國立交通大學

應用化學系碩士班

碩 士 論 文

二甲基甲醯胺：獨特的醣質化調控分子

Dimethylformamide: An Unusual Glycosylation Modulator

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中 華 民 國 一百 年 七 月

Abstract

A convenient pre-activation DMF-modulating glycosylation method is developed. The method employs DMF as a modulator to convert the highly reactive oxocarbenium ion to less reactive glycosyl imidate; subsequent coupling of the imidate with an acceptor leads to the formation of glycosylation product. In addition, there is a quantity-selectivity relationship between the amount of DMF modulator and the degree of α-selectivity in glycosylation. High to excellent 1,2-*cis* and 1,2-*trans* α-selectivities are achieved by this simple method without invoking any atypical protecting functions.

Regarding the reaction mechanism, VT-NMR study is performed, which clearly identifies the α-glycosyl imidate by detection of characteristic signals deriving from the imidate function. In addition, glycosyl formate deriving from the side reaction of the glycosyl donor is also observed on some occasions. Based on such evidence, a possible mechanism is proposed. The interception of oxocarbenium ions with DMF generates a mixture of α/β-glycosyl iminium ions. Empirically, the β-iminium intermediate is more reactive than the α one and is able to react predominantly with the alcohol acceptor through a S_N2-like pathway leading to 1,2-*cis* α-glycosidic bond formation.

摘要

此論文成功建立一套藉由預活化(pre-activation)的方式，透過二甲基甲醯胺(dimethylformamide)的調控達到高 alpha 選擇性醣質化反應。此方法利用二甲基甲醯胺，把高反應性的 oxocarbenium ion 轉變成相對反應性較低的 glycosyl imidate。之後加入醣受體與上述的 glycosyl imidate 反應形成醣質化產物。另外，二甲基甲醯胺的當量與 alpha 選擇性有正相關性。此方法不需要使用特殊的保護基，就能達到極高的 alpha 選擇性。

利用變溫核磁共振儀(VT-NMR)研究，觀察到α-glycosyl imidate 的特徵訊號，以及分離出副反應的 glycosyl formate。根據以上的證據，提出了此方法合理的反應機制。二甲基甲醯胺與 oxocarbenium 進行反應產生 glycosyl iminium ions 的 alpha, beta 混和物(α/β-glycosyl iminium ions)。而 beta 的 glycosyl iminium 反應性比 alpha 的 glycosyl iminium 較佳，會先與醣受體進行 S_N2-like 的反應，產生 1,2-*cis* 的醣苷鍵。

致謝

時間回到當初來交大報到的那一天，充滿期待的我希望能找到理想的實驗室度過這兩年的碩士生涯。在大學時有機學的不是很好，但卻很戲劇性的加入了有機合成的實驗室。

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劭儒

Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
All	Allyl
AgOTf	Silver trifluoromethanesulfonate
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
DMF	*N*,*N*-dimethylformamide
DMA	*N*,*N*-dimethylacetamide
Et	Ethyl
Fmoc	Fluorenylmethyloxycarbonyl
Fuc	Fucose
Gal	Galactose
Glc	Glucose
HMPA	Hexamethyl phosphoramide
Man	Mannose
Me	Methyl
MS	Molecular sieve
NIS	*N*-iodosuccinimide
Nu	Nucleophile
Ph	Phenyl
Phth	Phthalate
Rha	Rhamnose

TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Tf_2O	Trifluoromethanesulfonic anhydride
TsOH	*p*-toluenesulfonic acid
TEA	Triethylamine
TES	Triethylsilane
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
2-Nap	2-naphthylmethyl

Table of Contents

Index of Figures

Index of Tables

Index of Schemes

1. Introduction of α-stereoselective *O*-glycosylation

1.1 Oligosaccharides

Glycoconjugates are ubiquitous components of all living organisms. They play an important role in different biological activities, for examples, viral infection, cellular trafficking, cell proliferation, differentiation, cell apoptosis and immune response etc.[1] Most of these activities are closely associated with carbohydrate-protein interactions (**Figure 1.**).[2]

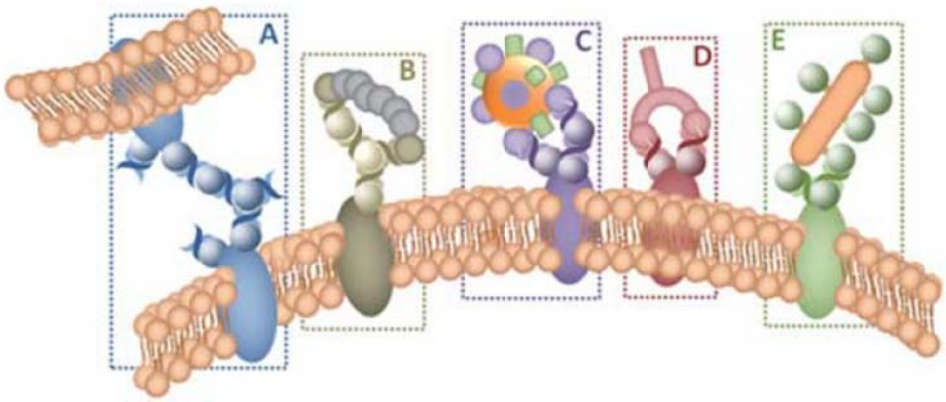


Figure 1. Participation of cell surface carbohydrates in recognition events with another cell (A), toxins (B), viruses (C), antibodies (D) and bacteria (E)

Some cancer diseases, one of the leading causes of mortality in many countries are closely associated with glycoconjugates. Scientists have found that particular oligosaccharide conjugates are over-expressed by cancer cell, such as Globo-H in breast cancer,[3] Gb_3 in Burkitt lymphoma,[4] GM_1 in lung cancer,[5] etc. Accordingly, development of synthetic carbohydrate vaccines to cure the cancer disease draws particular interest of scientists. Moreover, other applications of oligosaccharide conjugates include the preparation of bioconjugated hybrid materials, which is used for neutralization of antibody to alleviate

the immune response in organ transplant rejection.[6]

In order to study the biological function of the natural oligosaccharides, researchers needs sufficient quantity of biological relevant oligosaccharide structures in high purity and homogeneity. However, extraction of glycoconjugates from natural resources is inefficient and tedious, and they are unable to fulfill the above requirements; as such, chemical synthesis of oligosaccharides provides access to meet these demands.

The chemistry in oligosaccharide synthesis involved protecting group manipulation and glycosidic bond formations. Protecting group manipulation is always time-consuming and tedious, but the regioselectivity and stereoselectivity in glycosidic bond formations remain challenging. For example, any pair of six-carbon monosaccharides can be coupling in 11 different ways (Figure 2.). Regioselective glycosylation of a particular hydroxyl functions can be achieved by one-pot regioselective protection strategy.[7] However, selective formation of α- and β-glycosidic bonds is the main theme in glycosylation studies.

In recent decades, advances in synthetic methodologies have been achieved in construction of complex oligosaccharides. A number of synthetic strategies have emergred, which include the advances in traditional solution-phase glycosylations, and solid-phase synthesis. Among these advancements, we herein discuss three classes glycosylation chemistries that are widely used in contemporary carbohydrate chemistry. Some of them are elaborated to one-pot

oligosaccharide synthesis that significantly streamlines the traditional coupling processes.

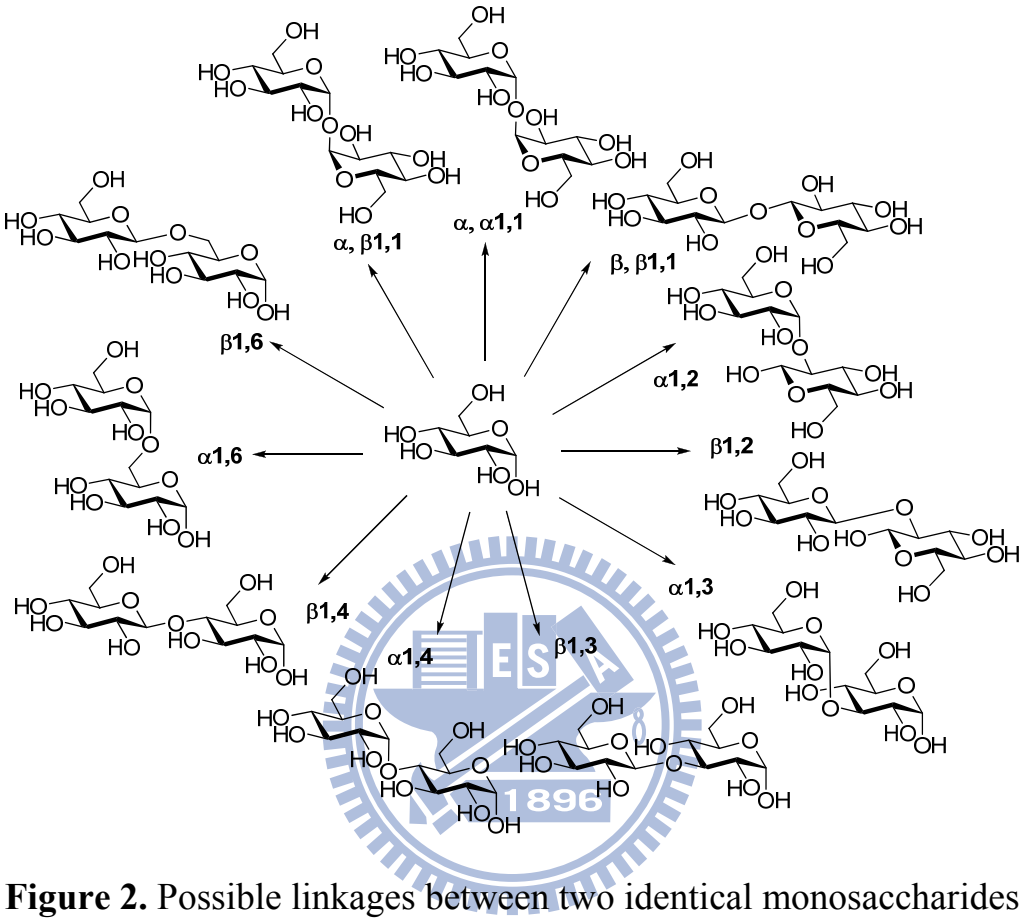


Figure 2. Possible linkages between two identical monosaccharides

1.2 Glycosylation strategies

The three classes of glycosylation chemistry to achieve the glycosylation coupling of saccharide units are the orthogonal, chemoselective and pre-activated iterative glycosylations. They have both advantages and disadvantages. Followings outline the key features of these strategies.

1.2.1 Orthogonal glycosylations

The difference in reactivity between glycosyl substrates was obtained by using various types of anomeric leaving groups. As such, by varying the promoter, a glycosyl donor e.g. bromide, trichloroacetimidate or thioglycosides, can be selectively activated by judicious use of appropriate promoters, which can then be coupled with a glycosyl acceptor and the anomeric function at the acceptor remains untouched. The advantage of an orthogonal strategy is that this strategy allows the condensation of building blocks, independent of their relative reactivity. However, the excessive synthetic work required to obtain building blocks with orthogonal anomeric functions complicates the scheme and therefore decreases the overall efficiency (**Figure 3**).

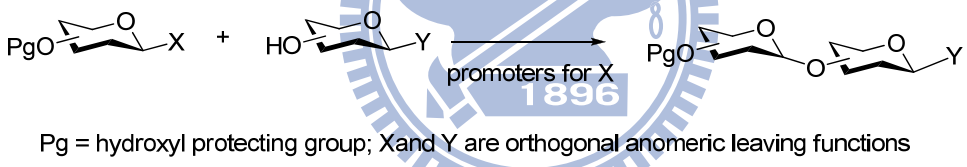


Figure 3. Concept of orthogonal glycosylation strategy

1.2.2 Chemoselective glycosylation strategy

In the chemoselective strategy, different protecting groups are employed to create a reactivity profile for glycosyl substrates. In general, the anomeric leaving groups become more nucleophilic by electron-donating protecting functions (an armed condition) and less nucleophilic by electron-withdrawing groups (a disarmed condition). Highly nucleophilic leaving group is more reactive toward electrophilic activation, while weakly nucleophilic leaving group is less reactive

toward electrophilic activation (**Figure 4**). Hans Paulsen firstly documented the viability of this so-called armed-disarmed concept[8] and later realized by Fraser-Reid *et al.*[9] Further studies by Ley and Wong translate this qualitative concept into quantitative reactivity-based glycosylations.[10]Besides protective groups manipulations at the multiple hydroxyl functions, other variables such as the nature of the anomeric leaving groups or the effect of the solvent on the donors' reactivity can be also exploited to facilitate efficient oligosaccharide one-pot synthesis.

Comparison with the orthogonal glycosylations, an apparent advantage of chemoselective glycosylations is that only one type of anomeric leaving group is required. However, such an advantage is partly compromised by the requirement to creating a reactivity difference for the glycosyl substrates concerned, which, as a consequence, invokes additional synthetic steps.

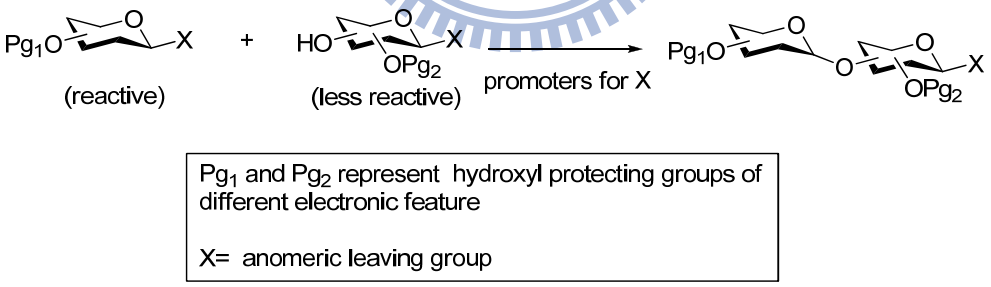


Figure 4. Concept of chemoselective glycosylation strategy

1.2.3 Pre-activated Iterative Glycosylations

The most straightforward way to assemble an oligosaccharide would be to use the same set of anomeric function, and be independent of the substituent pattern of the coupling partners. The pre-activation strategy

is certain to be a good choice.

This strategy combines the advantage of both reactivity-based (activation under only one set of glycosylation condition) and orthogonal strategy (independent of reactivity).

In the absence of acceptor, the glycosyl donors is pre-activated, which generates a reactive intermediate. After addition of acceptor to the pre-activated donor, a disaccharide is formed which can be activated in the same way. The process can be repeated several times in the same flask until the desired oligosaccharide is obtained (**Figure 5**).

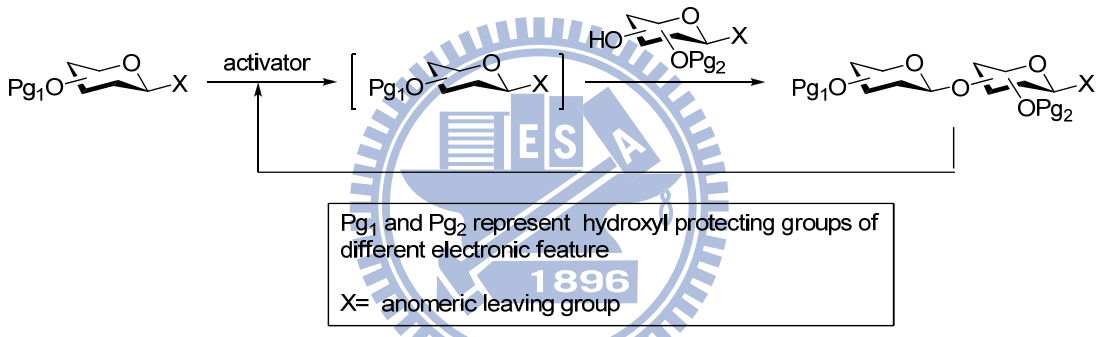
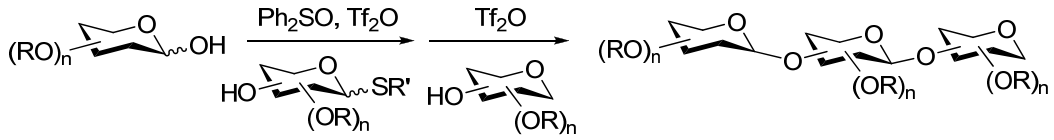


Figure 5. Concept of pre-activation strategy

However, some requisites need to be fulfilled to have an efficient reaction[11] : (i) the promoter utilized should be stoichiometric in activation of a wide range of glycosyl donors in order to prevent further activation of the following building blocks; (ii) the intermediate generated after pre-activation must be sufficiently stable until the addition of acceptor but reactive enough for a high-yielding coupling; (iii) side products formed during the reaction should not interfere with the glycosylation process.

In 2003, Van der Marel and co-workers reported a new glycosylation

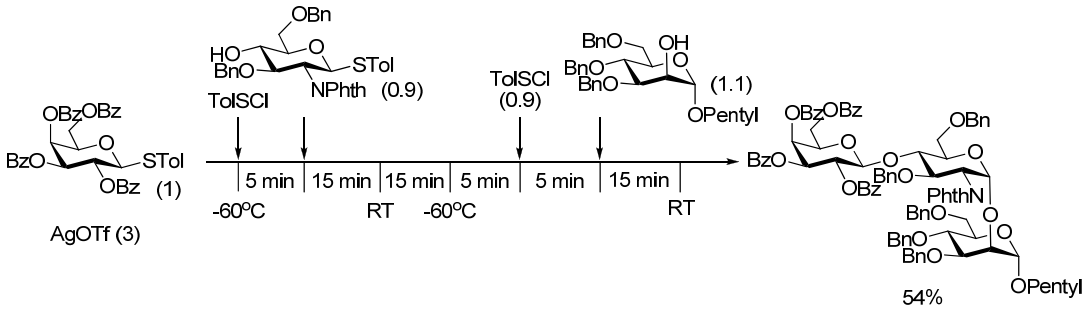
procedure in which the Ph_2SO/Tf_2O-mediated dehydrative condensation of 1-hydroxyl donors with thioglycosides affords in good yield the thiodisaccharides, which in turn can be activated by the same activator system to furnish trisaccharides (**Scheme 1**). The α-Gal epitope and a hyaluronan trisaccharide were efficiently assembled in a one-pot procedure.[12]



Scheme 1. Sequential One-Pot Glycosylations using 1-Hydroxyl and 1-Thiodonors

Pre-activation of thioglycosides was first reported by Crich et al.[13 14] They try to get highly reactive α-mannosyl triflate by pre-activating thioglycosides. The α-mannosyl triflate could undergo S_N2-type substitution, leading to the formation of the challenging β-mannosidic bond. In 2004, for the first time Huang and co-workers established the concept of iterative one-pot synthesis of oligosaccharides based on the pre-activation strategy.[15] *p*-TolSCl-AgOTf was used as a promoter in the iterative one-pot synthesis of trisaccharide (**Scheme 2**).

Pre-activation of disarmed galactoside using a stoichiometric amount of *p*-TolSOTf (formed in situ from *p*-TolSCl and AgOTf) was followed by addition of the more armed glucosamine. After the reaction was completed, the intermediate disaccharide was pre-activated using the same activator. Subsequent addition of the mannoside led to the formation of trisaccharide in 54% yield.



Scheme 2 One-pot synthesis of trisaccharide. The values given in parentheses denote the number of equivalents of each reagent.

Compare with the traditional reactivity-based strategy, this approach is a significantly improved strategy. This approach has also been applied to the assembly of chitotetroses[16], Globo-H[17] and hyaluronic acid oligosaccharides[18]; the results are satisfactory.

Though the above glycosylation chemistries are effective for 1,2-trans β-glycosidic bond formation, in many cases, poor α-stereoselectivity of glycosidic bond formation hampers the efficiency of the glycosylation method. In general, neighboring group participation by C-2 esters will often give 1,2-*trans* *β*-glycosides, while there is no general solution for 1,2-cis α-glycosidic bond formations. In the past, some elegant approaches address this synthetic problem. We are going to introduce some of the representation works in this regard (**Figure 6**).

1.3 The method of 1,2-*cis* *O*-Glycosylation

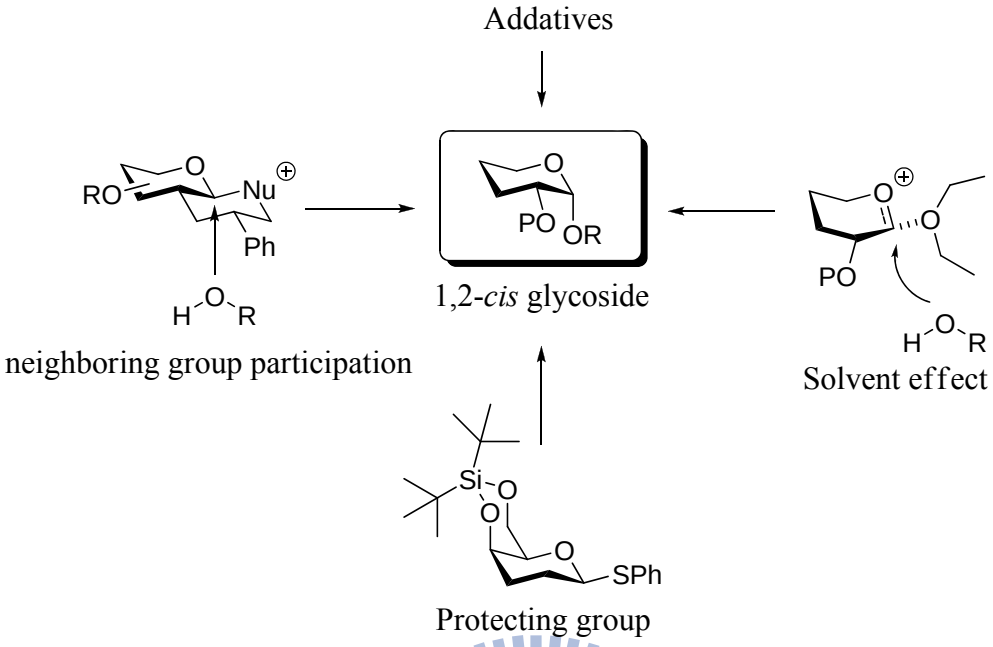
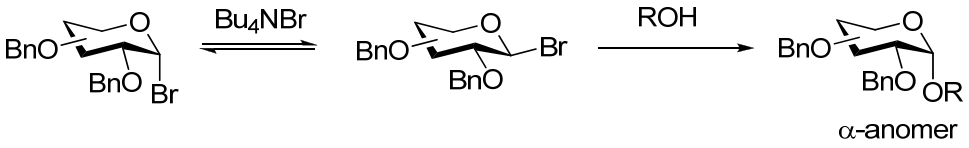


Figure 6. Factors influencing the stereoselectivity of glycosylation

1.3.1 Lemieux's *in situ* anomerization strategy

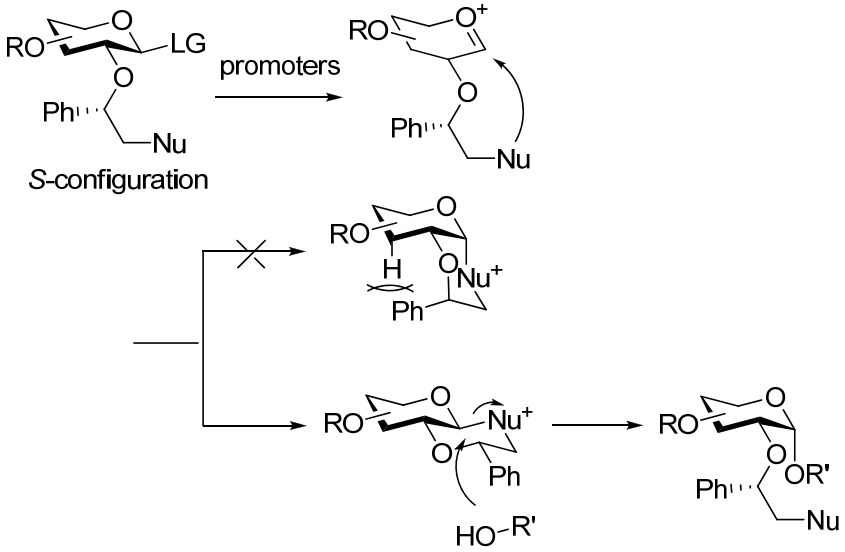
In 1975, Lemieux first introduced the concept of *in situ* anomerization, so-called "halide ion catalyzed glycosylation reactions" (**Scheme 3**). It was documented that a rapid equilibrium could be established between relatively stable α-glycosyl halides and the more reactive β-glycosyl halides by tetrabutyl ammonium bromide (Bu_4NBr). The energy barrier for the attack of glycosyl acceptor with β-glycosyl halide to give *cis*-glycoside is lower than the corresponding *trans*-formation of α-glycosyl halides into *trans*-glycosides. The formation of *cis*-glycosides is preferred. To date, this method provides by far better a α-selectivity in glycosylations for D-glucose, D-galactose, and L-fucose substrates. It has proven to be applicable for the synthesis of complex oligosaccharides especially. [19]



Scheme 3 Lemieux *in situ* anomerization for 1,2-*cis*-glycoside formation

1.3.2 α-selective glycosylation by neighboring group participation

The formation of 1,2-*cis*-glycosides can be also controlled by the certain participating groups. Boons and co-workers have developed a novel general method for the formation of 1,2-*cis* glycosides by utilizing the (*1S*)-phenyl-2-(phenylsulfanyl)ethyl group at the C-2 position[20]. The participating group of the chiral auxiliary gives a quasi-stable anomeric sulfonium ion formed as a *trans*-decalin ring system due to steric and electronic factors. Thus, acceptors could only attack the sulfonium ion intermediate from the bottom face to give α-glycosides (**Scheme 4**).

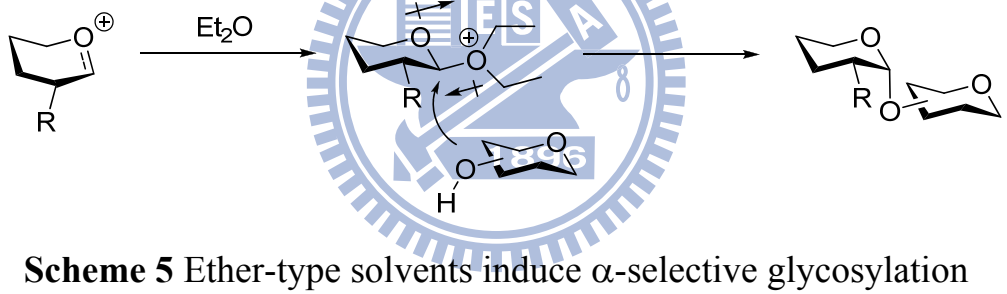


Scheme 4 Concept of the glycosylation with C-2-*S*-auxiliary glycosyl

donor

1.3.3 Solvent influence in α-selective glycosylation

Another important factor which influences the stereoselectivity of glycosylations is the type of solvent used. If the formation of α-glycosides is desired, the ether type solvents such as diethyl ether (Et_2O), THF and 1,4-dioxane are the suitable choice (**Scheme 5**).[21] The solvent molecules coordinate with oxocarbenium ions to preferentially occupy at the β-face. Therefore, the attack of the acceptor is restricted to the α-face, leading toward axial glycosidic bond formation. Nitroethane was also employed as a suitable solvent for 1,2-*cis* glycosylation. [22]



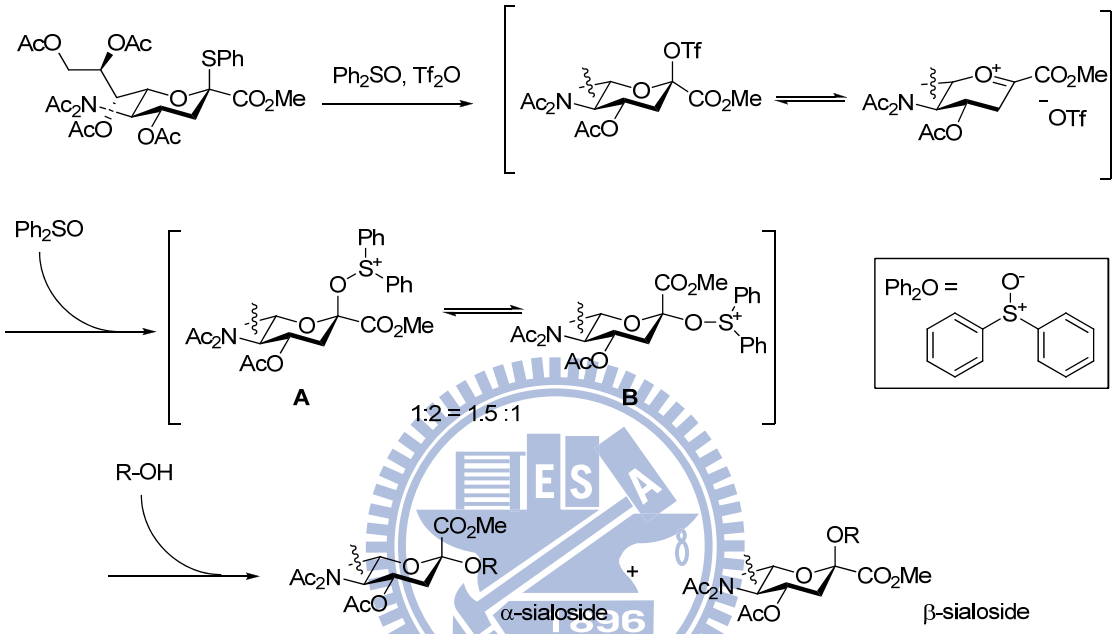
Scheme 5 Ether-type solvents induce α-selective glycosylation

1.3.4 α-selective *O*-glycosylation by additives

Moreover, additives also significantly influence the stereoselectivity. Bogusiak *et al*. reported the selective 1,2-*cis* glycofuranoside synthesis is improved by the addition of a catalytic amount of hexamethyl phosphoramide (HMPA) as an additive.[23]

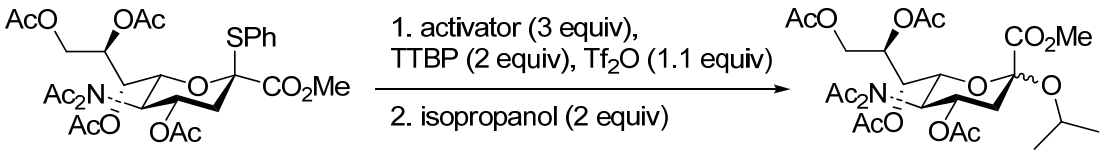
Few years later, Crich and his coworker have shown that the challenging α-sialylation can be performed by using diphenyl sulfoxide (Ph_2SO) and trifluoromethanesulfonic anhydride (Tf_2O).[24] The excess amount of diphenyl sulfoxide is shown to play an important role in

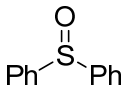
couplings and to suppress the formation of elimination product (**Scheme 6**). They demonstrated that the diphenyl sulfoxide is not only a promoter in glycosylation but it also traps the first-formed oxocarbenium ions. They also investigated the use of a series of sulfoxides in place of diphenyl sulfoxide (**Table 1**).

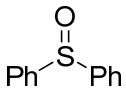
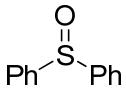
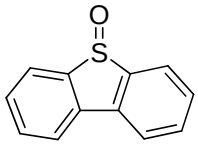


Scheme 7 Glycosylation of a phenyl thiosialoside donor with diphenyl sulfoxide (Ph_2O) and triflic anhydride (Tf_2O).

Table 1. The effective of additives and sulfoxides

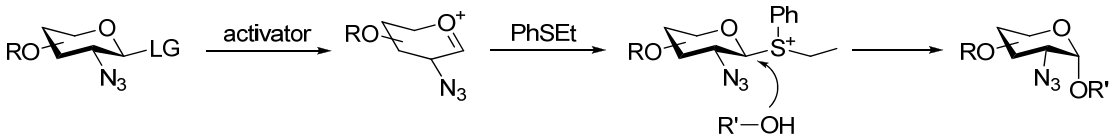


Entry	Activator	Solvent (temp)	% yield[a] (α:β)[b]
1		CH_2Cl_2(-60)	82%

			(2.2:1)
2		CH_2Cl_2/CH_3CN1:1(-78)	89% (1.8:1)
3		CH_3CH_2CN(-78)	77% (2:1)
4	(4-NO_2-Ph)PhSO	CH_2Cl_2(-78)	75% (2.7:1)
5	(4-OMe-Ph)PhSO	CH_2Cl_2(-78)	50% (2:1)
6		CH_2Cl_2(-78)	50% (6:1)

[a] Isolated yields. [b] Determined by ^{1}H NMR on the crude reaction mixture.

In 2007, Boons *et al.* presented an excellent α-selective glycosylation of 2-azido-2-deoxy-glucosyl trichloroacetimidates, when performed at a relatively high reaction temperature in the presence of PhSEt or thiophene.[25] With NMR and computational studies, β-anomeric sulfonium intermediate formed due to steric hindrance. As a result, the acceptor will come from α-side (**Scheme 8**).



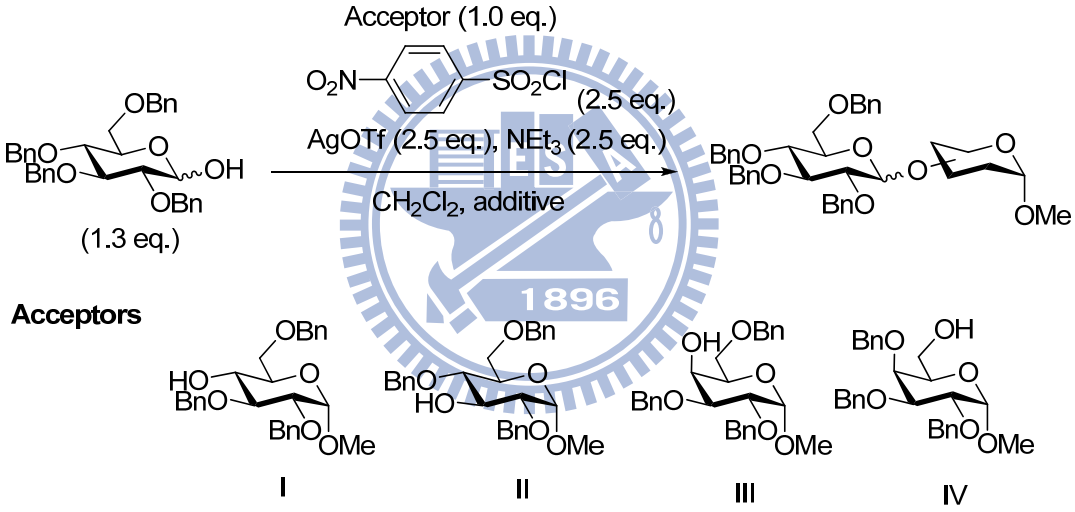
Scheme 8. Boons's method the glycosylation of 2-azido-2-deoxy glucosides using sulfonium ions.

1.3.5 α-Selective *O*-glycosylation by amide-type molecules

Koto first published the stereoselctive α-glucosylation in the

presence of a quaternary mixture of 4-nitobenzenesulfonyl chloride, silver trifluoromethanesulfonate, *N*,*N*-dimethylacetamide, and triethylamine (**Table 2**).[26] They proposed a plausible pathway that the alcohol may react with the hypothetical intermediate of β-iminium ion to form the corresponding α-glucoside. The intermediate α-iminium ion is more stable than intermediate β-iminium ion thermodynamically, but intermediate β-iminium ion is more reactive to form the α-glucoside. But they didn't show any physical data to support their hypothesis.

Table 2. α-glucosylation by using DMA (DMF) as an additive

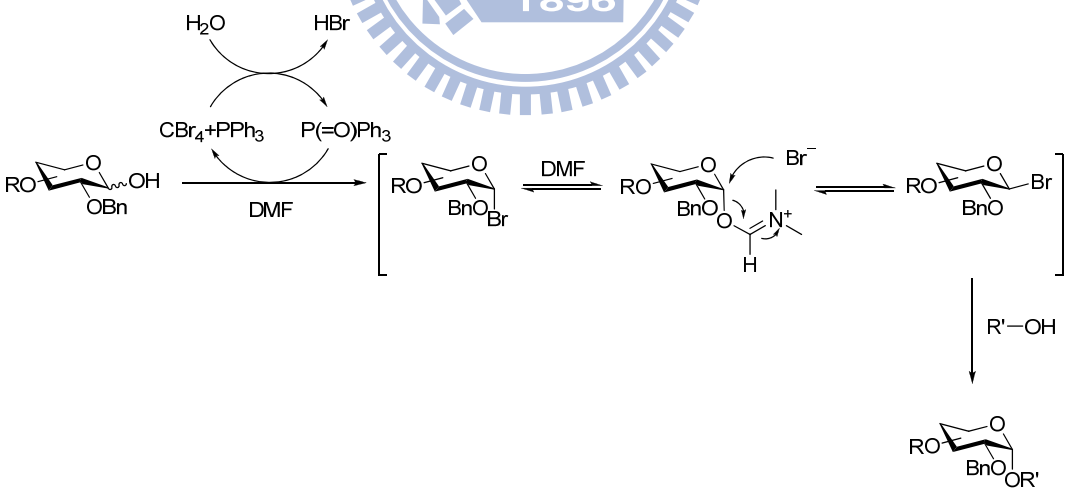


Entry	Acceptor	additives	Yield	α/β ratio
1	I	DMF[a]	58%	77:23
2	I	DMF (2.5)	92%	88:12
3	I	DMA (2.5)	86%	93:7
4	I	DMA (5.0)	73%	86:14
5	II	DMA (2.5)	85%	89:11
6	III	DMA (2.5)	87%	90:10

7	IV	DMA (2.5)	91%	47:53
8	IV	DMA (5.0)	88%	73:27
9	IV	DMA (10.0)	54%	72:28

[a] As a solvent.

In 2003, Nishida and his coworker reported a practical glycosylation by one-pot method using Appel agents in *N*,*N*-dimethylformamide.[27] The role of DMF is demonstrated according to the evident ^{1}H NMR spectra. The signals indicated that the α-glycosyl bromide by using Appel agent could be transformed to α-glycosyl iminium species when the solvent is DMF. (**Scheme 9**) Though Lemieux and co-workers[19a] reported a similar solvent effect, they didn't indicate the occurrence of such DMF-glycosyl adducts.



Scheme 9 Overview of One-pot α-glycosylation Using Appel agents in DMF

Two years later, they still speculate not only β-glycosyl bromide but also β-glycosyl imidate could be the species to induce the

stereoselectivity.[28] Compare to α-glycosyl imidate, the β-glycosyl imidate is more reactive and it may not be accessible by NMR at the room temperature due to the rapid equilibration. Furthermore, at the lower temperature DMF will be frozen. Nowadays, there is no mean to identify the real species in this reaction.

2 Motivation

1,2-*cis*-glycosidic bonds are widely occurred in numerous natural oligosaccharides, glycosides, and glycoconjugates, which are widely distributed in living tissues. These compounds are also found in the human milk, in blood group compounds, in bacterial lipopolysaccharide antigens, and many other sources. Such as Lewis (Le) antigens, *O*-linked glycoproteins, α-Gal Ceramide (KRN7000), polysulfated glycosaminoglycans, globotriaosylceramide (Gb_3) and *N*-linked glycoproteins. But there is no general solution for 1,2-*cis* α-glycosidic bond formations by chemical preparation.

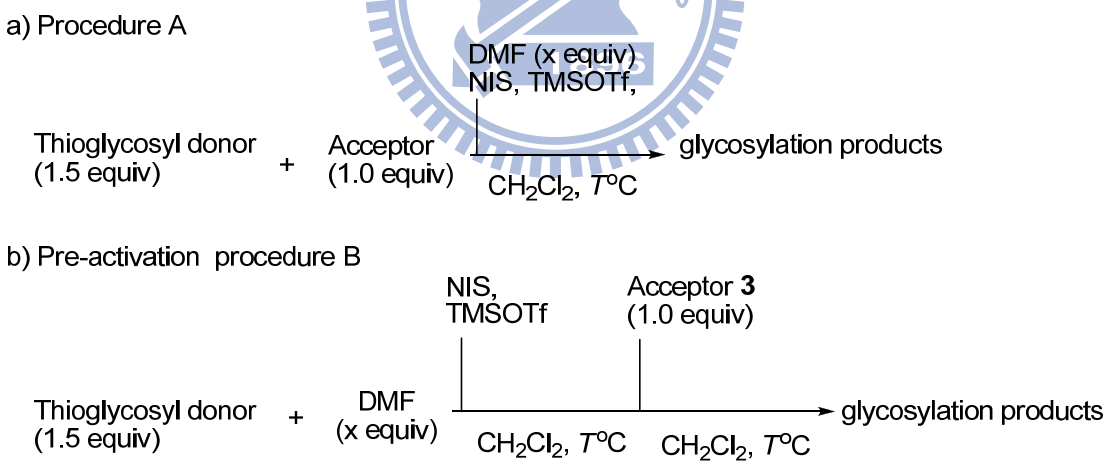
Based on the literatures described before, DMF has been used for the stereoselective glycosylation several times. But the exact role of DMF is still out there. To date, the reported examples only use glycosyl halides as donors. Could we apply it to other glycosyl donor, for example common-used thioglycoside? According to the literature survey, DMF can participate the glycosylation to form more stable intermediate, Could we apply it to pre-activation strategy and elevate it to iterative glycosylation? We herein reported the investigation and findings based on the above context and initial finding in our laboratory.

3 Results and discussion

Based on the preliminary studies of glycosyl chlorides, we observed that residual DMF in the glycosylation mixture promoted 1,2-*cis* α-glycosidic bond formation. Along this line, we hypothesize that this α-glycosylation should also be applicable to thioglycosyl donors, which as a stable glycosyl donor, open access to elucidation of the reaction mechanism. To the best of our knowledge, such investigations have not been reported.

3.1 Optimize the conditions for DMF-modulating glycoslations

In this thesis, we investigated two DMF-modulating glycosylation procedures, and they were depicted in Schemes 9a and 9b.

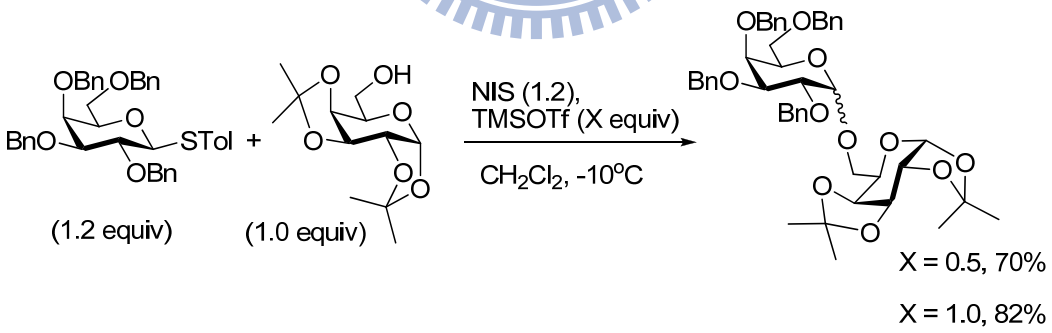


Scheme 10. (a) DMF-modulating glycosylation procedure (procedure A). (b) DMF-modulating glycosylation procedure (procedure B).

In procedure A, as adapted from standard glycosylation protocol, a mixture of thioglycosyl donor, glycosyl acceptor and DMF is treated with

N-iodosuccinimide (NIS) and trimethylsilyl triflate (TMSOTf) (**Scheme 10a**).[29] In procedure B, the thioglycosyl donor is firstly pre-activated with NIS and TMSOTf in the presence of DMF. Upon completion of activation, glycosyl acceptor is added and, it reacts with a presumably glycosyl imidate to furnish desired glycosylation product (**Scheme 10b**).

At the outset, the procedure A was applied to couple commercially available galactosyl acceptor **3** with **a** perbenzyl thiogalactoside **1**. After some experimentations, one molar equivalent of TMSOTf (with respect to glycosyl donor) was required for effective activation of the donor (**Scheme 11**). A larger amount of TMSOTf may be probably attributed due to a mild Lewis basicity nature of DMF. Nevertheless, the DMF modulator exhibits an α-directing effect in glycosylations using thioglyosyl donors, which is in line with our previous findings in glycosyl chlorides.[30]



Scheme 11. The influence of the equivalent of TMSOTf.

In addition, we observed a quantity-selectivity dependent relationship between the stoichiometric amount of DMF addition and the degree of

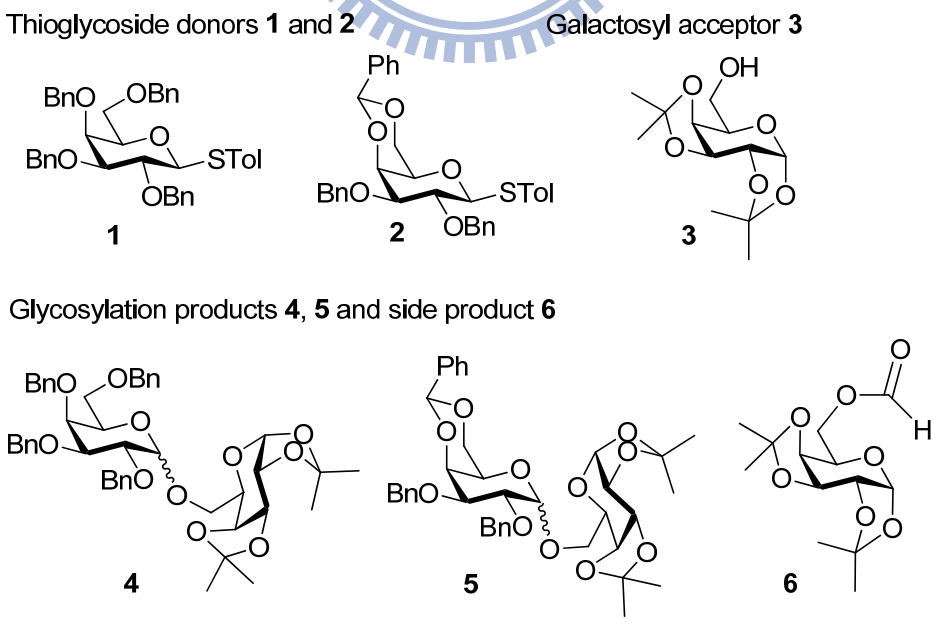
glycosylation selectivity. Explicitly speaking, when the amount of DMF increased from zero to 1.5 equiv, the α/β-anomer-ratio of the glycosylation product **4** increased from 1/1 to 3/1 (**Table 3**, entries 1–4). However, this moderate selectivity is still inadequate for synthetic application, but further increase in amount of DMF addition (>1.5 equiv.) aiming at selectivity improvement was prohibited due to the formation of a side-product, namely the formyl transfer product **6**.[26] Our rationale for this moderate α-selectivity in glycosylation is that the arming benzyl groups of donor **1** may promote the departure of DMF from glycosyl imidate; as a consequence, the α-directing effect of DMF was attenuated.[21]

Based on such a notion, a conformational restrain benzylidene thiogalactoside **2** is used in place of **1**.[22] However, replacing the donor alone did not bring about satisfactory improvement, and a 6/1 α/β-anomer ratio of glycosylation product **5** was obtained (**Table 3**, entry 5). Nonetheless, adopting the pre-activation procedure B in conjunction with an increase in DMF addition (from 1.5 to 6.0 equiv) did improve the α/β-anomer ratio of **5** to 19/1 (**Table 3**, entries 6–8). One may question about whether the ethereal type solvent (as mentioned in the introduction section) could result in similar α-directing effect as implicated in previous cases.[21b] Thus, glycosylation of **3** with **2** was repeated in tetrahydrofuran (THF), 1/3 CH_2Cl_2/Et_2O and 1/2 toluene/dioxane mixture using procedure A. In these experiments, the procedure B is not applicable because this procedure does not work in the absence of DMF. Donor **2** was poorly soluble in pure diethyl ether so

that a 1/3 CH_2Cl_2/ether mixture was employed. The 1/2 toluene/dioxane mixture was found aggregating at −10˚C so that the glycosylation in 1/2 toluene/dioxane mixture was conducted at 0˚C. No significant selectivity was observed for glycosylations irrespective of the type of ethereal solvent (**Table 3**, entry 5 vs 9−12).

In the past, dimethylacetamide (DMA) was used as an additive to promote the α-selectivity of glycosylation.[26] We were curious to examine if DMA could substitute for DMF in our procedure. Thus, glycosylation of **3** with **2** following the procedure B, was repeated with DMA addition, but the observed selectivity was not attractive (**Table 3**, entry 13).

Table 3. Investigation of DMF-modulating glycosylation procedures A and B with galactosyl acceptor **3**.



Entry	Donor (equiv)	DMF (equiv)	*T* (˚C)	Time (h)	Product, yield%, α/β[a]
1	**1** (1.2)[b]	0	-25	0.5	**4**, 90, 1/1
2	**1** (1.2)[b]	0.8	-10	1.0	**4**, 70, 3/2
3	**1** (1.2)[b]	0.8	0	1.0	**4**, 77, 3/2
4	**1** (1.2)[b]	1.5	0	1.0	**4**, 80, 3/1
5	**2** (1.5)[b]	1.5	-10	2.0	**5**, 82, 6/1
6	**2** (1.5)[c]	1.5	-10	2.0	**5**, 80, 8/1
7	**2** (1.5)[c]	3.0	-10	2.0	**5**, 87, 15/1
8	**2** (1.5)[c]	6.0	-10	2.0	**5**, 87, 19/1
9	**2** (1.5)[b]	0[d]	-10	0.3	**5**, 90, 1/1
10	**2** (1.5)[b]	0[e]	-10	0.2	**5**, 85, 1.5/1
11	**2** (1.5)[b]	0[f]	-10	0.5	**5**, 83, 1/1.5
12	**2** (1.5)[b]	0[f]	0	4.0	**5**, 40, 1/1.5
13	**2** (1.5)[c]	-[g]	-10	3.0	**5**, 80, 4/1

[a] α/β ratios were determined by HPLC (conditions given in SI). [b] Procedure A was used. [c] Procedure B was applied. [d] 1/3 CH_2Cl_2/Et_2O mixture was used as solvent. [e] THF was used as solvent. [f] 1:2 Toluene/dioxane was used as solvent. [g] 6 equiv of DMA was added.[26]

3.2 Test the scope of pre-activated DMF-mediated glycoslation

After confirming the effectiveness of the pre-activated DMF-modulating glycosylation (procedure B), this study next investigated its scope of application. In this regard, aglycon acceptors **10–13,** and *O*-glycoside acceptors **14–17** were coupled with thioglycosyl donors **2** (**Figure 7**, Table 4). For comparison the effectiveness of this method to conventional method as well as provision of reference data for HPLC analysis, all glycosylations were performed with and without addition of DMF.

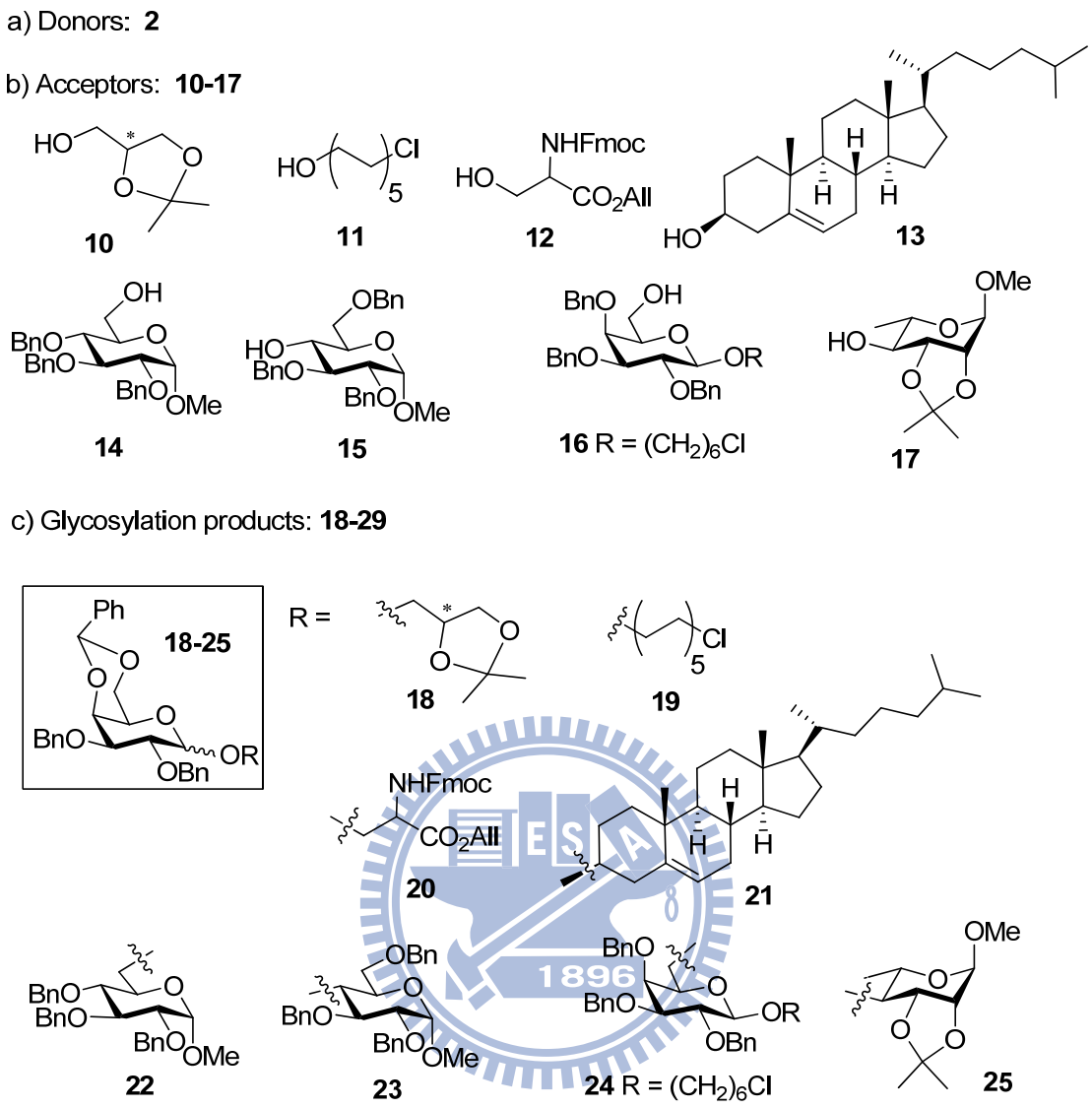
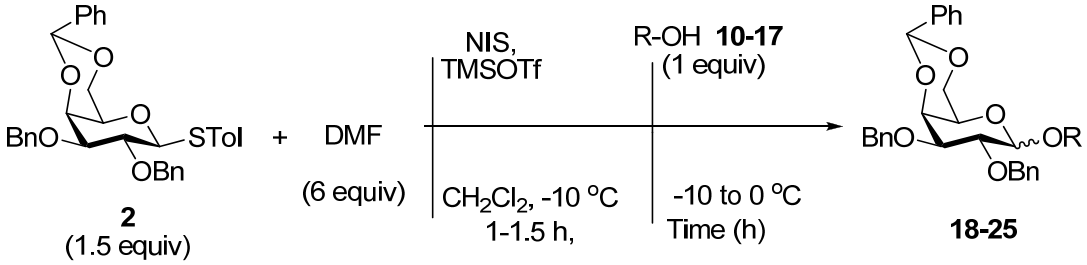


Figure 7. (a) Thioglycosyl donors: **2**. (b) Acceptors: **10**–**17**; (c) Glycosylation products: **18**–**25**.

Generally, reaction rates were lower in the presence of DMF than with its absence; nonetheless, the time required for completion of DMF-modulating glycosylation remained acceptable (2 to 6 h). Regarding the stereochemical control, DMF exerted a powerful α-directing effect on all glycosylations. In some cases, the selectivity was dramatically reversed (**Table 4**, entries 2, 4, 5, 11, and 12).

Table 4. Results of glycosylation of acceptors **10**−**17** using glycosylation procedure B.



Entry	D[a]	A[a]	*T* (˚C)	Time (h)	Product, yield%, α/β[b]		
					18-25	with DMF	no DMF[c]
1	**2**	**10**	-10	2	**18**	83, 12/1	80, 1/1
2	**2**	**11**	-10	2	**19**	76, 8/1	85, 2/5
3	**2**	**12**	-10	6	**20**	45, 19/1	50,15/1
4	**2**	**13**	0	2	**21**	79, 8/1	73, 2/5
5	**2**	**14**	-10	5.5	**22**	75, 12/1	80, 2/3
6	**2**	**15**	0	6	**23**	80, 49/1	50, 2/1
7	**2**	**16**	-10	2	**24**	82, 12/1	80, 3/2
8	**2**	**17**	0	4	**25**	60, 25/1	63, 5/1

[a] D referred to donor and A referred to acceptor. [b] α/β-Anomer ratios were determined by HPLC (settings were given in experimental). [c] Routine glycosylation (without DMF addition) was applied.

3.2.1 Application of DMF-modulating glycosylation to other thioglycoside donors

Encouraged by the results of DMF-modulating glycosylations, we moved on to investigate the application of our method to prepare 1,2-*cis*-*O*-linkage with other thioglyucoside donors. As such, we decided to choose some thiofucoside **7**, thiorhamnoside **8** and thioglucopyranoside **9** to evaluate their performance in glycosylations of acceptors **14**, **15** and **17** (**Figure 8**). For comparison, conventional glycosylations in the absence of DMF modulator were also carried out in parallel.

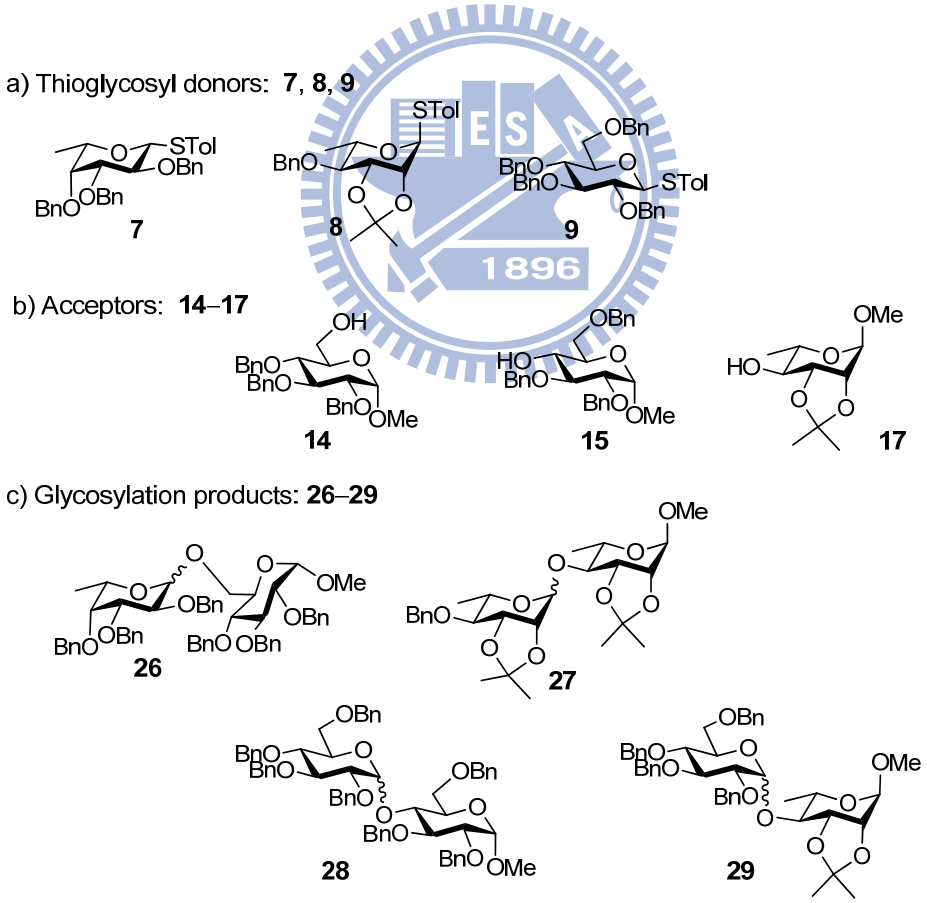
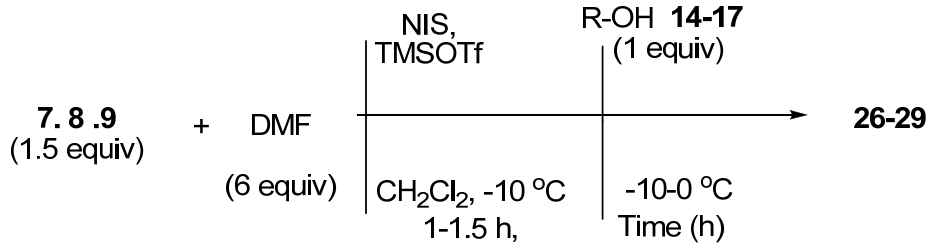


Figure 8. The pairs of thioglycosyl donor, acceptors and their corresponding glycosylation product.

Table 5. Results of glycosylation using glycosylation procedure B



Entry	D	A	*T* (˚C)	Time (h)	Product, yield%, α/β		
					Product	with DMF	no DMF
1	**7**	**14**	-10	4.5	**26**	75, 5/1	77, 1/1
2	**8**	**17**	-10	4	**27**	70, 49/1	80, 5/1
3	**9**	**15**	0	6	**28**[a]	76, 49/1[a]	60, 2/3
4	**9**	**17**	0	5	**29**[a]	75, 9/1[a]	70, 2/5

[a]The glycosylation was performed under ultra-sonification.

3.3 Application of DMF-modulating glycosylation to thioglycoside acceptors

A unique feature of the DMF-modulating glycosylation is the entrapment of oxocarbenium ions as glycosyl imidates. This feature provides an opportunity for development of a new pre-activated glycosylation procedure. In a typical oligosaccharide synthesis, introduction of different anomeric functions to glycosyl donor and acceptor is required such that the activation of the former does not affect the later. Though the reactivities of glycosyl donor and acceptor can also be tuned to create reactivity disparity that allowing their coupling by reactivity-based glycosylation, this strategy requires a long protecting

group manipulation for building block preparation.[10b, 11a, 31] The merit of a pre-activated glycosylation is to allow coupling of glycosyl substrates with the same anomeric function rendering the use of different anomeric function or the tuning of chemical reactivity, unnecessary. Such an approach not only shortens the synthetic steps in oligosaccharide synthesis, but it also paves the way to iterative one-pot glycosylation method.[11a] To the best of our knowledge, there is no pre-activation procedure that endows with α-directing capability.[15] To demonstrate the applicability of the DMF-modulating procedure, thioglycoside acceptors **30**–**40** were glycosylated with thioglycoside donors **2**, **7**, **8**, and **9** following procedure B (**Figure 9**). Preparations and references of thioglycosyl acceptors **30**–**40** were given in experimental section. Table 6 summarizes the yields and α/β-anomer ratios of corresponding glycosylation products **41**–**55**.

A known side-reaction in glycosylations of thioglycosides is the transfer of the thio-acetal function from acceptor to donor.[32] Gratifyingly, such transfer reaction did not occur in the DMF-modulating procedure perhaps due to masking of the reactive oxocarbenium ion by DMF molecule. The glycosylations in this study proceeded smoothly and the corresponding α-anomers were furnished in 45 to 85% yields with high to excellent α-selectivities. However, the reaction yields were on average lower than those produced from glycosylations of *O*-glycosides. We attributed this to the activation of thioglycoside product by residual NIS and/or some side reactions stemming from the imidate intermediates. To re-validate the α-directing effect of DMF, the glycosylation of **36** with **2**

was repeated by using a lesser amount of DMF (1.5 equiv) and the α/β-anomer ratio of glycosylation product **47** decreased sharply to 4/1 (data not shown).

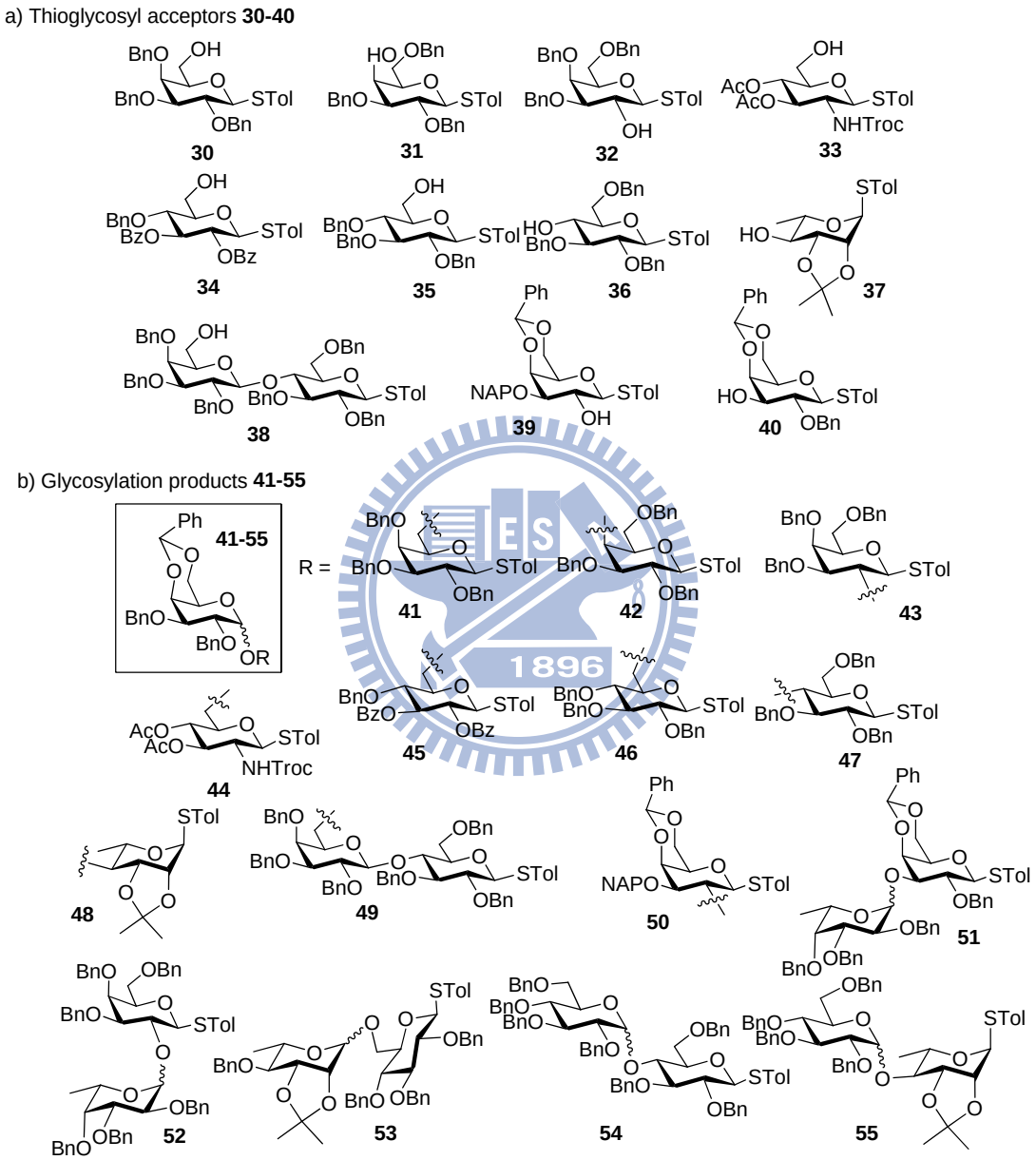
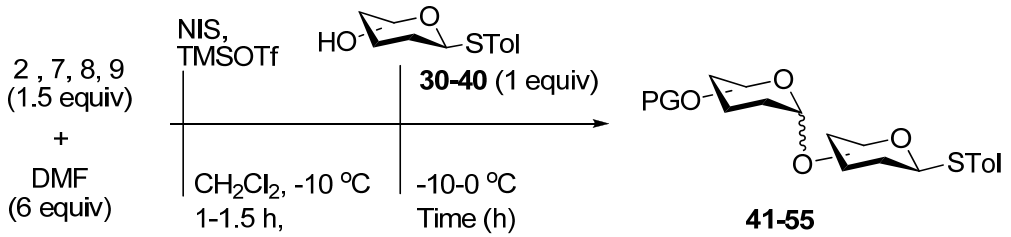


Figure 9. (a) Thioglycosyl acceptors **30**–**40**; (b) Glycosylation products: **41**–**55**.

Table 6. Results of glycosylation of thioglycosyl acceptors **30**–**40** using glycosylation procedure B

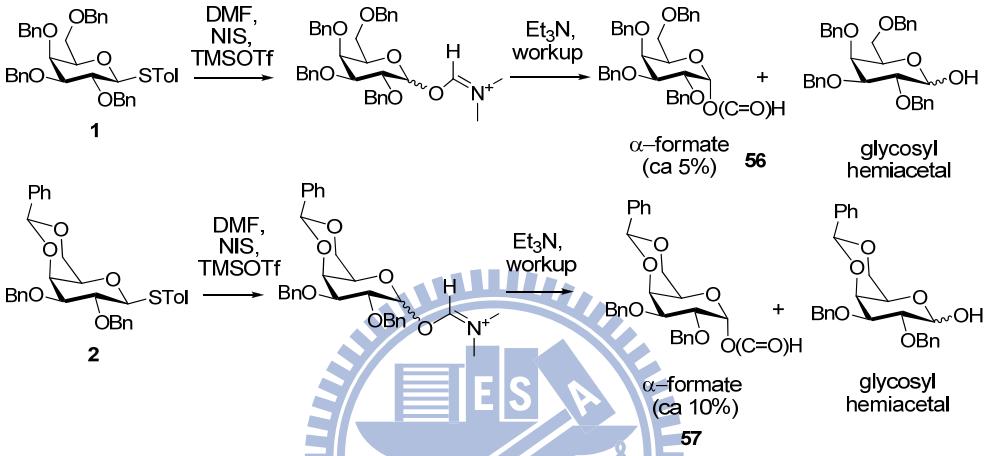


Entry	Donor	Acceptor	*T* (˚C)	Time (h)	α-anomer (yield%),[a] α/β[b]
1	**2**	**30**	-10	3	**41** (60), 36/1
2	**2**	**31**	0	6	**42** (55), 6/1
3	**2**	**32**	0	3	**43** (55), 11/1
4	**2**	**33**	-10	3	**44** (45), 11/1
5	**2**	**34**	-10	3	**45** (85), 49/1
6	**2**	**35**	-10	2	**46** (65), 12/1
7	**2**	**36**	0	4	**47** (70), 49/1[31]
8	**2**	**37**	0	2	**48** (50), 13/1
9	**2**	**38**	-10	3	**49** (75), 19/1
10	**2**	**39**	0	4	**50** (85), 49/1
11	**7**	**40**	-10	3	**51** (56), 49/1
12	**7**	**32**	-10	6	**52** (61), 49/1
13	**8**	**35**	-10	3	**53** (55), 6/1
14	**9**	**36**	0	5	**54** (50), 49/1[c]
15	**9**	**37**	0	3	**55** (55), 8/1[c]

[a] Glycosylation procedure B was applied and the yield (%) referred to isolated α-anomer. [b] α/β Ratios of glycosylation products were determined by HPLC analysis (HPLC conditions was given in experimental). [c] The glycosylation was performed under ultrasonification.[33]

3.4 Mechanistic investigations

3.4.1 Isolate the hydrolysis product of glycosyl imidate



Scheme 12 Isolate the hydrolysis product of glycosyl imidate.

Previous ^{1}H NMR spectroscopy was employed to detect the glycosyl imidates under different reaction context.[34] We reasoned that the glycosyl imidates if formed should undergo hydrolysis in work-up to give the glycosyl formates; and isolation of such formate products would indicate the existence of imidates. Thus, thiogalactosides **1** and **2** were activated in the presence of DMF, and the reaction was subsequently quenched by triethylamine (TEA) without the addition of acceptor. Upon standard workup, α-glycosyl formates (**56**, **57**) could be isolated in 5 and 10% respectively along with ca 80% of glycosyl hemiacetals, which were presumably the hydrolyzed products of glycosyl formates. Both glycosyl formates **56** and **57** were unstable, which accounted for the poor isolated

yields (**Scheme 12**). Chemical identities of **56** and **57** were evidenced by (1) the chemical shifts of anomeric protons (6.40 ppm for **56**, 6.47 ppm for **57**); (2) ^{3}J coupling constants of anomeric protons (3.4 Hz for **56**, 3.6 Hz for **57**); and (3) the characteristic chemical shifts of formate protons at 8.14 ppm for both **56** and **57**. However, we were not able to obtain the corresponding β-glycosyl formate, which might be attributed to its poor stability for standard isolation.

Try to prove the presence of β-glycosyl imidate, we turned to real-time monitoring of the activation process by ^{1}H NMR spectroscopy.

3.4.2 Real-time variable temperature NMR study

Since glycosyl imidate formation is the key step in DMF-modulating glycosylation, the detection of glycosyl imidate is crucial to support the proposed mechanism. In this regard, we prepared a simpler 4,6-*O*-benzylidene-2,3-di-*O*-methyl thiogalactoside **58**, which was activated with NIS and TMSOTf promoters in $CDCl_3$ and followed by the glycosylation of acceptor **59** using procedure B (**Figure 10a**). ^{1}H-, ^{13}C-, and HSQC-NMR spectroscopy of the reaction mixture were taken at 0, 90, and 180 min time points. Figures 9b-d showed selected regions of corresponding ^{1}H NMR spectra. Comparing the spectra of the pre-activated reaction mixture at 0 min and the TMSOTf activated mixture at 90 min (**Figure 10b** and **10c**), a new set of ^{1}H NMR signals are clearly identified, including an anomeric proton at 6.39 ppm (^{3}J = 3 Hz, **60**-H^{a}), a benzylidene proton at 5.60 ppm (**60**-H^{b}), an imidoyl proton at 8.90 ppm (**60**-H^{c}), and *N*,*N*-dimethyl protons at 3.40, and 3.32 ppm

(**60**-H^d). These signals are generated from the presumably α-glycosyl imidate **60**.[34a] The relative downfield positions of **60**-$H^{a,c,d}$ indicate their close proximity to an electron-deficient center. Following the addition of acceptor **59**, the signals stemming from imidate **60** vanished, and another two sets of signals emerged. One set includes an anomeric proton at 5.13 ppm (^3J = 3 Hz, **61**-H^a) and a benzylidene proton at 5.59 ppm (**61**-H^b) corresponding to the expected α-glycoside **61**. Another set (indicated by asterisks in **Figure 10d**) was originated from a α-*N*-galactosyl succinimide, which is a common side-product produced in NIS promoted glycosylation.[31]

As the real-time NMR study provided evidence for the presence of the α-glycosyl imidate, it is reasonable to propose the formation of α/β-glycosyl imidates in DMF-modulating glycosylations. And the β-glycosyl imidate, due to a more reactive nature, reacts preferentially with the acceptor to give the α-glycosylating product. At this time, we are not able to detect the presence of β-imidate.

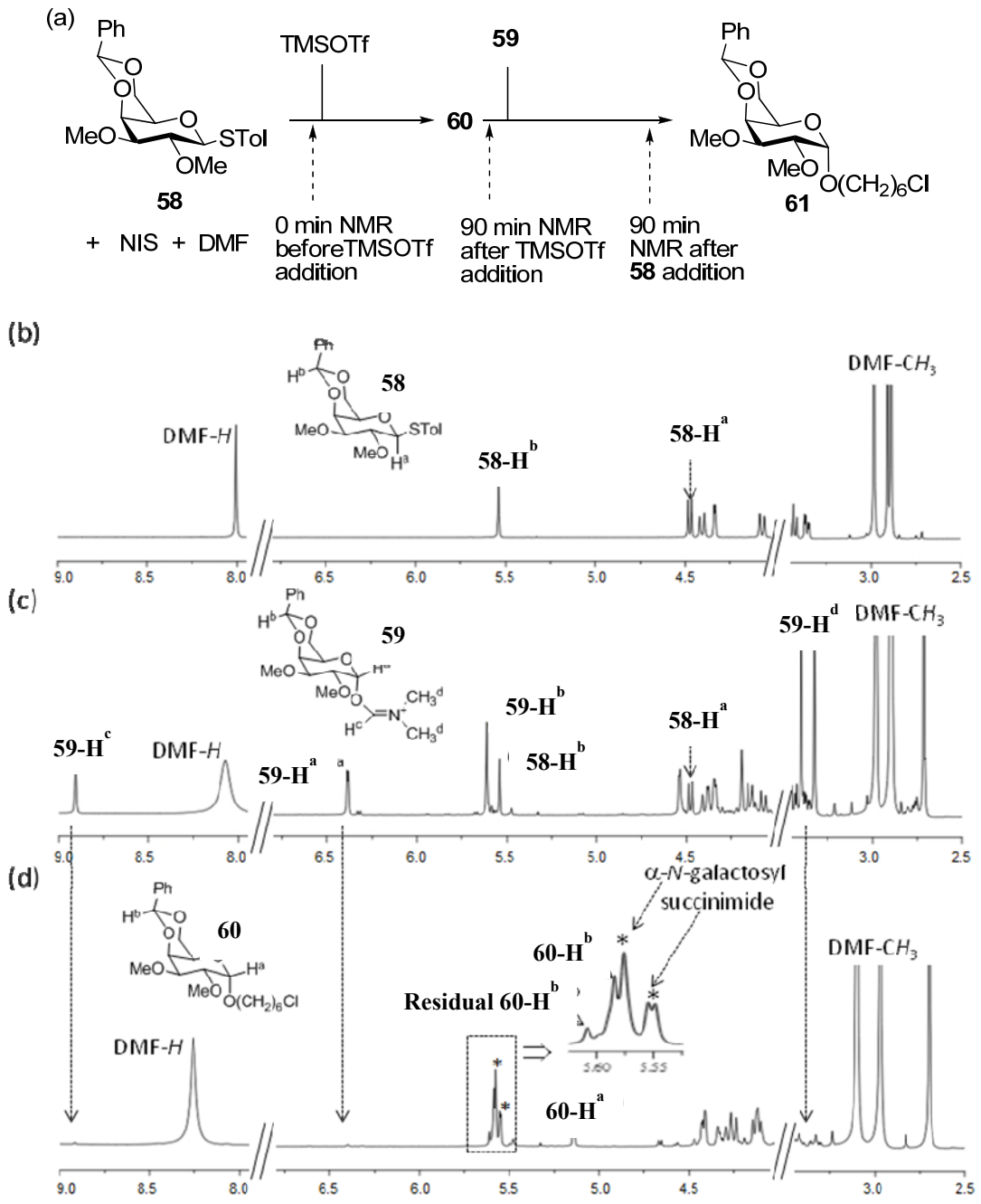
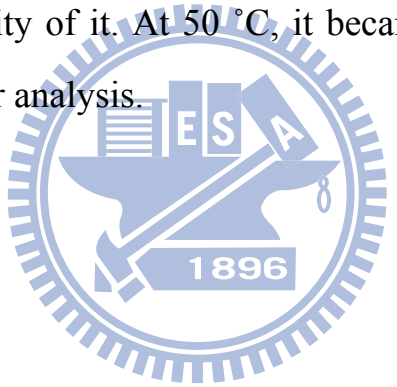


Figure 10. (a) Glycosylation of **58** with **59** following procedure B. (b) ^{1}H NMR spectrum taken just prior to TMSOTf addition (0 min). (c) ^{1}H NMR spectrum taken at 90 min following TMSOTf addition (90 min). (d) ^{1}H NMR spectrum taken at 90 min after addition of **59**.

3.4.3 Temperature profile using VT-NMR

Due to the life time of the β-glycosyl imidate is short via NMR analysis, we try to trap it under a lower reaction temperature. In addition, a variable NMR study may also study the stability of α-glycosyl imidate intermediate. Because of the melting point and boiling point of $CDCl_3$ and DMF, the range of temperature allowed in these experiments is ranged from −50 to 50 ˚C.

From −50 to 40 ˚C, there is no significant signal appeared. We didn't observe the signals of β-glycosyl imidate. Furthermore, among this temperature range the signals of α-glycosyl imidate still appeared, it indicate the high stability of it. At 50 ˚C, it became difficult to lock the NMR signals for further analysis.



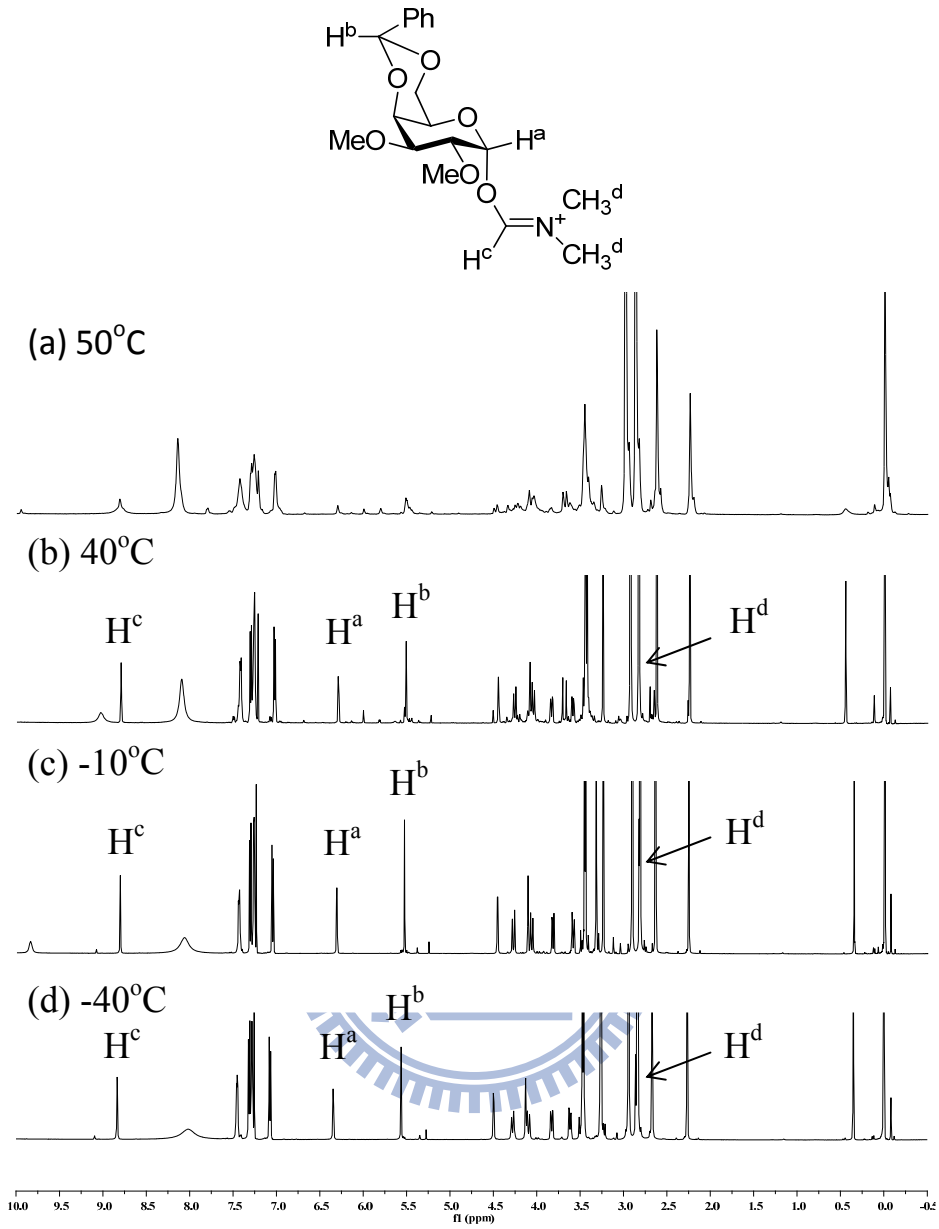


Figure 11. Temperature profile diagram by using VT-NMR from -50°C to 50°C

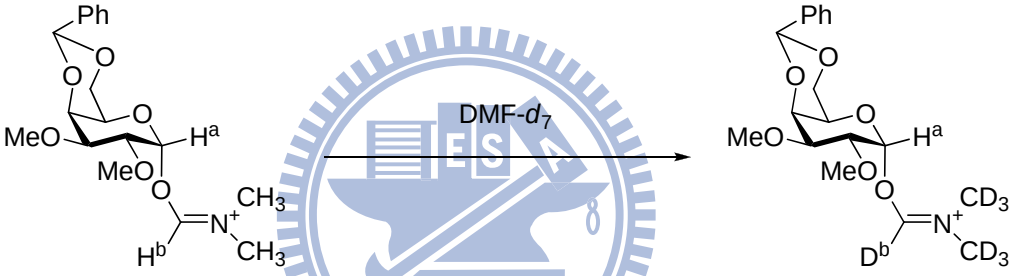
3.4.4 DMF-d_7 substitution experiment

In order to obtain more information about the reaction mechanism, we also did the DMF-d_7 exchange experiment. In the presence of DMF, the donor of thioglycoside was pre-activated in $CDCl_3$ at -10°C by NIS/TMSOTf promoters. After 30 minutes, we added DMF-d_7 and

examined the ^{1}H spectra at 0 and 30 minute.

From spectra, we observed the signals of glycosyl imidate decreased when the DMF-d_7 was added. This is estminated by comparing the ratio of anomeric proton (non-exchangeable) to the formamide proton (exchangneable), the ratios of H-1/formamide-H decreased from 1/1 to 1/0.2 (**Figure 12**). This information indicate that the α-glycosyl imidate have an equilibrium with DMF. Or β-glycosyl imidate react with DMF-d_7 first, then α-glycosyl imidate become β-glycosyl imidate by equilibrium.

It remains too early to exclude the possibility of other mechanism.[35] For elucidation, further experimental investigations are in progress.



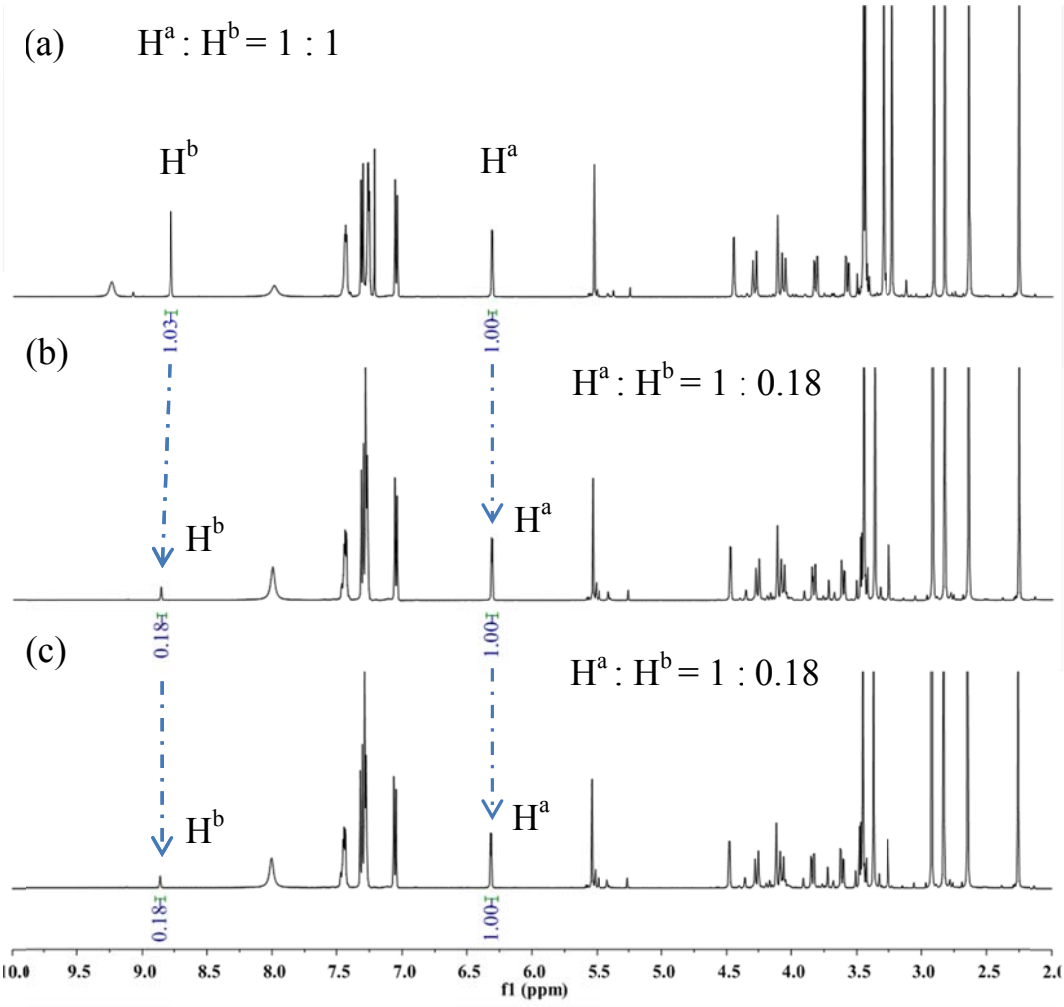
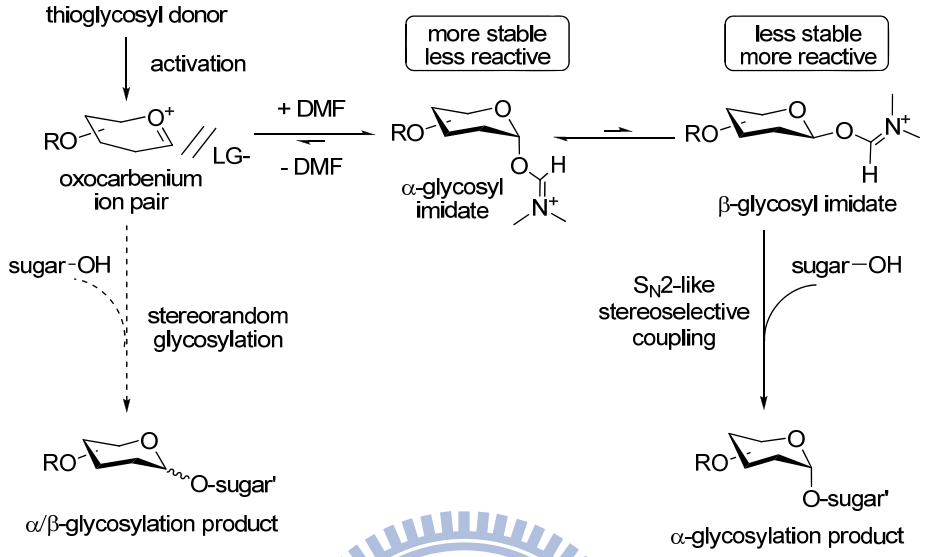


Figure 12. DMF-d_7 substitution experiment. (a) ^{1}H NMR spectrum taken just prior to DMF-d_7 addition. (b) ^{1}H NMR spectrum taken at 0 min after addition of DMF-d_7. (c) ^{1}H NMR spectrum taken at 30 min after addition of DMF-d_7.

3.5 Plausible mechanism of DMF-modulated pre-activated glycosylation



Scheme 13. Proposed mechanism of DMF modulating glycosylation.

On the basis of above experiment, we hypothesized that the activation of thioglycoside generates an oxocarbenium ion pair, which after trapped by a nucleophilic DMF, gives rise to an equilibrium mixture of α-/β-glycosyl imidates. Assuming that the β-imidate is more reactive than its α-counterpart; subsequent coupling of the β-imidate with an acceptor produces the desired α-anomer as a major product (**Scheme 13**). Since DMF plays as a modulating function in the reaction, we coined this new glycosylation strategy as a DMF-modulating glycosylation strategy.

4 Conclusions

In summary, a novel DMF-modulating glycosylation strategy is developed, which achieves excellent α-selectivity in glycosylation by simple addition of DMF. Further elaboration leads to the development of a practical pre-activated α-selective glycosylation strategy. Considering the availability of DMF, we anticipate that the synthesis concept mentioned above will find broad application in oligosaccharide synthesis. This work is accepted for publication in *Angewandte Chime* international edition 2011.

5 Experimental

5.1 General experiment procedure:

Reagent-grade chemicals were purchased from commercial vendors and used without further purification. Dichloromethane (CH_2Cl_2) was dried by Asianwong solvent purification system (AWS-1000). *N*,*N*-Dimethylformamide (DMF) was stocked with flame-dried molecular sieves (MS) under N_2. Progress of reactions was monitored by thin-layer chromatography on silica gel 60 F-254 plate and visualized under UV illumination and/or by staining with acidic ceric ammonium molybdate or *p*-anisaldehyde. HPLC analysis was performed over Mightysil column (Si-60 250-4.6) and eluted with EtOAc/hexane/CH_2Cl_2 mixture at a 0.8 mL min^{-1} flow rate by the gradient pump (L-2130) and UV detector (L-2400) from Hitachi. Silica gel (Geduran Si-60, 0.063-0.200 mm) for chromatography was obtained from Merck. NMR spectra were recorded at 300 MHz and 75 MHz spectrometers in Brüker console or 500 MHz and 125 MHz in Varian console as specified. Sonification was provided by standard bench top ultra-sonicator (Branson 2210R-MT). Real time NMR study of glycosylation of acceptor **59** with donor **58** was performed with 500 MHz in Varian console. The chemical shifts were calibrated against the residual proton signal and ^{13}C signals of deuterated chloroform. Coupling constants in Hz was calculated from chemical shifts of ^{1}H NMR spectra. Acceptors **3**, **10**, **11**, and **13** are commercially available, glycosyl donors **1**,[36] **2**,[36] **7**,[36] **8**,[37] **9**,[36] and glycosyl acceptors **12**,[38] **14**,[39] **15**,[39] **17**,[39] **30**,[39] **31**,[15] **32**,[17] **33**,[40] **35**,[15] **36**,[41] **37**,[42] and **40**[36] are prepared on the base of literature procedures.

5.2 General pre-activated DMF-modulating glycosylation procedure (procedure B).

Mixture of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene β-thiogalactopyranoside **2**[39] (166 mg, 0.3 mmol, 1.5 equiv) and flame-dried molecular sieve (AW300) was suspended in dried CH_2Cl_2 (4.0 mL) such that the final concentration of **2** was 75 mM. Then, DMF (93 μL, 1.2 mmol, 6.0 mol equiv) was added to the mixture. The resulting mixture was stirred at RT for 10 min and at -10 ˚C cooling bath for an additional 10 min. Subsequently, *N*-iodosuccinimide (NIS) (77 mg, 0.34 mmol, 1.5 equiv) and trimethylsilyltriflate (TMSOTf) (54 μL, 0.3 mmol, 1.5 equiv) were added, and the reaction progress was monitored by TLC with either EtOAc/hexane or EtOAc/hexane/CH_2Cl_2 mixture as the developing solvent. Upon completion of activation of glycosyl donor (**2**, **7**, **8**, **9** and **58**), acceptor (**3**, **10**−**17**) or thioglycoside acceptor (**30**−**40**) (1.0 equiv) was added to the reaction mixture. Exact amounts of glycosyl donor (**2**, **7**, **8**, and **9**), acceptor (**3**, **10**−**17**, and **30**−**40**), promoting reagents (NIS and TMSOTf), temperature for coupling reaction, time for coupling reaction and glycosylation yield were summarized in **Tables S1** and **S2**. Ultra-sound irradiation was applied to glycosylations with perbenzyl thioglucoside **9** (Ultra-sonication was generated from Branson 2210R-MT sonicator). The progress of glycosylation was monitored by TLC (judged by disappearance of the glycosyl imidate). Upon completion of reaction, satd. $NaHCO_3$ (ca 1 mL) and small lumps of $Na_2S_2O_{3(s)}$ (ca 0.5 g) were added to the mixture, followed by vigorous stirring until the

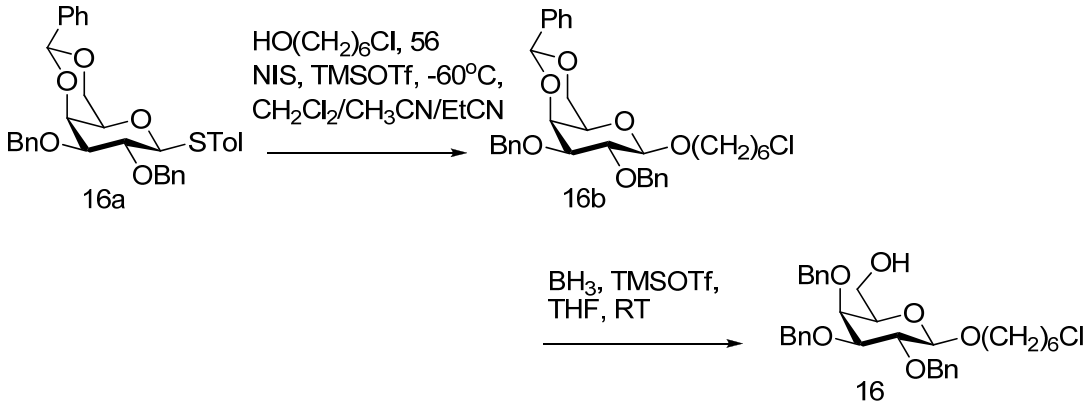
fading away of the deep red coloration of the reaction mixture. The resulting mixture was dried (over $MgSO_4$), filtered, and concentrated for flash chromatography purification over silica gel to furnish the glycosylation product (**5**, **18**−**29**, **41**−**55 and 61**). A small portion of the crude reaction mixture was eluted over a short pad of silica gel to obtain crude α/β mixture for HPLC analysis of α/β-anomer ratio.

5.3 Procedures and experimental data.

2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→6)-1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose 5.[43] Galactosyl acceptor **3** (52 mg, 0.2 mmol) was reacted with thiogalactosyl donor **2** (166.3 mg, 0.3 mmol) according to general pre-activated DMF-modulating glycosylation procedure. Compound **5** (125 mg, 87%) as a white glassy material was obtained by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 3/1/1). For α-anomer of **5**, $[\alpha]^{37.9}_D$= +29.1 (c= 1.2, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.53-7.24 (m, 2H, Ar*H*), 7.51-7.23 (m, 13H, Ar*H*), 5.50 (d, *J* = 6 Hz, 1H, H-1), 5.47 (s, 1H, benzylidene-C*H*), 5.05 (d, *J* = 3.3 Hz, 1H, H-1'), 4.82 (dd, *J* = 6, 12 Hz, 2H), 4.72 (dd, *J* = 6, 12 Hz, 2H), 4.58 (dd, *J* = 3, 7 Hz, 1H), 4.31-4.27 (m, 2H), 4.20-4.18 (m, 2H), 4.10-3.69 (m, 4H), 3.78-3.69 (m, 3H), 1.52 (s, 3H, C*H*$_3$), 1.44 (s, 3H, C*H*$_3$), 1.26 (s, 3H, C*H*$_3$), 1.24 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 138.6, 138.5, 137.7, 128.7, 128.1, 127.9, 127.6, 127.5, 127.40, 127.36, 126.2, 109.1 (isopropylidene-*C*), 108.4 (isopropylidene-*C*), 100.9 (benzylidene-*C*), 98.0 (C-1), 96.1 (C-1'), 75.7, 75.3, 74.5, 73.0, 71.8, 70.9, 70.4, 70.3, 69.3, 66.8, 66.4, 62.4, 25.9, 25.8,

24.8, 24.4.

6-chlorohexyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside 16.

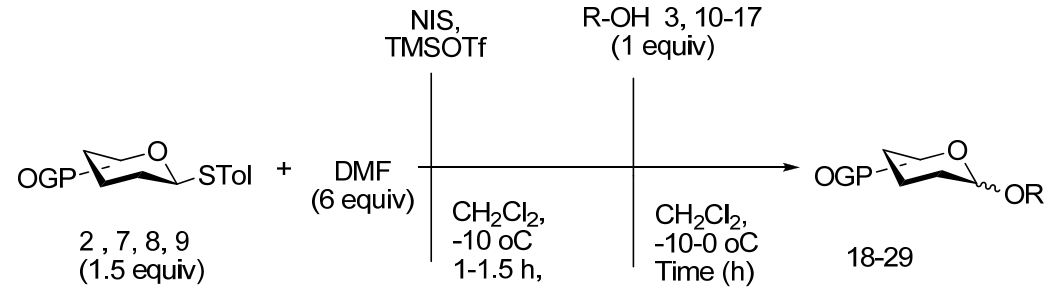


Scheme 14. Preperation of 6-chlorohexyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside 16

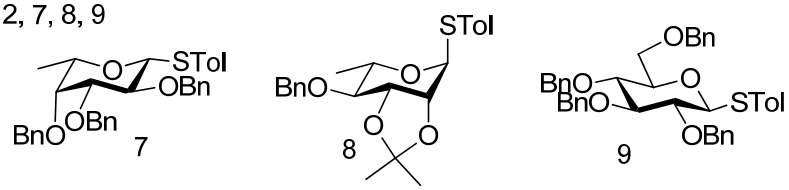
Known **16a** (1 g, 1.8 mml),[39] 6-chlorohexanol **59** (0.35 mL, 2.7 mmol) and activated molecular sieve (10 g) were suspended in 1/2/1 $CH_2Cl_2/CH_3CN/EtCN$ solvent mixture (150 mL) and stirred at 60 ˚C for 30 min. NIS (0.44 g, 1.95 mmol) and TMSOTf (68 μL, 0.38 mmol) were added and the mixture was stirred for additional 180 min at 60 ˚C under N_2 before quenched with TEA (ca 0.2 mL). Satd. $NaHCO_3$ (1 mL) and few pieces of solid $Na_2S_2O_3$ were added, followed by vigorous stirring at RT. The mixture was filtered over celite and the filtrate was concentrated for column chromatography (Elution: Hexane/CH_2Cl_2/EtOAc 3/1/1) to give target galactoside **16b** (0.52 g, 50%). The galactoside **16b** (0.52 g, 50%) was then treated with 1 M BH_3.THF (3.72 mL, 3.7 mmol) and TMSOTf (25 μL, 0.14 mmol), followed by stirring at RT for 2 h. The reaction was quenched with triethylamine (TEA) and methanol (MeOH) mixture. The resulting

mixture was concentrated for column chromatography purification (Elution: Hexane/CH_2Cl_2/EtOAc 3/1/1 to 2/1/1) to give target acceptor **16** as an oily substance (0.24 g, 45%). For compound **16**, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.23 (m, 15 H, Ar*H*), 4.97-4.91 (m, 2H), 4.82-4.71 (m, 3H), 4.65 (d, J = 12 Hz, 1H), 4.35 (d, J = 7.5 Hz, 1H, H-1), 4.00-3.92 (m, 1H), 3.89-3.75 (m, 3H), 3.72-3.47 (m, 5H), 3.36 (t, J = 6 Hz, 1H), 1.76-1.63 (m, 4H, CH_2 × 2), 1.25 (s, CH_2 × 2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.4, 138.2, 128.6, 128.4, 128.2, 127.9, 127.88, 127.5, 127.62, 127.55, 126.50, 104.0 (C-1), 82.2, 79.6, 75.1, 74.5, 74.1, 73.3, 72.9, 69.8, 61.9 (*C*H_2O) , 45.0 (*C*H_2Cl), 32.4, 29.5, 26.6, 25.4.

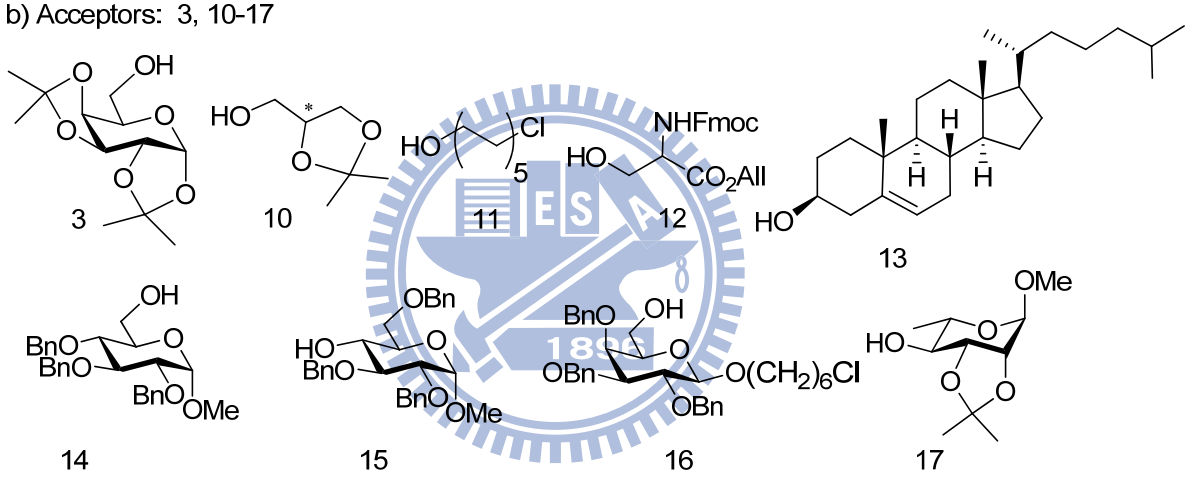
Table 7. Experimental details for glycosylation of acceptor **3**, **10**−**17** with donors **2**, **7**, **8** and **9**.



a) Donors: 2, 7, 8, 9



b) Acceptors: 3, 10-17



Entry	Donor (mg, mmol)	Acceptor (mg, mmol)	Time (h)	*T* (°C)	Glycosylation product	
					Yield (mg, %)	α/β[a]
1	**2** (166, 0.3)	**10** (26, 0.2)	2	-10	**18** (92.5, 83)	12/1
2	**2** (166, 0.3)	**11** (38, 0.2)	2	-10	**19** (95.6, 76)	8/1
3	**2** (166, 0.3)	**12** (74, 0.2)	6	-10	**20** (71.7, 45)	19/1
4	**2** (166, 0.3)	**13** (81, 0.2)	2	0	**21** (128, 79)	8/1
5	**2** (166, 0.3)	**14** (93, 0.2)	5.5	-10	**22** (129, 75)	12/1

6	**2** (166, 0.3)	**15** (93, 0.2)	6	0	**23** (141, 80)	49/1
7	**2** (166, 0.3)	**16** (71, 0.2)	2	-10	**24** (144, 82)	12/1
8	**2** (166, 0.3)	**17** (43, 0.2)	4	0	**25** (77, 60)	25/1
9	**7** (190, 0.36)	**14** (111, 0.24)	4.5	-10	**26** (159, 75)	5/1
10	**8** (144, 0.36)	**17** (52, 0.24)	4	-10	**27** (76, 70)	49/1
11	**9** (194, 0.3)	**15** (93, 0.2)	6	0	**28** (144, 76)	49/1[b]
12	**9** (194, 0.3)	**17** (44, 0.2)	5	0	**29** (111, 75)	9/1[b]

[a]Ratios were determined by Hitachi HPLC system (Mightysil column (Si-60 250-4.6); Elution: EtOAc/hexane/CH_2Cl_2 mixture at 0.8 mL min^{-1} flow rate; HPLC pump (L-2130) and UV detector (L-2400) were employed. [b]Ultra-sonification was applied.

1,2-isopropylidene-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galacto-pyranosyl)-*rac*-glycerol 18. Preparation of **18** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S1, entry 1). Compound **18** as a white glassy material was obtained by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 5/1/1). For α-anomer of **18**, R_f 0.3 (Hexane/EtOAc/CH_2Cl_2 2/1/1); $[\alpha]^{37.9}_D$= +18.5 (c= 0.44, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.53 (m, 2H, Ar*H*), 7.42-7.25 (m, 13H, Ar*H*), 5.48 (s, 1H, benzylidene-C*H*), 5.08 (d, J = 3.6 Hz, 1H, H-1), 4.88-4.71 (m, 3H), 4.66 (dd, J = 2.7, 12 Hz, 1H), 4.37-4.28 (m, 1H), 4.22 (d, J = 3Hz, 1H), 4.18 (d, J = 2.4 Hz, 1H), 4.09-3.95 (m, 4H), 3.78-3.62 (m, 3H), 3.59-3.43 (m, 1H), 1.39 (d, J = 3.9 Hz, 3H, CH_3), 1.35 (d, J = 1.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 138.72, 138.65,

137.8, 128.8, 128.28, 128.26, 128.1, 127.9, 127.8, 127.6, 127.52, 127.48, 126.3, 109.4 (isopropylidene-*C*), 101.0 (benzylidene-*C*H), 98.7 (C-1), 75.9, 75.7, 75.6, 75.53, 74.7, 74.6, 74.4, 73.6, 73.4, 72.1, 72.0, 69.6, 69.4, 69.3, 68.7, 66.8, 66.6, 62.7, 62.6, 26.9 (CH_3), 26.7 (CH_3), 25.5 (CH_3), 25.4 (CH_3); HRMS (MALDI-TOF): calcd for $C_{33}H_{38}O_8Na$ $[M + Na]^+$ requires 585.2464, found *m/z* 585.2425.

10-chlorodecanyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galacto-pyranoside 19. Preparation of **19** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S1, entry 2). Compound **19** as a white glassy material was obtained by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 7/0.5/2). For α-anomer of **19**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 7/0.5/2); $[\alpha]^{37.9}_D$= +15.4 (c= 0.9, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.50 (m, 2H, Ar*H*), 7.42-7.25 (m, 13H, Ar*H*), 5.47 (s, 1H, benzylidene-*H*), 4.90 (d, *J* = 3.3 Hz, 1H, H-1), 4.86 (d, *J* = 10.2 Hz, 1H), 4.82 (d, *J* = 10.2 Hz, 1H), 4.75-4.64. (m, 2H), 4.20 (dd, *J* = 1.2, 12.3 Hz, 1H), 4.19 (d, *J* = 3 Hz, 1H), 4.08-3.97 (m, 3H), 3.66-3.58 (m, 2H), 3.5 (t, *J* = 6.6 Hz, 2H, C*H*$_2$), 3.44(m, 1H), 1.8-1.7 (m, 2H, C*H*$_2$), 1.6-1.5 (m, 2H, C*H*$_2$), 1.44-1.37 (m, 2H, C*H*$_2$), 1.28 (broad, 10H, C*H*$_2$ × 5); ^{13}C NMR (75 MHz, $CDCl_3$): ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.8, 137.8, 128.8, 128.2, 128.0, 127.8, 127.57, 127.52, 127.4, 126.33, 101.1 (benzylidene-*C*H), 98.0 (C-1), 76.1, 75.8, 74.8, 73.4, 72.1, 69.4, 68.4, 62.6 (CH_2O), 45.1 (CH_2Cl), 32.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 26.8 (CH_2), 26.1 (CH_2). For β-anomer of **19**, R_f 0.3 (Hexane/EtOAc/CH_2Cl_2 7/0.5/2); ^{1}H NMR (300 MHz, $CDCl_3$): δ

7.58-7.55 (m, 2H, Ar*H*), 7.40-7.25 (m, 13H, Ar*H*), 5.5 (s, 1H, benzylidene-*H*), 4.95 (d, *J* = 11.1 Hz, 1H), 4.82-4.77 (m, 3H), 4.38 (d, *J* = 9.6 Hz, 1H, H-1), 4.36 (d, *J* = 12.3 Hz, 1H), 4.11 (d, *J* = 3.6 Hz, 1H), 4.03-3.95 (m, 2H), 3.84 (dd, *J* = 7.8, 9.6, 1H), 3.58-3.46 (m, 4H), 3.3 (s, 1H), 1.76 (m, 2H, CH_2), 1.7-1.6 (m, 2H, CH_2), 1.47-1.35 (m, 4H, CH_2), 1.28 (m, 8H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 138.4, 137.8, 128.8, 128.3, 128.2, 128.04, 127.98, 127.7, 127.6, 127.45, 126.46, 103.6 (benzylidene-*C*H), 101.3 (C-1), 79.2, 78.4, 75.2, 74.0, 72.0, 69.9, 69.2, 66.3 (*C*H_2O), 45.1 (*C*H_2Cl), 32.6 (*C*H_2), 29.7 (*C*H_2), 29.42 (*C*H_2), 29.39 (*C*H_2), 29.36 (*C*H_2), 28.8 (*C*H_2), 26.8 (*C*H_2), 26.1 (*C*H_2); HRMS (FAB): calcd for $C_{37}H_{47}ClO_6Na$ $[M + Na]^+$ requires 645.2959, found *m/z* 645.2947.

2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl *N*-(fluoren-9-ylmethoxycarbonyl)-L-serine allyl ester 20. Preparation of **20** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S1, entry 3). Compound **20** as a white powder was obtained by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 6/1/2). For α-anomer of **20**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 4/1/1); $[\alpha]^{37.9}_D$= +64.8 (c= 0.36, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.59 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.54-7.52 (m, 2H, Ar*H*) 7.42-7.25 (m, 19H, Ar*H*), 6.14 (d, *J* = 8.4 Hz, 1H, N*H*), 5.85 (m, 1H, =C*H*), 5.47 (s, 1H, benzylidene-C*H*), 5.29 (d, *J* = 17.4 Hz, 1H, =C*H*), 5.19 (d, *J* = 10.5 Hz, 1H, =C*H*), 4.86-4.71 (m, 4H), 4.65-4.58 (m, 2H), 4.55-4.32 (m, 4H), 4.22-4.18 (m, 4H), 4.08 (dd, *J* = 3.6, 10.2 Hz, 1H), 3.94-3.90 (m, 2H),

3.84 (dd, J = 2.7, 11.1 Hz, 1H), 3.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (*C*=O), 156.0 (*C*=O), 143.7, 141.26, 141.23, 138.6, 138.5, 137.7, 131.4, 128.8, 128.3, 128.3, 128.1, 127.8, 127.7, 127.6, 127.09, 127.04, 126.2, 125.1, 125.0, 120.0 (=*C*H), 118.7 (=*C*H), 100.9 (benzylidene-*C*H), 100.3 (C-1), 75.6, 75.3, 74.3, 73.6, 72.0, 70.6, 69.2, 67.2, 66.2, 63.3, 54.7, 47.0; HRMS (MALDI-TOF): calcd for $C_{48}H_{49}NO_{10}Na$ $[M + Na]^+$ requires 820.3098, found *m/z* 820.3092.

Cholesteryl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranoside 21. Preparation of **21** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S1, entry 4). Compound **21** as a white powder was obtained by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 16/0.3/4). For α-anomer of **21**, R_f 0.5 (Hexane/EtOAc/CH_2Cl_2 8/1/1); $[\alpha]^{37.9}_D$= +75.2 (c= 0.79, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.50 (m, 2H, Ar*H*), 7.42-7.25 (m, 13H, Ar*H*), 5.47 (s, 1H, benzylidene-C*H*), 5.32 (d, J = 5.1 Hz, 1H, =C*H*), 5.00 (d, J = 3.3 Hz, 1H, H-1), 4.86 (d, J = 5.1 Hz, 1H), 4.82 (d, J = 5.4 Hz, 1H), 4.70-4.60 (m, 2H), 4.22-4.19 (m, 2H), 4.10-3.90 (m, 3H), 3.7 (s, 1H), 3.50 (m, 1H), 2.41 (bt, J = 12. 5 Hz, 1H), 2.25 (dt, J = 4.5, 13.2 Hz, 1H), 2.0-1.8 (m, 5H), 1.56-0.85 (m, 33H), 0.68 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 139.0, 138.7, 137.9, 128.8, 128.25, 128.22, 128.0, 127.9, 127.5, 127.4, 126.3, 121.7, 101.0 (benzylidene-*C*H), 95.9 (C-1), 76.9, 76.3, 75.5, 74.8, 73.4, 72.1, 69.5, 62.6, 56.7, 56.1, 50.0, 42.3, 39.9, 39.7, 39.5, 37.0, 36.8, 36.2, 35.8,31.89, 31.85, 28.2, 27.0, 27.5 24.3, 23.8, 22.8, 22.5, 21.0, 19.4, 18.7, 11.8; HRMS (FAB): calcd for

$C_{54}H_{72}O_6Na$ $[M + Na]^+$ requires 839.5227, found *m/z* 839.5236.

Methyl

2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 22. Preparation of **22** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S1, entry 5). Compound **22** was obtained as a white amorphous solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 5.5/1/1.5). For α-anomer of **22**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 4/1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.48 (m, 2H, Ar*H*), 7.36-7.17 (m, 28H, Ar*H*), 5.43 (s, 1H, benzylidene-C*H*), 5.04 (d, J = 3.3 Hz, 1H), 4.97 (d, J = 11.1 Hz, 1H), 4.88 (d, J = 11.4 Hz, 1H), 4.81 (d, J = 2.7 Hz, 1H), 4.77-4.73 (m, 3H), 4.68-4.65 (m, 2H), 4.59-4.50 (m, 3H), 4.1-4.0 (m, 3H), 3.97-3.90 (m, 2H), 3.85-3.67 (m, 4H), 3.57 (t, J = 9.6 Hz, 1H), 3.46-3.41 (m, 2H), 3.3 (s, 3H, OC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.77, 138.73, 138.6, 138.5 138.1, 137.8, 128.8, 128.34, 128.28, 128.21, 128.18, 128.0, 127.9, 127.77, 127.69, 127.51, 127.46, 127.41, 127.3, 126.29, 101.0 (benzylidene-*C*H), 98.3 (C-1), 97.8 (C-1'), 82.0, 80.1, 77.9, 75.61, 75.57, 74.86, 74.75, 73.27, 72.78, 71.8, 70.1, 69.3, 66.4, 62.5, 54.9; HRMS (FAB): calcd for $C_{55}H_{58}O_{11}Na$ $[M + Na]^+$ requires 917.3877, found *m/z* 917.3892.

Methyl

2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→4)-2,3,6-tr

i-*O*-benzyl-α-D-glucopyranoside 23. Preparation of **23** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S1, entry 6). Compound **23** was obtained as a white amorphous solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 6/1/1.5). For α-anomer of **23**, R_f 0.35 (Hexane/EtOAc/CH_2Cl_2 4/1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.47 (m, 2H, Ar*H*), 7.38-7.20 (m, 28H, Ar*H*), 5.80 (d, J = 3.3 Hz, 1H, H-1), 5.37 (s, 1H, benzylidene-C*H*), 4.96 (d, J = 11.7 Hz, 1H), 4.84-4.79 (m, 2H), 4.70-4.66 (m, 3H), 4.57 (d, J = 3.6 Hz, 1H), 4.55-4.50 (m, 4H), 4.10-3.83 (m, 7H), 3.71 (dd, J = 3.9, 11.1 Hz, 1H), 3.62 (d, J = 5.4 Hz, 1H), 3.59-3.53 (m, 2H), 3.45 (s, 1H), 3.39 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 138.7, 138.3, 138.0, 137.9, 137.79, 128.75, 128.3, 128.3, 128.15, 128.11, 128.0, 127.8, 127.7, 127.6, 127.53, 127.49, 127.3, 127.0, 126.6, 126.2, 100.7 (benzylidene-*C*H), 97.8 (C-1), 97.6 (C-1'), 81.8, 80.3, 76.3, 74.8, 74.3, 74.2, 74.0, 73.4, 72.3, 71.7, 69.5, 69.3, 69.1, 62.9, 55.1; HRMS (FAB): calcd for $C_{55}H_{58}O_{11}Na$ $[M + Na]^+$ requires 917.3877, found *m/z* 917.3869.

6-chlorohexyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-galactopyranoside 24. Preparation of **24** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S1, entry 7). Compound **24** was obtained as a white glassy solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 7/1/2). For α-anomer of **24**, R_f 0.35 (Hexane/EtOAc/CH_2Cl_2 5/1/1); $[\alpha]^{37.9}_D$= +73.3 (c= 1, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.50 (m, 2H, Ar*H*),

7.40-7.20 (m, 28H, Ar*H*), 5.47 (s, 1H, benzylidene-C*H*), 4.90-4.80 (m, 6H), 4.76-4.66 (m, 3H), 4.64 (d, *J* = 4.5 Hz, 1H), 4.60 (d, *J* = 4.2 Hz, 1H), 4.31 (d, *J* = 7.5 Hz, 1H, H-1), 4.23-4.16 (m, 2H), 4.1-3.9 (m, 3H), 3.87-3.75 (m, 4H), 3.6- 3.5 (m, 3H), 3.5-3.4 (m, 4H), 1.78-1.69 (m, 2H, CH_2), 1.66-1.55 (m, 2H, CH_2), 1.50-1.33 (m, 4, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 138.46, 138.39, 138.32, 137.8, 128.8, 128.3, 128.2, 128.1, 128.0, 127.96, 127.86, 127.6, 127.5, 126.3, 103.8 (C-1), 101.0 (benzylidene-*C*H), 98.2 (C-1'), 82.1, 79.4, 75.9, 75.2, 75.1, 74.5, 74.2, 73.8, 73.6, 73.15, 73.14, 71.7, 69.50, 69.45 67.3, 62.5 (O*C*H_2), 45.0 (*C*H_2Cl), 32.4 (*C*H_2), 29.5 (*C*H_2), 26.6 (*C*H_2), 25.5 (*C*H_2); HRMS (ESI): calcd for $C_{60}H_{67}ClO_{11}Na$ $[M + Na]^+$ requires 1021.4270, found *m/z* 1021.4264.

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→4)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside 25. Preparation of **25** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S1, entry 8). Compound **25** was obtained as a white amorphous substance by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 8/1/2). For α-anomer of **25**, R_f 0.25 (Hexane/EtOAc/CH_2Cl_2 5/1/1); $[\alpha]^{37.9}_D$= +62.8 (c= 0.79, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H, Ar*H*), 7.42-7.25 (m, 13H, Ar*H*), 5.48 (s, 1H, benzylidene-C*H*), 5.1 (d, *J* = 3.6 Hz, 1H, H-1'), 4.87 (d, *J* = 12 Hz, 1H), 4.85 (s, 1H, H-1), 4.76-4.69 (m, 3H), 4.23 (d, *J* = 3.3 Hz, 1H), 4.19 (dd, *J* = 1.2, 12.3 Hz, 1H), 4.14-3.99 (m, 6H), 3.7 (m, 1H), 3.4 (m, 1H), 3.3 (s,

3H, OCH_3), 1.5 (s, 3H, CH_3), 1.3 (m, 6H, CH_3 × 2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.3, 137.9, 128.8, 128.3, 128.1, 127.7, 127.6, 126.3, 109.0 (isopropylidene-*C*), 101.0 (benzylidene-*C*H), 99.0 (C-1'), 97.7 (C-1), 79.5, 76.2, 75.3, 74.6, 74.4, 71.8, 69.4, 65.1, 62.5, 54.6, 28.1 (*C*H_3), 26.4 (*C*H_3), 17.2 (*C*H_3); HRMS (FAB): calcd for $C_{37}H_{44}O_{10}Na$ $[M + Na]^+$ requires 671.2832, found *m/z* 617.2842.

Methyl 2,3,4-tri-*O*-benzyl-L-fucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 26. Preparation of **26** was referred to the general pre-activated braking glycosylation and the exact amounts of reagents used were given (Table S1, entry 9). Compound **26** was obtained as a white glassy powder by column chromatography purification (Elution: Hexane/EtOAc 4.5/1). For α-anomer of **26**, R_f 0.4 (Hexane/EtOAc 3/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.15 (m, 30H, Ar*H*), 4.99 (d, *J* = 4.5 Hz, 1H), 4.95 (d, *J* = 3.6 Hz, 1H), 4.89 (d, *J* = 3.3 Hz, 1H), 4.85-4.62 (m, 10H), 4.58 (d, *J* = 3.3 Hz, 1H), 4.06-3.94 (m, 3H), 3.89 (q, *J* = 6.6, 12.9 Hz, 1H), 3.82 (d, *J* = 10.8 Hz, 1H), 3.75 (dd, *J* = 3.9, 10.2 Hz, 1H), 3.68-3.56 (m, 3H), 3.51 (dd, *J* = 3.6, 9.6 Hz, 1H), 3.31 (s, 3H, OCH_3), 1.10 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.65, 138.5, 138.3, 138.2, 128.35, 128.33, 128.30, 128.27, 128.10, 128.09, 127.95, 127.92, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 97.9 (C-1', C-1), 82.0, 79.9, 79.1, 77.6, 76.1, 75.7, 74.9, 74.7, 73.2, 73.1, 72.8, 70.0, 66.3, 66.2, 55.0, 16.5; HRMS (MALDI-TOF): calcd for $C_{55}H_{60}O_{10}Na$ $[M + Na]^+$ requires 903.40842, found *m/z* 903.4140.

Methyl 2,3-*O*-isopropylidene-4-*O*-benzyl-L-rhamnopyranosyl-α-(1→4)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside 27. Preparation of **27** was referred to the general pre-activated DMF-modulating glycosylation and the exact amounts of reagents used were given (Table S1, entry 10). Compound **27** was obtained as a yellowish glassy solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 0.5/5/1). For α-anomer of **27**, R_f 0.45 (Hexane/EtOAc/CH_2Cl_2 7/1/2); $[\alpha]^{37.9}_D$= -133.2 (c= 0.52, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H, Ar*H*), 5.59 (s, 1H, H-1'), 4.9 (d, J = 11.7 Hz, 1H), 4.86 (s, 1H, H-1), 4.64 (d, J = 11.4 Hz, 1H), 4.25-4.14 (m, 3H), 4.08 (d, J = 5.4 Hz, 1H), 3.74-3.54 (m, 3H), 3.36 (d, J = 0.6 Hz, 3H, OCH_3), 3.24 (dd, J = 7.5, 9.9 Hz, 1H), 1.54 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.27 (m, 6H, CH_3 × 2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 128.3, 128.1, 127.7, 109.4, 109.0, 97.9 (C-1), 95.5 (C-1'), 80.8, 78.5, 78.5, 76.41, 76.35, 76.0, 73.2, 64.9, 63.8, 54.8, 28.0, 27.9, 26.3, 17.9, 17.5; HRMS (MALDI-TOF): calcd for $C_{26}H_{38}O_9Na$ $[M + Na]^+$ requires 517.24135, found *m/z* 517.2429.

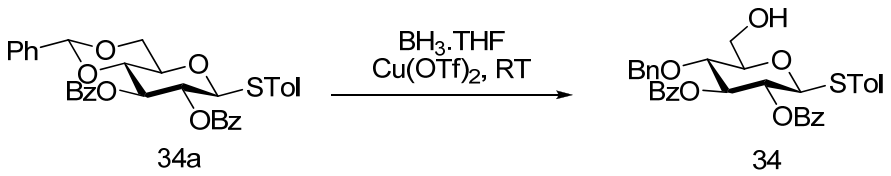
Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside 28.[44] Preparation of **28** was referred to the general pre-activated DMF-modulating glycosylation and the exact amounts of reagents used were given (Table S1, entry 11). Compound **28** was obtained as a yellowish amorphous solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 7/1/1). For α-anomer of **28**, R_f 0.3 (Hexane/EtOAc/CH_2Cl_2 5/1/1); ^{1}H NMR (300 MHz, $CDCl_3$):

7.28-7.19 (m, 33H, Ar*H*), 7.10-7.07 (m, 2H, Ar*H*), 5.72 (d, *J* = 3.6 Hz, 1H), 5.05 (d, *J* = 11.4 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.82-4.76 (m, 3H), 4.07 (d, *J* = 12.3 Hz, 1H), 4.62-4.48 (m, 7H), 4.40 (d, *J* = 10.8 Hz, 1H), 4.25 (d, *J* = 12.3 Hz, 1H), 4.13-4.03 (m, 2H), 3.94-3.80 (m, 3H), 3.72-3.58 (m, 4H), 3.35-3.46 (m, 2H), 3.37 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 138.6, 138.4, 138.0, 137.8, 137.76, 128.4, 128.28, 128.24, 128.19, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.47, 127.3, 127.1, 127.06, 126.7, 97.7 (C-1'), 96.5 (C-1), 82.0, 80.1, 79.3, 75.5, 74.8, 74.4, 73.4, 73.2, 73.0, 71.9, 70.8, 69.4, 68.8, 67.9, 55.1.[S12]

Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside 29. Preparation of **29** was referred to the general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S1, entry 12). Compound **29** was obtained as a milky white glassy substance by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 5/1/1). For α-anomer of **29**, R_f 0.3 (Hexane/EtOAc/CH_2Cl_2 5/1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.23 (m, 18H, Ar*H*), 7.18-7.15 (m, 2H, Ar*H*), 4.98-4.95 (m, 2H), 4.88-4.78 (m, 4H), 4.73-4.60 (m, 2H), 4.52 (d, *J* = 7.5 Hz, 1H), 4.48 (d, *J* = 9 Hz, 1H), 4.12-4.04 (m, 3H), 3.98 (t, *J* = 9.3 Hz, 1H), 3.82-3.70 (m, 3H), 3.65-3.58 (m, 2H), 3.34 (q, *J* = 10.8, 17.1 Hz, 1H), 3.33 (s, 3H, OCH_3), 1.43 (s, 3H, CH_3), 1.31 (d, *J* = 6.3 Hz, 3H, CH_3), 1.25 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.3, 137.9, 137.8, 128.39, 128.38, 128.34, 128.30, 128.24, 127.92, 127.89, 127.8, 127.65, 127.63, 127.5, 108.9 (isopropylidene-*C*), 98.3 (J_{CH} = 168 Hz,

C-1'), 97.7 (J_{CH} = 166 Hz, C-1), 82.2, 80.7, 79.7, 77.74, 77.75, 75.8, 75.5, 75.1, 74.2, 73.5, 70.2 67.9, 64.7, 54.6, 28.1, 26.3, 17.4; HRMS (MALDI-TOF): calcd for $C_{44}H_{52}O_{10}Na$ $[M + Na]^+$ requires 763.34527, found *m/z* 763.3478.

***p*-tolyl 4-*O*-benzyl-2,3-di-*O*-benzoyl-thio-β-D-glucopyranoside 34**.

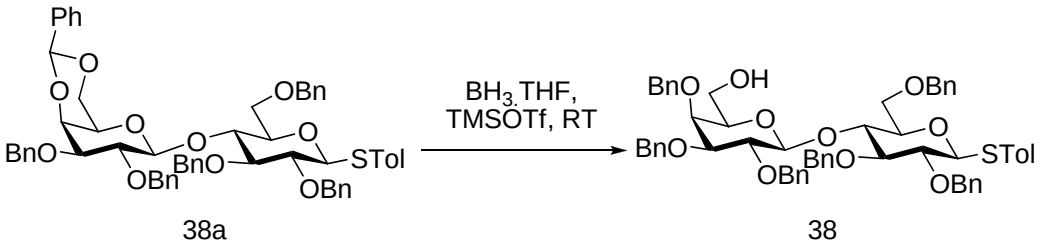


Scheme 15. Preperation of *p*-tolyl 4-*O*-benzyl-2,3-di-*O*-benzoyl-thio-β-D-glucopyranoside 34.[45]

Thioglucopyranoside **34a**[17] (2 g, 3.43 mmol) was then treated with BH_3 (1 M in THF) (17 mL) and $Cu(OTf)_2$ (186 mg, 0.51 mmol) at RT under N_2. Upon completion of reductive ring opening, the reaction mixture was cooled to 0 ˚C and neutralized with NEt_3, excess BH_3 was quenched with MeOH at 0 ˚C. The resulting mixture was concentrated and purified by column chromatography (Elution: hexane/EtOAc/CH_2Cl_2 6/1/1 to 2/1/1) to afford thioglucopyranoside **34** as a white amorphous solid (1.72 g, 86% from **34a**). For **34**, $[\alpha]^{37.9}_D$= +56.5 (c= 0.48, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00-7.93 (m, 4H, Ar*H*), 7.57-7.50 (m, 2H, Ar*H*), 7.43-7.36 (m, 6H, Ar*H*), 7.21-7.16 (m, 7H, Ar*H*), 5.78 (t, *J* = 10 Hz, 1H), 5.38 (t, *J* = 10 Hz, 1H), 4.94 (d, *J* = 10 Hz, 1H, H-1), 4.62 (s, 2H, C*H*$_2$), 4.02 (d, *J* = 18 Hz, 1H), 3.94 (t, *J* = 10 Hz, 1H), 3.86-3.82 (m, 2H), 3.65 (m, 1H), 2.36 (s, 3H, C*H*$_3$), 2.19 (bs, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (*C*=O), 165.3 (*C*=O), 138.5, 137.0, 133.3, 133.2, 133.1, 129.8, 129.7, 129.6, 129.3, 129.2, 128.3, 128.15, 128.11, 127.9, 86.3

(C-1), 79.5, 75,2, 74.8, 70.8, 61.6, 21.1 (CH_3); HRMS (ESI): calcd for $C_{66}H_{70}NaO_{12}S$ $[M + Na]^+$ 1109.4480, found *m/z* 1109.4454.

***p*-tolyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-thio-β-D-glucopyranoside 38**.



38a 38

Scheme 16. Preparation of *p*-tolyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-thio-β-D-glucopyranoside 38.

Known **38a**[39] (1.5 g, 1.52 mmol) was treated with 1 M BH_3.THF (6.1 mL, 6.1 mmol) under N_2, followed by the addition of TMSOTf (41 μL, 0.23 mmol). The mixture was stirred at RT for 2 h before quenching with triethylamine (TEA) (0.1 mL) and MeOH (2 mL) at 0 ˚C. The reaction crude was then concentrated for column chromatography (Elution: Hexane/EtOAc/CH_2Cl_2 1/3/1) to furnish **38** as a glassy material (0.94 g, 63%). For **38**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 2/1/1); $[\alpha]^{37.9}_D$= -0.85 (c= 3.32, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J = 8.1 Hz, 2H, Ar*H*), 7.41-7.25 (m, 27H, Ar*H*), 7.19-7.12 (m, 4H, Ar*H*), 7.00 (d, J = 7.8 Hz, 2H, Ar*H*), 5.08 (d, J = 10.5 Hz, 1H, Ar*H*), 4.95 (d, J = 11.7 Hz, 1H), 4.84-4.68 (m, 7H), 4.61-4.50 (m, 3H), 4.42-4.38 (m, 2H), 3.92 (t, J = 9.6Hz, 1H), 3.84-3.75 (m, 3H), 3.61 (t, J = 8.7 Hz, 1H), 3.56-3.50 (m,

1H), 3.44-3.31 (m, 4H), 3.17 (dd, J = 5.4, 6.6Hz, 1H), 2.26 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.98, 138.96, 138.9, 138.8, 138.6, 138.0, 133.0, 130.1, 130.0, 129.3, 128.8, 128.72, 128.66, 128.64, 128.61, 128.59, 128.51, 128.48, 128.4, 128.2, 128.1, 128.00, 127.98, 127.9, 127.83, 127.78, 103.2 (C-1'), 88.1 (C-1), 85.3, 82.9, 80.6, 80.3, 79.7, 77.0, 76.2, 75.9, 75.6, 75.4, 74.8, 74.1, 73.5, 73.3, 68.6, 62.1, 21.5 (*C*H_3); ESI: calcd for $C_{61}H_{64}NaO_{10}S$ $[M + Na]^+$ 1011.4, found *m/z* 1011.6.

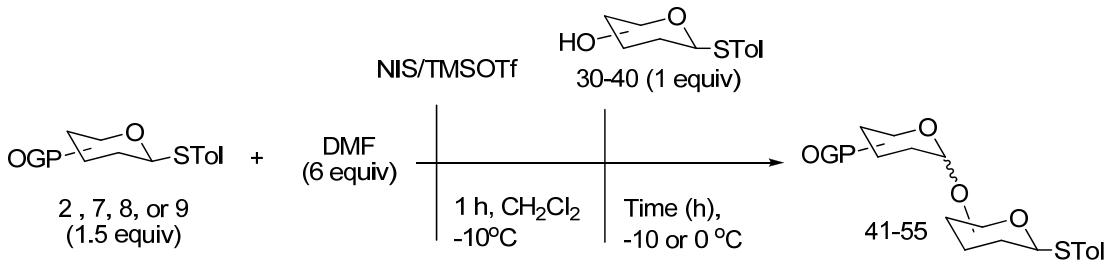
4,6-*O*-benzylidene-3-*O*-(2-naphthyl)-thio-β-D-galactopyranoside 39.

Scheme 17. Preparation of 4,6-*O*-benzylidene-3-*O*-(2-naphthyl)-thio-β-D-galactopyranoside **39**.

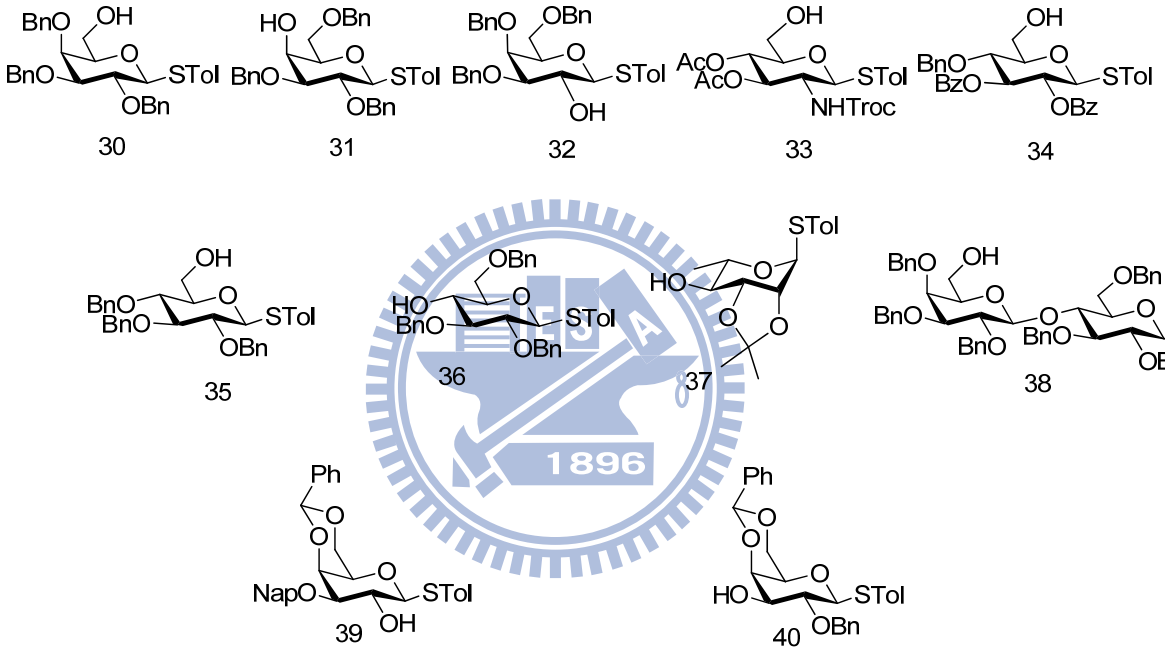
A suspension of known **39a**[46] (1 g, 2.67 mmol) and dibutyl tin oxide (Bu_2SnO) (1 g, 4.0 mmol) in toluene (25 mL) was heated to reflux (ca 135 ˚C) under Dean-Stark condensation for 15 h. After then, the mixture was concentrated by removal of toluene (to 15 mL), followed by stirring at RT. Subsequently, 2-naphthalene bromide (2-NapBr) (0.89 g, 4 mmol) and CH_3CN (10 mL) were added to the residue. The mixture was stirred at 70 ˚C for 6 h, followed by addition of 2 N $NaOH_{(aq)}$ (1 mL) and CH_2Cl_2 (20 mL). The resulting emulsion was filtered through celite and the filtrate was concentrated for column chromatography purification (Elution: Hexane/CH_2Cl_2/EtOAc 4/3/1) to give **39** as a white amorphous

powder (0.95 g, 71% from re-precipitation in hexane/EtOAc). For acceptor **39**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 2/1/1); $[\alpha]^{37.9}_D$= +6.7 (c= 1.73, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83-7.73 (m, 4H, Ar*H*), 7.58 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.50-7.44 (m, 3H, Ar*H*), 7.42-7.33 (m, 5H, Ar*H*), 7.06 (d, *J* = 8.1 Hz, 1H, Ar*H*), 5.39 (s, 1H, benzylidene-C*H*), 4.88 (s, 2H), 4.45 (d, *J* = 9.6 Hz, 1H, H-1), 4.32 (bt, *J* = 12.3 Hz, 1H), 4.12 (d, *J* = 3Hz, 1H), 3.95-3.87 (m, 2H), 3.54 (dd, *J* = 3.3, 9.3 Hz, 1H), 3.39 (s, 1H), 2.49 (d, *J* = 1.8 Hz, 1H, O*H*), 2.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 137.8, 135.5, 134.4, 133.1, 133.0, 129.7, 129.0, 128.2, 128.0, 127.8, 127.7, 126.7, 126.6, 126.4, 126.1, 126.0, 125.7, 101.1 (benzylidene-*C*H), 87.0 (C-1), 80.0, 73.4, 71.8, 70.0, 69.3, 67.1, 21.2 (*C*H_3); ESI: calcd for $C_{31}H_{30}NaO_5S$ $[M + Na]^+$ 537.2, found *m/z* 537.1.

Table 8. Experimental details for glycosylation of thioglycosyl acceptors **30**−**40** using procedure B



Thioglycoside acceptors 30-40



Entry	Donor (mg, mmol)	Acceptor (mg, mmol)	Time (h)	*T* (˚C)	Glycosylation product	
					Yield (mg, %),	α/β[a]
1	**2** (166.3, 0.3)	**30** (111.2, 0.2)	3	-10	**41** (118.3, 60)	36/1
2	**2** (166.3, 0.3)	**31** (111.2, 0.2)	6	0	**42** (108.5, 55)	6/1
3	**2** (166.3,	**32** (111.2, 0.2)	3	0	**43** (108.5, 55)	11/1

	0.3)					
4	**2** (166.3, 0.3)	**33** (108.6, 0.2)	3	-10	**44** (87.1, 45)	11/1
5	**2** (166.3, 0.3)	**34** (116.8, 0.2)	3	-10	**45** (172.2, 85)	49/1
6	**2** (166.3, 0.3)	**35** (111.2, 0.2)	2	-10	**46** (127.9, 65)	12/1
7	**2** (166.3, 0.3)	**36** (111.2, 0.2)	4	0	**47** (138.1, 70)	49/1
8	**2** (166.3, 0.3)	**37** (62, 0.2)	2	0	**48** (73.6, 50)	13/1
9	**2** (166.3, 0.3)	**38** (197.7, 0.2)	3	-10	**49** (212.8, 75)	19/1
10	**2** (166.3, 0.3)	**39** (102.8, 0.2)	4	0	**50** (160.2, 85)	49/1
11	**7** (100, 0.2)	**40** (70, 0.15)	3	-10	**51** (64, 56)	49/1
12	**7** (700, 1.3)	**32** (560, 1.0)	6	-10	**52** (518, 61)	49/1
13	**8** (96, 0.24)	**35** (55.6, 0.2)	3	-10	**53** (91.5, 55)	6/1
14	**9** (155, 0.24)	**36** (91, 0.2)	5	0	**54** (107.8, 50)	49/1[b]
15	**9** (155, 0.24)	**37** (62, 0.2)	3	0	**55** (91.5, 55)	8/1[b]

[a]α/β Ratios were determined by Hitachi HPLC system (Mightysil column (Si-60 250-4.6); Elution: EtOAc/hexane/CH_2Cl_2 mixture at 0.8 mL min^{-1} flow rate; HPLC pump (L-2130) and UV detector (L-2400) were employed. [b]Ultra-sonification was applied (Branson 2210R-MT).

***p*-tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-thio-β-D-galactopyranoside 41.** Preparation of **41** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 1). Compound **41** was obtained as a white glassy material by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 7/1/2). For α-anomer of **41**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 5/1/2); $[\alpha]^{37.9}_D$= +42.6 (c= 1.04, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.47 (m, 2H, Ar*H*), 7.42-7.22 (m, 30H, Ar*H*), 7.57-7.50 (m, 2H, Ar*H*), 6.98 (d, *J* = 7.8 Hz, 2H, Ar*H*), 5.42 (s, 1H, benzylidene-C*H*), 4.93 (d, *J* = 12.0 Hz, 1H), 4.84 (d, *J* = 12 Hz, 1H), 4.80-4.68 (m, 8H), 4.64-4.56 (m, 2H), 4.15 (dd, *J* = 1.2, 12.5 Hz, 1H), 4.08-4.01 (m, 2H), 3.95 (d, *J* = 3.3 Hz, 1H), 3.92 (d, *J* = 2.7 Hz, 1H), 3.89-3.76 (m, 3H), 3.68(s, 1H), 3.64 (t, *J* = 3.9 Hz, 1H), 3.59 (dd, *J* = 2.7, 9.3 Hz, 1H), 3.33 (dd, *J* = 3.9, 10.2 Hz, 1H), 2.25 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 139.0, 138.9, 138.7, 138.6, 138.4, 137.2, 131.3, 131.1, 130.1, 129.3, 128.96, 128.84, 128.80, 128.78, 128.74, 128.54, 128.49, 128.3, 128.2, 128.1, 128.0, 127.9, 126.78, 101.4 (benzylidene-*C*H), 98.5 (C-1'), 87.4 (C-1), 84.6, 77.8, 77.6, 76.8, 76.2, 75.8, 74.8, 74.7, 74.42, 74.38, 73.5, 72.2, 70.0, 68.2, 62.9, 21.6 (*C*H$_3$); HRMS (FAB): calcd for $C_{61}H_{62}O_{10}SNa$ $[M + Na]^+$ requires 1009.3961, found *m/z* 1009.3956.

***p*-tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-thio-β-D-galactopyranoside 42**. Preparation of **42** was referred to general pre-activated DMF-modulating glycosylation

procedure and the exact amounts of reagents used were given (Table S2, entry 2). Compound **42** was obtained as a white glassy solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 7/1/2). For α-anomer of **42**, R_f 0.5 (Hexane/EtOAc/CH_2Cl_2 5/1/2); $[\alpha]^{37.9}_D$= +50.7 (c= 1.32, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J = 8.1 Hz, 2H, Ar*H*), 7.50-7.17 (m, 30H, Ar*H*), 7.06 (d, J = 8.1 Hz, 2H, Ar*H*), 5.34 (s, 1H, benzylidene-C*H*), 5.18 (d, J = 3.3 Hz, 1H, H-1'), 5.05 (d, J = 11.7 Hz, 1H), 4.76-4.72 (m, 5H), 4.65 (d, J = 5.7 Hz, 1H), 4.54 (d, J = 9.6 Hz, 1H, H-1), 4.35-4.25 (m, 3H), 4.21-4.15 (m, 2H), 4.10-3.98 (m, 4H), 3.80 (t, J = 9.3 Hz, 1H), 3.66-3.49 (m, 5H), 3.40 (dd, J = 1.2, 12.6 Hz, 1H), 2.17 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 139.3, 138.7, 138.54, 138.46, 138.3, 137.4, 132.5, 130.5, 130.1, 129.3, 128.9, 128.80, 128.77, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.4, 126.8, 101.2 (benzylidene-*C*H), 100.6 (C-1'), 87.5 (C-1), 83.3, 76.4, 76.1, 75.7, 74.9, 74.5, 73.7, 73.3, 72.5, 71.3, 69.8, 67.6, 63.0, 21.5 (*C*H_3); HRMS (FAB): calcd for $C_{61}H_{62}O_{10}SNa$ $[M + Na]^+$ requires 1009.3961, found *m/z* 1009.3981.

***p*-tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-thio-β-D-galactopyranoside 43**. Preparation of **43** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 3). Compound **43** was obtained as a white amorphous solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 6/1/2). For α-anomer of **43**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 5/1/2);

$[\alpha]^{37.9}_{D}$= +61.9 (c= 0.43, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.19 (m, 30H, Ar*H*), 7.06-7.03 (m, 2H, Ar*H*), 6.96 (d, *J* = 7.8 Hz, 2H, Ar*H*), 5.89 (d, *J* = 3.6 Hz, 1H, H-1'), 5.19 (s, 1H, benzylidene-C*H*), 4.90 (dd, *J* = 1.5, 11.4 Hz, 1H), 4.83-4.77 (m, 3H), 4.73-4.62 (m, 3H), 4.51-4.41 (m, 2H), 4.30 (t, *J* = 9.3 Hz, 1H), 4.24 (d, *J* = 10.2, 1H), 4.11-4.06 (m, 2H), 3.97 (s, 1H), 3.88 (dd, *J* = 3.6, 10.2, 1H), 3.80 (dd, *J* = 0.9, 12.3, 1H), 3.70-3.63 (m, 5H), 3.01 (dd, *J* = 1.2, 12.3 Hz, 1H), 2.28 (s, 1H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 139.2, 138.8, 138.4, 138.2, 137.9, 137.6, 132.0, 130.3, 130.1, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.54, 128.50, 128.46, 128.4, 128.2, 128.02, 127.96, 126.8, 101.3 (benzylidene-*C*H), 97.2 (C-1'), 88.3 (C-1), 84.2, 77.9, 77.5, 77.3, 77.1, 76.1, 76.0, 75.2, 75.1, 74.2, 73.9, 73.4, 72.8, 72.5, 71.4, 69.5, 69.0, 62.5, 21.6 (*C*H_3); HRMS (FAB): calcd for $C_{61}H_{62}O_{10}SNa$ $[M + Na]^+$ requires 1009.3961, found *m/z* 1009.3961.

_p_-tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→6)-3,4-di-*O*-acetyl-2-deoxy-2-trichloroethoxycarbamyl-thio-β-D-glucopyranoside 44. Preparation of **44** was referred to pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 4). Compound **44** was obtained as a white glassy material by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 3/1/1). For α-anomer of **44**, R_f 0.3 (Hexane/EtOAc/CH_2Cl_2 3/1/1); $[\alpha]^{37.9}_{D}$= +44.4 (c= 0.76, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H, Ar*H*), 7.42-7.25 (m, 15H, Ar*H*), 7.11 (d, *J* = 8.1 Hz, 2H, Ar*H*), 5.77 (d, *J* = 9.3 Hz, 1H, N*H*), 5.44 (s, 1H, benzylidene-C*H*), 5.18 (t, *J* = 7.8 Hz, 1H), 4.92-4.88 (m, 2H),

4.78-4.55 (m, 7H), 4.15-3.94 (m, 5H), 3.89-3.67 (m, 4H), 3.58 (s, 1H), 2.35 (s, 1H, CH_3), 2.04 (s, 3H, CH_3), 1.93 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.92 (*C*=O), 170.85 (*C*=O), 154.6 (*C*=O), 138.9, 138.7, 138.6, 138.1, 133.6, 130.1, 129.4, 129.3, 128.9, 128.8, 128.6, 128.4, 128.1, 126.7, 101.4 (benzylidene-*C*H), 100.3 (C-1'), 95.9 (*C*Cl_3), 87.2 (C-1), 76.0, 75.1, 74.9, 74.7, 74.5, 74.0, 72.4, 69.7, 64.3, 63.8, 55.2, 21.6 (*C*H_3), 21.4 (*C*H_3), 21.3 (*C*H_3); HRMS (FAB): calcd for $C_{47}H_{50}Cl_3NO_{13}SNa$ $[M + Na]^+$ requires 996.1966, found *m/z* 996.1953.

_p_-tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→6)-4-*O*-benzyl-2,3-di-*O*-benzoyl-thio-β-D-glucopyranoside 45.

Preparation of **45** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 5). Compound **45** was obtained as a white glassy material by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 6/1/3). For α-anomer of **45**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 6/1/3); $[\alpha]^{37.9}_D$= +78.7 (c= 0.85, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.79 (d, *J* = 7.5, 2H, Ar*H*), 7.57-7.53 (m, 2H, Ar*H*), 7.51-7.45 (m, 2H, Ar*H*), 7.43-7.21 (m, 19H, Ar*H*), 7.10-7.04 (m, 7H, Ar*H*), 5.69 (t, *J* = 9.3, 1H), 5.48 (s, 1H, benzylidene-C*H*), 5.33 (t, *J* = 9.6 Hz, 2H), 5.17 (d, *J* = 3.3 Hz, 1H, H-1), 4.87-4.73 (m, 4H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.49 (s, 2H), 4.22 (d, *J* = 12.3, 1H), 4.11-4.07 (m, 2H), 4.01-3.83 (m, 5H), 3.79-3.74 (m, 1H), 3.65 (s, 1H), 2.23 (s, 1H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1 (*C*=O), 165.7 (*C*=O), 139.2, 139.0, 138.7, 138.4, 137.8, 133.6, 133.5, 130.32, 130.25, 129.84, 129.76, 129.4, 128.93, 128.78, 128.7,

128.6, 128.5, 128.4, 128.2, 128.1, 128.04, 128.00, 126.8, 101.5 (benzylidene-*C*H), 98.5 (C-1'), 86.2 (C-1), 80.0, 77.9, 77.5, 77.1, 76.8, 76.5, 76.4, 76.0, 75.1, 74.0, 72.4, 71.3, 69.9, 66.1, 63.1, 21.6 (CH_3); HRMS (FAB): calcd for $C_{61}H_{58}O_{12}SNa$ $[M + Na]^+$ requires 1037.3547, found, *m/z* 1037.3541.

***p*-tolyl**

2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-thio-β-D-glucopyranoside 46. Preparation of **46** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 6). Compound **46** was obtained as a white amorphous solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 6/1/3) and both α/β-anomers were isolated for NMR characterization. For α-anomer of **46**, R_f 0.5 (Hexane/EtOAc/CH_2Cl_2 6/1/3; $[\alpha]^{37.9}{}_D$= +63.1 (c= 0.85, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 2.4, 7.8, 2H, Ar*H*), 7.42-7.20 (m, 30H, Ar*H*), 7.07 (d, *J* = 7.8 Hz, 2H, Ar*H*), 5.43 (s, 1H, benzlidene-C*H*), 5.04 (d, *J* = 3.3, 1H, H-1'), 4.91-4.72 (m, 8H), 4.65 (dd, *J* = 2.1, 9.9 Hz, 2H), 4.56 (d, *J* = 11.4, 1H), 4.15 (d, *J* = 12.6, 1H), 4.07 (dd, *J* = 3.3, 9.9 Hz, 1H), 4.03 (d, *J* = 3.3, 1H), 3.96 (dd, *J* = 3.3, 10.2, 1H), 3.85-3.77 (m, 2H), 3.74-3.70 (m, 1H), 3.67 (d, *J* = 9, 1H), 3.63 (s, 1H), 3.60-3.55 (m, 2H), 3.32 (t, *J* = 9 Hz, 1H), 2.26 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 138.9, 138.6, 138.4, 138.3, 137.8, 131.9, 130.8, 130.2, 129.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.14, 128.11, 128.08, 128.03, 127.95, 127.88, 126.8, 101.4 (benzylidene-*C*H), 98.6 (C-1'), 87.7 (C-1), 87.1, 81.3, 79.0, 78.4, 77.9,

77.5, 77.1, 76.2, 76.1, 75.9, 75.3, 75.1, 73.5, 72.5, 69.9, 67.1, 62.9, 21.5 (CH_3). For β-anomer of **46**, R_f 0.3 (Hexane/EtOAc/CH_2Cl_2 6/1/3); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.55 (m, 2H, Ar*H*), 7.46-7.15 (m, 30H, Ar*H*), 7.00 (d, J = 7.8 Hz, 2H, Ar*H*), 5.49 (s, 1H, benzylidene-C*H*), 4.95-4.86 (m, 3H), 4.82-4.69 (m, 6H), 4.65-4.57 (m, 2H), 4.41 (d, J = 7.8 Hz, 1H, H-1'), 4.29-4.20 (m, 2H), 4.08 (d, J = 3.3 Hz, 1H), 3.97 (d, J = 11.1, 1H), 3.90-3.76 (m, 2H), 3.69 (t, J = 8.4 Hz, 1H), 3.62-3.48 (m, 3H), 3.42 (t, J = 9.3 Hz, 1H), 3.20 (s, 1H), 2.20 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 138.88, 138.86, 138.7, 138.5, 138.3, 137.9, 132.5, 130.4, 130.2, 129.4, 128.9, 128.84, 128.80, 128.64, 128.60, 128.5, 128.3, 128.2, 128.14, 128.09, 127.8, 127.0, 104.1 (C-1'), 101.8 (benzylidene-*C*H), 88.0 (C-1), 87.1, 81.1, 79.7, 79.3, 78.8, 78.4, 76.1, 75.8, 75.7, 75.3, 74.4, 72.5, 69.6, 68.6, 66.9, 21.5 (CH_3); HRMS (FAB): calcd for $C_{61}H_{62}O_{10}S$ Na $[M + Na]^+$ requires 1009.3961, found *m/z* 1009.3964.

***p*-tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-thio-β-D-glucopyranoside 47**. Preparation of **47** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 7). Compound **47** was obtained as a milk white glassy material by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 7/1/2). For α-anomer of **47**, R_f 0.3 (Hexane/EtOAc/CH_2Cl_2 7/1/2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.47 (m, 4H, Ar*H*), 7.33-7.14 (m, 28H, Ar*H*), 7.03 (d, J = 7.8 Hz, 2H, Ar*H*), 5.77 (d, J = 3.3 Hz, 1H, H-1'), 5.38 (s, 1H, benzylidene-C*H*), 4.92-4.81 (m, 3H), 4.78-4.74 (m, 1H), 4.68 (s,

2H), 4.63-4.48 (m, 5H), 4.09 (d, J = 5.4 Hz, 1H), 4.04 (d, J = 8.1, 2H), 3.97-3.93 (m, 2H), 3.81-3.67 (m, 4H), 3.58-3.48 (m, 3H), 2.29 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.0, 138.7, 138.6, 138.27, 138.25, 133.2, 130.1, 129.9, 129.2, 128.82, 128.78, 128.71, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 126.9, 126.7, 101.2 (benzylidene-*C*H), 98.4 (C-1'), 87.9 (C-1), 87.2, 81.4, 79.2, 77.9, 77.5, 77.1, 76.8, 75.7, 75.0, 74.7, 74.6, 74.0, 72.5, 72.0, 69.8, 69.6, 63.4, 21.6 (*C*H_3); HRMS (FAB): calcd for $C_{61}H_{62}O_{10}SNa$ $[M + Na]^+$ requires 1009.3961, found *m/z* 1009.4016.

***p*-tolyl**

2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→4)-2, 3-isopropylidene-thio-α-L-rhamnopyranoside 48. Preparation of **48** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 8). Compound **48** was obtained as a pale yellowish glassy material by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 7/1/2) and both α/β-anomers were isolated for NMR characterization. For α-anomer of **48**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 6/1/2); $[\alpha]^{37.9}_D$= -34.1 (c= 0.34, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.52 (m, 2H, Ar*H*), 7.43-7.24 (m, 15H, Ar*H*), 7.12 (d, J = 7.8 Hz, 2H, Ar*H*), 5.67 (s, 1H, H-1), 5.48 (s, 1H, benzylidene-C*H*), 5.08 (d, J = 3 Hz, 1H, H-1'), 4.91 (d, J = 11.4 Hz, 1H), 4.82-4.70 (m, 3H), 4.31-4.00 (m, 9H), 3.51 (dd, J = 7.8, 9.9 Hz, 1H), 2.33 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.32 (s, 1H, CH_3), 1.25 (d, J = 6.3, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 138.6, 138.4, 138.3, 132.9, 130.3, 129.94, 129.3, 128.8, 128.6, 128.2, 128.0, 126.8,

109.6 (isopropylidene-*C*), 101.5 (benzylidene-*C*H), 99.6 (C-1'), 84.4 (C-1), 80.4, 77.9, 77.5, 77.3, 77.2, 77.1, 75.6, 75.2, 74.9, 72.3, 69.9, 67.2, 63.0, 28.6, 27.1, 21.6 (CH_3), 17.6. For β-anomer of **48**, R_f 0.3 (Hexane/EtOAc/CH_2Cl_2 6/1/2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (m, 2H, Ar*H*), 7.46-7.29 (m, 15H, Ar*H*), 7.13 (d, J = 7.8 Hz, 2H, Ar*H*), 5.64 (s, 1H, H-1), 5.48 (s, 1H, benzylidene-C*H*), 4.95-4.86 (m, 2H), 4.81-4.71 (m, 3H), 4.31-4.21 (m, 3H), 4.18-4.08 (m, 2H), 4.01-3.97 (m, 1H), 3.82-3.73 (m, 2H), 3.59 (dd, J = 3.6, 9.6 Hz, 1H), 3.28 (s, 1H), 2.33 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.33-1.30 (m, 6H, CH_3 × 2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 139.0, 138.5, 138.4, 133.1, 130.3, 130.1, 129.5, 128.80, 128.75, 128.7, 128.6, 128.2, 128.1, 128.0, 127.0, 109.8 (isopropylidene-*C*), 101.9 (benzylidene-*C*), 101.8 (C-1'), 84.6 (C-1), 79.7, 79.4, 79.0, 78.3, 77.0, 75.8, 74.6, 72.7, 69.7, 66.8, 66.7, 28.4 (CH_3), 26.9 (CH_3), 21.6 (CH_3), 18.2 (CH_3); HRMS (FAB): calcd for $C_{43}H_{48}O_9SNa$ [M + Na]$^+$ requires 763.2917, found *m/z* 763.291.

***p*-tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-thio-β-D-glucopyranoside 49.** Preparation of **49** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 9). Compound **49** was obtained as a white glassy solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 9/1/3). For α-anomer of **49**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 8/1/3); $[\alpha]^{37.9}_D$= +33.6 (c= 0.54, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.11 (m, 47H, Ar*H*), 7.00 (d, J = 7.8Hz, 2H, Ar*H*), 5.35 (s, 1H, benzylidene-C*H*), 5.04 (d, J = 9.9 Hz, 1H),

4.95 (d, J = 11.4 Hz, 1H), 4.87-4.43 (m, 18H), 4.12-3.73 (m, 12H), 3.60 (t, J = 9.0 Hz, 1H), 3.53-3.34 (m, 6H), 2.27 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 139.2, 139.1, 138.93, 138.90, 138.7, 138.3, 138.2, 133.2, 130.1, 130.1, 129.3, 129.2, 128.9, 128.8, 128.76, 128.70, 128.64, 128.55, 128.53, 128.4, 128.3, 128.1, 128.04, 127.99, 127.9, 127.8, 126.8, 102.9 (C-1'), 101.4 (benzylidene-*C*H), 98.9 (C-1''), 88.2 (C-1), 85.5, 83.0, 80.9, 80.5, 79.8, 76.9, 76.6, 76.2, 76.0, 75.8, 75.7, 75.0, 74.8, 74.3, 74.2, 73.7, 73.5, 73.2, 72.2, 69.8, 68.8, 67.0, 62.9, 21.6 (*C*H_3); HRMS (FAB): calcd for $C_{88}H_{90}O_{15}SNa$ $[M + Na]^+$ requires 1441.5898, found *m/z* 1441.5893.

***p*-tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosyl-(1→2)-4,6-*O*-benzylidene-3-*O*-(2-naphthyl)-thio-β-D-galactopyranoside 50**. Preparation of **50** was referred to general pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 10). Compound **50** was obtained as white amorphous solid by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 5/1/1 to 2/1/1). For α-anomer of **50**, R_f 0.5 (Hexane/EtOAc/CH_2Cl_2 2/1/1); $[\alpha]^{37.9}_D$= +69.5 (c= 0.38, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83-7.67 (m, 4H, Ar*H*), 7.51-7.25 (m, 25H, Ar*H*), 6.99 (d, J = 7.8 Hz, 2H, Ar*H*), 5.92 (d, J = 3.6 Hz, 1H, H-1), 5.48 (s, 1H, benzylidene-C*H*), 5.07 (s, 1H), 4.94 (d, J = 11.4 Hz, 1H), 4.81-4.73 (m, 4H), 4.65 (d, J = 12.3 Hz, 1H), 4.49 (d, J = 11.1 Hz, 1H), 4.36-4.29 (m, 2H), 4.23 (t, J = 9.0 Hz, 1H), 4.08 (dd, J = 3.3, 9.5 Hz, 1H), 4.00-3.91 (m, 3H), 3.81-3.73 (m, 3H), 3.43 (s, 1H), 2.99 (dd, J = 1.2, 12.3 Hz, 1H), 2.30 (s, 1H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 138.9,

138.40, 138.35, 138.0, 135.6, 133.6, 133.4, 133.3, 130.2, 129.6, 129.2, 128.9, 128.8, 128.69, 128.66, 128.5, 128.2, 128.1, 128.0, 127.5, 127.1, 127.0, 126.8, 126.7, 126.6, 101.7 (benzylidene-*C*H), 101.1(benzylidene-*C*H), 97.2 (C-1'), 87.0 (C-1), 81.2, 77.9, 77.7, 77.1, 76.22, 76.17, 75.1, 74.2, 72.9, 72.4, 71.5, 70.4, 69.9, 69.7, 62.8, 21.7 (*C*H_3); HRMS (FAB): calcd for $C_{58}H_{56}SO_{10}Na$ $[M + Na]^+$ requires 967.3486, found *m/z* 967.3478.

***p*-tolyl**

2,3,4-tri-*O*-benzyl-L-fucopyranosyl-α-(1→3)-2-*O*-benzyl-4,6-*O*-benzyl idene-thio-β-D-galactopyranoside 51. Preparation of **51** was referred to pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 11). Compound **51** was obtained as a glassy material by column chromatography purification (Elution: Hexane/EtOAc 4/1). For α-anomer of **51**, R_f 0.2 (Hexane/EtOAc/CH_2Cl_2 3/1); $[\alpha]^{37.9}_D$= -56.7 (c= 0.08, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J = 8.1 Hz, 2H, Ar*H*), 7.47-7.16 (m, 26H, Ar*H*), 7.01 (d, J = 8.1 Hz, 1H), 5.47 (s, 1H, benzylidene-C*H*), 5.09 (d, J = 10.2 Hz, 3H), 4.95-4.92 (m, 2H), 4.84 (d, J = 12.3 Hz, 1H), 4.74-4.57 (m, 5H), 4.45 (d, J = 10.2 Hz, 1H), 4.39-4.34 (m, 2H), 4.10-3.96 (m, 4H), 3.77 (t, J = 9.3 Hz, 3H), 3.66 (dd, J = 3.0, 9.0 Hz, 1H), 3.56 (s, 1H), 3.48 (s, 1H), 2.33 (s, 3H, CH_3), 0.98 (d, J = 6.6Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.40, 139.38, 139.1, 139.0, 138.5, 138.0, 134.0, 130.0, 129.5, 129.1, 128.8, 128.72, 128.66, 128.61, 128.60, 128.58, 128.5, 128.41, 128.36, 128.0, 127.9, 127.8, 127.75, 127.7, 127.0, 101.7 (benzylidene-*C*H), 101.4 (C-1'), 87.0 (C-1), 85.3, 79.4, 78.2, 76.6, 76.4,

75.8, 75.3, 74.7, 73.5, 73.3, 70.0, 69.9, 67.5, 21.7 (CH_3), 17.3 (CH_3); HRMS (ESI): calcd for $C_{54}H_{56}O_9SNa$ $[M + Na]^+$ requires 903.3543, found 903.3527.

***p*-tolyl**

2,3,4-tri-*O*-benzyl-L-fucopyranosyl-α-(1→2)-3,4,6-tri-*O*-benzyl-thio-β-D-galactopyranoside 52. Preparation of **52** was referred to pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 12). Compound **52** was obtained as a white solid material by column chromatography purification (Elution: Hexane/EtOAc 5/1). For α-anomer of **52**, R_f 0.4 (Hexane/EtOAc 4/1); $[\alpha]^{37.9}_D$= -114.5 (c= 0.71, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.32 (m, 28H, Ar*H*), 7.17-7.08 (m, 3H, Ar*H*), 7.06-6.99 (m, 4H, Ar*H*), 5.85 (d, J = 3.3 Hz, 1H, H-1'), 4.92 (d, J = 11.7 Hz, 1H), 4.81-4.70 (m, 5H), 4.65-4.59 (m, 2H), 4.55-4.44 (m, 4H), 4.40-4.32 (m, 3H), 4.07-3.97 (m, 3H), 3.76 (dd, J = 2.4, 9.0 Hz, 1H), 3.71 (s, 1H), 3.62-3.59 (m, 3H), 2.28 (s, 3H, C*H*$_3$), 1.13 (d, J = 6.6 Hz, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3, 139.1, 138.9, 138.8, 138.2, 137.4, 131.9, 131.1, 130.0, 128.8, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 126.7, 98.2 (C-1'), 87.8 (C-1), 86.3, 80.0, 78.2, 75.9, 75.1, 74.8, 74.0, 73.4, 73.2, 72.3, 72.1, 71.1, 69.3, 67.8, 21.5 (CH_3), 17.0 (CH_3).; HRMS (ESI): calcd for $C_{61}H_{64}O_9SNa$ $[M + Na]^+$ requires 995.4169, found *m/z* 995.4163.

***p*-tolyl 4-*O*-benzyl-2,3-*O*-isopropylidene-L-rhamnopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-thio-β-D-glucopyranoside 53**. Preparation of **53** was referred to pre-activated DMF-modulating glycosylation procedure and the exact amounts of reagents used were given (Table S2, entry 13). Compound **53** was obtained as a white amorphous material by column chromatography purification (Elution: Hexane/EtOAc/CH_2Cl_2 5/0.5/1). For α-anomer of **53**, R_f 0.4 (Hexane/EtOAc/CH_2Cl_2 7/1/2); $[\alpha]^{37.9}_D$= -18.4 (c= 0.35, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.24 (m, 22H, Ar*H*), 7.09-7.07 (d, *J* = 7.8 Hz, 2H, Ar*H*), 4.94-4.82 (m, 6H), 4.74-4.63 (m, 2H), 4.60-4.56 (m, 1H), 4.27 (t, *J* = 6.6 Hz, 1H), 4.09 (d, *J* = 5.7 Hz, 1H), 3.94 (d, *J* = 10.5 Hz, 1H), 3.78-3.67 (m, 2H), 3.56-3.42 (m, 4H), 3.22 (dd, *J* = 7.2, 9.6 Hz, 1H), 2.26 (s, 3H, C*H*$_3$), 1.52 (s, 3H, C*H*$_3$), 1.38 (s, 3H, C*H*$_3$), 1.26 (s, 3H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 138.8, 138.5, 138.3, 133.2, 130.1, 130.0, 129.98, 128.95, 128.9, 128.7, 128.5, 128.40, 128.36, 128.2, 128.0, 109.7 (isopropylidene-*C*), 97.6 (C-1'), 87.9 (C-1), 87.3, 81.5, 81.3, 79.2, 78.7, 78.1, 76.4, 76.3, 75.9, 75.5, 73.4, 66.7, 65.0, 28.5 (*C*H$_3$), 26.9 (*C*H$_3$), 21.5 (*C*H$_3$), 18.3 (*C*H$_3$); HRMS (MALDI-TOF): calcd for $C_{50}H_{56}O_9SNa$ $[M + Na]^+$ requires 855.3543, found *m/z* 855.3577.

***p*-tolyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-thio-β-D-glucopyranoside 54.** Preparation of **54** was referred to pre-activated DMF-modulating glycosylation procedure (B) and the exact amounts of reagents used were given (Table S2, entry 14). Compound **54** was obtained as a white glassy material by column chromatography purification (Elution: Hexane/Et_2O/CH_2Cl_2 7/1/2). For α-anomer of **54**, R_f

0.4 (Hexane/Et_2O/CH_2Cl_2 7/1/2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J = 8.1 Hz, 2H, Ar*H*), 7.30-7.23 (m, 27H, Ar*H*), 7.19-7.08 (m, 8H), 7.04 (d, J = 7.8 Hz, 2H), 5.64 (d, J = 3.6 Hz, 1H, H-1'), 4.89-4.76 (m, 5H), 4.63-4.51 (m, 6H), 4.47-4.40 (m, 1H), 4.29 (d, J = 12.0 Hz, 1H), 4.09 (t, J = 9.0 Hz, 1H), 3.94-3.83 (m, 2H), 3.81-3.75 (m, 2H), 3.66 (d, J = 9.0 Hz, 1H), 3.61-3.47 (m, 4H), 3.41 (dd, J = 1.2, 10.4 Hz, 1H), 2.31 (s, 1H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.1, 139.0, 138.9, 138.8, 138.33, 138.30, 138.21, 133.27, 130.2, 129.9, 128.84, 128.79, 128.77, 128.75, 128.7, 128.5, 128.3, 128.23, 128.15, 128.1, 128.0, 127.91, 127.86, 127.6, 126.9, 97.5 (C-1'), 87.8 (C-1), 87.3, 82.5, 81.3, 79.7, 79.1, 78.1, 76.0, 75.7, 75.4, 74.8, 73.92, 73.85, 73.7, 72.9, 71.4, 69.5, 68.6, 21.6 (*C*H_3); HRMS (ESI): calcd for $C_{68}H_{70}O_{10}SNa$ $[M + Na]^+$ requires 1101.4587, found *m/z* 1101.4582.

***p*-tolyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3-*O*-isopropylidene-thio-α-L-rhamnopyranoside 55.** Preparation of **55** was referred to pre-activated DMF-modulating glycosylation procedure (B) and the exact amounts of reagents used were given (Table S2, entry 15). Compound **55** was obtained as a white glassy material by column chromatography purification (Elution: Hexane/Et_2O/CH_2Cl_2 6/1/1). For α-anomer of **55**, R_f 0.3 (Hexane/EtOAc/CH_2Cl_2 6/1/1); $[\alpha]^{37.9}_D$= -56.2 (c= 0.23, $CHCl_3$)^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.24 (m, 21H, Ar*H*), 7.19-7.10 (m, 4H, Ar*H*), 5.64 (s, 1H, H-1'), 5.00-4.69 (m, 6H), 4.64-4.47 (m, 3H), 4.28-4.14 (m, 3H), 4.10-3.98 (m, 2H), 3.83-3.76 (m, 2H), 3.66-3.58 (m, 2H), 3.43-3.37 (m, 1H), 2.33 (s, 3H, CH_3), 1.43 (s, 3H), 1.24 (d, J = 6.6 Hz,

6H, C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.2, 138.8, 138.4, 138.3, 132.9, 130.3, 130.1, 128.91, 128.88, 128.86, 128.8, 128.7, 128.43, 128.41, 128.3, 128.1, 128.0, 109.6 (isopropylidene-*C*), 98.9 (C-1'), 84.5 (C-1), 82.7, 81.7, 80.3, 78.3, 76.1, 75.6, 74.7, 74.0, 70.8, 68.4, 66.9, 28.6 (*C*H$_3$), 27.0 (*C*H$_3$), 21.6 (*C*H$_3$), 17.8 (*C*H$_3$); HRMS (MALDI-TOF): calcd for $C_{50}H_{56}O_9SNa$ $[M + Na]^+$ requires 855.3543, found *m/z* 855.3570.

***p*-tolyl**

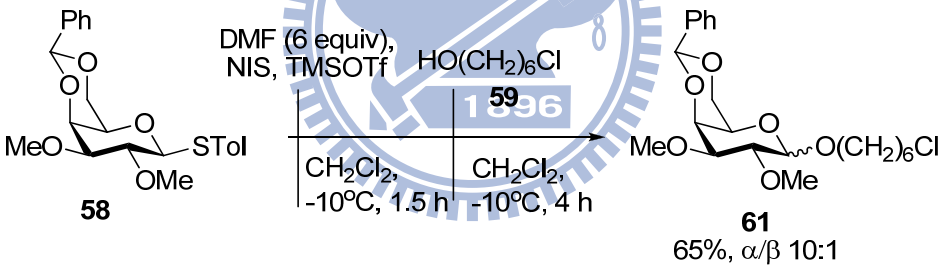
4,6-*O*-benzylidene-2,3-di-*O*-methyl-thio-β-D-galactopyranoside 58

Scheme 18. Preparation of *p*-tolyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-thio-β-D-galactopyranoside 58

Known **58a**[43] (1.5 g, 4 mmol) was dissolved in DMF (13 mL), and stirred at ice bath under N_2. To the DMF solution was added iodomethane (0.65 mL, 10.4 mml) and 60% NaH in oil mist (0.5 g, 20 mmol). The mixture was stirred from 0 ˚C to RT for 3 h, followed by quenching with satd. NH_4Cl (20 mL). Product in the mixture was extracted with CH_2Cl_2 (20 mL × 2), and the CH_2Cl_2 solution was then washed with 1 N $HCl_{(aq)}$, brine, dried ($MgSO_4$) and concentrated for chromatography purification to obtain **58** as a glassy material (1.1 g, 65%). For compound **58**, $[\alpha]^{37.9}{}_D$= -15.2 (c= 0.94, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, J = 8.1

Hz, 2H, Ar*H*), 7.49-7.46 (m, 2H, Ar*H*), 7.37-7.35 (m, 3H, Ar*H*), 7.05 (d, *J* = 8.1 Hz, 2H, Ar*H*), 5.12 (s, 1H, benzylidene-C*H*), 4.45 (d, *J* = 9.3 Hz, 1H, H-1), 4.38 (dd, *J* = 1.5, 11 Hz, 1H), 4.29 (d, *J* = 3 Hz, 1H), 4.02 (d, *J* = 1.5, 11 Hz, 1H), 3.55 (s, 3H, CH_3), 3.53(s, 3H, CH_3), 3.46-3.42 (m, 2H), 3.31 (dd, *J* = 3.3, 6 Hz, 1H), 2.32 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.75, 138.72, 133.7, 129.5, 129.1, 128.4, 128.2, 126.7, 101.5 (benzylidene-*C*H), 86.4 (C-1), 83.5, 76.8, 73.0, 69.7, 69.5, 60.9 (O*C*H_3), 57.7 (O*C*H_3), 21.2 (*C*H_3). ESI: calcd for $C_{22}H_{26}NaO_5S$ $[M + Na]^+$ 425.1, found *m/z* 425.0.

6-chlorohexyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-D-galacto pyranoside 61



Scheme 19. Preparation of 6-chlorohexyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-D-galacto pyranoside 61

61 (54 mg, 65%, α/β = 10/1) was prepared from coupling of 6-chlorohexanol **59** (26 μL mg) and thiogalactopyranoside **61** (121 mg, 0.3 mmol) according to general pre-activated DMF-modulating glycosylation procedure. Purification of **61** was achieved by column chromatography (Elution: Hexane/EtOAc 2/1/1). For α-anomer of **61**, $[\alpha]^{37.9}_D$= +124.1 (c= 0.26, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$):

δ 7.54-7.51 (m, 2H, Ar*H*), 7.38-7.31 (m, 3H, Ar*H*), 5.56 (s, 1H, benzylidene-C*H*), 5.10 (d, J = 3.3 Hz, 1H, H-1), 4.36 (dd, J = 0.9, 3.6 Hz, 1H), 4.26 (dd, J = 1.5, 12.6 Hz, 5H), 4.09 (dd, J = 1.8, 12.6Hz, 3H), 3.80 (dd, J = 3.3, 10.2Hz, 2H), 3.74-3.66 (m, 3H), 3.56-3.52 (m, 9H), 1.79 (quintet, J = 6.6 Hz, 2H, CH_2), 1.72-1.62 (m, 2H, CH_2), 1.53-1.33 (m, 4H, CH_2 × 2); ^{13}C NMR (75 MHz, $CDCl_3$): δ ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2, 129.4, 128.6, 126.9, 101.7 (benzylidene-*C*H), 97.7 (C-1), 77.8, 77.6, 74.1, 70.0, 68.6, 63.1, 59.3, 58.1, 45.5, 32.9, 29.7 (*C*H_2), 27.1 (*C*H_2), 25.9 (*C*H_2); HRMS (MALDI-TOF): calcd for $C_{21}H_{31}ClO_6Na$ $[M + Na]^+$ requires 437.1701, found *m/z* 437.1704.

6 Reference:

1. (a) Bertozzi, C. R.; Kiessling, L. L., Chemical glycobiology. *Science* **2001,** *291* (5512), 2357-64; (b) Seeberger, P. H.; Werz, D. B., Synthesis and medical applications of oligosaccharides. *Nature* **2007,** *446* (7139), 1046-51; (c) Dwek, R. A., Glycobiology: Toward Understanding the Function of Sugars. *Chem Rev* **1996,** *96* (2), 683-720.
2. Pashkuleva, I.; Reis, R. L., Sugars: burden or biomaterials of the future? *J Mater Chem* **2010,** *20* (40), 8803-8818.
3. (a) Bilodeau, M. T.; Park, T. K.; Hu, S. H.; Randolph, J. T.; Danishefsky, S. J.; Livingston, P. O.; Zhang, S. L., Total Synthesis of a Human Breast-Tumor Associated Antigen. *J Am Chem Soc* **1995,** *117* (29), 7840-7841; (b) Zhu, T.; Boons, G. J., A Two-Directional and Highly Convergent Approach for the Synthesis of the Tumor-Associated Antigen Globo-H. *Angew Chem Int Ed Engl* **1999,** *38* (23), 3495-3497.
4. Stoffyn, P.; Stoffyn, A.; Hauser, G., Structure of trihexosylceramide isolated from rat spleen. *Biochim Biophys Acta* **1973,** *306* (2), 283-6.
5. Mong, T. K.; Lee, H. K.; Duron, S. G.; Wong, C. H., Reactivity-based one-pot total synthesis of fucose GM1 oligosaccharide: a sialylated antigenic epitope of small-cell lung cancer. *Proc Natl Acad Sci U S A* **2003,** *100* (3), 797-802.
6. Tirelli, N., Glyco-materials: using saccharides and their interactions for designing new biomaterials. *Macromolecular Bioscience* **2006,** *6* (8), 575-8.
7. Wang, C. C.; Lee, J. C.; Luo, S. Y.; Kulkarni, S. S.; Huang, Y. W.; Lee, C. C.; Chang, K. L.; Hung, S. C., Regioselective one-pot protection of carbohydrates. *Nature* **2007,** *446* (7138), 896-9.
8. Paulsen, H., Advances in Selective Chemical Syntheses of Complex Oligosaccharides. *Angewandte Chemie-International Edition in English* **1982,** *21* (3), 155-173.
9. Fraser-Reid, B.; Burgey, C. S.; Vollerthun, R., Carbohydrates to densely functionalized carbocycles: 'Armed and disarmed' effects in an approach to tetrodotoxin. *Pure Appl Chem* **1998,** *70* (2), 285-288.
10. (a) Boons, G. J.; Entwistle, D. A.; Ley, S. V.; Woods, M., Dispiroketals in Synthesis .4. Enantioselective Desymmetrization of Glycerol Using a C2-Symmetrical Disubstituted Bis-Dihydropyran. *Tetrahedron Lett* **1993,** *34* (35), 5649-5652; (b) Zhang, Z. Y.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C. H., Programmable one-pot oligosaccharide synthesis. *J Am Chem Soc* **1999,** *121* (4), 734-753.
11. (a) Wang, Y.; Ye, X. S.; Zhang, L. H., Oligosaccharide assembly by one-pot multi-step strategy. *Org Biomol Chem* **2007,** *5* (14), 2189-200; (b) Boltje, T. J.;

Buskas, T.; Boons, G. J., Opportunities and challenges in synthetic oligosaccharide and glycoconjugate research. *Nat Chem* **2009,** *1* (8), 611-22.
12. Codee, J. D.; van den Bos, L. J.; Litjens, R. E.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A., Sequential one-pot glycosylations using 1-hydroxyl and 1-thiodonors. *Org Lett* **2003,** *5* (11), 1947-50.
13. (a) Crich, D.; Sun, S. X., Direct formation of beta-mannopyranosides and other hindered glycosides from thioglycosides. *J Am Chem Soc* **1998,** *120* (2), 435-436; (b) Crich, D., Chemistry of glycosyl triflates: Synthesis of beta-mannopyranosides (Reprinted from Glycochemistry: Principles, Synthesis, and Applications, pg 53-75, 2001). *J Carbohyd Chem* **2002,** *21* (7-9), 667-690.
14. Crich, D.; Sun, S., Formation of beta-Mannopyranosides of Primary Alcohols Using the Sulfoxide Method. *J Org Chem* **1996,** *61* (14), 4506-4507.
15. Huang, X.; Huang, L.; Wang, H.; Ye, X. S., Iterative one-pot synthesis of oligosaccharides. *Angew Chem Int Ed Engl* **2004,** *43* (39), 5221-4.
16. Huang, L.; Wang, Z.; Li, X.; Ye, X. S.; Huang, X., Iterative one-pot syntheses of chitotetroses. *Carbohydr Res* **2006,** *341* (10), 1669-79.
17. Wang, Z.; Zhou, L.; El-Boubbou, K.; Ye, X. S.; Huang, X., Multi-component one-pot synthesis of the tumor-associated carbohydrate antigen Globo-H based on preactivation of thioglycosyl donors. *J Org Chem* **2007,** *72* (17), 6409-20.
18. Huang, X. F.; Huang, L. J., Highly efficient syntheses of hyaluronic acid oligosaccharides. *Chem-Eur J* **2007,** *13* (2), 529-540.
19. (a) Lemieux, R. U.; Driguez, H., The chemical synthesis of 2-O-(alpha-L-fucopyranosyl)-3-O-(alpha-D-galactopyranosyl)-D-galactose. The terminal structure of the blood-group B antigenic determinant. *J Am Chem Soc* **1975,** *97* (14), 4069-75; (b) Lemieux, R. U.; Bundle, D. R.; Baker, D. A., The properties of a "synthetic" antigen related to the human blood-group Lewis a. *J Am Chem Soc* **1975,** *97* (14), 4076-83; (c) Shingu, Y.; Nishida, Y.; Dohi, H.; Matsuda, K.; Kobayashi, K., Convenient access to halide ion-catalyzed alpha-glycosylation free from noxious fumes at the donor synthesis. *J Carbohyd Chem* **2002,** *21* (6), 605-611.
20. Kim, J. H.; Yang, H.; Khot, V.; Whitfield, D.; Boons, G. J., Stereoselective glycosylations using (R)- or (S)-(ethoxycarbonyl)benzyl chiral auxiliaries at C-2 of glycopyranosyl donors. *Eur J Org Chem* **2006,** (22), 5007-5028.
21. (a) Ishiwata, A.; Munemura, Y.; Ito, Y., Synergistic solvent effect in 1,2-cis-glycoside formation. *Tetrahedron* **2008,** *64* (1), 92-102; (b) Demchenko, A.; Stauch, T.; Boons, G. J., Solvent and other effects on the stereoselectivity of thioglycoside glycosidations. *Synlett* **1997,** (7), 818-&.
22. Uchiro, H.; Mukaiyama, T., A significant effect of a lithium salt in the stereocontrolled synthesis of alpha-D-ribofuranosides. *Chem Lett* **1996,** (4),

271-272.
23. (a) Bogusiak, J.; Szeja, W., Polar additives as cocatalyst in glycosidation. *Synlett* **1997,** (6), 661-662; (b) Bogusiak, J.; Szeja, W., Studies on the synthesis of 1,2-cis pentofuranosides from S-glycofuranosyl dithiocarbamates, dithiocarbonates and phosphorodithioates. *Carbohyd Res* **2001,** *330* (1), 141-144.
24. (a) Crich, D.; Li, W., Efficient glycosidation of a phenyl thiosialoside donor with diphenyl sulfoxide and triflic anhydride in dichloromethane. *Org Lett* **2006,** *8* (5), 959-62; (b) Haberman, J. M.; Gin, D. Y., Dehydrative sialylation with C2-hemiketal sialyl donors. *Organic Letters* **2003,** *5* (14), 2539-2541.
25. Park, J.; Kawatkar, S.; Kim, J. H.; Boons, G. J., Stereoselective glycosylations of 2-azido-2-deoxy-glucosides using intermediate sulfonium ions. *Organic Letters* **2007,** *9* (10), 1959-1962.
26. Koto, S.; Morishima, N.; Owa, M.; Zen, S., A Stereoselective Alpha-Glucosylation by Use of a Mixture of 4-Nitrobenzenesulfonyl Chloride, Silver Trifluoromethanesulfonate, N,N-Dimethylacetamide, and Triethylamine. *Carbohyd Res* **1984,** *130* (Jul), 73-83.
27. Nishida, Y.; Shingu, Y.; Dohi, H.; Kobayashi, K., One-pot alpha-glycosylation method using Appel agents in N,N-dimethylformamide. *Org Lett* **2003,** *5* (14), 2377-80.
28. Shingu, Y.; Miyachi, A.; Miura, Y.; Kobayashi, K.; Nishida, Y., One-pot alpha-glycosylation pathway via the generation in situ of alpha-glycopyranosyl imidates in N,N-dimethylformamide. *Carbohyd Res* **2005,** *340* (14), 2236-2244.
29. Veeneman, G. H.; Vanleeuwen, S. H.; Vanboom, J. H., Iodonium Ion Promoted Reactions at the Anomeric Center .2. An Efficient Thioglycoside Mediated Approach toward the Formation of 1,2-Trans Linked Glycosides and Glycosidic Esters. *Tetrahedron Lett* **1990,** *31* (9), 1331-1334.
30. Chang, S. S.; Lin, C. C.; Li, Y. K.; Mong, K. K., A straightforward alpha-selective aromatic glycosylation and its application for stereospecific synthesis of 4-methylumbelliferyl alpha-T-antigen. *Carbohydr Res* **2009,** *344* (4), 432-8.
31. Mong, K. K.; Wong, C. H., Reactivity-based one-pot synthesis of a Lewis Y carbohydrate hapten: a colon-rectal cancer antigen determinant. *Angew Chem Int Ed Engl* **2002,** *41* (21), 4087-90.
32. Li, Z.; Gildersleeve, J. C., Mechanistic studies and methods to prevent aglycon transfer of thioglycosides. *J Am Chem Soc* **2006,** *128* (35), 11612-9.
33. Deng, S.; Gangadharmath, U.; Chang, C. W., Sonochemistry: a powerful way of enhancing the efficiency of carbohydrate synthesis. *J Org Chem* **2006,** *71* (14), 5179-85.
34. (a) Nishida, Y.; Shingu, Y.; Dohi, H.; Kobayashi, K., One-pot

alpha-glycosylation method using appel agents in N,N-dimethylformamide. *Org Lett* **2003,** *5* (14), 2377-2380; (b) Shingu, Y.; Miyachi, A.; Miura, Y.; Kobayashi, K.; Nishida, Y., One-pot alpha-glycosylation pathway via the generation in situ of alpha-glycopyranosyl imidates in N,N-dimethylformamide. *Carbohydr Res* **2005,** *340* (14), 2236-44.

35. (a) Barresi, F.; Hindsgaul, O., Synthesis of Beta-Mannopyranosides by Intramolecular Aglycon Delivery. *J Am Chem Soc* **1991,** *113* (24), 9376-9377; (b) Ishiwata, A.; Munemura, Y.; Ito, Y., NAP ether mediated intramolecular aglycon delivery: A unified strategy for 1,2-cis-glycosylation. *Eur J Org Chem* **2008,** (25), 4250-4263.

36. Wong, C. H.; Zhang, Z. Y.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T., Programmable one-pot oligosaccharide synthesis. *J Am Chem Soc* **1999,** *121* (4), 734-753.

37. Verma, P. R.; Mukhopadhyay, B., Synthesis of a tetrasaccharide related to the O-antigen from Azospirillum lipoferum SR65. *Carbohydr Res* **2010,** *345* (3), 432-6.

38. Valencia, M. E.; Gil, A.; Lavilla, P.; Pintado, V.; Lopez Dupla, J. M., [Drug surveillance for adverse reactions in patients with human immunodeficiency virus infection]. *An Med Interna* **1990,** *7* (11), 591-8.

39. Chao, C. S.; Li, C. W.; Chen, M. C.; Chang, S. S.; Mong, K. K., Low-concentration 1,2-trans beta-selective glycosylation strategy and its applications in oligosaccharide synthesis. *Chemistry* **2009,** *15* (41), 10972-82.

40. Lin, P. C.; Adak, A. K.; Ueng, S. H.; Huang, L. D.; Huang, K. T.; Ho, J. A.; Lin, C. C., DAST-mediated regioselective anomeric group migration in saccharides. *J Org Chem* **2009,** *74* (11), 4041-8.

41. Ye, X. S.; Fan, Q. H.; Li, Q.; Zhang, L. H., Regioselective benzylation of azido-containing monosaccharides. *Synlett* **2006,** (8), 1217-1220.

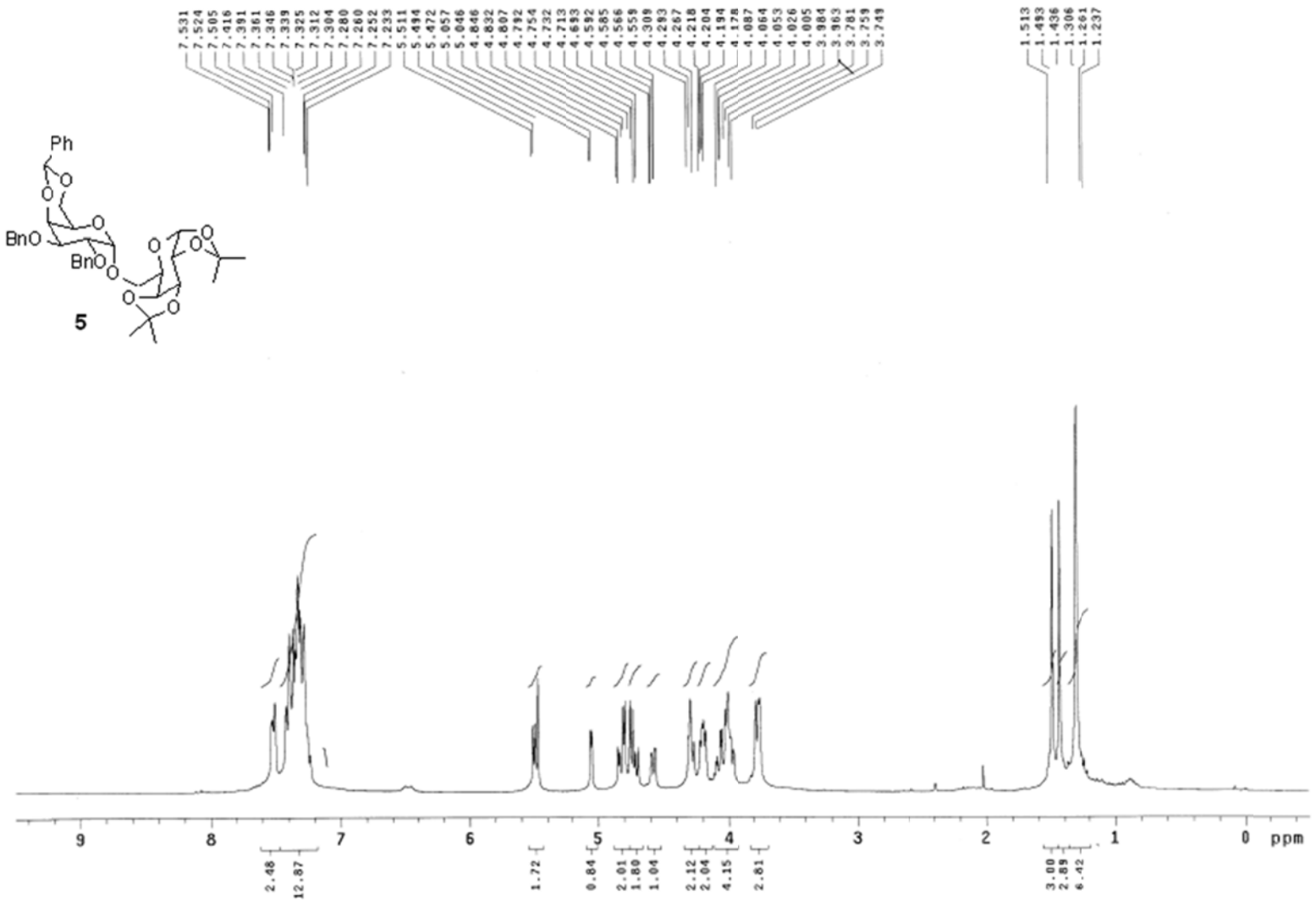
42. Mukhopadhyay, B.; Field, R. A., Convergent synthesis of a trisaccharide as its 2-(trimethylsilyl)ethyl glycoside related to the flavonoid triglycoside from Gymnema sylvestre. *Carbohydr Res* **2006,** *341* (10), 1697-701.

43. Mong, K. K. T.; Chang, C. W.; Chang, S. S.; Chao, C. S., A mild and general method for preparation of alpha-glycosyl chlorides. *Tetrahedron Lett* **2009,** *50* (31), 4536-4540.

44. Omura, S.; Shirahata, T.; Matsuo, J.; Teruya, S.; Hirata, N.; Kurimoto, T.; Akimoto, N.; Sunazuka, T.; Kaji, E., Improved catalytic and stereoselective glycosylation with glycosyl N-trichloroacetylcarbamate: application to various 1-hydroxy sugars. *Carbohyd Res* **2010,** *345* (6), 740-749.

45. Mong, K. K. T.; Chao, C. S.; Yen, Y. F.; Hung, W. C., Solvent Participation in a One-Pot Glycosylation Strategy (SPOG). *Adv Synth Catal* **2011,** *353* (6), 879-884.

46. Ye, X. S.; Wang, C. N.; Li, Q.; Wang, H. S.; Zhang, L. H., A new one-pot synthesis of Gb(3) and isoGb(3) trisaccharide analogues. *Tetrahedron* **2006,** *62* (50), 11657-11662.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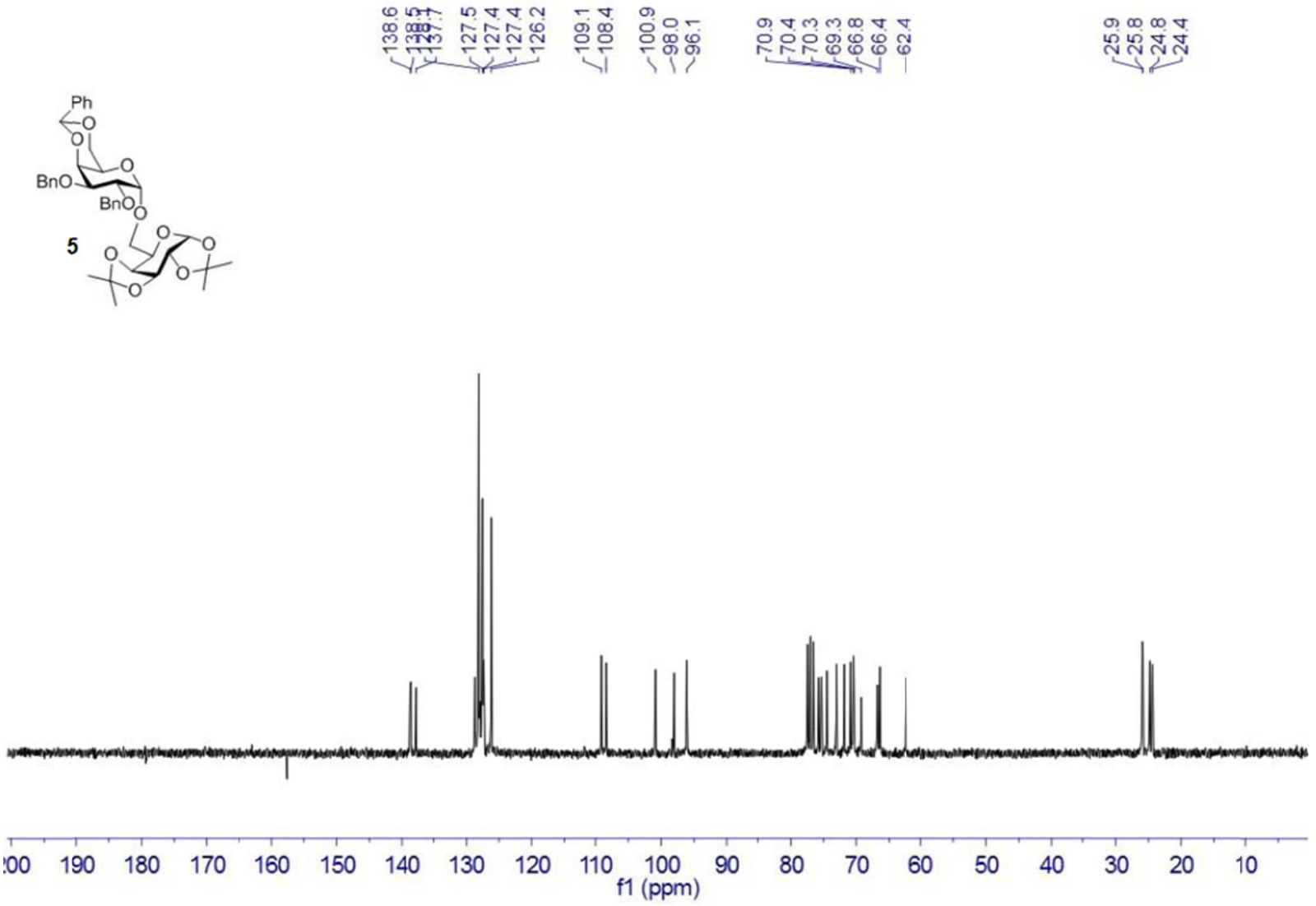
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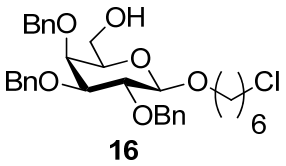
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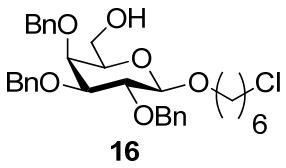
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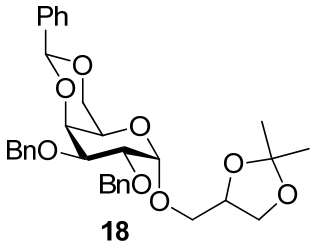
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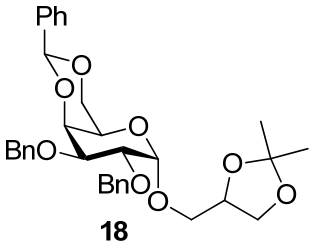
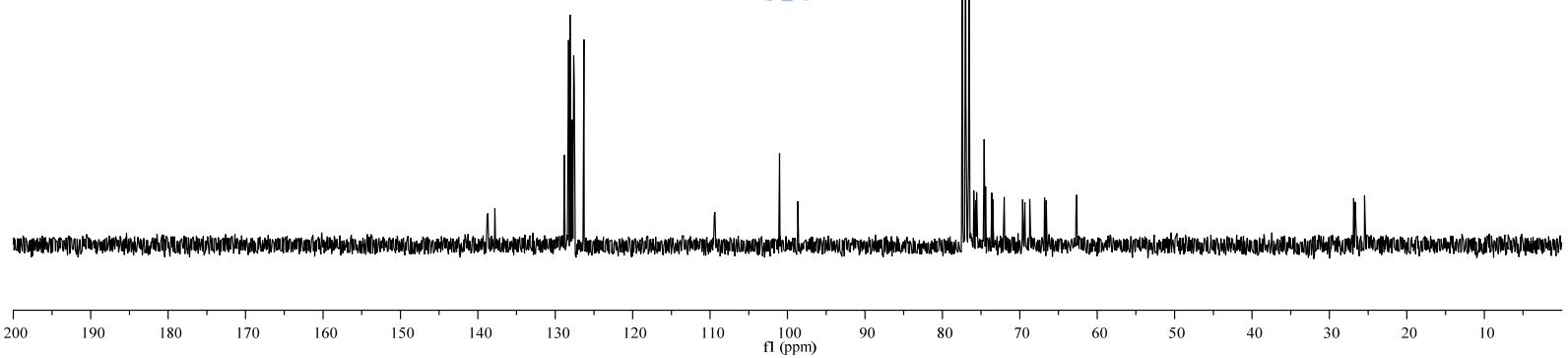
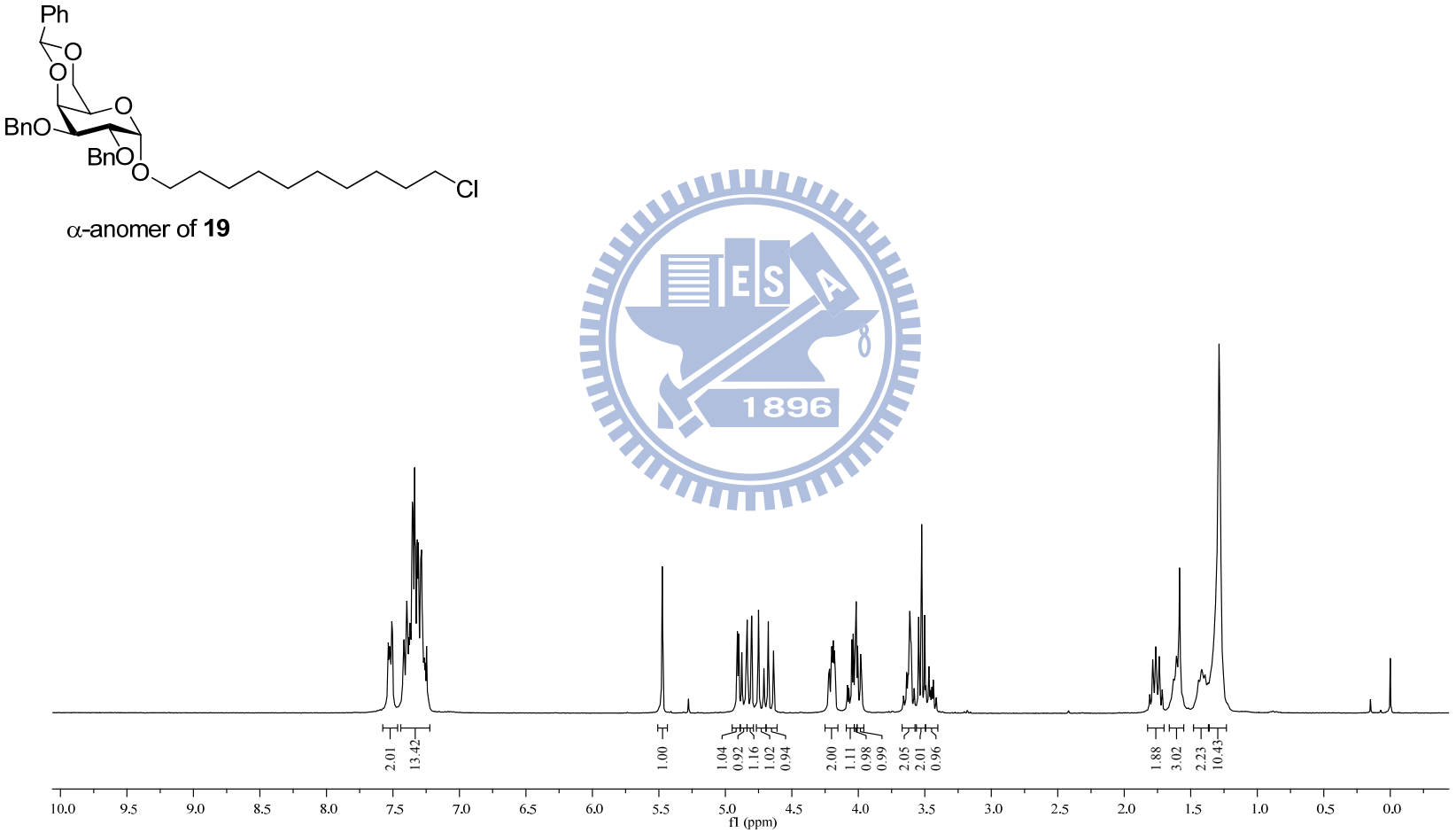
f1 (ppm)



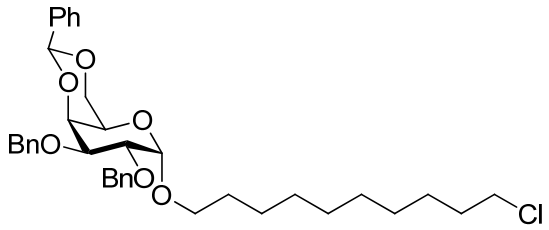
18

137.791
137.791
128.289
128.078
127.851
127.789
127.619
127.527
126.292
109.365
101.035
101.035
98.673
98.673
76.991
75.567
74.680
74.595
74.419
73.612
73.434
72.007
68.714
66.570
62.647
62.647
26.875
26.875
26.688
26.688
25.473
25.473
25.389
25.389

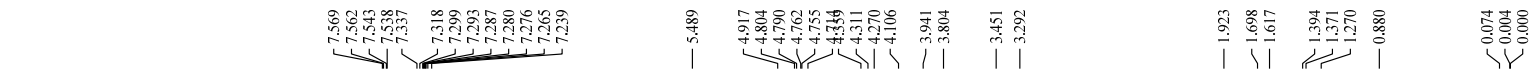


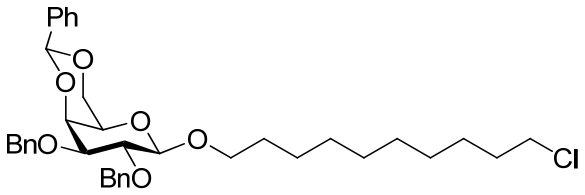


α-anomer of **19**

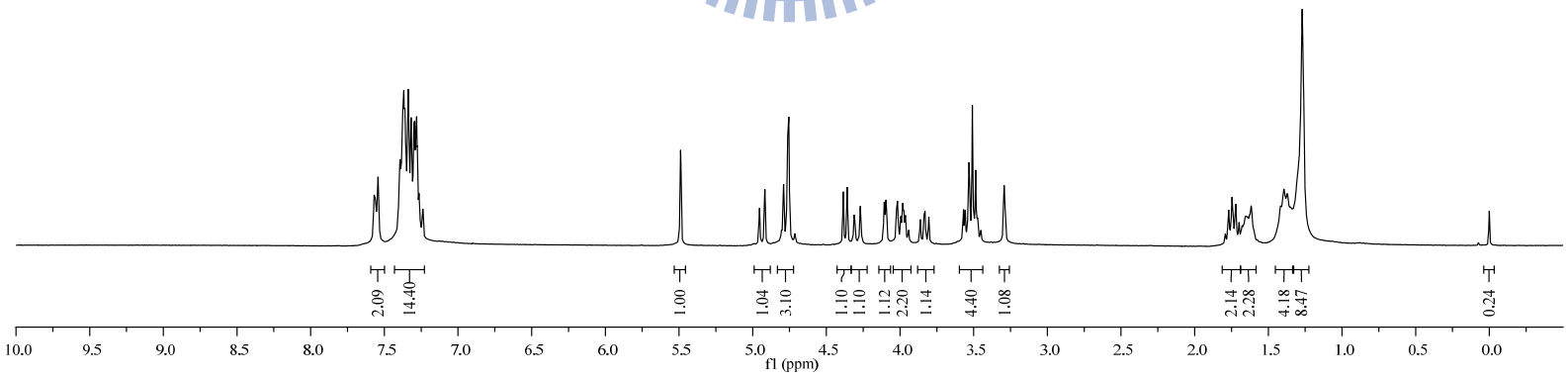


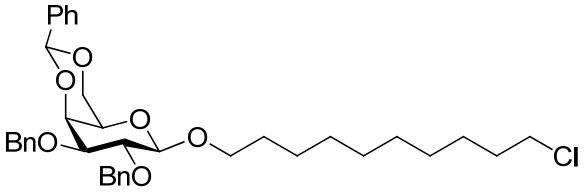
α-anomer of **19**



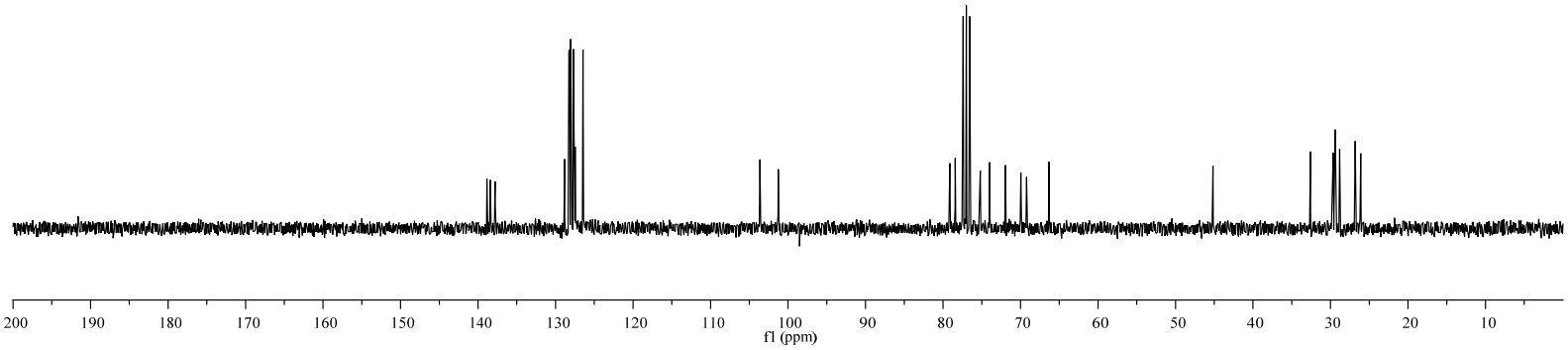


β-anomer of **19**

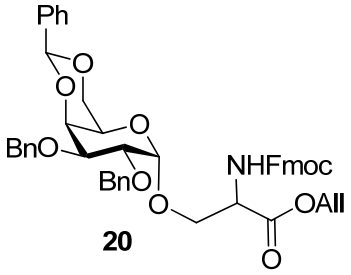




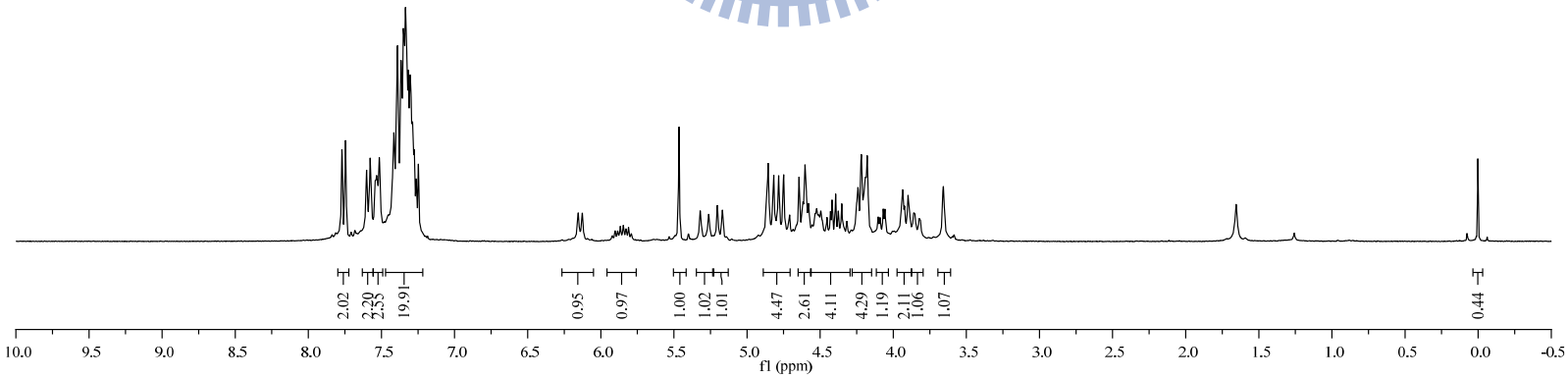
β-anomer of **19**

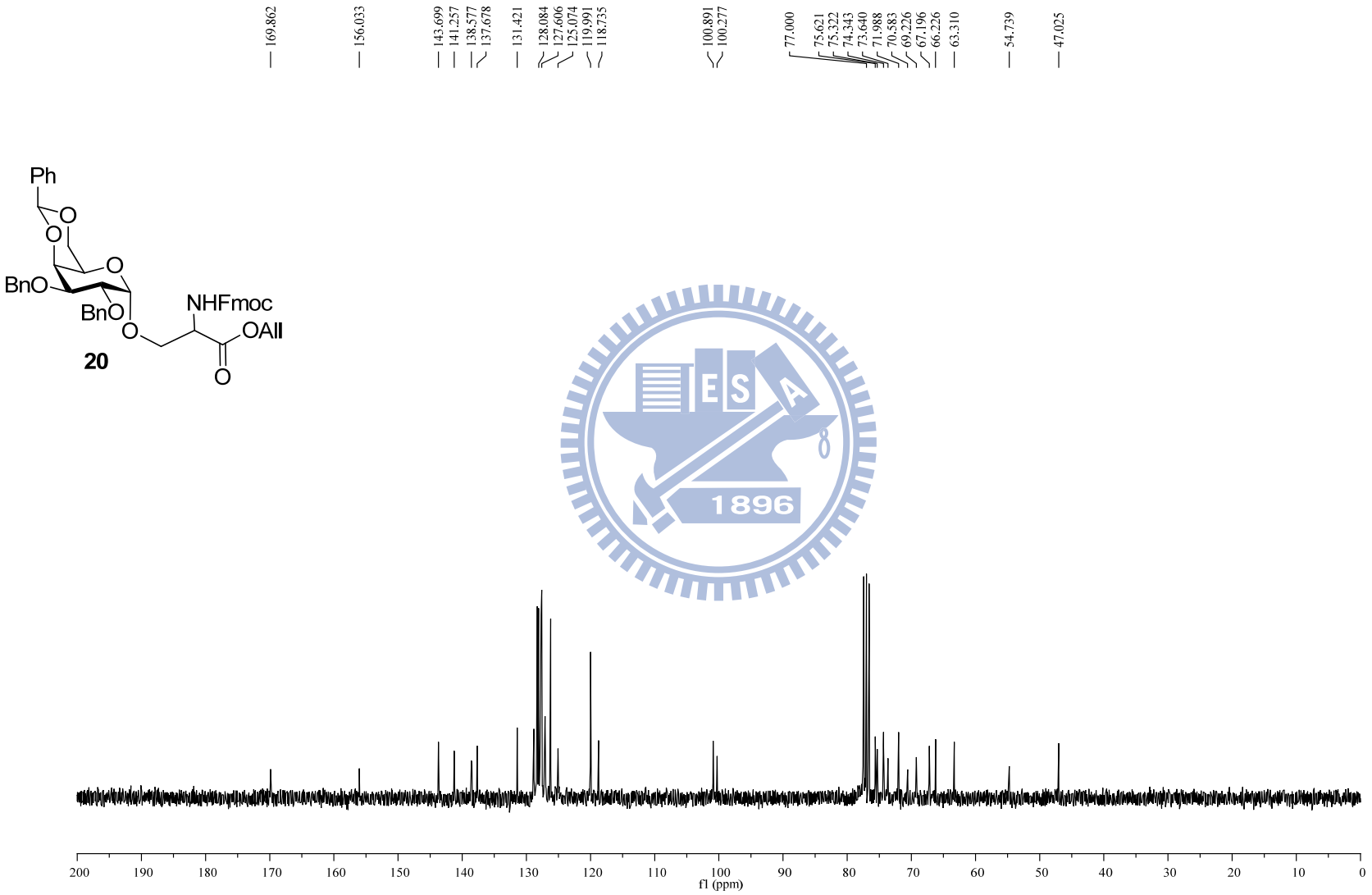


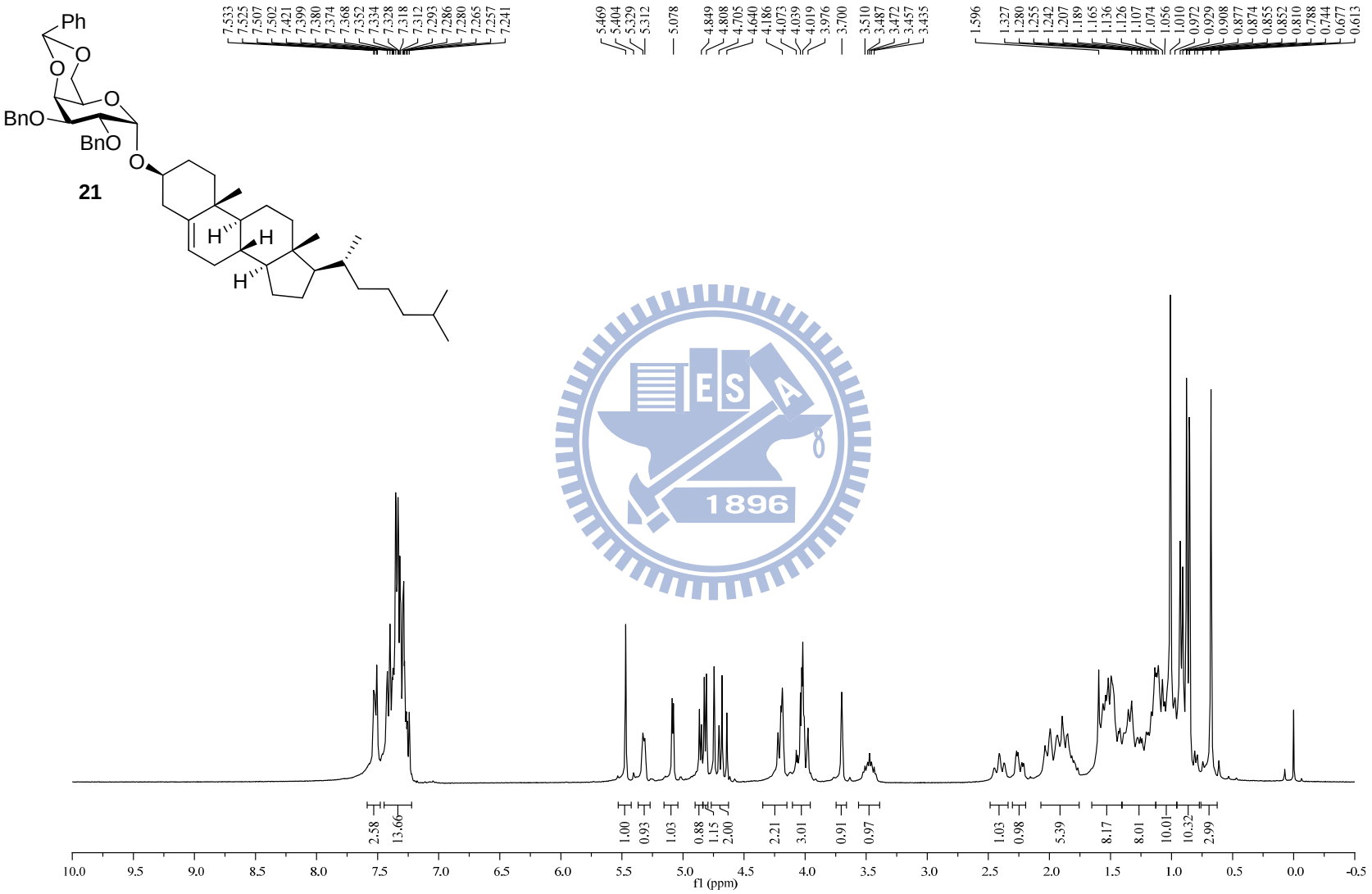

7.838
7.813
7.770
7.745
7.707
7.682
7.601
7.577
7.541
7.533
7.515
7.415
7.391
7.366
7.351
7.345
7.335
7.316
7.303
7.299
7.290
7.276
7.262
7.247
7.184
6.154
6.126
5.867
5.791
5.465
5.261
5.203
4.603
4.524
4.429
4.375
4.242
4.178
4.068
3.936
3.860
3.814
3.657
3.584
1.655
1.257
0.077
0.002

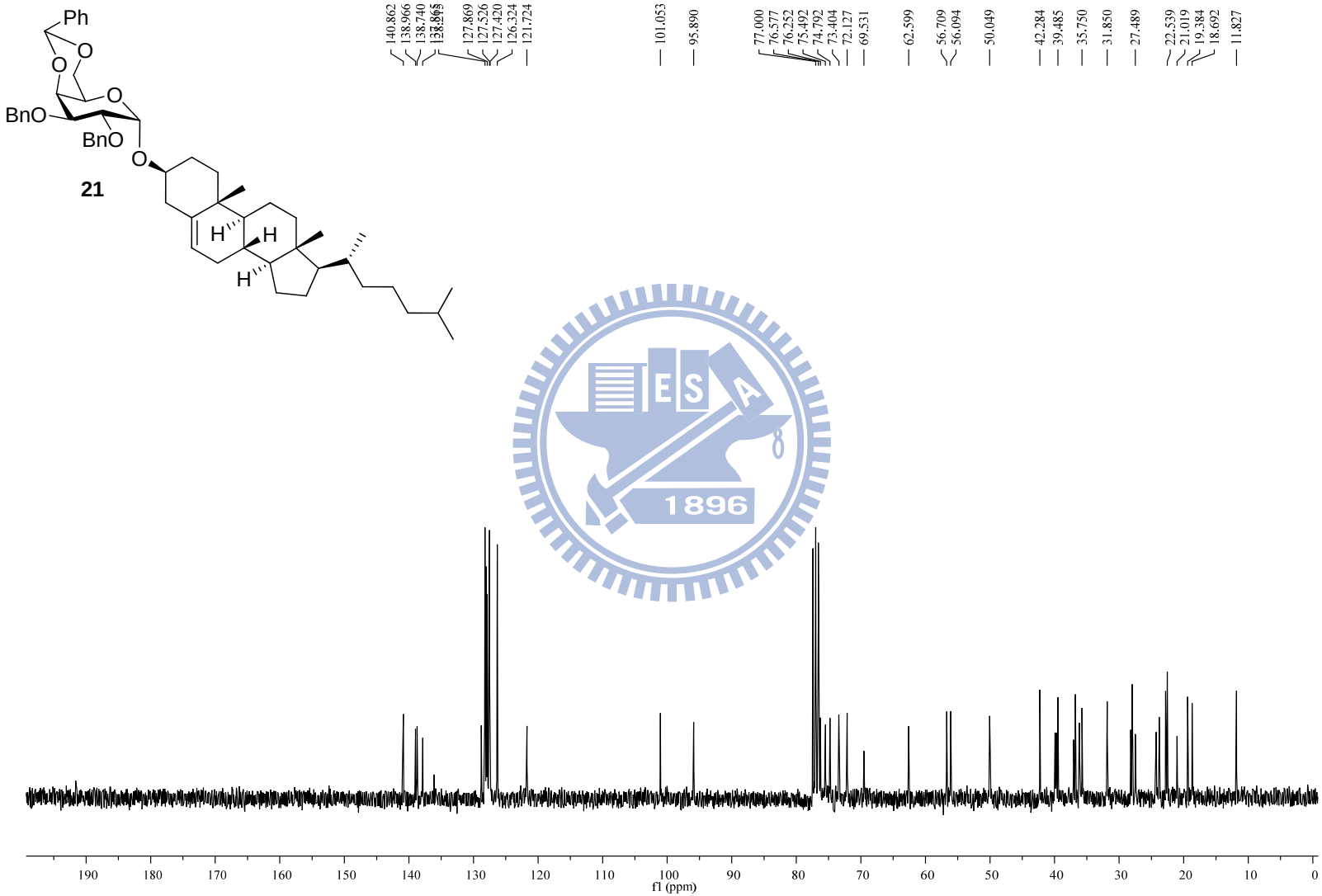

Ph
O
O
O
BnO
BnO
O
NHFmoc
OAll
O

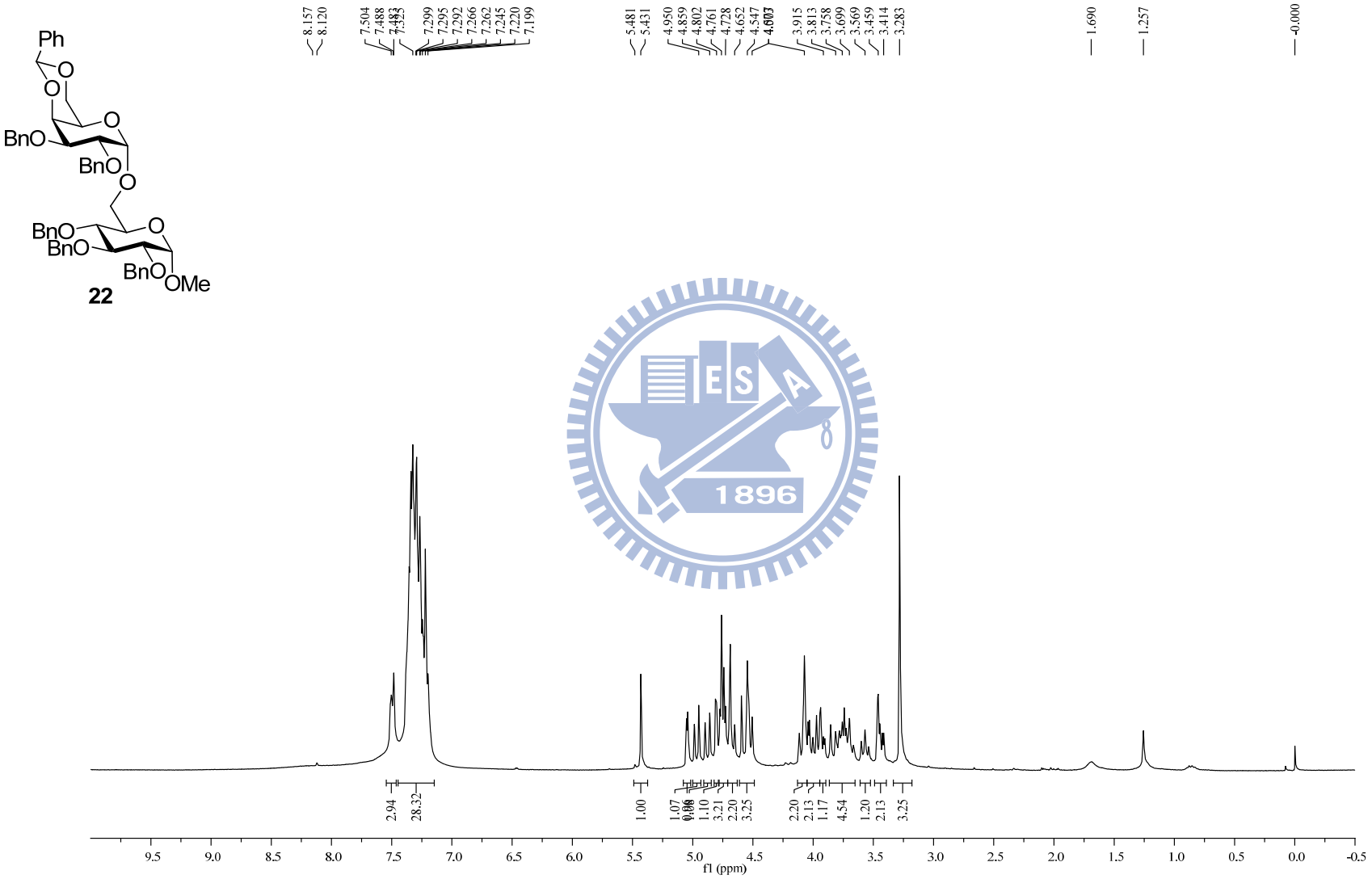
20

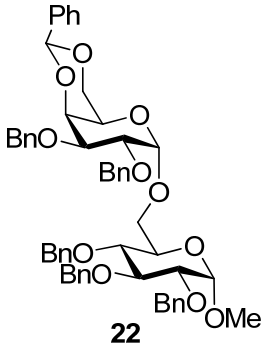

2.02
2.20
2.35
19.91
0.95
0.97
1.00
1.02
1.01
4.47
2.61
4.11
4.29
1.19
2.11
1.06
1.07
0.44
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


169.862
156.033
143.699
141.257
138.577
137.678
131.421
128.084
127.606
125.074
119.991
118.735
100.891
100.277
77.000
75.621
75.322
74.343
73.640
71.988
70.583
69.226
67.196
66.226
63.310
54.739
47.025
Ph
O
O
O
BnO
BnO
O
NHFmoc
OAll
O
20
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Ph
O
O
O
BnO
BnO
O
21
H
H
H
7.533
7.525
7.507
7.502
7.421
7.399
7.380
7.374
7.368
7.352
7.334
7.328
7.318
7.312
7.293
7.286
7.280
7.265
7.257
7.241
5.469
5.404
5.329
5.312
5.078
4.849
4.808
4.705
4.640
4.186
4.073
4.039
4.019
3.976
3.700
3.510
3.487
3.472
3.457
3.435
1.596
1.327
1.280
1.255
1.242
1.207
1.189
1.165
1.136
1.126
1.107
1.074
1.056
1.010
0.972
0.929
0.908
0.877
0.874
0.855
0.852
0.810
0.788
0.744
0.677
0.613
2.58
13.66
1.00
0.93
1.03
0.88
1.15
2.00
2.21
3.01
0.91
0.97
1.03
0.98
5.39
8.17
8.01
10.01
10.32
2.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

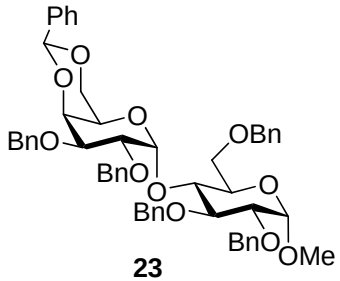

Ph
O
O
O
BnO
BnO
O
21
H
H
H
140.862
138.966
138.740
127.869
127.526
127.420
126.324
121.724
101.053
95.890
77.000
76.577
76.252
75.492
74.792
73.404
72.127
69.531
62.599
56.709
56.094
50.049
42.284
39.485
35.750
31.850
27.489
22.539
21.019
19.384
18.692
11.827
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Ph
O
O
O
BnO
BnO
O
BnO
BnO
O
BnO
OMe
22
8.157
8.120
7.504
7.488
7.483
7.323
7.299
7.295
7.292
7.266
7.262
7.245
7.220
7.199
5.481
5.431
4.950
4.859
4.802
4.761
4.728
4.652
4.547
4.503
3.915
3.813
3.758
3.699
3.569
3.459
3.414
3.283
1.690
1.257
-0.000
2.94
28.32
1.00
1.07
1.10
3.21
2.20
3.25
2.20
2.13
1.17
4.54
1.20
2.13
3.25
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


Ph
O
O
O
BnO
BnO
O
BnO
BnO
O
BnO
OMe

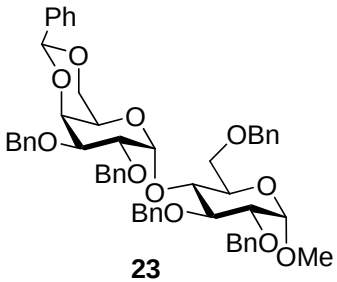
22

138.770
138.596
138.460
138.097
127.911
127.768
127.692
127.511
127.464
127.405
127.330
126.285
100.975
98.300
97.819
77.416
76.568
75.605
74.855
74.747
73.269
72.782
71.801
70.072
69.284
66.372
62.541
54.944
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Ph
O
O
O
BnO
BnO
O
BnO
OBn
O
BnO
OMe

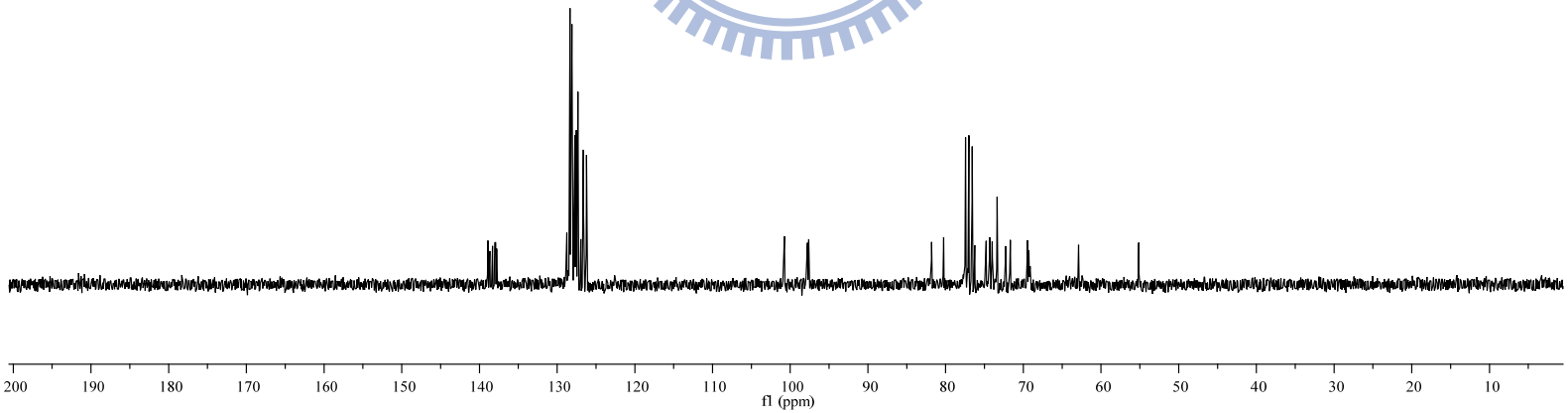
23

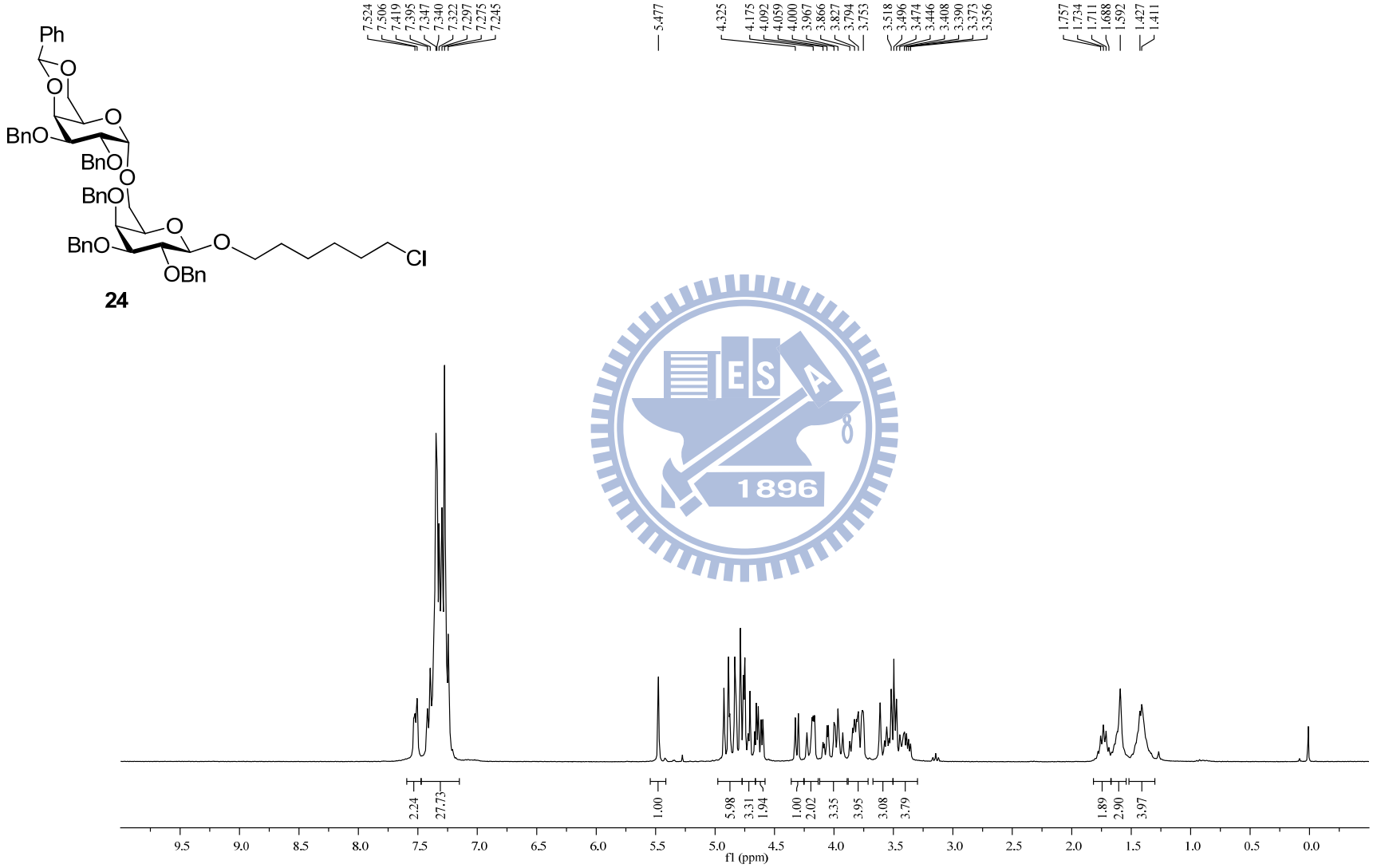
8.184
8.048
7.874
7.357
7.343
7.322
7.297
7.282
7.257
7.235
7.230
7.199
7.131
6.057
5.808
5.754
5.544
5.508
5.209
5.143
4.753
4.696
4.580
4.544
4.455
4.036
3.883
3.731
3.682
3.588
3.572
3.528
3.319
3.171
2.168
2.034
1.911
1.602
1.466
1.225
1.029
0.941
0.883
0.369
0.076
0.047
0.004
-0.000
-0.559
2.70
30.79
0.96
1.00
1.05
2.27
2.93
1.31
3.71
7.39
1.13
1.23
1.95
1.11
2.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



23

138.917
138.659
138.316
138.028
137.918
139.344
127.835
127.719
127.619
127.530
127.322
126.952
126.636
126.229
100.740
97.785
97.618
81.799
80.259
77.000
74.337
73.358
71.675
69.285
62.893
55.138




Ph
O
O
O
BnO
BnO
O
BnO
O
BnO
O
OBn
Cl
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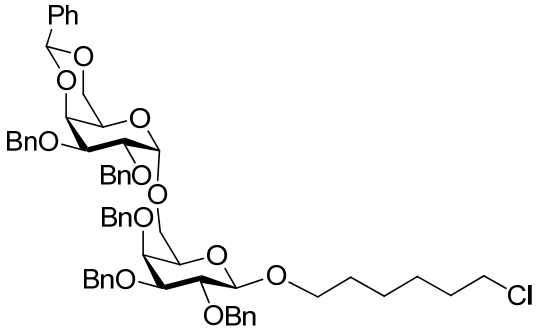
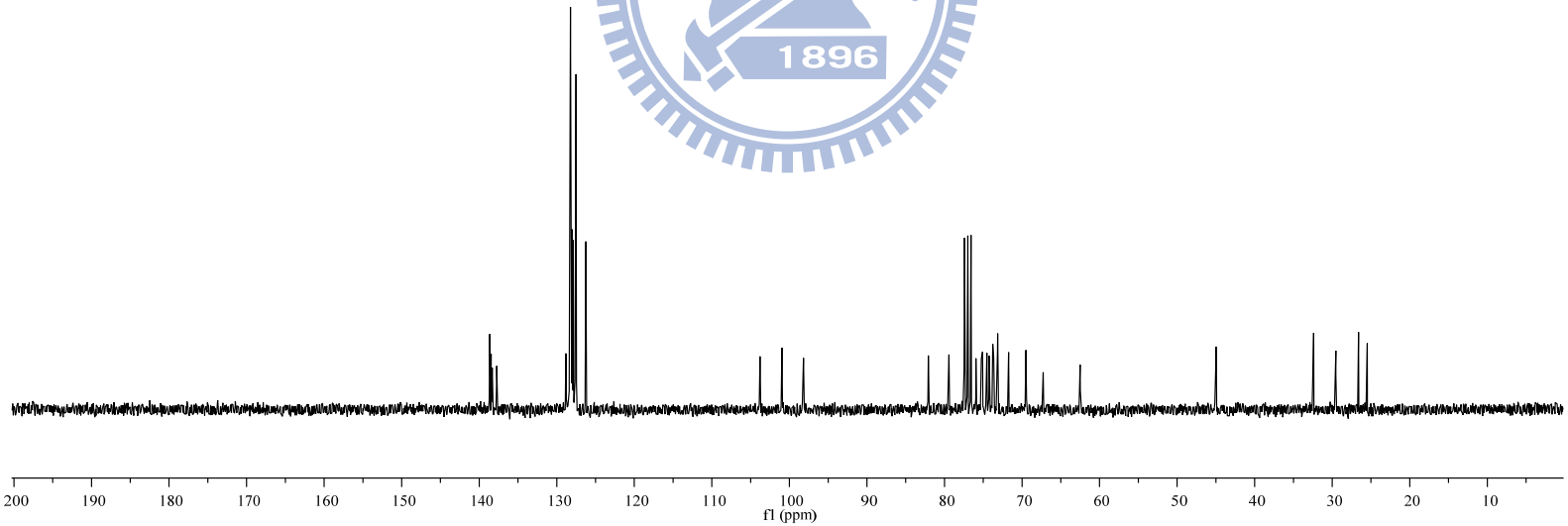
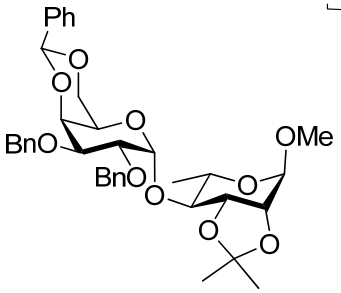
7.506
7.419
7.395
7.347
7.340
7.322
7.297
7.275
7.245
5.477
4.325
4.175
4.092
4.059
4.000
3.967
3.866
3.827
3.794
3.753
3.518
3.496
3.474
3.446
3.408
3.390
3.373
3.356
1.757
1.734
1.711
1.688
1.592
1.427
1.411
2.24
27.73
1.00
5.98
3.31
1.94
1.00
2.02
3.35
3.95
3.08
3.79
1.89
2.90
3.97
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



24

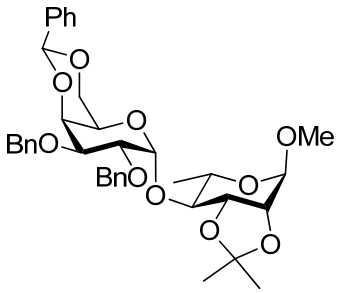
138.649
138.464
138.386
138.323
128.229
128.141
128.043
127.956
127.861
127.609
127.509
126.253
103.782
100.968
98.187
82.087
77.000
75.935
75.097
74.232
73.647
71.732
67.277
62.500
44.957
32.399
29.539
26.613
25.486




Ph
O
O
O
BnO
BnO
O
O
O
O
OMe

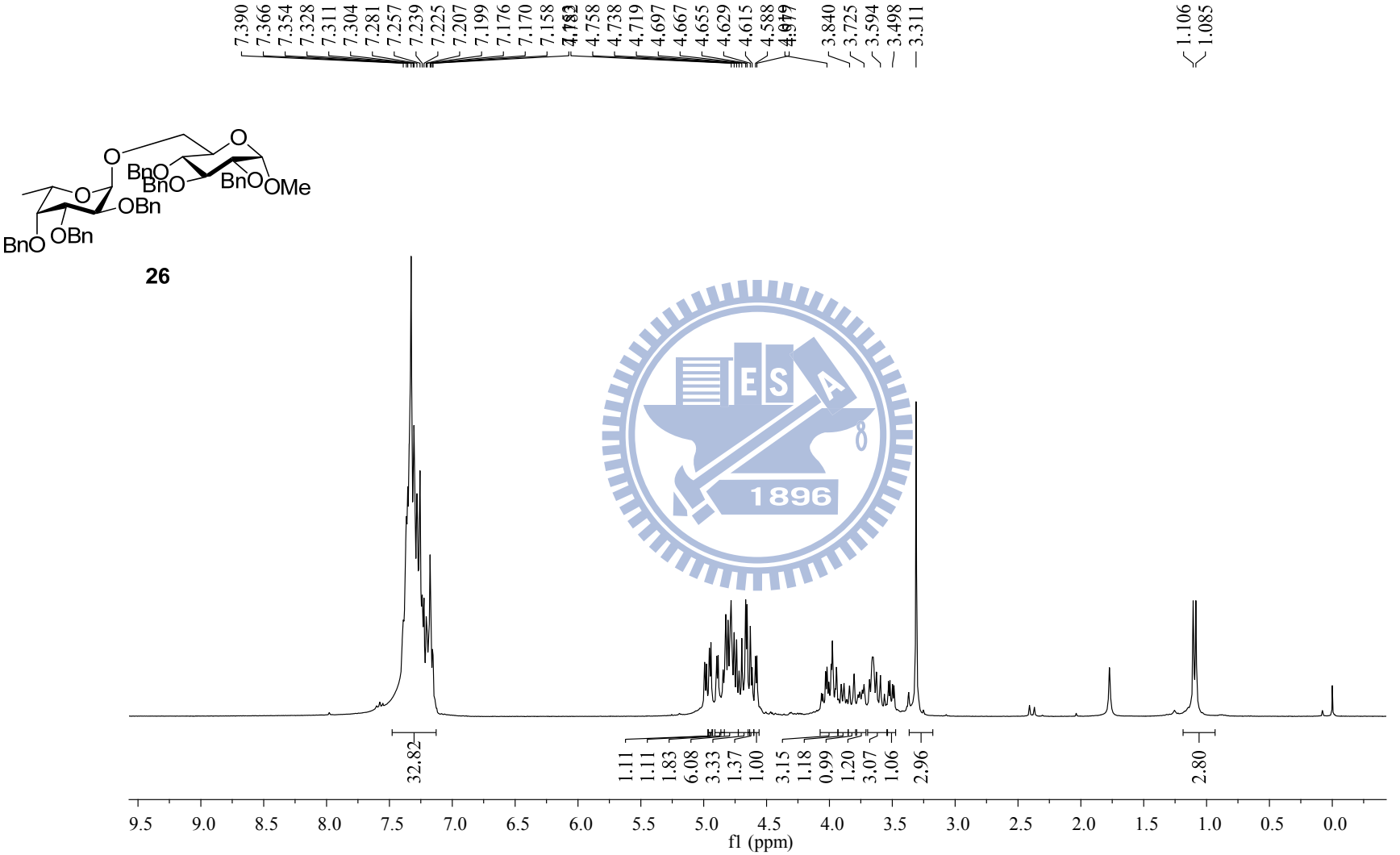
25

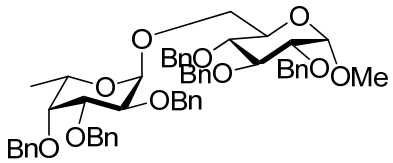
7.537
7.530
7.511
7.506
7.415
7.409
7.389
7.373
7.361
7.355
7.351
7.342
7.337
7.321
7.313
7.306
7.303
7.296
7.287
7.280
7.273
7.259
7.246
5.475
5.089
5.077
4.872
4.797
4.732
4.688
4.208
4.128
4.082
4.034
3.988
3.456
3.445
3.437
3.421
3.411
3.403
3.387
3.379
3.332
1.495
1.321
1.304
1.253
2.13
13.46
1.00
1.02
2.17
2.95
1.89
6.22
1.05
0.88
3.05
3.09
6.42
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


Ph
O
O
O
BnO
BnO
O
O
O
O
OMe

25

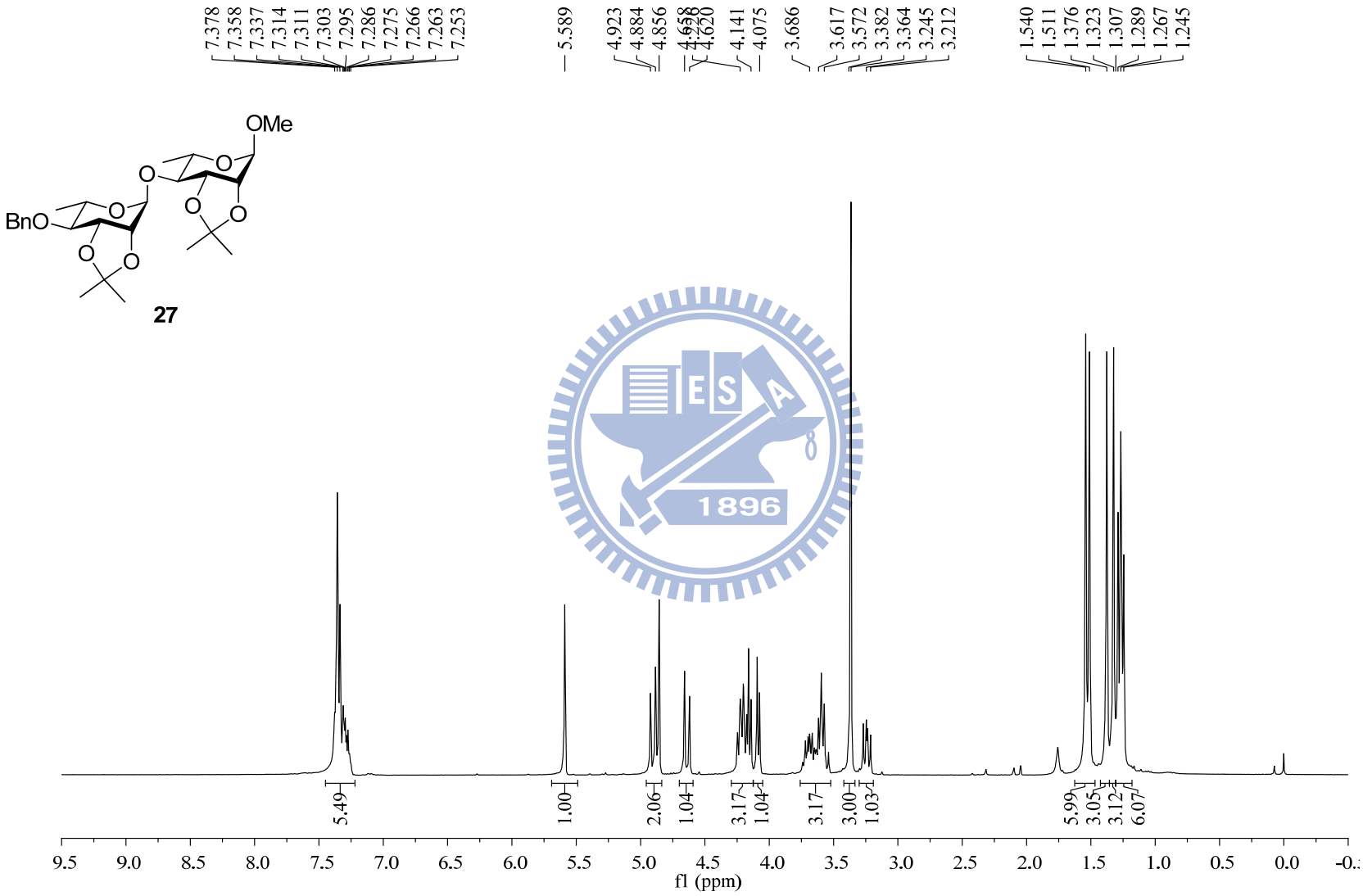
143.200
138.725
137.937
128.802
128.275
128.064
127.691
127.550
126.308
108.995
101.007
99.017
97.664
77.426
77.000
76.577
76.162
75.254
74.614
74.442
71.750
69.436
65.071
62.521
54.588
28.092
26.436
17.270
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.390
7.366
7.354
7.328
7.311
7.304
7.281
7.257
7.239
7.225
7.207
7.199
7.176
7.170
7.158
4.758
4.738
4.719
4.697
4.667
4.655
4.629
4.615
4.588
3.840
3.725
3.594
3.498
3.311
1.106
1.085
BnO
BnO
BnO
OMe
OBn
BnO
OBn
26
32.82
1.11
1.11
1.83
6.08
3.33
1.37
1.00
3.15
1.18
0.99
1.20
3.07
1.06
2.96
2.80
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
BnO
BnO
BnO
OMe
O
OBn
BnO
OBn

26

138.723
138.660
138.528
138.323
138.202
128.359
128.096
127.929
127.659
127.507
127.273
97.882
77.426
76.576
75.752
74.734
73.100
69.983
66.302
66.191
55.004
16.556
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.337
7.314
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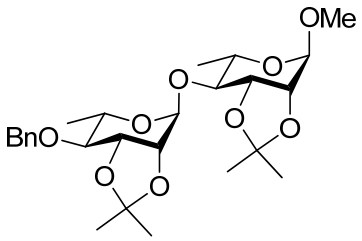
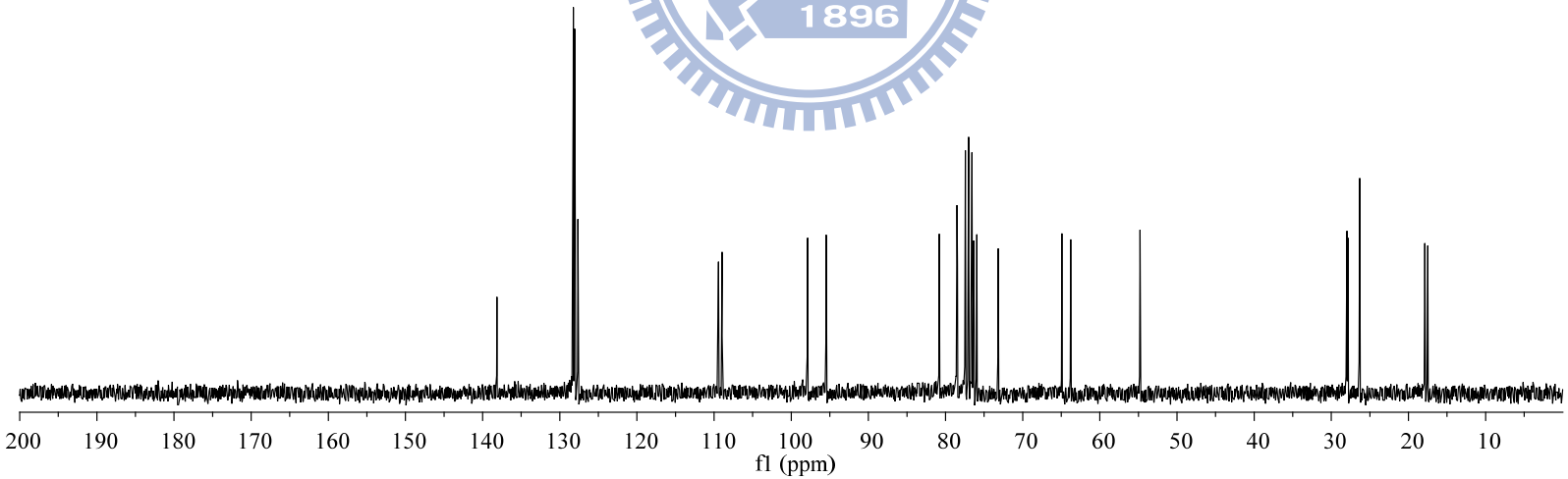
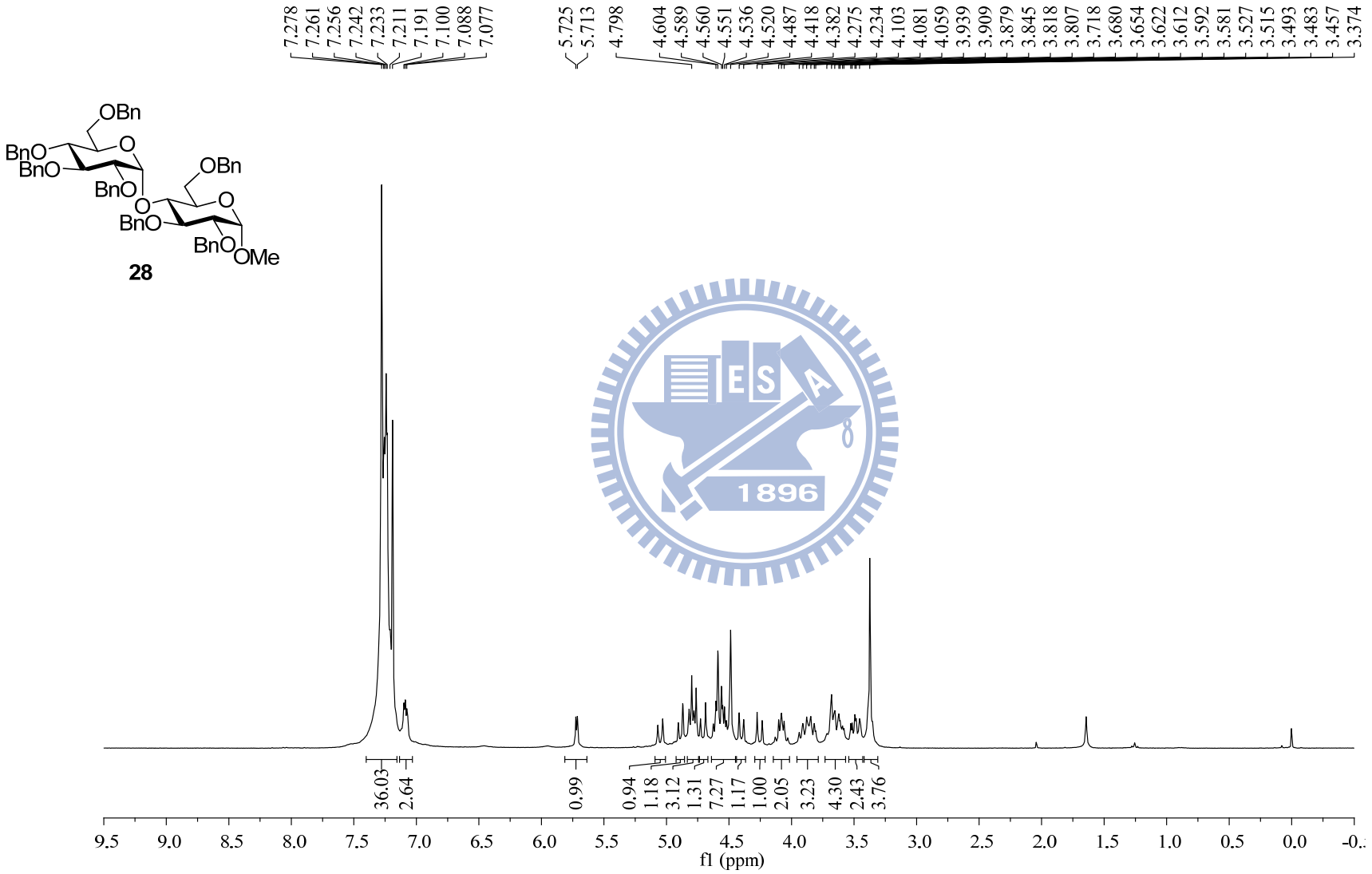
7.303
7.295
7.286
7.275
7.266
7.263
7.253
5.589
4.923
4.884
4.856
4.658
4.620
4.141
4.075
3.686
3.617
3.572
3.382
3.364
3.245
3.212
1.540
1.511
1.376
1.323
1.307
1.289
1.267
1.245
OMe
BnO
O
27
5.49
1.00
2.06
1.04
3.17
1.04
3.17
3.00
1.03
5.99
3.05
3.12
6.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



27

138.146
128.250
128.052
127.654
109.419
108.972
97.884
95.469
77.000
76.576
76.412
76.346
75.951
73.177
64.908
63.777
54.783
27.973
27.860
26.323
17.876
17.491

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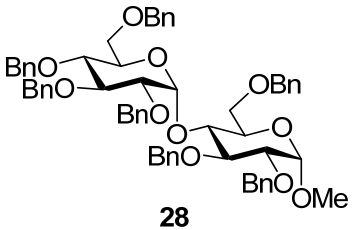
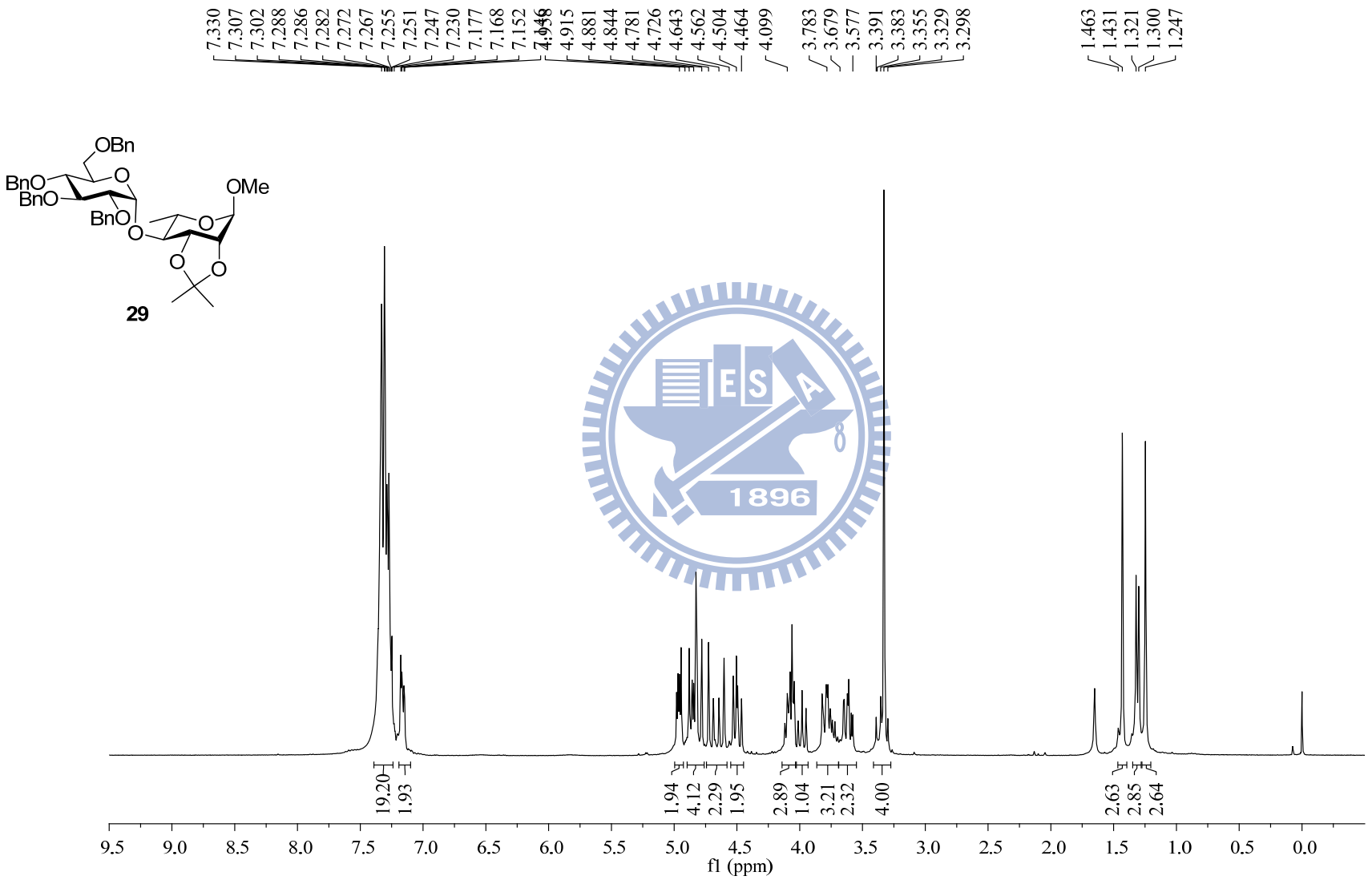
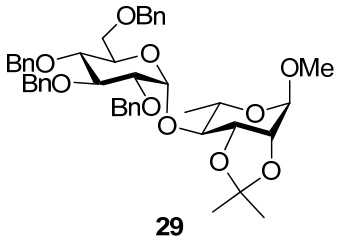
7.261
7.256
7.242
7.233
7.211
7.191
7.100
7.088
7.077
5.725
5.713
4.798
4.604
4.589
4.560
4.551
4.536
4.520
4.487
4.418
4.382
4.275
4.234
4.103
4.081
4.059
3.939
3.909
3.879
3.845
3.818
3.807
3.718
3.680
3.654
3.622
3.612
3.592
3.581
3.527
3.515
3.493
3.483
3.457
3.374
OBn
BnO
BnO
BnO
O
OBn
O
BnO
O
BnO
BnO
OMe
28
36.03
2.64
0.99
0.94
1.18
3.12
1.31
7.27
1.17
1.00
2.05
3.23
4.30
2.43
3.76
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OBn
BnO
BnO
O
BnO
O
OBn
O
BnO
BnO
OMe

28

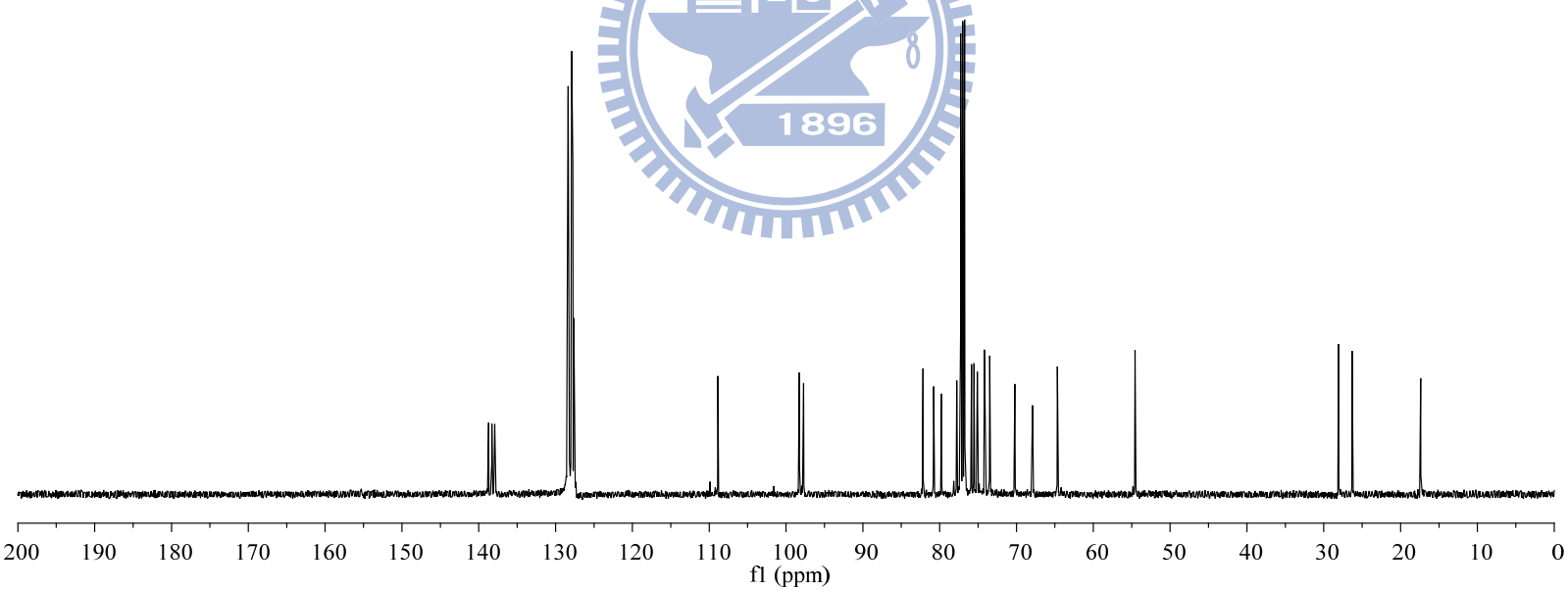
138.795
138.629
138.351
138.030
137.844
137.757
128.240
128.019
127.777
127.598
127.472
127.126
126.690
97.672
96.515
77.000
74.385
73.353
73.194
73.008
71.926
70.823
69.358
68.847
67.930
55.090
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

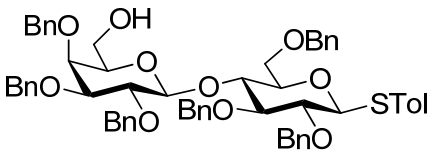

7.330
7.307
7.302
7.288
7.286
7.282
7.272
7.267
7.255
7.251
7.247
7.230
7.177
7.168
7.152
4.915
4.881
4.844
4.781
4.726
4.643
4.562
4.504
4.464
4.099
3.783
3.679
3.577
3.391
3.383
3.355
3.329
3.298
1.463
1.431
1.321
1.300
1.247
OBn
BnO
BnO
BnO
O
O
O
O
O
OMe
29
19.20
1.93
1.94
4.12
2.29
1.95
2.89
1.04
3.21
2.32
4.00
2.63
2.85
2.64
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



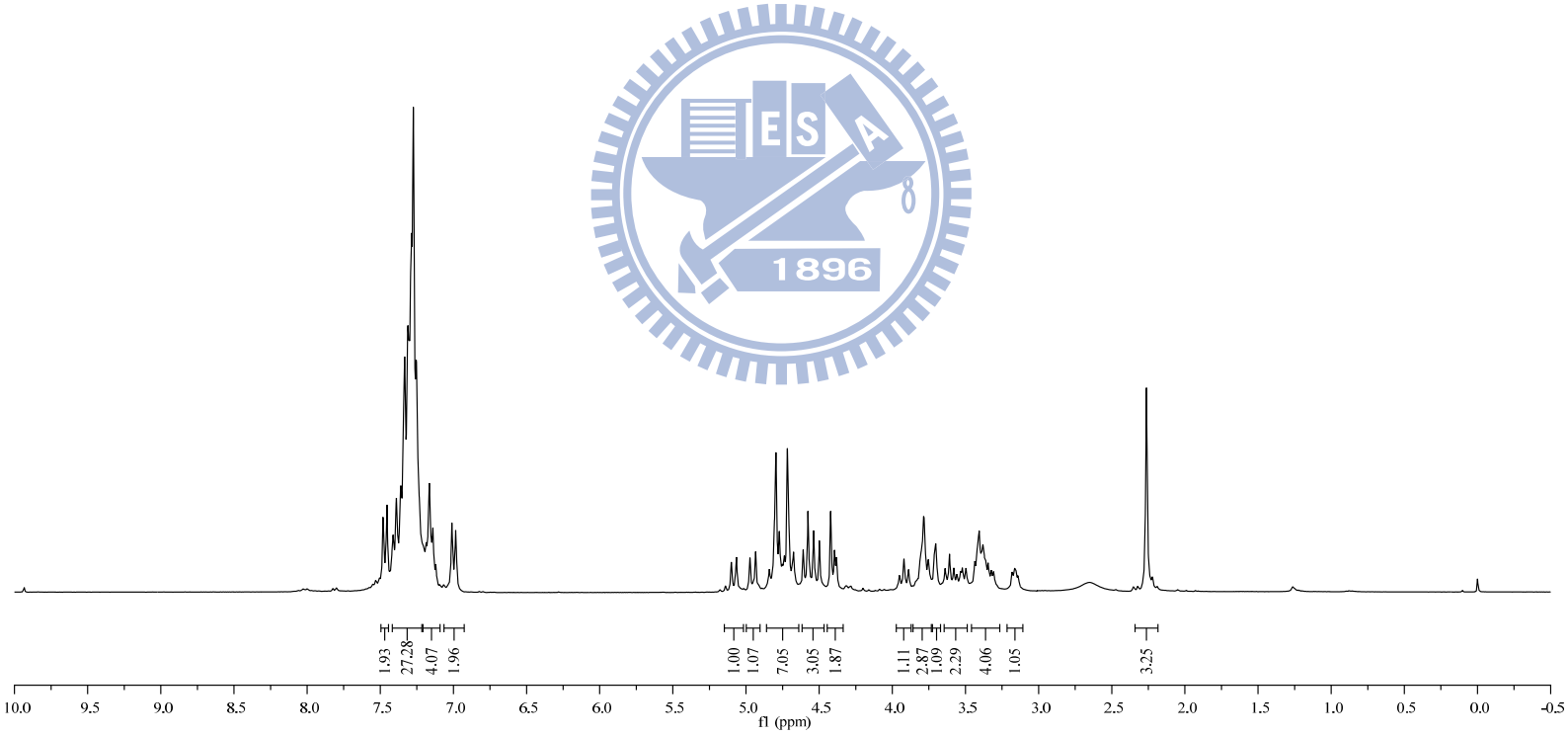
29

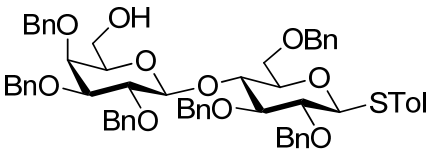
138.722
138.298
137.792
127.908
127.756
127.619
127.523
108.876
98.259
97.721
76.746
75.848
75.535
75.092
74.182
73.491
70.211
67.910
64.685
54.562
28.090
26.306
17.384




BnO
OH
O
BnO
BnO
O
OBn
O
BnO
STol
BnO

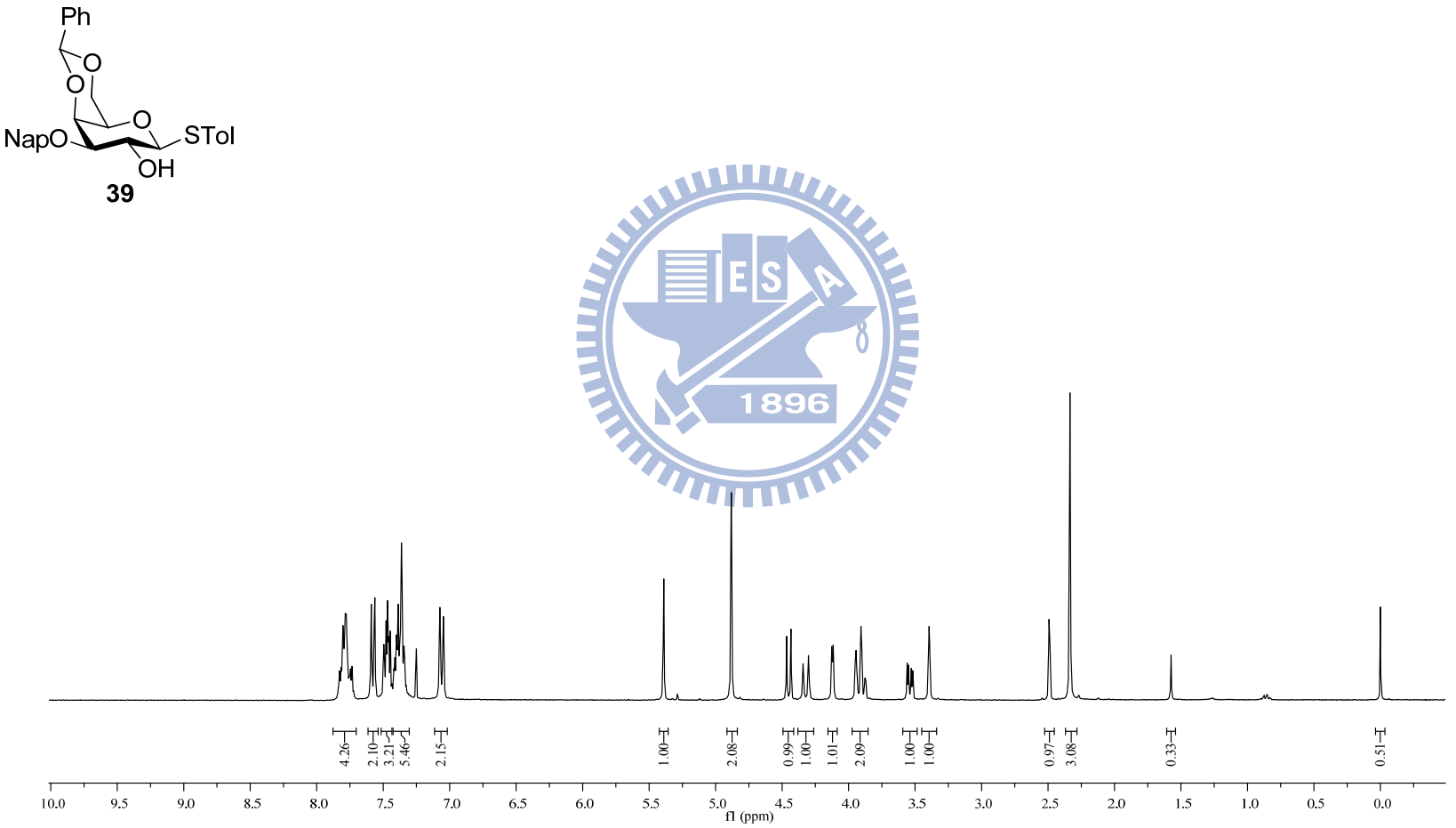
38

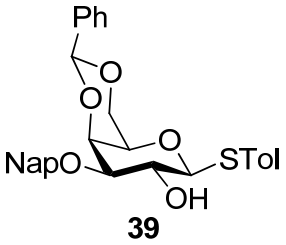

7.481
7.454
7.412
7.389
7.359
7.334
7.311
7.302
7.286
7.274
7.254
7.186
7.164
7.140
7.121
7.010
6.984
5.066
4.934
4.841
4.795
4.773
4.751
4.738
4.717
4.675
4.609
4.576
4.538
4.498
4.422
4.383
3.610
3.559
3.521
3.436
3.390
3.345
3.308
3.181
3.163
3.141
2.263
1.93
27.28
4.07
1.96
1.00
1.07
7.05
3.05
1.87
1.11
2.87
1.09
2.29
4.06
1.05
3.25
f1 (ppm)


BnO
OH
O
BnO
BnO
O
BnO
OBn
O
BnO
STol

38

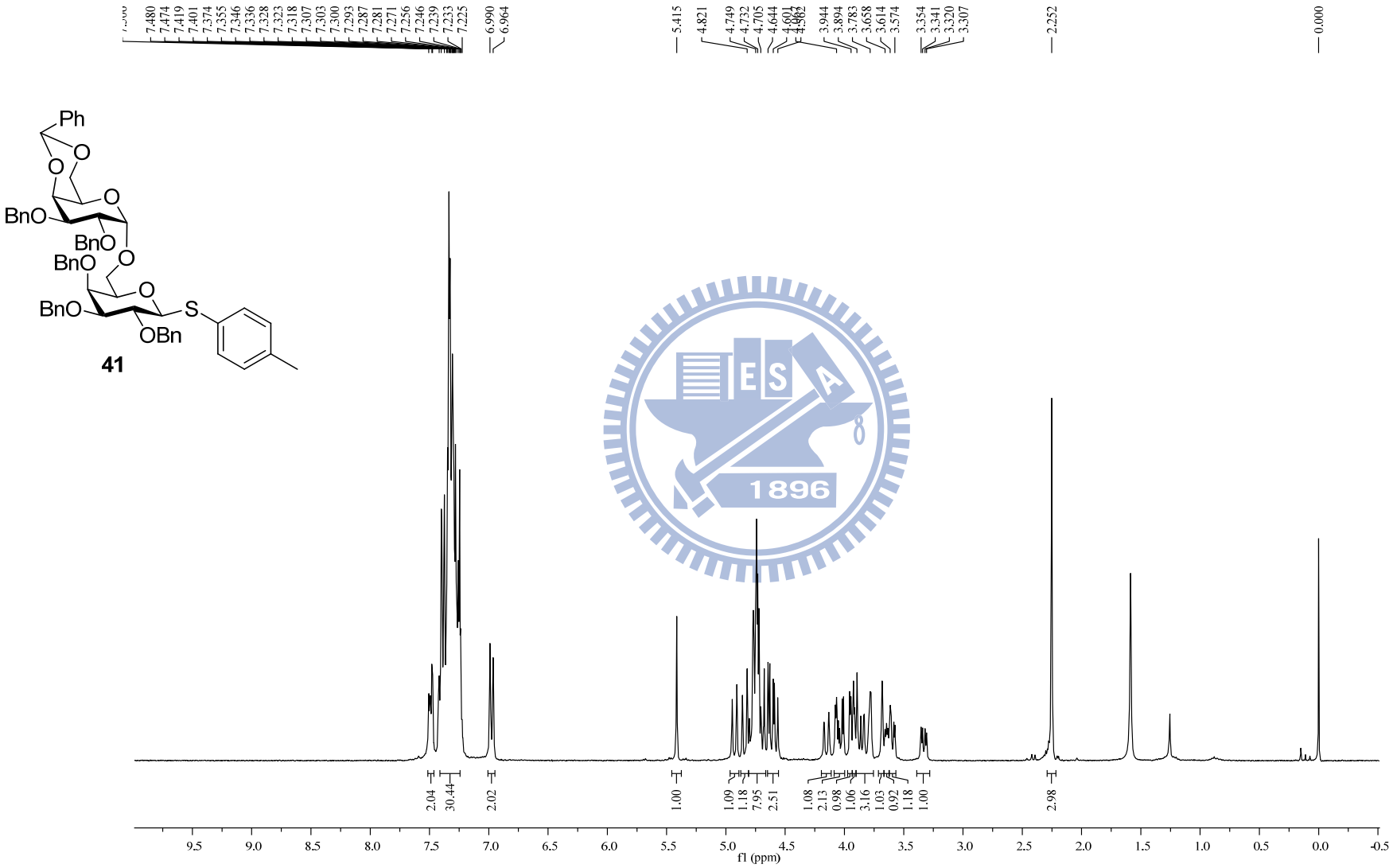
138.985
138.960
138.921
138.746
138.600
137.948
132.995
128.640
128.593
128.478
128.217
127.997
127.857
127.783
103.237
88.092
85.266
82.940
79.692
77.076
75.850
74.827
73.247
68.639
62.054
21.467
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.828
7.817
7.803
7.785
7.777
7.755
7.746
7.735
7.468
7.412
7.339
7.074
7.047
5.390
4.882
4.465
4.433
4.342
4.301
4.116
3.907
3.871
3.548
3.517
3.394
2.492
2.486
2.335
Ph
O
O
O
NapO
STol
OH
39
4.26
2.10
3.21
5.46
2.15
1.00
2.08
0.99
1.00
1.01
2.09
1.00
1.00
0.97
3.08
0.33
0.51
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Ph
O
O
O
NapO
STol
OH

39

138.373
137.795
134.361
132.995
129.653
127.661
126.679
126.599
126.404
126.143
125.986
125.745
101.131
87.038
80.051
76.566
73.368
71.826
69.955
69.329
67.125
21.210
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.480
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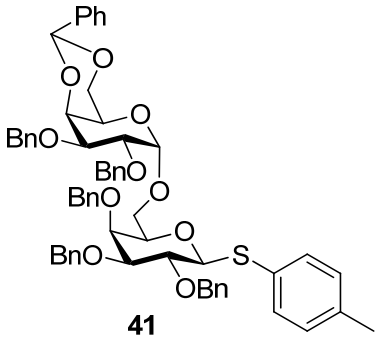
7.374
7.355
7.346
7.336
7.328
7.323
7.318
7.307
7.303
7.300
7.293
7.287
7.281
7.271
7.256
7.246
7.239
7.233
7.225
6.990
6.964
5.415
4.821
4.749
4.732
4.705
4.644
4.601
4.582
3.944
3.894
3.783
3.658
3.614
3.574
3.354
3.341
3.320
3.307
2.252
0.000
Ph
O
O
O
BnO
BnO
BnO
O
O
BnO
S
OBn
41
2.04
30.44
2.02
1.00
1.09
1.18
7.95
2.51
1.08
2.13
0.98
1.06
3.16
1.03
0.92
1.18
1.00
2.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



41

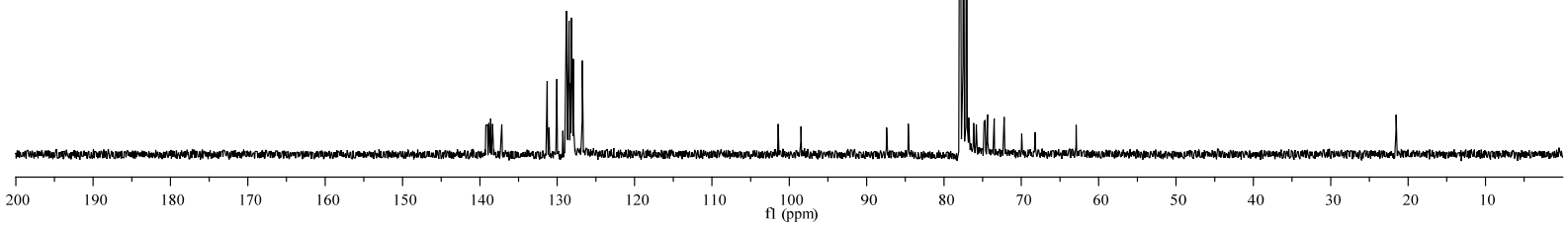
139.224
139.223
139.013
139.013
138.853
138.853
138.661
138.661
138.597
138.597
138.353
138.353
137.169
128.804
128.781
128.543
128.481
128.172
128.114
127.916
126.766

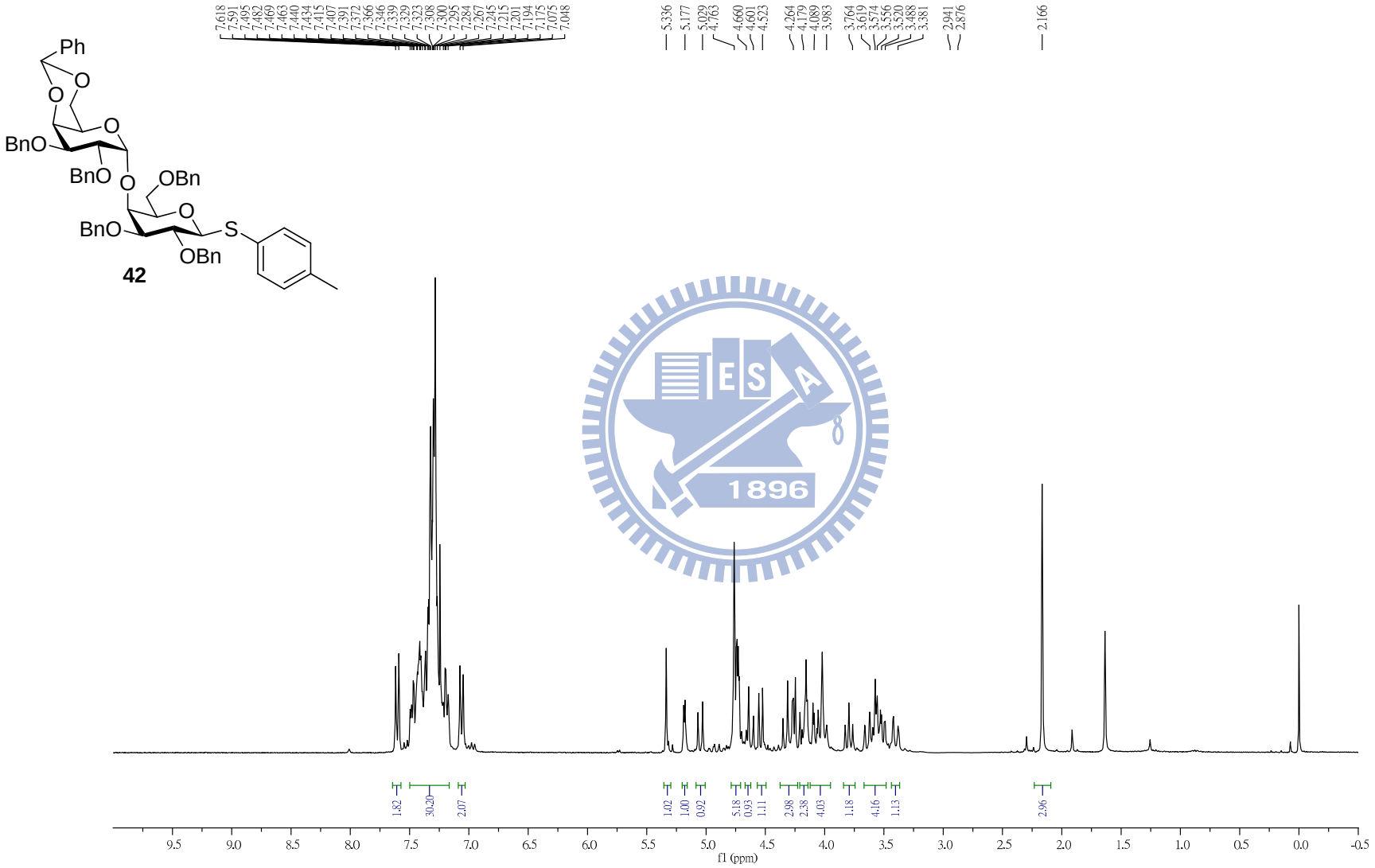
101.429
101.427
98.493
98.492

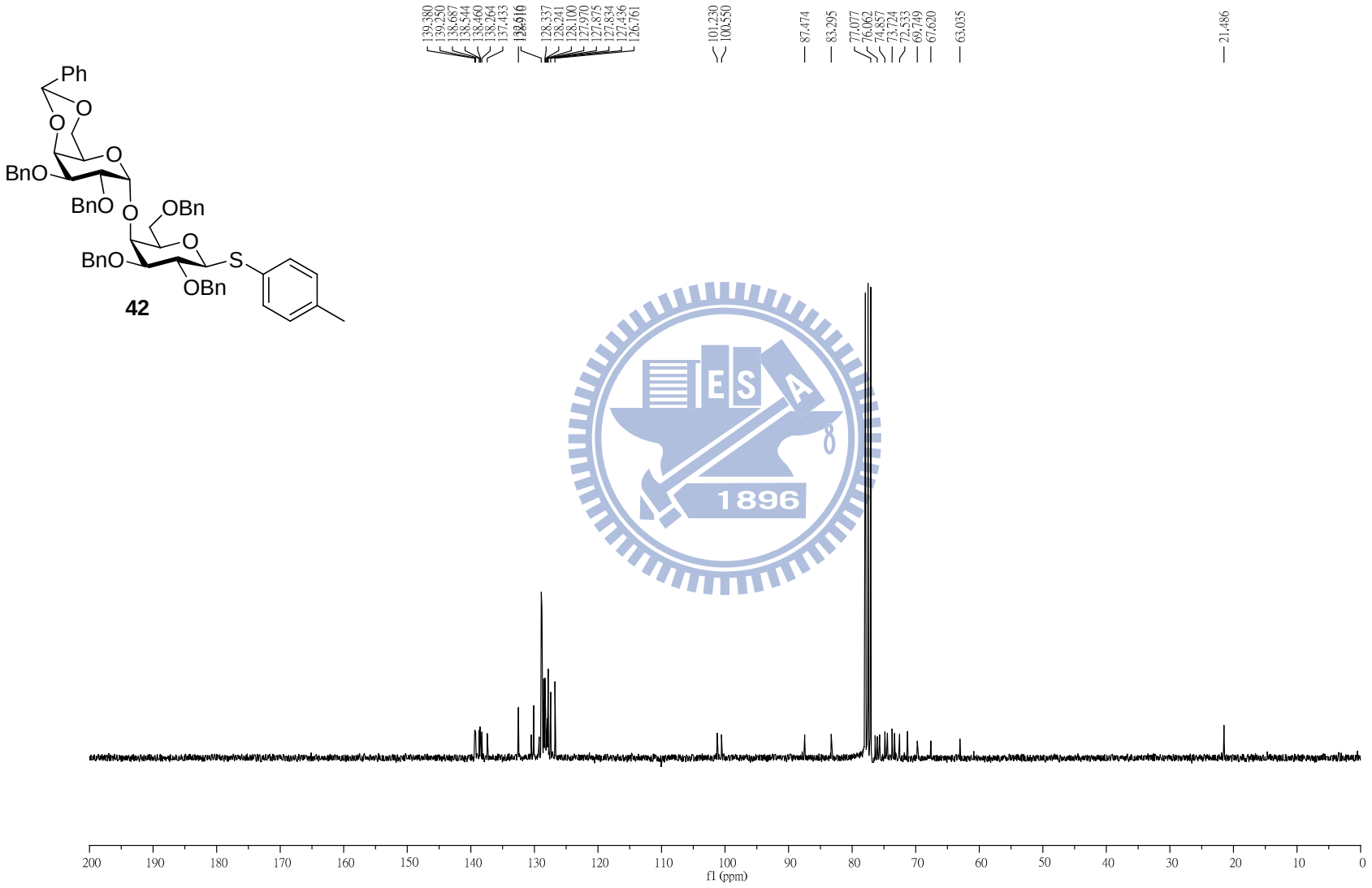
87.418
87.417
84.619
84.618
77.500
76.800
74.809
74.420
72.227
68.207

62.902
62.901

21.550
21.549




Ph
O
O
O
BnO
BnO
O
OBn
O
BnO
S
OBn
42
7.618
7.591
7.495
7.482
7.469
7.463
7.440
7.434
7.415
7.407
7.391
7.372
7.366
7.346
7.339
7.329
7.323
7.308
7.300
7.295
7.284
7.267
7.245
7.215
7.201
7.194
7.175
7.075
7.048
5.336
5.177
5.029
4.763
4.660
4.601
4.523
4.264
4.179
4.089
3.983
3.764
3.619
3.574
3.556
3.520
3.488
3.381
2.941
2.876
2.166
1.83
30.20
2.07
1.02
1.00
0.92
5.18
0.93
1.11
2.98
2.38
4.03
1.18
4.16
1.13
2.96
f1 (ppm)


Ph
O
O
O
BnO
BnO
O
OBn
O
BnO
S
OBn
42
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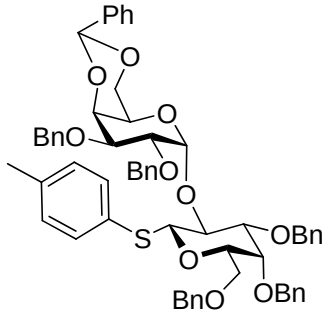
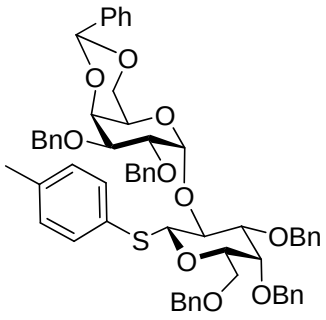
139.250
138.687
138.544
138.460
138.264
137.433
128.337
128.241
128.100
127.970
127.875
127.834
127.436
126.761
101.230
100.550
87.474
83.295
77.077
76.062
74.857
73.724
72.533
69.749
67.620
63.035
21.486
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

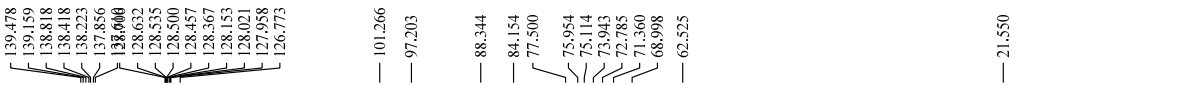

Ph
O
O
O
BnO
BnO
O
S
OBn
O
BnO
OBn

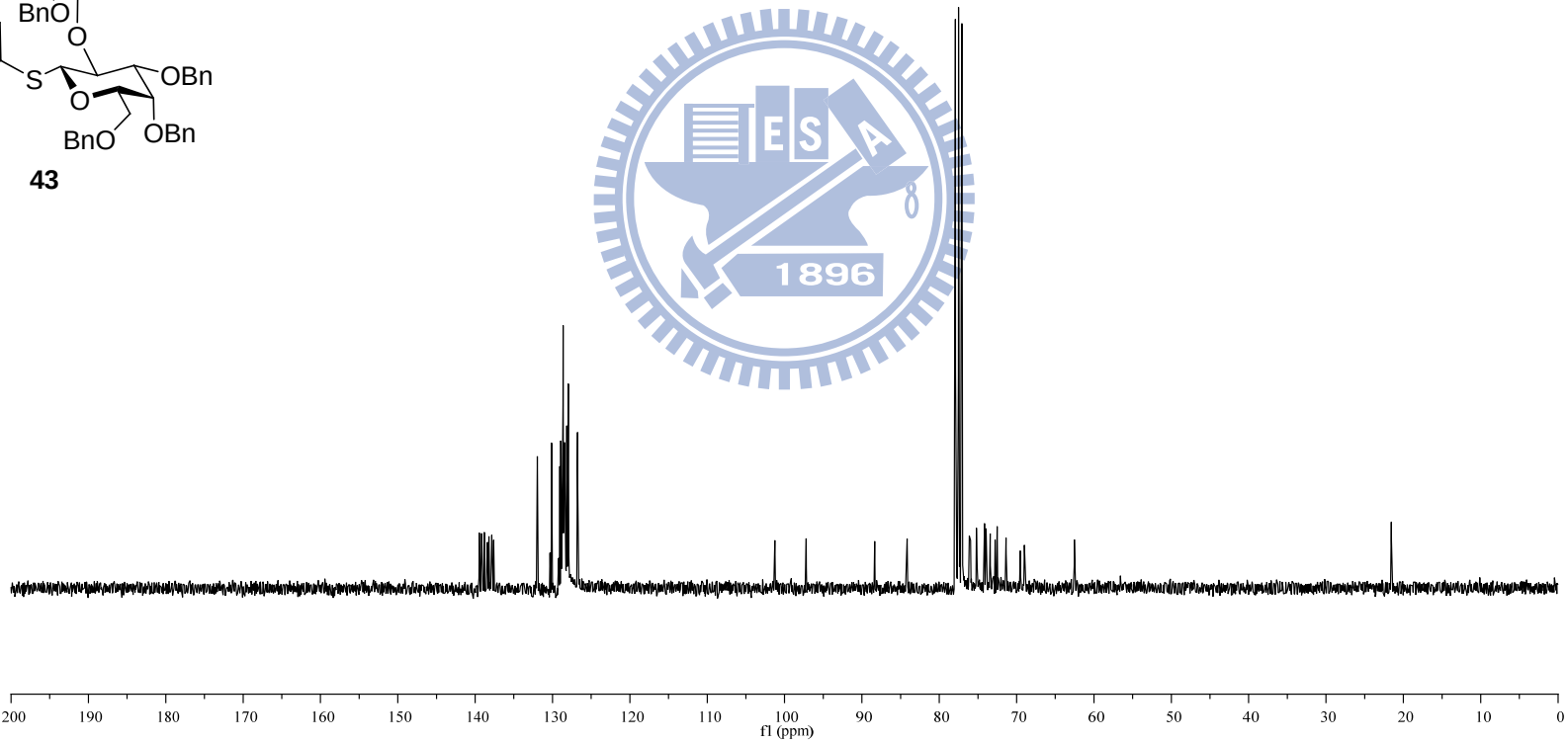
43

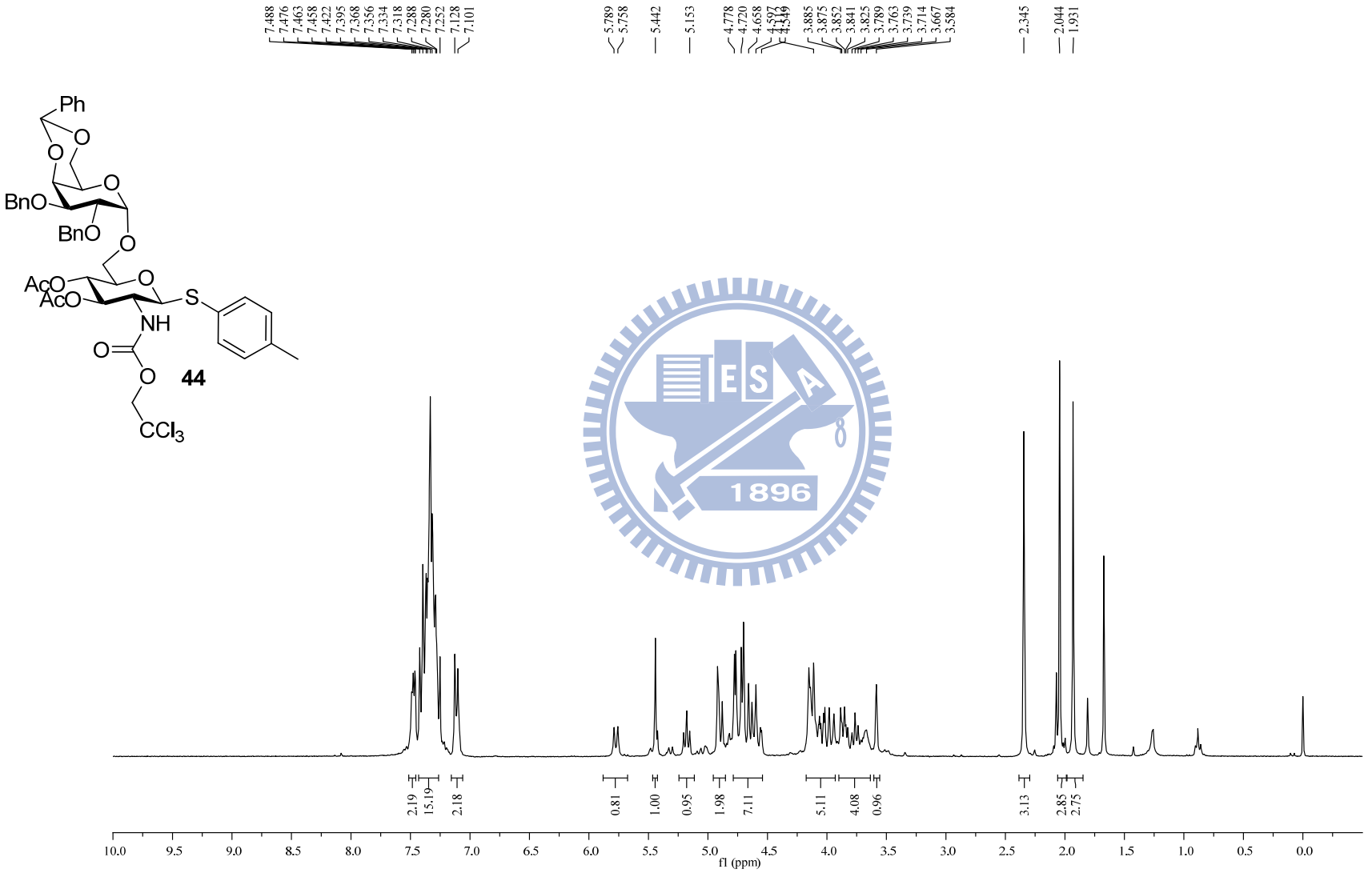
7.442
7.435
7.424
7.387
7.380
7.359
7.351
7.343
7.336
7.320
7.311
7.305
7.295
7.281
7.276
7.265
7.242
7.232
7.226
7.218
7.210
7.207
7.203
7.192
7.058
7.036
7.031
6.969
6.943
5.893
5.881
4.661
4.513
4.450
4.333
4.270
4.220
4.099
4.072
3.969
3.892
3.858
3.784
3.669
3.639
3.030
2.993
2.276
1.589
0.000
30.49
2.13
2.02
1.00
1.00
2.05
3.25
3.30
2.25
2.12
1.04
5.13
1.01
2.98
f1 (ppm)

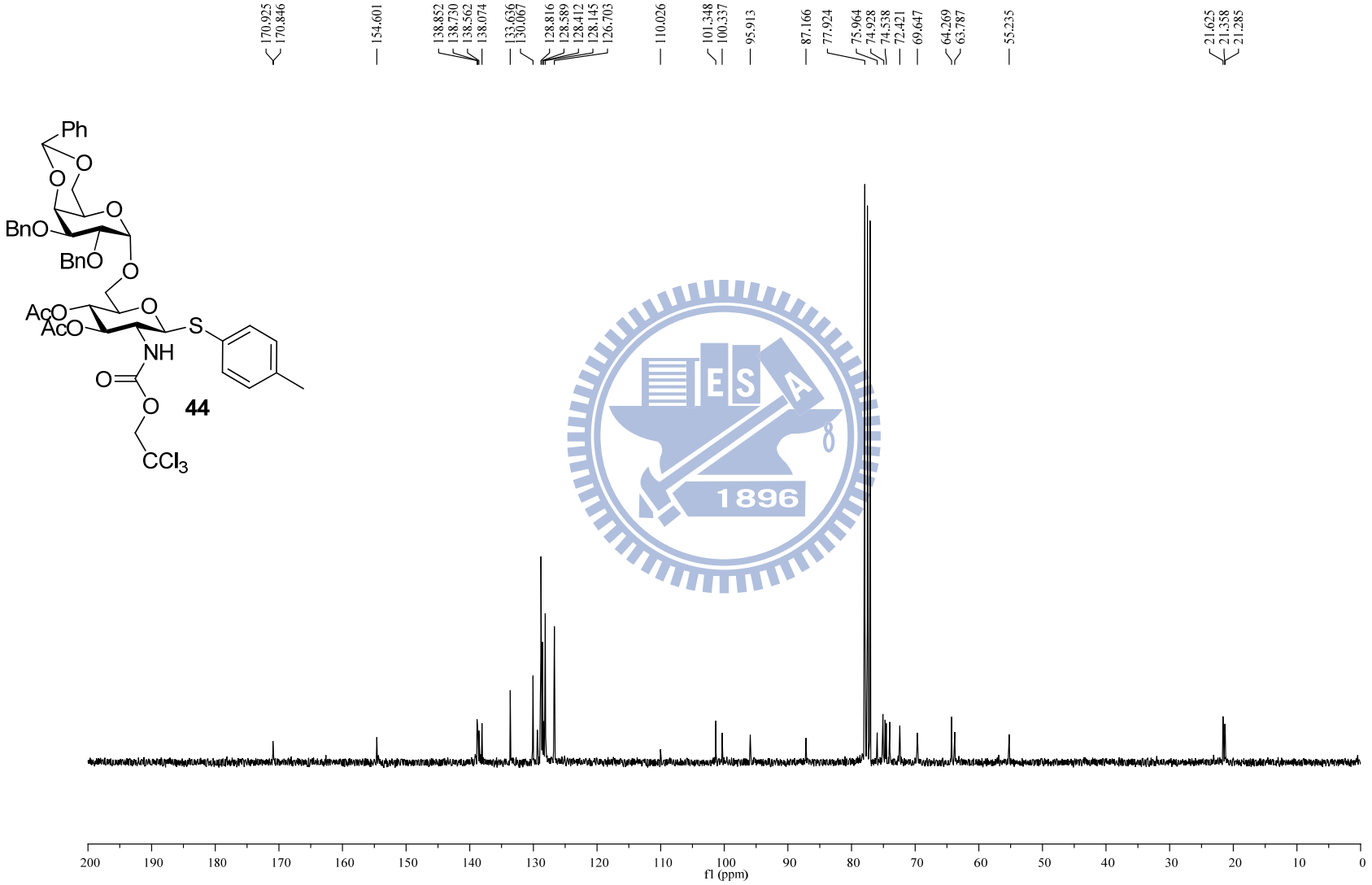

Ph
O
O
O
BnO
BnO
O
S
OBn
O
BnO
OBn

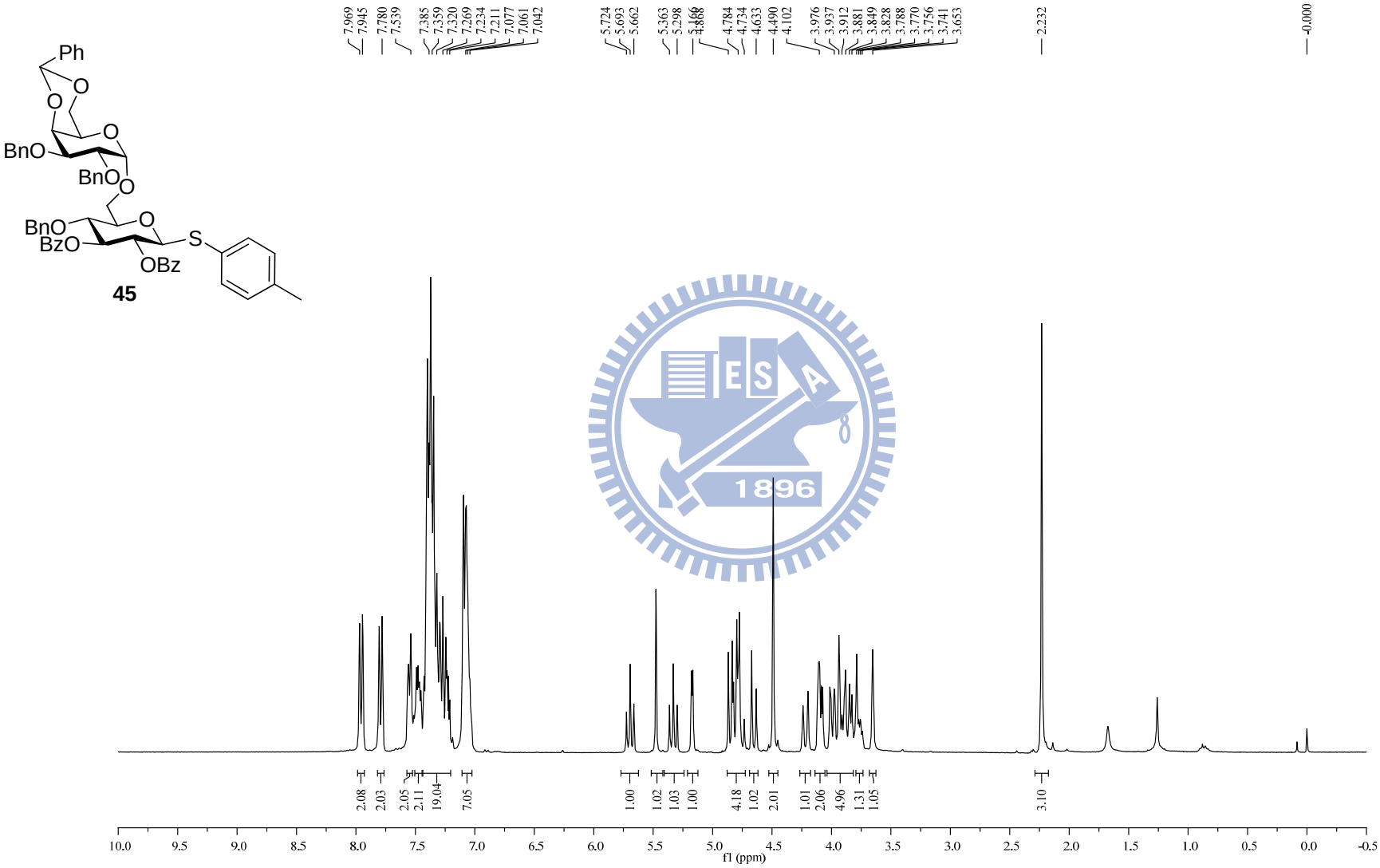
43

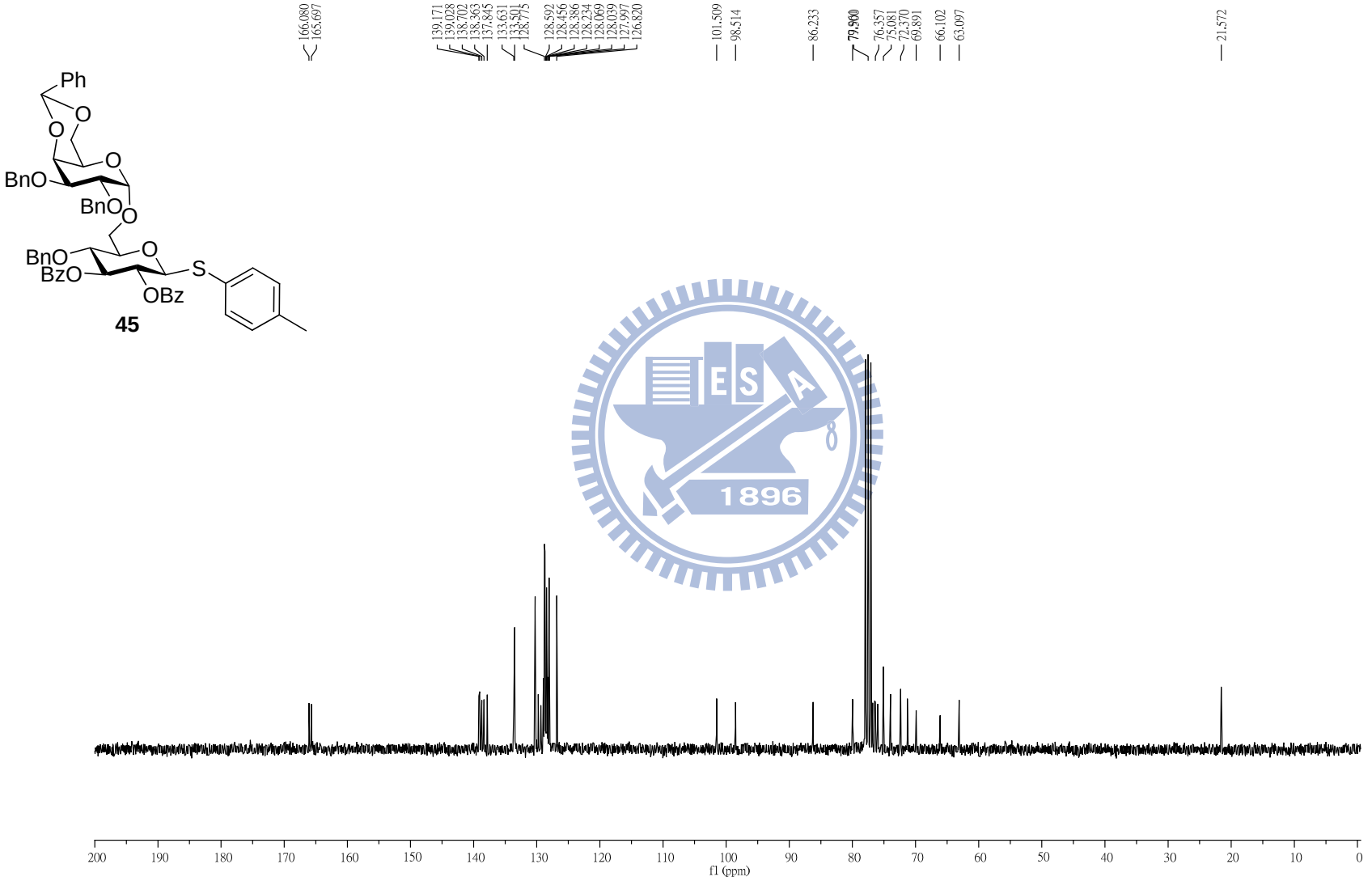

139.478
139.159
138.818
138.418
138.223
137.856
128.632
128.535
128.500
128.457
128.367
128.153
128.021
127.958
126.773
101.266
97.203
88.344
84.154
77.500
75.954
75.114
73.943
72.785
71.360
68.998
62.525
21.550

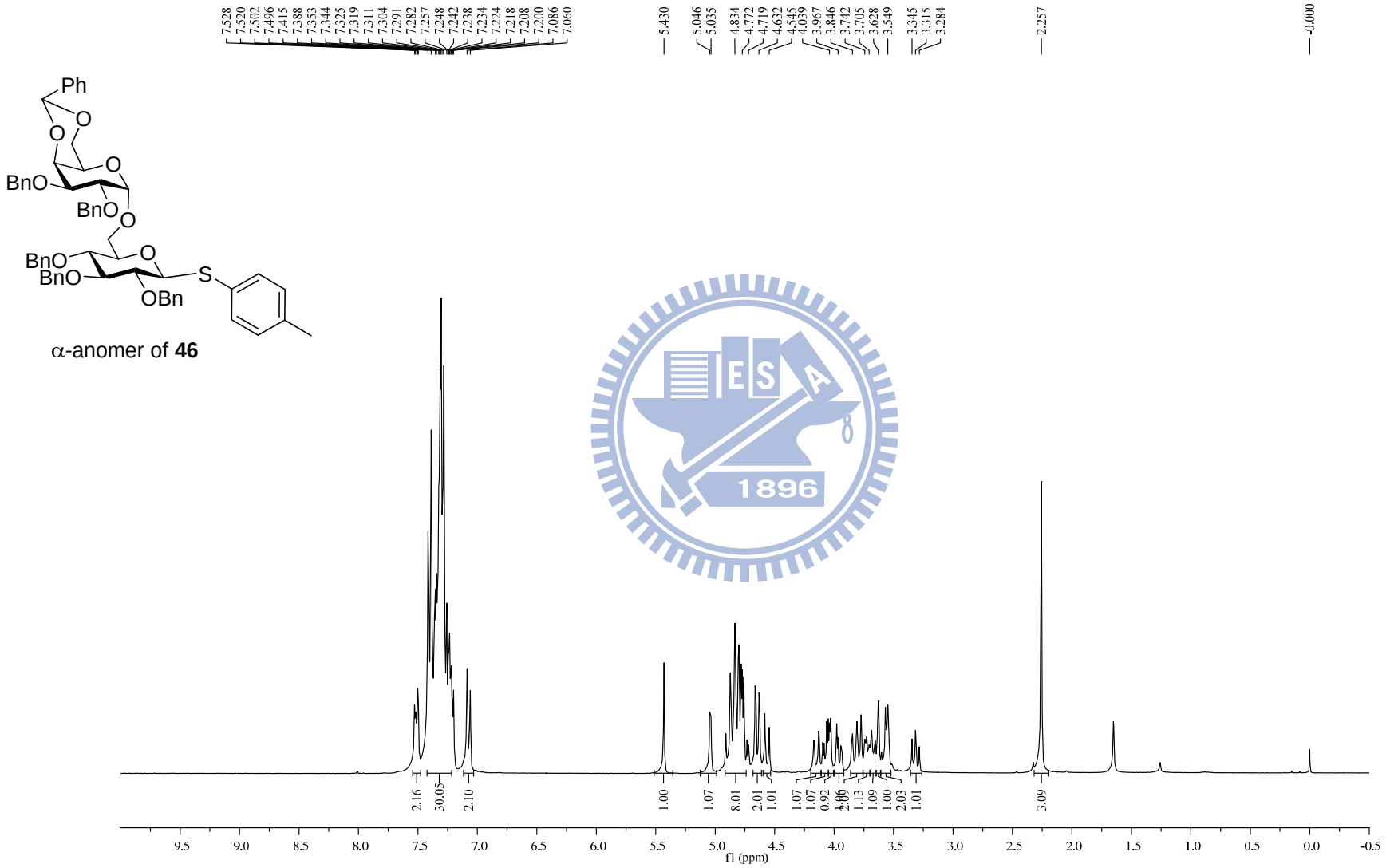

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.488
7.476
7.463
7.458
7.422
7.395
7.368
7.356
7.334
7.318
7.288
7.280
7.252
7.128
7.101
5.789
5.758
5.442
5.153
4.778
4.720
4.658
3.885
3.875
3.852
3.841
3.825
3.789
3.763
3.739
3.714
3.667
3.584
2.345
2.044
1.931
Ph
BnO
BnO
AcO
AcO
NH
S
44
CCl3
2.19
15.19
2.18
0.81
1.00
0.95
1.98
7.11
5.11
4.08
0.96
3.13
2.85
2.75
f1 (ppm)

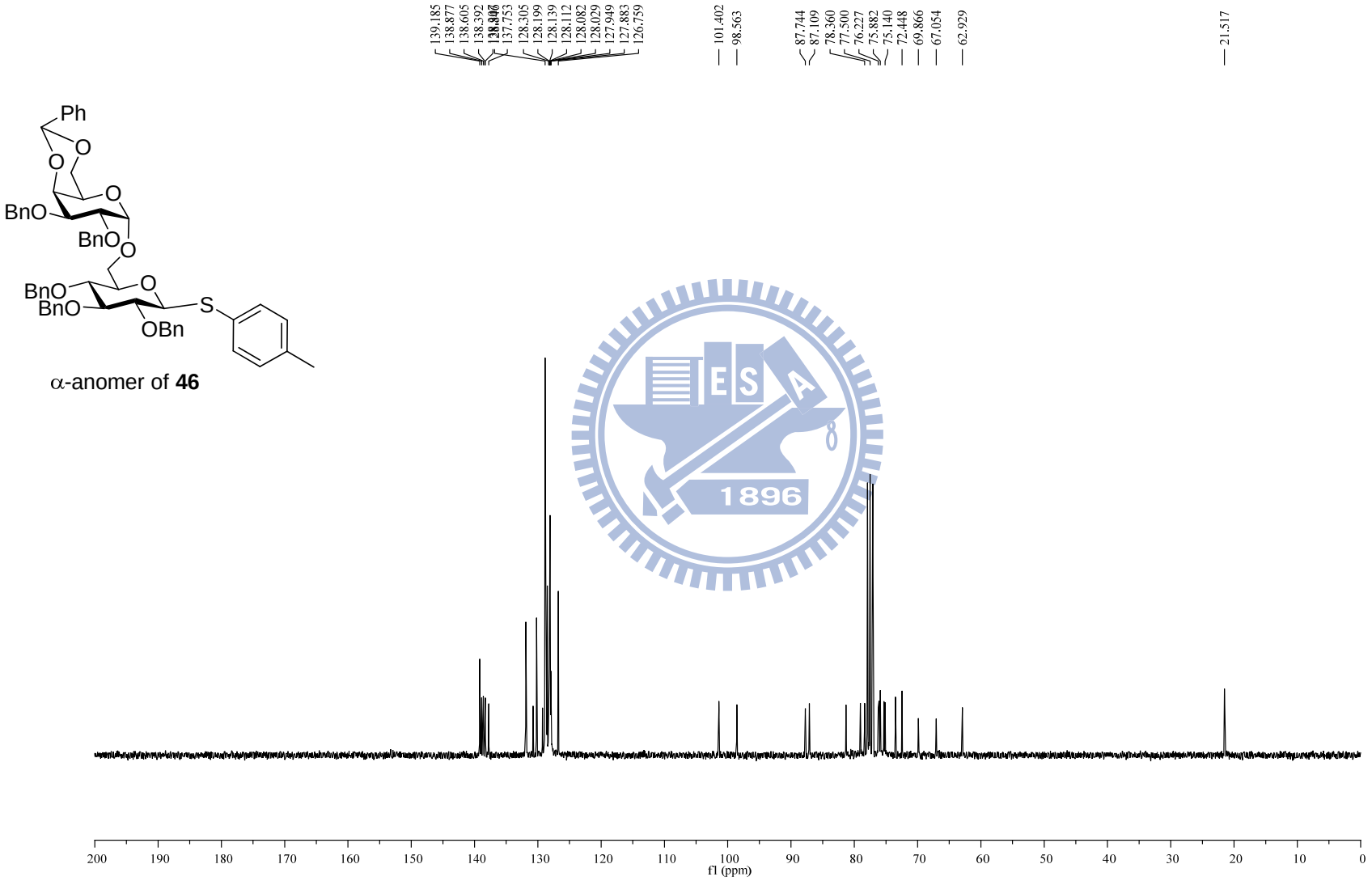

170.925
170.846
154.601
138.852
138.730
138.562
138.074
133.636
130.067
128.816
128.589
128.412
128.145
126.703
110.026
101.348
100.337
95.913
87.166
77.924
75.964
74.928
74.538
72.421
69.647
64.269
63.787
55.235
21.625
21.358
21.285
Ph
BnO
BnO
AcO
AcO
NH
S
44
CCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Ph
O
O
O
BnO
O
BnO
O
BnO
O
BzO
S
OBz
45
7.969
7.945
7.780
7.539
7.385
7.359
7.320
7.269
7.234
7.211
7.077
7.061
7.042
5.724
5.693
5.662
5.363
5.298
4.784
4.734
4.633
4.490
4.102
3.976
3.937
3.912
3.881
3.849
3.828
3.788
3.770
3.756
3.741
3.653
2.232
-0.000
2.08
2.03
2.05
2.11
19.04
7.05
1.00
1.02
1.03
1.00
4.18
1.02
2.01
1.01
2.06
4.96
1.31
1.05
3.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

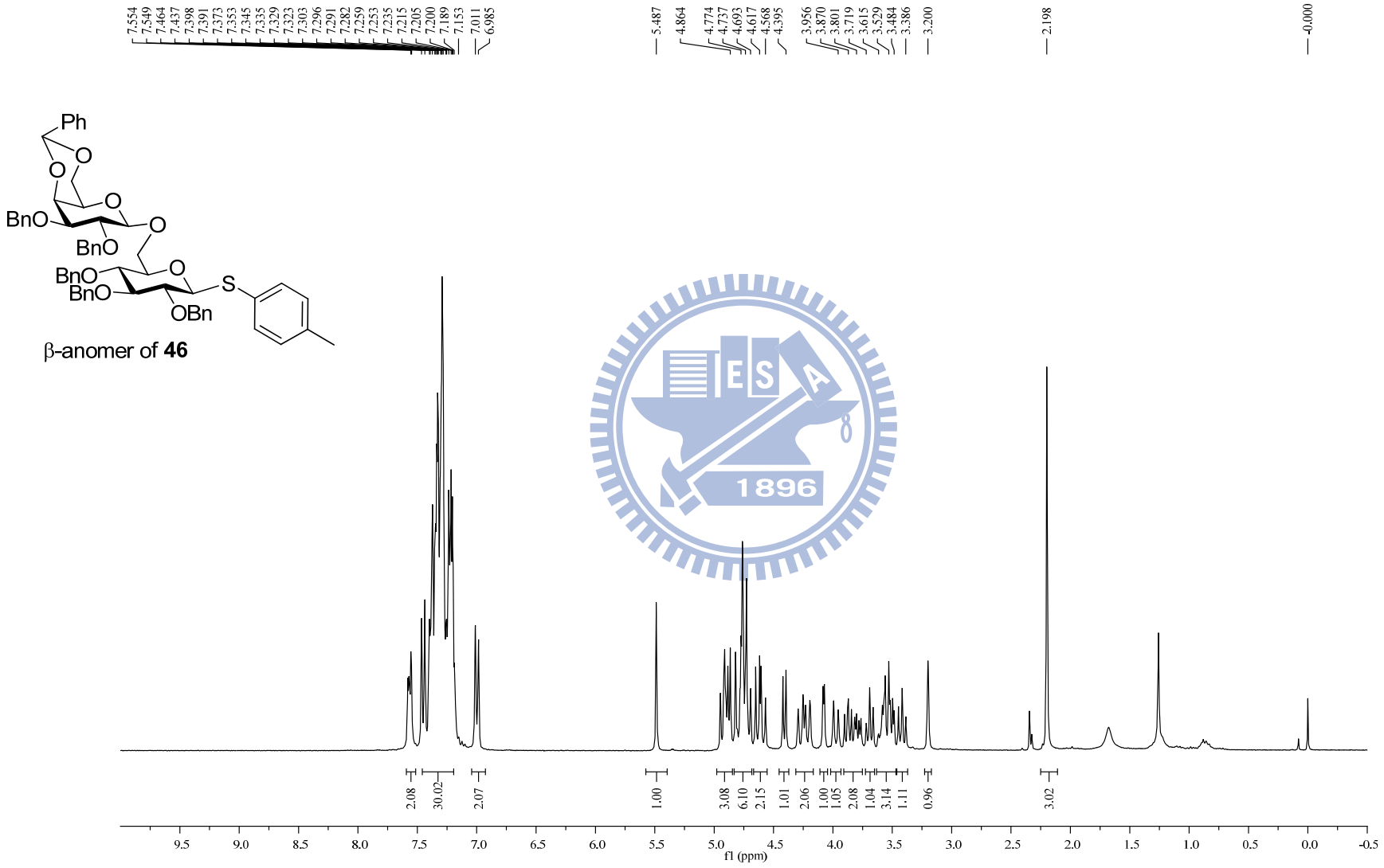

166.080
165.697
139.171
139.028
138.702
138.363
137.845
133.631
133.501
128.775
128.592
128.456
128.386
128.234
128.069
128.039
127.997
126.820
101.509
98.514
86.233
79.960
79.900
76.357
75.081
72.370
69.891
66.102
63.097
21.572
Ph
O
O
O
BnO
BnO
O
BnO
BzO
O
S
OBz
45
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

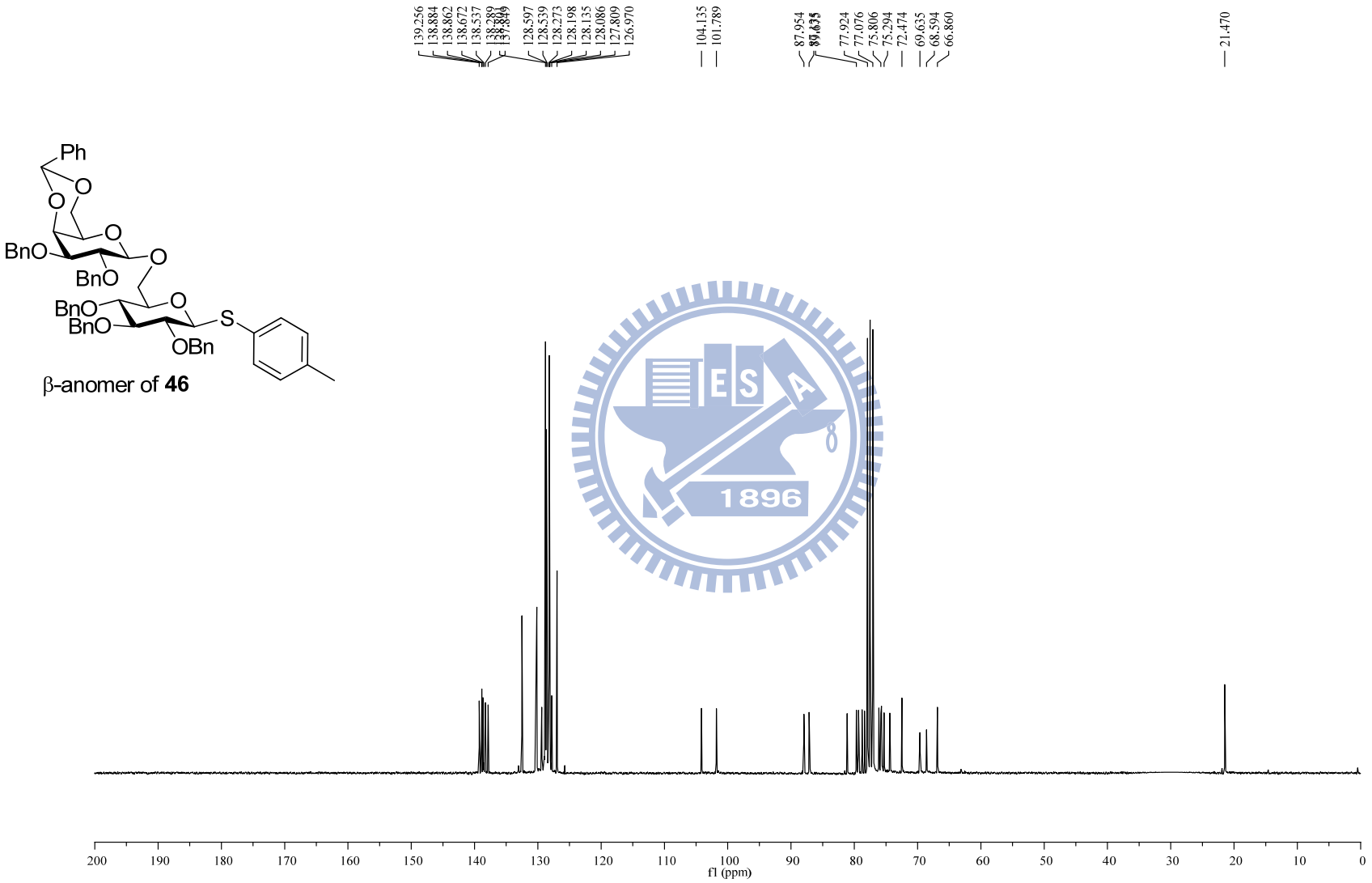


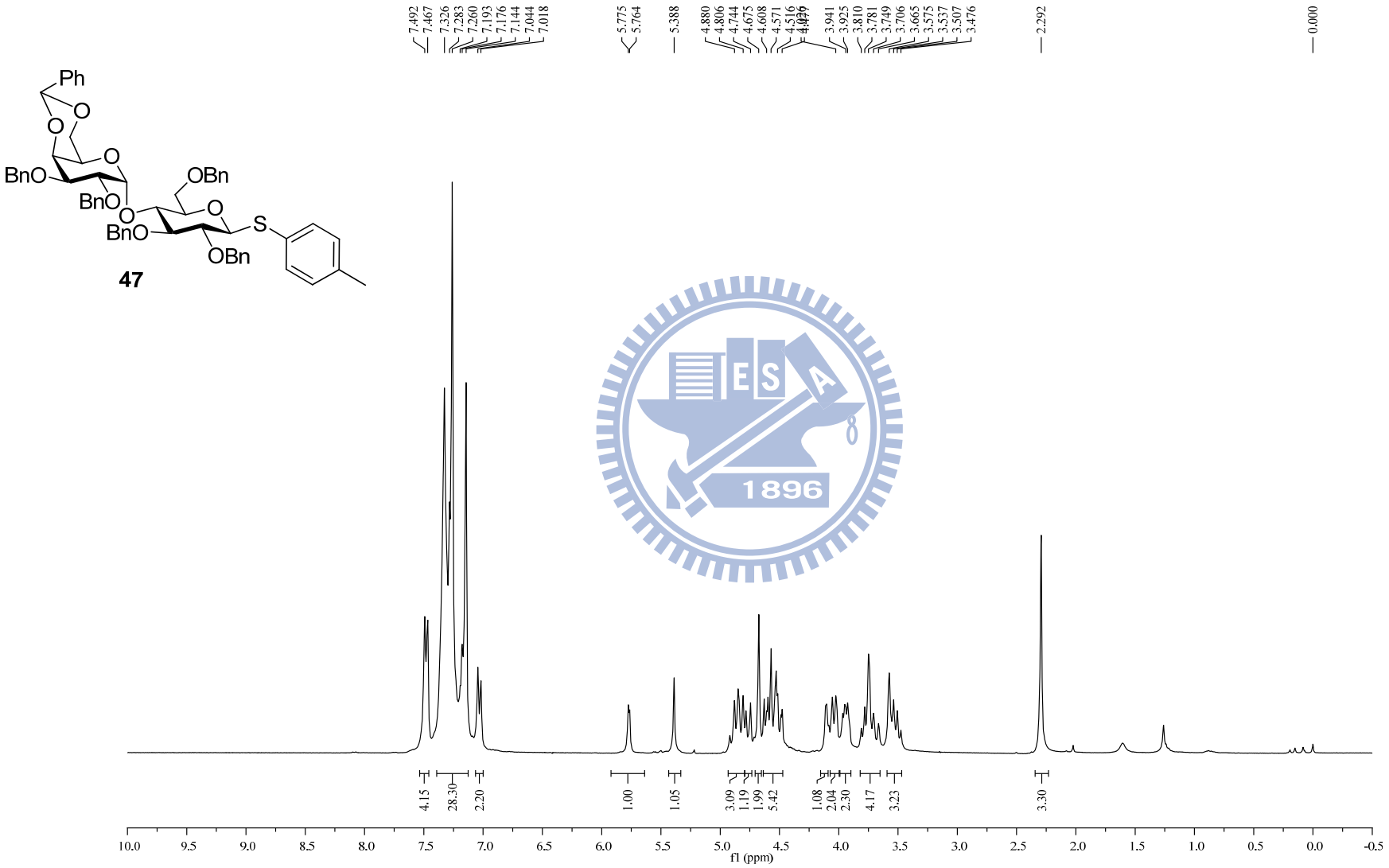
α-anomer of **46**

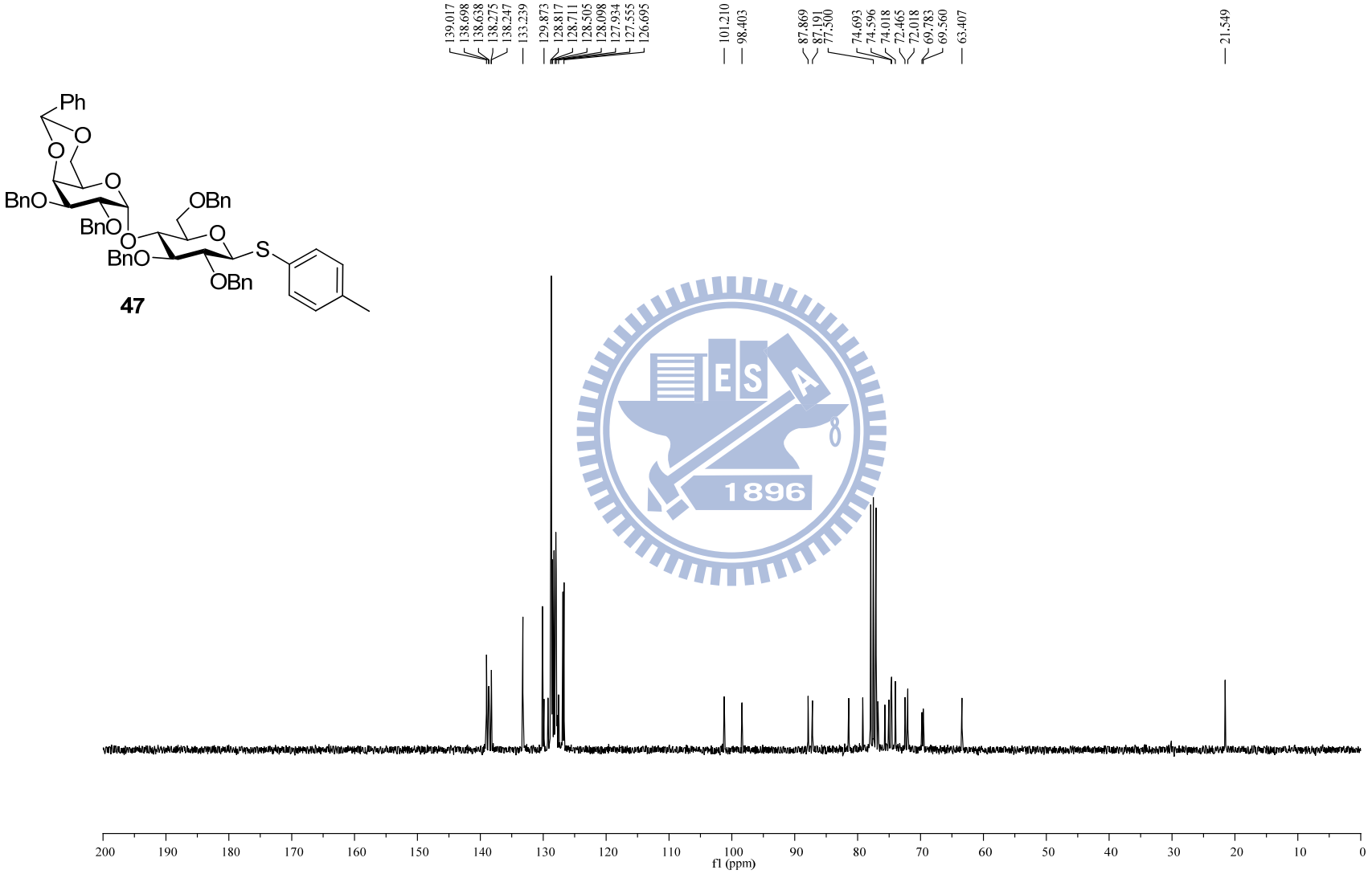


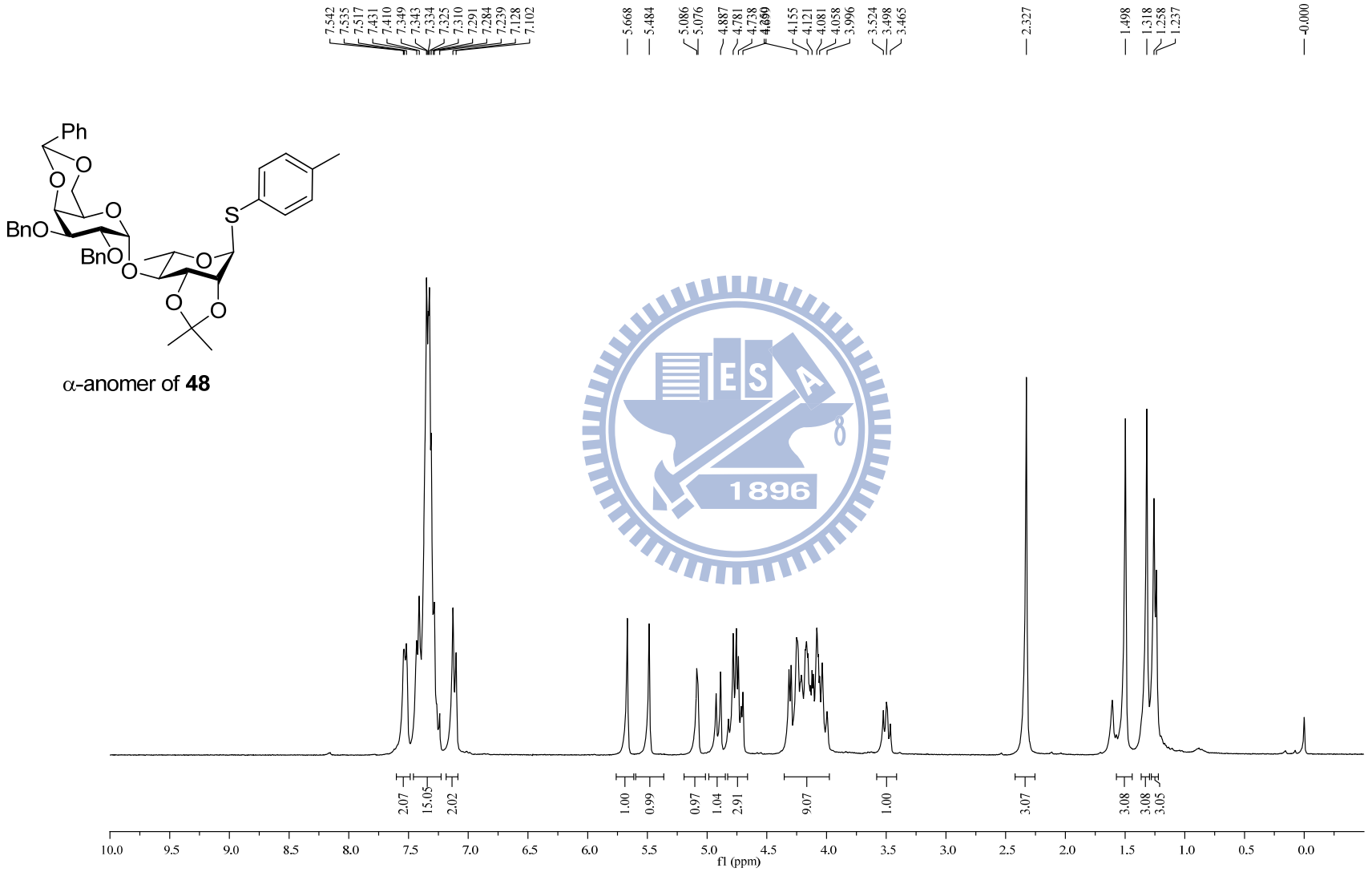
α-anomer of **46**


7.554
7.549
7.464
7.437
7.398
7.391
7.373
7.353
7.345
7.335
7.329
7.323
7.303
7.296
7.291
7.282
7.259
7.253
7.235
7.215
7.205
7.200
7.189
7.153
7.011
6.985
5.487
4.864
4.774
4.737
4.693
4.617
4.568
4.395
3.956
3.870
3.801
3.719
3.615
3.529
3.484
3.386
3.200
2.198
-0.000
Ph
O
O
O
O
BnO
BnO
O
BnO
BnO
S
OBn
β-anomer of 46
2.08
30.02
2.07
1.00
3.08
6.10
2.15
1.01
2.06
1.00
1.05
2.08
1.04
3.14
1.11
0.96
3.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

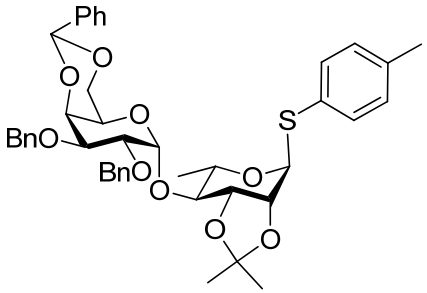

139.256
138.884
138.862
138.672
138.537
128.597
128.539
128.273
128.198
128.135
128.086
127.809
126.970
104.135
101.789
87.954
77.924
77.076
75.806
75.294
72.474
69.635
68.594
66.860
21.470
Ph
O
O
O
O
BnO
BnO
O
BnO
BnO
S
OBn
β-anomer of **46**
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Ph
O
O
O
BnO
BnO
O
BnO
OBn
O
S
OBn
47
7.492
7.467
7.326
7.283
7.260
7.193
7.176
7.144
7.044
7.018
5.775
5.764
5.388
4.880
4.806
4.744
4.675
4.608
4.571
4.516
3.941
3.925
3.810
3.781
3.749
3.706
3.665
3.575
3.537
3.507
3.476
2.292
0.000
4.15
28.30
2.20
1.00
1.05
3.09
1.19
1.99
5.42
1.08
2.04
2.30
4.17
3.23
3.30
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

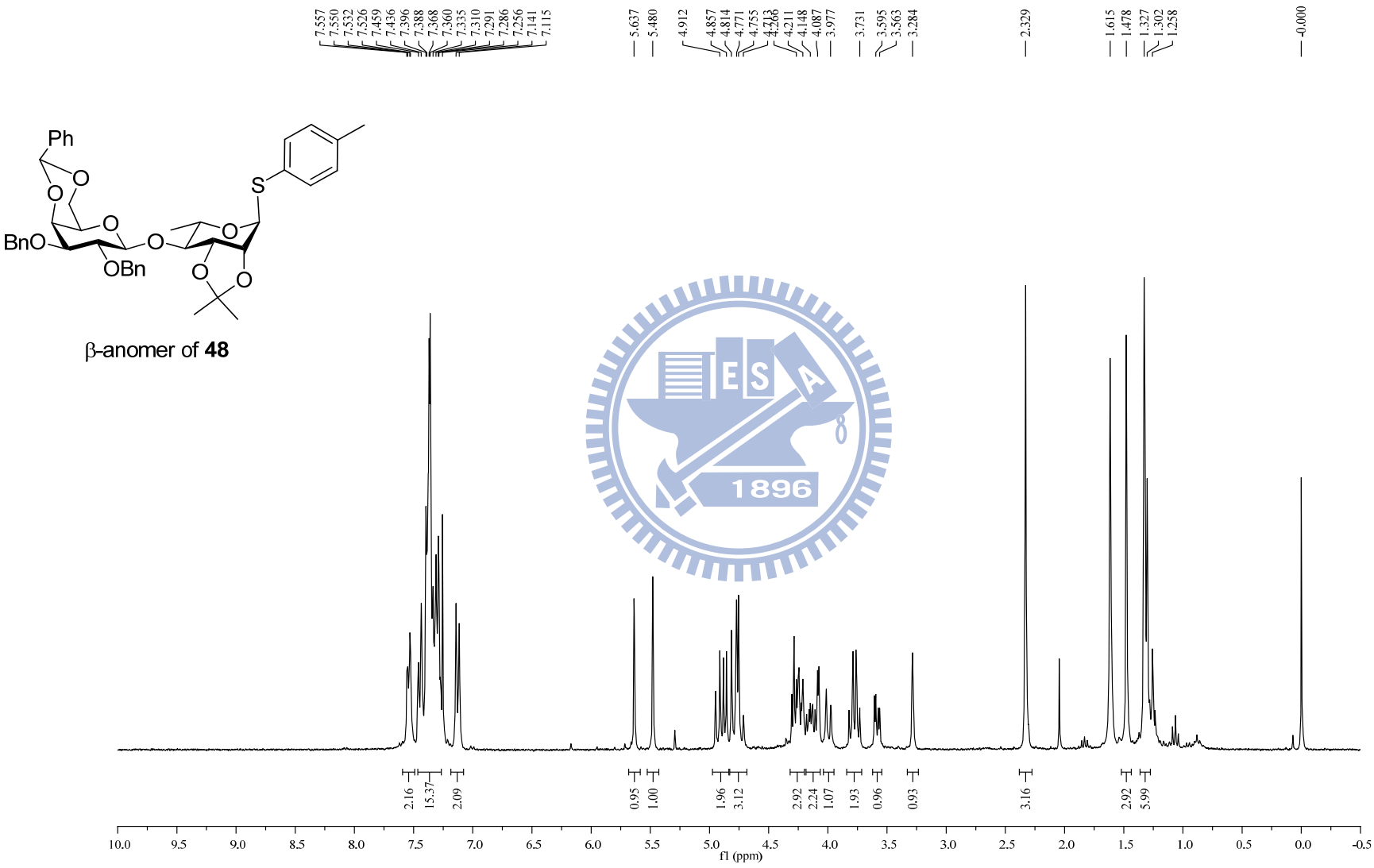

139.017
138.698
138.638
138.275
138.247
133.239
129.873
128.817
128.711
128.505
128.098
127.934
127.555
126.695
101.210
98.403
87.869
87.191
77.500
74.693
74.596
74.018
72.465
72.018
69.783
69.560
63.407
21.549
Ph
O
O
O
BnO
BnO
O
BnO
OBn
O
S
OBn
47
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



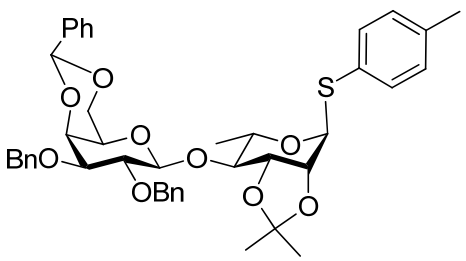
α-anomer of **48**



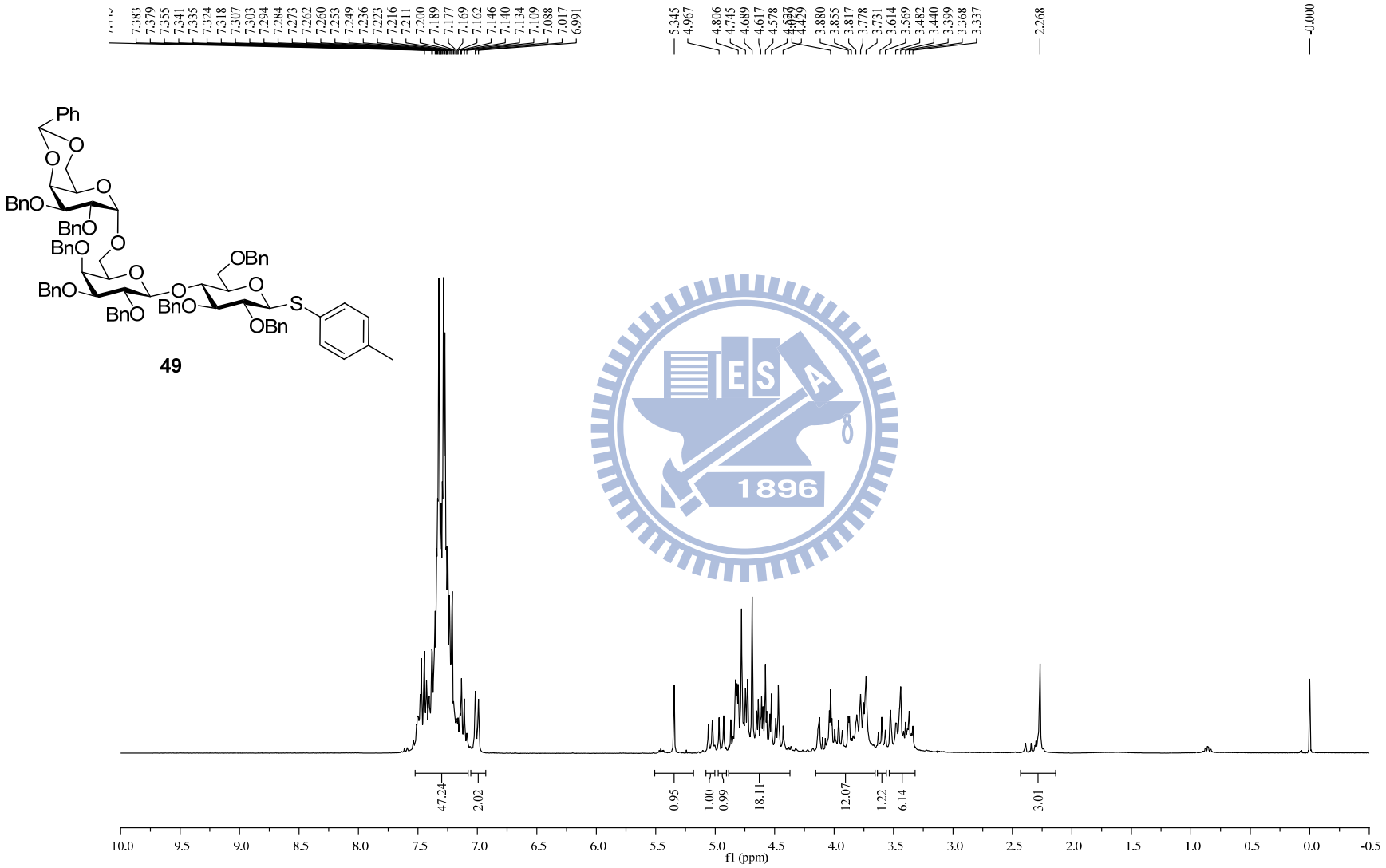
α-anomer of **48**

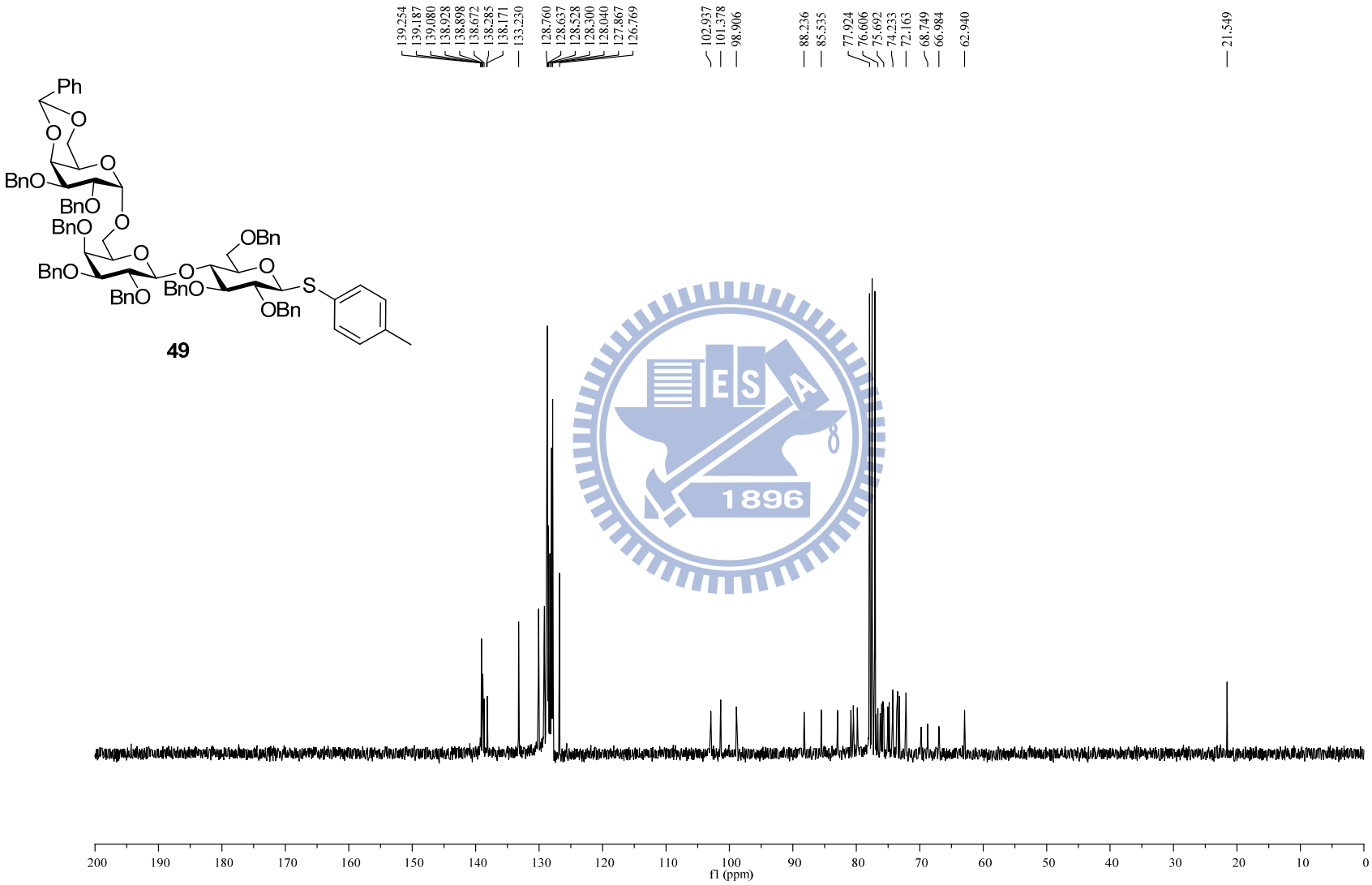


β-anomer of **48**

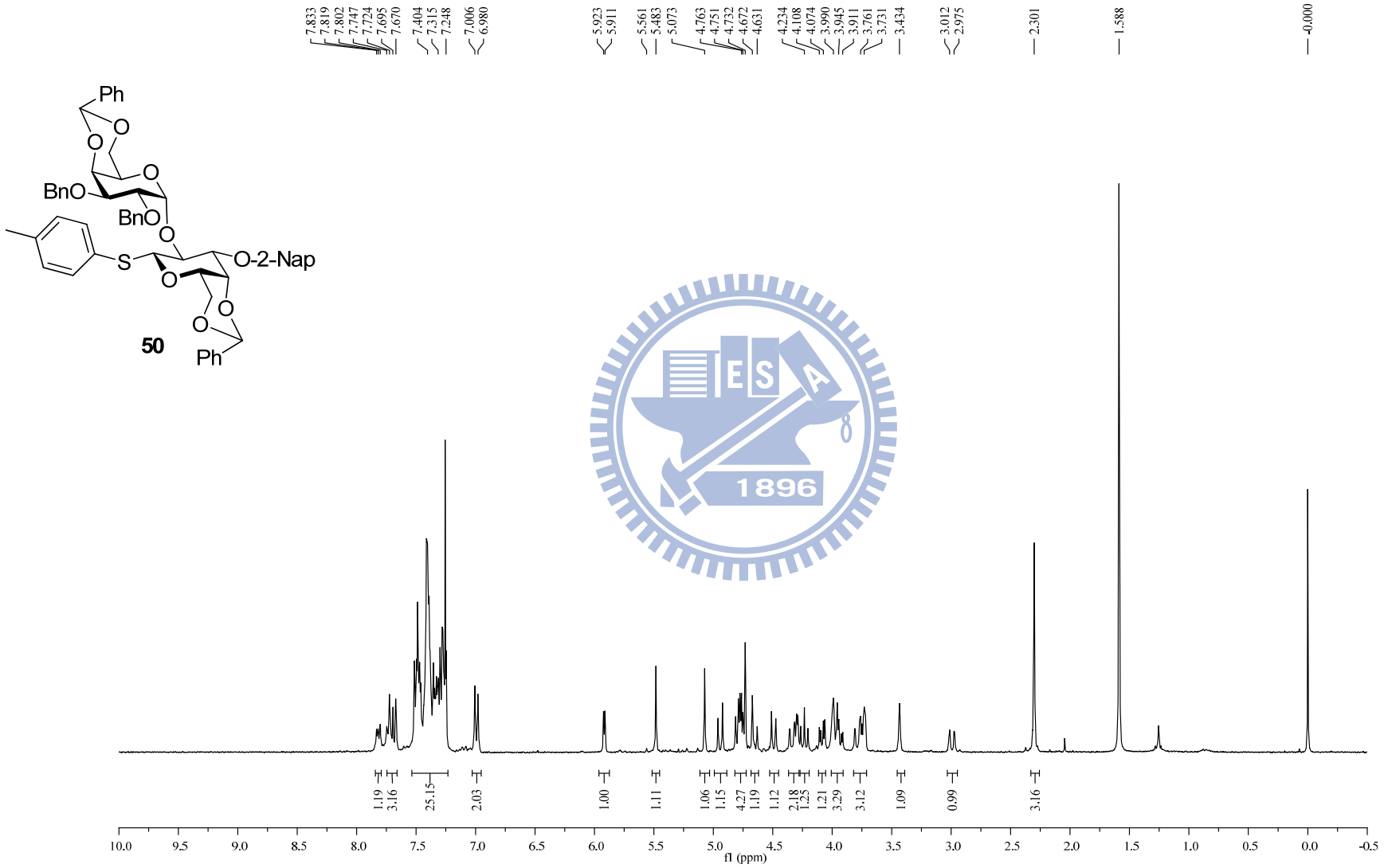


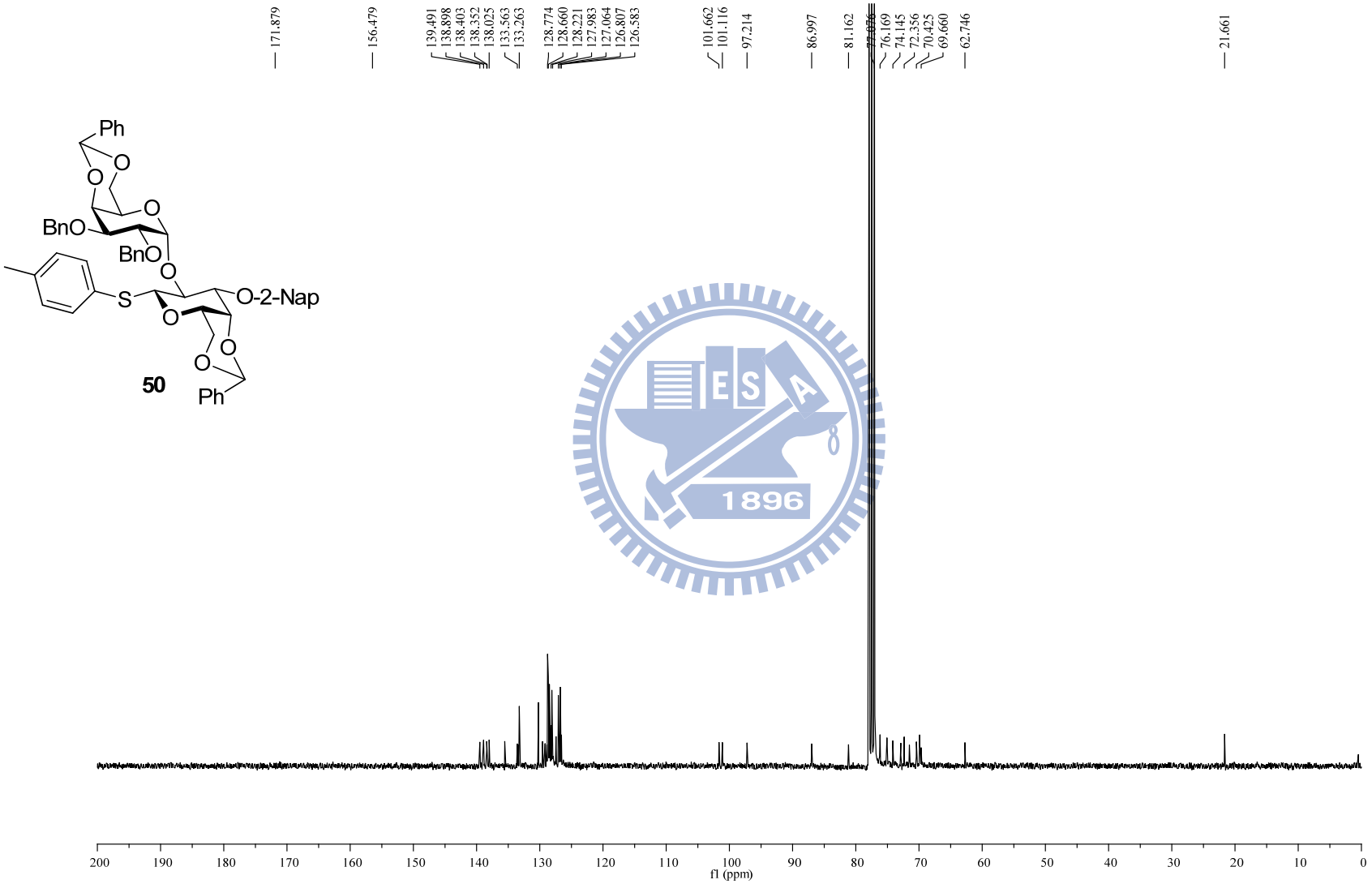
β-anomer of **48**

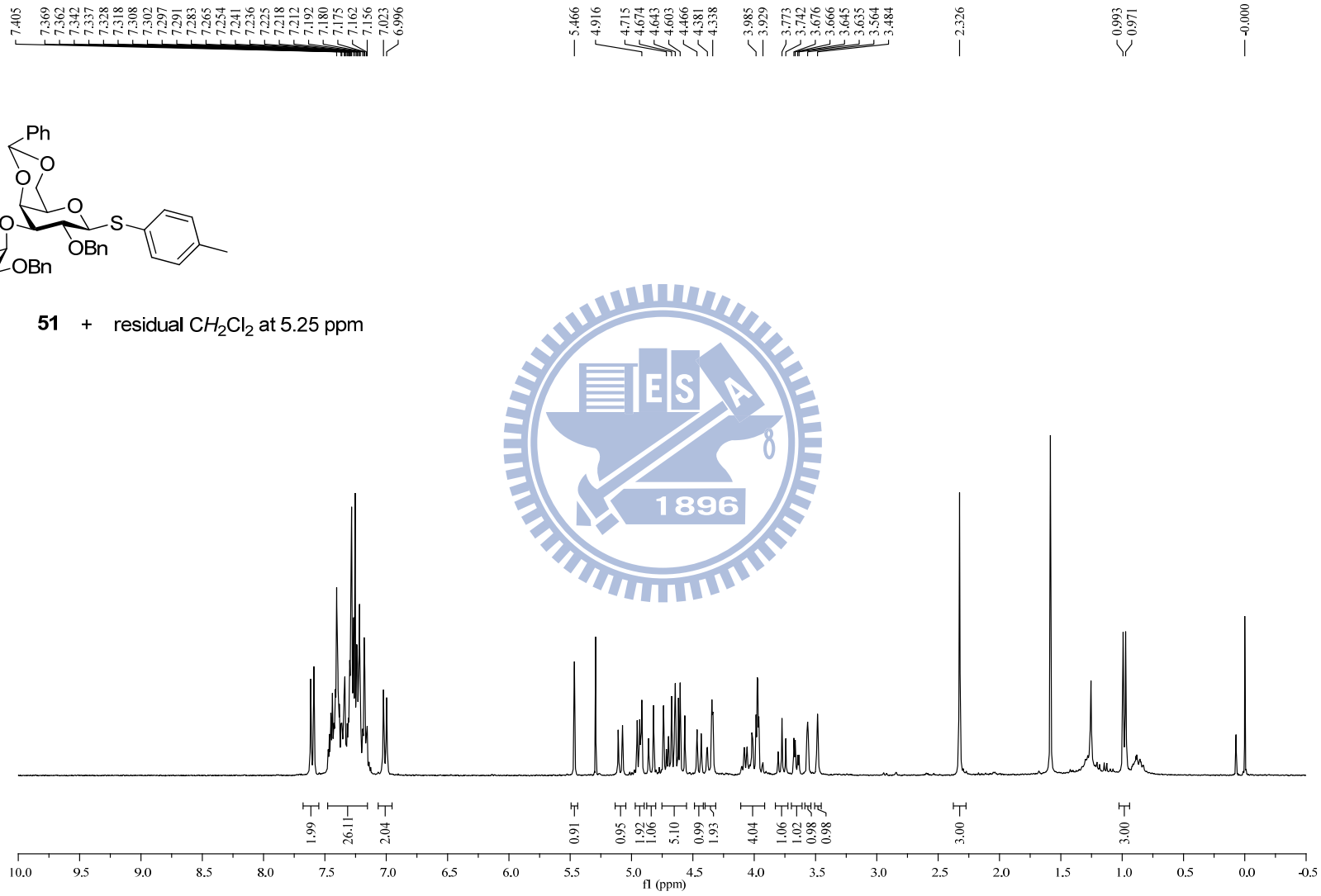

7.383
7.379
7.355
7.341
7.335
7.324
7.318
7.307
7.303
7.294
7.284
7.273
7.262
7.260
7.253
7.249
7.236
7.223
7.216
7.211
7.200
7.189
7.177
7.169
7.162
7.146
7.140
7.134
7.109
7.088
7.017
6.991
5.345
4.967
4.806
4.745
4.689
4.617
4.578
4.429
3.880
3.855
3.817
3.778
3.731
3.614
3.569
3.482
3.440
3.399
3.368
3.337
2.268
-0.000
Ph
BnO
BnO
BnO
BnO
BnO
BnO
OBn
OBn
S
49
47.24
2.02
0.95
1.00
0.99
18.11
12.07
1.22
6.14
3.01
f1 (ppm)


139.254
139.187
139.080
138.928
138.898
138.672
138.285
138.171
133.230
128.760
128.637
128.528
128.300
128.040
127.867
126.769
102.937
101.378
98.906
88.236
85.535
77.924
76.606
75.692
74.233
72.163
68.749
66.984
62.940
21.549
Ph
O
O
O
BnO
BnO
BnO
O
O
BnO
BnO
O
BnO
OBn
O
S
OBn
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

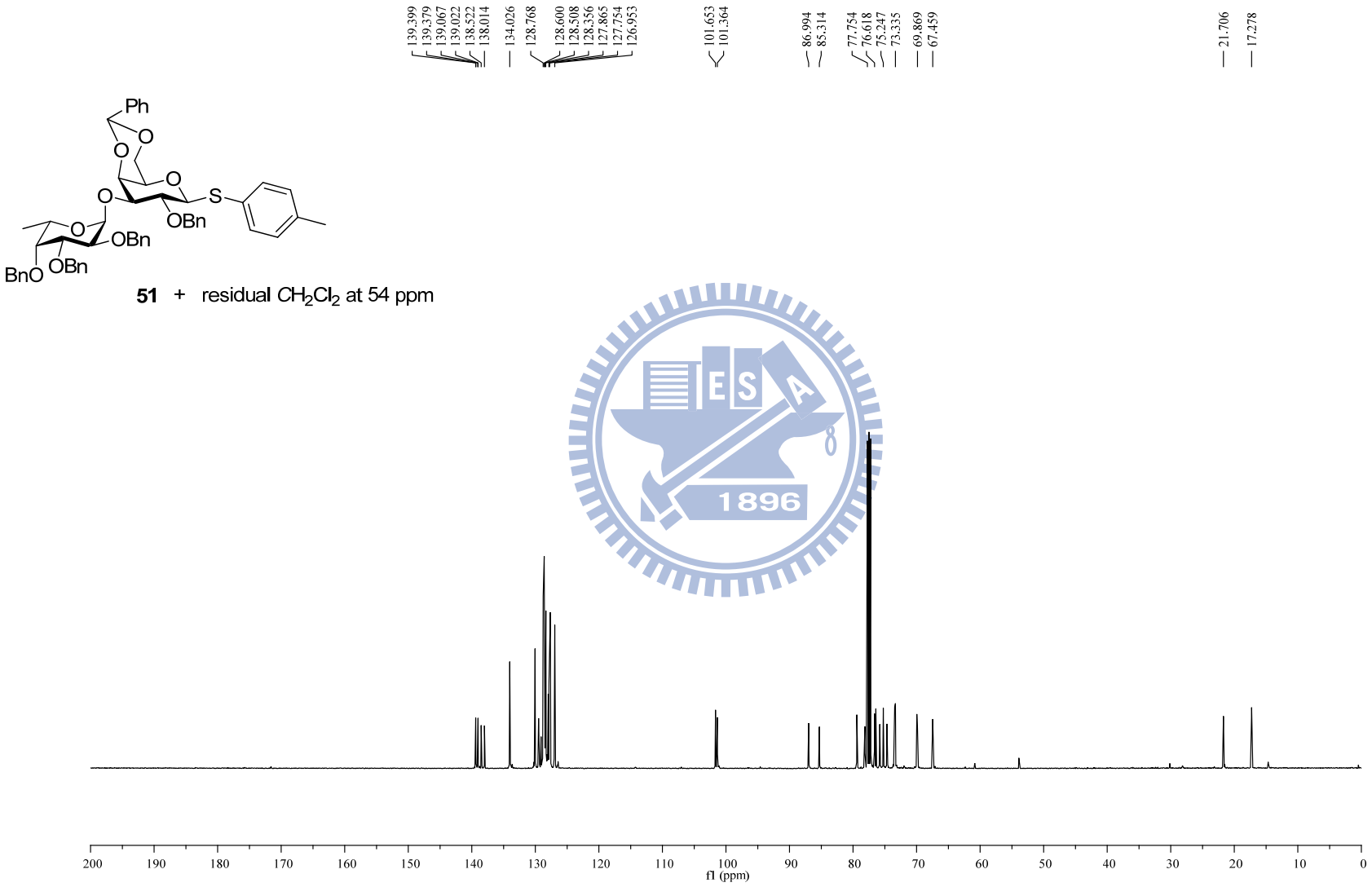
49


7.833
7.819
7.802
7.747
7.724
7.695
7.670
7.404
7.315
7.248
7.006
6.980
5.923
5.911
5.561
5.483
5.073
4.763
4.751
4.732
4.672
4.631
4.234
4.108
4.074
3.990
3.945
3.911
3.761
3.731
3.434
3.012
2.975
2.301
1.588
-0.000
Ph
O
O
O
BnO
BnO
O
S
O
O-2-Nap
O
O
Ph
50
1.19
3.16
25.15
2.03
1.00
1.11
1.06
1.15
4.27
1.19
1.12
2.18
1.25
1.21
3.29
3.12
1.09
0.99
3.16
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


171.879
156.479
139.491
138.898
138.403
138.352
138.025
133.563
133.263
128.774
128.660
128.221
127.983
127.064
126.807
126.583
101.662
101.116
97.214
86.997
81.162
77.036
76.169
74.145
72.356
70.425
69.660
62.746
21.661
Ph
O
O
BnO
O
BnO
O
S
O
O-2-Nap
O
O
Ph
50
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

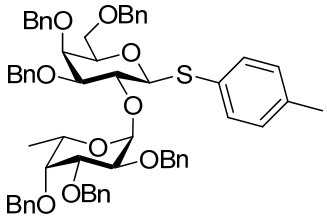


51 + residual CH_2Cl_2 at 5.25 ppm

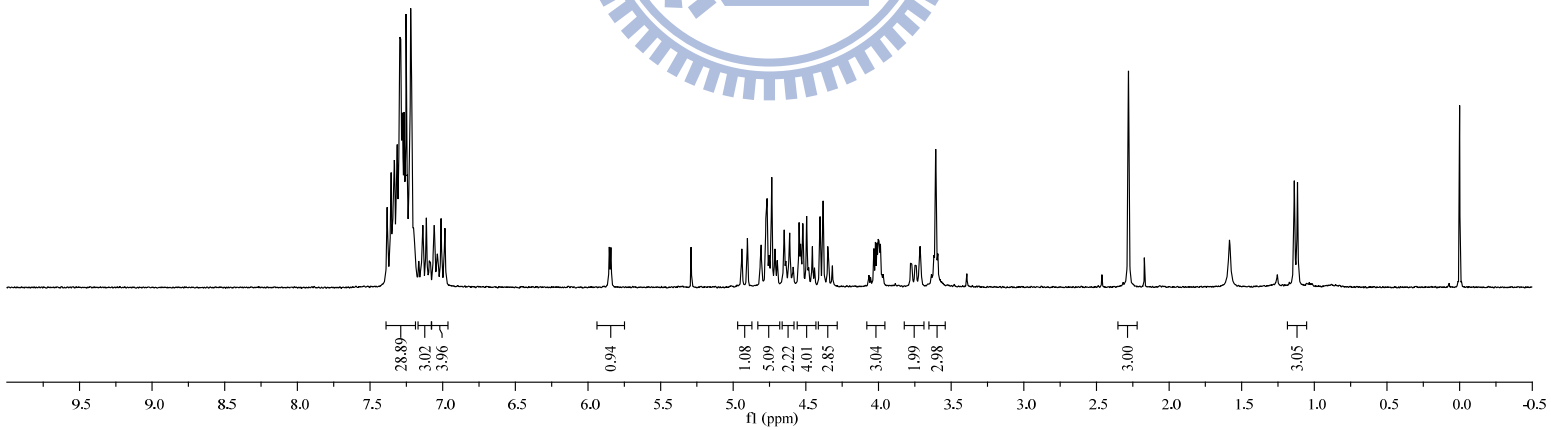


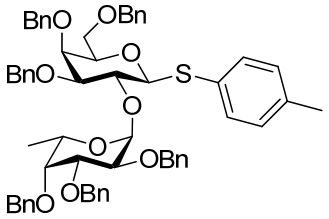
51 + residual CH_2Cl_2 at 54 ppm


7.382
7.355
7.332
7.313
7.302
7.296
7.288
7.276
7.265
7.251
7.220
7.200
7.165
7.142
7.137
7.112
7.092
7.084
7.058
7.037
7.012
6.985
5.853
5.842
4.774
4.753
4.713
4.649
4.611
4.547
4.522
4.482
4.441
4.381
4.118
4.010
3.987
3.779
3.771
3.749
3.741
3.714
3.606
3.592
2.279
1.138
1.116
0.000


BnO
OBn
O
BnO
S
O
O
OBn
BnO
OBn

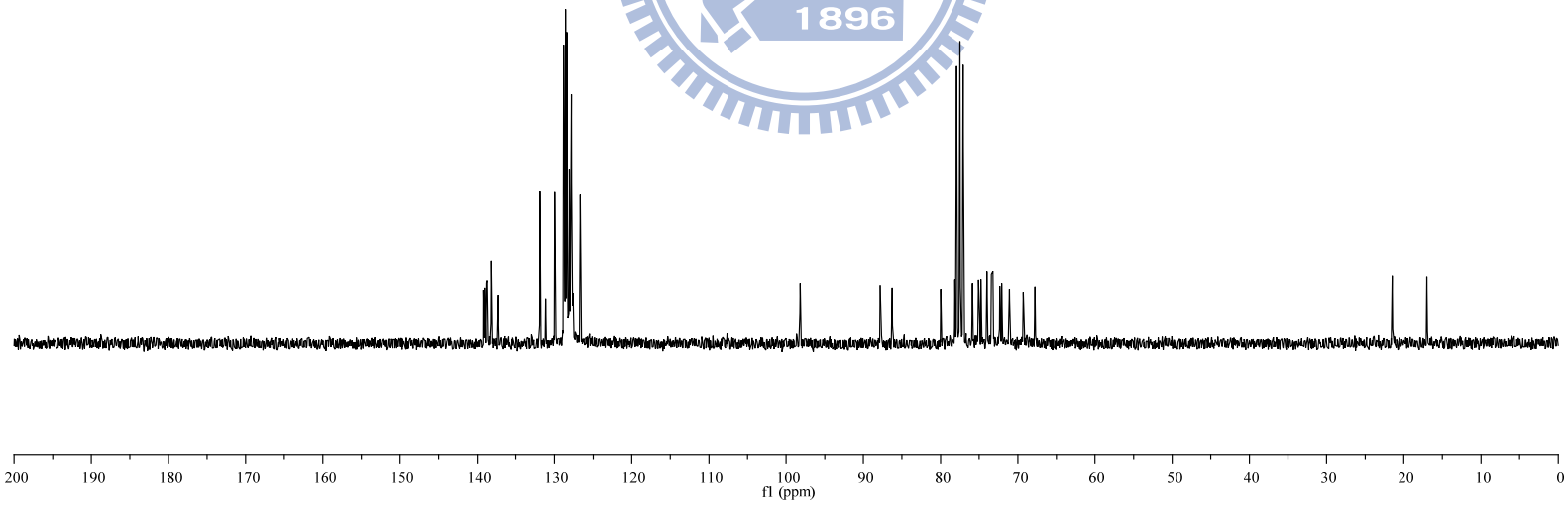
52

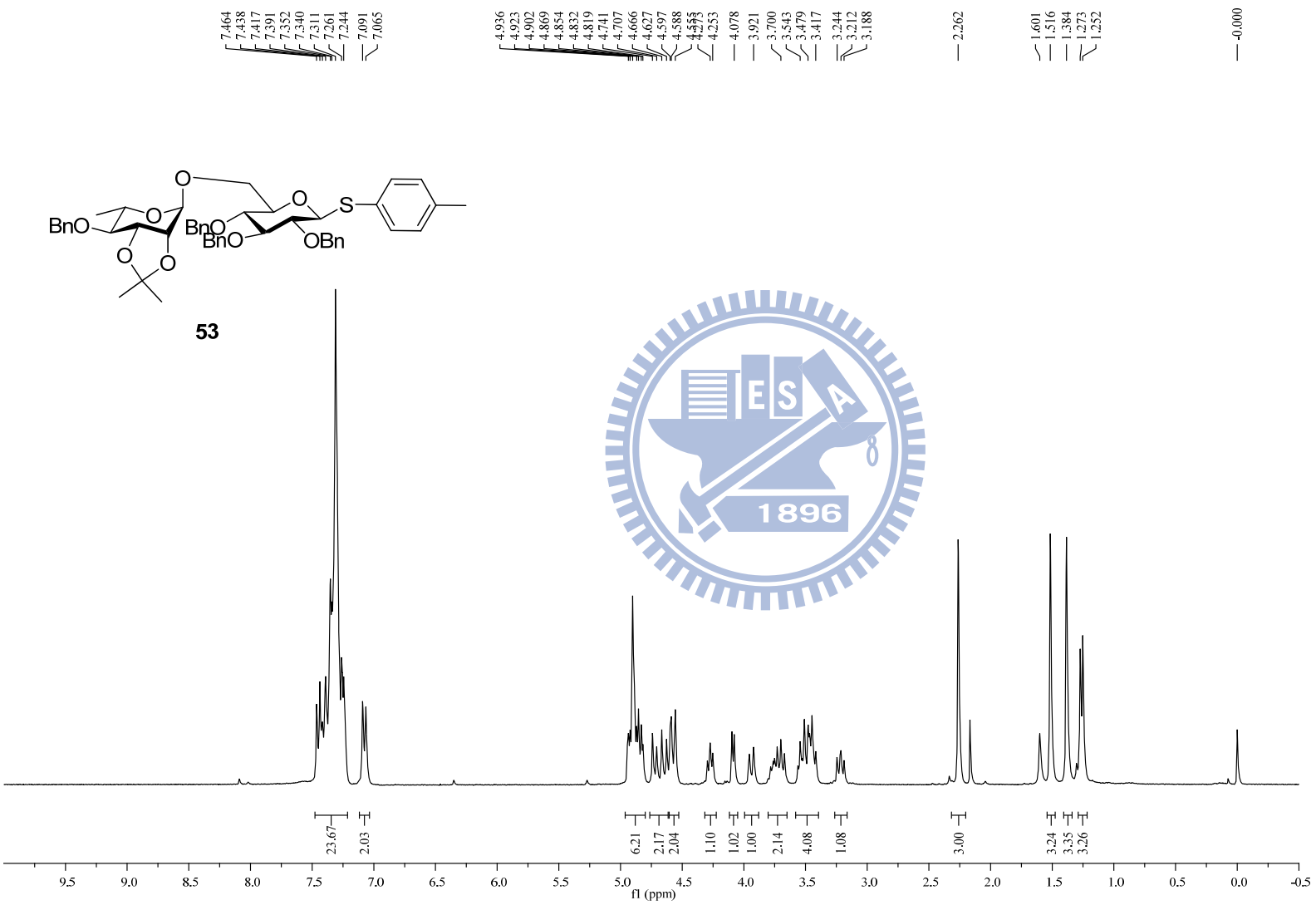

28.89
3.02
3.96
0.94
1.08
5.09
2.22
4.01
2.85
3.04
1.99
2.98
3.00
3.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



52

139.247
139.095
138.852
138.781
138.242
128.563
128.381
128.210
128.063
127.901
127.810
127.725
127.634
126.669
98.191
87.823
86.270
79.976
78.145
77.919
77.496
77.071
75.859
75.076
74.770
74.002
73.424
73.223
72.343
72.096
71.077
69.293
67.770
21.500
17.020




7.464
7.438
7.417
7.391
7.352
7.340
7.311
7.261
7.244
7.091
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BnO
BnO
OBn
S
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2.17
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1.10
1.02
1.00
2.14
4.08
1.08
3.00
3.24
3.35
3.26
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8.5
8.0
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7.0
6.5
6.0
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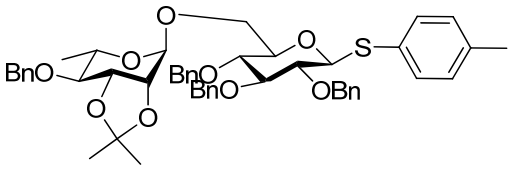
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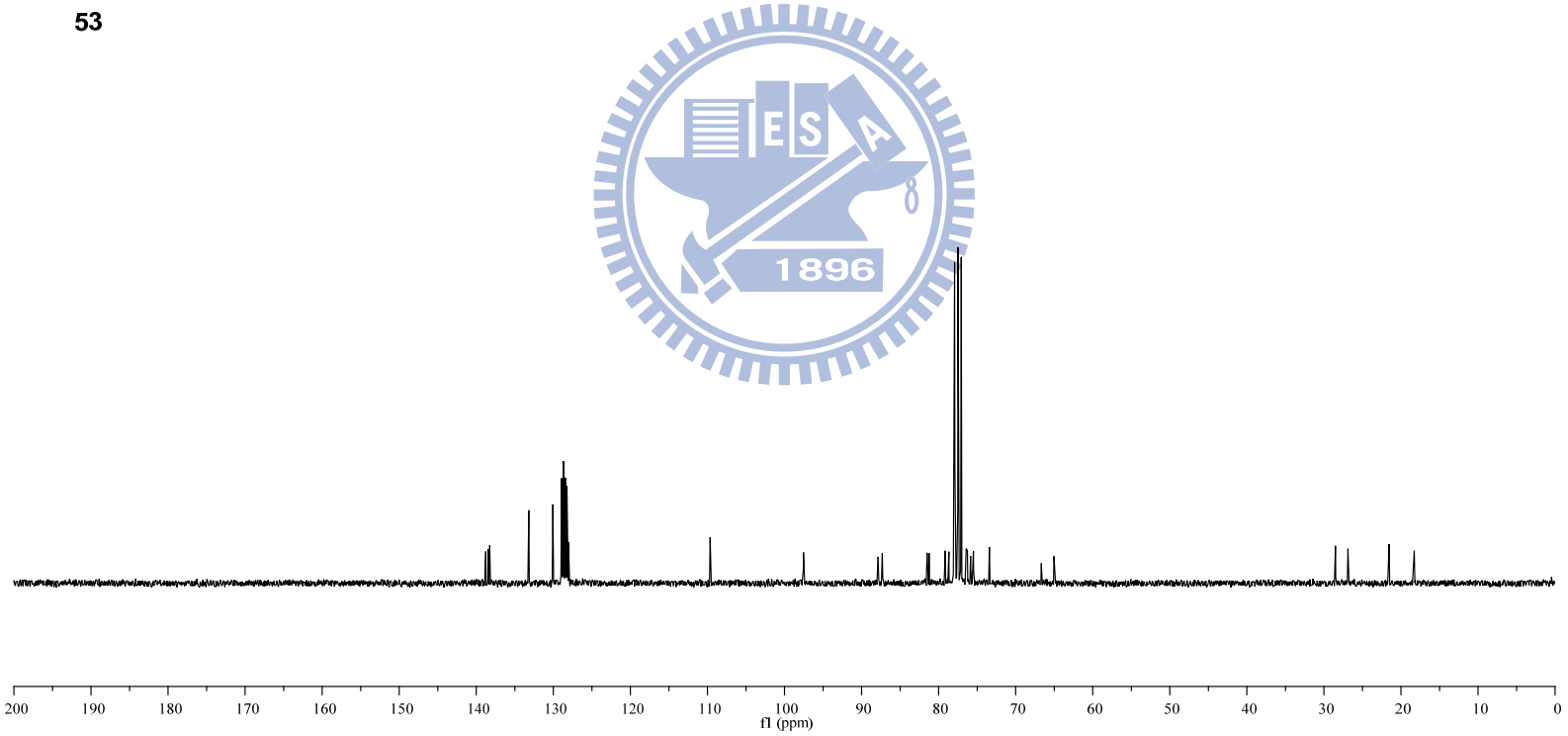
53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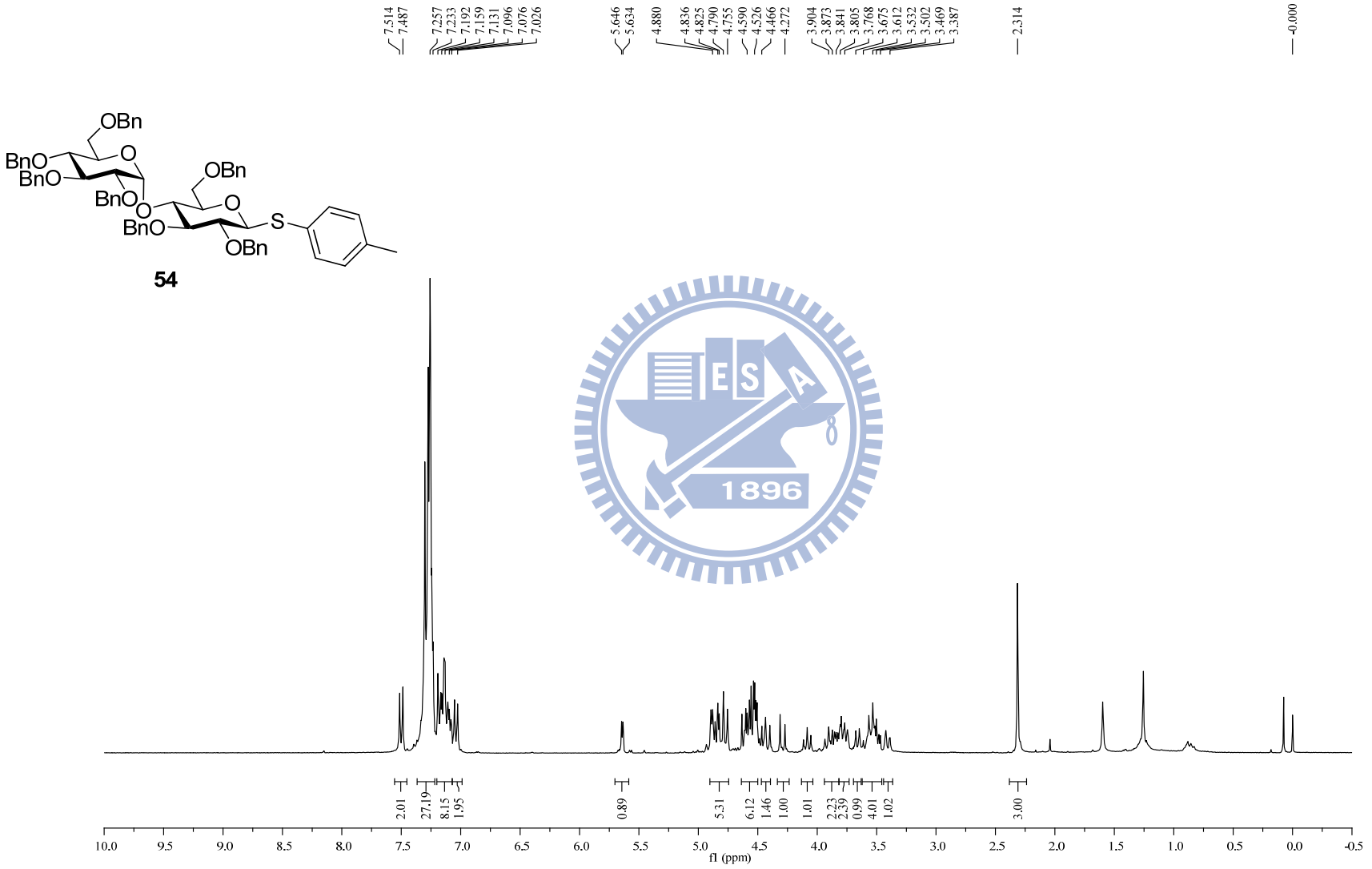
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BnO
BnO
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BnO
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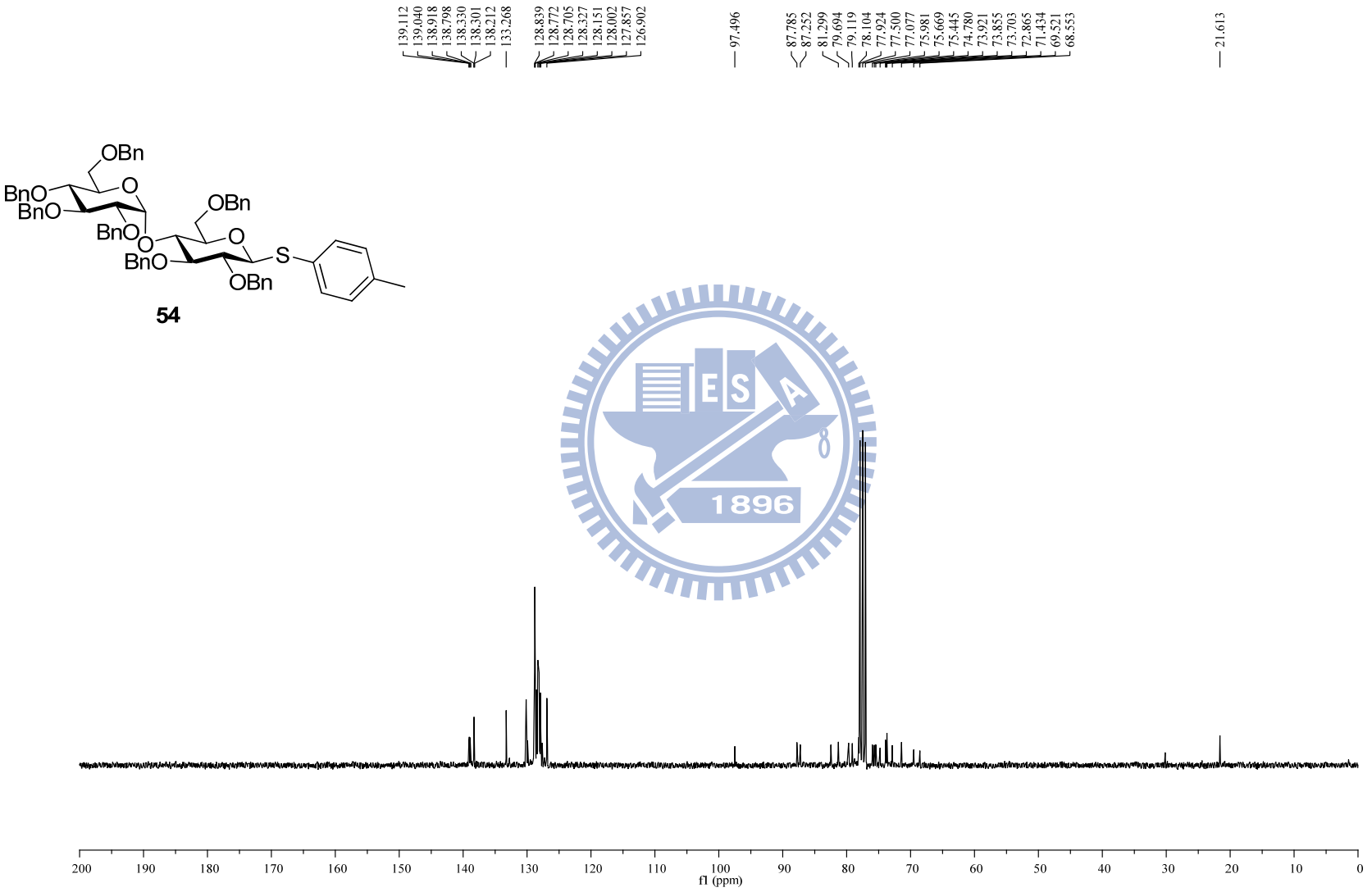
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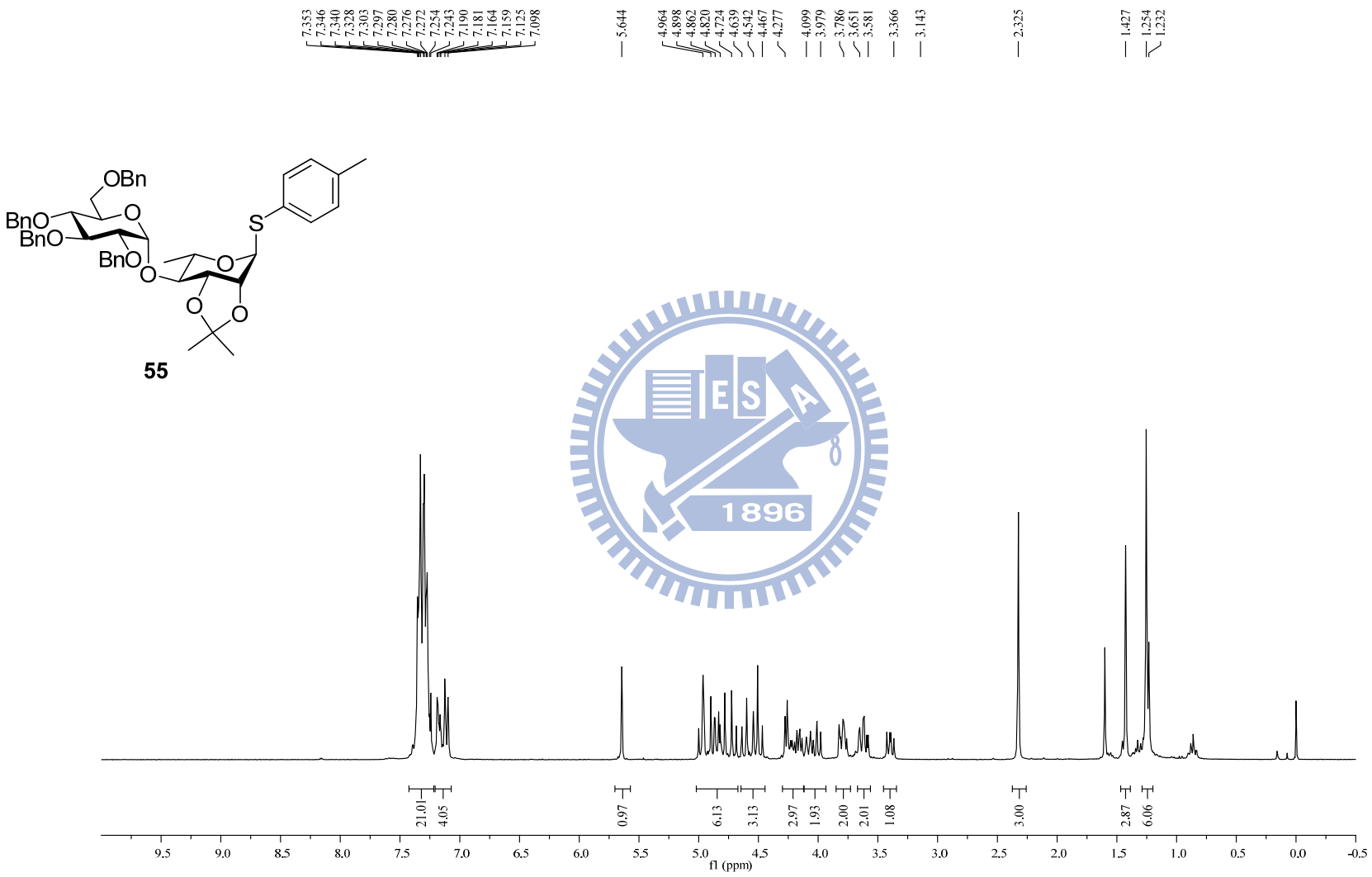
f1 (ppm)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1.232
OBn
BnO
BnO
BnO
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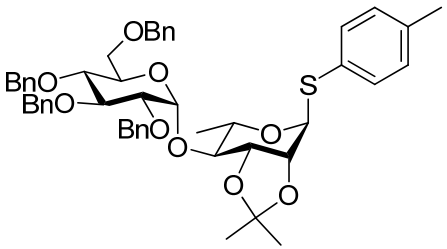
-0.5
f1 (ppm)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BnO
BnO
O
O
O
O
O
S

55


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132.935
130.050
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128.815
128.433
128.270
128.043
109.556
98.863
78.290
77.924
77.500
77.076
76.064
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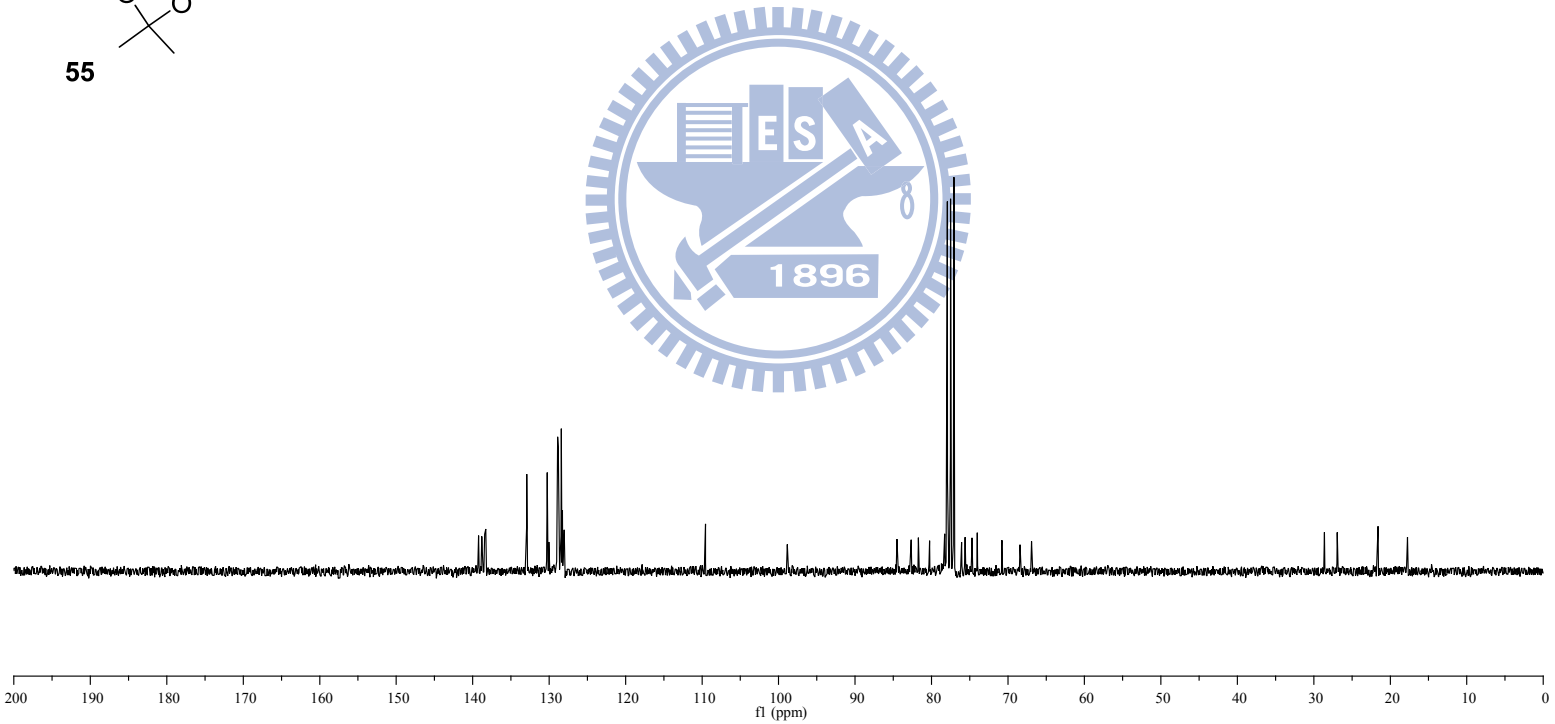
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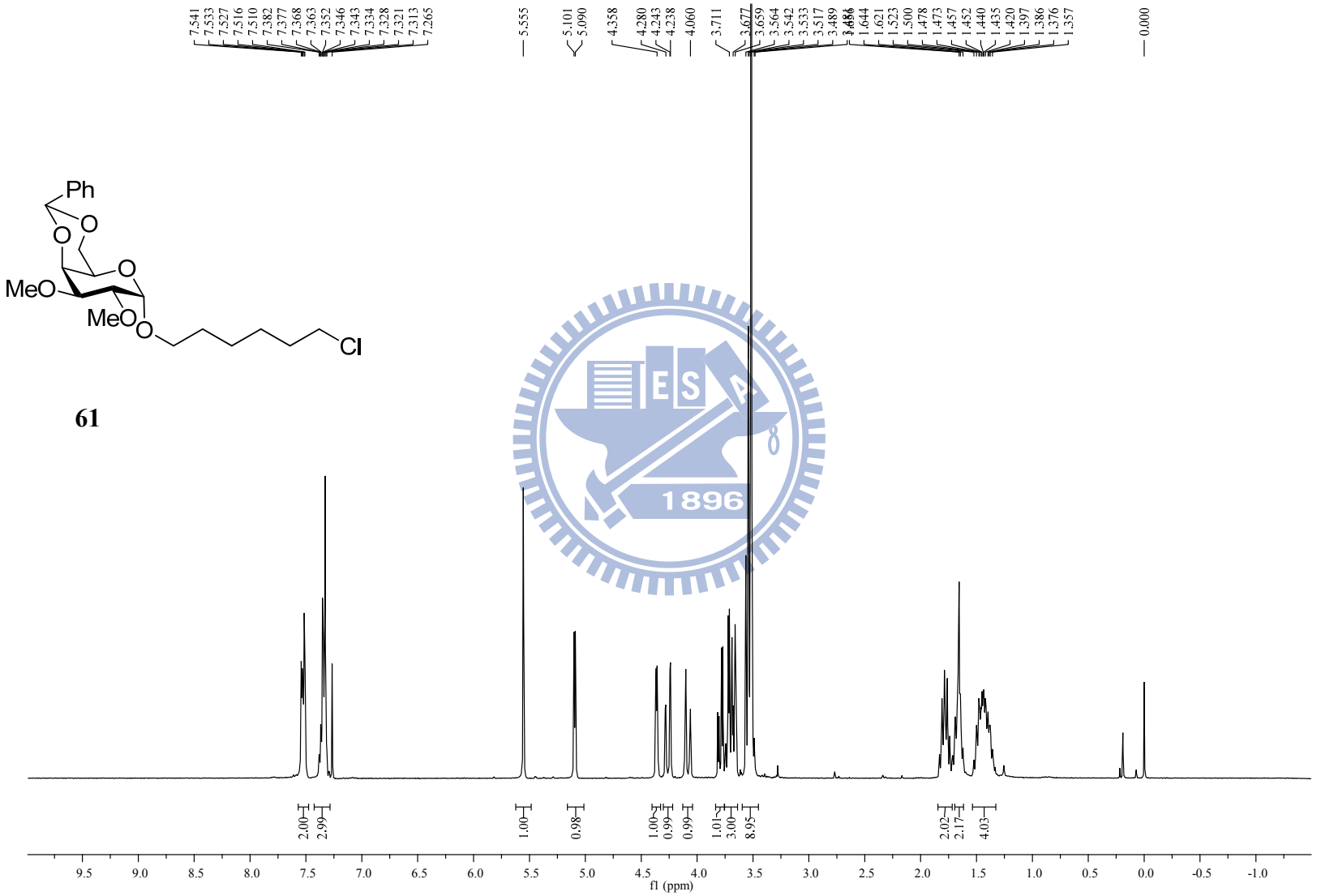
0
f1 (ppm)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MeO
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Cl
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0.99
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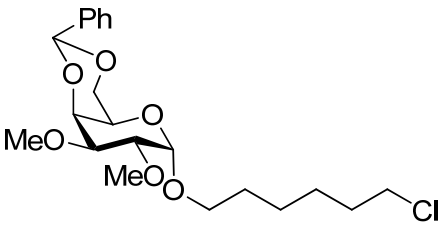
2.17
4.03
f1 (ppm)

61


Ph
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O
MeO
MeO
O
Cl

61

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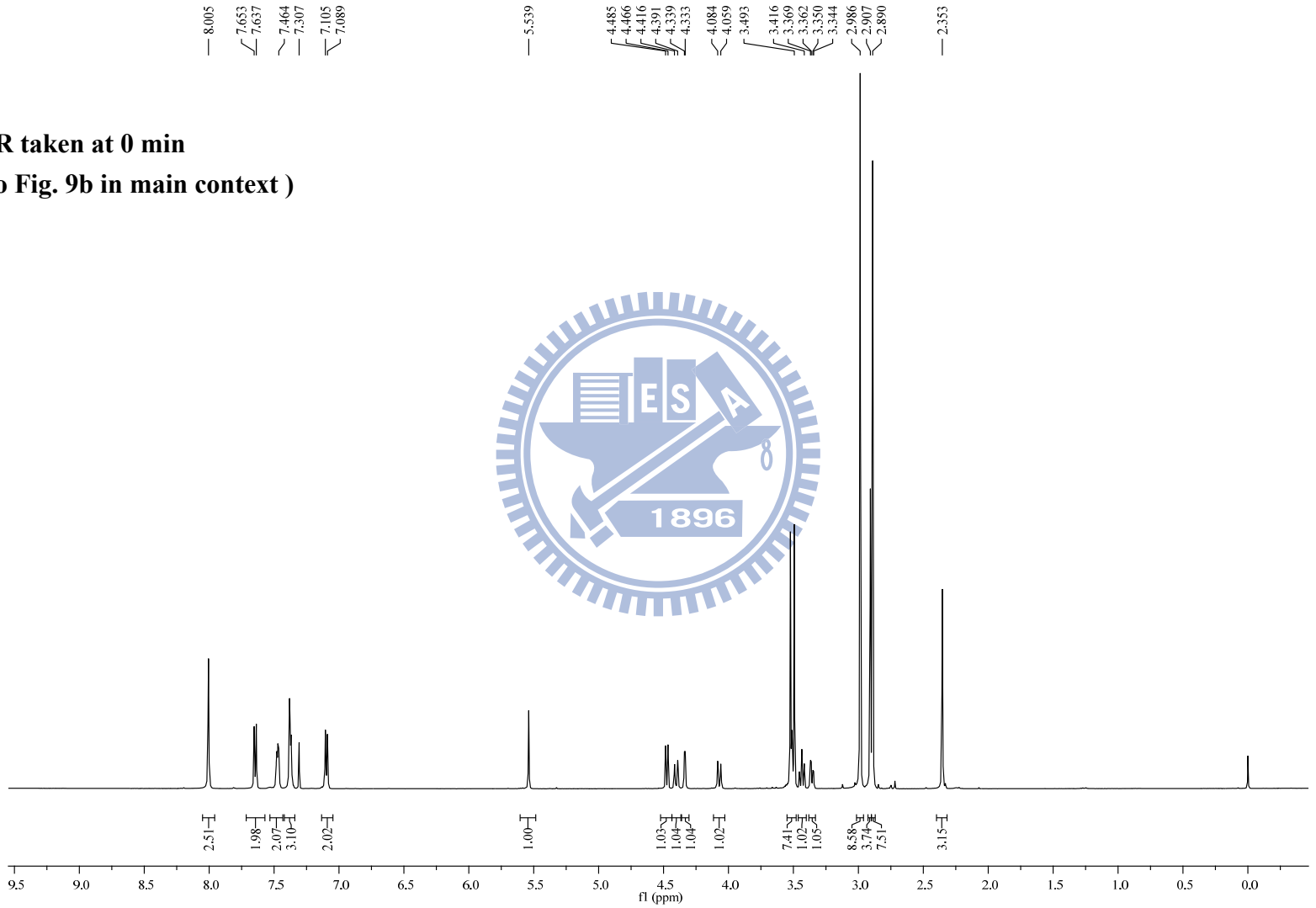
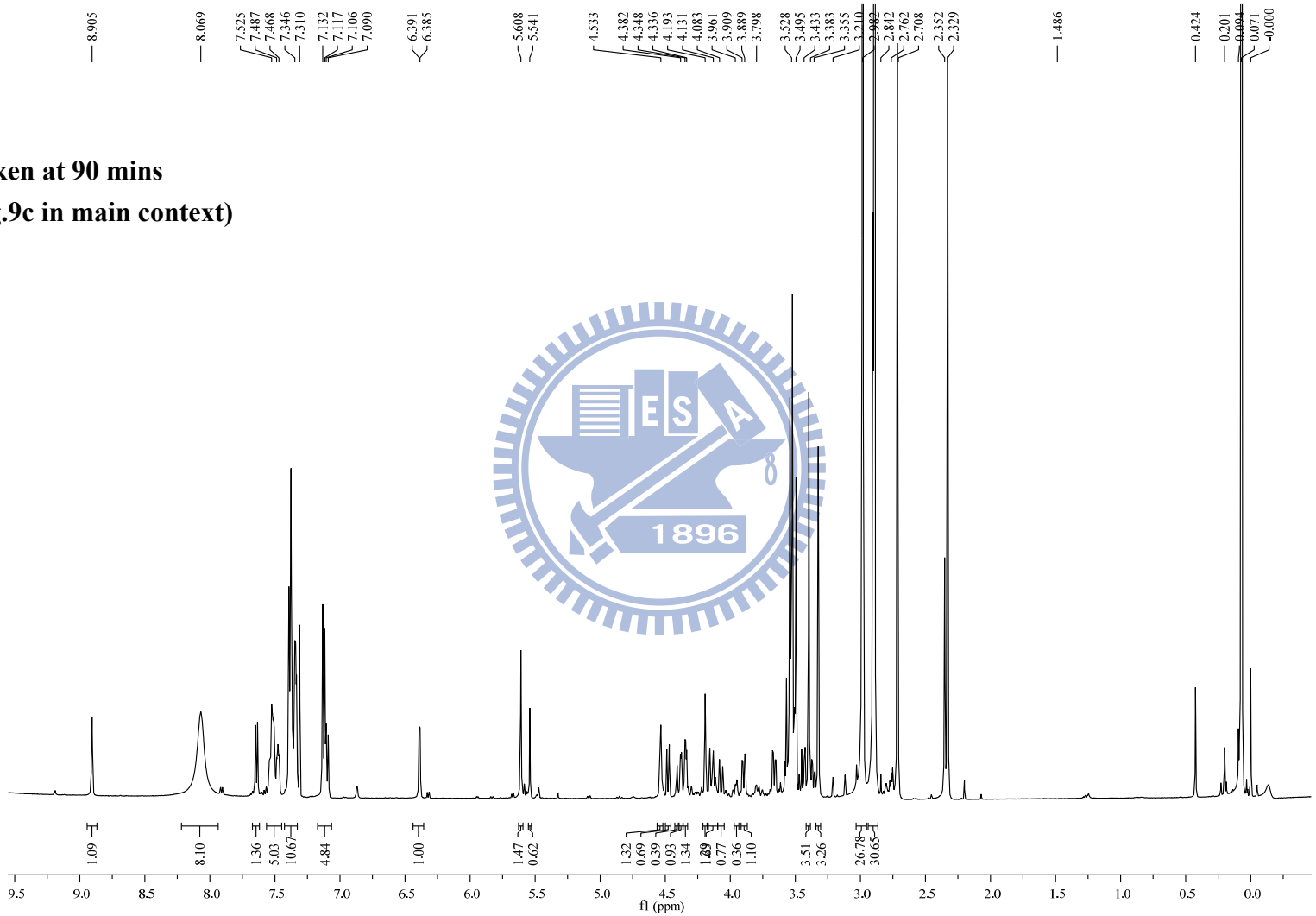
129.388
128.583
126.854
101.689
97.669
77.923
77.811
77.636
77.500
77.076
74.109
69.998
68.580
63.143
59.294
58.056
45.483
32.927
29.707
27.067
25.904
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

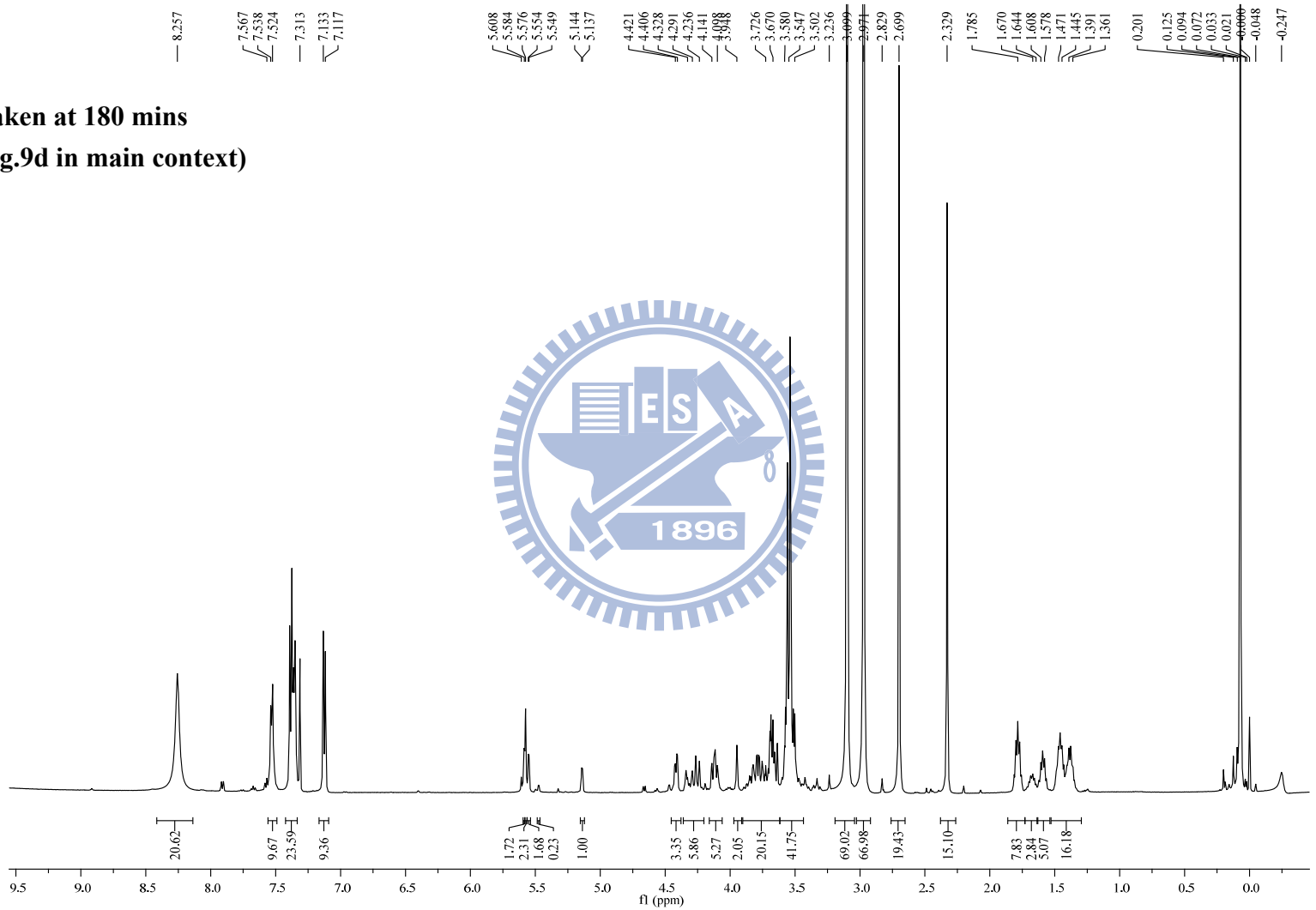
^{1}H NMR taken at 0 min
(refer to Fig. 9b in main context)



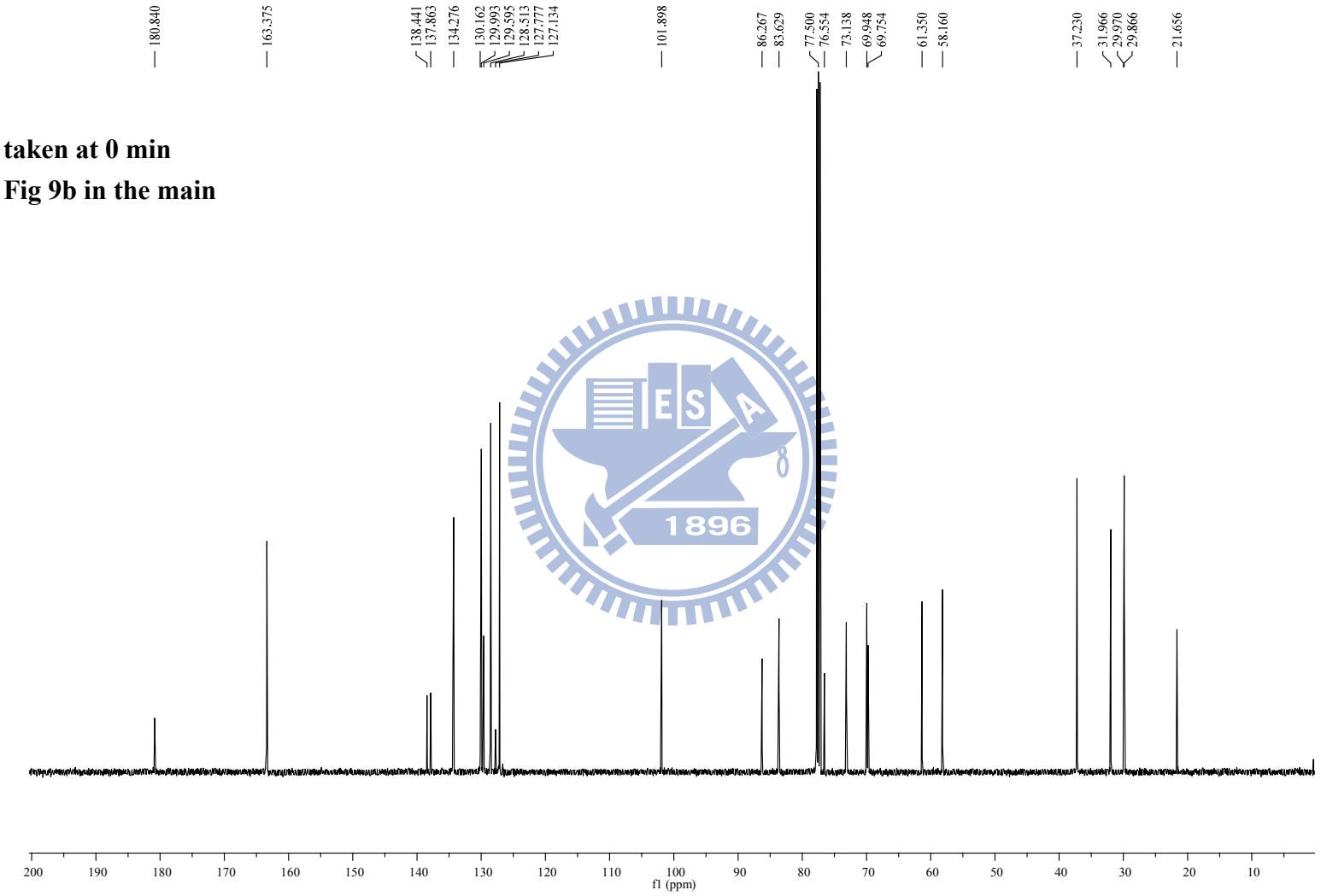
^{1}H NMR taken at 90 mins
(refer to Fig.9c in main context)

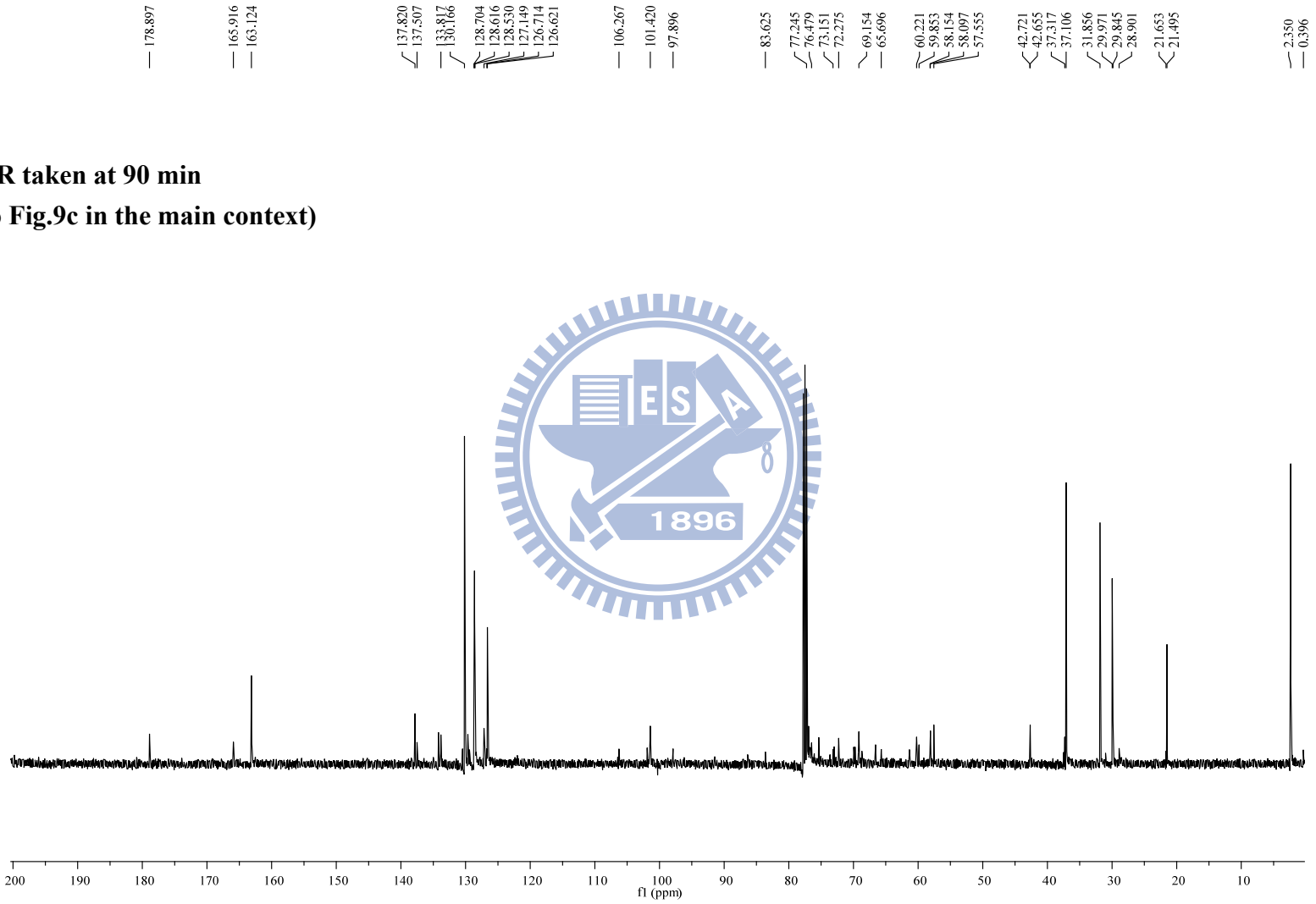


^{1}H NMR taken at 180 mins
(refer to Fig.9d in main context)



^{13}C NMR taken at 0 min
(refer to Fig 9b in the main context)



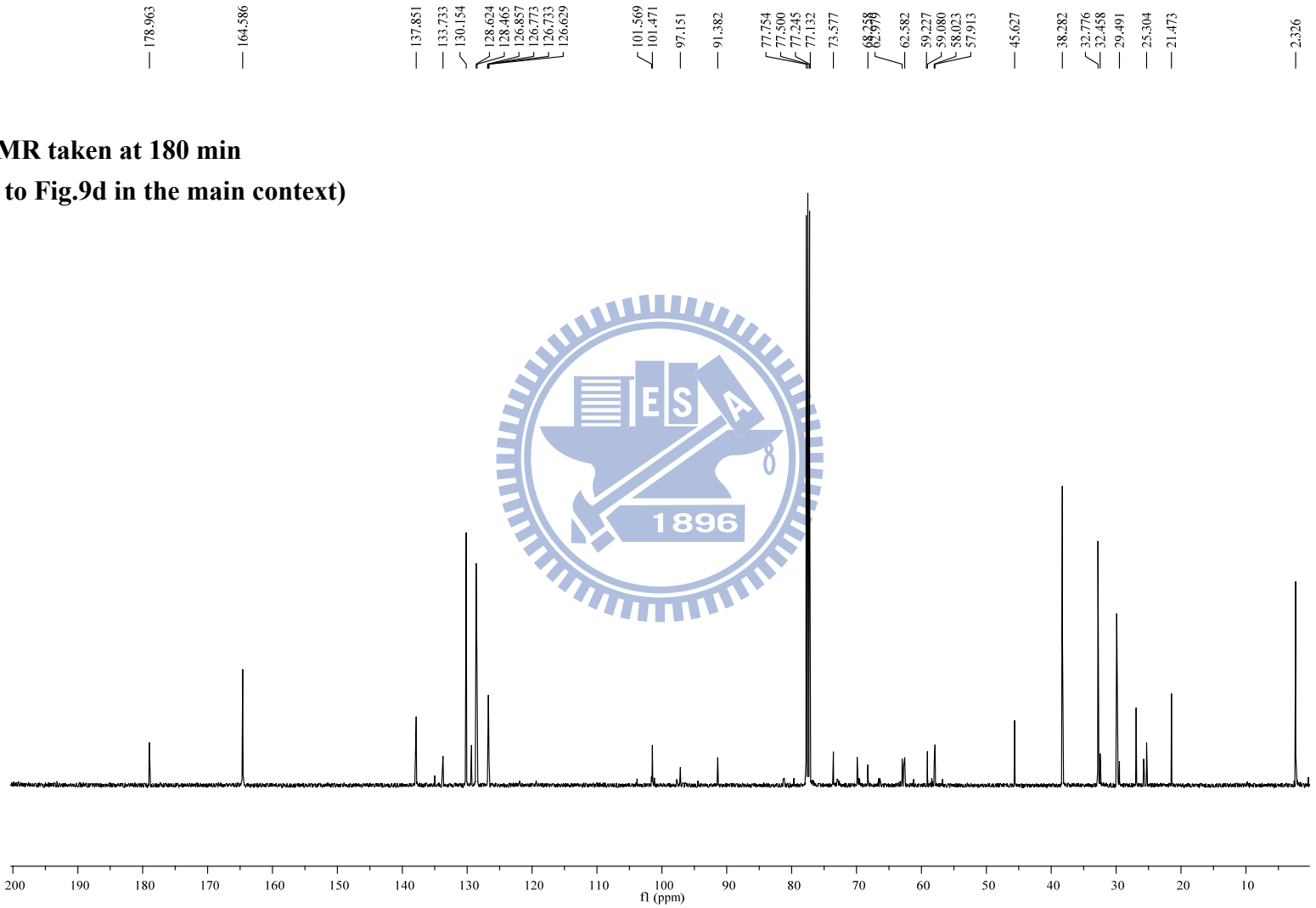


^{13}C NMR taken at 90 min

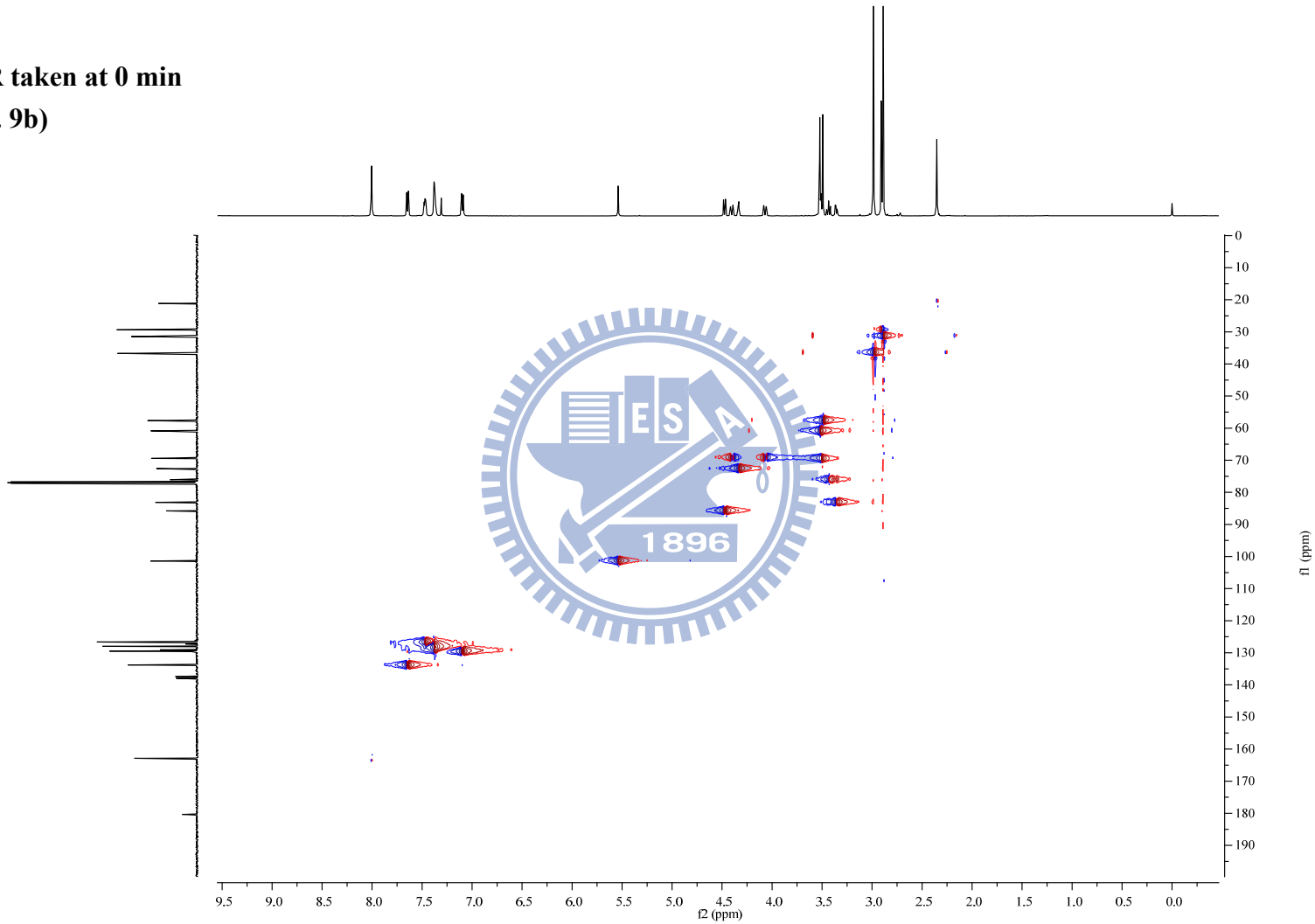
(refer to Fig.9c in the main context)

^{13}C NMR taken at 180 min

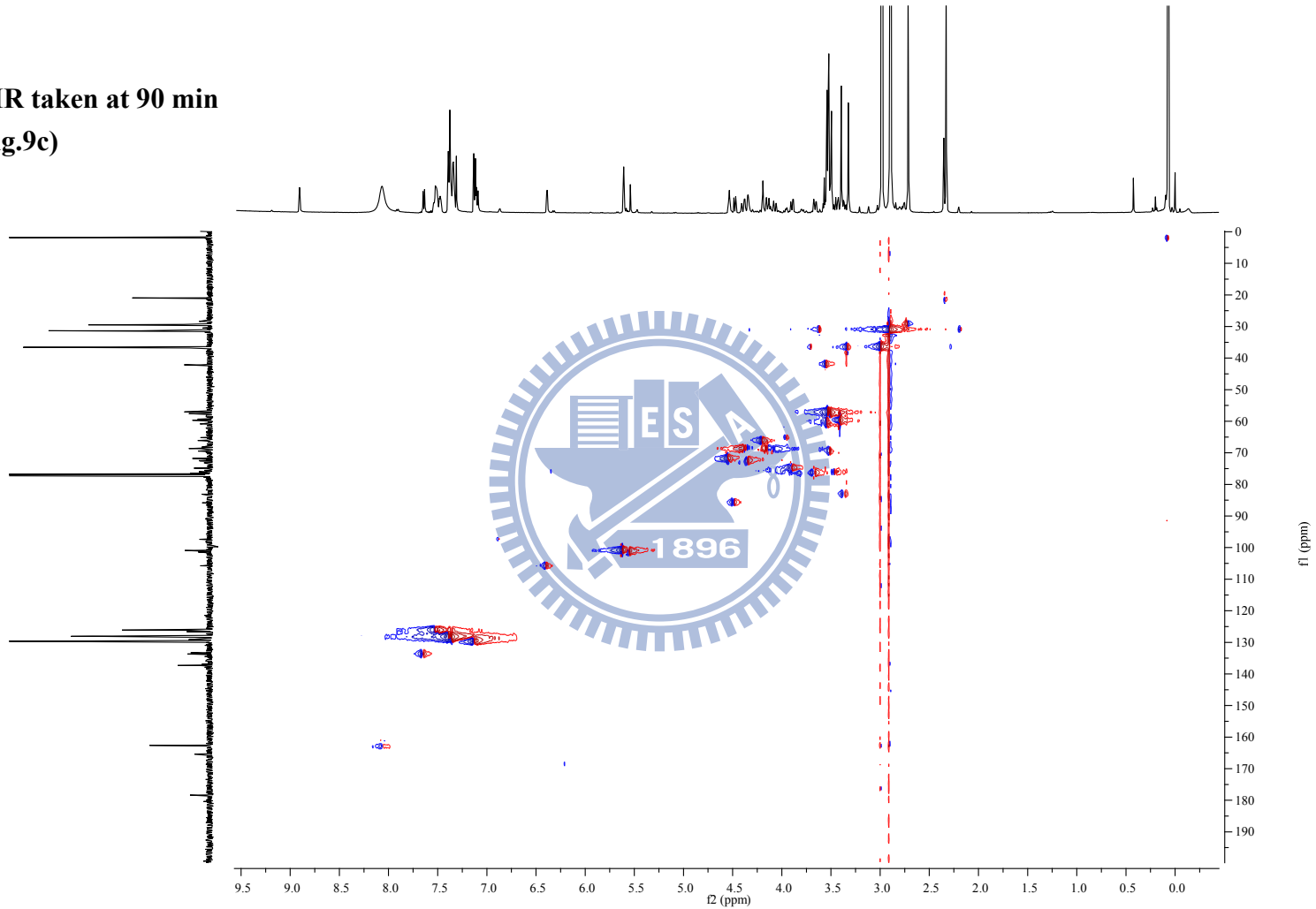
(refer to Fig.9d in the main context)



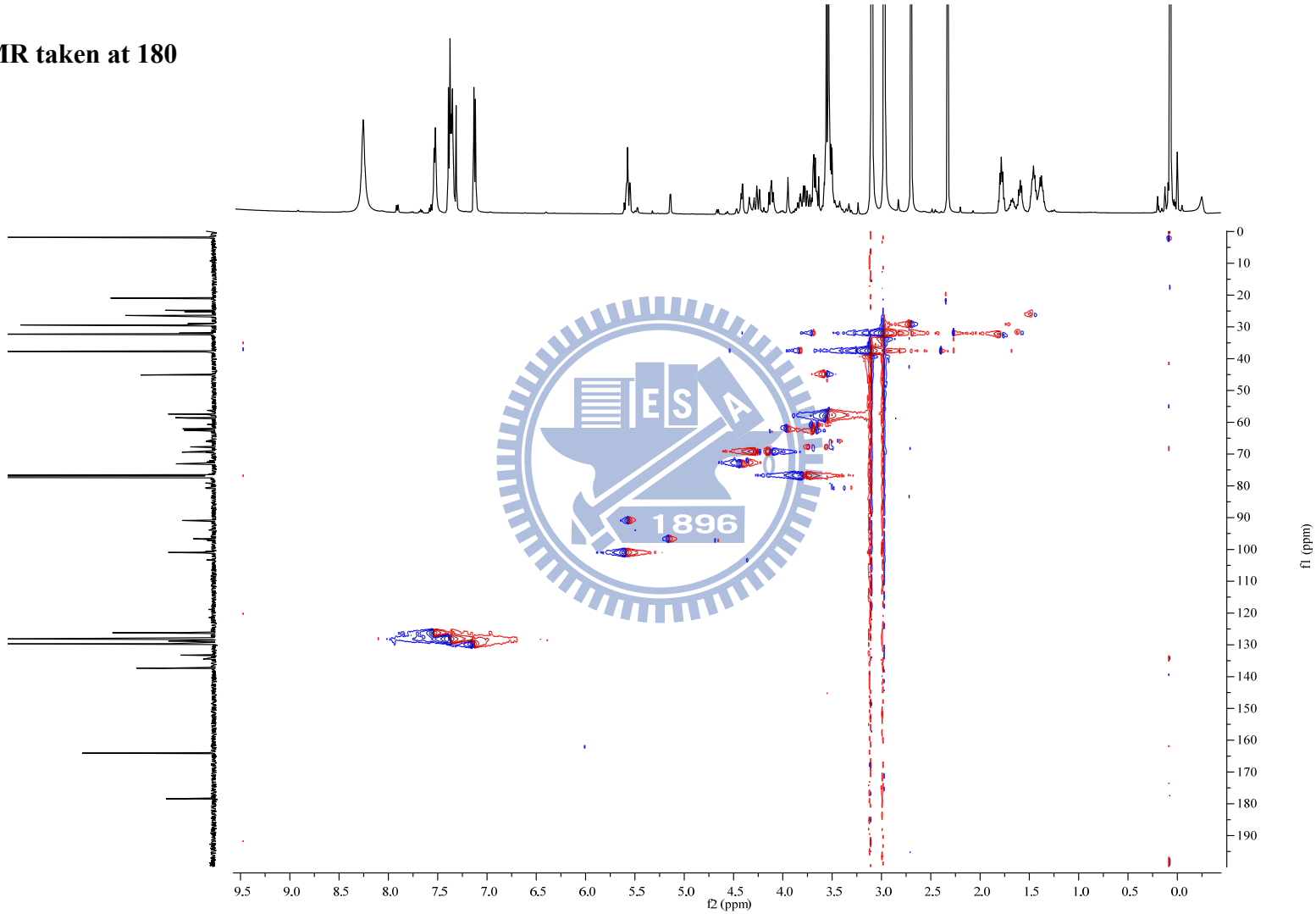
HSQC NMR taken at 0 min
(refer to Fig. 9b)



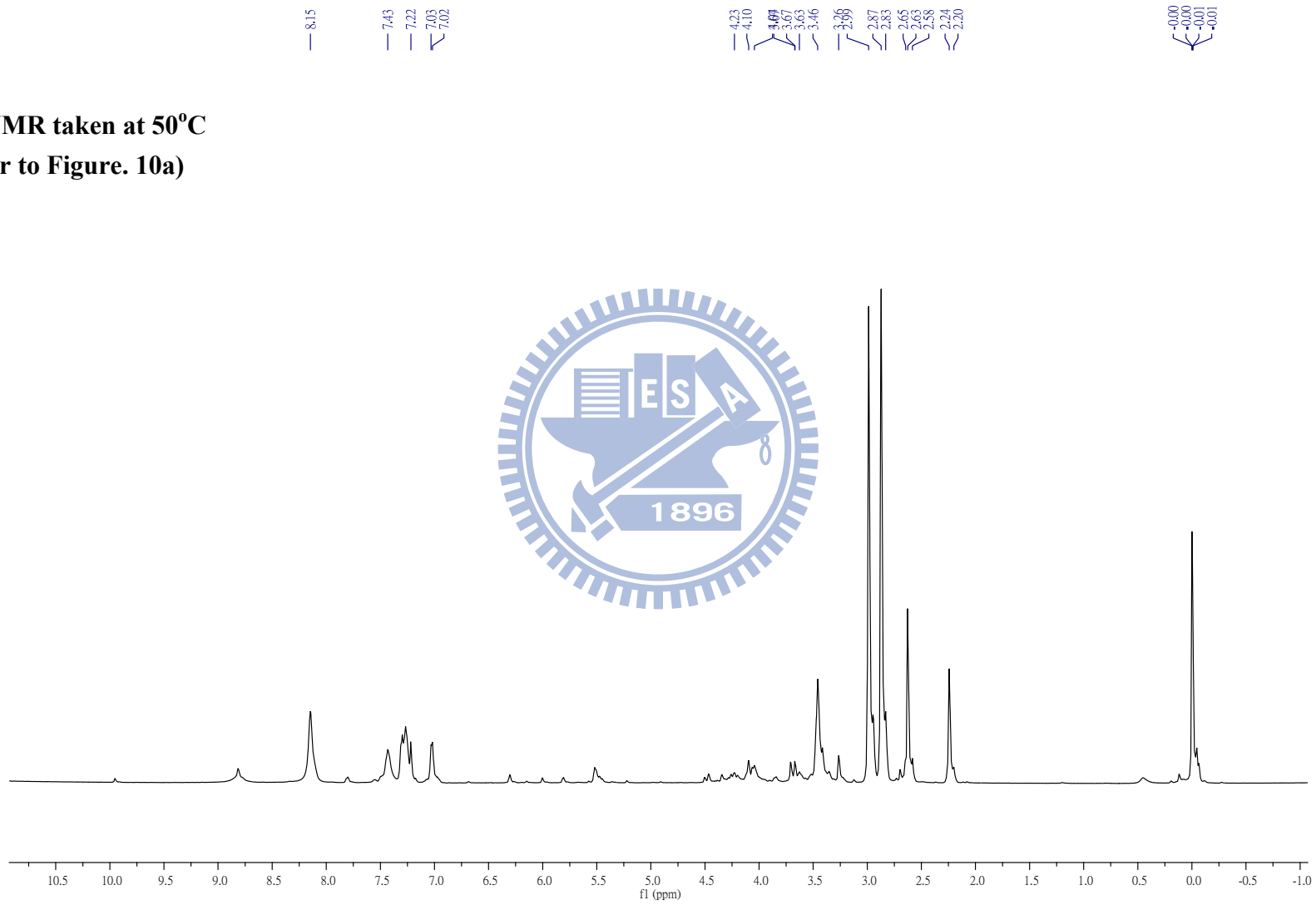
HSQC NMR taken at 90 min
(refer to Fig.9c)



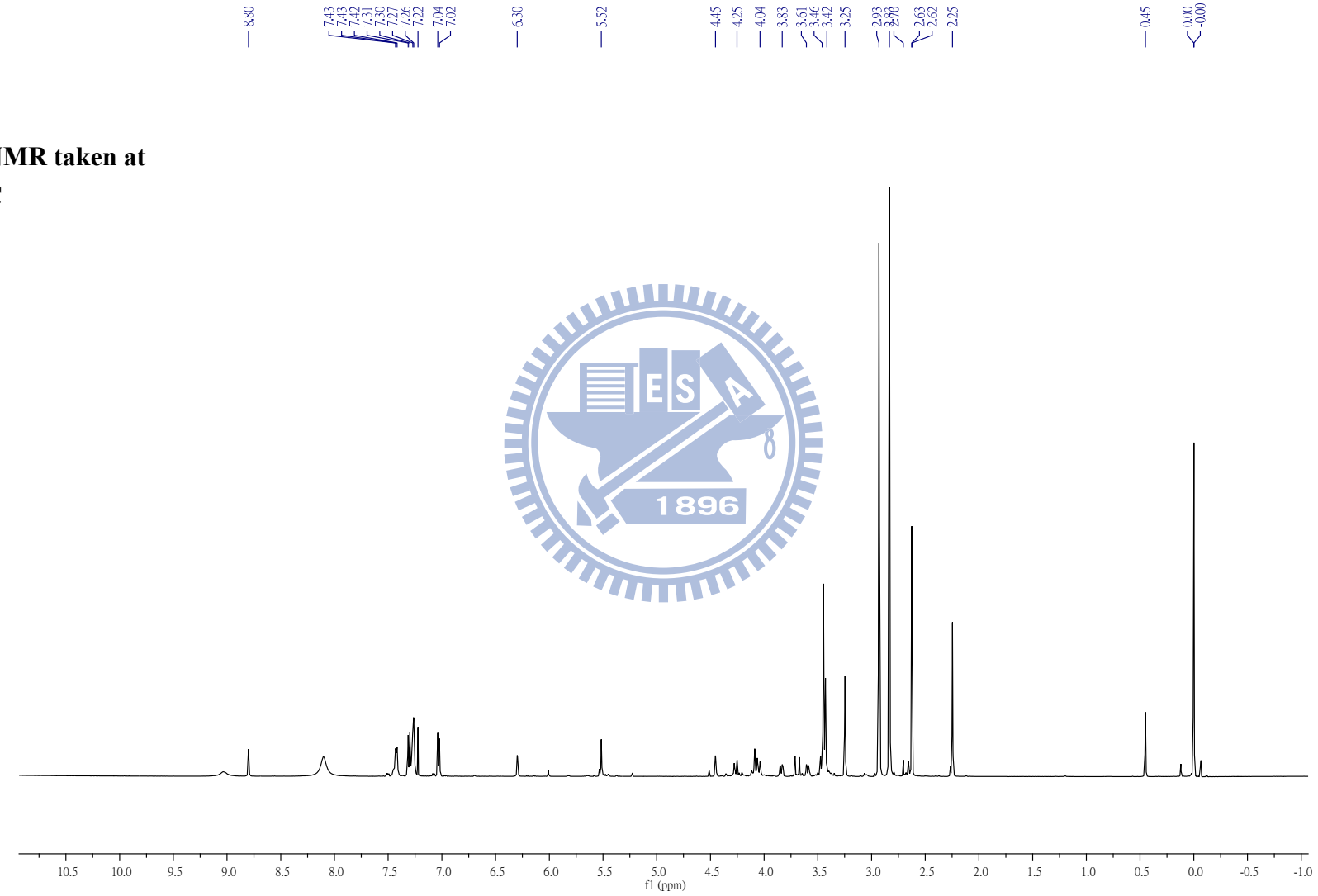
HSQC NMR taken at 180 min



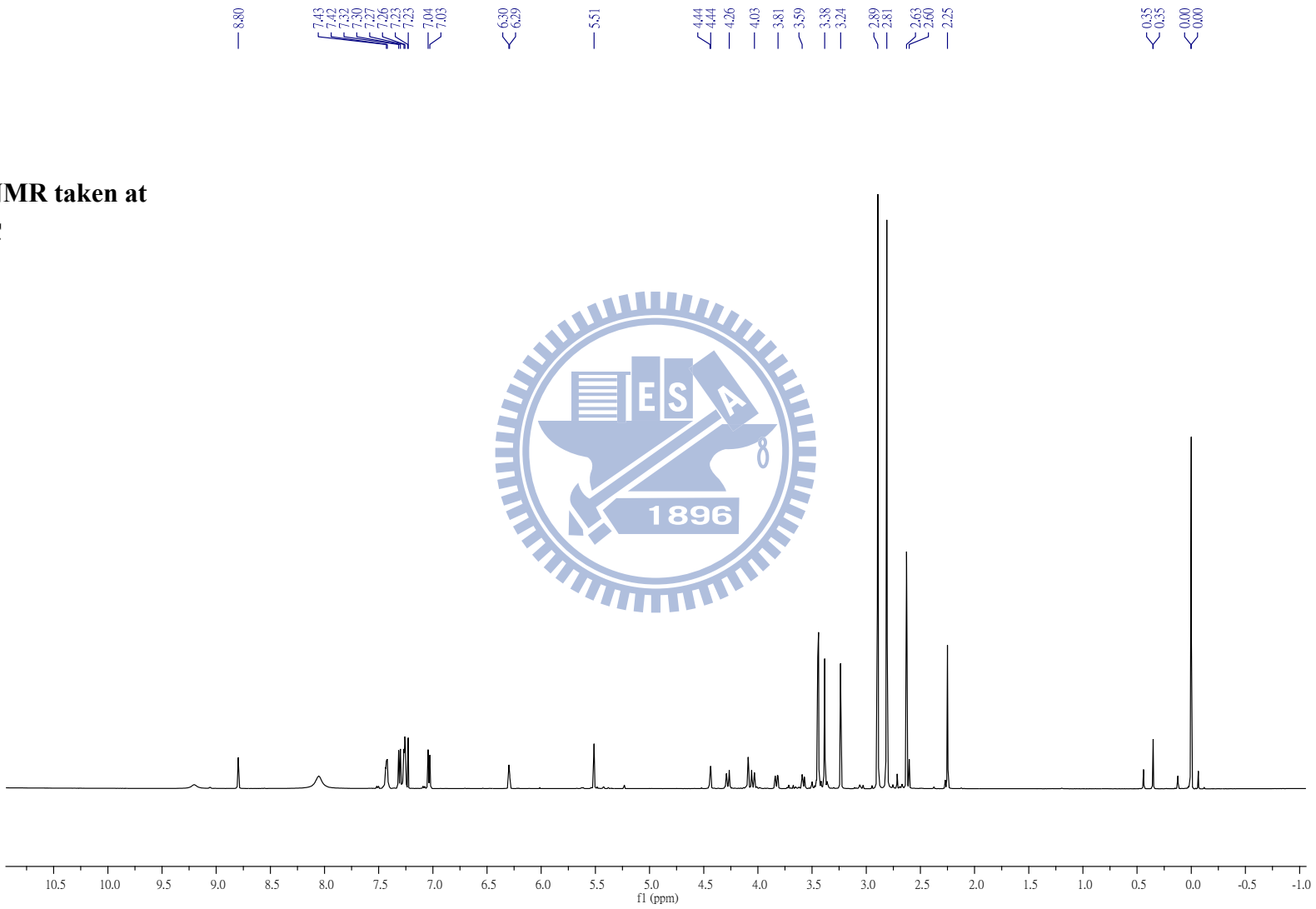
^{1}H NMR taken at 50^{o}C
(refer to Figure. 10a)



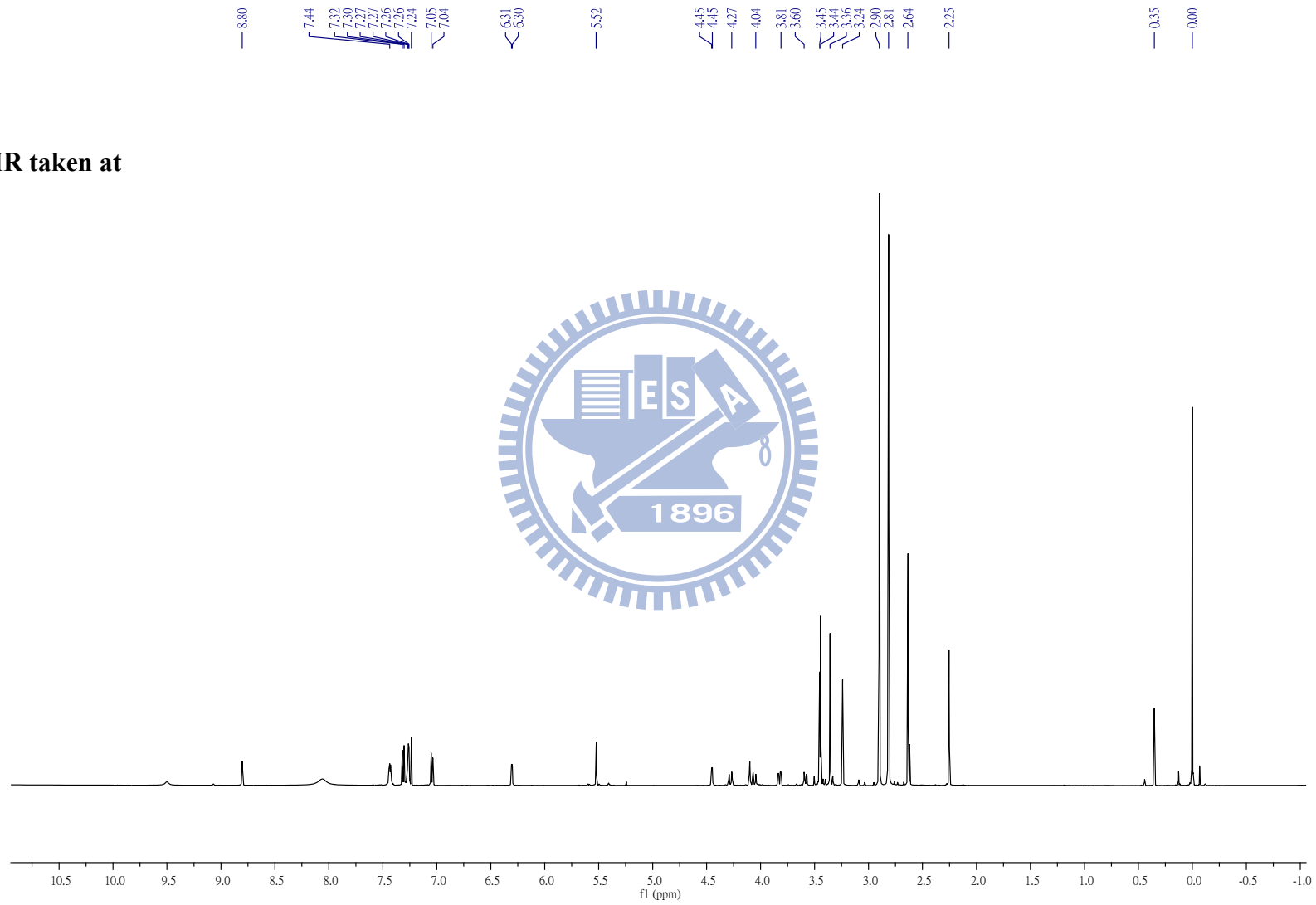
^{1}H NMR taken at
40^{o}C



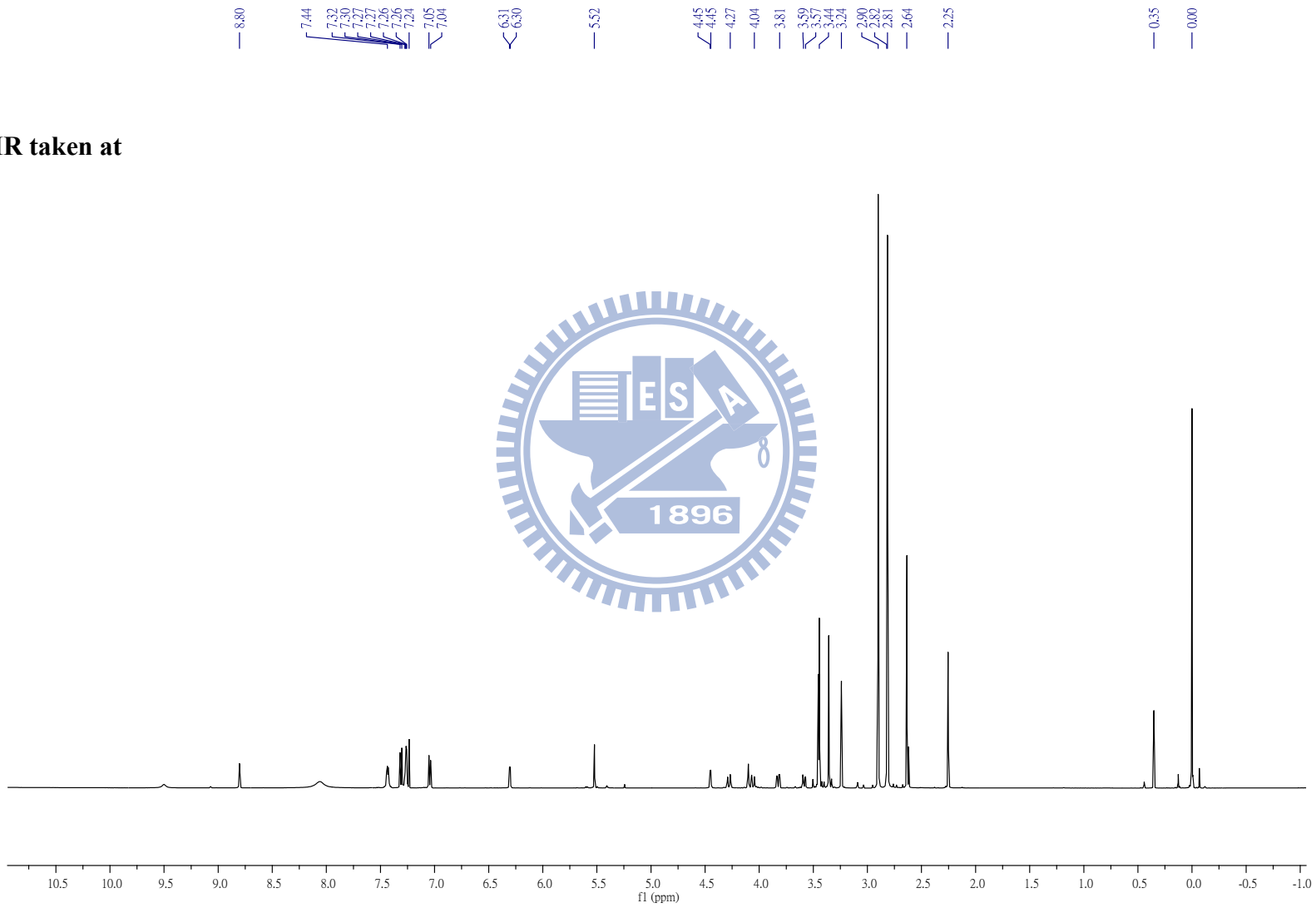
^{1}H NMR taken at
30^{o}C



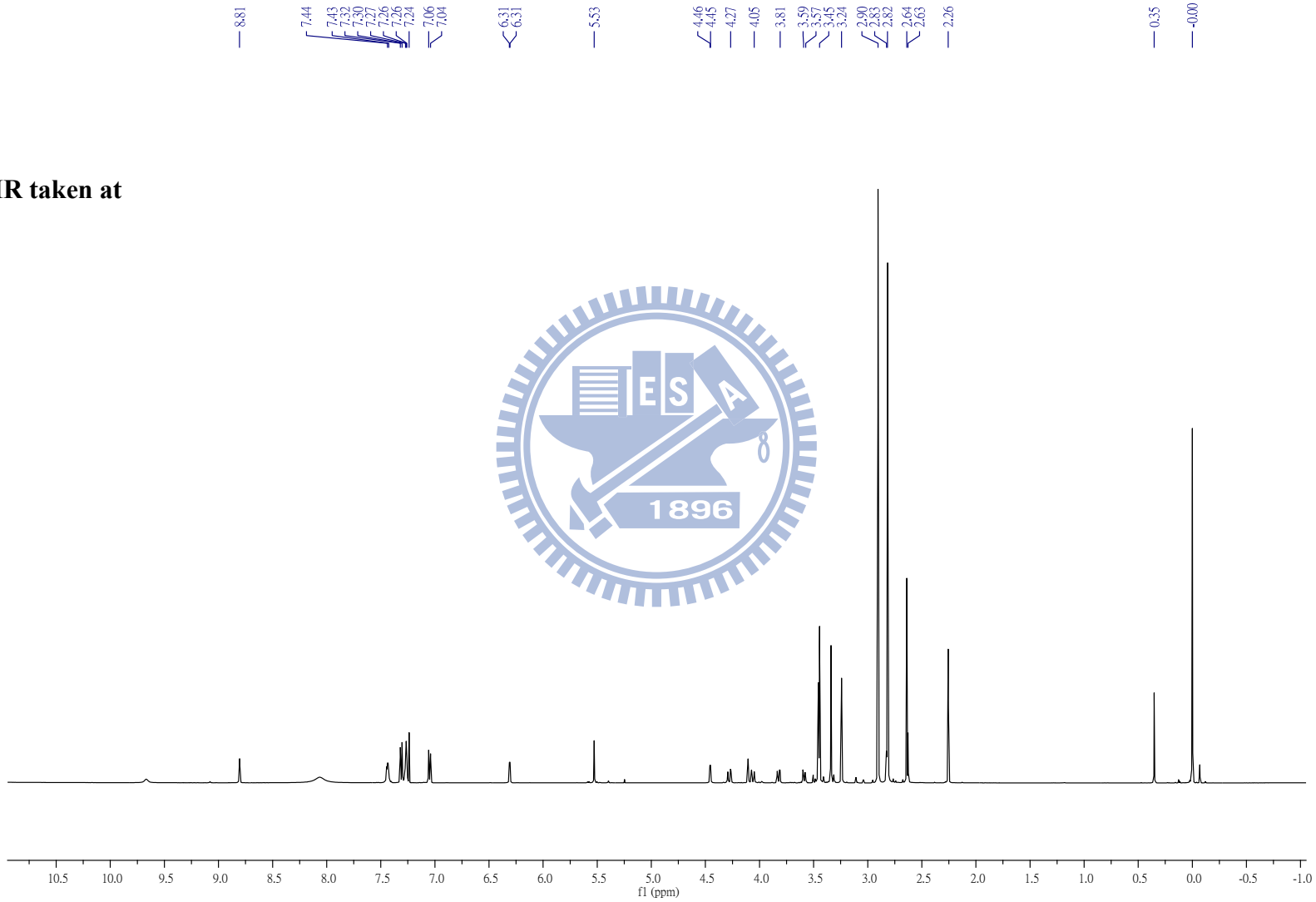
^{1}H NMR taken at
20^{o}C



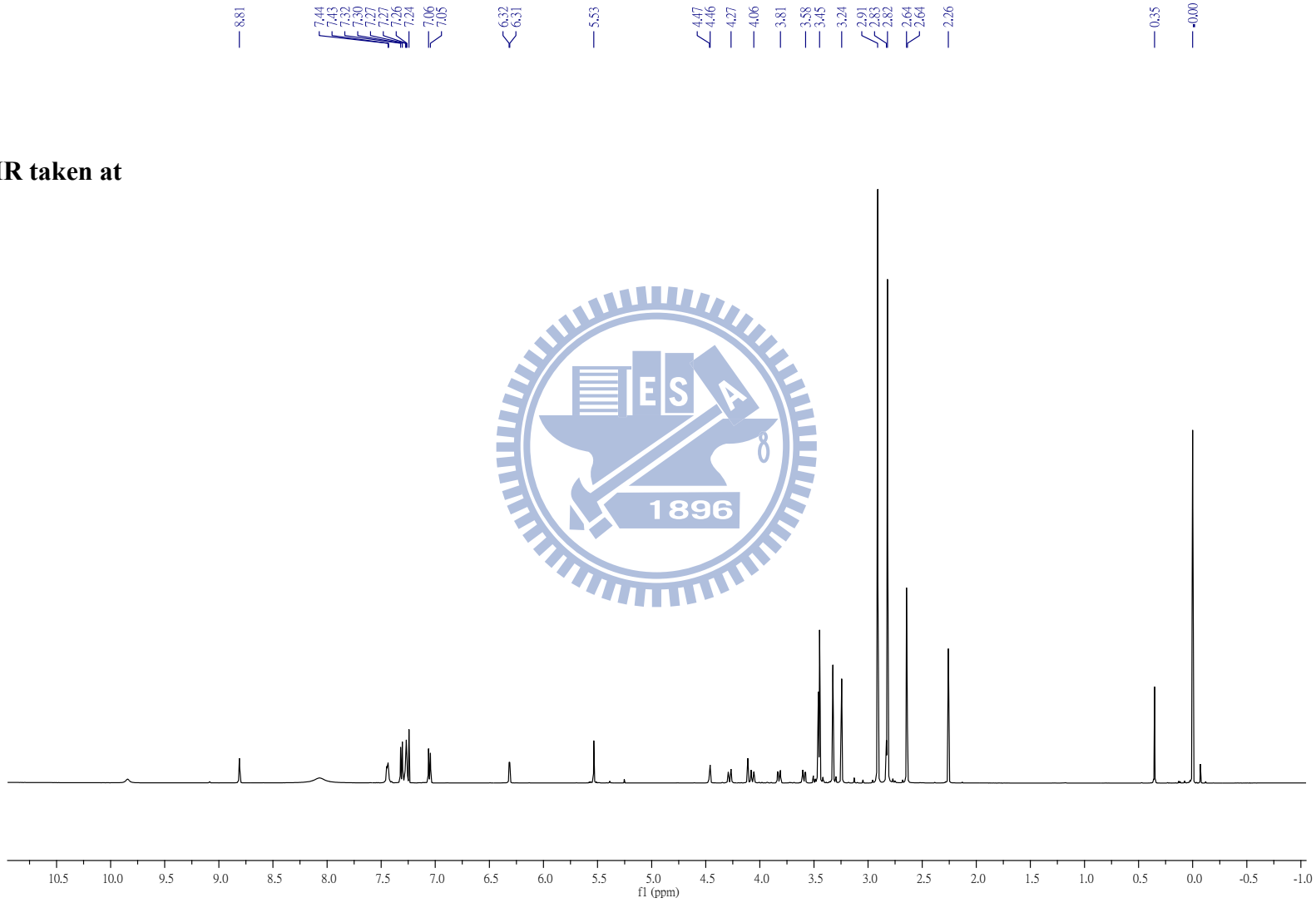
^{1}H NMR taken at
10^{o}C



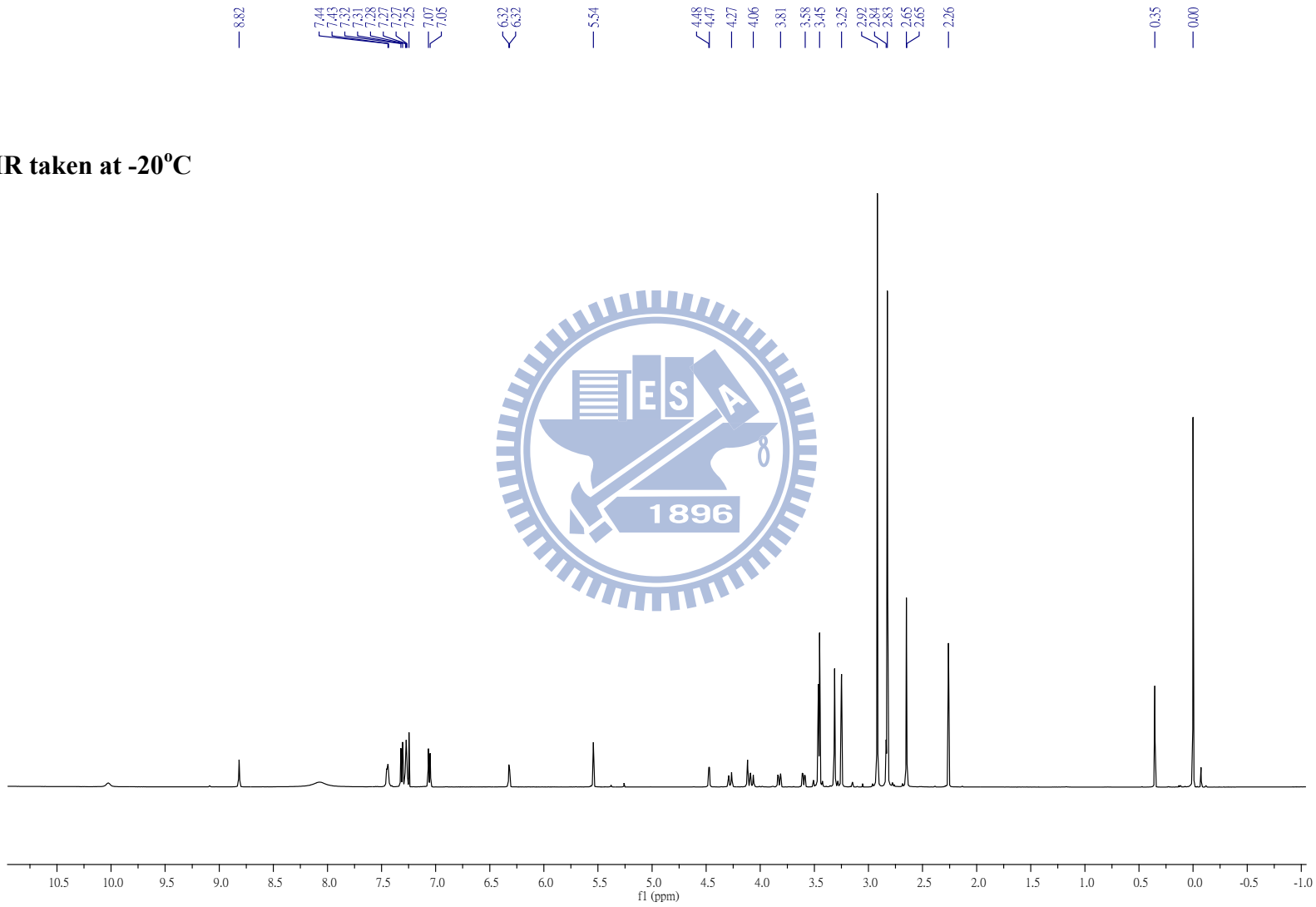
^{1}H NMR taken at 0^{o}C



^{1}H NMR taken at
-10^{o}C



^{1}H NMR taken at -20^{o}C



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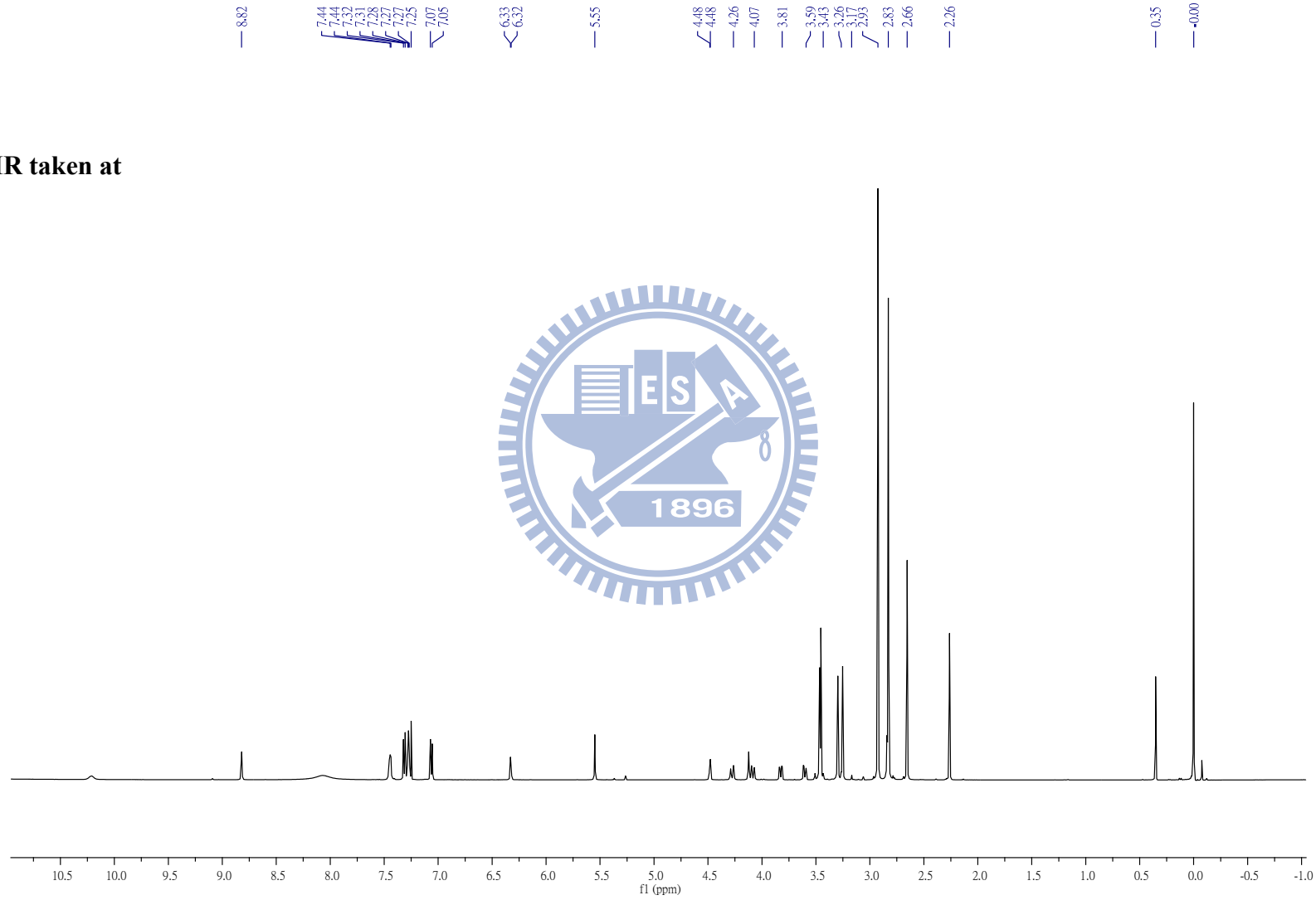
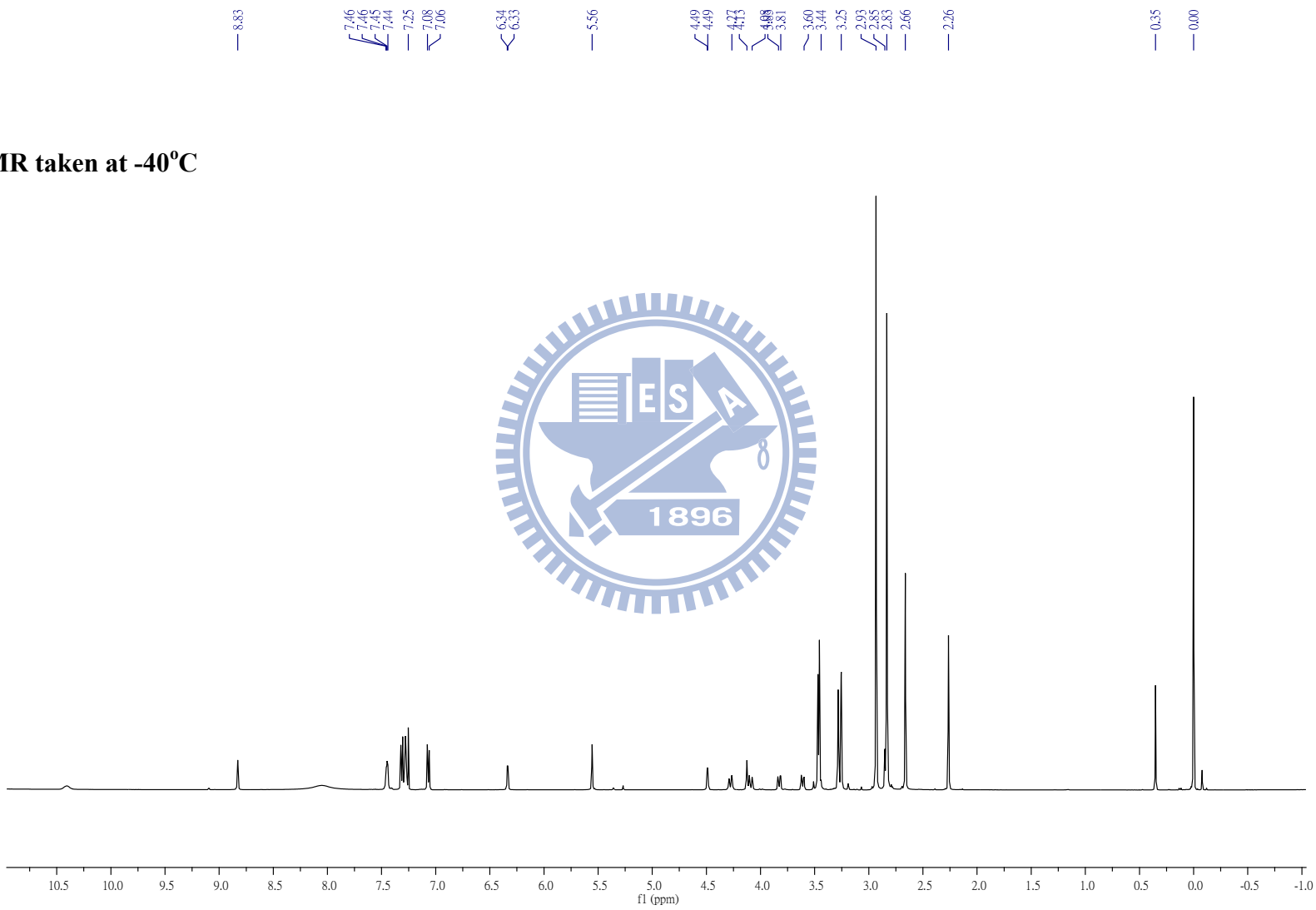


^{1}H NMR taken at -40^{o}C



^{1}H NMR taken at
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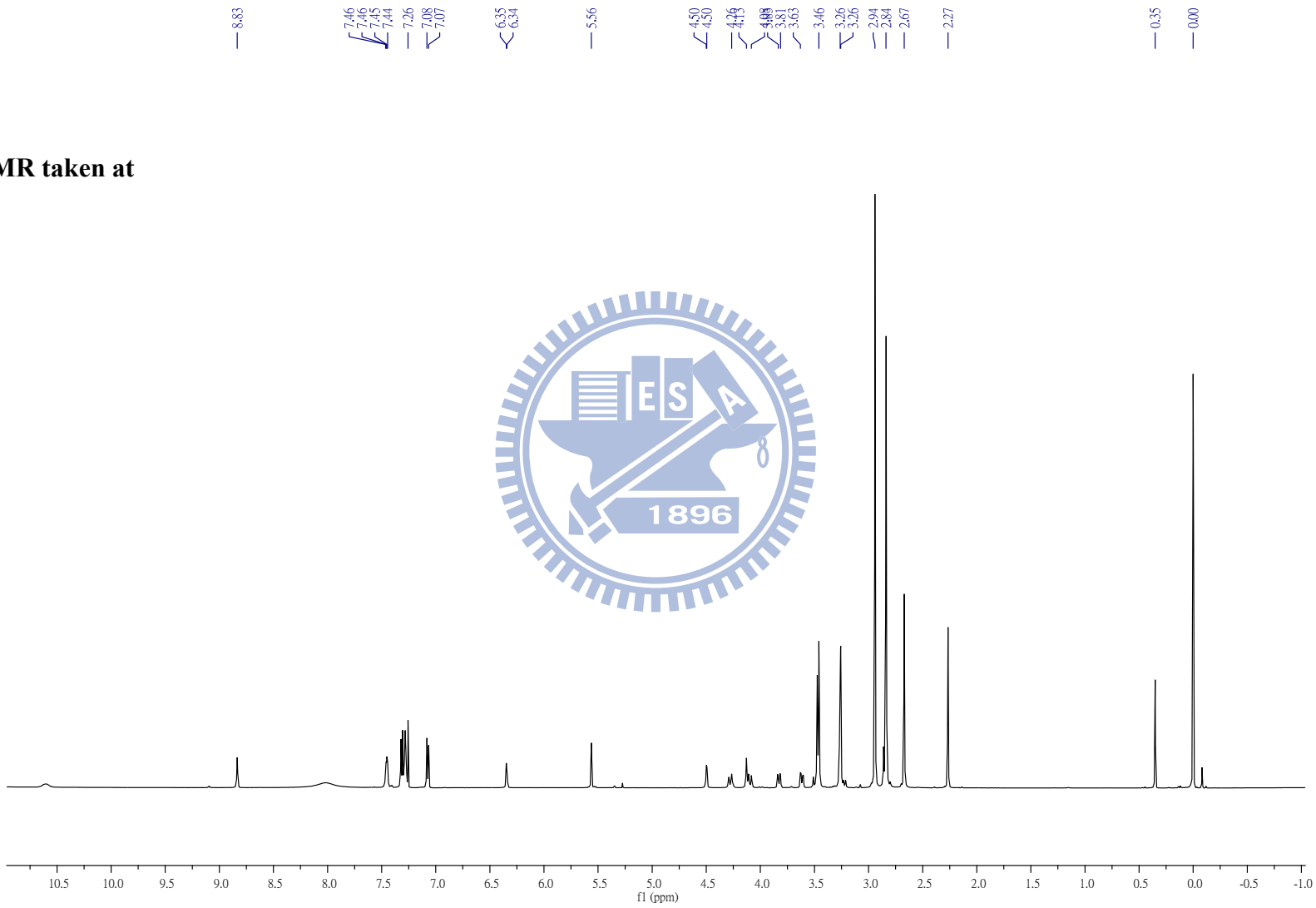
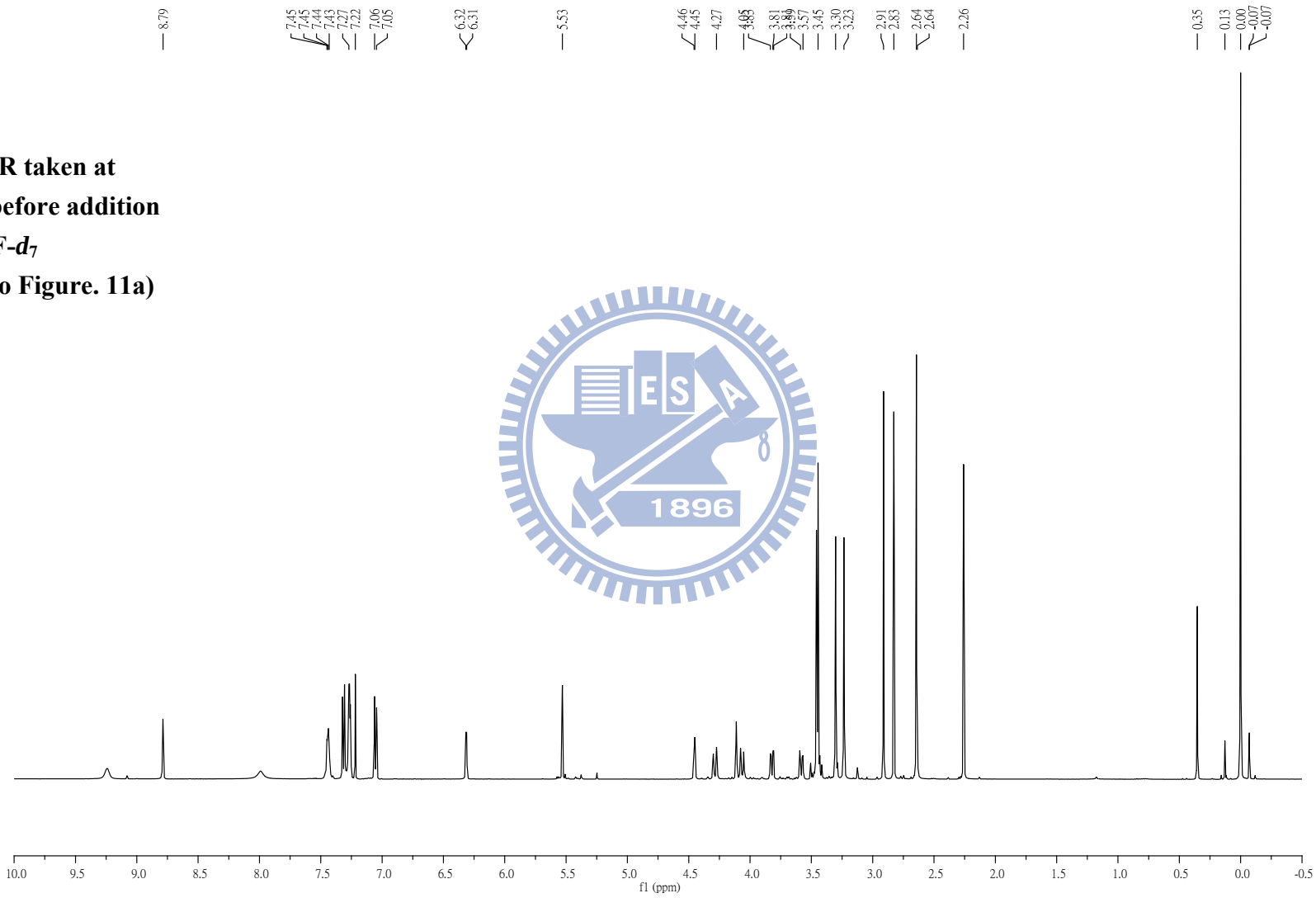
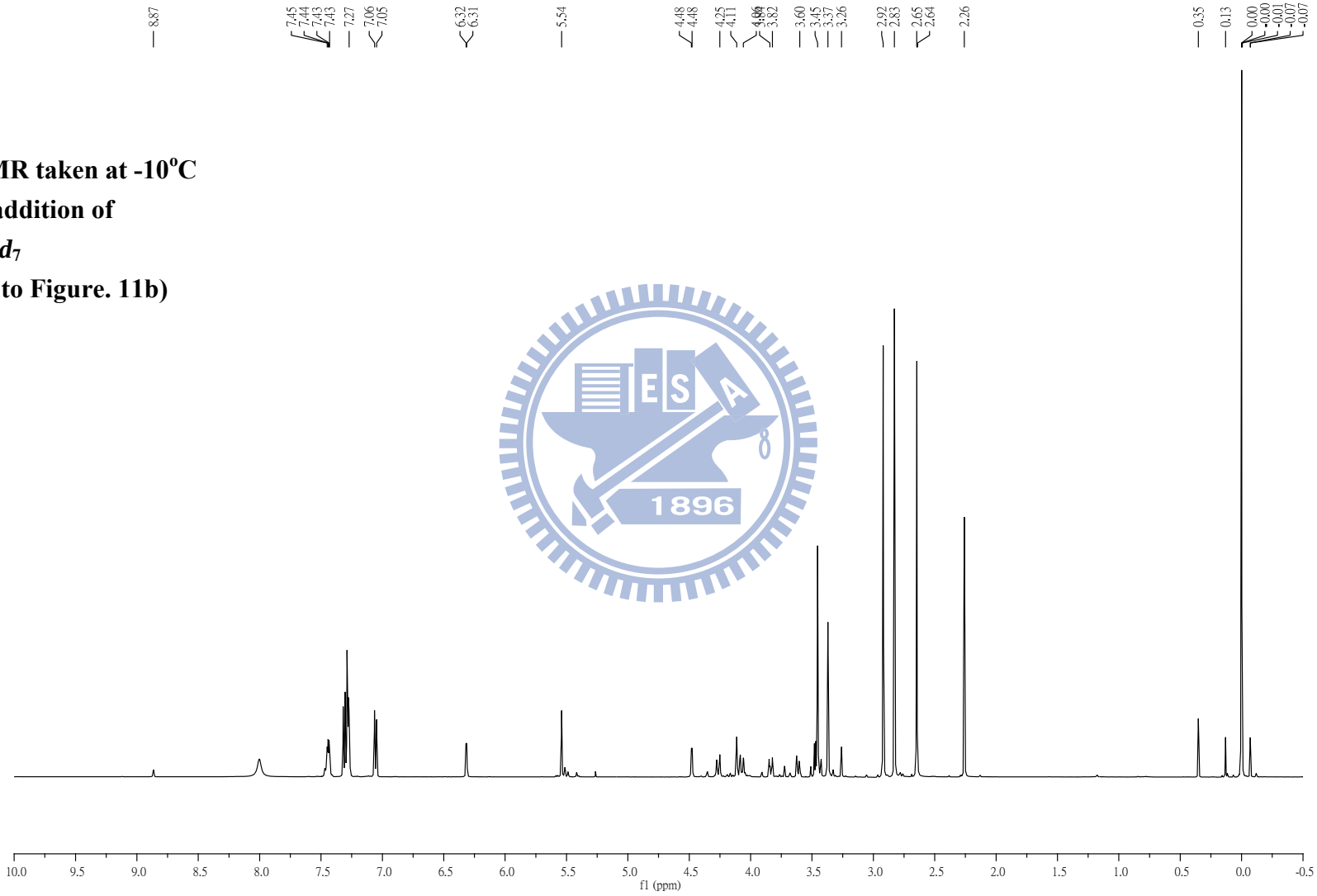


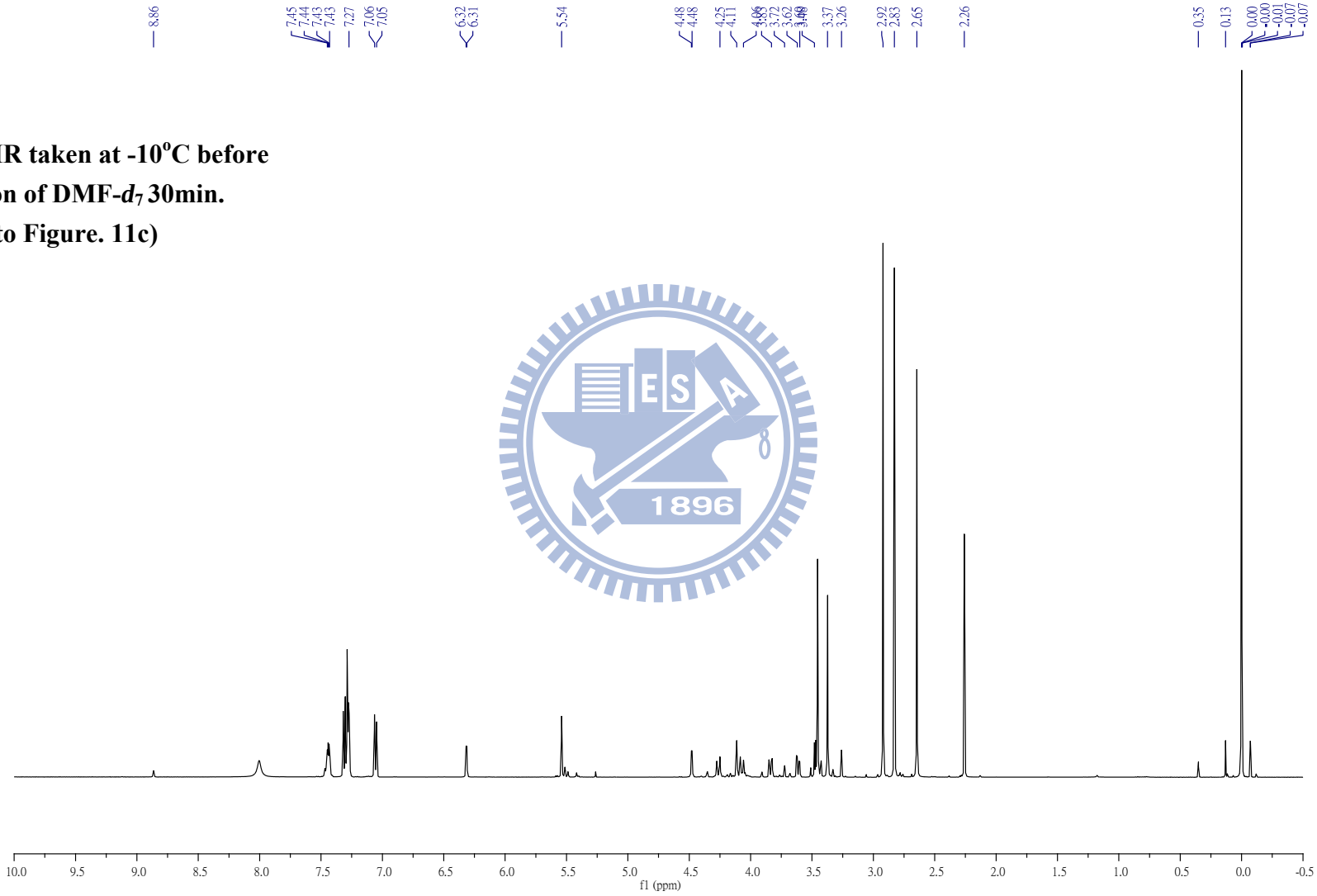
^{1}H NMR taken at
-10^{o}C before addition
of DMF-d_7
(refer to Figure. 11a)



^{1}H NMR taken at -10^{o}C after addition of DMF-d_7 (refer to Figure. 11b)



^{1}H NMR taken at -10^{o}C before addition of DMF-d_7 30min. (refer to Figure. 11c)

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Glycosylation

DOI: 10.1002/anie.201100076

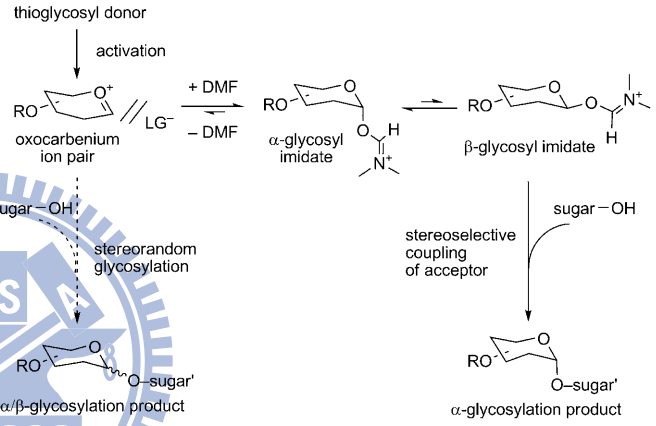
Dimethylformamide: An Unusual Glycosylation Modulator**

*Shao-Ru Lu, Yen-Hsun Lai, Jiun-Han Chen, Chih-Yueh Liu, and Kwok-Kong Tony Mong**

Dedicated to Professor Chi-Huey Wong

The key steps in oligosaccharide synthesis are protecting-group manipulation and stereoselective glycosylation.[1] Various strategies have emerged to expedite glycosylation, and some of these strategies have been elaborated for automated solid-phase synthesis[2] and one-pot cascade glycosylation.[3] Most glycosylation strategies rely on traditional methods for stereochemical control over glycosidic-bond formation. Although such tactics work well for the formation of 1,2-*trans* β-glycosidic bonds,[4] there is no straightforward solution for the formation of a 1,2-*cis* α-glycosidic bond.[1a,5] Existing methods often require extensive optimization of the reaction conditions, including the selection of an ethereal solvent,[6] a transition-metal-complex promoting system,[7] a remote participating group,[8] a silylidene protecting group,[9] and a chiral or achiral accessory group at the C2 position,[10–13] or the installation of a fluoride substituent at the C2 position.[14] However, most of these methods require additional steps for the installation of a specific functionality and are therefore less convenient for routine synthesis. Herein, we report a simple and general α-glycosylation method in which *N*,*N*-dimethylformamide (DMF) is used as a modulating molecule to direct the stereochemical course of glycosylation. Further elaboration of this approach led to a practical α-selective procedure based on preactivation that is useful for the glycosylaton of both O-glycoside and thioglycoside acceptors.

In a previous study of the chlorination of glycosyl hemiacetals, we observed that residual DMF in the glycosylation mixture promoted the formation of 1,2-*cis* α-glycosidic bonds.[15] A search of the literature revealed that DMF has been utilized as a glycosylation solvent[16] and as a component in the Vilsmeier–Haack reaction for glycosylations.[17] Koto et al. reported the use of DMF as an additive to effect α-glycosylation; however, this protocol suffered from undesired glycosyl formate formation.[17d] Lemieux and Driguez employed DMF (20–30 vol%) as one component of a mixed solvent system in particular glycosylations; however, such reactions required 4 days to reach completion, and the role of DMF was not stated.[18] We hypothesized that the activation of a thioglycoside generates an oxocarbenium ion pair, which upon trapping by nucleophilic DMF gives rise to an equilibrium mixture of α-/β-glycosyl imidates. Assuming that the β imidate is more reactive than its α counterpart; subsequent coupling of the β imidate with an acceptor produces the desired α anomer as the major product (Scheme 1). Since DMF has a modulating function in the reaction, we coined the term DMF-modulated glycosylation strategy for this approach.



Scheme 1. Proposed mechanism of the DMF-modulated glycosylation.

Initially, we examined two DMF-modulated procedures (Scheme 2a,b). In procedure A, adapted from a standard glycosylation protocol, a mixture of a thioglycosyl donor, a glycosyl acceptor, and DMF is treated with *N*-iodosuccinimide (NIS) and trimethylsilyl triflate (TMSOTf) (Scheme 2a).[19] In procedure B, the thioglycosyl donor is first preactivated with NIS and TMSOTf in the presence of DMF. Following activation, the glycosyl acceptor is added and reacts with the glycosyl imidate to furnish the desired glycosylation product (Scheme 2b).

At the outset, we followed procedure A to couple the commercially available galactosyl acceptor **3** with the perbenzyl thiogalactoside **1**.[20] After some experimentation, we found that one molar equivalent of TMSOTf (with respect to the glycosyl donor) was required for effective activation of the donor, probably owing to the mild Lewis basicity of DMF. DMF exhibited an α-directing effect in glycosylation reactions: a result which is in line with our previous findings.[15] We observed a quantity–selectivity dependence between the stoichiometric amount of DMF added and the degree of glycosylation selectivity. Explicitly, when the amount of DMF was increased from 0 to 1.5 equivalents, the α/β-anomer ratio of the glycosylation product **4** increased from 1:1 to 3:1

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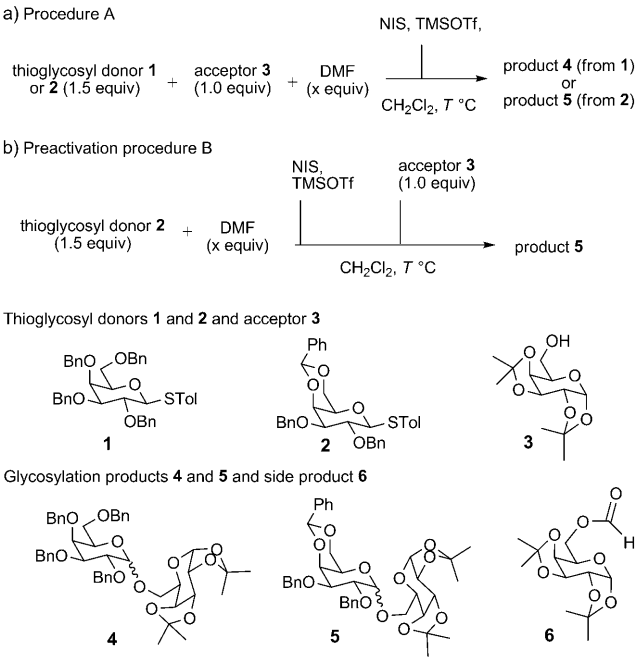


Scheme 2. a) First DMF-modulated glycosylation procedure (procedure A). b) Second DMF-modulated glycosylation procedure (procedure B). Bn = benzyl, Tol = *p*-tolyl.

(Table 1, entries 1–4). However, such moderate selectivity remains inadequate for synthetic utility; a further increase in the amount of DMF added (> 1.5 equiv) did not improve the selectivity owing to the formation of a formyl-transfer product **6**.[17d] We reasoned that the arming benzyl groups of donor **1** may promote the departure of DMF from the glycosyl imidate; consequently, the α-directing effect of DMF was attenuated.[21] Therefore, a conformationally restrained benzylidene thiogalactoside **2** was used in place of **1**.[20] However, the replacement of the donor alone did not bring about significant improvement: glycosylation product **5** was obtained with a 6:1 α/β-anomer ratio (Table 1, entry 5). Nevertheless, when the preactivation procedure B was adopted in conjunction with an increase in the amount of DMF added (from 1.5 to 6.0 equivalents), the α/β-anomer ratio of **5** was increased to 19:1 (Table 1, entries 6–8). To investigate whether an ethereal solvent could reproduce the α-directing effect, as implicated in previous studies,[6a] we repeated the glycosylation of **3** with **2** in pure THF, CH_2Cl_2/Et_2O (1:3), and toluene/dioxane (1:2) by procedure A, as procedure B does not work in the absence of DMF.[22] No significant selectivity was observed in these glycosylation reactions, irrespective of the type of ethereal solvent used (Table 1, entries 9–12). In the past, dimethylacetamide (DMA) has been used as an additive to promote α selectivity in glycosylation reactions.[17d] We were curious whether DMA could replace DMF in our procedure and repeated the glycosylation of **3** with **2** according to procedure B with the addition of DMA; however, the observed selectivity was not attractive (Table 1, entry 13).

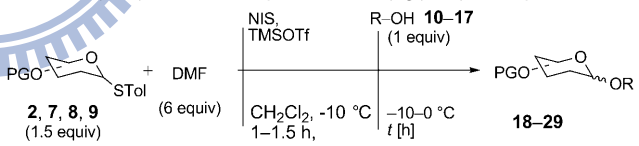
After confirming the effectiveness of the preactivation glycosylation procedure B, we next investigated its scope of application. Thus, aglycone acceptors **10**–**13** and O-glycoside acceptors **14**–**17** were coupled with thioglycosyl donors **2**, **7**, **8**, and **9** (Scheme 3, Table 2).[23] For comparison, these glycosylation reactions were performed with and without the addition of DMF. Generally, reaction rates were lower in the presence of DMF than in its absence; nonetheless, the time required for the completion of DMF-modulated glycosylation remained acceptable (2–6 h). Regarding stereochemical control, DMF exerted a powerful α-directing effect on all glycosylations. In some cases, the selectivity was reversed dramatically by the addition of DMF (Table 2, entries 2, 4, 5,

Table 1: Investigation of DMF-modulated glycosylation procedures A and B with galactosyl acceptor **3**.

Entry	Donor (equiv)	DMF [equiv]	*T* [°C]	*T* [h]	Product, yield [%], α/β[a]
1	**1** (1.2)[b]	0	−25	0.5	**4**, 90, 1:1
2	**1** (1.2)[b]	0.8	−10	1.0	**4**, 70, 3:2
3	**1** (1.2)[b]	0.8	0	1.0	**4**, 77, 3:2
4	**1** (1.2)[b]	1.5	0	1.0	**4**, 80, 3:1
5	**2** (1.5)[b]	1.5	−10	2.0	**5**, 82, 6:1
6	**2** (1.5)[c]	1.5	−10	2.0	**5**, 80, 8:1
7	**2** (1.5)[c]	3.0	−10	2.0	**5**, 87, 15:1
8	**2** (1.5)[c]	6.0	−10	2.0	**5**, 87, 19:1
9	**2** (1.5)[b]	0[d]	−10	0.3	**5**, 90, 1:1
10	**2** (1.5)[b]	0[e]	−10	0.2	**5**, 85, 1.5:1
11	**2** (1.5)[b]	0[f]	−10	0.5	**5**, 83, 1:1.5
12	**2** (1.5)[b]	0[f]	0	4.0	**5**, 40, 1:1.5
13	**2** (1.5)[c]	–[g]	−10	3.0	**5**, 80, 4:1

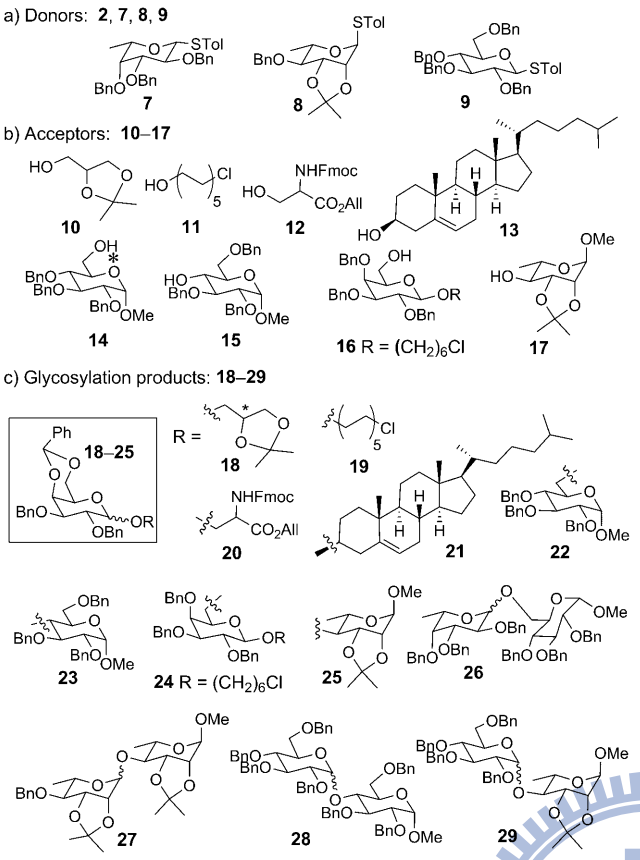
[a] The α/β ratio was determined by HPLC (conditions given in the Supporting Information). [b] Procedure A was used. [c] Procedure B was applied. [d] A 1:3 CH_2Cl_2/Et_2O mixture was used as the solvent. [e] THF was used as the solvent. [f] A 1:2 toluene/dioxane mixture was used as the solvent. [g] DMA (6 equiv) was added.[17d]

Table 2: Glycosylation of acceptors **10**–**17** by glycosylation procedure B.



Entry	D[a]	A[a]	*T* [°C]	*t* [h]	Product	Yield [%], α/β[b] with DMF	without DMF[c]
1	**2**	**10**	−10	2	**18**	83, 12:1	80, 1:1
2	**2**	**11**	−10	2	**19**	76, 8:1	85, 2:5
3	**2**	**12**	−10	6	**20**	45, 19:1	50, 15:1
4	**2**	**13**	0	2	**21**	79, 8:1	73, 2:5
5	**2**	**14**	−10	5.5	**22**	75, 12:1	80, 2:3
6	**2**	**15**	0	6	**23**	80, 49:1	50, 2:1
7	**2**	**16**	−10	2	**24**	82, 12:1	80, 3:2
8	**2**	**17**	0	4	**25**	60, 25:1	63, 5:1
9	**7**	**14**	−10	4.5	**26**	75, 5:1	77, 1:1
10	**8**	**17**	−10	4	**27**	70, 49:1	80, 5:1
11	**9**	**15**	0	6	**28**[d]	76, 49:1	60, 2:3
12	**9**	**17**	0	5	**29**[d]	75, 9:1	70, 2:5

[a] D is the donor; A is the acceptor. [b] The α/β-anomer ratio was determined by HPLC (settings are given in the Supporting Information). [c] A routine glycosylation (without the addition of DMF) was carried out. [d] The glycosylation was performed with ultrasonification.[24] PG = protecting group.

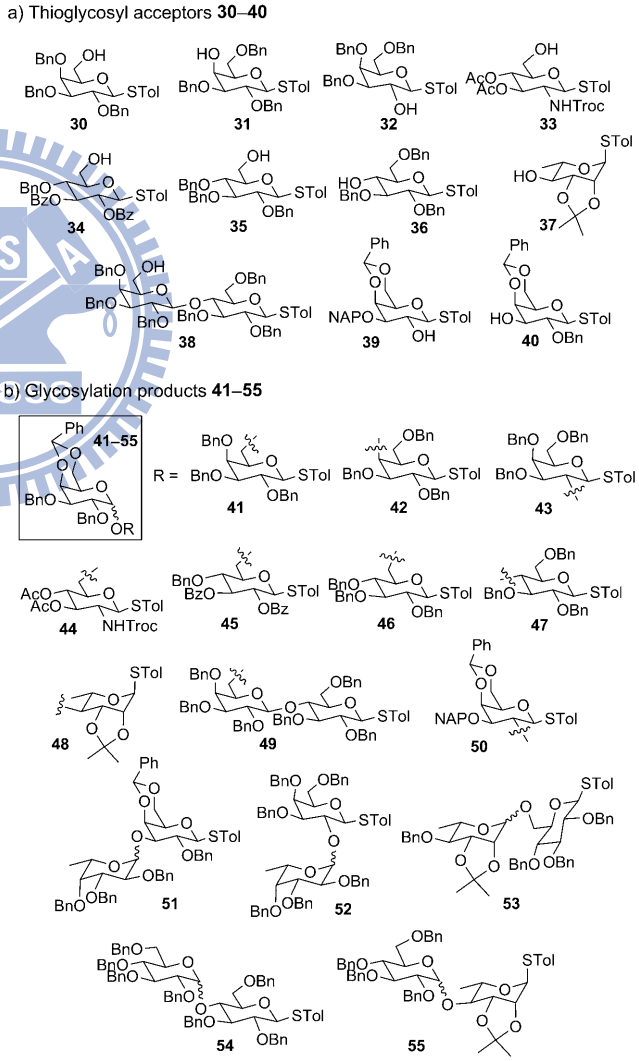


Scheme 3. Structures of a) thioglycosyl donors **7**–**9**; b) acceptors **10**–**17**; c) glycosylation products **18**–**29**. All = allyl, Fmoc = 9-fluorenylmethoxycarbonyl.

11, and 12). More importantly, this effect was not restricted to galactosyl donors, but also occurred with L-thiofucoside **7**, L-thiorhamnoside **8**, and D-thioglucoside **9** (Table 2, entries 9–12). However, the stereoelectronic features of a particular donor does affect the reaction efficiency. Therefore, some optimization of the reaction conditions is required. For example, the glycosylations of **15** and **17** with thioglucoside donor **9** were conducted with ultrasound irradiation to shorten the reaction time (Table 2, entries 11 and 12).[24]

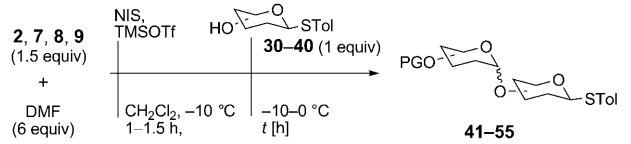
A unique feature of the DMF-modulated glycosylation is the entrapment of oxocarbenium ions as glycosyl imidates. This feature provides an opportunity for the development of a new glycosylation procedure with preactivation. In a typical oligosaccharide synthesis, the introduction of different anomeric functional groups in the glycosyl donor and acceptor is required so that the activation of the former does not affect the later. Although the reactivities of the glycosyl donor and acceptor can also be tuned to create reactivity disparity that enables their coupling by reactivity-based glycosylation, this strategy requires extensive protecting-group manipulation for building-block preparation.[3,21a,25] The merit of a glycosylation involving preactivation is that it enables the coupling of glycosyl substrates with the same anomeric functionality and thus renders the use of different anomeric functionalities or the tuning of chemical reactivity unnecessary. Such an approach not only shortens the synthetic route in oligosaccharide synthesis, but it also paves the way to an iterative one-pot glycosylation method.[3] To the best of our knowledge, there is no previously reported preactivation procedure that causes an α-directing effect.[26] To demonstrate the applicability of the DMF-modulated procedure, thioglycoside acceptors **30**–**40** were glycosylated with thioglycoside donors **2**, **7**, **8**, and **9** according to procedure B (Scheme 4).[27] Table 3 summarizes the yields and α/β-anomer ratios of the corresponding glycosylation products **41**–**55**.

A known side reaction in glycosylations of thioglycosides is the transfer of the thioacetal functionality from the acceptor to the donor.[28] Gratifyingly, such a transfer reaction did not occur in the DMF-modulated procedure, perhaps as a result of masking of the reactive oxocarbenium ion by a DMF molecule. The glycosylations in this study proceeded smoothly, and the corresponding α anomers were furnished in 45–85 % yield with high to excellent α selectivity. However, the reaction yields were on average lower than those observed for the glycosylation of O-glycosides. We attributed the lower



Scheme 4. Structures of a) thioglycosyl acceptors **30**–**40**; b) glycosylation products **41**–**55**. Bz = benzoyl, NAP = 2-naphthylmethyl, Troc = trichloroethoxycarbonyl.

Table 3: Glycosylation of thioglycosyl acceptors **30–40** by glycosylation procedure B.



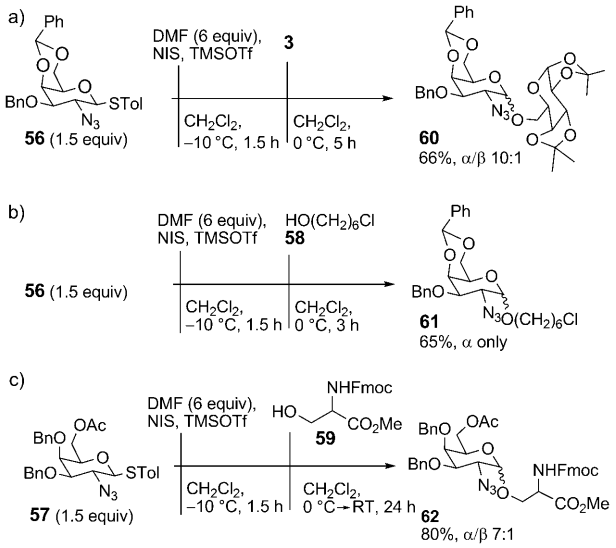
Entry	Donor	Acceptor	T [°C]	t [h]	α anomer (yield [%]),[a] α/β[b]
1	**2**	**30**	−10	3	**41** (60), 36:1
2	**2**	**31**	0	6	**42** (55), 6:1
3	**2**	**32**	0	3	**43** (55), 11:1
4	**2**	**33**	−10	3	**44** (45), 11:1
5	**2**	**34**	−10	3	**45** (85), 49:1
6	**2**	**35**	−10	2	**46** (65), 12:1
7	**2**	**36**	0	4	**47** (70), 49:1[29]
8	**2**	**37**	0	2	**48** (50), 13:1
9	**2**	**38**	−10	3	**49** (75), 19:1
10	**2**	**39**	0	4	**50** (85), 49:1
11	**7**	**40**	−10	3	**51** (56), 49:1
12	**7**	**32**	−10	6	**52** (61), 49:1
13	**8**	**35**	−10	3	**53** (55), 6:1
14	**9**	**36**	0	5	**54** (50), 49:1[c]
15	**9**	**37**	0	3	**55** (55), 8:1[c]

[a] The yield of the isolated α anomer is given. [b] The α/β ratio of the glycosylation product was determined by HPLC analysis (HPLC conditions are given in the Supporting Information). [c] The glycosylation was performed with ultrasonification.[24]

yields to the activation of the thioglycoside product by residual NIS and/or side reactions stemming from the imidate intermediates. To revalidate the α-directing effect of DMF, the glycosylation of **36** with **2** was repeated with a smaller amount of DMF (1.5 equiv); under these conditions, the α/β-anomer ratio of glycosylation product **47** decreased sharply to 4:1 (results not shown).[29]

Encouraged by the aforementioned results, we extended the applicability of the DMF-modulated glycosylation to 2-amino-2-deoxyglycosyl donors. Thus, 2-azido-2-deoxythiogalactosides **56** and **57** were coupled with acceptors **3**, **58**, and **59** by glycosylation procedure B (Scheme 5).[30] The α-directing effect of DMF was observed in all reactions examined, but the reaction time was generally longer than that required for non-amino glycosyl donors. The glycosylation of serine acceptor **59** with **57** was repeated in the absence of DMF, under which conditions **62** was produced with a 1:1 α/β-anomer ratio (results not shown). This comparison distinguishes the intrinsic selectivity of the serine acceptor from the α-directing effect of DMF. However, glycosylation with 2-azido-2-deoxythioglucosides has not met with success so far; further optimization of the reaction conditions is required.

Since the formation of a glycosyl imidate is the key step in DMF-modulated glycosylation, the detection of the glycosyl imidate is crucial for validation of the proposed mechanism (see Scheme 1). In this regard, we prepared a simpler 4,6-*O*-benzylidene-2,3-di-*O*-methylthiogalactoside **63**, which was activated with NIS and TMSOTf in $CDCl_3$ and then used for the glycosylation of acceptor **58** by procedure B (Figure 1 a).[31] ^{1}H, ^{13}C, and HSQC NMR spectroscopy of the reaction mixture was carried out at 0, 90, and 180 min time points. Figure 1 b–d shows selected regions of the corresponding ^{1}H NMR spectra. Comparison of the spectra of the preactivated reaction mixture at 0 min and the TMSOTf-activated mixture at 90 min (Figure 1 b,c) showed the appearance of a new set of clearly identifiable ^{1}H NMR signals, including those for an anomeric proton at $\delta = 6.39$ ppm ($^3J =$ 3 Hz, **64**-H^a), a benzylidene proton at $\delta = 5.60$ ppm (**64**-H^b), an imidoyl proton at $\delta = 8.90$ ppm (**64**-H^c), and *N*,*N*-dimethyl protons at $\delta = 3.40$ and 3.32 ppm (**64**-H^d). These signals are presumably generated from the α-glycosyl imidate **64**.[16a,b,31,32] The relative downfield positions of **64**-H^{a,c,d} indicate the close proximity of these hydrogen atoms to an electron-deficient center. Following the addition of acceptor **58**, the signals stemming from imidate **64** vanished, and another two sets of signals emerged. One set includes the signals for an anomeric proton at $\delta = 5.13$ ppm ($^3J = 3$ Hz, **65**-H^a) and a benzylidene proton at $\delta = 5.59$ ppm (**65**-H^b); these signals correspond to the expected α-glycoside **65**. Another set (indicated by asterisks in Figure 1 d) originated from an α-*N*-galactosyl succinimide: a common side product in NIS-promoted glycosylation reactions.[25]



Scheme 5. Glycosylation of acceptors **3**, **58**, and **59** with 2-azido-2-deoxythiogalactosides **56** and **57** by glycosylation procedure B.

As the real-time NMR spectroscopic study provided evidence for the presence of the α-glycosyl imidate, it is reasonable to propose the formation of α-/β-glycosyl imidates in DMF-modulated glycosylations. The β-glycosyl imidate, owing to its more reactive nature, reacts preferentially with the acceptor to give the α-glycosylation product. Until now, we have not been able to detect the presence of the β imidate; therefore, it is too early to exclude the possibility of the other mechanism outlined in Scheme 1.[33,34] Further experimental investigations toward the elucidation of the reaction mechanism are in progress.

In summary, we have described a new DMF-modulated glycosylation strategy which enables excellent α selectivity in glycosylation reactions through the simple addition of DMF. Further elaboration led to the development of a useful α-selective glcyosylation procedure involving preactivation. Considering the availability of DMF, we anticipate that the

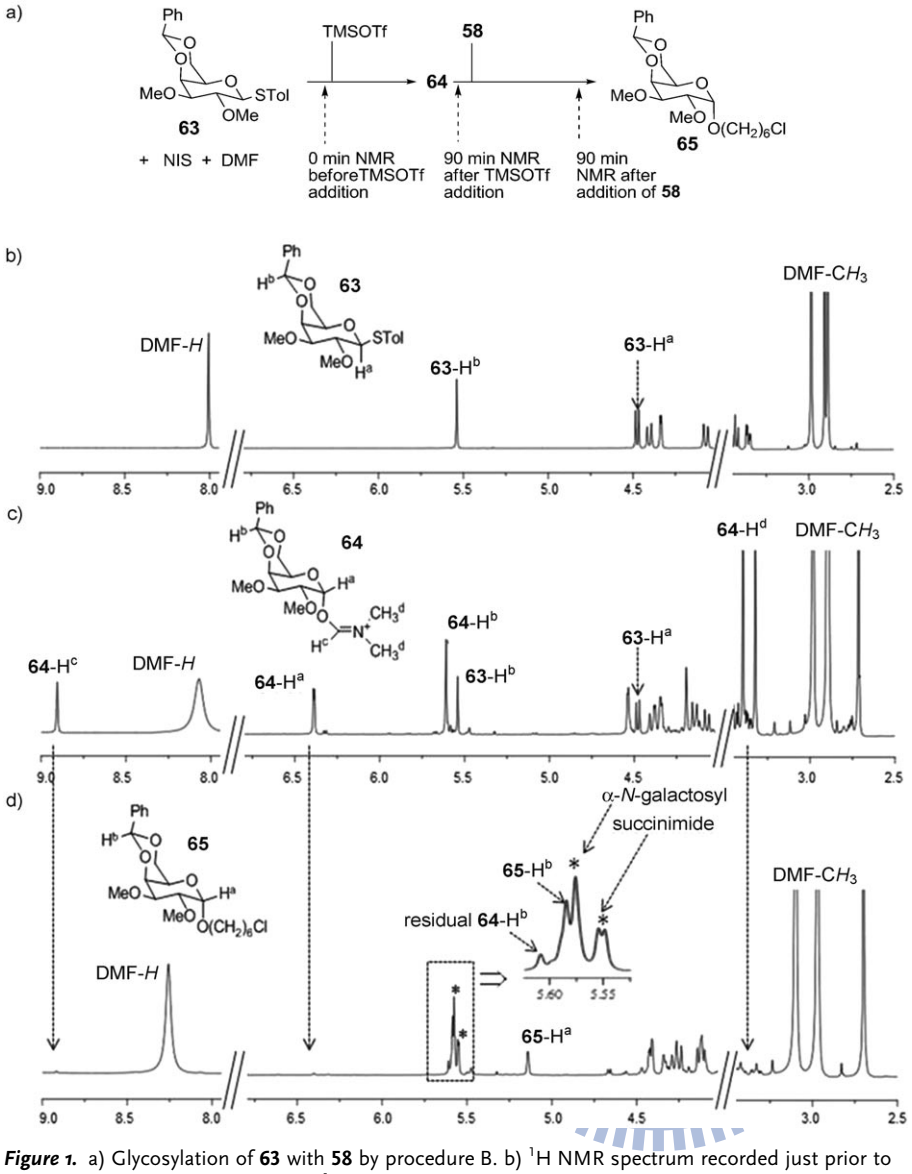


Figure 1. a) Glycosylation of **63** with **58** by procedure B. b) ^{1}H NMR spectrum recorded just prior to the addition of TMSOTf (0 min). c) ^{1}H NMR spectrum recorded 90 min after the addition of TMSOTf (90 min). d) ^{1}H NMR spectrum recorded 90 min after the addition of **58**.

synthetic concept described herein will find broad application in oligosaccharide synthesis.

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[1] a) K. L. Mydock, A. V. Demchenko, *Org. Biomol. Chem.* **2010**, *8*, 497–510; <lit b> X. Zhu, R. R. Schmidt, *Angew. Chem.* **2009**, *121*, 1932–1967; *Angew. Chem. Int. Ed.* **2009**, *48*, 1900–1934.
[2] P. H. Seeberger, *Chem. Soc. Rev.* **2008**, *37*, 19–28.
[3] Y. Wang, X.-S. Ye, L.-H. Zhang, *Org. Biomol. Chem.* **2007**, *5*, 2189–2200.
[4] a) C.-U. Pittman, S.-P. McManus, J. W. Larsen, *Chem. Rev.* **1972**, *72*, 357–438; b) L. Goodman, *Adv. Carbohydr. Chem. Biochem.* **1967**, *22*, 109.
[5] A.-V. Demchenko, *Synlett* **2003**, 1225–1239.
[6] a) A.-V. Demchenko, G.-J. Boons, *Synlett* **1997**, 818–820; b) A. Ishiwata, Y. Munemura, Y. Ito, *Tetrahedron* **2008**, *64*, 92–102; c) M. Koshiba, N. Suzuki, R. Arihara, T. Tsuda, H. Namba, S. Kakamura, S. Hashimoto, *Chem. Asian J.* **2008**, *3*, 1664–1677.
[7] P. Pornsuriyasak, C. Vetter, S. Kaeothip, M. Kovermann, J. Balbach, D. Steinborn, A. V. Demchenko, *Chem. Commun.* **2009**, 6379–6381.
[8] a) Y. P. Cheng, H.-T. Chen, C.-C. Lin, *Tetrahedron Lett.* **2002**, *43*, 7721–7723; b) A. V. Demchenko, G. J. Boons, *Tetrahedron Lett.* **1999**, *40*, 6523–6526.
[9] A. Imamura, A. Hiromune, S. Korogi, G. Tanabe, O. Muraoka, H. Ishida, M. Kiso, *Tetrahedron Lett.* **2003**, *44*, 6725–6728.
[10] M. A. Fascione, S. J. Adshead, S. A. Stalford, C. A. Kilner, A. G. Leach, W. B. Turnbull, *Chem. Commun.* **2009**, 5841–5843.
[11] J.-H. Kim, H. Yang, V. Khot, D. Whitfield, G.-J. Boons, *Eur. J. Org. Chem.* **2006**, 5007–5028.
[12] J.-H. Kim, H. Yang, G.-J. Boons, *Angew. Chem.* **2005**, *117*, 969–971; *Angew. Chem. Int. Ed.* **2005**, *44*, 947–949.
[13] D. J. Cox, A. J. Fairbanks, *Tetrahedron: Asymmetry* **2009**, *20*, 773–780.
[14] C. Bucher, R. Gilmour, *Angew. Chem.* **2010**, *122*, 8906–8910; *Angew. Chem. Int. Ed.* **2010**, *49*, 8724–8728.
[15] C.-W. Chang, S.-S. Chang, C.-S. Chao, K. K. T. Mong, *Tetrahedron Lett.* **2009**, *50*, 4536–4540.
[16] a) Y. Nishida, Y. Shingu, H. Dohi, K. Kobayashi, *Org. Lett.* **2003**, *5*, 2377–2380; b) Y. Shingu, A. Miyachi, Y. Miura, K. Kobayashi, Y. Nishida, *Carbohydr. Res.* **2005**, *340*, 2236–2244; c) C. Satgé, J. Le Bras, F. Henin, J. Muzart, *Tetrahedron* **2005**, *61*, 8405–8409.
[17] a) V. Dourtoglou, B. Gross, *J. Carbohydr. Chem.* **1983**, *2*, 57–73; b) J. Bogusiak, W. Szeja, *Synlett* **1997**, 661–662; c) Y. Kobashi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 910–916; d) S. Koto, N. Morishima, M. Owa, S. Zen, *Carbohydr. Res.* **1984**, *130*, 73–83; e) J. Park, S. Kawatkar, J.-H. Kim, G.-J. Boons, *Org. Lett.* **2007**, *9*, 1959–1962; f) T. Nokami, A. Shibuya, S. Manabe, Y. Ito, J. Yoshida, *Chem. Eur. J.* **2009**, *15*, 2252–2255.
[18] R. U. Lemieux, H. Driguez, *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062; R. U. Lemieux, H. Driguez, *J. Am. Chem. Soc.* **1975**, *97*, 4063–4068; R. U. Lemieux, H. Driguez, *J. Am. Chem. Soc.* **1975**, *97*, 4069–4075.
[19] G.-H. Veeneman, S.-H. van Leeuwen, J. H. van Boom, *Tetrahedron Lett.* **1990**, *31*, 1331–1334.

[20] For the preparation of thiogalactosides **1** and **2**, see: Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734–753.
[21] a) Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734–753; b) D. R. Mootoo, P. Konradsson, U. E. Udodong, B. Fraser-Raid, *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584.
[22] Donor **2** was poorly soluble in pure diethyl ether, so a 1:3 CH_2Cl_2/ether mixture was employed. The 1:2 toluene/dioxane mixture was found to aggregate at −10 °C, so the glycosylation in toluene/dioxane (1:2) was conducted at 0 °C.
[23] The preparation of and/or references to aglycone acceptors **10**–**13**, O-glycoside acceptors **14**–**17**, and thioglycosyl donors **7**–**9** are given in the Supporting Information.
[24] a) S. Deng, U. Gangadharmath, C.-W. Chang, *J. Org. Chem.* **2006**, *71*, 5179–5185; b) D. V. Jarikote, C. O'Reilly, P. V. Murphy, *Tetrahedron Lett.* **2010**, *51*, 6776–6778.
[25] K.-K. T. Mong, C.-H. Wong, *Angew. Chem.* **2002**, *114*, 4261–4264; *Angew. Chem. Int. Ed.* **2002**, *41*, 4087–4090.
[26] X. Huang, L. Huang, H. Wang, X.-S. Ye, *Angew. Chem.* **2004**, *116*, 5333–5336; *Angew. Chem. Int. Ed.* **2004**, *43*, 5221–5224.
[27] The preparation of and/or references to thioglycosyl acceptors **30**–**40** are given in the Supporting Information.
[28] Z. Li, J. C. Gildersleeve, *J. Am. Chem. Soc.* **2006**, *128*, 11612–11619.
[29] One of the referees suggested that we compare the α-directing ability of DMF with that of an ethereal solvent. However, procedure B as used for the reactions in Table 3 does not work in the absence of DMF. We decreased the amount of DMF from the optimal 6 equivalents to suboptimal 1.5 equivalents in the glycosylation of **36** with **2** to demonstrate the quantity–selectivity relationship mentioned earlier.
[30] The preparation of and/or references to 2-azido-2-deoxythiogalactosides **56** and **57** and the protected serine acceptor **59** are given in the Supporting Information.
[31] For the preparation of thiogalactoside **63**, see the Supporting Information.
[32] The corresponding anomeric and imidoyl carbon signals of **64** were identified at $\delta = 105.8$ and 165 ppm in an HSQC study.
[33] F. Barresi, O. Hindsgaul, *J. Am. Chem. Soc.* **1991**, *113*, 9376–9377.
[34] A. Ishiwata, Y. Munemura, Y. Ito, *Eur. J. Org. Chem.* **2008**, 4250–4263.

