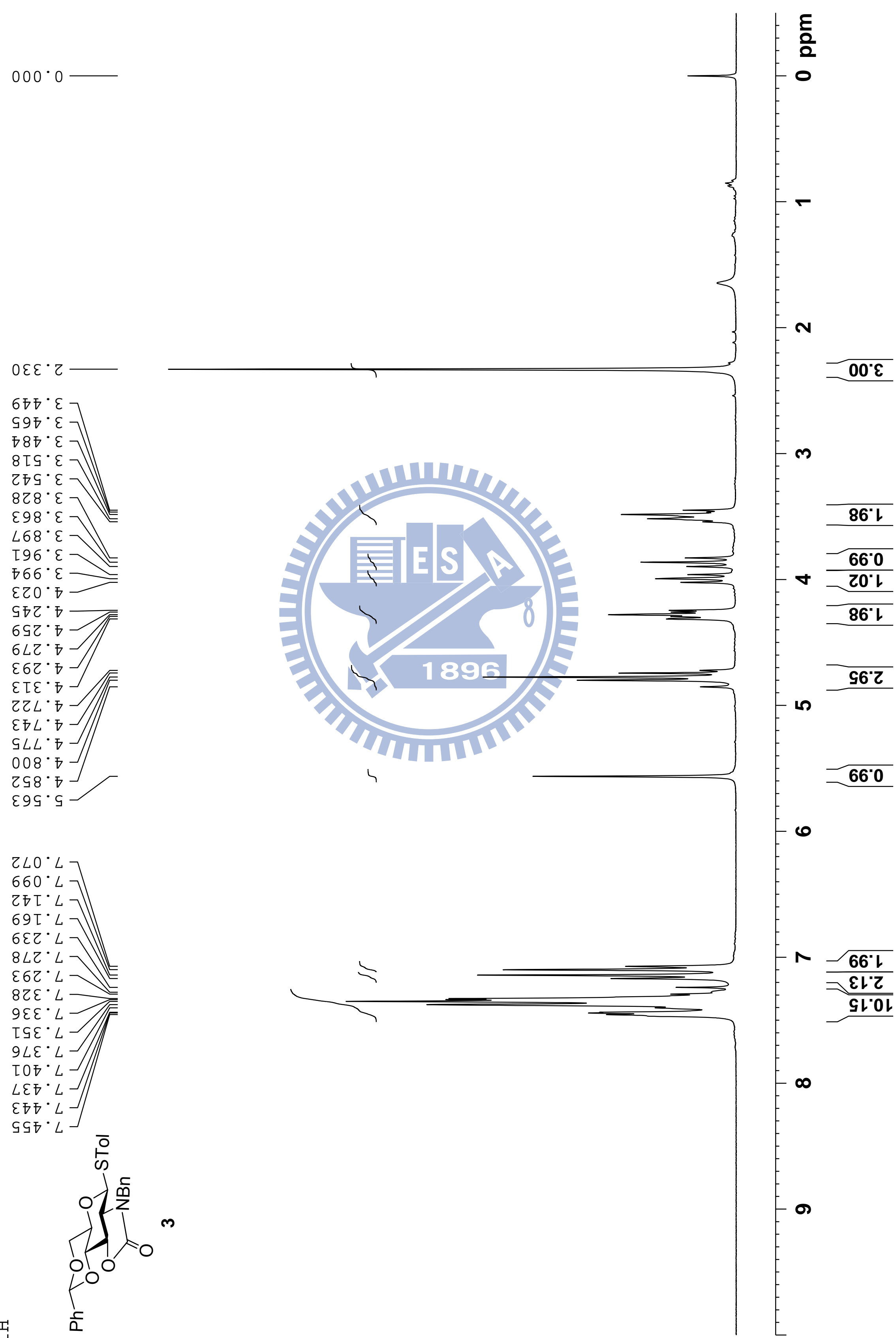
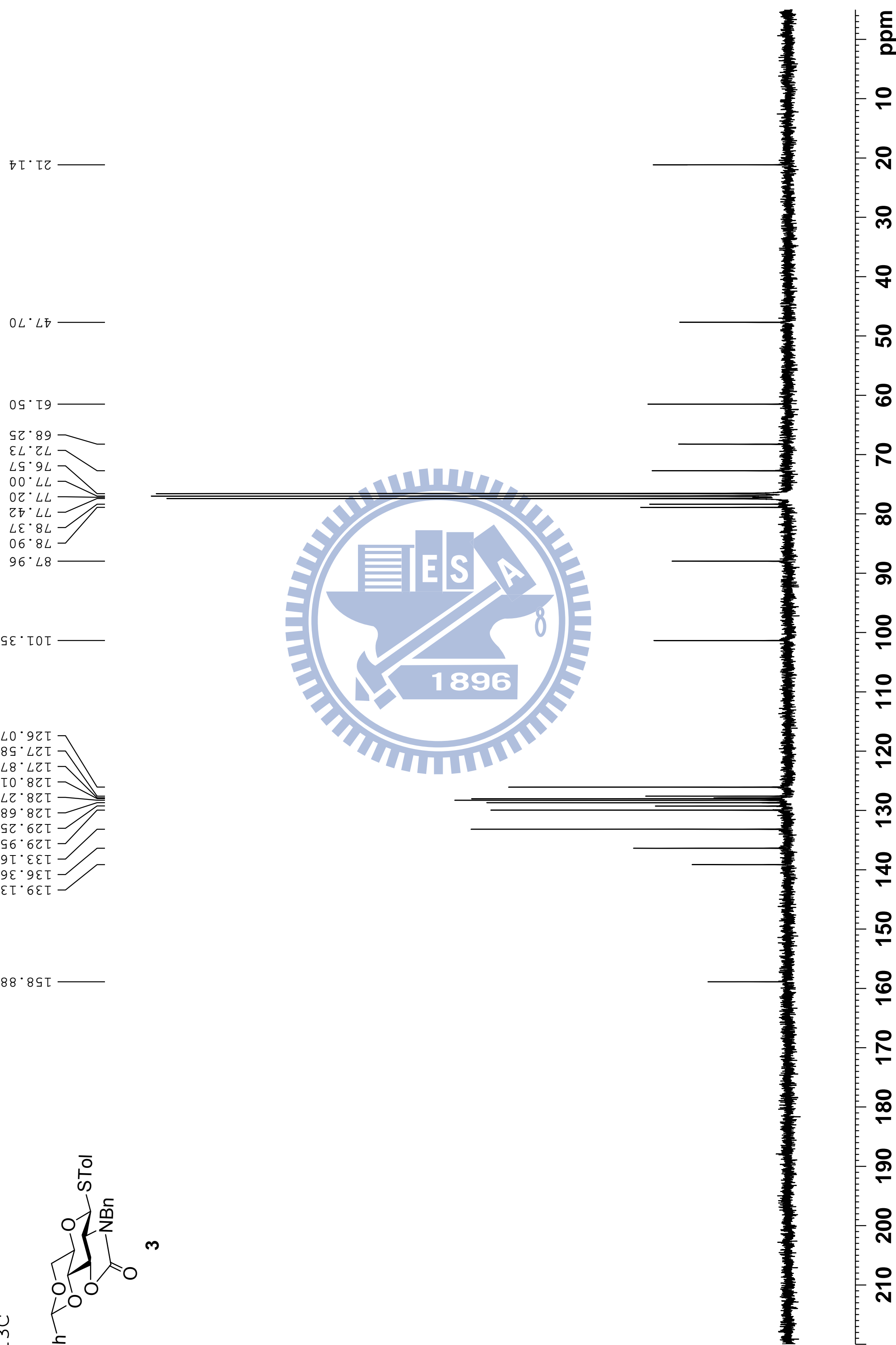
Appendix

[1]H spectrum of *p*-Tolyl *N*-Benzyl-2-amino-4,6-*O*-benzylidene-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**3**)



^{13}C spectrum of *p*-Tolyl *N*-Benzyl-2-amino-4,6-*O*-benzylidene-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**3**)



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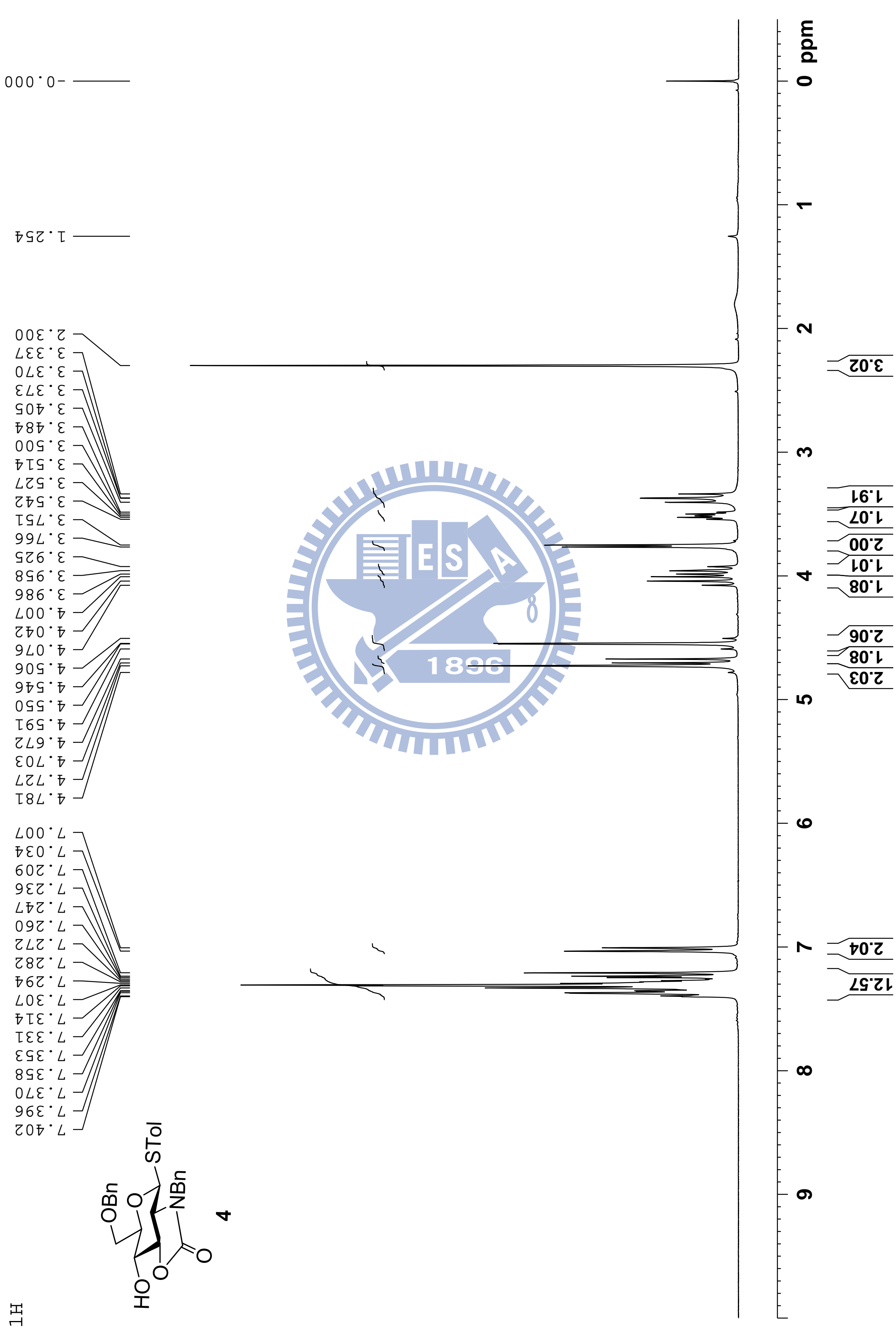
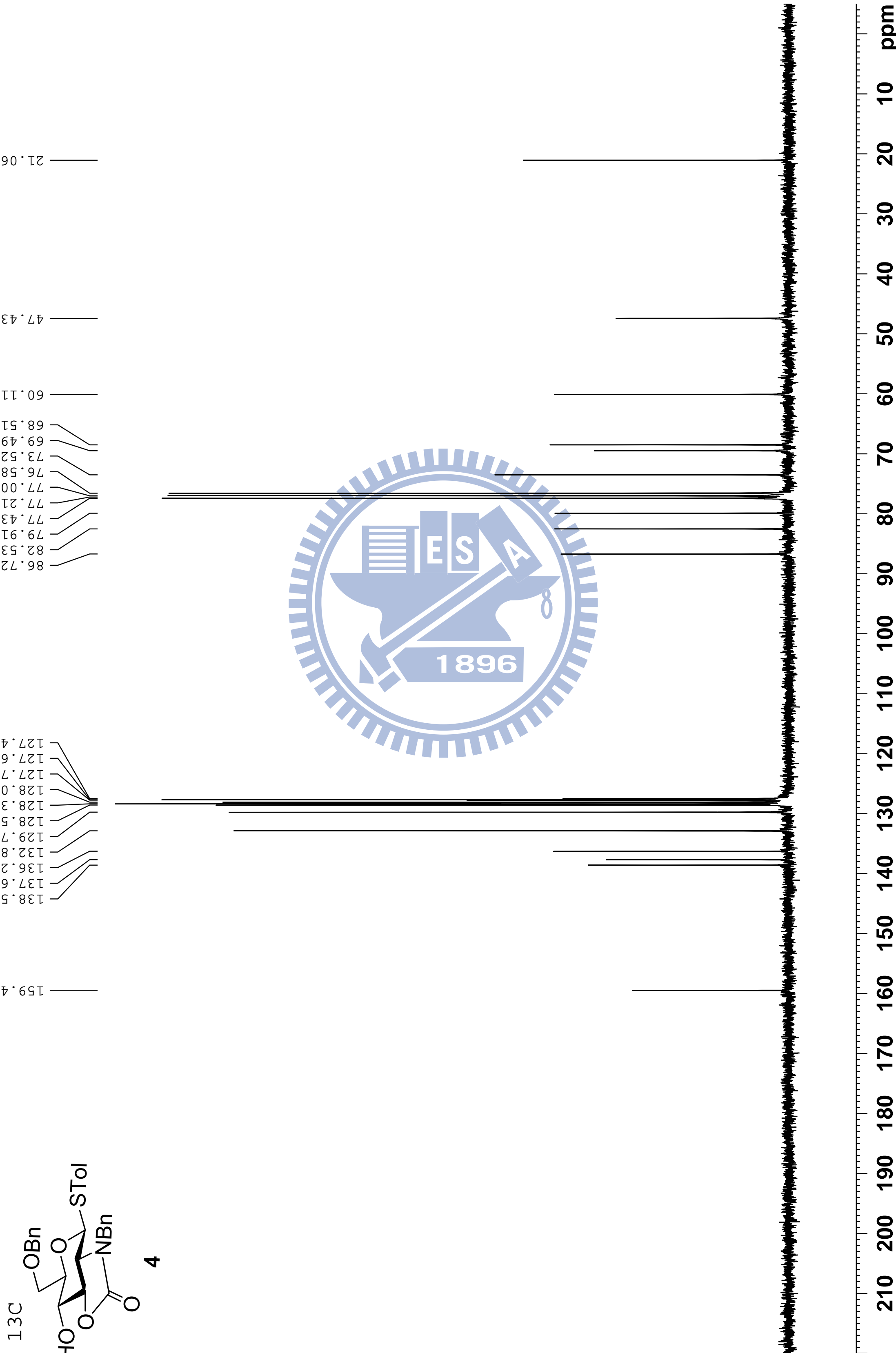
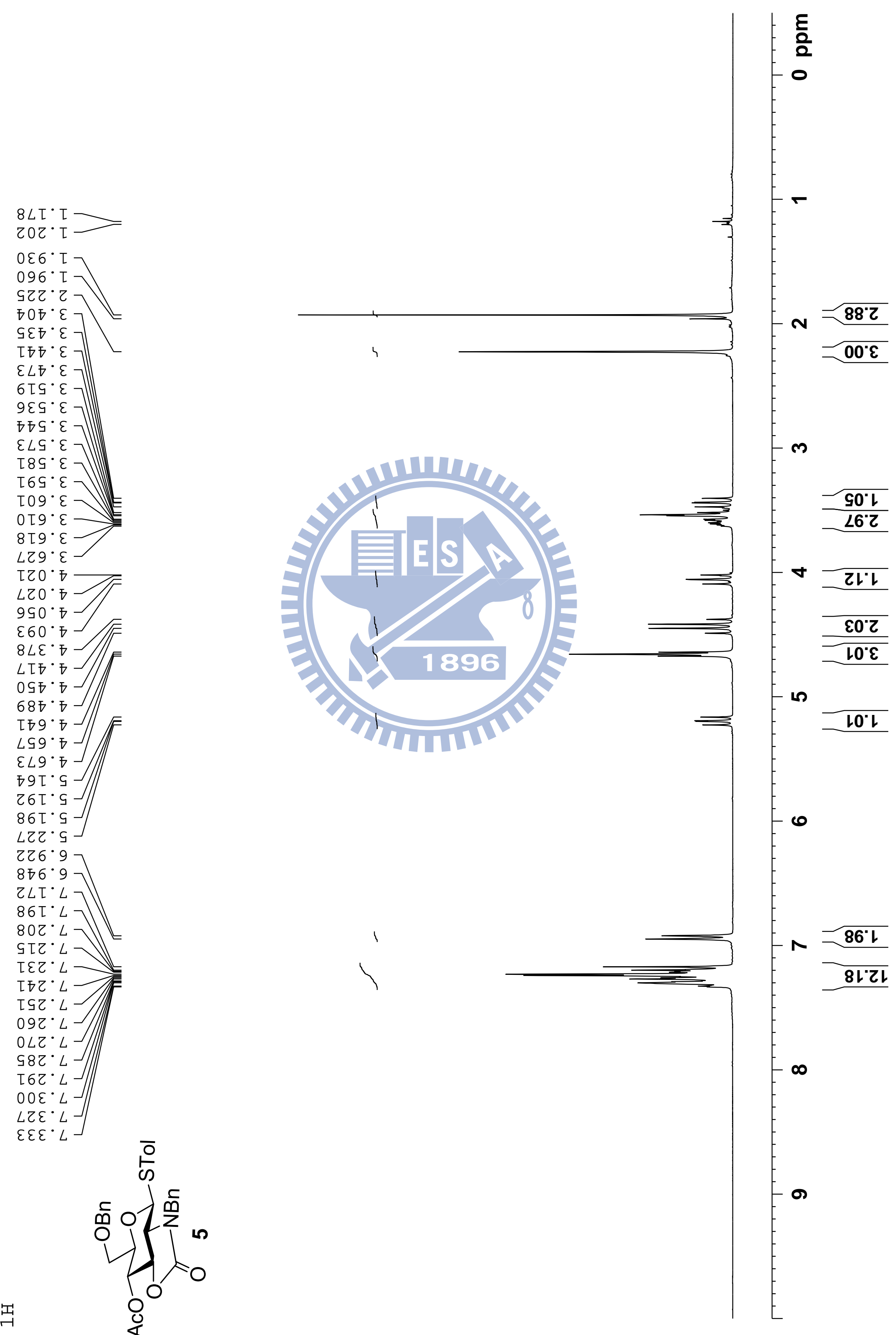


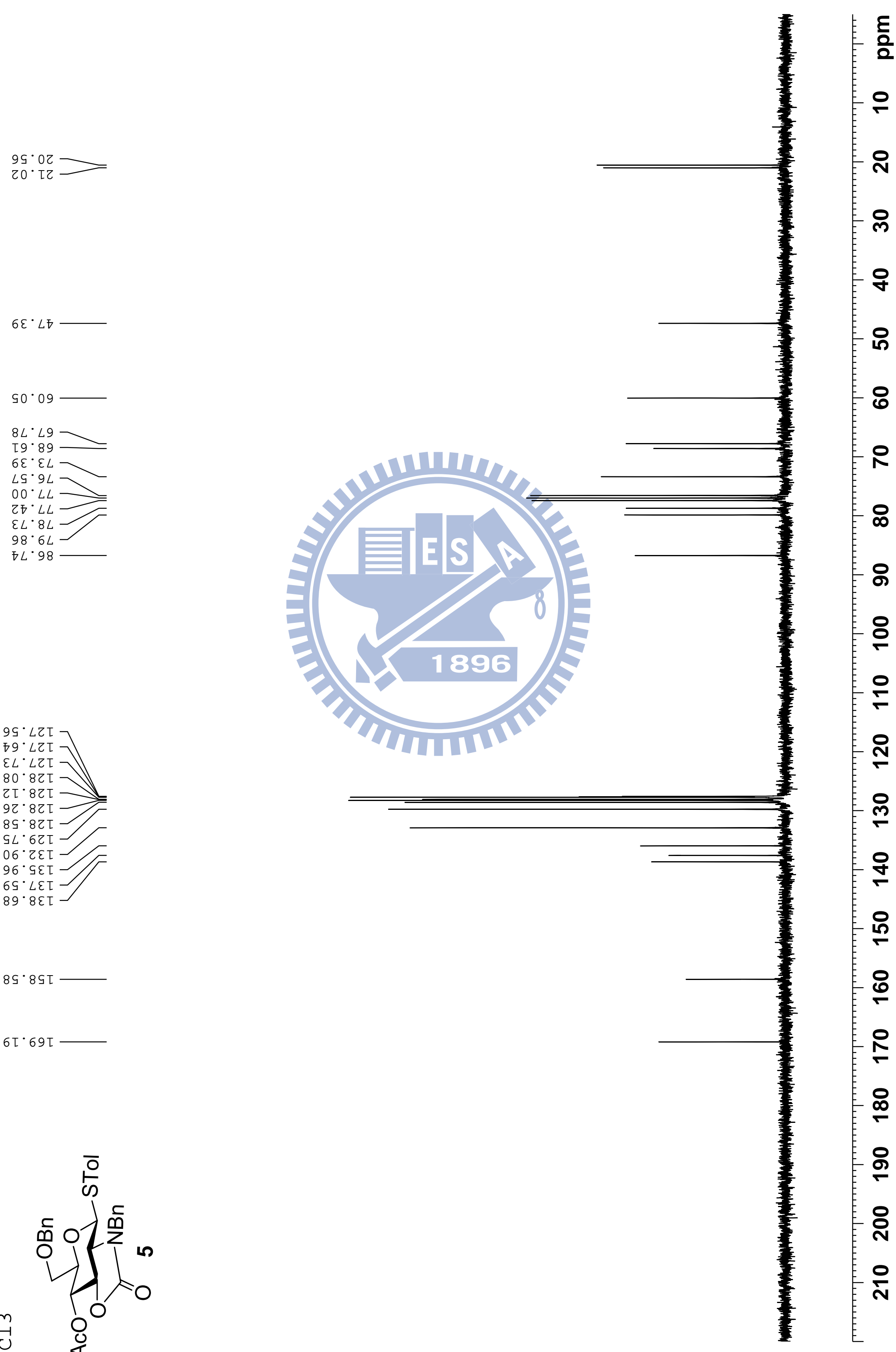
^{13}C spectrum of *p*-Tolyl *N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**4**)



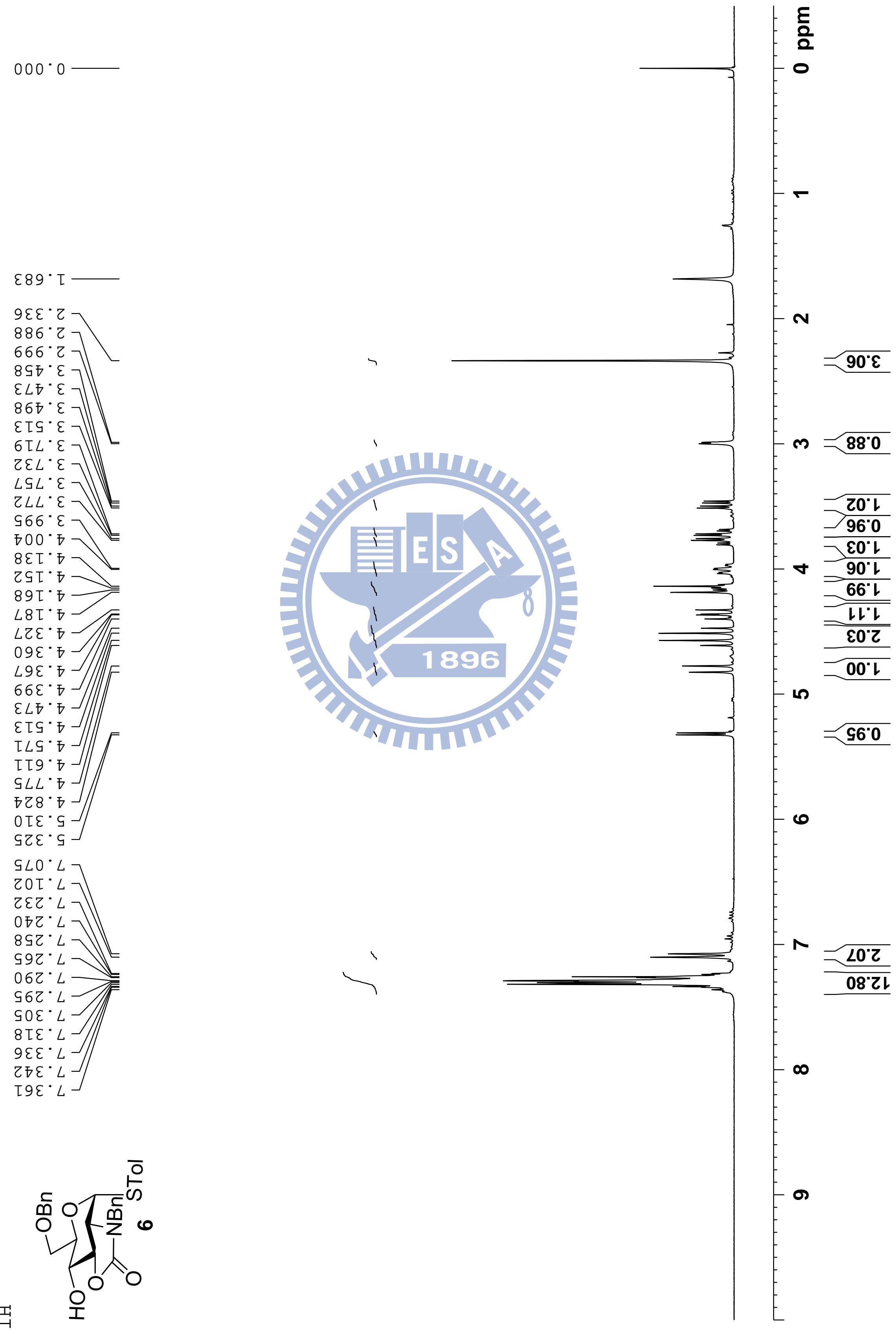
[1]H spectrum of *p*-Tolyl *N*-Benzyl-2-amino-4-acetyl-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio- β-D-glucopyranoside (**5**)



^{13}C spectrum of *p*-Tolyl *N*-Benzyl-2-amino-4-acetyl-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio- β-D-glucopyranoside (**5**)



[1]H spectrum of *p*-Tolyl *N*-Benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2- deoxy-1-thio-α-D-glucopyranoside (**6**)



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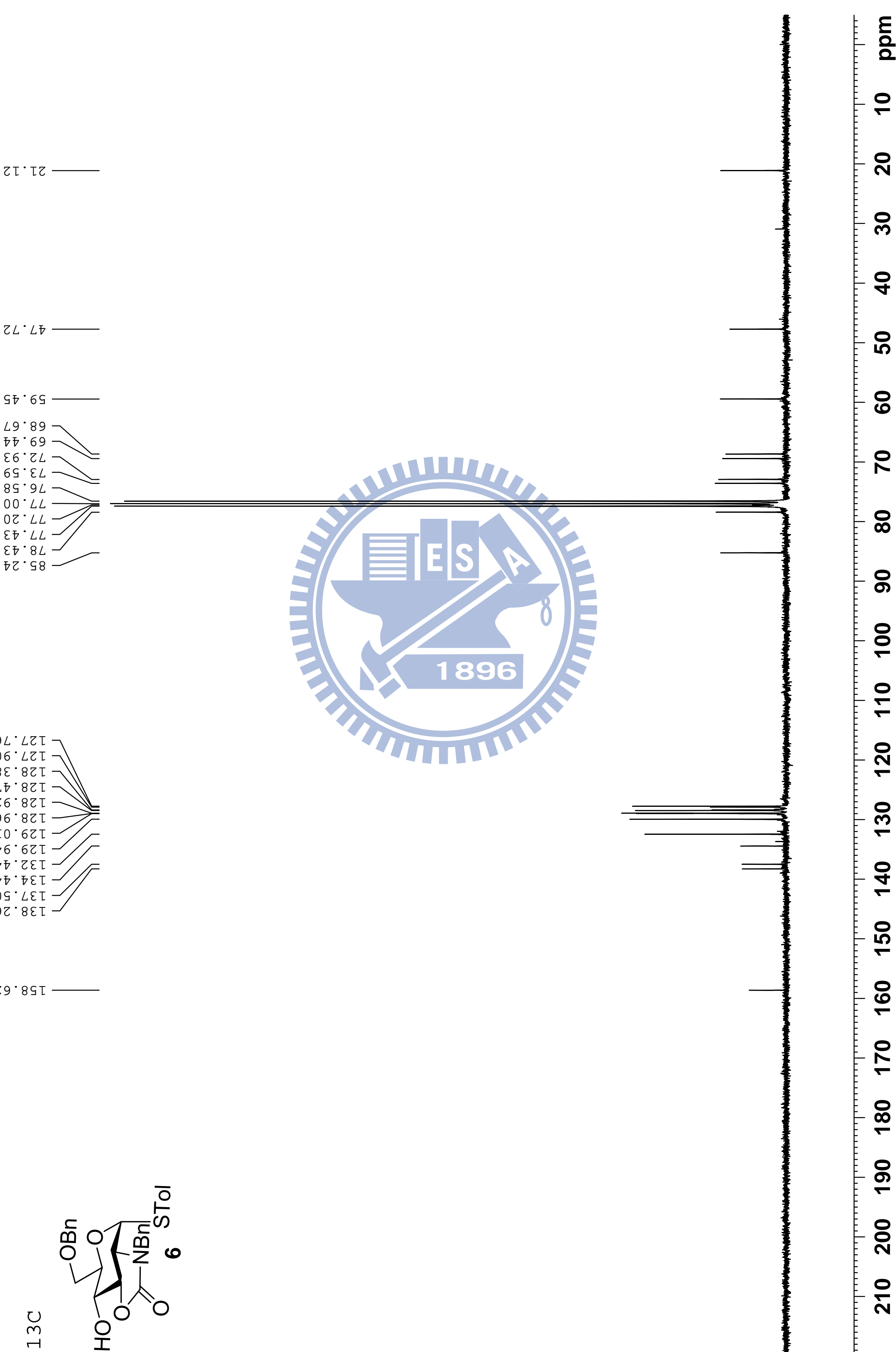
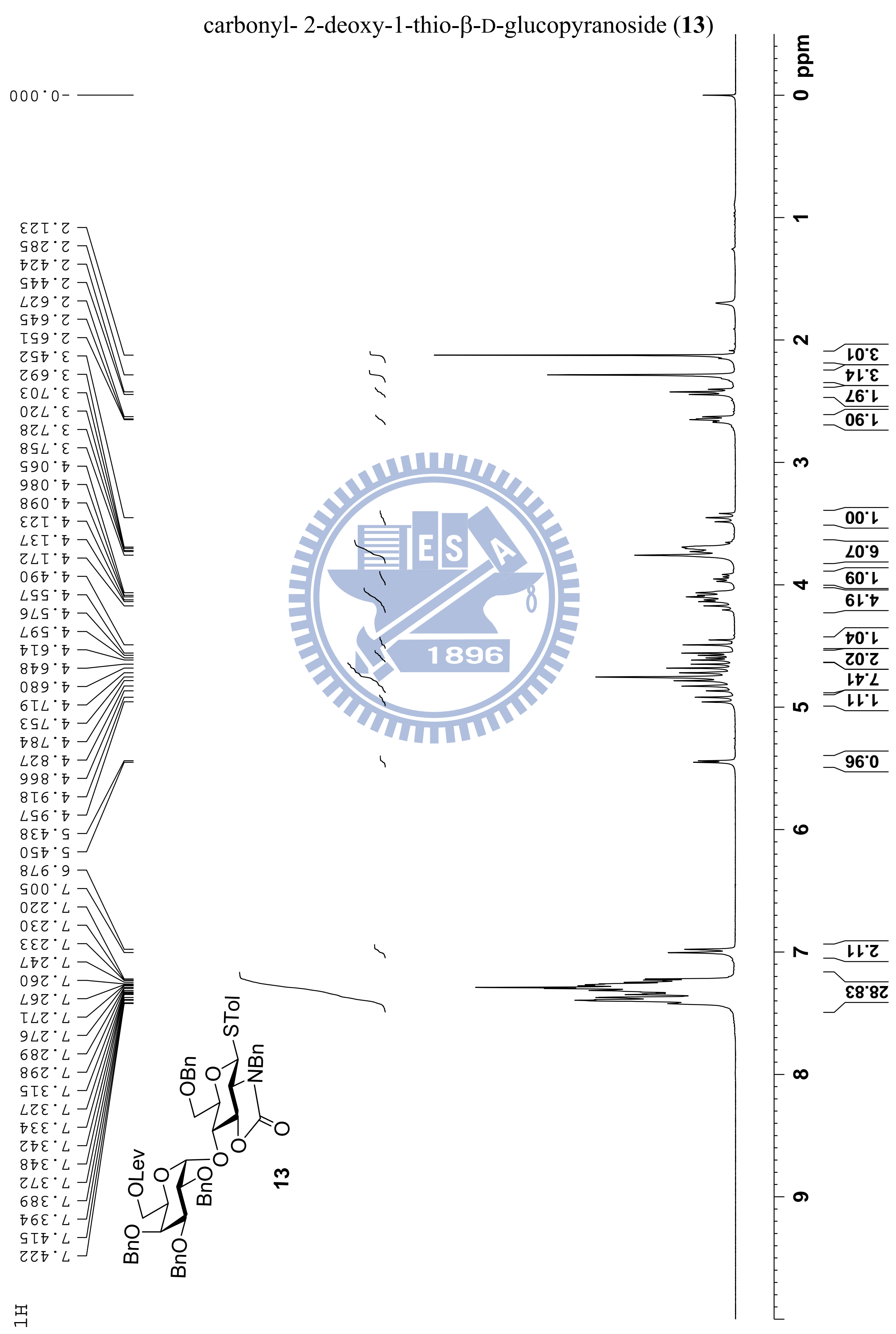
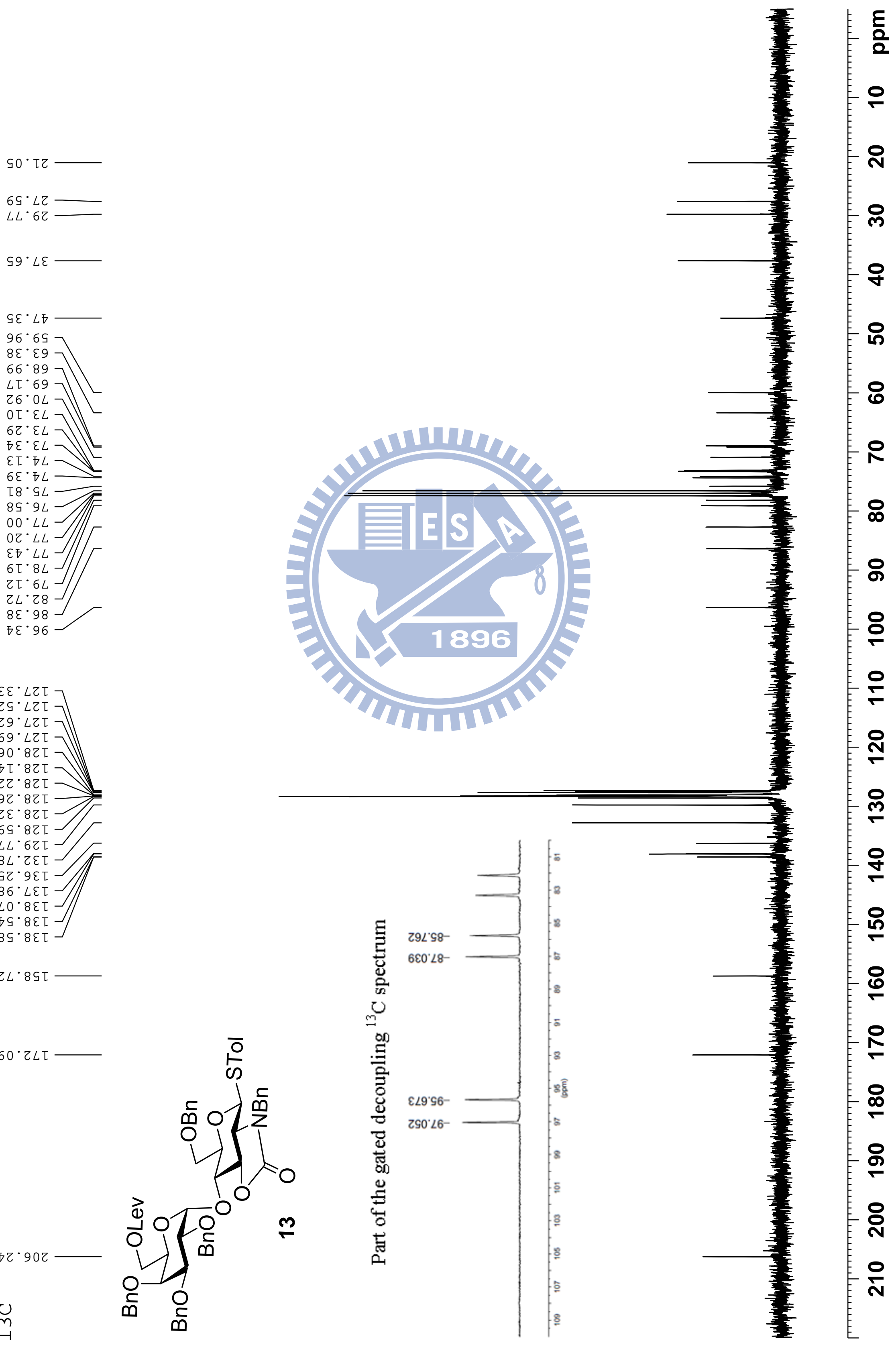


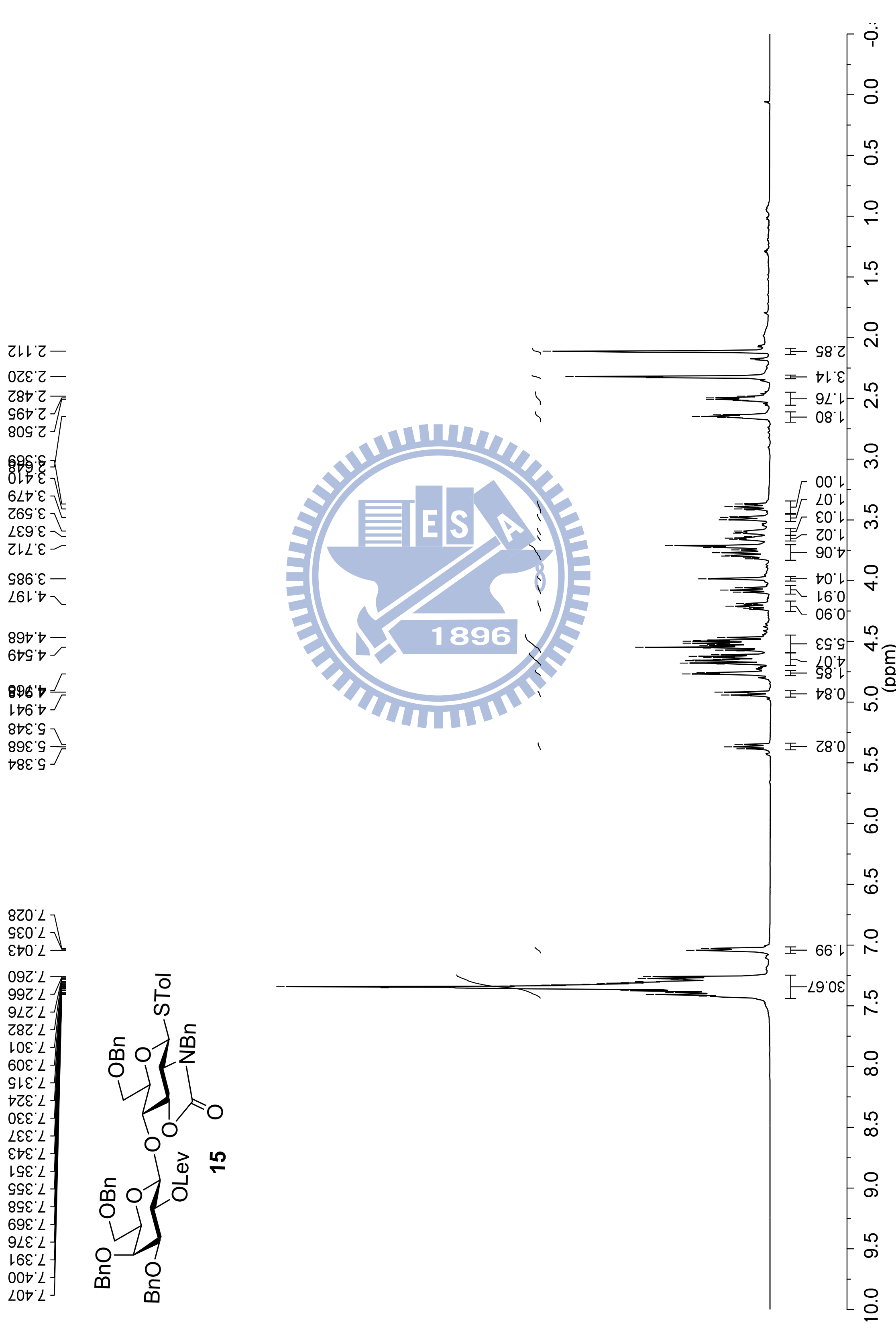
^{1}H spectrum of *p*-Tolyl 2,3,4-Tri-*O*-benzyl-6-*O*-levulinoyl-α-D-galacto-pyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl- 2-deoxy-1-thio-β-D-glucopyranoside (**13**)



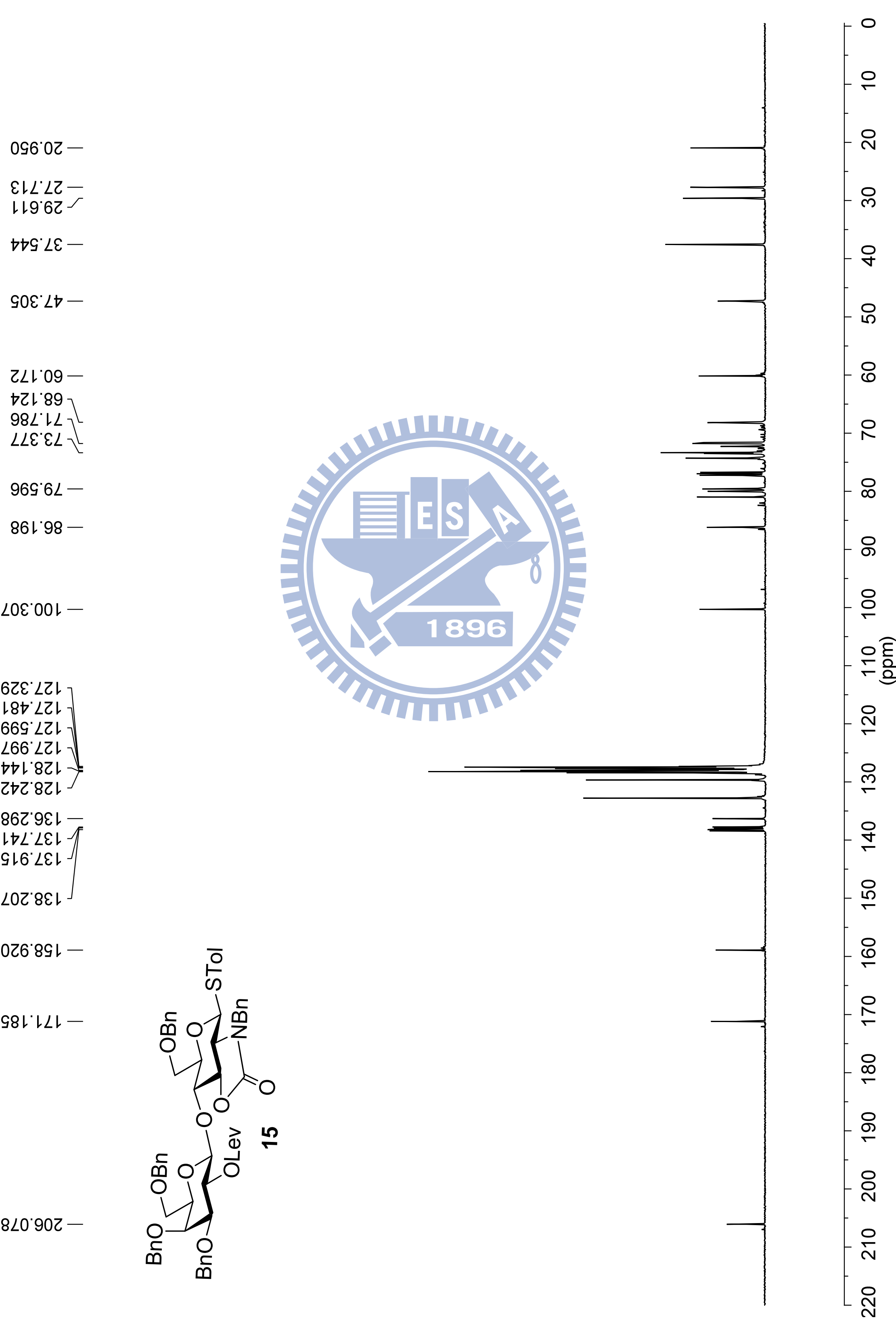
[13]C spectrum of *p*-Tolyl 2,3,4-Tri-*O*-benzyl-6-*O*-levulinoyl-α-D-galacto-pyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl- 2-deoxy-1-thio-β-D-glucopyranoside (**13**)



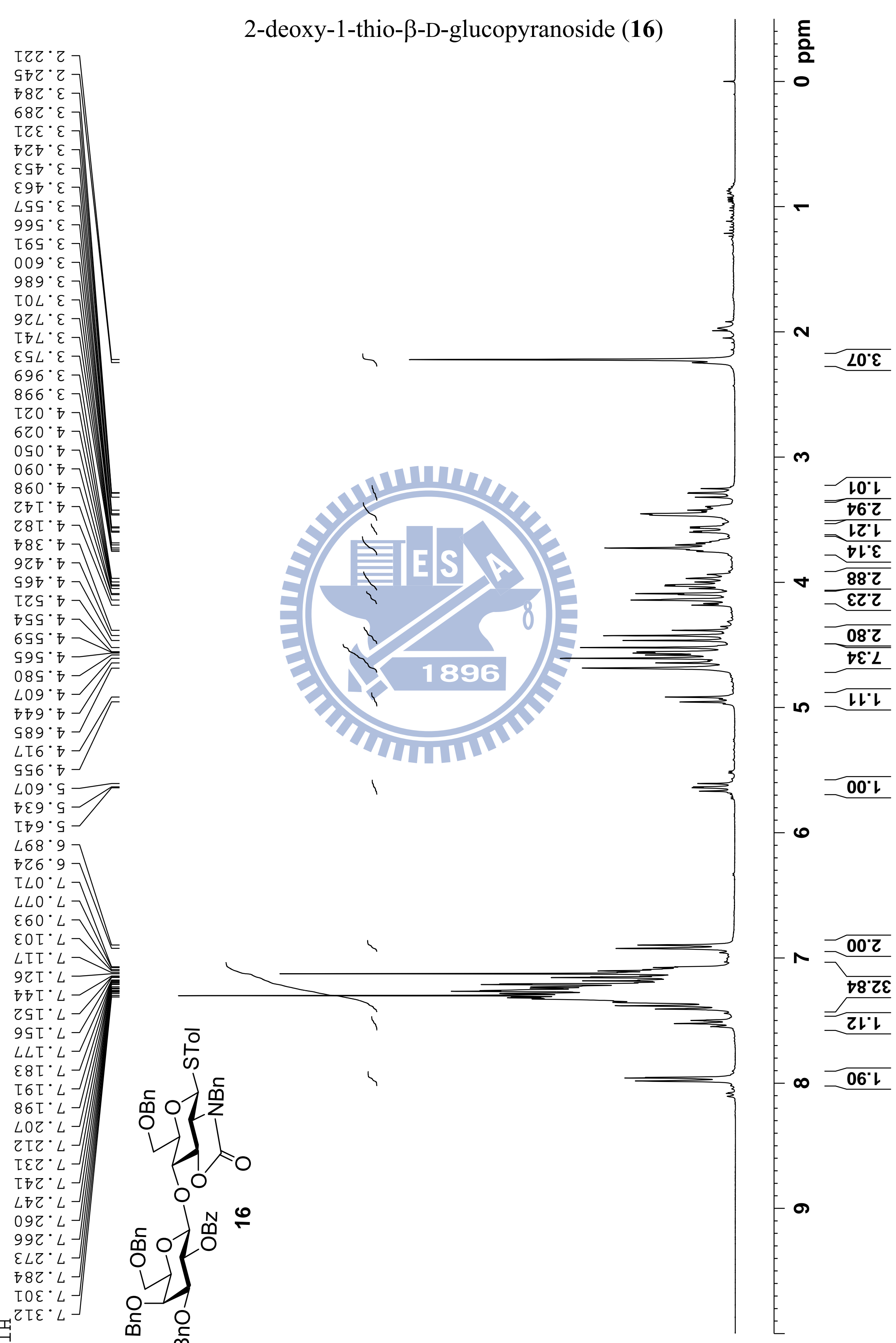
^{1}H spectrum of *p*-Tolyl 3,4,6-Tri-*O*-benzyl-2-*O*-levulinoyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl -2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**15**)



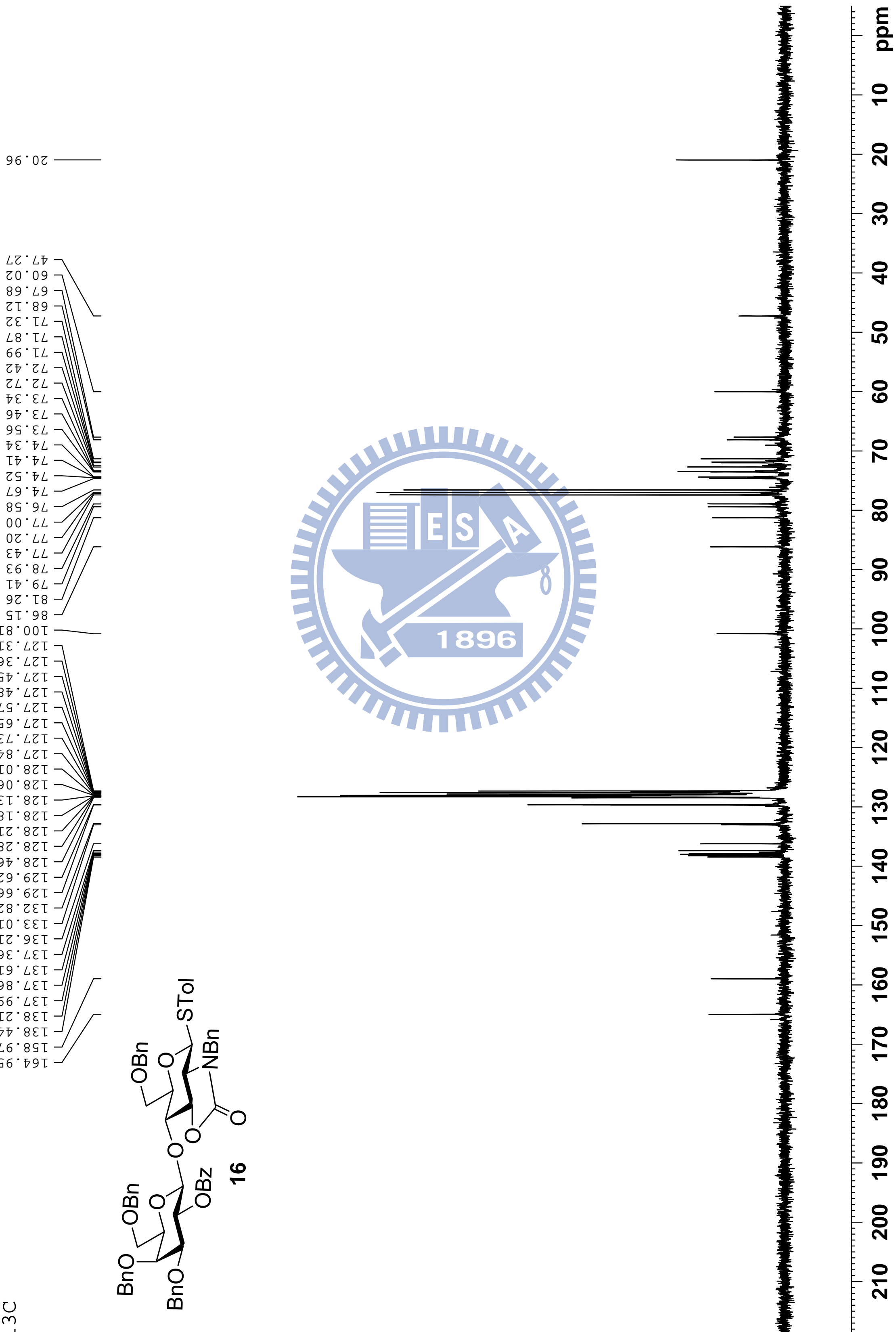
^{13}C spectrum of *p*-Tolyl 3,4,6-Tri-*O*-benzyl-2-*O*-levulinoyl-β-D-galacto-pyranosyl-(1→4)-*N*-benzyl -2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**15**)



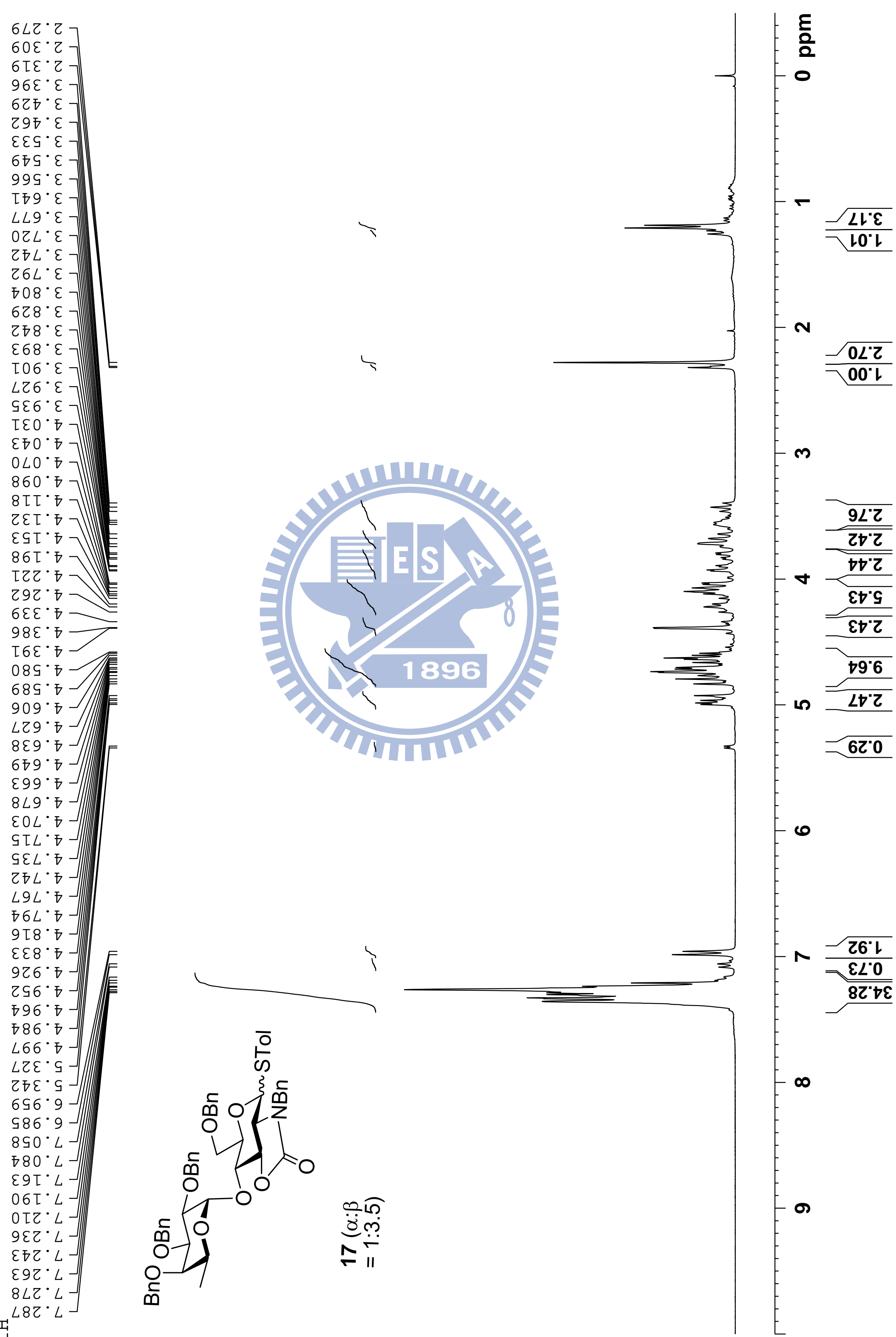
[1]H spectrum of *p*-Tolyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**16**)



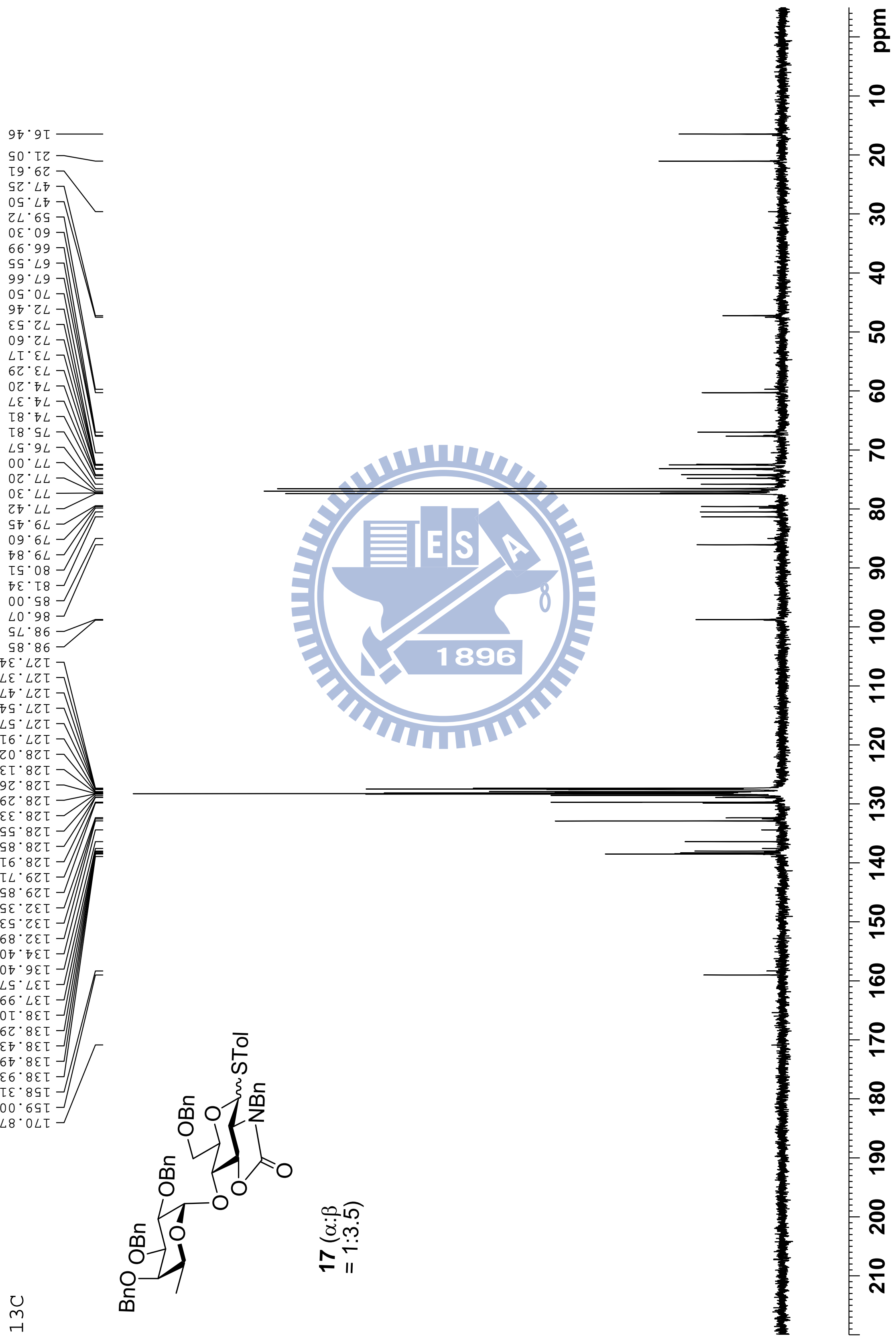
[13]C spectrum of *p*-Tolyl 2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**16**)



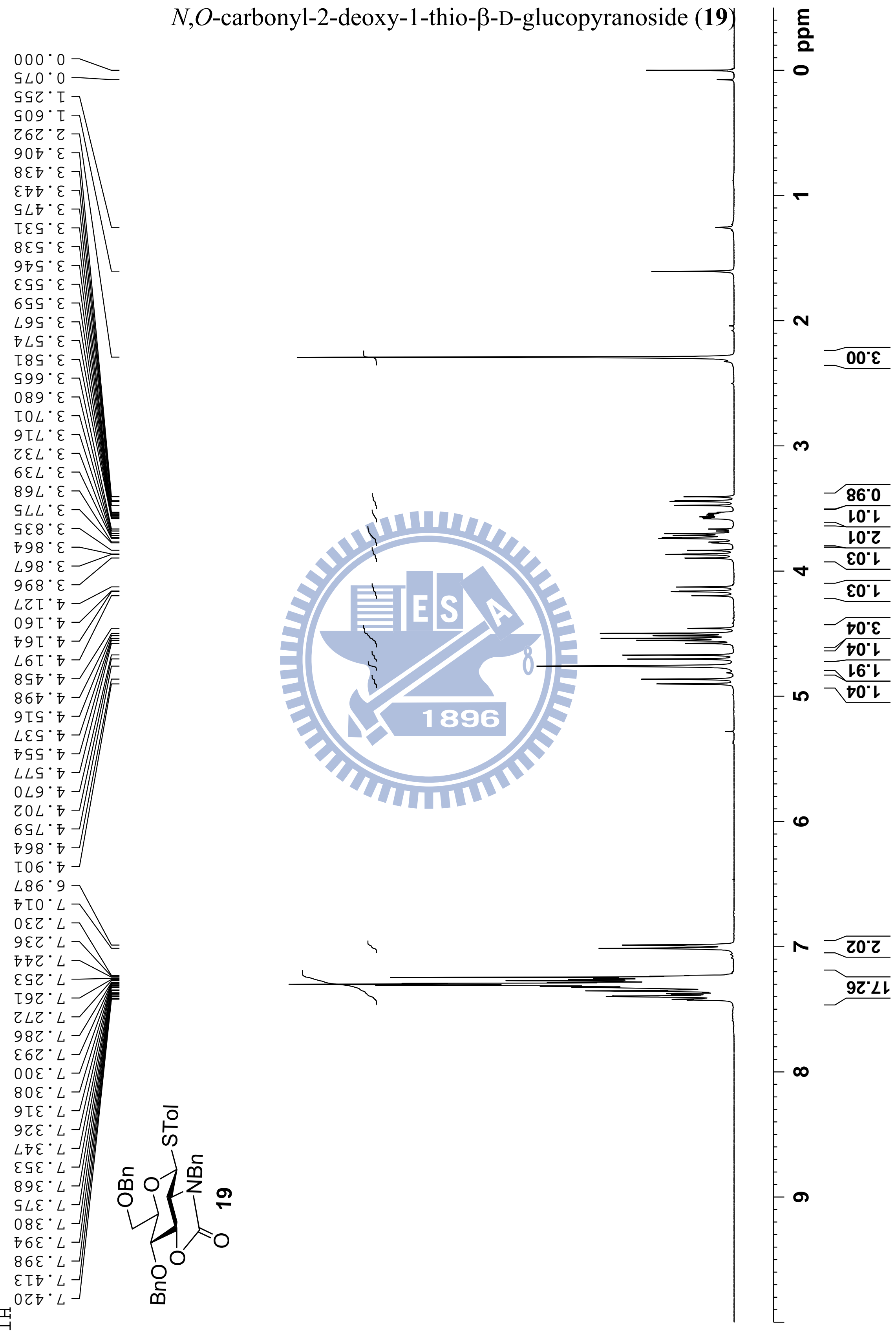
[1]H spectrum of *p*-Tolyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-D-glucopyranoside (**17**)



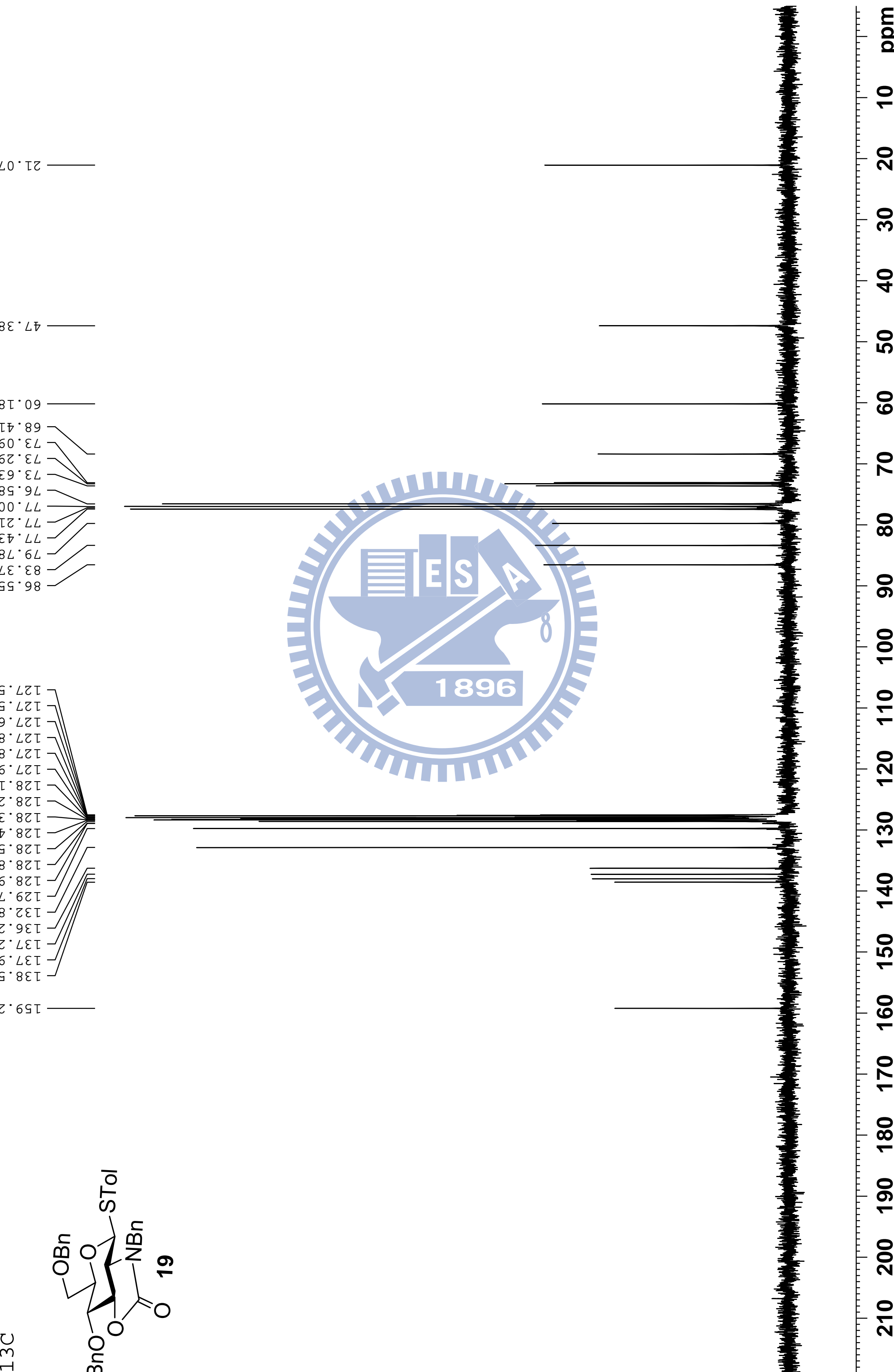
^{13}C spectrum of *p*-Tolyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-D-glucopyranoside (**17**)



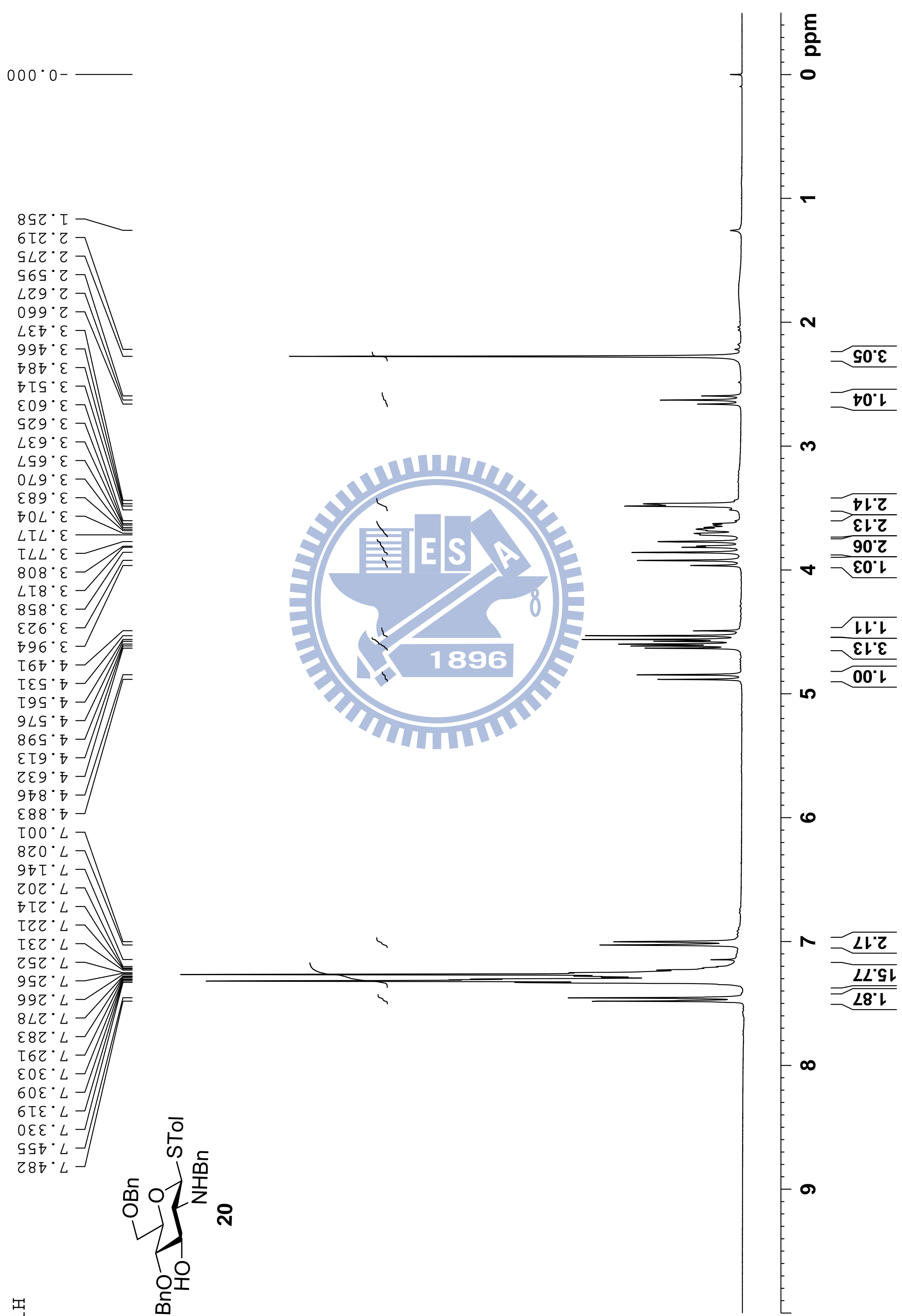
^{1}H spectrum of *p*-Tolyl *N*-Benzyl-2-amino-4,6-di-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**19**)



^{13}C spectrum of *p*-Tolyl *N*-Benzyl-2-amino-4,6-di-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (**19**)

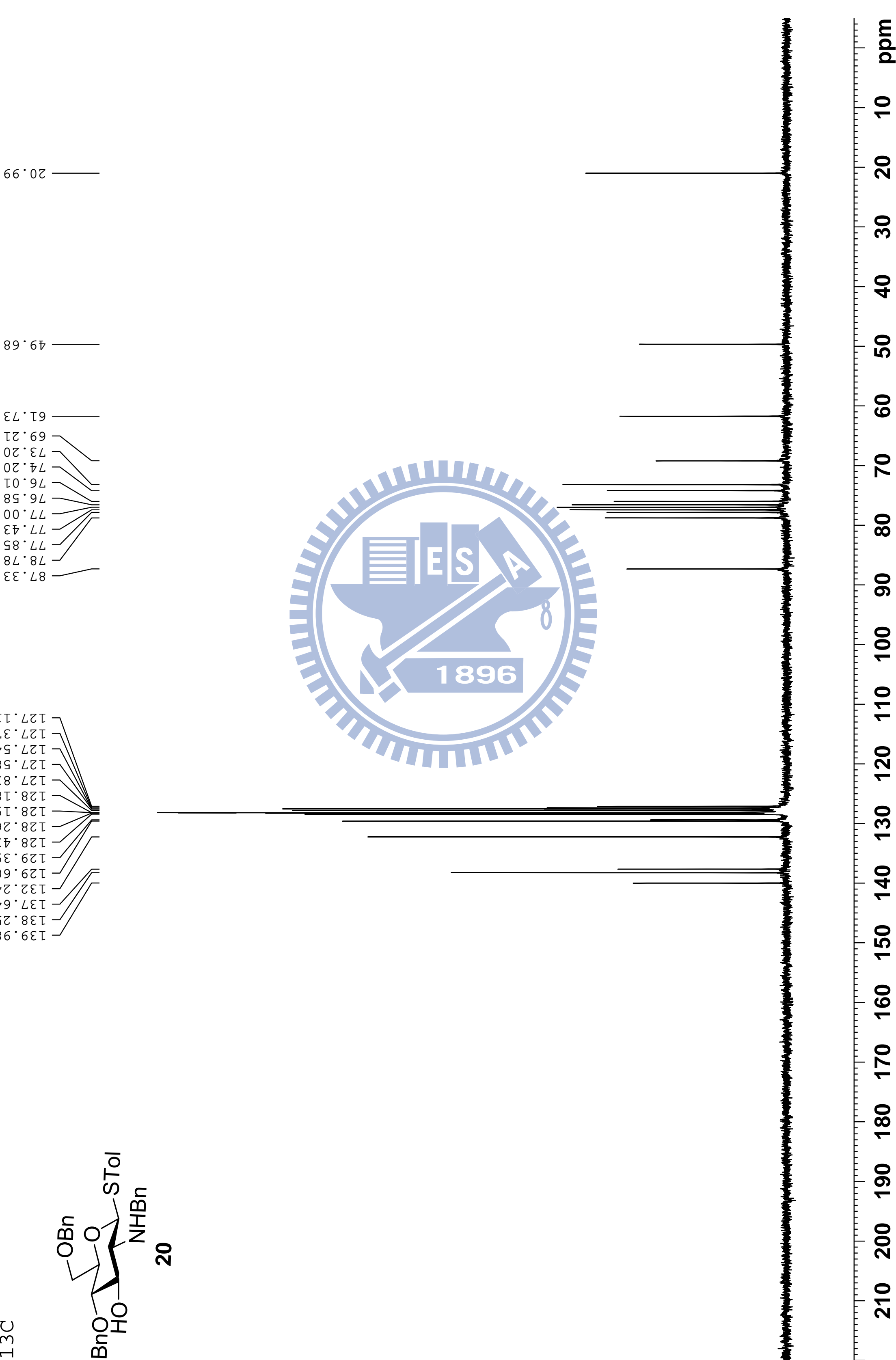


[1]H spectrum of *p*-Tolyl *N*-Benzyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (**20**)

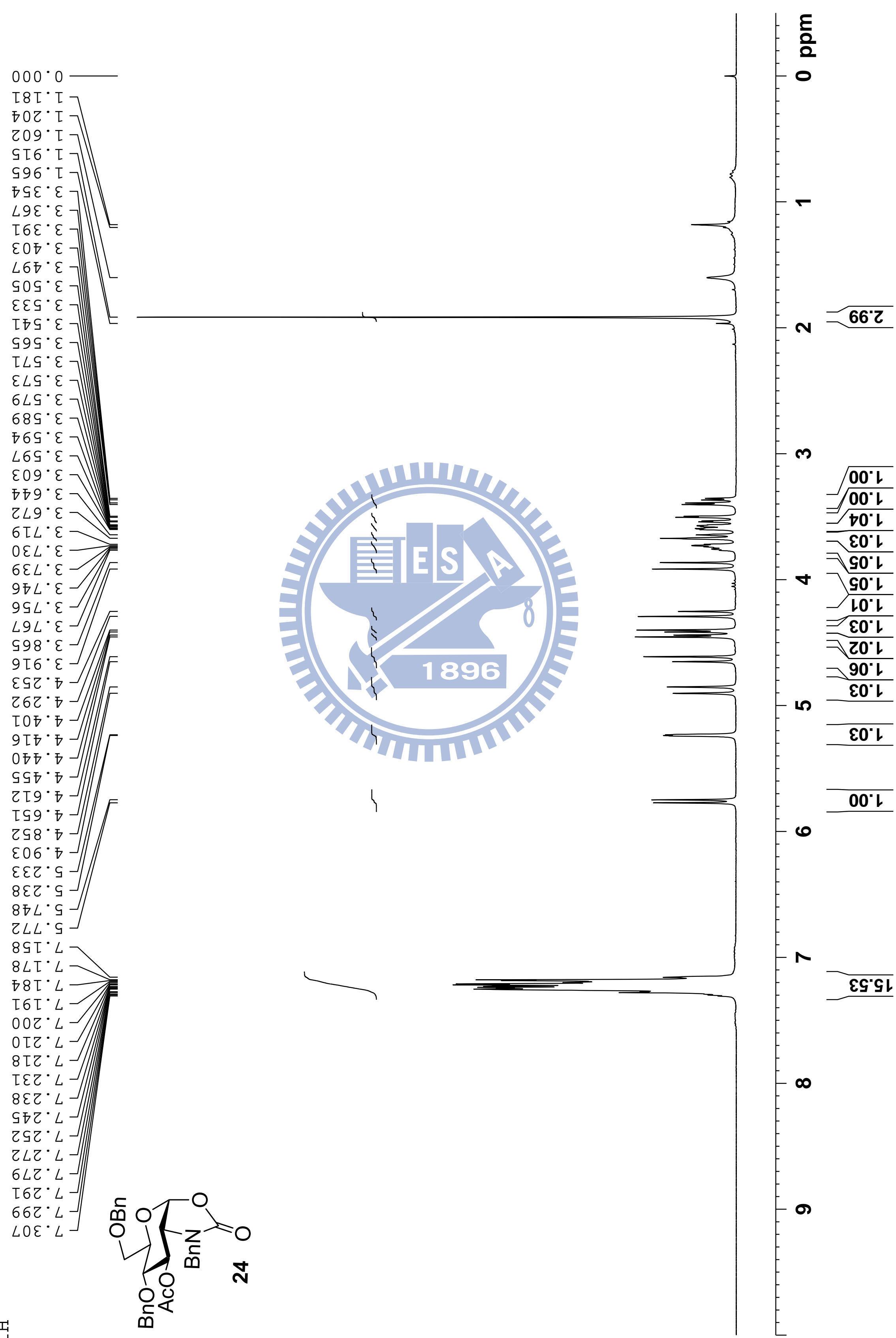


^{13}C spectrum of *p*-Tolyl *N*-Benzyl-2-amino-4,6-di-*O*-benzyl-

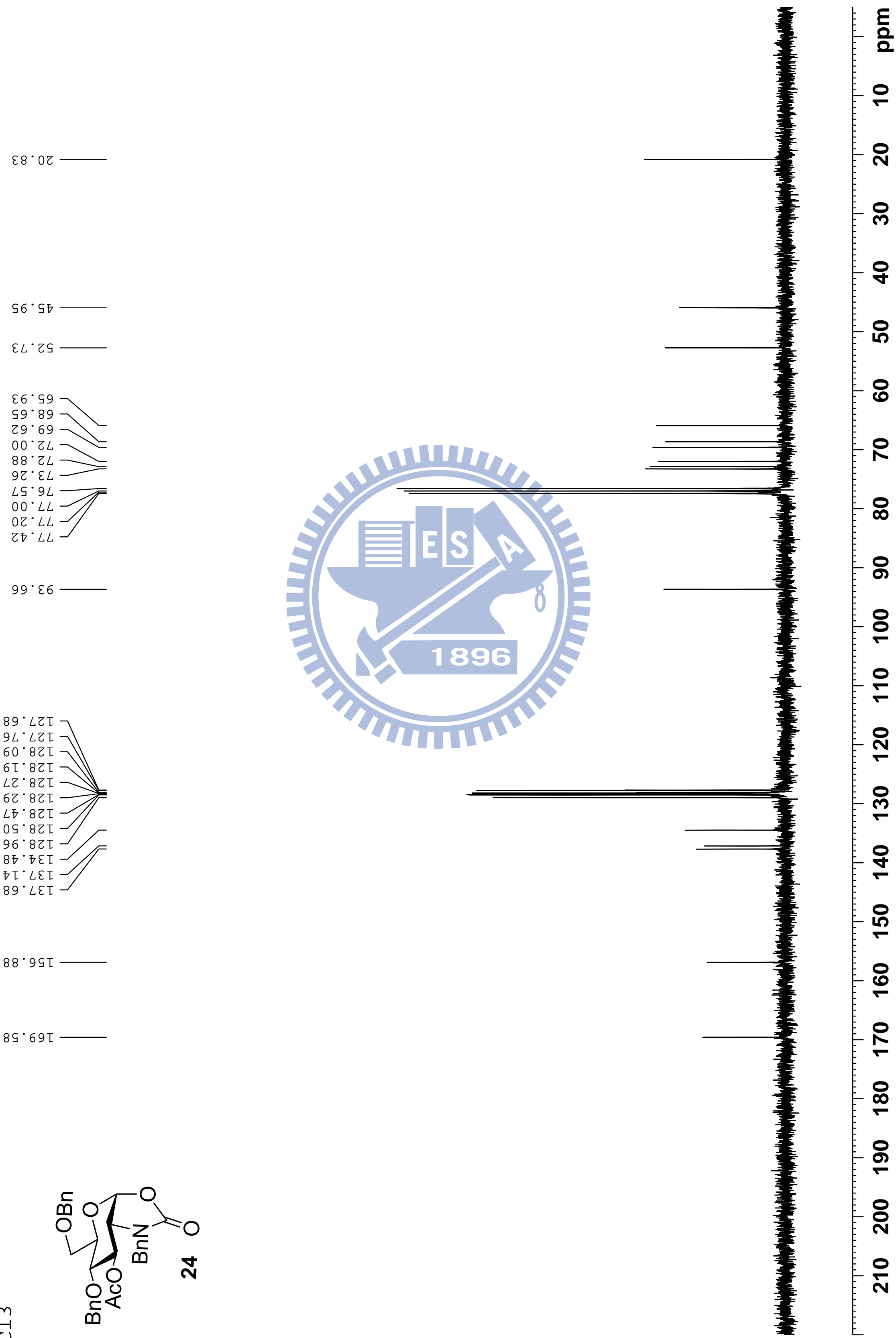
2-deoxy-1-thio-β-D-glucopyranoside (**20**)



[1]H spectrum *N*-Benzyl-2-amino-3-*O*-acetyl-4,6-di-*O*-benzyl-1,2-*cis*-*O*,*N*-carbonyl-2-deoxy-D-glucopyranoside (**24**)



[13]C spectrum *N*-Benzyl-2-amino-3-*O*-acetyl-4,6-di-*O*-benzyl-1,2-*cis*-*O*,*N*-carbonyl-2-deoxy-D-glucopyranoside (**24**)



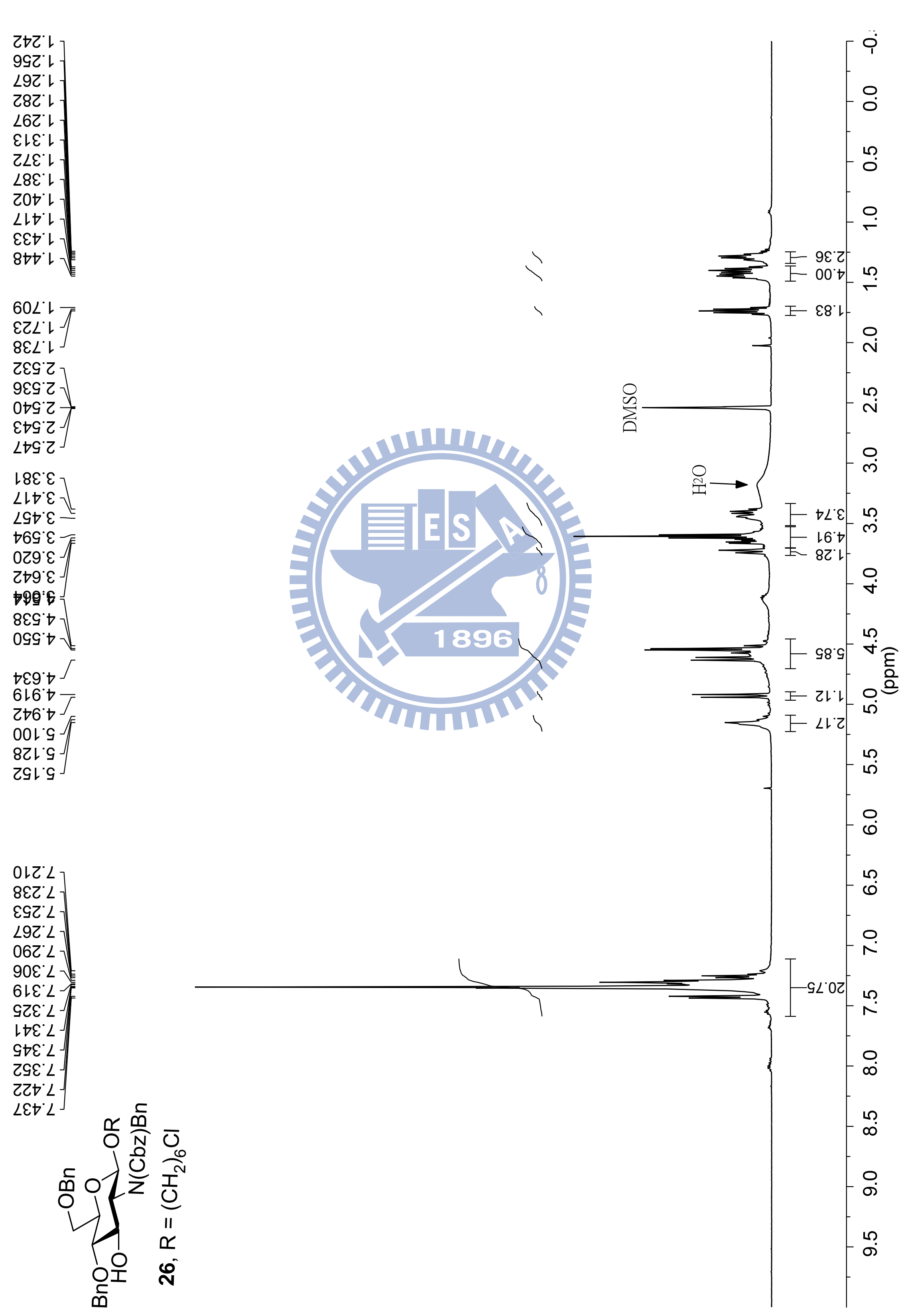
VT-NMR ^{1}H spectrum stacked plot of 6-Chlorohexyl *N*-Benzyl-

N-benzyloxycarbonyl-2-amino-4,6-di-*O*-benzyl-

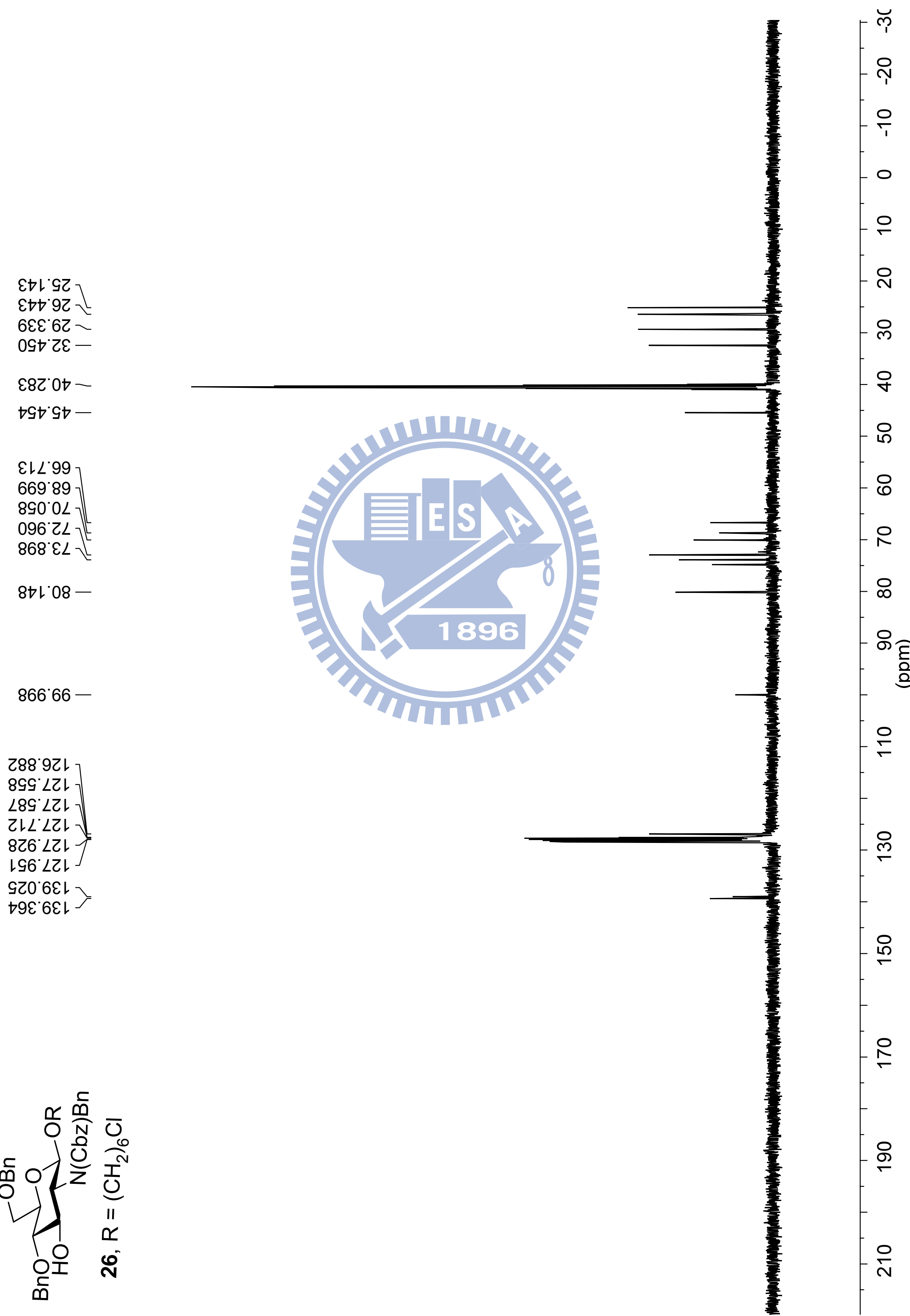
2-deoxy-β-D-glucopyranoside (**26**)

^{1}H spectrum (100 °C) of 6-Chlorohexyl *N*-Benzyl-*N*-benzyloxycarbonyl-

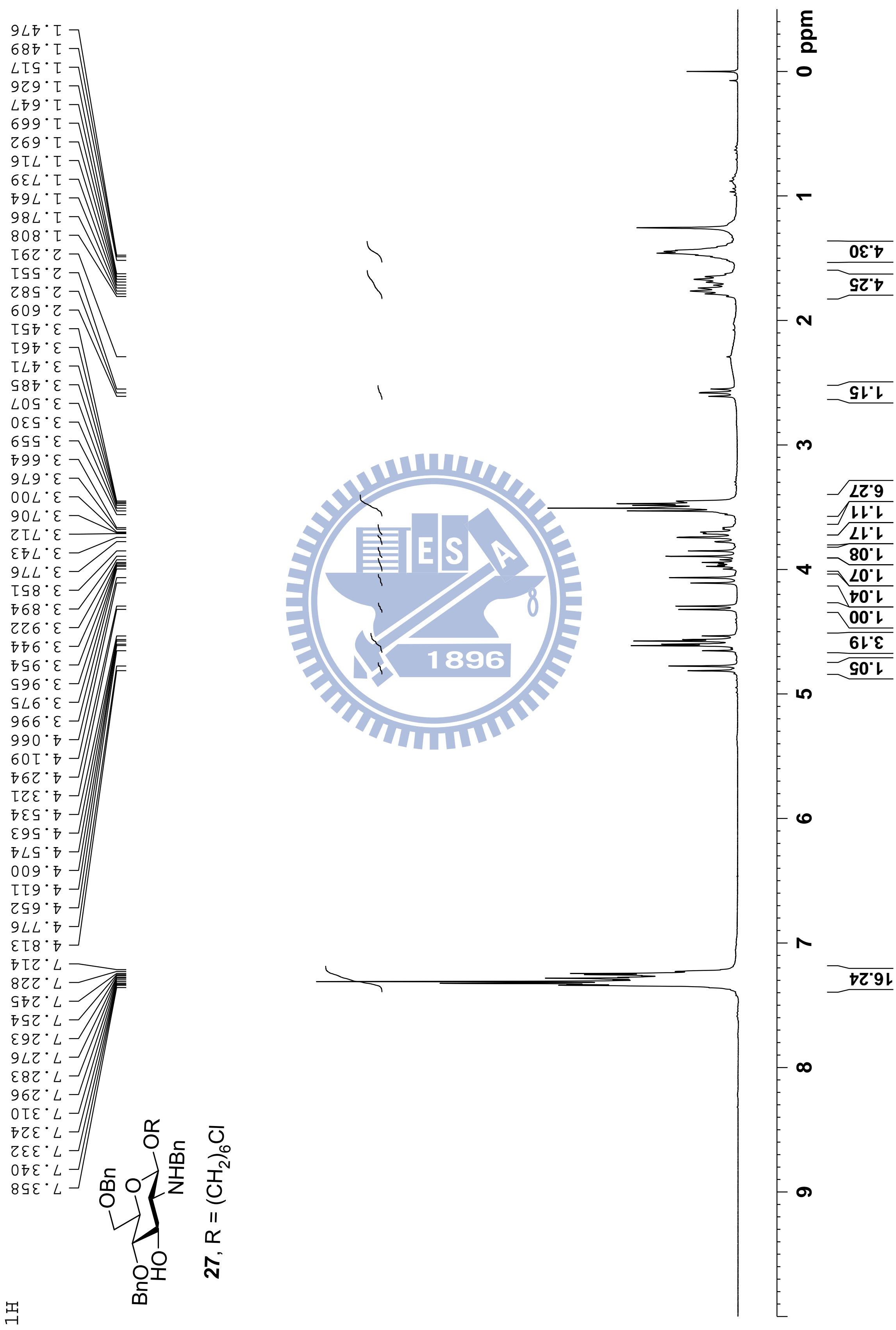
2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**26**)



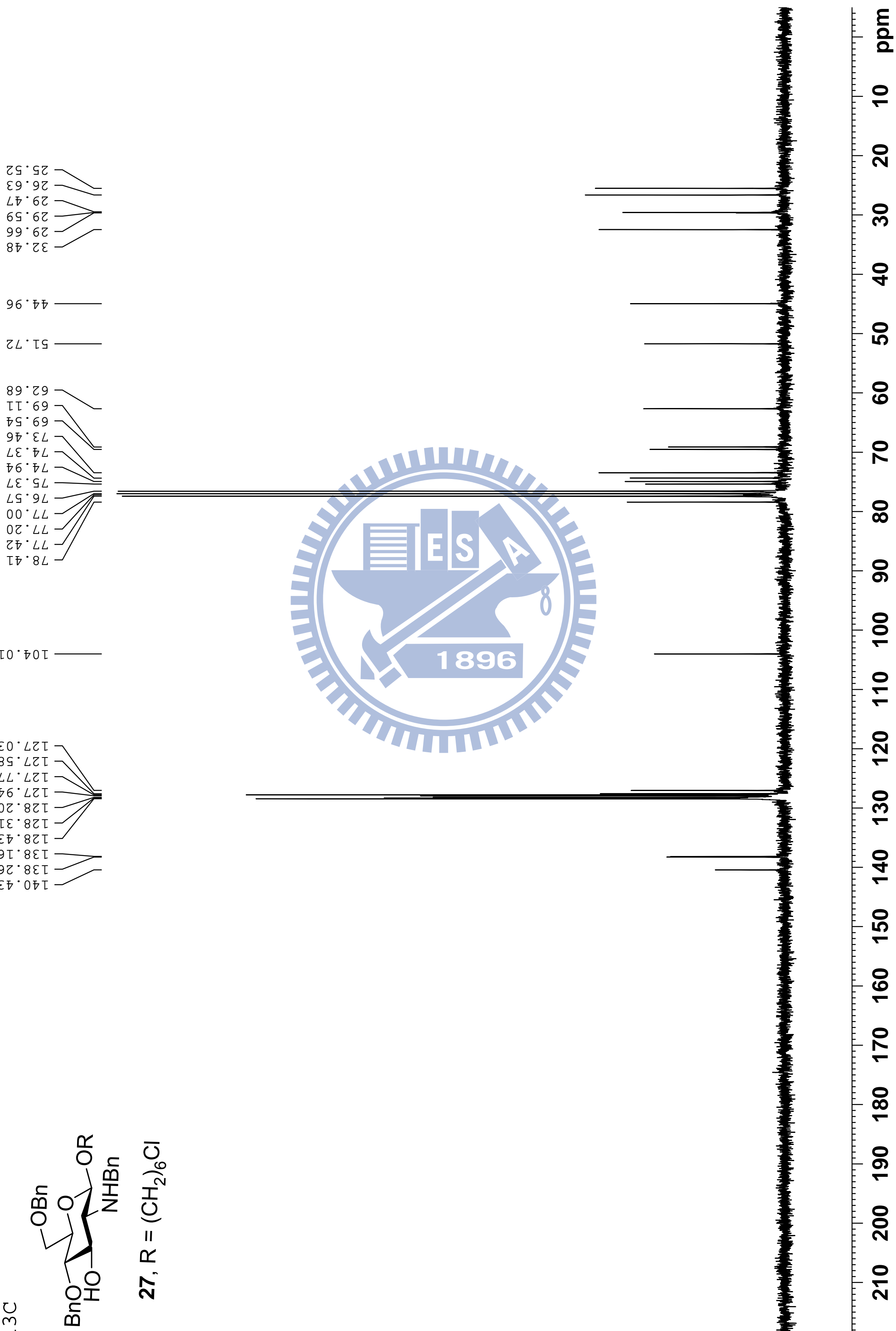
^{13}C spectrum (100 °C) of 6-Chlorohexyl *N*-Benzyl-*N*-benzyloxycarbonyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**26**)



[1]H spectrum of 6-Chlorohexyl *N*-Benzyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**27**)

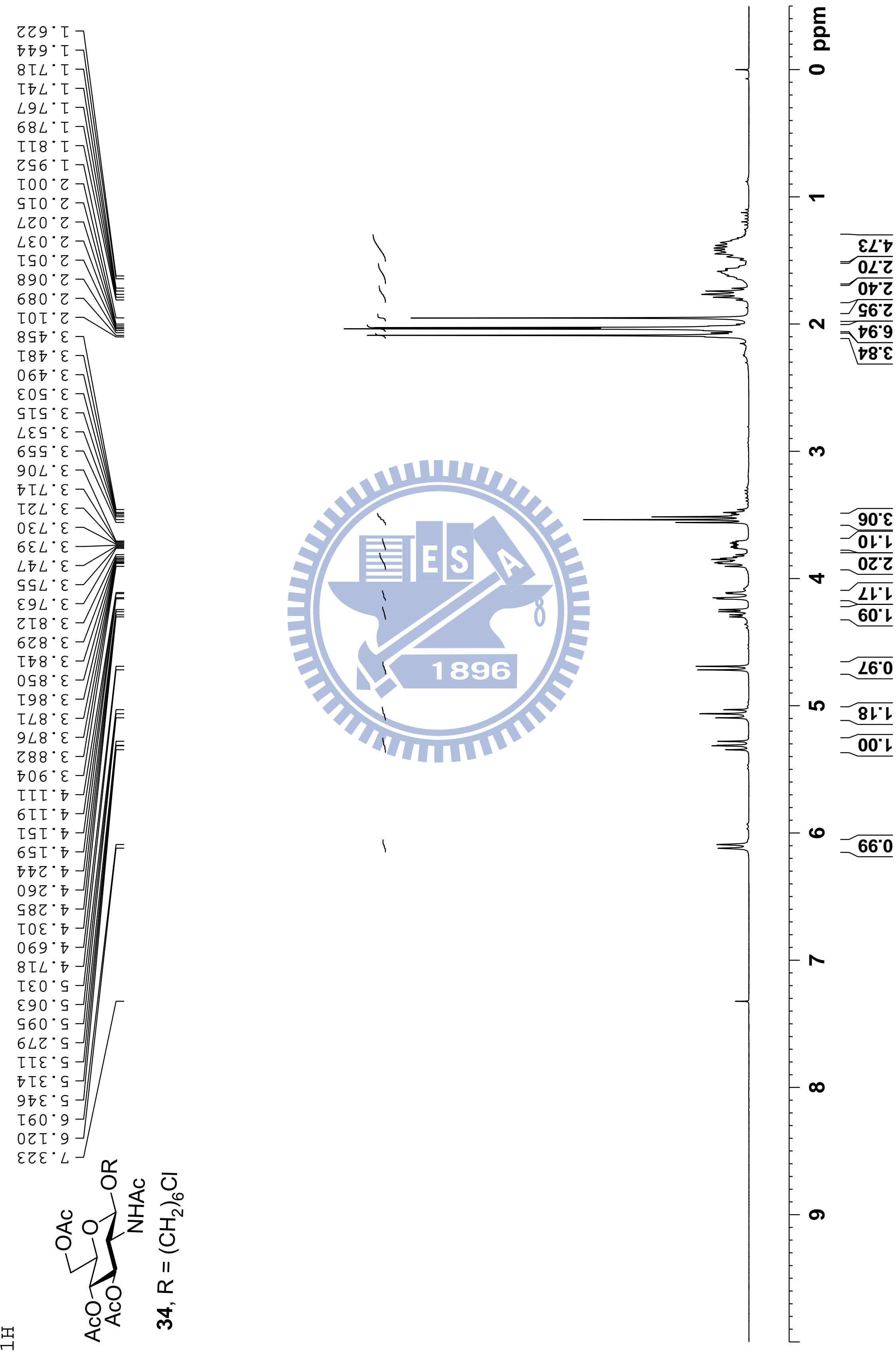


^{13}C spectrum of 6-Chlorohexyl *N*-Benzyl-2-amino-4,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**27**)



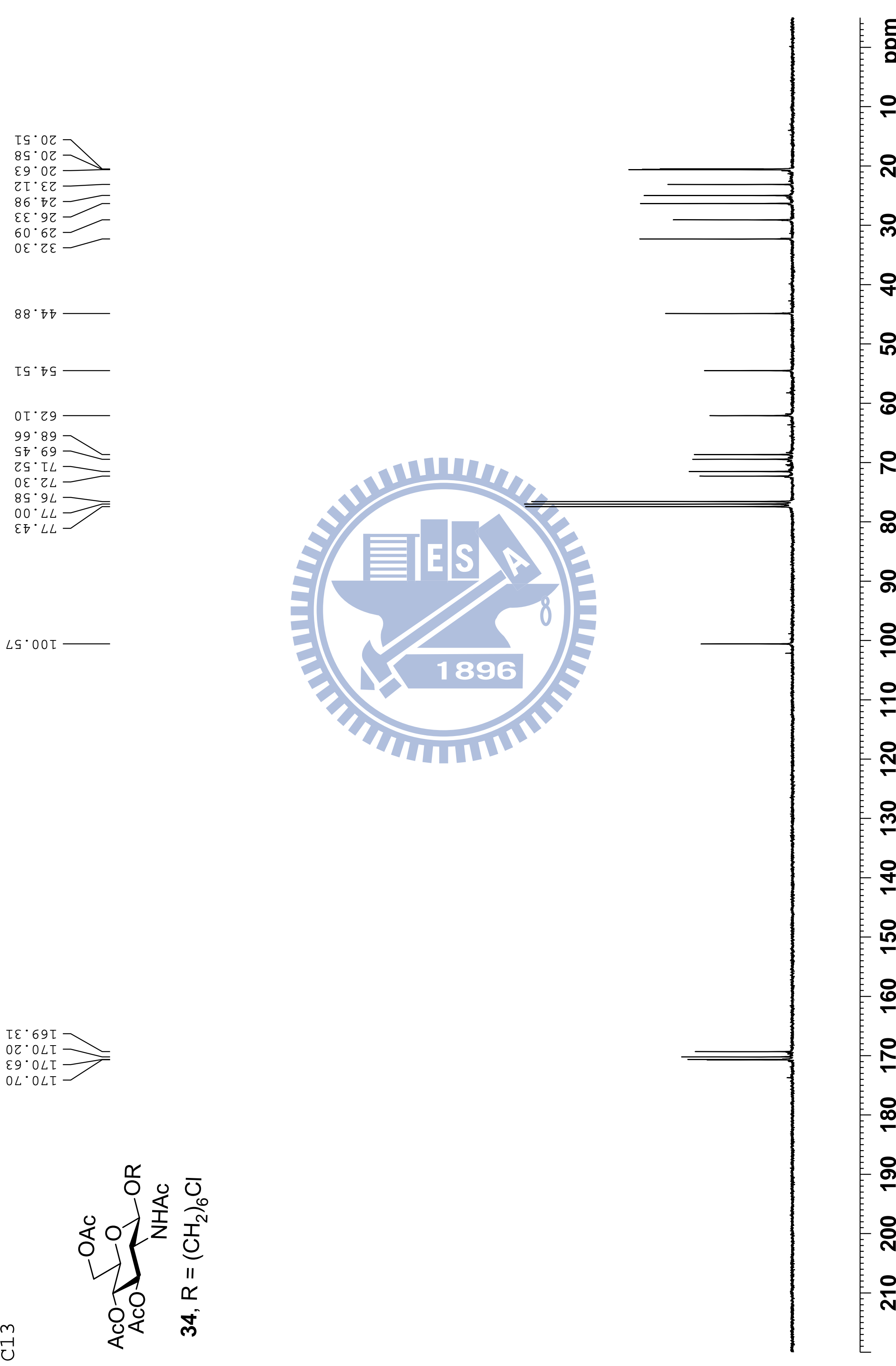
^{1}H spectrum of 6-Chlorohexyl 2-acetamido-3,4,6-tri-*O*-acetyl-

β-D-glucopyranoside (**34**)

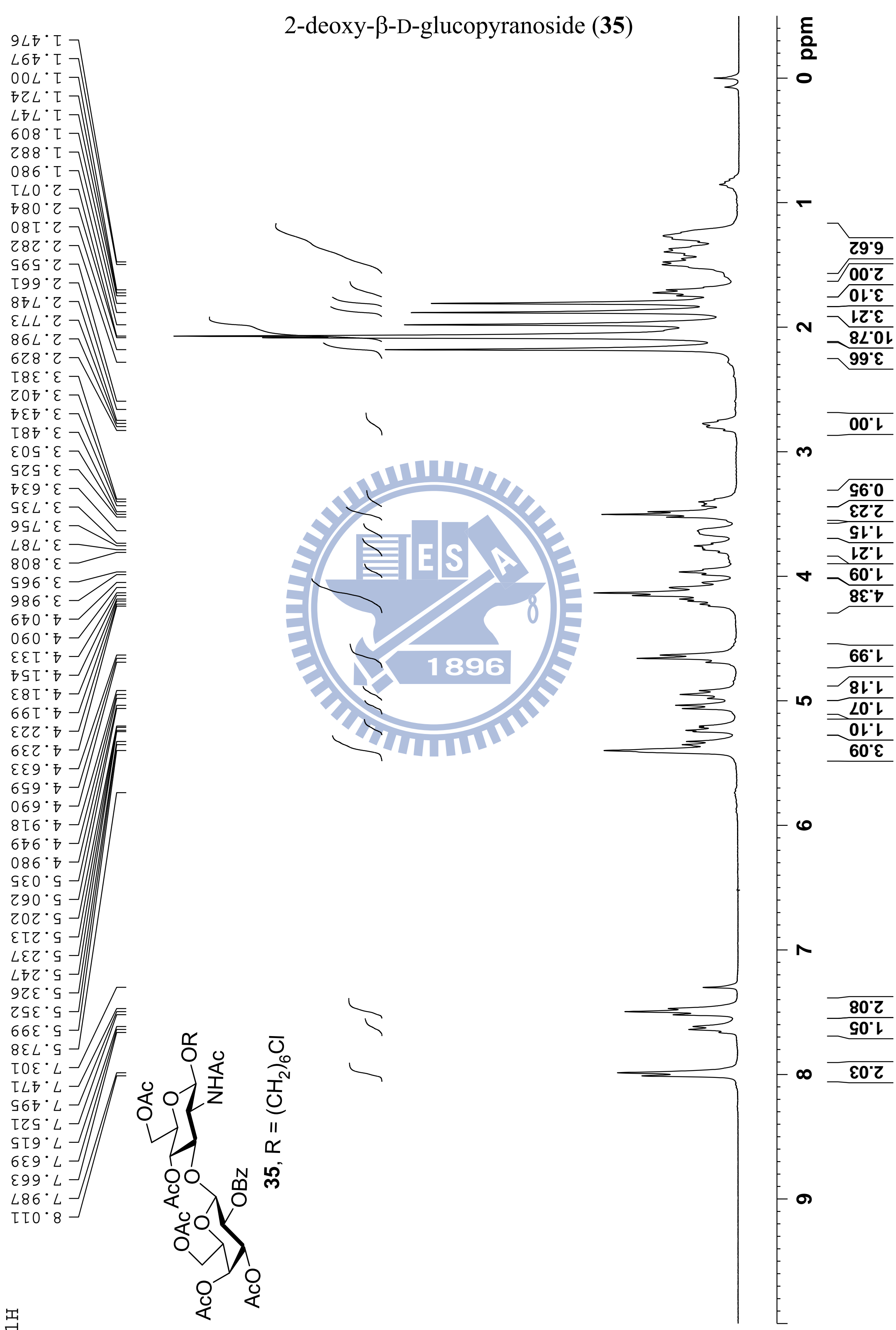


^{13}C spectrum of 6-Chlorohexyl 2-acetamido-3,4,6-tri-*O*-acetyl-

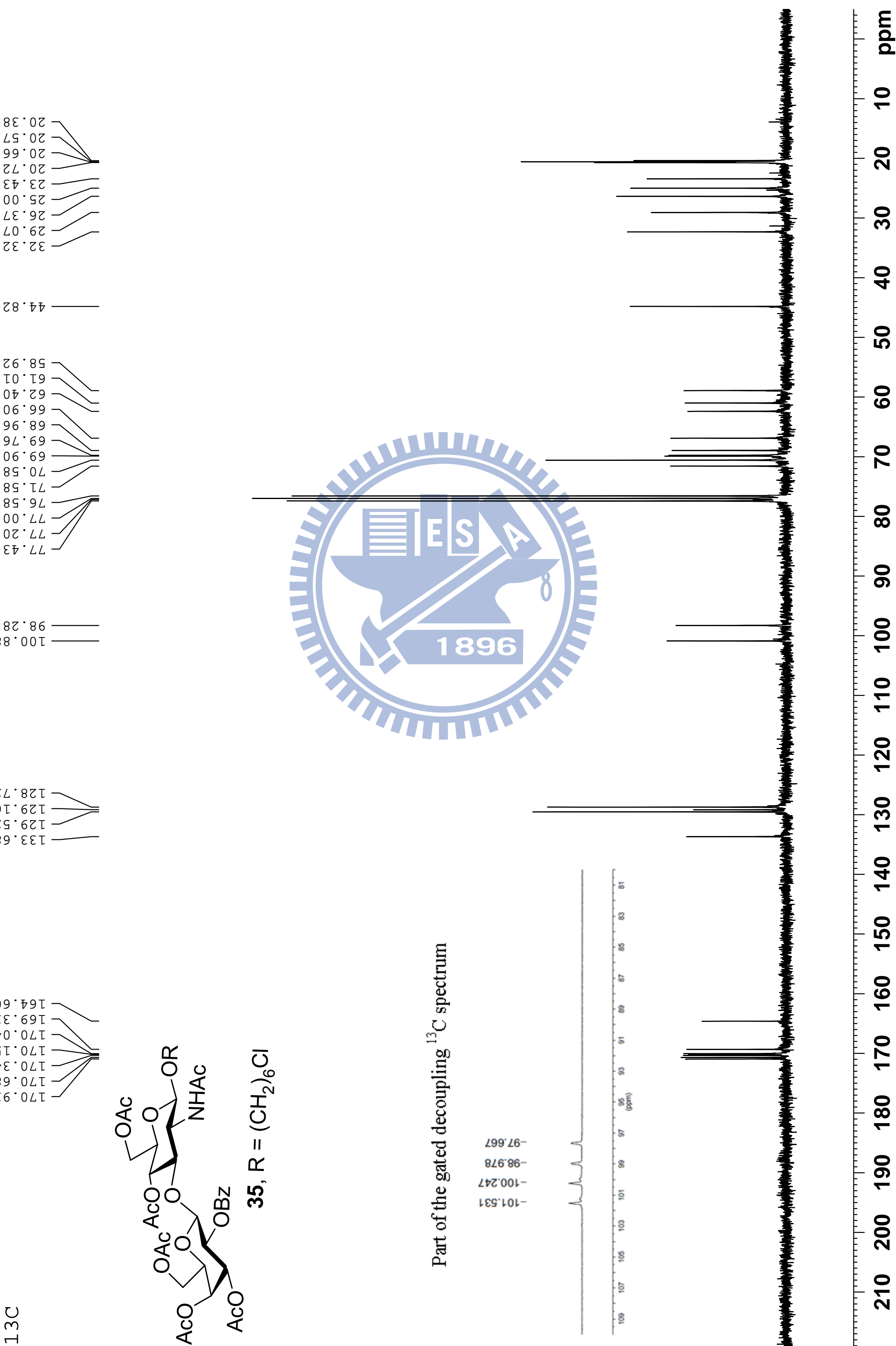
β-D-glucopyranoside (**34**)



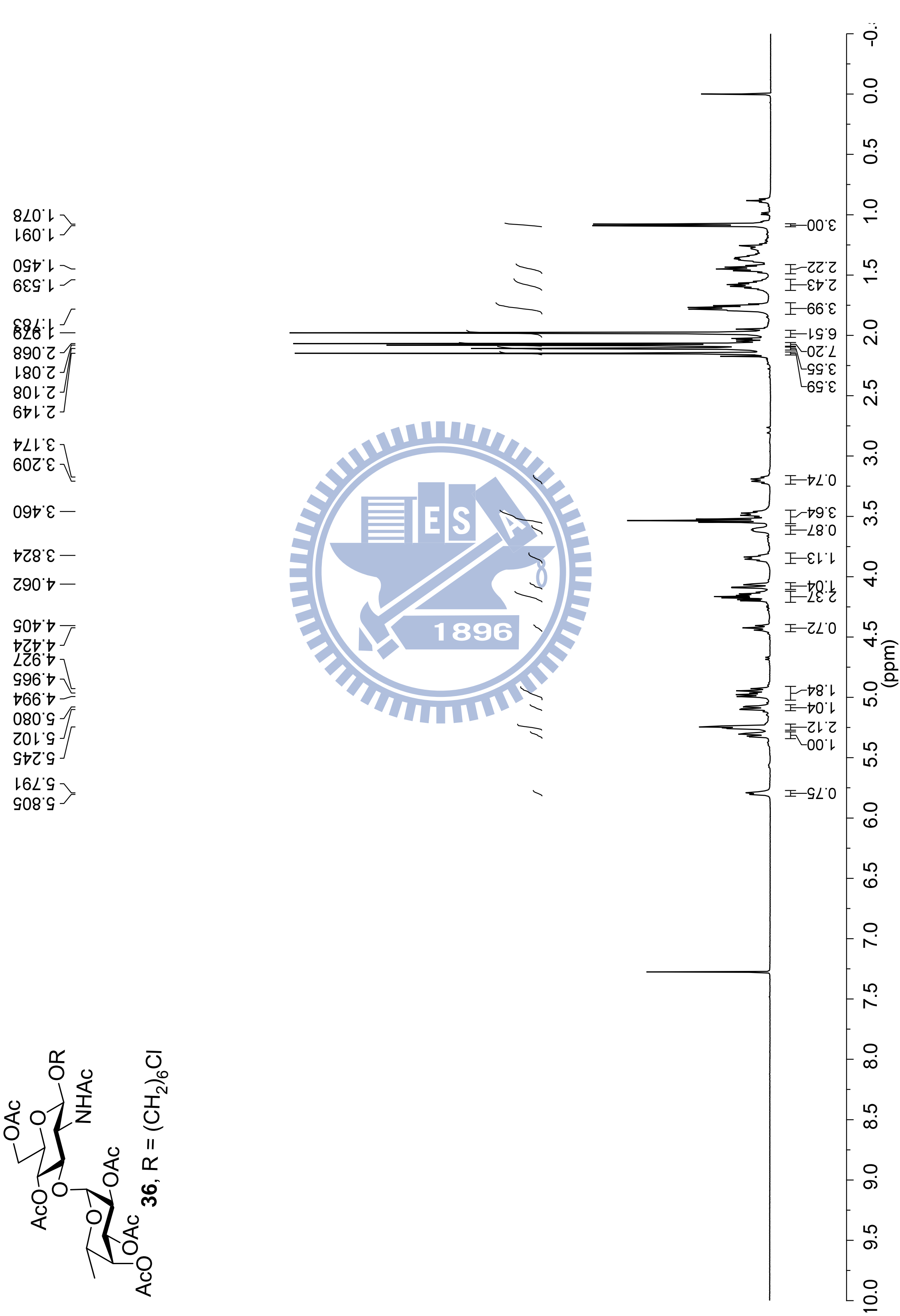
[1]H spectrum of 6-Chlorohexyl 3,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-β-D-galactopyranosyl-(1→3)-2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**35**)



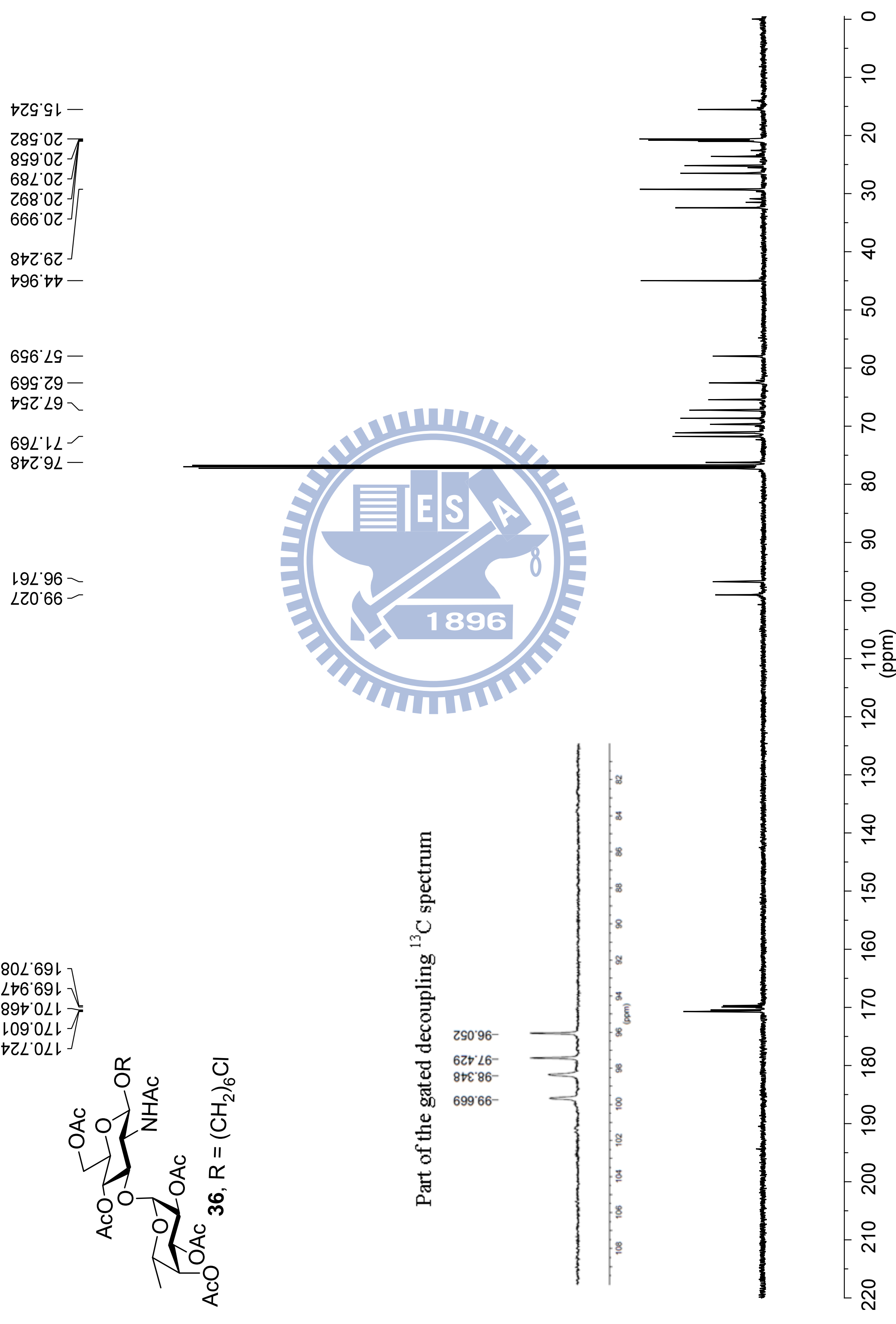
^{13}C spectrum of 6-Chlorohexyl 3,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-β-D-galactopyranosyl-(1→3)-2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**35**)



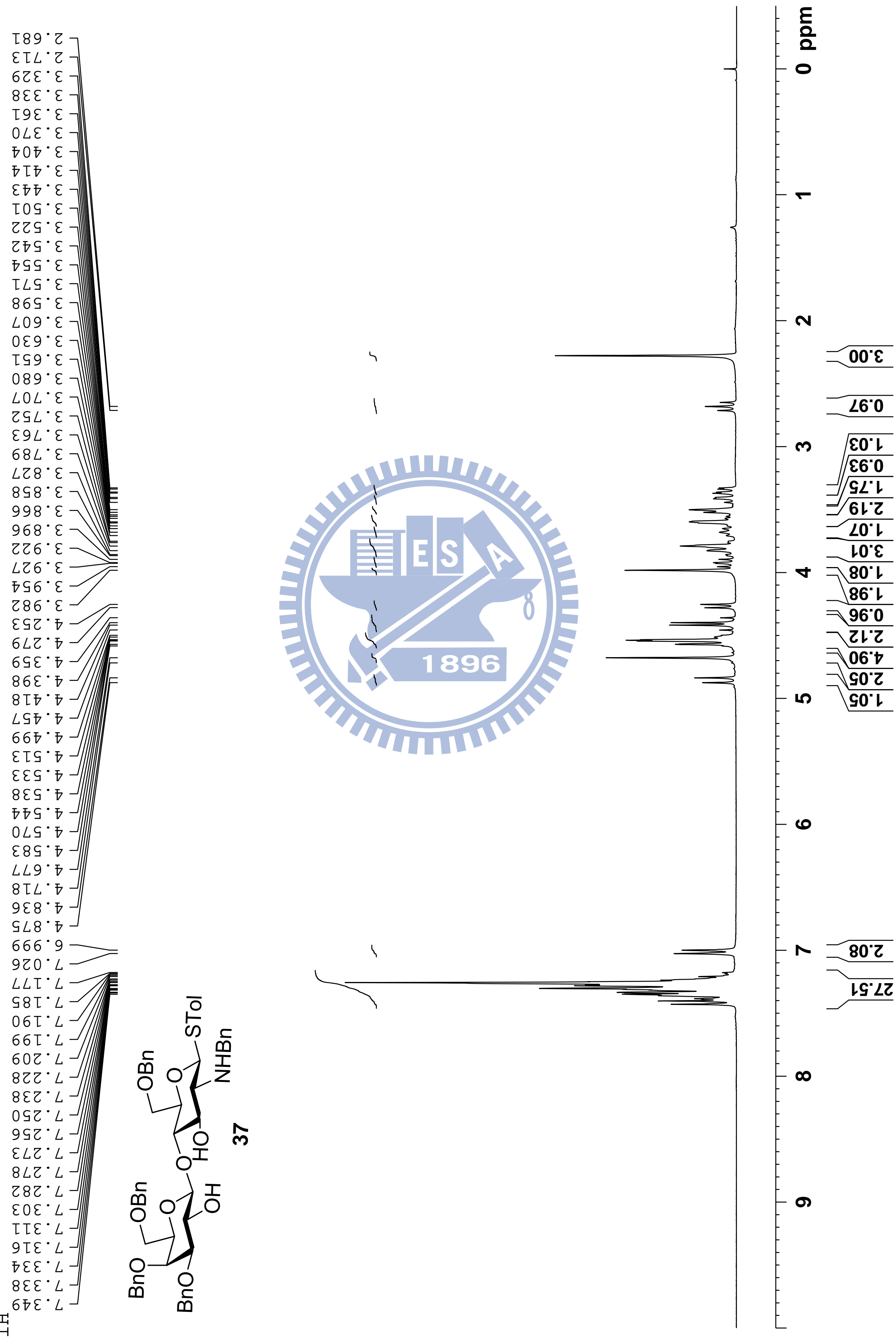
^{1}H spectrum of 6-Chlorohexyl 2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)-2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**36**)



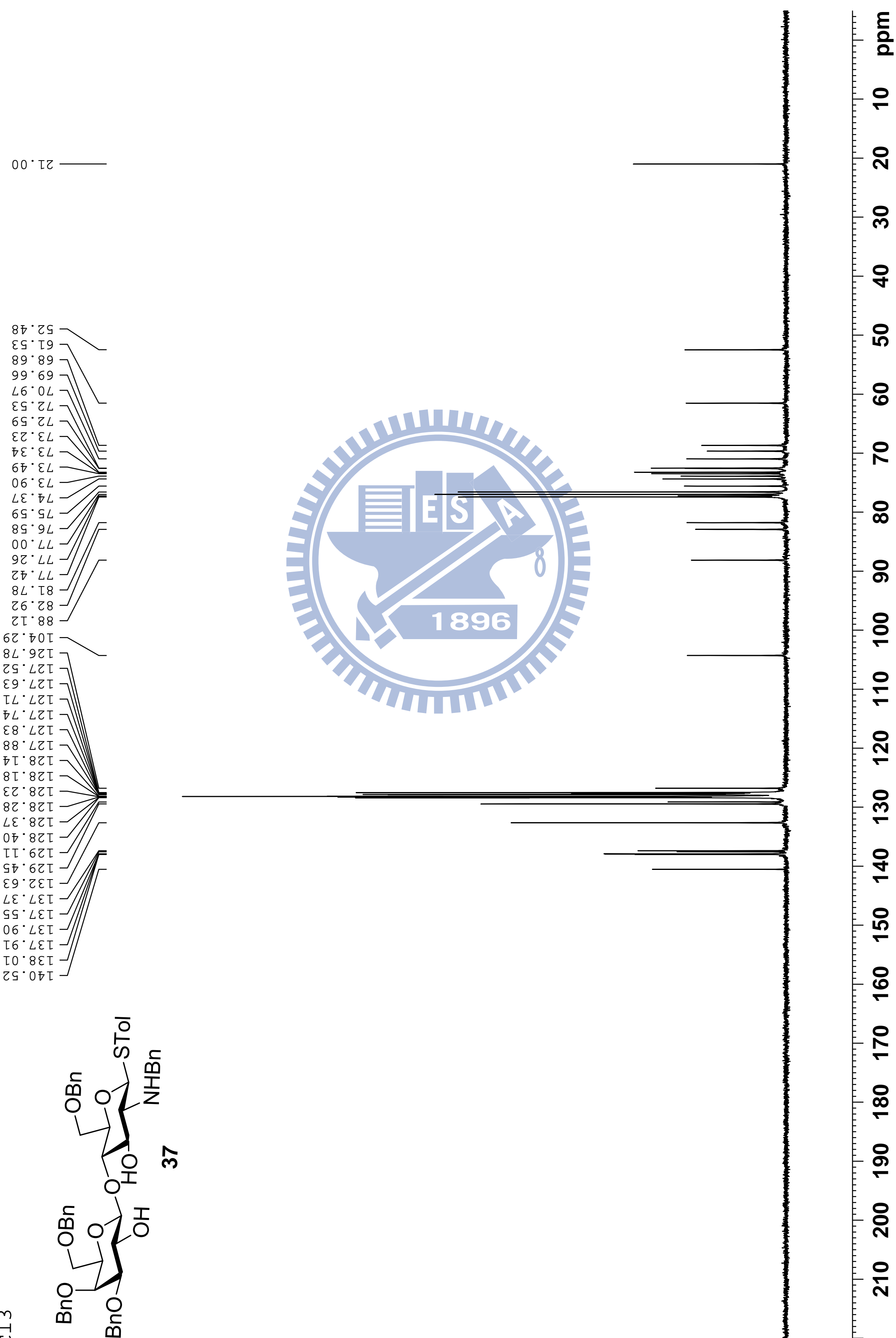
^{13}C spectrum of 6-Chlorohexyl 2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-(1→3)-2-acetamido-4,6-di-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**36**)



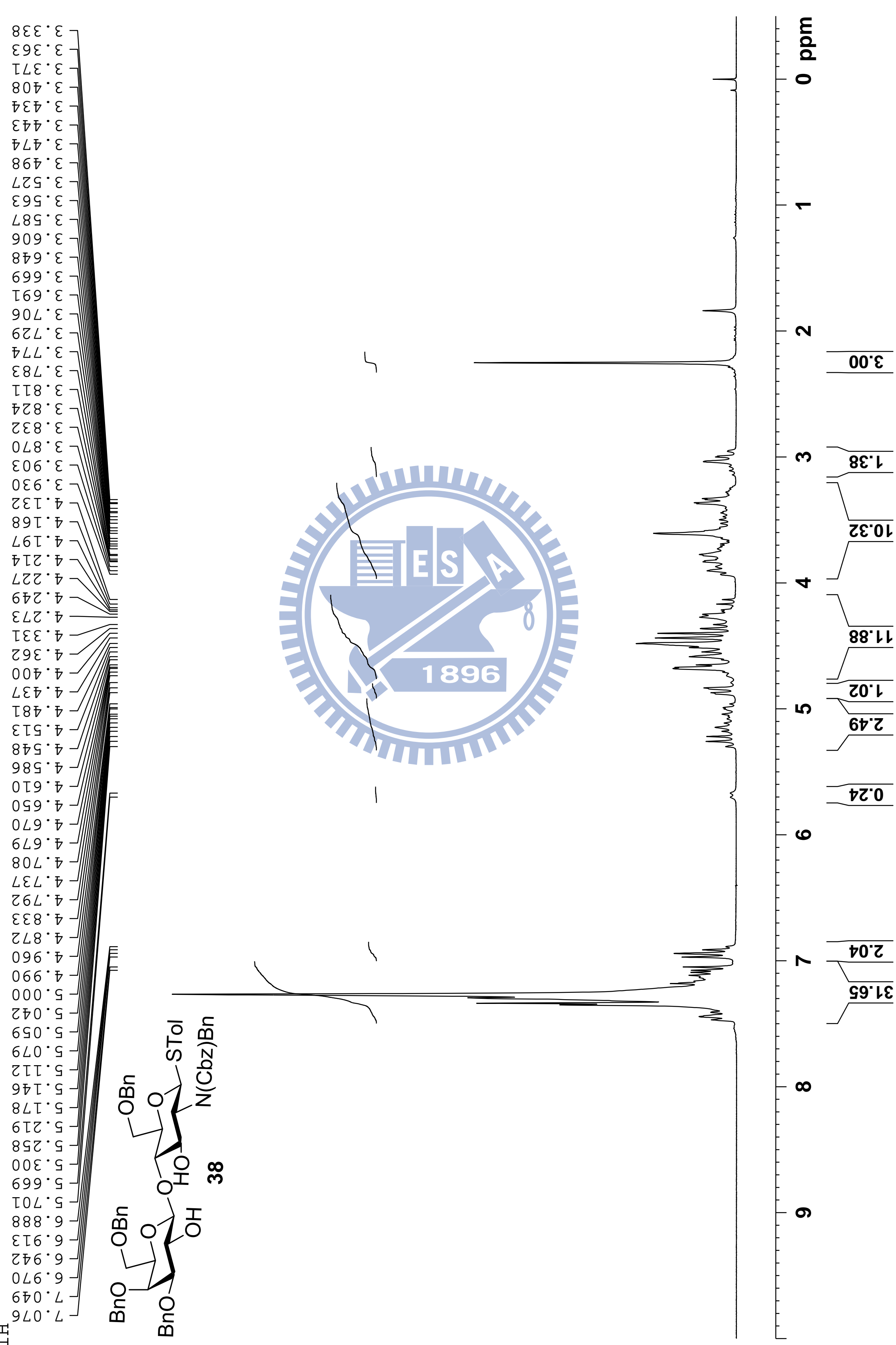
[1]H spectrum of *p*-Tolyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*- benzyl-2-deoxy-1-thio-β-D-glucopyranoside (**37**)



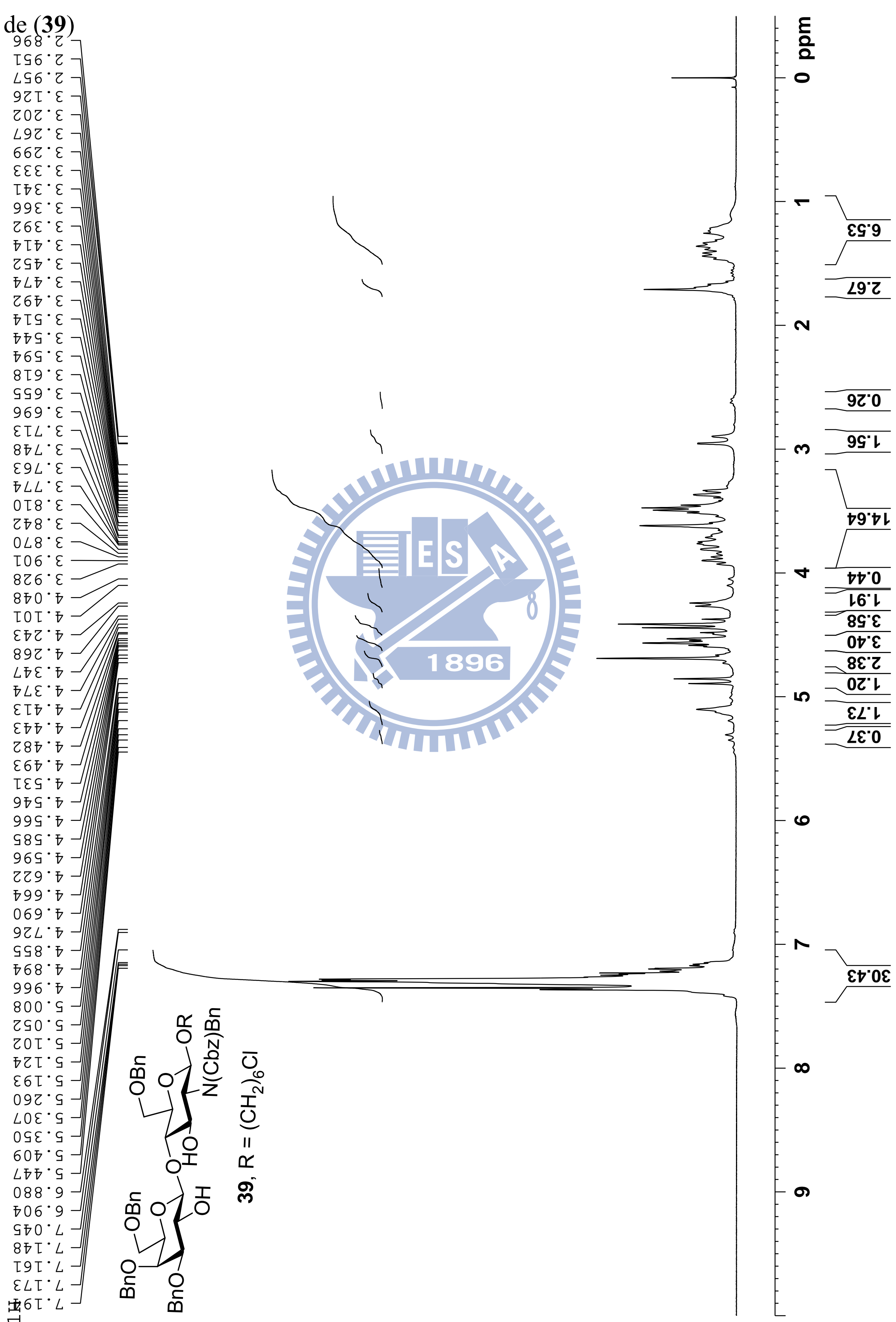
^{13}C spectrum of *p*-Tolyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-2-amino-6-*O*- benzyl-2-deoxy-1-thio-β-D-glucopyranoside (**37**)



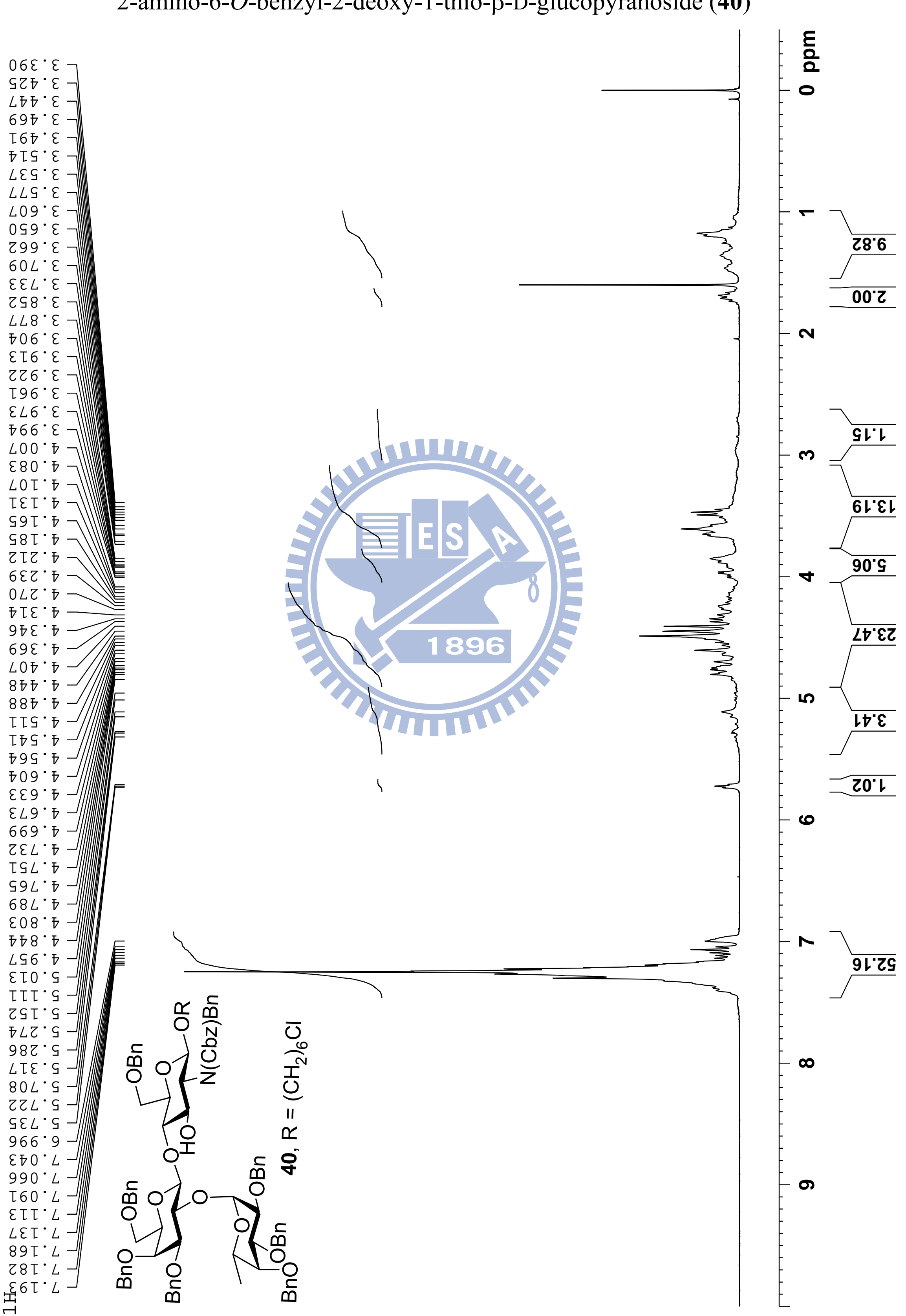
[1]H spectrum of *p*-Tolyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-*N*-benzyloxy- carbonyl-2-amino-6-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (**38**)



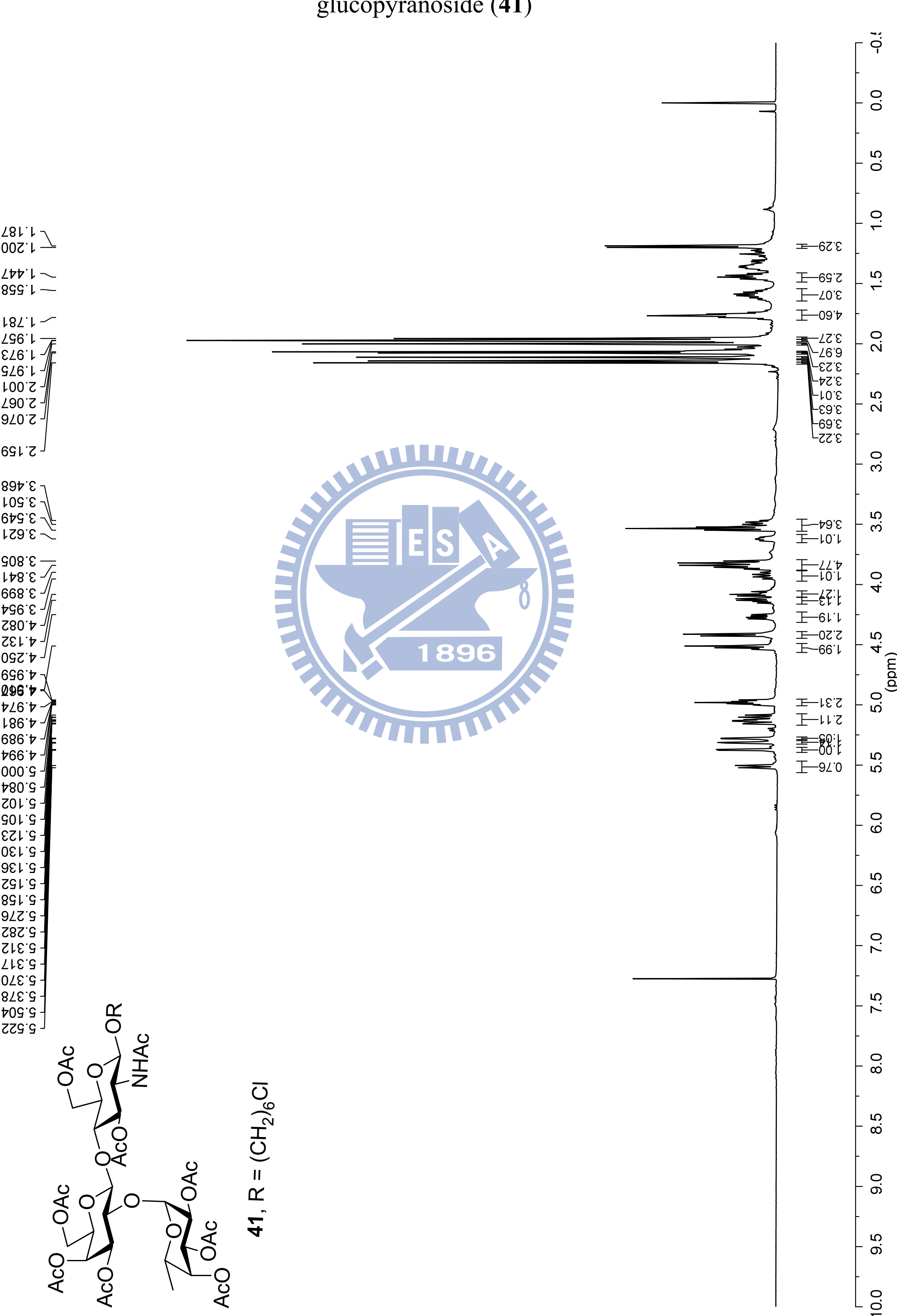
^{1}H spectrum of 6-Chlorohexyl 3,4,6-Tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-*N*-benzyloxycarbonyl-2-amino-6-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (**39**)



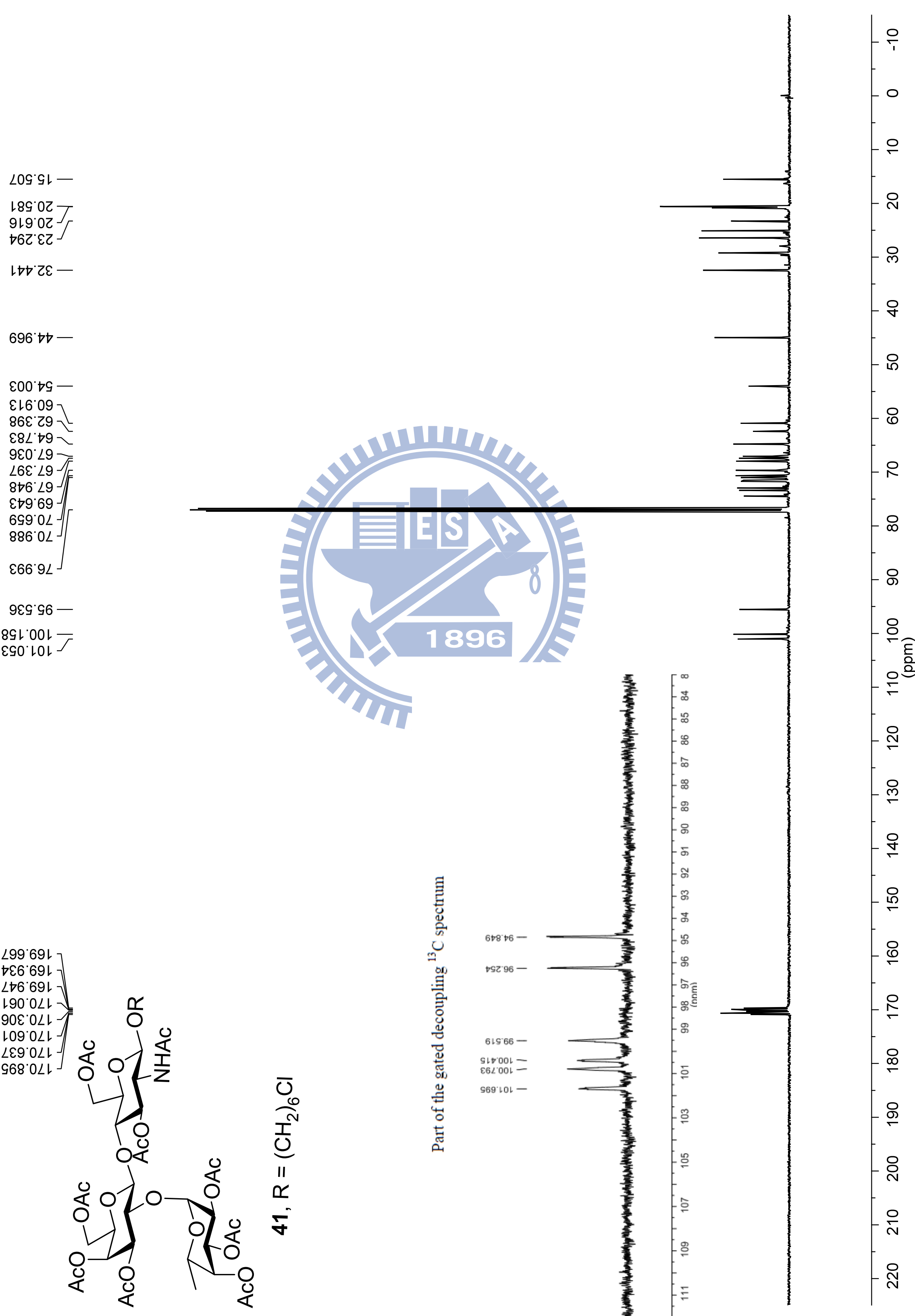
^{1}H spectrum of 6-Chlorohexyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-*N*-benzyl-*N*-benzyloxycarbonyl-2-amino-6-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (**40**)



^{1}H spectrum of 6-Chlorohexyl 2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2-acetamido-3,6-di-*O*-acetyl-β-D-glucopyranoside (**41**)



^{13}C spectrum of 6-Chlorohexyl 2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2-acetamido-3,6-di-*O*-acetyl-β-D-glucopyranoside (**41**)



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Note

Versatile acetylation of carbohydrate substrates with bench-top sulfonic acids and application to one-pot syntheses of peracetylated thioglycosides

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Abstract—Inexpensive and readily available sulfonic acids, *p*-toluenesulfonic acid, and sulfuric acid are versatile and efficient catalysts for the peracetylation of a broad spectrum of carbohydrate substrates in good yield and in a practical time frame. Three appealing features in sulfonic acid-catalyzed acetylation of free sugars were explored including (1) suppression of furanosyl acetate formation for D-galactose and L-fucose; (2) high yielding chemoselective acetylation of sialic acid under appropriate conditions; and (3) peracetylation of amino sugars with different amino protecting functions. Simple one-pot two step acetylation–thioglycosidation methods for the expeditious synthesis of *p*-tolyl per-*O*-acetyl thioglycosides were also delineated.
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Keywords: *p*-Toluenesulfonic acid; Acid-catalyzed acetylation; Amino sugars; One-pot protecting group manipulation

Chemical synthesis of oligosaccharides is a two-stage process that comprises the preparation of glycosyl building blocks followed by their assemblage.[1] Different synthetic strategies have emerged to speed up the assembling process, which include the armed-disarmed approach,[2] orthogonal glycosylation,[3] reactivity-based one-pot glycosylation,[4] sequential iterative glycosylation,[5] and automated solid phase oligosaccharide synthesis.[6] The implementation of these strategies relies heavily on the facile synthesis of glycosyl building blocks. Thioglycoside derivatives constitute a major class of glycosyl building blocks for oligosaccharide synthesis,[7] which are mainly derived from per-*O*-acetyl thioglycosides.

Conventional preparation of per-*O*-acetyl thioglycosides involves peracetylation and subsequent thioglycosidation.[8] However, classical carbohydrate acetylation uses excess pyridine; not only is pyridine highly toxic, but the presence of excess basic reagent makes the one-pot operation impossible.[9] Provided that the first peracetylation is an acid-catalyzed process, which is compatible to the second thioglycosidation; a one-pot acetylation–thioglycosidation is foreseeable. Thus, various one-pot strategies for the preparation of per-*O*-acetyl thioglycosides have been developed, although most of the existing methods have pitfalls originating from the peracetylation process.[10] For example, the formation of undesired furanosyl acetates for some sugars in acid-catalyzed acetylation compromises the yield in the subsequent thioglycosidation.[10c,e,11] The strong Lewis acid character of some acids makes them less suitable for the peracetylation of N-protected amino sugars and thus limits the scope of application to carbohydrate substrates without amino functions.[10d,e,12–14] Herein, we report a versatile and high yielding (75–95%) carbohydrate peracetylation protocol that can overcome the above drawbacks by using common sulfonic acids in the appropriate reaction conditions. Subsequent development of the simple one-pot two step acetylation–thioglycosidation protocols for the expeditious syntheses of *p*-tolyl per-*O*-acetyl thioglycosides was also delineated.

p-Toluenesulfonic acid monohydrate (TsOH)[15] and sulfuric acid (H_2SO_4)[16,17] are known catalysts for

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hydroxyl acetylation in the presence of excess acetic anhydride, however their efficiency with near stoichiometric acetic anhydride has not been explored. In addition, TsOH has never been used for the acetylation of free sugar substrates. Although silica-supported H_2SO_4 and $HClO_4$ have been used for carbohydrate acetylation, the additional immobilization step makes these protocols less convenient and the use of potentially explosive $HClO_4$ is also discouraged.[14a,b] Our initial observations showed that both neat H_2SO_4 and TsOH exhibited sufficient catalytic efficiency (1 mol % per OH group of the sugar) for the acetylation of D-glucose with a near stoichiometric amount of Ac_2O. Peracetylation of D-glucose with H_2SO_4 was completed in 0.2 h while with TsOH the reaction needed 8 h; such a difference should be useful for the selective peracetylation of sugars under different reaction conditions.

In the standard protocol, TsOH (1 or 2 mol % per OH group of the sugar) in Ac_2O (Table 1, entries a–c, h, and m) or in a mixture of Ac_2O and acetonitrile (CH_3CN) (Table 1, entries d–g, i–l, and n–o) was added to the carbohydrate substrate with stirring at 0 °C for 1 h. Subsequently, the reaction mixture was warmed to the optimal reaction temperature; detailed experimental conditions are given in Table S1 of Supplementary data. In general, a near stoichiometric amount of Ac_2O (1.2 mol equiv per OH group of the sugar) was employed. For carbohydrate substrates without amino functions, the desired peracetylated glycosyl acetates were furnished in good to excellent (75–95%) yield (Table 1, entries a, b, c, m, n, and o).

Acetylation of D-galactose and L-fucose requires special attention as both are prone to form undesired furanosyl acetates. Such furanosyl isomers were also formed from the sugars with our standard TsOH-catalyzed acetylation protocol (30% relative to total peracetyl acetates for D-galactose, 26% relative to total peracetyl acetates for L-fucose).[10c,e,11] Gratifyingly, the furanosyl isomer derived from D-galactose was gradually reduced by decreasing the reaction temperatures and nearly complete elimination was accomplished at 0 °C.[10e,15b] At such low reaction temperature, the more reactive H_2SO_4 was needed. However for the acetylation of L-fucose, 7% of furanosyl isomer was formed at 0 °C and thus further decrease in the temperature to −20 °C was required. Under the optimal reaction conditions, the formation of furanosyl isomer was reduced to less than 2% (see spectroscopic in Supplementary data page S23).

After examining the simple carbohydrate substrates, we turned to the amino sugars, which occur in the majority of natural oligosaccharides. Although pyridine-catalyzed acetylation works well for the acetylation of amino sugars, the less toxic TsOH-catalyzed protocol should provide a desirable alternative.[9] As different amino protecting functions have been used in oligosaccharide synthesis, it would be worthy knowing the compatibility of our protocol to such protecting functions. To this end, D-glucosamines with trichloroethoxycarbonyl (Troc), trichloroacetyl (TCA), acetyl (Ac), azido (N_3), and benzylethoxycarbonyl (Cbz) functions were prepared and acetylated with the standard TsOH-catalyzed protocol (Table 1, entries f–j).[18] To our delight, the desired peracetylated products **6**–**10** were furnished within 3–6 h in respectable 85–94% yield. For the acetylation of *N*-acetyl neuraminic acid methyl ester (NANA methyl ester), 4,7,8,9-tetra-*O*-acetyl NANA methyl ester **11** was obtained exclusively in 90% yield without any trace of the pentaacetylated product (Table 1, entry k). Such chemoselectivity is superior to the conventional $HClO_4$-catalyzed protocol.[19] To obtain the pentaacetyl product, a higher reaction temperature (45 °C) and excess Ac_2O were required, and 2,4,7,8,9-pentacetyl NANA methyl ester **12** was furnished in 80% yield along with 5% elimination product (Table 2, entry l). As **11** and **12** are valuable precursors for the synthesis of sialic acid-containing oligosaccharides, our new procedure should provide a more convenient alternative.

It should also be mentioned that the facile acetylation of amino sugars with the TsOH-catalyzed protocol was in sharp contrast to the reaction using I_2.[12] As a comparison, the amount of acid catalyst (in mol % per OH group), reaction time, and product yield for the acetylation of *N*-Troc glucosamine, *N*-acetyl glucosamine, and NANA methyl ester with I_2-catalyzed and TsOH-catalyzed protocols are provided in Table 1 (entries f, h, k and l). For the acetylation of *N*-Troc glucosamine with I_2, the reported experimental procedure was followed and 250 mg I_2 per g of *N*-Troc glucosamine (9 mol % per OH group) was used.[12] For the I_2-catalyzed acetylation of GlcNAc and NANA methyl ester, a much higher catalyst loading was applied (either 5 or 13 mol % per OH group for the I_2-catalyzed acetylation versus 2 mol % per OH group for the TsOH-catalyzed acetylation) (Table 1, entries, h, k, and l). Even at such a high I_2 concentration, it still took two days for the complete acetylation of *N*-acetyl glucosamine (Table 1, entry h). In addition, no significant acetylation was observed for *N*-Troc glucosamine when I_2 catalyst was used (Table 1, entry f).

Regarding the α-/β-selectivity of the process, α-glycosyl acetates were formed preferentially in majority of the cases, which can be explained by thermodynamics (Table 1, entries a–e, g–h, and m). Nevertheless, for the acetylation of *N*-Troc and 2-azido-2-deoxy-glucosamines, β-glycosyl acetates were the major anomers obtained (Table 1, entries f and i). Apparently, the strong participatory effect of trichloroethoxylcarbamyl function outweighed the anomeric effect in *N*-Troc glucosamine, while the reason for β-selectivity in 2-azido-2-dexoy-glucosoamine is not clear.

Table 1. Sulfonic acid-catalyzed acetylation for carbohydrate substrates with different complexities

Entry	Carbohydrate substrate	Per-*O*-acetyl glycosyl acetate	Acid (mol % per OH)	Temp (°C)	Time (h)	Yield % (α:β)
a	D-Glucose	**1**	TsOH (2)	0–27	6	95 (71:29)
b	D-Mannose	**2**	TsOH (2)	0–27	5	94 (45:11)
c	L-Rhamnose·H_2O	**3**	TsOH (2)	0–27	4	92 (58:42)
d	D-Galactose	**4**	H_2SO_4 (2)	−20 to 0	18	92 (76:24)[a]
e	L-Fucose	**5**	H_2SO_4 (2)	−30 to −20	8	93 (9:1)[a]
f	2-Trichloroethoxy carbamyl-2-deoxy-D-glucopyranose	**6** (NHTroc)	TsOH (2) I_2 (9)	0–27 0–27	6 >24	90 (27:73)[a] No reaction[b]
g	2-Trichloroacetamido-2-deoxy-D-glucopyranose	**7** (NHTCA)	TsOH (2)	0–55	5	93 (77:23)[a]
h	2-Acetamido-2-deoxy-D-glucopyranose	**8** (NHAc)	TsOH (2) I_2 (5)	0–50 0–27	5 48	90 (61:39) 98 (2.5:1)[b,c]
i	2-Azido-2-deoxy-D-glucopyranose	**9** (N_3)	TsOH (2)	0–27	4	85 (23:77)[a]
j	2-Benzyloxycarbamyl-2-deoxy-D-glucopyranose	**10** (NHCbz)	TsOH (2)	0–40	3	94 (not determined)[a]
k	*N*-Acetyl neuraminic acid methyl ester	**11**	TsOH (2) I_2 (6.5) I_2 (13)	0–27 0–27 0–27	4 Sluggish 20 min	90 (1:4)[a] Not determined[b,c] 70 (not determined)[b,c]
l	*N*-Acetyl neuraminic acid methyl ester	**12**	TsOH (2) I_2 (13)	0–45 0–35	12 60 min	80 (β only)[a,b] 90 (1:3.5)[b,c]
m	D-Lactose·H_2O	**13**	TsOH (2)	0–40	4	90 (3:2)

(*continued on next page*)

Table 1 (*continued*)

Entry	Carbohydrate substrate	Per-*O*-acetyl glycosyl acetate	Acid (mol % per OH)	Temp (°C)	Time (h)	Yield % (α:β)
n	β-Cylcodextrin	per-*O*-acetyl-β-cylcodextrin **14**	TsOH (1)	0–40	10	90[a]
o	D(+)-Melezitose·H_2O	per-*O*-acetyl-D(+)-Melezitose **15**	TsOH (1)	0–30	6	75[a]

[a] CH_3CN was added to the reaction mixture.
[b] Excess Ac_2O was used.
[c] Ref. 12.

Table 2. One-pot syntheses of per-*O*-acetyl thioglycosides

HO– (sugar) –OH, OH (or *N*-protected) → One-pot [Ac_2O, cat. sulfonic acid + Tol-SH, Lewis acid], 1–2 d → AcO– (sugar) –STol, OAc (or *N*-protected)

Entry	Carbohydrate substrate	Thioglycoside	Yield % (α:β)
a	D-Glucose	**16**	75 (β only)[a]
b	D-Mannose	**17**	80 (α only)[a]
c	L-Rhamnose·H_2O	**18**	84 (5:1)[a]
d	D-Galactose	**19**	68 (β only)[a]
e	L-Fucose	**20**	75 (β only)[a]
f	2-Trichloroethoxy carbamyl-2-deoxy-D-glucopyranose	**21**	72 (β only)[a]
g	2-Trichloroacetamido-deoxy-D-glucopyranose	**22**	65 (β only)[a]
h	2-Acetamido-2-deoxy-D-glucopyranose	**23**	65 (β only)[b]
i	*N*-Acetyl neuraminic acid methyl ester	**24**	72 (β only)[a]
k	D-Lactose·H_2O	**25**	75 (β only)[a]

[a] $BF_3 \cdot Et_2O$ was used for thioglycosidation.
[b] $SnCl_4$ was used for thioglycosidation.

With the sulfonic acid-catalyzed acetylation protocols in hand, we next explored a simple one-pot two step acetylation–thioglycosidation approach for the preparation of per-*O*-acetyl thioglycosides. In the one-pot TsOH-catalyzed acetylation–thioglycosidation, the sugar substrate was firstly peracetylated with the

described TsOH-catalyzed acetylation, followed by the solvent removal, and the addition of *p*-thiocresol (1.5 mol equiv) in dichloromethane (CH_2Cl_2) and the appropriate Lewis acid catalyst ($BF_3 \cdot Et_2O$ or $SnCl_4$) (Table 2, entries a–c and f–k). The optimal reaction conditions and exact amount of reagents used are detailed in Table S2 of Supplementary data. In the one-pot H_2SO_4-catalyzed acetylation–thioglycosidation of D-galactose and L-fucose, complete removal of solvent led to undesired dehydration; thus 1.2 equiv of methanol was added to quench the remaining Ac_2O, followed by the addition of thiocresol (2 mol equiv) in CH_2Cl_2 and $BF_3 \cdot Et_2O$ (2 mol equiv). Simple hexopyranoses (Table 2, entries a–e), glucosamines with different amino protecting functions (Table 2, entries f–h), NANA methyl ester (Table 2, entry i), and lactose (Table 2, entry k) were smoothly converted to the expected per-*O*-acetyl thioglycosides **15**–**25** in respectable yields (65–84%) within 1–2 days. Both *N*-Cbz and N_3 protecting functions were dismantled under these thioglycosidation conditions. Due to the participation of the group at C2, the 1,2-*trans* thioglycosidic bond was formed exclusively in most cases, whereas for L-rhamnose, a 5:1 α- to β-thioglycosides mixture was furnished, which also agreed with previous finding (Table 2, entry c).[10e] For NANA methyl ester, the β-thioglycoside **24** was formed exclusively, which could be attributed to the anomeric effect (Table 2, entry i).

In conclusion, cheap and readily available sulfonic acids, TsOH, and H_2SO_4 are versatile and efficient catalysts for the acetylation of carbohydrates. Contrary to most acid catalysts, which are mainly restricted to the acetylation of simple carbohydrates without amino functions,[10d,e,12–14] our versatile protocol can be applied to different carbohydrate substrates including mono-, di-, tri-, and hepta-saccharides, amino sugars with different amino protecting functions, and oligosaccharides containing fragile furanosyl glycosidic bonds. Additional features include the chemoselective formation of tetra-*O*-acetyl- and penta-*O*-acetyl-NANA esters. In addition, the simple one-pot two step acetylation–thioglycosidation protocols were also developed for the direct access of a panel of *p*-tolyl per-*O*-acetyl thioglycosides including the first one-pot preparation of a sialyl thioglycoside.

1. Experimental

1.1. General methods

All chemicals were purchased as reagent grade and used without further purification. TsOH was dried over P_2O_5 under vacuum and stored in desiccators. 99.99% H_2SO_4 used was purchased from a known chemical vendor. CH_3CN and CH_2Cl_2 were distillated over calcium hydride under N_2 before use. Flash column chromatography was performed on silica gel 60 (70–230 mesh, E. Merck). ^1H and ^{13}C NMR spectra of the prepared compounds were recorded with 300 MHz and 75 MHz Bruker spectrometers. Chemical shift (δ ppm) was measured against TMS, generated from the residual $CHCl_3$ lock signal at δ 7.26 ppm against the residual proton signal of deuterated chloroform, and the ^{13}C resonance signal is calibrated against the ^{13}C signal of deuterated chloroform. Coupling constant(s) in Hertz (Hz) were obtained from ^1H NMR spectra.

1.2. TsOH-catalyzed acetylation procedure for the preparation of per-*O*-acetyl glycosyl acetates 1–3 and 6–15

To 0.5 g of mono-, di-, tri-, or hepta-saccharides was added Ac_2O (or a mixture of Ac_2O and CH_3CN) in which a catalytic amount of TsOH was dissolved. The mixture was firstly stirred at 0 °C for 1 h and then stirred at the optimal reaction temperature.[19] Upon complete acetylation, the mixture was diluted with EtOAc (20 mL), which was washed with cold satd $NaHCO_3$ (20 mL × 2), water (20 mL × 1), brine (20 mL × 1), dried over $MgSO_4$, filtered, and then concentrated. Except for melezitose and N-protected amino sugars, the crude concentrate after work-up was directly characterized with NMR spectroscopy. For the peracetylated products of melezitose and N-protected amino sugars, flash chromatography purification with EtOAc–hexane elution was performed.

1.3. H_2SO_4-catalyzed acetylation procedure for the preparation of per-*O*-acetyl glycosyl acetates 4 and 5

To a suspension of 0.5 g of D-galactose in a mixture of Ac_2O–CH_3CN at −20 °C (or −30 °C for L-fucose) was added catalytic amount of H_2SO_4 in CH_3CN (neat H_2SO_4 was diluted with CH_3CN to a 10% v/v solution). The exact amount of reagents used and specific reaction conditions were detailed in Supplementary data.[19] After stirring for 1 h at −20 °C (or −30 °C for L-fucose), the temperature was gradually warmed up to 0 °C (−20 °C for L-fucose) and the stirring was continued till the end of the reaction. The workup procedure was processed as described above.

1.4. One-pot TsOH-catalyzed acetylation–thioglycosidation procedure for the preparation of per-*O*-acetyl thioglycosides of 16–18 and 21–25

The peracetylation procedure was performed at 0.5 g sugar substrate scale as described above. Upon complete acetylation, the reaction solvent was removed and co-evaporated twice with an equal volume of toluene on a rotary evaporator. Thiocresol (1.5 mol equiv) in CH_2Cl_2 was added to the crude residue at 0 °C, followed

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by the addition of Lewis acid (either 2 mol equiv of $BF_3{\cdot}Et_2O$ or 1.1 mol equiv of $SnCl_4$), and the mixture was stirred initially at 0 °C under N_2. After the addition of the reagents, the reaction temperature was raised to 27 °C and the reaction mixture stirred until the end of the reaction, except for *N*-acetyl-D-glucosamine **8**, in which the reaction mixture was warmed up to 40 °C. Upon completion of the reaction, the mixture was diluted with cold EtOAc (50 mL), which was sequentially washed with cold satd $NaHCO_3$ (30 mL × 2), brine (30 mL × 1), dried over $MgSO_4$, filtered, and then concentrated for flash column chromatography to furnish the per-*O*-acetyl thioglycosides **16–18** and **21–25**.

1.5. One-pot H_2SO_4-catalyzed acetylation–thioglycosidation procedure for the preparation of per-*O*-acetyl thioglycosides 19 and 20

The peracetylation procedure of D-galactose or L-fucose was performed at 0.5 g scale as described above. Upon complete acetylation, 1.2 equiv of methanol was added and the mixture was stirred for 1 h at 0 °C; subsequent addition of thiocresol (1.5 mol equiv) in CH_2Cl_2 and $BF_3{\cdot}Et_2O$ followed. The mixture was stirred initially at 0 °C and then gradually warmed to room temperature (27 °C) under N_2. Upon completion of the reaction, the mixture was diluted with cold EtOAc (50 mL), which was washed with cold satd $NaHCO_3$ (30 mL × 2), brine (30 mL × 1), dried over $MgSO_4$, filtered, and then concentrated for flash column chromatography to furnish the per-*O*-acetyl thioglycosides **19** and **20**.

1.6. *p*-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (16)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, *J* = 8.1 Hz, 2H, ArH), 7.10 (d, *J* = 7.9 Hz, 2H, ArH), 5.20 (dd, *J* = 9.3, 9.4 Hz, 1H, H-3), 5.01 (dd, *J* = 9.3, 9.9 Hz, 1H, H-4), 4.92 (dd, *J* = 9.3, 10.0 Hz, 1H, H-2), 4.63 (d, *J* = 9.9 Hz, 1H, H-1), 4.20–4.14 (m, 2H, H-6, H-6), 3.70 (ddd, *J* = 2.6, 4.7, 10.1 Hz, 1H, H-5), 2.33 (s, 3H, STol CH_3), 2.09 (s, 3H, Ac), 2.08 (s, 3H, Ac), 2.01 (s, 3H, Ac), 1.98 (s, 3H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.97, 170.58, 169.78, 169.63, 139.2, 134.2, 130.2, 130.1, 127.9, 86.2, 76.1, 70.3, 68.6, 62.5, 21.58, 21.16, 21.12, 20.97.

1.7. *p*-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (17)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 8.1 Hz, 2H, ArH), 7.12 (d, *J* = 8.1 Hz, 2H, ArH), 5.50 (dd, *J* = 1.5, 2.5 Hz, 1H), 5.42 (d, *J* = 1.0 Hz, 1H, H-1), 5.34–5.32 (m, 2H), 4.57–4.56 (m, 1H), 4.30 (dd, *J* = 12.3, 6.0 Hz, 1H), 4.10 (dd, *J* = 12.5, 2.6 Hz, 1H), 2.34 (s, 3H, STol CH_3), 2.15 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.08 (s, 3H, Ac), 1.99 (s, 3H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.0, 170.3, 170.22, 170.16, 138.8, 122.0, 130.4, 129.2, 86.4, 69.8, 69.7, 66.8, 62.9, 21.52, 21.27, 21.09, 21.03.

1.8. *p*-Tolyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside (18)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 8.1 Hz, 2H, ArH), 7.11 (d, *J* = 8.1 Hz, 2H, ArH), 5.48 (dd, *J* = 3.3, 1.5 Hz, 1H, H-2), 5.32 (d, *J* = 1.5 Hz, 1H, H-1), 5.27 (dd, *J* = 3.3, 9.9 Hz, 1H, H-2), 5.13 (t, *J* = 9.9 Hz, 1H, H-4), 4.41–4.32 (m, H-5), 2.32 (s, 3H, STol CH_3), 2.14 (s, 3H, Ac), 2.07 (s, 3H, Ac), 2.00 (s, 3H, Ac), 1.24 (s, 3H, CH_3-R); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.4, 170.3, 138.6, 132.8, 130.4, 130.3, 129.7, 86.4, 71.6 × 2, 69.7, 68.1, 21.52, 21.30, 21.21, 21.08, 17.7.

1.9. *p*-Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (19)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, *J* = 8.1 Hz, 2H, ArH), 7.10 (d, *J* = 7.8 Hz, 2H, ArH), 5.4 (dd, *J* = 1.0, 3.3 Hz, 1H, H-4), 5.22 (t, *J* = 9.9 Hz, 1H, H-2), 5.03 (dd, *J* = 3.3, 10.0 Hz, H-3), 4.64 (d, *J* = 10.0 Hz, H-1), 4.19 (dd, *J* = 7.0, 11.3 Hz, 1H, H-6), 4.11 (dd, *J* = 6.3, 11.3 Hz, H-6), 3.92 (dt, *J* = 1.0, 6.1 Hz, H-5), 2.34 (s, 3H, STol CH_3), 2.12 (s, 3H, Ac), 2.10 (s, 3H, Ac), 2.04 (s, 3H, Ac), 1.97 (s, 3H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.8, 170.62, 170.48, 169.84, 138.8, 133.5, 130.0, 129.0, 87.3, 72.4, 67.7, 67.6, 61.9, 21.56, 21.27, 21.07, 21.04, 20.99.

1.10. *p*-Tolyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside (20)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 8.1 Hz, 2H, ArH), 7.13 (d, *J* = 7.9 Hz, 2H, ArH), 5.25 (dd, *J* = 0.7, 3.2 Hz, 1H, H-4), 5.19 (t, *J* = 9.9 Hz, 1H, 1H, H-2), 5.03 (dd, *J* = 3.3, 9.9 Hz, 1H, H-3), 4.64 (d, *J* = 9.8 Hz, 1H, H-1), 3.80 (q, *J* = 6.4 Hz, 1H, H-5), 2.33 (s, 3H, STol CH_3), 2.14 (s, 3H, Ac), 2.10 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.24 (d, *J* = 6.4 Hz, 3H, CH_3-R); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.1, 170.6, 169.9, 138.6, 133.3, 130.3, 130.0, 129.5, 8.2, 72.8, 70.7, 67.8, 21.6, 21.3, 21.09, 21.06, 16.8.

1.11. *p*-Tolyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-2-trichloroethoxycarbamyl-β-D-glucopyranoside (21)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 8.1 Hz, 2H, ArH), 7.13 (d, *J* = 7.8 Hz, 2H, ArH), 5.29–5.26 (m, 2H), 5.03 (t, *J* = 9.8 Hz, 1H, H-4), 4.79 (d, *J* = 10.8 Hz, 1H), 4.75 (d, *J* = 10.9 Hz, 1H), 4.23–4.17 (m, 2H), 3.74–3.65 (m, 2H), 2.36 (s, 3H, STol CH_3), 2.10 (s, 3H, Ac), 2.06 (s, 3H, Ac), 2.01 (s, 3H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.4, 171.0, 170.5, 169.8, 154.7, 139.0,

138.7, 134.1, 133.2, 130.3, 130.2, 95.8, 86.7, 75.1, 71.4, 63.8, 63.5, 55.7, 52.6, 21.5, 21.1, 21.07, 20.95.

1.12. *p*-Tolyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-trichloroacetamido-1-thio-β-D-glucopyranoside (22)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 (br m, 1H, N–H), 7.39 (d, $J = 8.1$ Hz, 2H, ArH), 7.10 (d, $J = 7.9$ Hz, 2H, ArH), 5.41 (dd, $J = 9.3$, 11 Hz, 1H, H-3), 5.03 (t, $J = 9.6$ Hz, 1H, H-4), 4.75 (d, $J = 9.8$ Hz, 1H, H-1), 4.23–4.01 (m, 3H, H-6, H-2), 3.76 (ddd, $J = 2.5$, 4.6, 10.0 Hz, 1H, H-5), 2.32 (s, 3H, STol CH_3), 2.06 (s, 3H, Ac), 1.98 (s, 3H, Ac), 1.78 (s, 3H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.8, 171.0, 170.0, 162.2, 139.4, 134.5, 130.1, 128.2, 92.8, 87.2, 76.2, 73.9, 68.9, 62.8, 54.5, 21.6, 21.1, 21.0, 20.6.

1.13. *p*-Tolyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (23)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, $J = 8.1$ Hz, 2H, ArH), 7.10 (d, $J = 7.9$ Hz, 2H, ArH), 5.92 (br d, $J = 12$ Hz, 1H, N–H), 5.23 (dd, $J = 9.3$, 10.9 Hz, 1H, H-3), 5.03 (dd, $J = 9.3$, 9.9 Hz, 1H, H-4), 4.79 (d, $J = 9.9$ Hz, 1H, H-1), 4.20–4.17 (m, 2H, H-6, H-6′), 4.00 (dd, $J = 9.3$, 10.0 Hz, 1H, H-2), 3.71 (ddd, $J = 2.6$, 4.7, 10.1 Hz, 1H, H-5), 2.34 (s, 3H, STol CH_3), 2.09 (s, 3H, Ac), 2.01 (s, 3H, Ac), 1.99 (s, 3H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.4, 171.0, 170.5, 169.8, 162.4, 139.4, 134.5, 130.1, 128.2, 87.2, 76.2, 73.9, 68.9, 62.8, 54.5, 21.5, 21.1, 21.07, 20.95.

1.14. *p*-Tolyl 2-thio-β-D-*N*-acetyl-neuraminic acid methyl ester (24)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (d, $J = 12.8$ Hz, 2H, ArH), 7.12 (d, $J = 7.9$ Hz, 2H, ArH), 5.92 (br d, 1H, N–H), 5.48 (s, 1H), 5.39 (td, $J = 1.1$, 4.2 Hz, H-4), 4.96 (d, $J = 13.9$ Hz, 1H), 4.64 (dd, $J = 2.3$, 10.5 Hz, 1H), 4.50 (dd, $J = 1.9$, 12.2 Hz, 1H), 4.13 (dd, $J = 4.3$, 13.4 Hz, 1H), 4.03 (dd, $J = 8.7$, 7.2 Hz, 1H), 3.59 (s, 3H, CH_3O), 2.64 (dd, $J = 9.1$, 4.7 Hz, 1H), 2.32 (s, 3H, STol CH_3), 2.14 (s, 3H, Ac), 2.12 (s, 3H, Ac), 2.08 (s, 3H, Ac), 1.95 (s, 3H, Ac), 1.89 (s, 3H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.66, 171.40, 170.66, 170.63, 168.66, 140.5, 136.6, 130.2, 125.6, 89.3, 73.6, 73.5, 69.2, 69.1, 63.2, 52.9, 49.7, 37.8, 23.5, 21.69, 21.49, 21.30, 21.13, 21.09.

1.15. *p*-Tolyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-1-thio-β-D-glucopyranoside (25)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (d, $J = 8.2$ Hz, 2H, ArH), 7.07 (d, $J = 8.0$ Hz, 2H, ArH), 5.30 (dd, $J = 1.0$, 3.3 Hz, H-4′), 5.16 (t, $J = 9.9$ Hz, 1H), 5.05 (dd, $J = 9.3$, 9.4 Hz), 5.03 (dd, $J = 9.3$, 9.9 Hz, 1H), 4.93 (dd, $J = 3.3$, 10.0 Hz, 1H), 4.82 (dd, $J = 9.3$, 10.0 Hz, 1H), 4.57 (d, $J = 10.0$ Hz), 4.47–4.43 (m, 2H), 4.09–4.03 (m, 3H), 3.84 (t, $J = 6.3$ Hz, 1H), 3.70 (t, $J = 7.7$ Hz, 1H), 3.64 (m, 1H), 2.29 (s, 3H, STol CH_3), 2.13–1.92 (m, 21H, $7 \times$ Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.69, 170.64, 170.52, 170.42, 170.09, 169.92, 169.41, 138.9, 134.1, 132.8, 130.3, 130.0, 128.1, 101.3, 85.9, 77.0, 74.3, 71.3, 71.2, 71.1, 70.0, 66.9, 62.4, 61.2, 21.55, 21.22, 21.17, 21.01, 20.99, 20.88.

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Supplementary data

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Joined use of oxazolidinone and desymmetric amino protection: a new strategy for protection of glucosamine

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ABSTRACT

Joined use of N-benzyl oxazolidinone and N-benzyl-N-benzyloxycarbonyl (N-BnCbz) desymmetric amino-protecting function is reported. The new synthetic approach enables the facile preparation of type 1 and type 2 LacNAc disaccharides in satisfactory yields. One-pot deprotection of N-BnCbz and O-benzyl ether is achieved by hydrogenolysis under mild conditions.

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A number of naturally occurring glycoconjugates contain N-acetyl glucosamines that glycosylate at C-3 and C-4 positions.[1] Typical examples are the Lewis blood group antigens, which contain either Gal-β(1→3)-GlcNAc (type 1 LacNAc) or Gal-β(1→4)-GlcNAc (type 2 LacNAc) backbone.[2] Some of these blood group antigens such as Lewis Y antigen have been proven to be specific tumor markers for cancer diseases; thus, they are attractive targets for various biomedical investigations.[3] To sustain these research activities, the supply of pure oligosaccharide samples and their conjugates is crucial. One of the important factors in oligosaccharide synthesis is the effective formation of glycosidic bonds. However, due to steric hindrance and hydrogen-bonding interaction, the C-3 and C-4 hydroxyl functions in N-acetyl glucosamine are weakly nucleophilic, and therefore glycosylations of these hydroxyl functions are often problematic.[4,5] To solve these problems, different amino-protecting groups have been designed, which include N-phthaloyl (N-Phth),[6] N-tetrachlorophthaloyl (N-TCPhth),[7] N-dithiasuccinoyl (N-Dts),[8] N-trichloroethoxycarbonyl (N-Troc),[9] N-trichloroacetyl (N-TCA),[10] N-trifluoroacetyl (N-TFA),[11] N,N-diacetyl (N-Ac_2),[12] N-p-nitrobenzyloxy-carbonyl (N-PNZ),[13] N-dimethylphosphoryl (N-DMP),[14] and others.[15] In routine practice, the amino function of glucosamine is often masked with a protecting function in the early stage of synthesis. After a series of protecting group manipulations and glycosylations, this amino-protecting group has to be removed in the final stage. This standard strategy demands the use of a robust protecting function to survive different conditions, but such a function has to be taken off in the end. Therefore, it is not easy to design a single protecting function embracing both features. A point in case is the use of N-Phth protection, which is stable to different reaction conditions,[5] but its removal is non-trivial.[15,16]

In 2001, Kerns and co-workers reported using N-unprotected oxazolidinone for the protection of C-3 hydroxyl and C-2 amino functions in glucosamine.[17] This function was later elaborated to N-acetyl[18–22] and N-benzyl oxazolidinone derivatives.[23–25] The primary goal of using oxazolidinone function is to search for a good α-directing glucosamine donor.[17] Subsequent studies reveal some degree of inconsistency in the stereochemical preference of glycosylations.[22,25,26] We speculated that other than stereochemical preference, the unique feature of N-benzyl oxazolidinone may impart additional utilities (Fig. 1).

Our rationale is grounded on the following facts. Firstly, the 'tied-up' C-3 hydroxyl and C-2 amino functions reduce the steric hindrance at C-4 position and therefore should facilitate its glycosylation.[21] Secondly, the oxazolidinone protection has been shown to decrease the reactivity of the anomeric-leaving function,[22,27] which paves the way for the reactivity-based glycosylation.[28] Thirdly, the hydrolytic opening of oxazolidinone and reprotection of amine function lead to the formation of desymmetric amino-protected glucosamine, which to the best of our knowledge has rarely been studied in the literature.[9b] In the light of the discussion above, this study reports a useful strategy for the protection of glucosamine capitalizing the N-benzyl oxazolidinone and its derived desymmetric N-benzyl-N-benzyloxycarbonyl (N-BnCbz) functions.

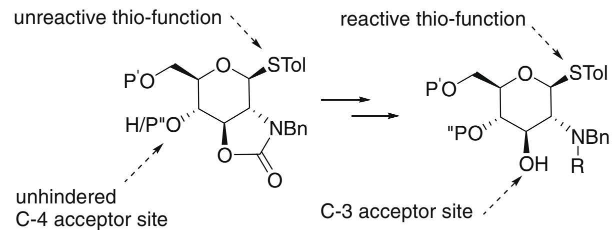

Figure 1. N-Benzyl oxazolidinone-protected glucosamine and its derived disubstituted-desymmetric amino-protected glucosamine.

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In the beginning, 2-Troc-2-deoxy thioglucopyranoside **1** prepared from glucosamine[28] was converted to 4,6-*O*-benzylidene-2*N*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy thioglucopyranoside **3** via benzylidene acetal intermediate **2** (Scheme 1).[25] However, the reductive ring opening of benzylidene acetal **3** required considerable experimentation (Table 1). Previous efforts using either sodium cyanoborohydride–hydrogen chloride ($NaBH_3CN/HCl$)[29] or triethylsilane–boron trifluoride etherate ($Et_3SiH/BF_3{\cdot}Et_2O$)[30] led to $\beta{\rightarrow}\alpha$ anomerization. This undesirable reaction is attributable to the coordination of BF_3 to ring oxygen atom that promotes the endocyclic cleavage of C1–O5 linkage.[24,31] After some investigations, using triethylsilane–trifluoroacetic acid (Et_3SiH/TFA) at low reaction temperature was found to be effective for the reduction of $\beta{\rightarrow}\alpha$ anomerization.[32] To our delight, *N*-benzyl-2,3-*N*,*O*-carbonyl-protected β-thioglucopyranoside **4b** was formed exclusively in high 80% yield at −20 °C (Table 1, entry 3). However, anomerization of **4b** to α-anomer **4a** and trace amount of complete deacetalation product **5** were observed at higher reaction temperatures (Table 1, entries 1 and 2). Noted that the use of the literature procedure resulted in a 1:6 α/β-anomeric mixture (Table 1, entry 4).[24] The β-anomeric configuration of **4b** was supported by the ^{13}C chemical shift at 86.7 ppm and $^1J_{CH}$ coupling constant of 161 Hz.[33]

After the preparation of glucosamine acceptor **4b**, this study proceeded to synthesize a desymmetric amino-protected glucosamine acceptor (Scheme 2). In this regard, *N*-benzyl oxazolidinone-protected glucosamine thioglycoside **6**[25] was treated with *t*-BuOK to produce benzylamine derivative **7**,[25] which was chemoselectively converted to desymmetric *N*-benzyl-*N*-benzyloxycarbonyl (*N*-BnCbz)-protected glucosamine thioglycoside **8**.[34] Subsequent glycosylation of aglycon acceptor **9** with thioglycoside **8** using *N*-iodosuccinimide (NIS) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as promoters furnished glucosamine glycoside **10**.[35] Noted that the assignment of ^1H NMR spectra of **8** and **10** was difficult due to the peak broadening of the resonance signals.[36] Nonetheless, their preliminary identifications were evidenced by HRMS.

Scheme 1. Synthesis of glucosamine acceptor **4b**.

Table 1
Reaction conditions and results of reductive benzylidene ring opening of thioglycoside **3**

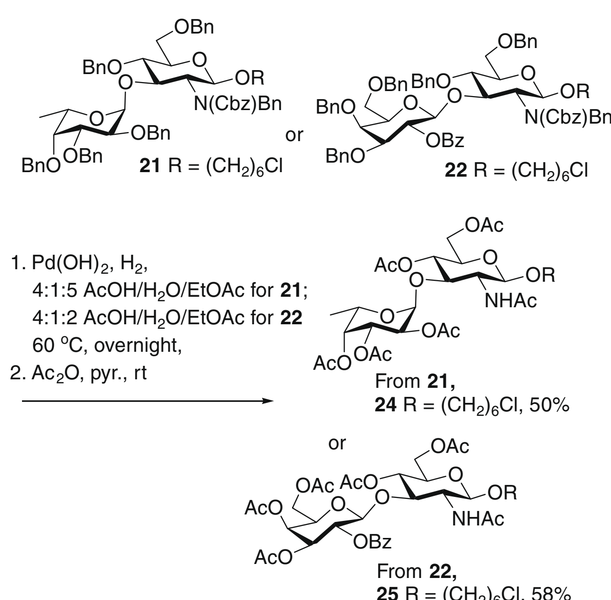
Entry	Acid (equiv)	Et_3SiH (equiv)	*T* (°C)	Yield (%) of **4**[a]	α:β
1	TFA (6)	5	25	35	1:1
2	TFA (6)	5	0	57	1:10
3	TFA (6)	5	−20	80	β only
4	BF_3 (2)	12	−20	65	1:6[b]

[a] Total yield of **4a** and **4b** after chromatography purification.
[b] The method was referred to Ref. 23.

Scheme 2. Synthesis of desymmetric (*N*-BnCbz)-protected glucosamine acceptor **10**.

Further support of their structures could be obtained by high temperature NMR spectroscopy, as demonstrated for glycoside **10** (ca VT-NMR from rt to 100 °C in deuterated DMSO solvent).[37] The broadening of resonance signal is due to the presence of the Cbz carbamate function because such a broadening phenomenon had gone for glucosamine glycoside **11**, in which the Cbz function was removed.

With glucosamine acceptors **4b** and **10** in hand, the stage was ready to study their glycosylations with known thioglycosides **12**–**16** (Table 2).[38] Glycosylations of **4b** with thiogalactopyranoside **12** and thiofucopyranoside **13** produced Gal-α(1→4)-GlcNAc disaccharide **17** and Fuc-α(1→4)-GlcNAc disaccharide **18** as the single anomers (Table 2, entries 1 and 2). Intriguingly, the thiotolyl function in thioglycoside **18** underwent $\beta{\rightarrow}\alpha$ anomerization forming an inseparable 1:3.5 α/β-anomeric mixture. Though this anomerization can be explained by C1–O5 endocyclic bond cleavage as described before,[31] it is unclear why the same anomerization did not occur in the glycosylation of **12**. Due to the deactivation of oxazolidinone function, self-condensation of **4b** did not occur under the present reaction conditions.[22,27] Glycosylations of **4b** with thioglycosides **14** and **15** furnished type 2 LacNAc disaccharides **19** and **20** in high yields (Table 2, entries 3 and 4). For glycosylations of



Scheme 3. Deprotection of disaccharides **21** and **22**.

Table 2
Glycosylation studies of glucosamine acceptors **4b** and **10**

thioglycoside donor **12**, **13**, **14**, **15** or **16**; + glucosamine acceptor **4b** or **10** → (NIS, cat. TMSOTf, 4A MS, CH_2Cl_2, T °C) disaccharide **17**, **18**, **19**, **20**, **21**, **22**, or **23**

Entry	Thioglycoside donor	Glucosamine acceptor	T (°C)	Disaccharide product	Yield (%)
1	**12**	**4b**	−70	**17**	70
2	**13**	**4b**	−60	**18** (α:β = 1:3.5)	85
3	**14**	**4b**	−65	**19**	65
4	**15**	**4b**	−70	**20**	80
5	**13**	**10**	−70	**21** (R = $(CH_2)_6Cl$)	93
6	**15**	**10**	−65	**22** (R = $(CH_2)_6Cl$)	80
7	**16**	**10**	−65	**23** (R = $(CH_2)_6Cl$)	73

glucosamine acceptor **10**, thioglycoside donors **13**, **15**, and **16** were employed. All the glycosylations furnished the expected disaccharide products **21**–**23** in high (73–93%) yields (Table 2, entries 5–7). For NMR spectroscopy of disaccharides **21**–**23**, the phenomenon of resonance peak broadening was also observed.

After studying the glycosylation properties of glucosamine acceptors **4b** and **10**, we next explored appropriate deprotection methods for selected disaccharide products. As the deprotection methods for oxazolidinone have already been developed,[23] this study focused on the deprotection of desymmetric amino protection of Fuc-α(1→3)-GlcNAc glycoside **21** and type 1 LacNAc glycoside **22** (Scheme 3). An advantage of using *N*-Cbz protection in glucosamine is that it can be removed along with the benzyl ether and benzylamine functions during Pd-catalyzed hydrogenolysis.[39]

In our hands, the optimization of reaction conditions was required. Ultimately, $Pd(OH)_2$ was found to be the most effective catalyst for the deprotection of *N*-BnCbz and *O*-Bn in **21** and **22** (Scheme 3).[23,40,41] Both hydrogenolysis reactions were performed in AcOH/H_2O/EtOAc solvent mixtures under 1 atm H_2 at 60 °C. For NMR characterization, the resulting debenzylated products were further acetylated to produce the peracetyl Fuc-α(1→3)-GlcNAc glycoside **24** and type 1 LacNAc glycoside **25**.

In summary, this study reports a versatile amino protection strategy for glucosamine by the joined use of *N*-benzyl oxazolidinone and desymmetric *N*-BnCbz function. The scope of investigation includes the installation, deprotection, and application of these protecting functions. As glucosamine constitutes the key component in different oligosaccharide structures, the results of this study should be found useful for their preparation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.021.

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