PROGRESS TOWARD THE SYNTHESIS OF GRISEOLIC ACID B AND GLYCOSYLATION OF NUCLEOSIDES AND PEPTIDES

by

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ABSTRACT OF THE DISSERTATION

Progress toward the Syntheis of Griseolic Acid B and Glycosylation of Nucleosides and Peptides

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This dissertation describes the total synthesis toward griseolic acid B and the direct glycosylation of nucleosides and peptides.

The first part of this thesis focuses on the total synthesis of the nucleoside griseolic acid B and its derivatives. The griseolic acids were of particular interest since they contain the highly unusual and strained 1,5-dioxabicyclo[3.3.0]oct-3-ene acting as a mimetic of the ribose phosphate in cyclic nucleotides. Using griseolic acids as templates, more selective and therefore therapeutically useful agents potentially can be identified for the treatment of cardiovascular problems, sexual dysfunction and inflammation. However, the existing reported synthetic strategy to griseolic acid using cis-sulfoxide elimination makes it is almost impossible to synthesize large amounts of material for biologic studies. Thus, a more flexible and efficient access to griseolic acids and their analogues is desired. Our proposed retrosynthetic analysis of griseolic acid B makes use of conjugate addition reaction and a late-stage Vorbrüggen glycosylation. The challenges and successes of this synthesis are described in detail. More specifically, the route to 1,5-

dioxabicyclo[3.3.0]oct-3-ene core integrates a stereoselective Michael addition reaction and the nucleobase is introduced by a facile and highly diastereoselective late-stage *N*-glycosylation. Unfortunately, the proposed last step, elimination of sulfonate confronts a disastrous roadblock. An alternative strategy is proposed for future work, which includes a palladium reduction of triflate to generate 1,5-dioxabicyclo[3.3.0]oct-3-ene core.

In chapter III, we describe mild and general experimental conditions for the efficient O-glycosylation of nucleoside ribofuranose hydroxyls despite competition from more Lewis basic sites on the purine or pyrimidine nucleobase. Indium(III) triflate serves both to activate the glycosyl donor, either a thioglycoside or glycosyl trichloroacetimidate, and to promote the isomerization of ancillary donor, heterocycle-glycosylated, intermediates to the desired nucleoside disaccharide. The isolation and characterization of (*O*-4)- and (*N*-3)-2″,3″,4″,6″-tetra-acetyl-*D*-glucopyranosyl derivatives of uridine 2′,3′,5′-triacetate provides evidence for the susceptibility of these sites to unintended or temporary glycosylation.

In chapter IV, we further demonstrate the efficient and elegant synthesis of *N*, *O*-glycopeptides by direct *N*, *O*-glycosylation of asparagine or serine/threonine containing peptides with glycosyl thio-glucoside utilizing a catalytic amount of copper triflate benzene complex in dichloroethane. The coupling method allows for the synthesis of the various *N*, *O*-glycopeptides from the primary amide or alcohol derivatives, which are effective biochemical probes for elucidation of the role of glycoproteins.

Chapter V includes the experimental procedures for the preparation of all compounds, backed up by full analytical characterization. In addition, ^{1}H- and ^{13}C-NMR spectra are given.

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CONTENTS

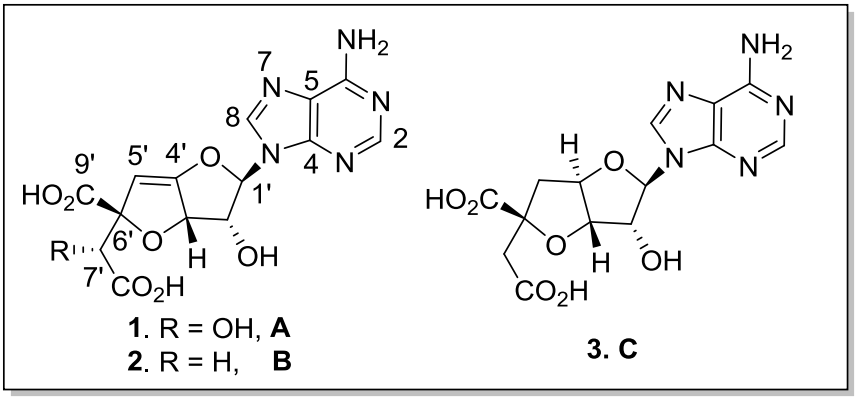
Chapter I

Introduction

1.1 Isolation and Significance

In 1985, Naito and coworkers at Sankyo Co. published the isolation and structural elucidation of griseolic acids A–C (**1-3, Figure 1**)[1]. The natural products are a family of complex nucleosides isolated from a cultured broth of *Streptomycetes griseoaurantiacus*.

Figure 1. Griseolic Acid A-C.



Spectroscopic and crystallographic analysis reveals griseolic acid skeletons that broadly resemble cyclic AMP. Studies have shown that griseolic acids and their derivatives have the ability to inhibit the activity of phosphodiesterases specific to various cyclic nucleotides.[2] These include, for example, 3', 5'-cyclic adenosine monophosphate (cAMP) phosphodiesterases (PDE) and 3', 5'-cyclic guanosine monophosphate (cGMP) PDE. This inhibition can potentially increase the level of a cyclic nucleotide, e.g. cAMP or cGMP, in the cells of a patient treated with such a compound.

It is well known that cAMP, which is well widely distributed in animal tissues, functions as a second messenger and mediates the effect of a large number of hormones. As a result, cAMP has a variety of very important physiological and biochemical roles.[3] It is known to have an effect on or participate in: division, proliferation and differentiation of cells; hematopoiesis; various activities of the central nervous system; immune reactions; and the liberation of insulin and histamine. Its concentration in tissues, and hence its effect upon these various functions, depends upon the balance between the enzyme that synthesizes cAMP and the enzyme that decomposes cAMP. Inhibitors such as griseolic acids that act against cAMP PDE would increase the level of cAMP in the cells. They are thus expected to have a variety of therapeutic uses, such as the treatment of cardiovascular problems, as antiasthmatic agents, as smooth muscle relaxants, as psychotropic or neurotropic agents, as anti-inflammatory agents, and as treatment for cancer and diabetes.

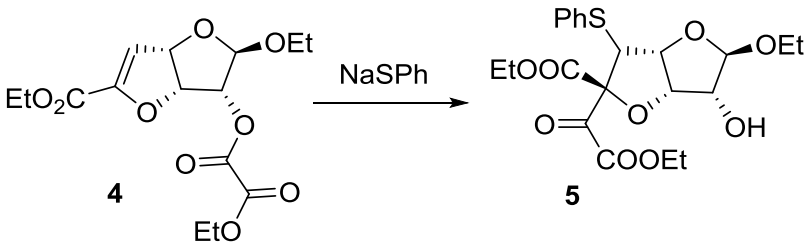
The naturally occurring griseolic acids A (**1**), B (**2**), and C (**3**) have been reported to inhibit a rat brain phosphodiesterase preparation (EC 3.1.4.17) with IC_{50} values of 0.16, 0.16, and 0.12 μM, respectively, when cAMP was the substrate.[1] The potent inhibitory activities of griseolic acids have drawn wide interests in the pharmaceutical industry. Extensive studies of griseolic acids and its analogues were carried out at Sankyo Company[4] and Schering-Plough Corporation.[5]

In this thesis, we mainly focus on griseolic acid A and B due to the synthetic challenge of their unique strained 1,5-dioxabicyclo[3.3.0]oct-3-ene ring system. Griseolic acid C on the other hand carries a relatively easily accessible saturated form of griseolic acid B with a D-*ribo* configuration.

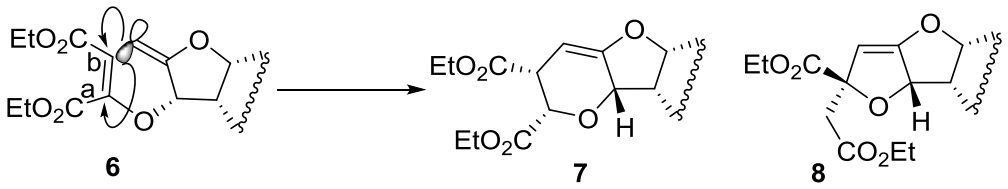
1.2 Published Synthetic Efforts to Griseolic Acid

The total synthesis of griseolic acids and analogues is hampered by the stereochemical and structural challenges that include the formation of: a strained 1,5 dioxabicyclo[3.3.0]oct-3-ene ring system, a quaternary stereogenic center at C-6′ with -COOH and -CH_2COOH substituents, a reactive C-4′ vinyl ether with a greater tendency to form a cation than the C-1′ acetal, and a purine with multiple Lewis basic sites. To date, there have been two known strategies to address the synthetic challenges of griseolic acids and analogues: (1) constructing the dioxabicyclic ring skeleton with -OR and -COOR groups and then the stereoselective introduction of two carbon acid units by using carbanion chemistry (Tulshian and co-worker,[5] shown in **Scheme 1**), and (2) achieving the bicyclic system with required substituents at C-6' by π-face-dependent radical cyclization (Knapp group,[8] shown in **Scheme 2**).

Scheme 1. Carbanion Chemistry to Build Griseolic Acid Core.



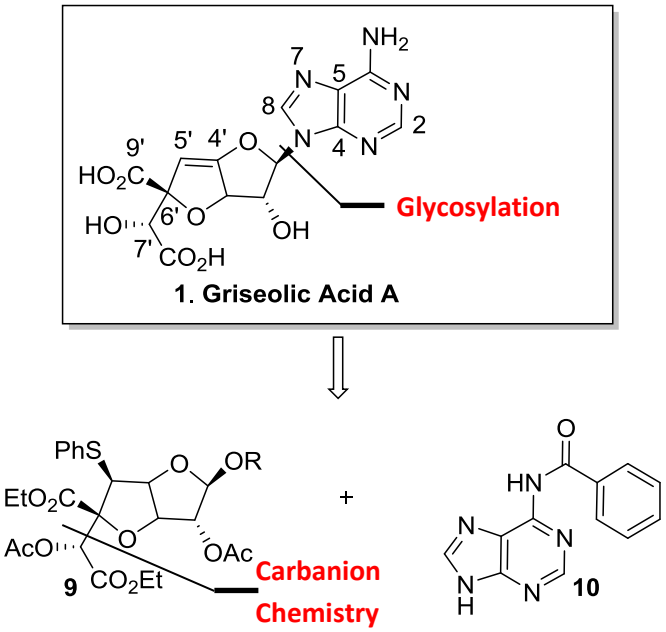
Scheme 2. π-face-dependent Radical Cyclization.



1.2.1 Tulshian's Synthesis of Griseolic Acid A

In order to use griseolic acids as a template to discover more selective and therefore more therapeutically useful antihypertensive agents, [5] Tulshian and co-workers at Schering-Plough Corporation began investigating the total synthesis Griseolic acid A in the 1990's. Their retrosynthetic approach began with the first disconnection, shown in **Scheme 3**, which arrived at dioxabicycle **9** and benzoyl protected purine base **10.** Carbanion chemistry at C-6' was envisioned to enable installation of a two-carbon unit in a stereoselective manner.

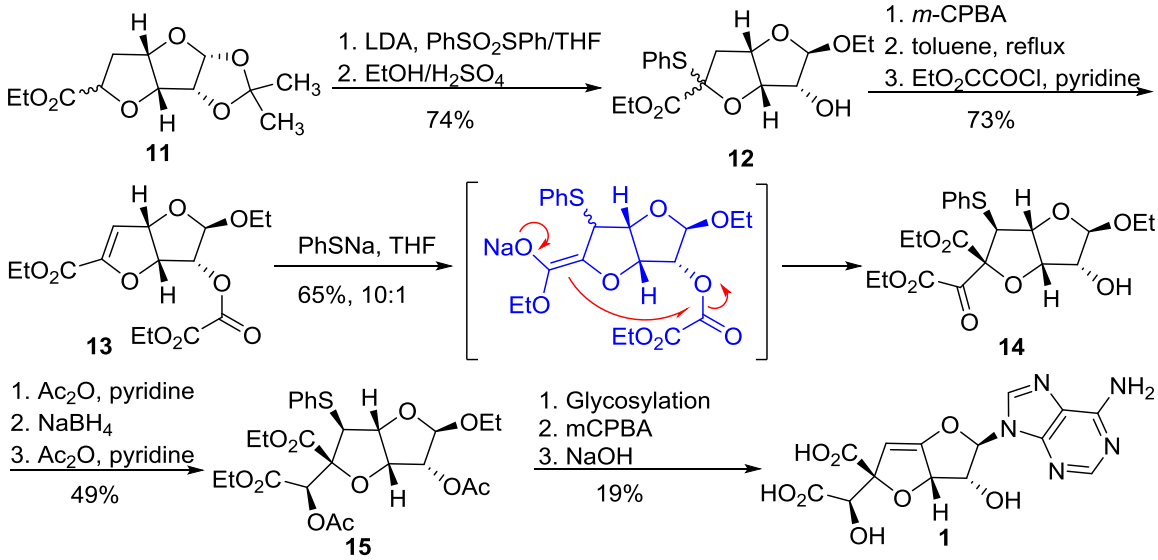
Scheme 3. Retrosynthesis of Griseolic Acid A.



The total synthesis started from anhydro sugar derivative **11**, shown in **Scheme 4**, which is readily available from diacetone-D-glucose.[5] To achieve their goal, their first strategy was to prepare **13** from **11** by sulfenylation, acid ethanolysis, and then oxidation with *m*-chloroperbenzoic acid. A thermal elimination and acylation afforded **13** in 45% overall yield. Tulshian was able to conduct the key transformation to **14** by nucleophilic

addition with sodium benzenethiolate to generate a carbon anion at C-6' to transfer the keto ester portion, thus installing a two-carbon unit at C-6' in a stereoselective manner (epimeric ratio = 10:1). The major isomer is formed by addition of mercaptide from the top face of the concave-shaped **13**. The next transformation was to set the correct stereochemistry at C-7', which was achieved by sodium borohydride reduction of **14**, affording a 5:1 mixture in favor of desired isomer. The desired isomer was acylated with pyridine/acetic anhydride in almost quantitative yield to give **15**. Completion of the synthesis of griseolic acid A required four steps: installation of the purine base by Vorbruggen reaction[6] with N^1,N^9-bis(trimethylsilyl)-N- benzoyladenine in the presence of trimethylsilyl trifluoromethanesulfonate; completing the assembly of the strained 1,5-dioxabicyclo[3.3.0]oct-3-ene ring by oxidation and thermal elimination; removal of the ethyl, acetyl and benzoyl groups in one step with 1 N NaOH aqueous solution.

Scheme 4. Total Synthesis of Griseolic Acid A.

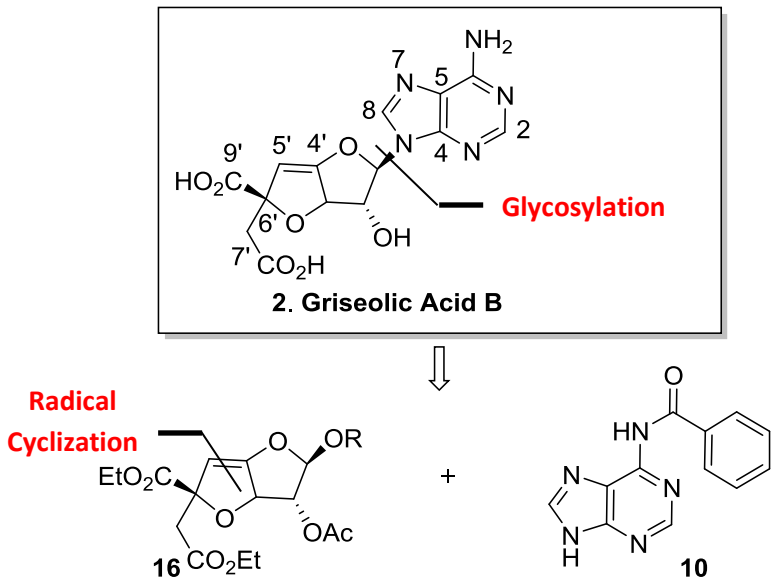


The Tulshian synthesis of griseolic acid A comprises 12 linear steps, starting from the known, highly functionalized, 3, 6-anhydro sugar derivative **11** in an overall yield of approximately 3%.

1.2.2 Knapp's Total Synthesis of Griseolic Acid B

The Knapp retrosynthetic approach also started with the disconnection of oxabicyclo ring core **16** and purine base **10** shown in **Scheme 5**. A radical cyclization strategy was envisioned to construct the dioxabicyclo **16** with the desired quaternary stereogenic center at C-6´.

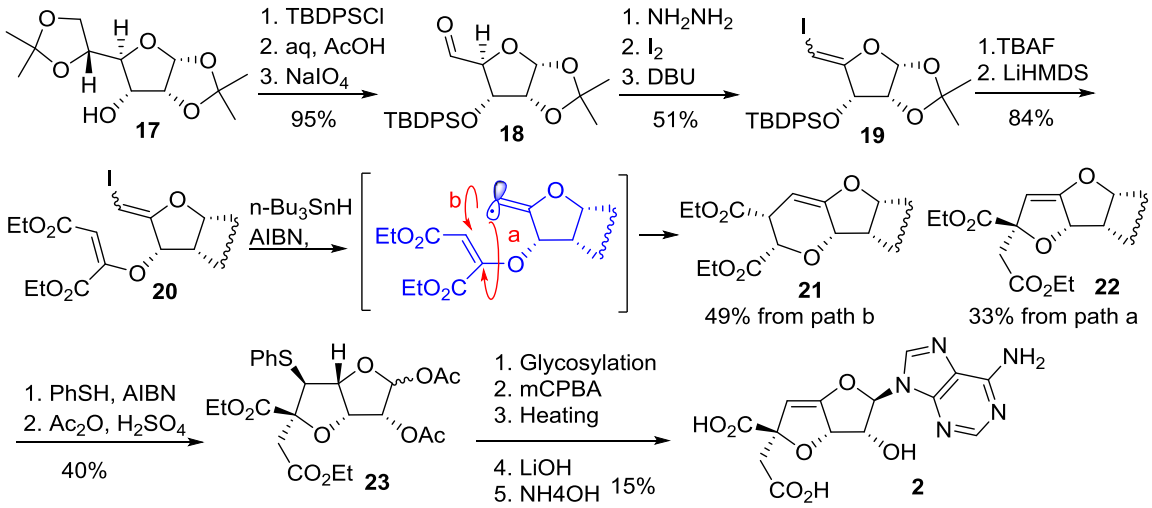
Scheme 5. Retrosynthesis of Griseolic Acid B.



The success of Knapp's synthetic strategy largely depended on whether the dioxabicyclo core **16** could be formed by radical cyclization reaction of precursor **20**. The synthesis began with the commercially available starting material, D-*allo*-furanose **17,** shown in **Scheme 6**. Aldehyde **18** was synthesized from **17** in 95% overall yield by

protection of the O-3' alcohol, selective hydrolysis of the 5,6-acetonide, and oxidation of the resulting diol with sodium periodate. Aldehyde **17** was then converted to vinyl iodide **19** (95:5 mixture of isomers) by iodination of the derived hydrazone. Deprotection at O-3' and addition of this hydroxyl to diethyl acetylenedicarboxylate under basic conditions afforded the key intermediate succinate derivative, **20,** in 84% overall yield. A variety of reducing reagents, initiators, solvents, concentrations, and temperatures were tried in order to generate the radical intermediate for cyclization. A solution of 0.05 M *n*-Bu_3SnH in refluxing benzene was identified as an effective combination to convert **20** into products **21** and **22** in a 3:2 ratio with 82% combined yield. However, the intermediate **22** cannot undergo glycosylation due to the reactive C-4' vinyl ether, which has greater tendency to form a cation than the C-1' acetal. To proceed from **22**, the double bond was temporarily protected by addition of thiophenol, followed by acetolysis to give the anomeric acetate **23**. From intermediate **23**, the total synthesis of griseolic acid B was finished by Vorbrüggen glycosylation,[7] thermal elimination and then deprotection.

Scheme 6. Total Synthesis of Griseolic Acid B

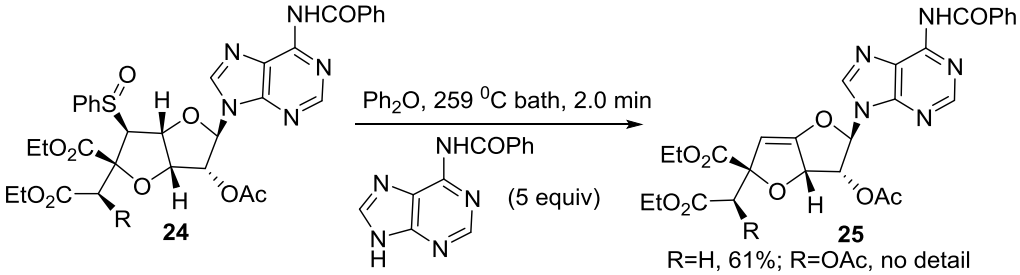


The Knapp's total synthesis of griseolic acid B comprises 16 linear steps starting from commercial available starting material D-allo-furanose **17** and gives an overall yield of approximately 0.8%.

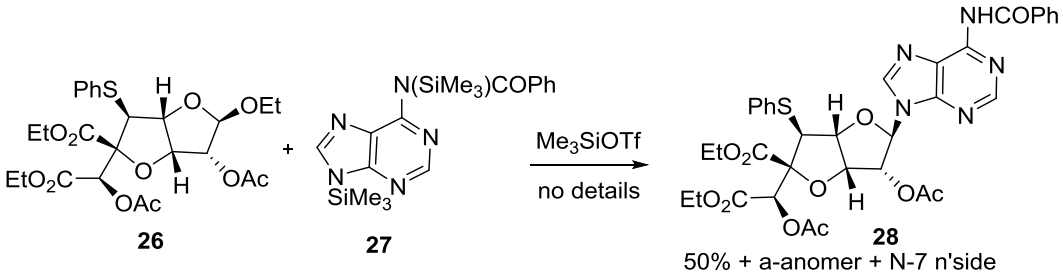
1.2.3 Limitations in the Existing Syntheses of Griseolic Acid A and B

In many aspects, the syntheses of griseolic acids A and B have overcome many barriers in the form of novel molecular motifs and stereochemical features through both the development and application of unique synthetic strategies and tactics.

Scheme 7. Cis-Elimination in the Syntheses of Griseolic Acids



Scheme 8. Glycosylation Step in the Synthesis of Griseolic Acid A



Intriguingly, though, neither journey was completely smooth in that each had to confront at least one unintended, and potentially disastrous, roadblock that resulted from their selected synthetic sequence. In the Knapp synthesis of griseolic acid B, the challenge was the cis-sulfoxide elimination that proceeded only at very high temperature.

After considerable screening of reaction conditions, the best conditions proved to be thermolysis in refluxing Ph_2O at 259 °C for 2.0 min in the presence of 5 equivalents of N^6-benzoyladenine, as shown in **Scheme 7**. This makes it is almost impossible to synthesize large quantity of Griseolic acid B. In the Tulshian griseolic acid A synthesis, the challenges were not only the anticipated *cis*-sulfoxide elimination for which very little experimental detail was reported, but also the glycosylation step shown in **Scheme 8,** in which tedious column chromatography separations were required to get rid of the multiple side products formed in the reaction.

Considering the limitations of existing synthetic routes for griseolic acid A and B, a synthetic route featuring implementation of a new strategy to generate the strained 1,5-dioxabicyclo[3.3.0]oct-3-ene ring system and an more efficient introduction of the purine base is desirable.

1.3 Research Objectives

Griseolic acid A and B are non-selective phosphodiesterases inhibitors. However, by using griseolic acid A or B as templates, more selective and therefore therapeutically useful agents have been indentified.[2] These agents have shown great potency in the treatment of cardiovascular problems, sexual dysfunction and inflammation. In this content, a more scalable synthetic route toward griseolic acids and their structural related analogues beyond the existing routes is valuable. Our investigations have tried to fulfill this need by exploring an alternative synthetic route to griseolic acids in which the roadblock step, namely, the *cis*-sulfoxide elimination, can be avoided. We hoped this alternative synthetic route would provide scalable griseolic acids and analogues that could allow systematic structure–activity relationship (SAR) studies.

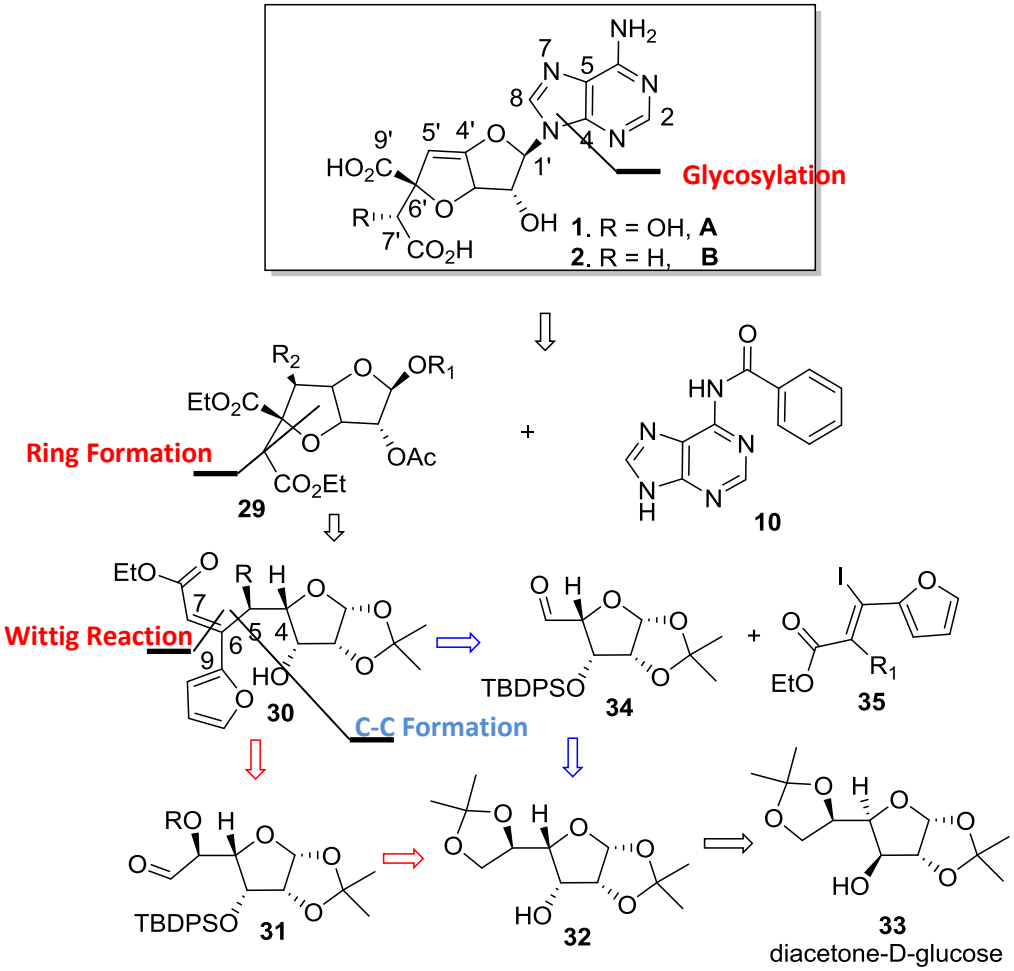
Chapter II

Progress toward the Synthesis of Griseolic Acid B

2.1 Retrosynthetic Analysis

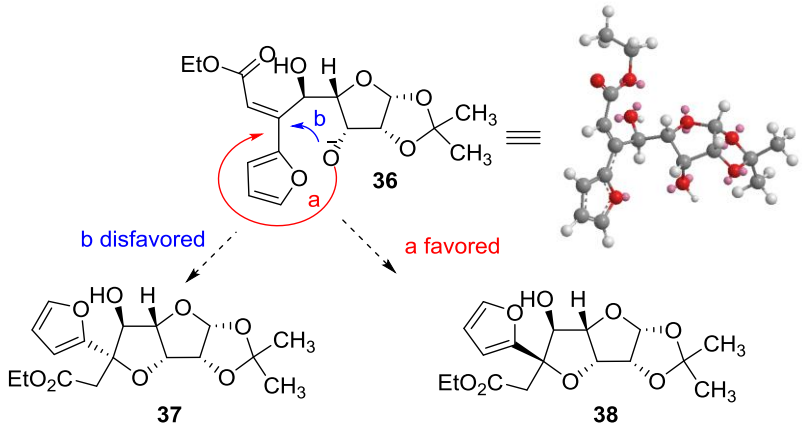
To avoid carrying the adenine group with multiple Lewis acid sites along the synthetic sequence, a late-stage Vorbrüggen glycosylation was chosen that disconnected griseolic Acid B into oxabicyclo ring **29** and purine base **10**, as shown in **Scheme 9**. This strategy is commonly used for complex nucleoside syntheses including Tulshian's synthesis of griseolic acid A and Knapp's synthesis of Griseolic acid B.

Scheme 9. Proposed Michael Addition Reaction to Build the Griseolic Acids Core.



Differing from the existing synthetic strategies, we envisioned the oxabicyclo core **29** as derivable from a derivative of α-D-gulofuranose, **30**, by an intramolecular conjugate addition reaction. The success of this strategy largely depends on the outcome of the steroselectivity of the conjugate addition reaction to install the tertiary center C-6'. Two possible pathways, shown in **Scheme 10**, may occur in which only path **a**, the *exo*-cyclization, will provide the desired oxabicyclic ring **38**. In support of the proposed the selectivity of the conjugate addition reaction, conformational analysis of **36** by MM2 reveals that the *exo*-cyclization might be favored due to the preference of the fur-2-yl group, a masked carboxylic acid, to locate above the β face of the bicyclic system.

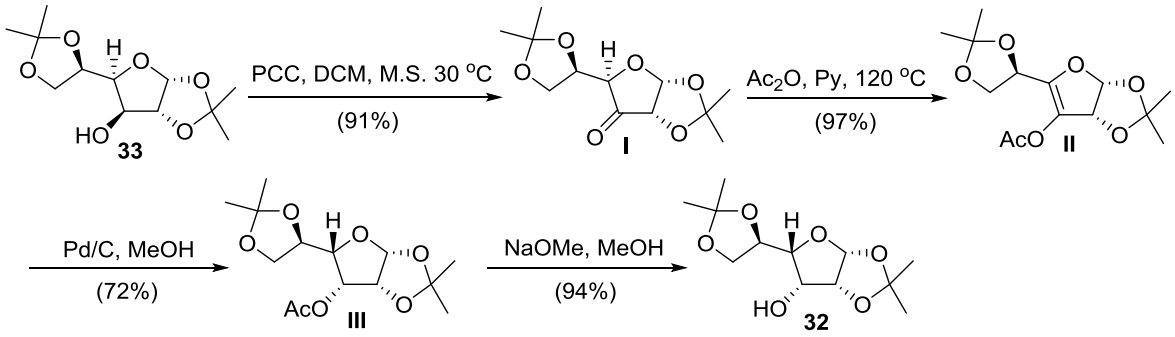
Scheme 10. Possible Pathway for Michael Addition Reaction



To take advantage of the stereochemical features of C-1', C-2', and C-3' in starting material **32** (all present in the griseolic acid core), the disconnection of compound **30** was chosen either between C-5' and C-6' or between C-6' and C-7'. We envisioned **34** and **35** being assembled by Grignard addition or similar organometallic reaction. Should this strategy succeed, it would allow access to key intermediate **29** in just a few steps. A complementary disconnection provides aldehyde **31**, but requires a longer linear

synthesis from starting material **33**. However, the drawback of this long linear strategy is partially compensated by the relatively straightforward chemistry that is well presented in the literature.[5]

Scheme 11. Synthesis of Starting Material **32**

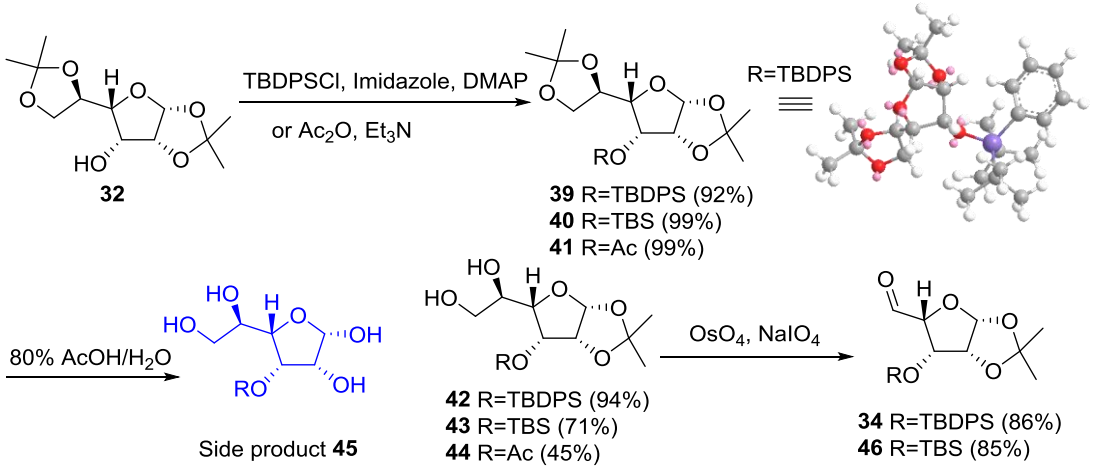


2.2 The Synthesis of Starting Material 32

The synthesis of griseolic acid commenced with the preparation of starting material **32**. As shown in Scheme **11**, the inversion of stereochemistry at the free OH and C4 of 1,2:5,6-diisopropylidene-D-glucose (diacetone-D-glucose, DAG) was achieved by a three-step process.[7] Oxidation by using PDC/Ac_2O in CH_2Cl_2 solution gave 1,2 :5,6-di-*O*-isopropylidene-α-ribo-hexofuranos-3-ulose **36** in 91% yield. Although different approaches have been reported for the synthesis of **I,**[8] the DMSO-based oxidation was not suitable in this case since traces of DMSO would inhibit a subsequent hydrogenation reaction.[9] Enolization by using pyridine/Ac_2O and heating gave the enol acetate, 3-O-acetyl-1,2 :5,6-di-O-isopropylidene- α-D-erythrohex-3-enofuranose (**II),** in almost quantitative yield. Conversion of the enol acetate by hydrogenation gave 3-O-acetyl-1,2 :5,6-di-Oisopropylidene-a-D-gulofuranose **III**. Almost 20% of DAG was formed in the hydrogenation reaction, but this can be removed by silica gel chromatography. The last

step is de-*O*-acetylation of **38** with catalytic NaOMe in MeOH; crystallization from hexane gave colorless **32**.

Scheme 12. Synthesis of Building Block **34**

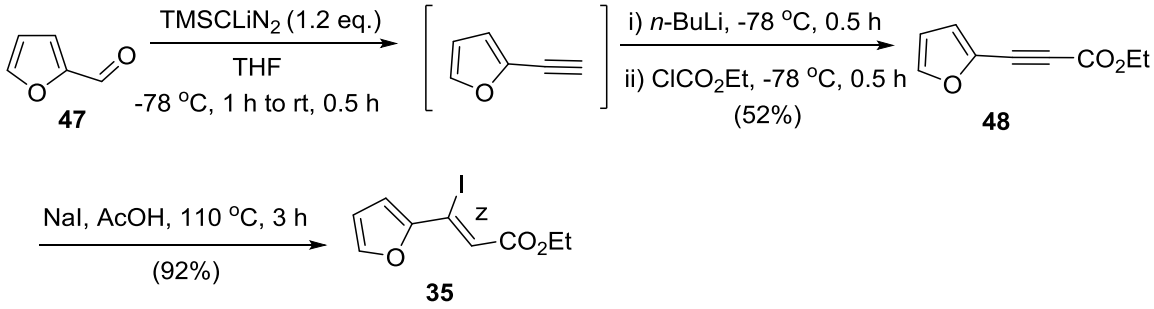


2.3 The Synthesis of Building Blocks 34 and 35

The preparation of 1,2:5,6-bis-*O*-(1-methylethylidene)-α-D-gulofuranose **32**, which serves as the starting material, was achieved on a multi-gram scale by applying modifications of the combined literature protocols shown in **Scheme 11**. The initial strategy was to protect the C-3 hydroxyl as the corresponding tert-butyldimethylsilyl ether by using TBDMSCl and imidazole in dry DMF solution. This afforded a quantitative yield of **40**. However, the next step, site selective hydrolysis of the 5,6-*O*-isopropylidene group in **40** with AcOH/H_2O (4:1, 25 °C) furnished diol **43** in only 71% yield (**Scheme 12**), with significant amounts of side product **45**. To improve the selectivity of the 5,6-O-isopropylidene hydrolysis, a bulkier tert-butyldiphenyl group was used to protect the C-3 hydroxyl in **32**, which provided **39**. Under the same AcOH/H_2O (4:1, 25 °C) conditions, the site selective ring opening of the 5,6-O-isopropylidene ring in

39 gave **42** in 94% yield. For comparison, when the less bulky group acetyl was used to protect the C-3 hydroxyl, the subsequent ring opening of the 5,6-O-isopropylidene moiety in **41** only afforded 45% yield of diol **44.** The last step was the oxidation of diol **42** or **43** with $OsO_4/NaIO_4$ to give aldehyde building block **34** or **46** in 86% yield.

Scheme 13. Synthesis of Building Block **35**

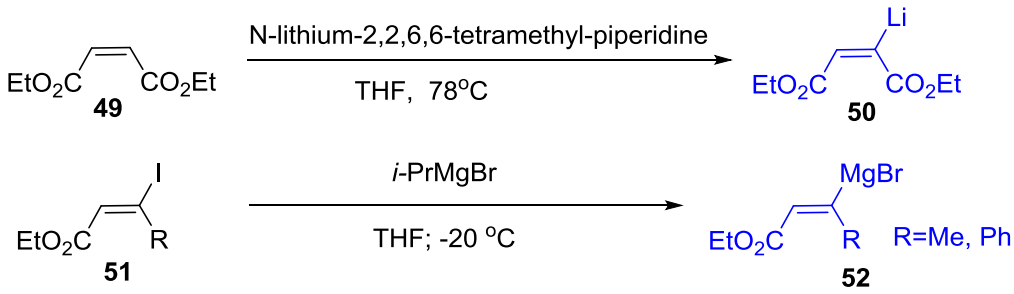


There are many known literature strategies to approach intermediate **48,** an intermediate one step away from building block **35**. 1) formation of **48** by Sonogashira coupling of 2-bromofuran with 2-propynoic acid ethyl ester[10] gave ~20% yield; 2) the formation of **48** by reacting lithium fur-2-ylethyne with ethyl chloroformate gave ~63% yield (the 2-ethynylfuran was made by Corey–Fuchs reaction[11] starting from furan-2-carbaldehyde); 3) a one-pot synthesis wherein furan-2-carbaldehyde reacted with lithium trimethylsilyldiazomethane [$TMSC(Li)N_2$] gave terminal acetylene via alkylidene carbene intermediates.[12] Without isolation, terminal acetylene was reacting with ethyl chloroformate to give **48** with moderate yield (52%). In this work, we adopted the one-pot synthesis shown in **Scheme 13**. Treated compound **48** with NaI in acetic acid at elevated temperature as reported in literature[13] gave the building block **35** in 92% yield.

2.4 The Coupling of Building Block 34 with 35

With grams of building blocks **34** and **35** in hand, we sought to establish the key intermediate **30** by the formation of the new (C-5) – (C-6) bond. To realize this transformation, the key is to make an organometallic intermediate out of **35** that can successfully react with electrophile **34**. There are literature precedents to make organolithium[14] and organomagnesium[15] species containing an ester group similar to **35** under appropriate reaction conditions as shown in **Scheme 14**. Most strikingly, the organomagnesium species **52** can be generated from a very mild magnesium-halogen exchange reaction by **51** with isopropylmagnesium bromide at –20 °C in THF solution. We decided to try the coupling of **34** and **35** using similar reaction conditions.

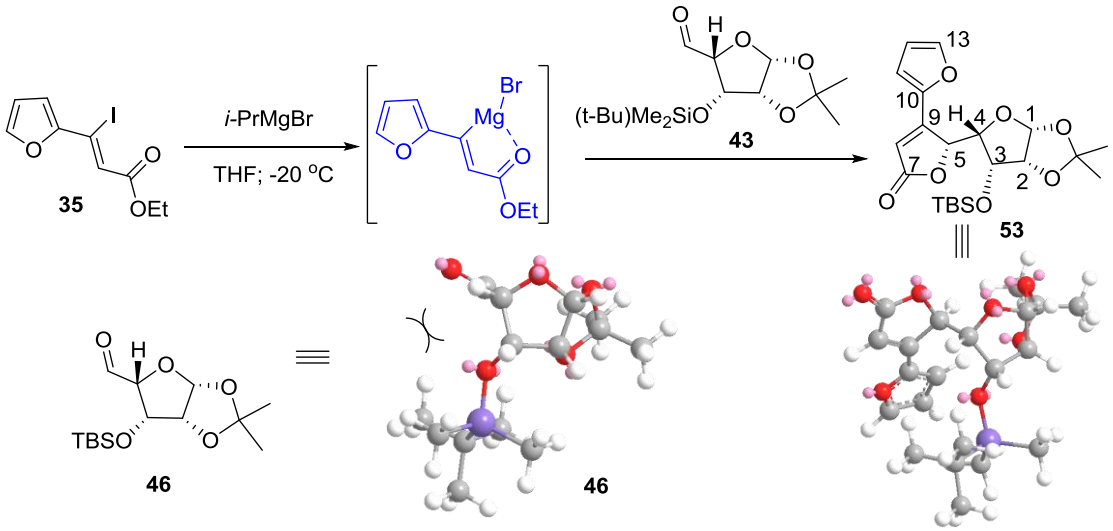
Scheme 14. Synthesis of **35** Related Organolithium and Organomagnesium Species



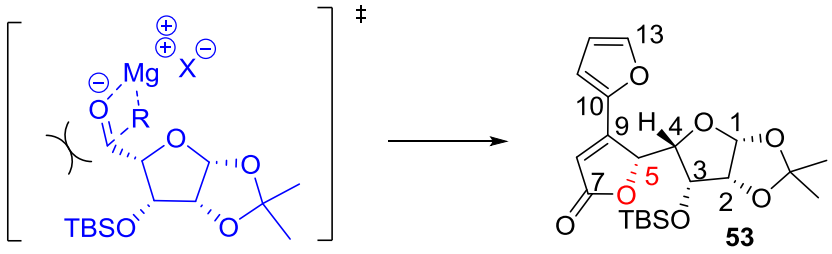
Treatment of **35** with 1 equivalent of isopropylmagnesium bromide for magnesium halogen exchange below –20 °C for 1 h, following by addition of electrophile **34** afforded a single diastereomerically pure lactone **53**, instead of the open-ring ester, in 60% yield. The major side products of the reaction are the reduced product from **35** as well as dark reddish decomposed products. The stereochemistry of C-5 in lactone **53** was determined as *R* by 2-D NMR studies in which showed that H-4 and H-5 are gauche to

each other ($J_{4,5}$ = ~1 Hz and prominent NOE between H-4 and H-5). Furthermore, a large NOE is observed between H-11 and H-4, which is only possible for the *R* isomer.

Scheme 15. Coupling of Building Block **34** with **35**



Scheme 16. Proposed Transition State for Formation of **53**

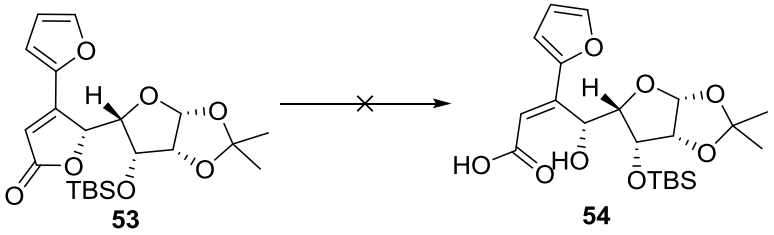


It is not unexpected that the reaction gives good diastereoselectivity, considering the chiral electrophile **34** used. According to the proposed transition-state model shown in **Scheme 16**, the large silyl protecting group at O-3 blocks the α-face, which leaves the β face more favored to afford the single diastereomer **53**.

2.5 Further Chemistry on Lactone 53

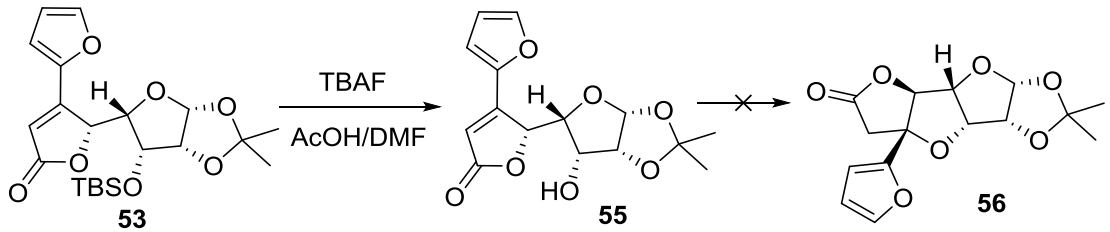
To approach **30** from lactone **53**, the most straightforward way is by hydrolysis of **53** to afford the corresponding acid **54**, followed by esterification. However, numerous attempts under basic conditions with LiOH, NaOH, KOH and acidic conditions with HCl failed to hydrolyze the lactone **53** to acid **54** (**Scheme 17**).

Scheme 17. Hydrolysis of Lactone 53



Another unsuccessful effort to convert **53** into **30** is shown in **Scheme 18**. Removal of the O-3 TBS with tetrabutylammonium fluoride in DMF solution in the presence of acetic acid afforded a quantitative yield of **55**. Treatment of **55** with bases such as NaOMe, NaOH, KO(t-Bu), and DBU failed to provide **56**, a potential precursor to **30**, but instead resulted in either no reation or decomposition.

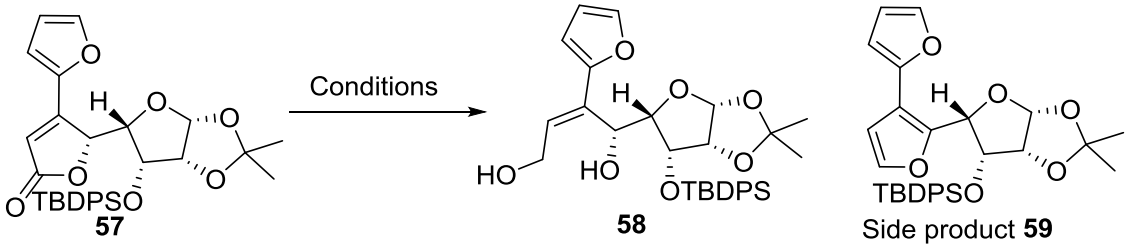
Scheme 18. Approach Compound 54 by Lactone Ring Opening



After the failure of initial efforts, we turned to an alternative way to approach **30** from **53**, through a multiple step sequence in which the first step was to open the lactone

ring by reduction to form the corresponding diol **58**. To realize this transformation, a range of reduction conditions was screened, as displayed in in **Table 1**. It was found that boron based reducing reagents such as lithium triethylborohydride and borane (**Table 1**, entries 5,6,7) resulted in messy reactions. DIBAL as the reducing reagent (**Table 1**, entry 3) only afforded lactol and side product **59**. A moderate yield of the desired diol was obtained with lithium aluminum hydride as reducing reagent (**Table 1**, entry 1, 2). Further optimizing the entry 1 and 3 to a two-step reduction sequence shown in entry 4 only resulted in a slight better yield. Under almost all conditions, the side product furan **59** was observed and sometimes even became the major product (**Table 1**, entries 1, 2 and 4). This result is not unexpected due to similar examples in the literature.[16]

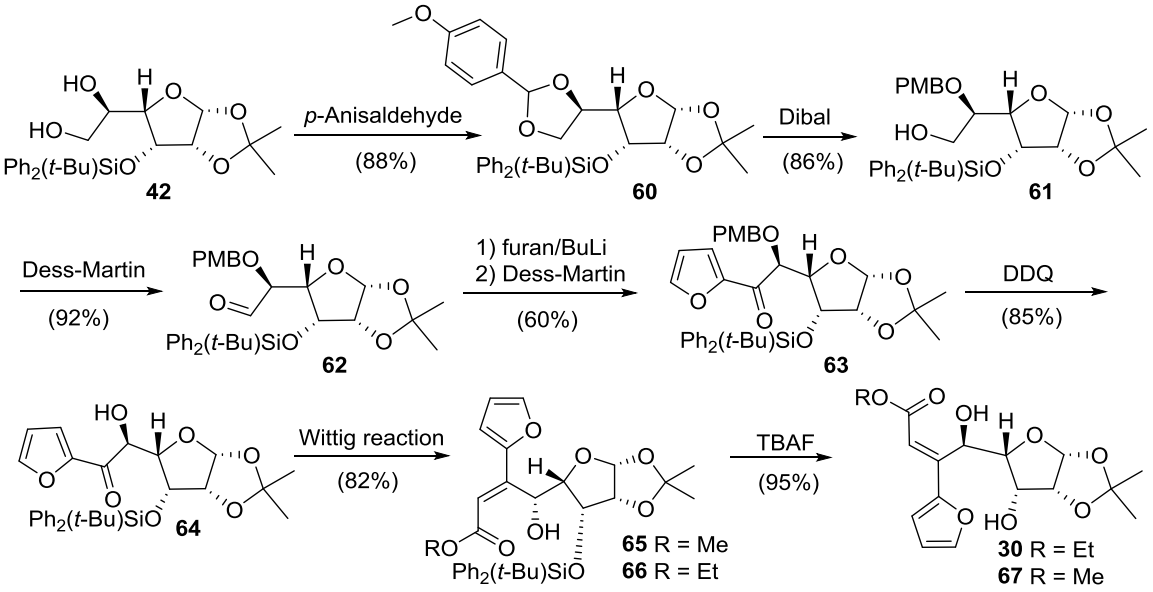
Table 1: Reaction Conditions to Reduce Lactone 51



Entry	Reaction Conditions	Isolated Yield
1	$LiAlH_4$, -78 ^oC-0 ^oC, 1 h	21%
2	TMEDA, $LiAlH_4$, Et_2O, 0 ^oC-RT, 1 h	25%
3	Dibal, DCM, -78 ^oC-RT, 1h	Lactol and side product
4	Dibal, DCM, -78 ^oC-RT, 1h; Then $LiAlH_4$, -78 ^oC-0 ^oC, 1 h	28%
5	Dibal, DCM, -78 ^oC-RT, 1h; Then $NaBH_4$ THF/H_2O, 0 ^oC, 1 h	Messy
6	BH_3, THF, 0 ^oC-RT, 24 h	Messy
7	Et_3BHNa, THF 0 ^oC	Messy

At this stage of the synthesis, the low yield of **58** made it very difficult to pursue intermediate **30** from lactone **57**. It was questionable whether **57** could be converted to the griseolic acid core in an efficient manner. Thus, we turned to the complementary linear route discussed previously.

Scheme 19. Linear Synthetic Sequence to Compound 30

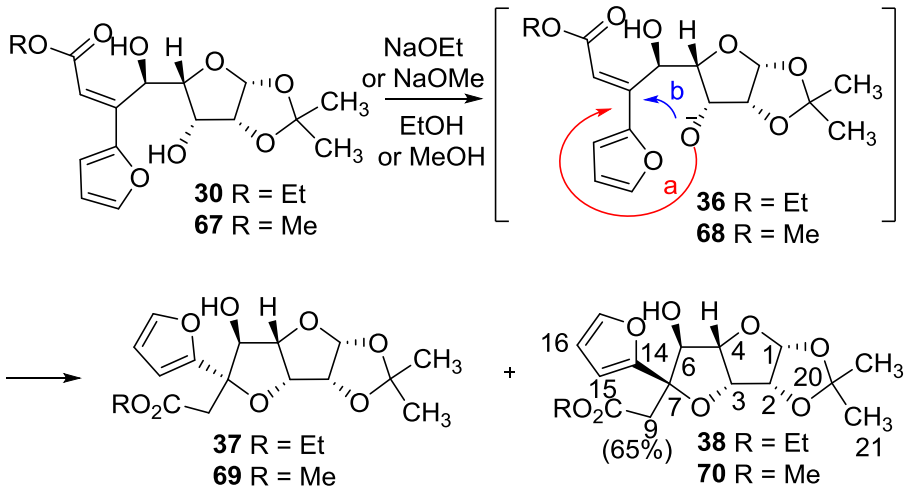


2.6 Linear Synthetic Sequence to 30

The linear sequence started with **42**, prepared as described previously, which was converted to *p*-methoxybenzylidene derivative **60** in 88% yield. Subsequent regioselective reductive ring-opening reaction with DIBAL-H in CH_2Cl_2 solution afforded the primary alcohol **61** in 86% yield. Compound **61** on oxidation with the Dess-Martin periodinane afforded aldehyde **62** in 90% yield. Subsequent exposure of this aldehyde to 2-lithiofuran in THF then leads smoothly to a diastereomeric mixture of alcohol intermediates, which was oxidized with the Dess-Martin periodinane to give

ketone **63** in 60% overall yield**.** After the removal of the 4-methoxybenzyl protecting group on O-5, the carbon scaffold was further extended by Wittig reaction to introduce a two-carbon side chain to afford **65** or **66**. The TBDPS protecting group in **65/66** was then removed upon treatment with TBAF in DMF in the presence of acetic acid to complete the synthesis of the key building blocks **30** and **67**.

Scheme 20 Cyclization of Compound 30



2.7 Cyclization of Compound 30 to 38

The stereoselectivity of the cyclization of **30** is remarkable. The presumed intermediate anion of **36**, shown in **Scheme 20,** must add to the α face of the acrylate C=C to set the stereochemistry at C-7 of **38** (red arrow), or to the opposite acrylate alkene face to set the stereochemistry at C-7 of **37** (blue arrow). In other words, the acrylate pi face that is exposed to the anion determines the stereochemistry of the product. In our experiment, **38** was observed as the only product, formation of which is supported by the MM2 conformational analysis shown previously. The stereochemistry at C-7 was determined by 2D NMR studies. The NOESY spectrum shows NOE'S between the

proton at C-15 with the protons at C-3 and C-4, consistent with the furan ring being located above the β face of the tricyclic system. The observation that the lower field α methyl-**21** resonance showed an NOE with the methylene-**9** is also consistent with the methylene-**9** located on the α face of the tricyclic system.

It is not unexpected that the reactions showed good diastereoselectivity, considering the size of the furyl group compared with methylene, as discussed previously. Apart from the impressive selectivity, the reaction gave only ~65% yield; significant amount of more polar dark reddish side product presumably came from decomposition of **30**. In an effort to optimize the reaction conditions, bases such as NaOMe, NaO*t*-Bu, KO*t*-Bu, DBU, and LiHMDS, and solvents such as THF and Et_2O were tried, but no better result was observed.

2.8 Last Few Steps toward Griseolic Acid B

The effort was then focused on the last few steps toward griseolic acid B, as shown in **Scheme 21**. Compound **70** was subjected to the action of MsCl and Et_3N in THF solution at 0 °C, giving mesylate **71** in 96% yield. Here**,** we hoped the methanesulfonyl can act as a protecting group for the C-5 hydroxyl as well as serve as a potential leaving group to generate the alkene in a subsequent step. As expected, the mesylate survived the $RuCl_3/NaIO_4$ conditions to convert the furan in **71** into a carboxylic acid, which in turn was treated with (trimethylsilyl)diazomethane to generate methyl ester **72** in 54% overall yield. Compound **72** was taken on via acetolysis in 1:1 acetic anhydride/acetic acid in the presence of catalytic H_2SO_4 to afford the anomeric acetate in almost quantitative yield. The Vorbruggen reaction of the anomeric acetate

with N^6,N,^{9}-bis(trimethylsilyl)-*N*-benzoyladenine in the presence of trimethylsilyl trifluoromethanesulfonate gave rise to nucleoside **73** in 71% overall yield. In this reaction, the side products include a small amount (~8%) of unwanted anomeric α nucleoside and N-7 alkylation product, which can be removed by flash column chromatography.

Scheme 21. Last Few Steps toward Griseolic Acid B

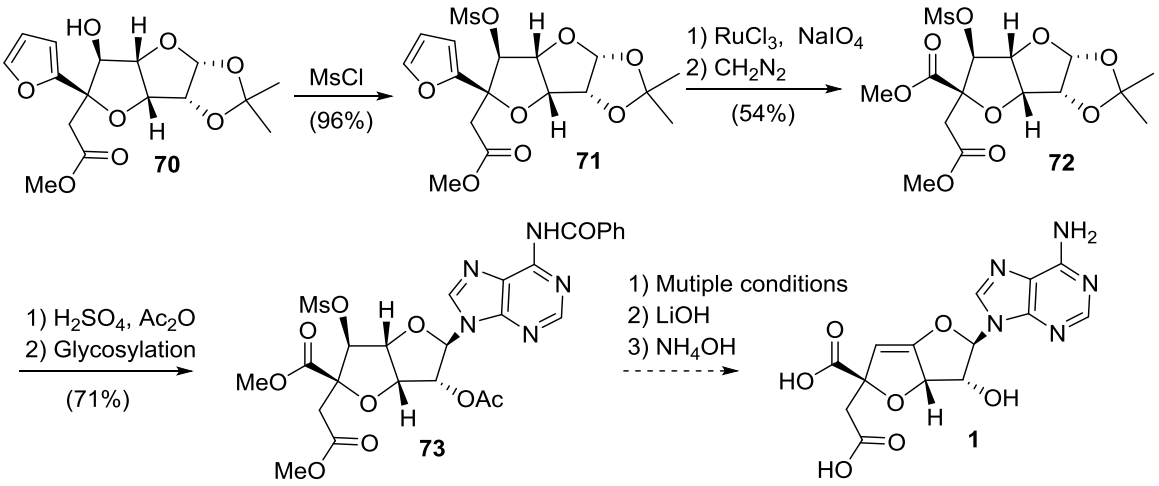
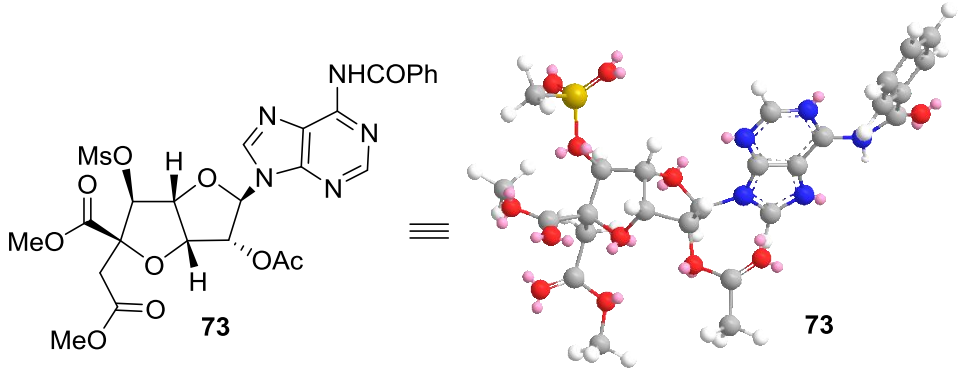


Figure 2. Conformational Analysis of 73 by MM2



Having reached the final stages of the total synthesis, we now faced the most challenging transformation: to generate the strained 1,5 dioxabicyclo[3.3.0]oct-3-ene ring

system by elimination of mesylate from **73.** The difficulty resided in the dihedral angle between the OMs at C-5' and the C-4' H, which is close to 10°, as shown in **Figure 2** (MM2 analysis). Inspired by E. J. Corey's work[17] on formation of olefins via pyrolysis of sulfonate esters, we decide to spend some effort to investigate the elimination reaction of **73**, the C2' acetate or ester group of which might participate from the β face as shown in **Scheme 22**.

Scheme 22. Proposed Elimination Pathway of Compound 73

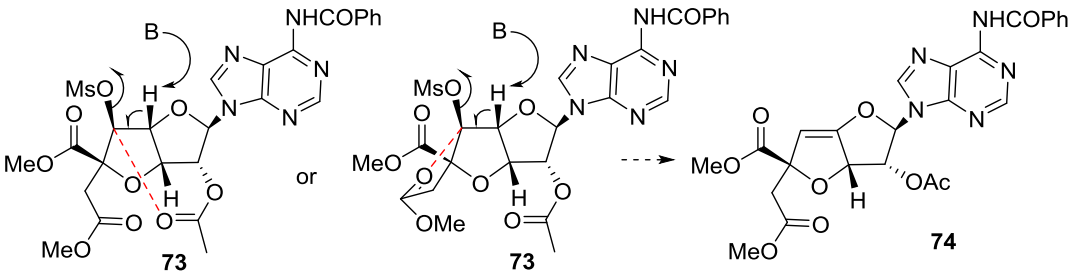
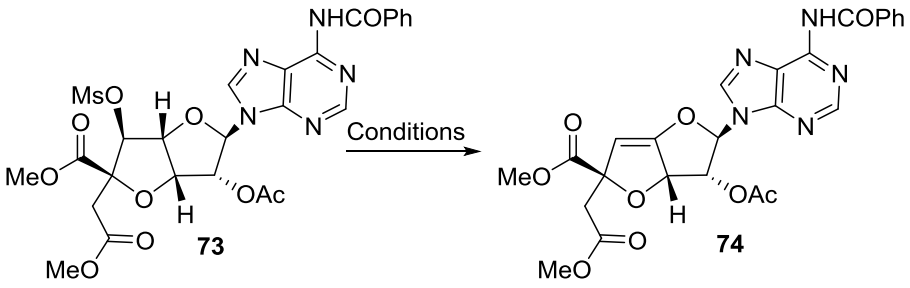


Table 2: Reaction Conditions for Elimination of Mesylate 73

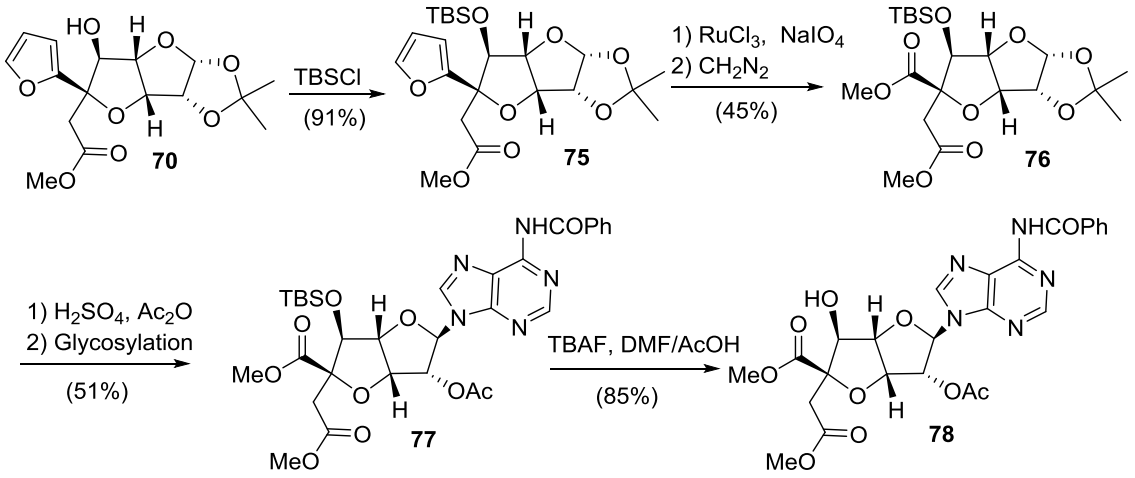


Entry	Reaction Conditions	Isolated Yield
1	t-BuOK, DMSO or THF, 0-RT	Decomposed
2	DBU or DBN, Toluene or DCM or DMF or THF, ACN, RT-150 °C	Decomposed at high T
3	TBAF, THF, RT-80°C	Decomposed at high T
4	LiBr or NaI DMF, Then Na, Zn	Decomposed
5	LiBr or NaI DMF, Then DBU, DBN	Decomposed

To test this hypothesis, a range of elimination conditions was tried, as shown in **Table 2**. A variety of bases such as DBU, DBN, TBAF and t-BuOK were used to treat **73** under varied solvent and temperature conditions (Entries **1, 2, 3**). However, no desired product was detected. These outcomes were not altogether surprising given that nucleoside **73** is not stable under strong basic conditions and high temperature, and deacylation, depurinylation and even demethylation might occur.

Further attempts were then focused on conversion of mesylate **73** to the corresponding bromide or iodide, and then treatment with a metal such as Zn or Na to generate the strained 1,5-dioxabicyclo[3.3.0]oct-3-ene ring (Entries **4**, **5**). Unfortunately, under several reaction conditions, **73** failed to form the corresponding bromide or iodide.

Scheme 23. Synthesis of Intermediate 78

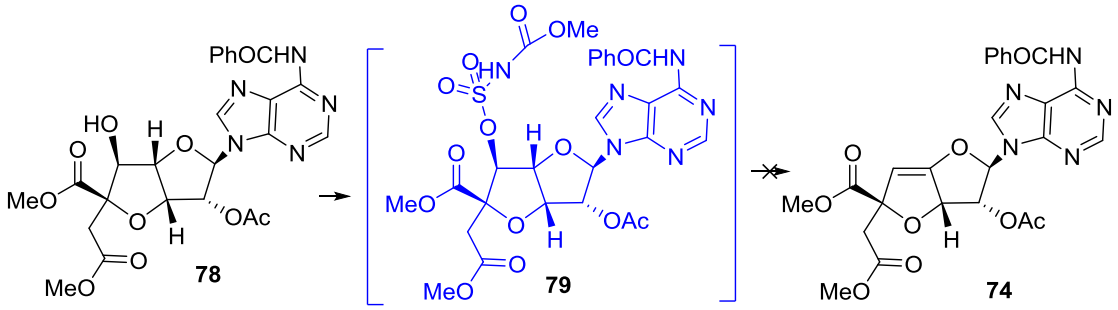


2.9 Alternative Strategies to synthesize the 1,5 dioxabicyclo[3.3.0]oct-3-ene ring

The failure of cis-mesylate elimination reactions forced us to come up with alternative strategies to build the 1,5 dioxabicyclo[3.3.0]oct-3-ene ring. Instead of installing a mesylate group at an early stage in **71,** we envisioned that the secondary

alcohol intermediate **78** might open more options to allow different leaving groups at a later stage. Starting from the **70**, nucleoside **77** was prepared essentially following the same procedure as nucleoside **73** , but with a slight lower overall yield. The TBS group was well tolerated under furyl oxidation and glycosylation conditions. Compound **77** was then treated with tetrabutylammonium fluoride in the presence of AcOH to provide the key intermediate, secondary alcohol **78**, in 85% yield.

Scheme 24. Attempted Elimination by using Burgess Reagent



Upon the formation of **78**, the immediate thought was to try the elimination reaction with Burgess reagent[18] in which alcohol dehydration takes place via syn elimination through an intramolecular pathway. The secondary alcohol **78** was exposed to Burgess reagent with THF or benzene as the solvent at elevated temperature, as shown in **Scheme 24**. Even though we have seen the formation of intermediate **79** in the reaction below 80 °C, there is no desired product **74**. Further raising the temperature of the reaction caused decomposition of **79**.

In order to install a better leaving group, the triflate derivative analogous to **80** was also made, and the elimination conditions listed in **Table 2** (Entries **1, 2, 3**) were tried. Unfortunately, no desired product was detected.

Scheme 25. Attempted Elimination of Triflate

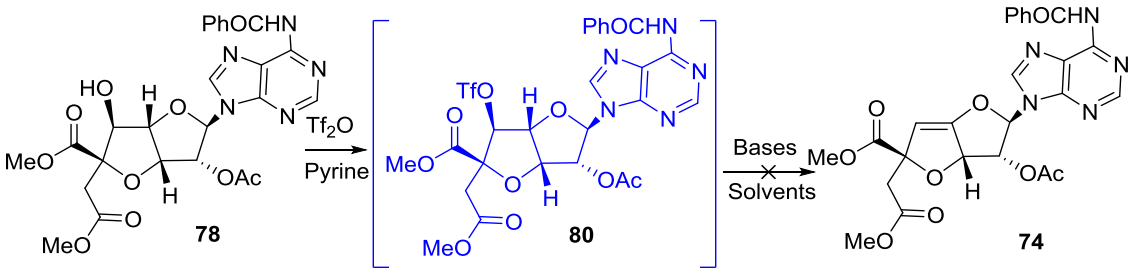
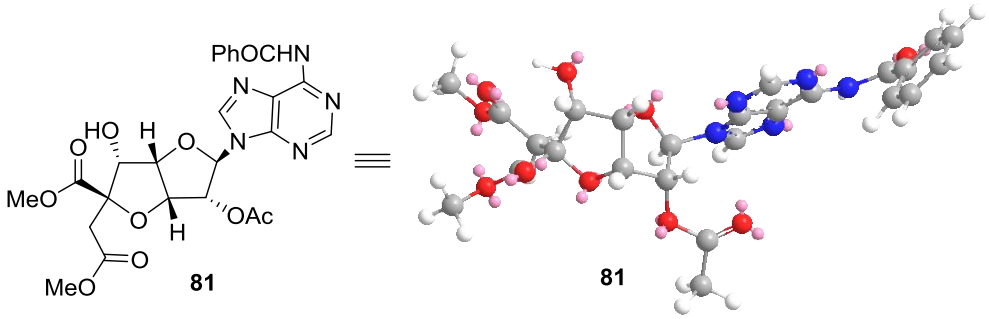


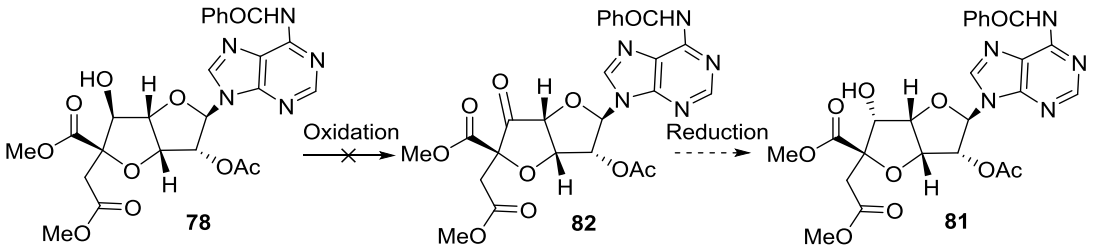
Figure 3. **Conformation Analysis of 81 by MM2**



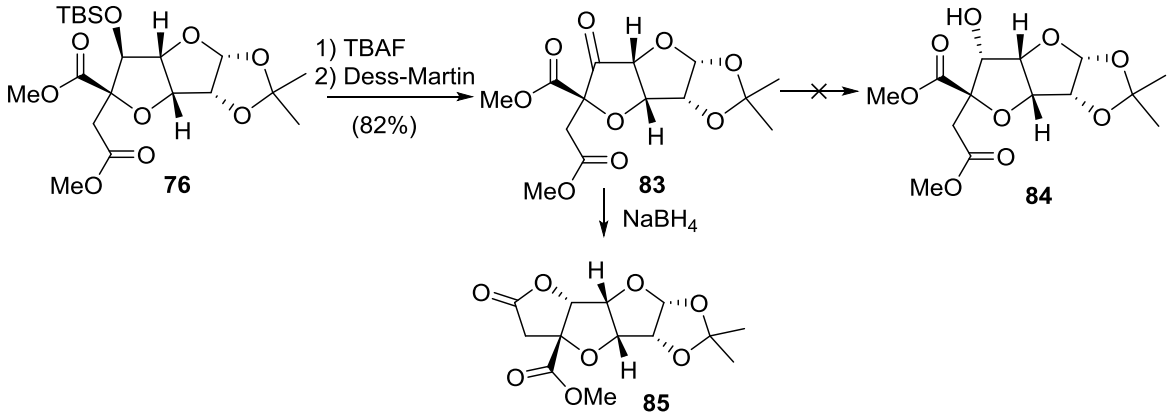
At this point, all the attempts at *cis* elimination had proved futile. We turned to the *trans* compound, **81**, with an inverted C-5' hydroxyl compare with **78**. We envisioned that **81** might be more successful even through the dihedral angle between C4' H and C5' hydroxyl is not ideal (~150° according to MM2 conformational analysis shown in **Figure 3**). To test this hypothesis, we initiated a two-step sequence to invert the C-5' hydroxyl of **78**, as shown in **Scheme 26**. The inversion of the C-5' hydroxyl was rationalized in that reducing reagents ought to deliver the hydride from the less steric hindered α face. Unfortunately, the seemingly straightforward oxidation of secondary **78** to ketone **82** turned out to be troublesome. Numerous reaction conditions with various oxidants such as Dess-Martin periodinane, Swern, PCC/PDC and TPAP all failed to

oxidize the nucleoside **78**. In most cases, either decomposition or recovery of starting material was observed.

Scheme 26. Synthetic Sequence to 81



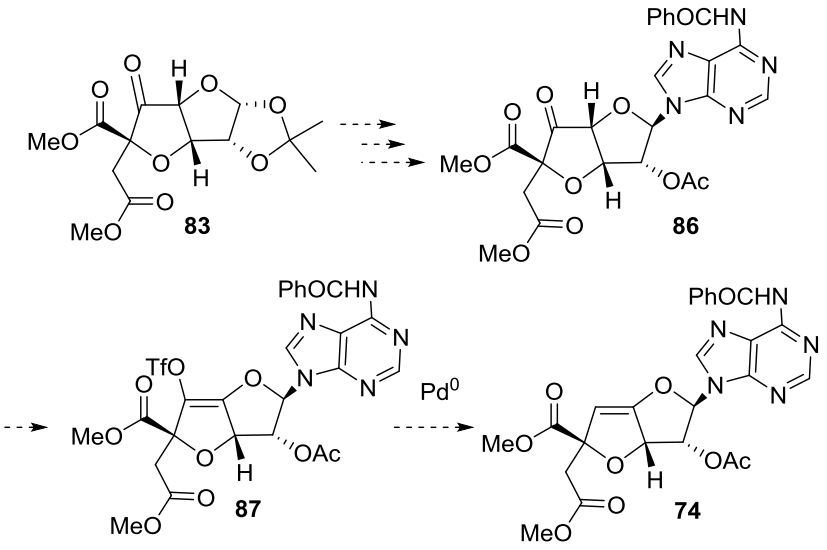
Scheme 27. Synthetic Sequence to84



The failure of oxidation of the nucleoside **78** was not altogether surprising given the oxidizable sites on the purine ring. To address this issue, we choose **75** the as starting point to invert the C-5' hydroxyl, as shown in **Scheme 27**. As expected, **76** was converted smoothly into the alcohol quantitatively by exposure to TBAF in the presence of acetic acid. The alcohol was then oxidized to ketone **83** with the Dess-martin periodinane in a combined 82% overall yield. Ketone **83** should allow exploration of ways to invert the stereochemistry of the C-5' hydroxyl. Unfortunately, instead of

formation of the desired **84**, reduction of **83** with $NaBH_4$ led to lactone **85** exclusively. This disappointing result has complicated our initially designed strategy to invert the C-5' hydroxyl of **76**.

Scheme 28. Pd Chemistry Strategy



2.10 Future Strategies to Synthesize the 1,5-Dioxabicyclo[3.3.0]oct-3-ene Ring

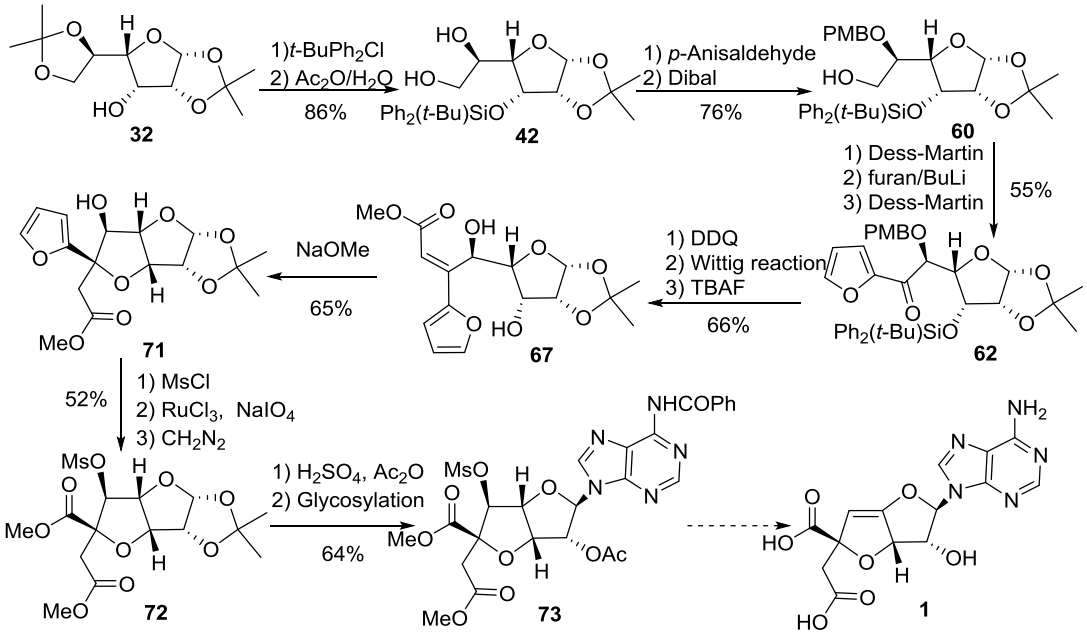
To rescue our proposed synthetic strategies, we envisioned that the Pd chemistry shown in Scheme **28** might show greater success rate in forming the 1,5 dioxabicyclo[3.3.0]oct-3-ene ring. There are literature precedents for the reduction of triflate in nucleosides.[19] The mild reductive conditions in general were well tolerated for carbohydrate substrates. However, this strategy also requires the challenging conversion of ketone **83** to nucleoside **87**.

A somewhat less attractive strategy involves exploring the *trans*-elimination starting from **81**. This will add multiple steps to the proposed synthetic sequence, and still requires finding a way to meet the trans-elimination challenge.

2.11 Conclusions

Two strategies of making griseolic acid B were evaluated. In strategy one, Grignard chemistry has been applied successfully to connect the key building blocks **35** and **43** to afford lactone **53**. As a way to generate **30** from **53**, the direct ring-opening strategy failed. The indirect multiple step sequence suffered from the low yield of reduction of lactone **53** to diol **57**. In strategy two, we reached the late stage mesylate **73** shown in S**cheme 29** and the corresponding secondary alcohol **78** shown in **Scheme 23**. However, even though significant effort was expended on the challenging elimination reaction to generate the 1, 5 dioxabicyclo[3.3.0]oct-3-ene ring (**73** and **78**), we failed to generate desired compound **74**. To rescue our proposal, a mild Pd reductive condition was envisioned to generate the 1,5 dioxabicyclo[3.3.0]oct-3-ene ring, thus enabling the total synthesis of griseolic acid B.

Scheme 29. Progress towards Griseolic Acid B



Chapter III

Glycosylation of Nucleosides

3.1 Introduction

Nucleoside disaccharides, various higher homologues, and other related modified complex nucleosides are an important class of natural products.[20,21] In particular, a stunning variety of complex nucleosides featuring the second glycosyl linkage, as well as components featuring lipid, heterocycle, sulfate, and amino acid subunits, have been found to show pronounced antibiotic and other activities. In many instances this results from an effective inhibition of bacterial cell wall biosynthesis.[22,23,24,25] Not surprisingly, the synthesis of the nucleoside disaccharide structural motif has been investigated by using not only the tactic of nucleosidation with pre-existing disaccharide donors, but also the *O*-glycosylation of pre-existing nucleoside acceptors.[26] The latter tactic, while synthetically more convergent, has an inherent problem: in most cases, the nucleoside heterocyclic base, a purine or a pyrimidine, features Lewis basic sites that are more reactive than the hydroxyl site where *O*-glycosylation is desired. There are several specific examples of complex nucleoside *O*-glycosylation in the literature in which glycosylation likely occurs preferentially on the nucleobase or other Lewis basic site, and completion of the reaction at the hydroxyl site requires a large excess of the donor.[27,28]

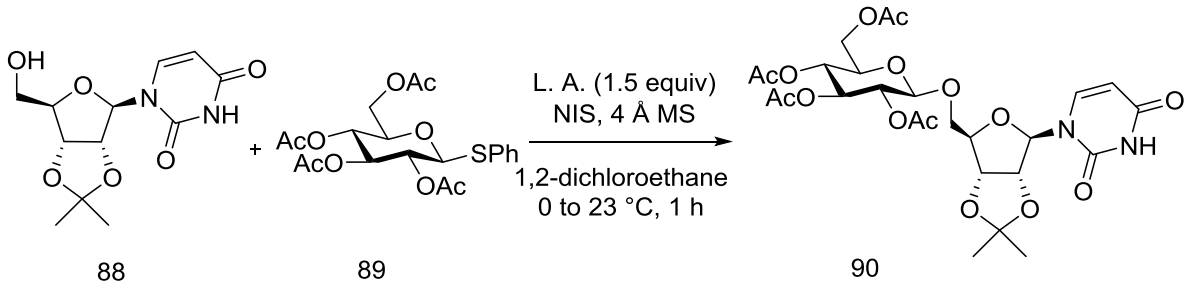
This is a fundamental issue in organic synthesis — how does one protect a more reactive site in a molecule so that the desired transformation can take place at a less reactive site? The attachment and subsequent cleavage of an effective protecting group, if one can be found, adds steps to the synthetic route. Some form of "transient protection" is

more attractive.[29] In the case of glycosylation, there are at least three "transient protection" scenarios by which the desired glycosylation selectivity could be achieved: (1) the donor, used in excess, reacts at both sites, and the glycosylated heterocycle portion is hydrolyzed during workup; (2) a Lewis acid, used in excess, blocks access to the more reactive nucleobase site; and (3) the Lewis acid promotes transfer of the glycosyl moiety from the nucleobase to the hydroxyl site. Because the glycosyl donor is typically more expensive than the Lewis acid, and sometimes considerably more so, options (2) and (3) are more attractive than (1). When this transformation occurs late in a total synthesis route, the freedom to optimize reaction conditions is often limited by the amounts of starting materials available.

We began an investigation into the selective *O*-glycosylation of nucleosides with the restrictions that the amount and complexity of the donor should be limited, the Lewis acid should be inexpensive relative to the donor (or better, commercially available), and the reaction conditions should be mild. Furthermore, thioglycosides were initially used as glycosyl donors because of their multiple advantages: they are easy to prepare, stable to storage and a variety of reaction conditions, and yet can be readily activated at modest temperatures with a wide range of electrophilic promoters.[30,31] Several syntheses of complex nucleoside antibiotics rely on thioglycoside intermediates to take advantage of these features.[32] A number of commendable glycosylation examples compliant with some of these criteria can be found in the literature;[33,34,35,36,37,38,39,40,41,42,43,44] however, we sought a protocol that could more generally inform future complex nucleoside synthesis efforts. We find that, after some adjustment of reaction conditions and protecting groups,

the Lewis acid indium(III) triflate proved to be particularly well suited to promote formation of nucleoside disaccharides by selective *O*-glycosylation.

Table 3. Nucleoside Glycosylation - Lewis Acid Screen



88 89 90

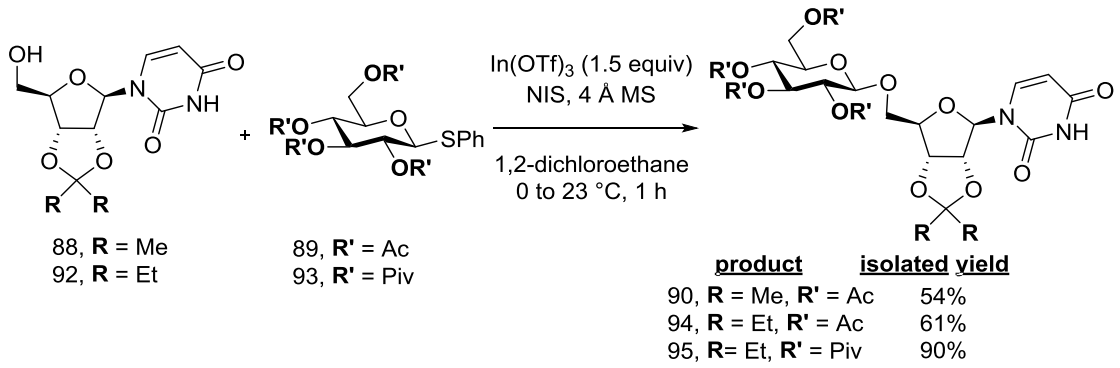
entry	Lewis acid (L.A.)	solvent	yield (HPLC)
1	TMS-OTf	1,2-dichloroethane	19%
2	$BF_3{\cdot}OEt_2$	1,2-dichloroethane	34%
3	AgOTf	1,2-dichloroethane	22%
4	CuOTf	1,2-dichloroethane	32%
5	$Cu(OTf)_2$	1,2-dichloroethane	37%
6	$Bi(OTf)_3$	1,2-dichloroethane	trace
7	$Y(OTf)_3$	1,2-dichloroethane	15%
8	$Ga(OTf)_3$	1,2-dichloroethane	33%
9	$Sc(OTf)_3$	1,2-dichloroethane	26%
10	**$Fe(OTf)_3$**	**1,2-dichloroethane**	**64%**
11	**$In(OTf)_3$**	**1,2-dichloroethane**	**68%**
12	"	acetonitrile	42%
13	"	propionitrile	35%
14	"	dichloromethane	54%
15	"	ether	8%
16	"	THF	trace

3.2 Results and discussion

An initial screen of Lewis acid activators was performed with 2',3'-*O*-isopropylidene)uridine[45] **88** as the acceptor and phenyl 1-thio-2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranoside[46] **89** as the acceptor. Combinations of *N*-iodosuccinimide (NIS) and various Lewis acids were examined, and the formation of the O-5' glycosylated

nucleoside[47] (**90**) was monitored by HPLC. Under conventional conditions,[48] namely 1.5 equiv each of trimethylsilyl trifluorosulfonate, NIS, and donor **89** in 1,2-dichloroethane solution for 1 h at room temperature, very little product **90** was formed (entry 1). This can be immediately attributed to interference, by the Lewis basic sites on the uracil base, with what should otherwise be an efficient *O*-glycosylation. Boron trifluoride etherate[49] offered a slight improvement (entry 2). Among a series of commercially available metal triflate activators (entries 3–11), two gave acceptable yields: iron(III) triflate and indium(III) triflate. Activation of thioglycosides by NIS in combination with metal triflates as a means to promote glycosylation of carbohydrate acceptors is known,[50] but the nucleoside case is more of a challenge. Further screening of several alternative solvents (entries 12–16) failed to improve on the combination of indium(III) triflate and 1,2-dichloroethane.[51]

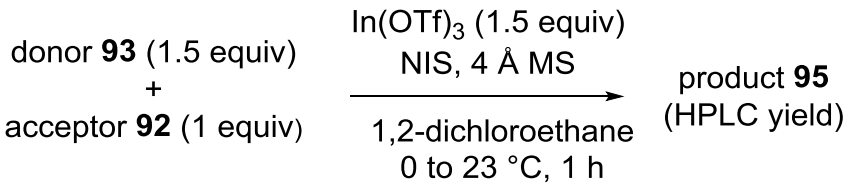
Scheme 30. Improvement of Protecting Groups



At this point, two protecting group modifications were made to improve the glycosylation (**Scheme 30**). First, the isopropylidene protecting group of **88** was replaced by a 3-pentylidene ketal[52] (see **92**), which provides greater stability and solubility. Second, the acetyls of **89** were replaced by pivaloyls ("Piv"; see **93**), which minimizes

interference by ortho ester formation during glycosylation of the primary hydroxyl.[53] As a result, product **95** could now be isolated in 90% yield, representing one of the best examples of such a nucleoside glycosylation.

Table 4. Effect of the Amount of $In(OTf)_3$ Activator

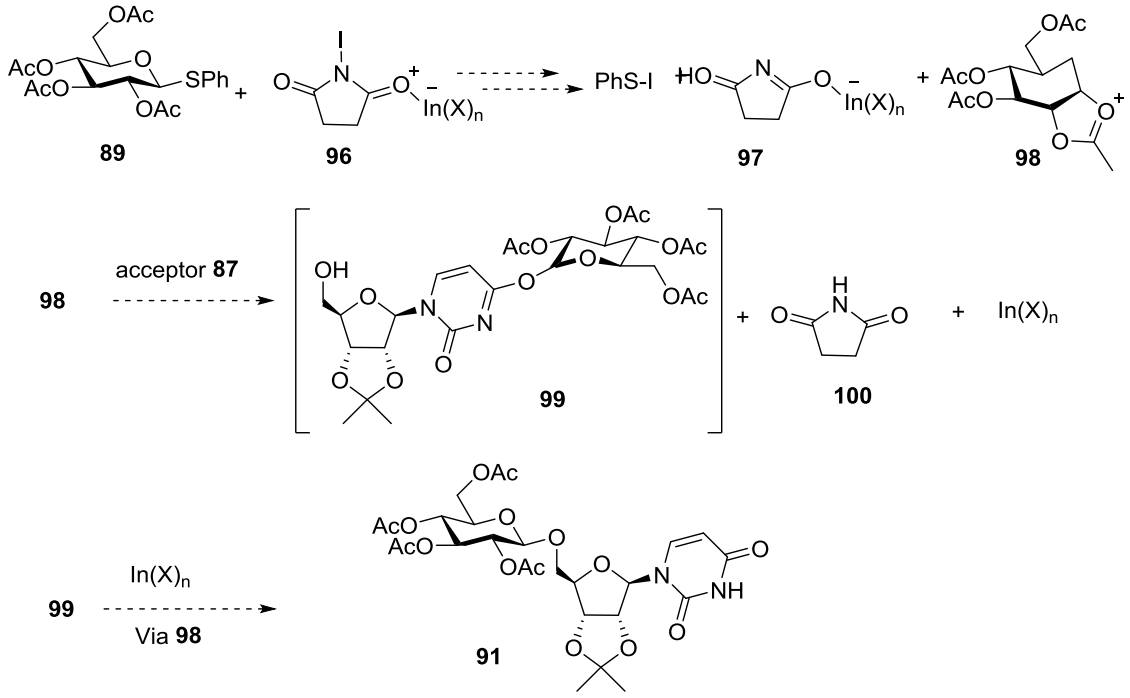


entry	equiv of $In(OTf)_3$	acceptor consumed	HPLC yield
1	0.1	27%	23%
2	0.5	82%	77%
3	1.0	92%	85%
4	**1.5**	**99%**	**91%**
5	2.0	95%	87%
6	3.0	92%	85%

With the amount of donor **93** held at 1.5 equiv, the amount of indium(III) triflate was varied in order to gain some insight into the role of the Lewis acid activator (Table 4). Yields, as determined by HPLC analysis, increase with the amount of In(III) triflate from 0.1 to 1.5 equiv (entries 1–4), but no additional benefit is observed beyond 1.5 equiv of activator. Without interference by the uracil base, a high glycosylation yield might have been expected with only catalytic In(III), since the Lewis acid can normally be recycled after initial NIS activation. Double glycosylation (once on the more reactive uracil ring and a second time on the 5' hydroxyl), followed by hydrolysis of the glycosylated heterocycle on workup, corresponds to scenario (1) in the introduction (above). As an exclusive path, this can be ruled out by the fact that yields exceed 75%,

the maximum for double glycosylation when only 1.5 equiv of donor is employed. Scenario (2), namely, Lewis acid blockage of the more reactive site on the nucleobase, is also ruled out as an exclusive path inasmuch as 0.5 equiv of In(III) would fail to block all the uracil sites, and yet still leads to a 77% yield for the glycosylation. Scenario (3), however, is consistent with observations: glycosylation can occur first on the uracil ring, and in the presence of sufficient In(III) the glycosyl group can be transferred to the desired 5' hydroxyl site.

Scheme 31. Possible Mechanism for Nucleoside Glycosylation

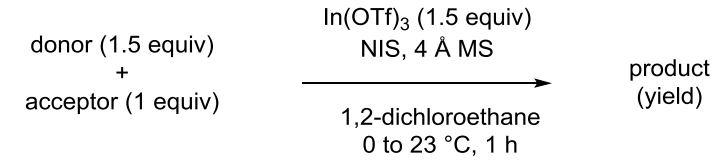


A proposed mechanism reflecting this process is outlined in Scheme 31. Succinimide (**100**) serves as the eventual proton acceptor. The integrity of the indium-triflate bonds is left unspecified.[54] Initial glycosylation by the participating intermediate, **98**, is suggested to occur at O-4 (see **99**), based on precedent that suggests that this site is the most Lewis basic on the uracil ring. Analogies may be found in the kinetic reaction of

the uracil ring of uridine derivatives at O-4 with silyl,[55] phosphoryl,[56] and sulfonyl[57] electrophiles. In contrast, N-3 glycosylation has been observed under Mitsunobu (i. e., basic) conditions,[58] which suggests that direct reaction at or isomerization to N-3 ought to be considered. In(III) promoted intermolecular isomerization of **99** to product **91** may occur, for example by, coordination of the metal at O-6. The isomerization could be promoted by catalytic In(III), but favored by the presence of additional Lewis acid, which would account for the respectable yield at 0.5 equiv and improved yields at 1.0 and 1.5 equiv. The failure of other Lewis acids (Table 1), which ought to promote anyway the activation of NIS (see **96** and **97**), to give high yields of O-5' glycosylated product **91** can be attributed to their inability to promote the O-4 to O-5' isomerization of **99** as effectively. Any remaining O-4 glycosylated product **99** would be hydrolyzed back to acceptor **88** upon aqueous workup.

The generality of these mild and practical reaction conditions, namely, slight excess (1.5 equiv) each of donor, NIS, and indium(III) triflate at 23 °C for 1 h, was explored for additional donors and acceptors, as shown in Table 5 (donors are shown; acceptors, which are described in the experimental section, are apparent from the structure of the product). Galactopyranoside donor **101** proved to be almost as effective (84%) as the gluco- donor, **93**, both using optimized uridine acceptor **92**. Ribofuranoside donor **103** was also employed successfully (80%). By mimicking uridine acceptor **95**, the analogous cytidine acceptor gave a good yield (85%) of nucleoside disaccharide **105**. Ribofuranoside donor **103** worked almost as well (78%).

Table 5. Additional Thioglycoside Donors and Nucleoside Acceptors



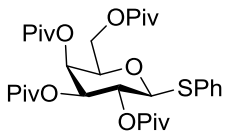
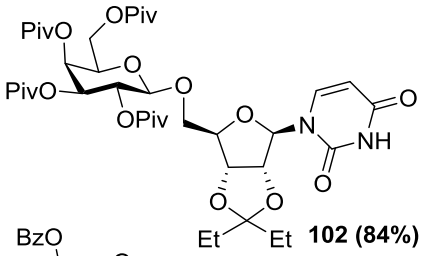
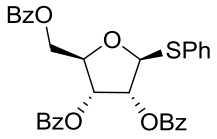
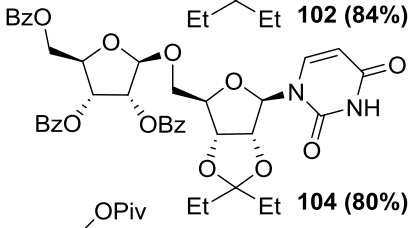
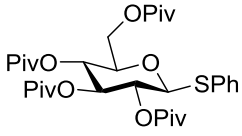
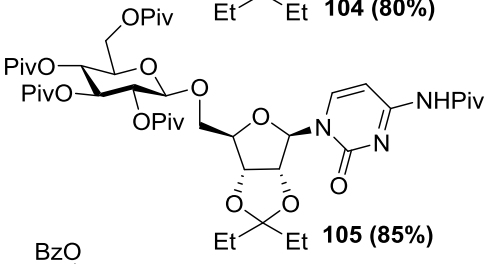
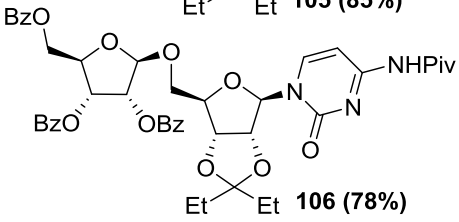
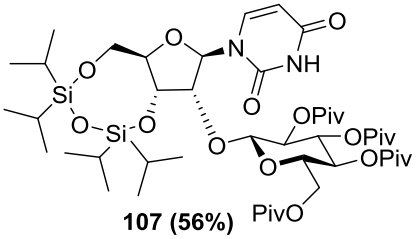
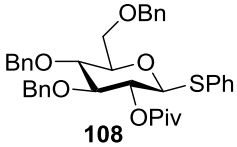
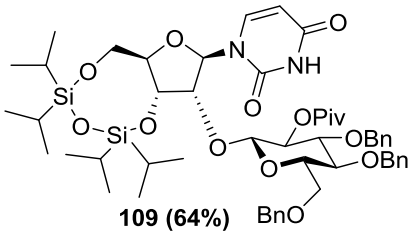
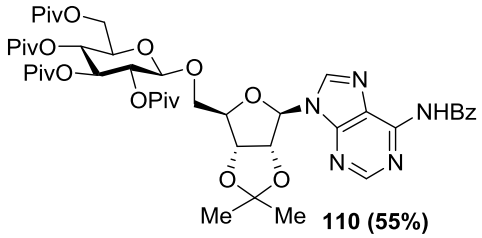
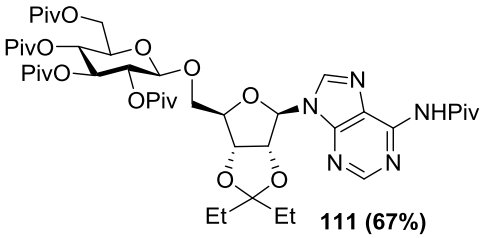
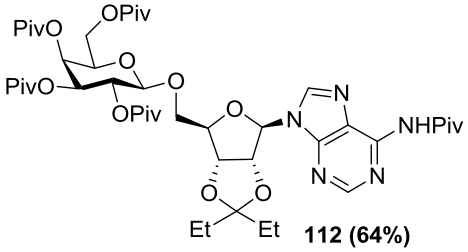
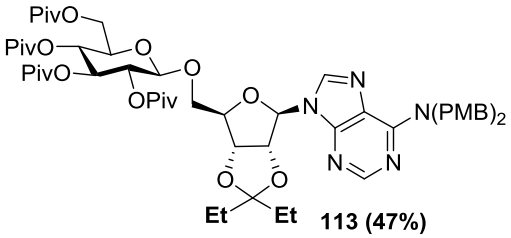
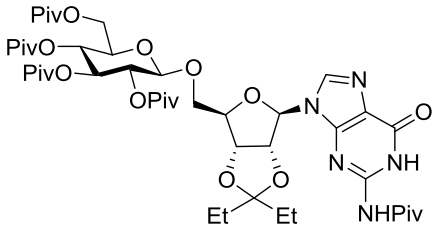
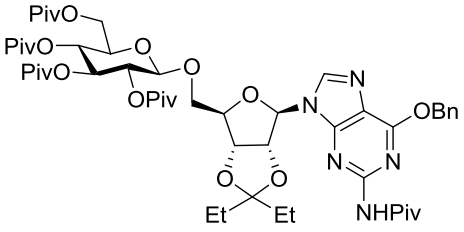
donor	product yield
 **101**	 **102 (84%)**
 **103**	 **104 (80%)**
 **93**	 **105 (85%)**
103	 **106 (78%)**
93	 **107 (56%)**
 **108**	 **109 (64%)**

Table 5 (continued). Additional Thioglycoside Donors and Nucleoside Acceptors

93		**110 (55%)**
93		**111 (67%)**
101		**112 (64%)**
93		**113 (47%)**
93		**114 (22%)**
93		**115 (61%)**

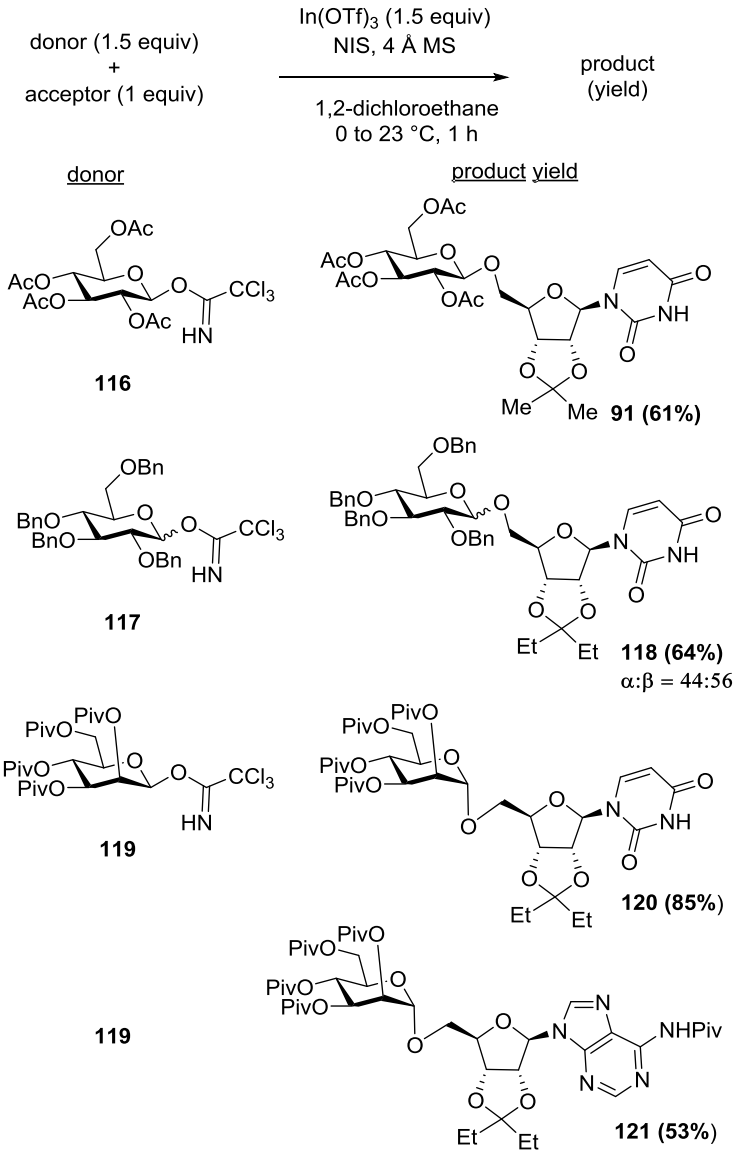
The relatively inaccessible [27b] secondary 2'-hydroxyl of an appropriately protected uridine acceptor was glycosylated in 56% yield by using 2 equiv of the dependable donor, **93**. The more activated ("armed") donor, **108**, worked even better (64%).

The purine nucleosides are intrinsically difficult to *O*-glycosylate because they readily de-purinylate, a process that occurs by way of competing N-7 glycosylation followed by loss of the ribofuranose at N-9.[27a, 27b, 60] Additionally, the protecting group at the C-6 heteroatom (N or O) should be chosen with a view to minimizing its ability to act as a glycosyl acceptor itself. Thus, the adenosine (N-6)-benzoyl acceptor could be improved upon by switching to (N-6)-pivaloyl (55% for **110** vs 67% yield for **111**). Galactopyranoside donor **101** also worked well (64%), but the (N-6)-bis(*p*-methoxybenzyl) acceptor was worse (47%). An (N-2)-protected guanosine acceptor performed poorly (**114**, 22%), but the situation was improved (**115**, 61%) by incorporation of an O-benzyl at C-6, blocking glycosylation at that site.

Trichloroacetimidate (Schmidt) donors,[59] such as **116** (Table 6), are often used for glycosylations because of their high reactivity. Indium triflate ought to activate such donors by coordinating to the imidate nitrogen atom, but without the need for NIS. This idea was explored in the context of nucleoside glycosylation for three pyranose donors and three nucleoside acceptors (Table 6). In each case, the reaction only required 1 h at 0 °C. Donor **116**,[39] which is analogous to thioglycoside **90**, gave the disaccharide **91** in somewhat better yield than **90**. The "armed" donor **117**, [60] gave a good yield of **118**, but without stereoselectivity. A new Schmidt donor, **119**, worked well with both a pyrimidine acceptor and a purine acceptor, providing disaccharides **120** and **121**, respectively.

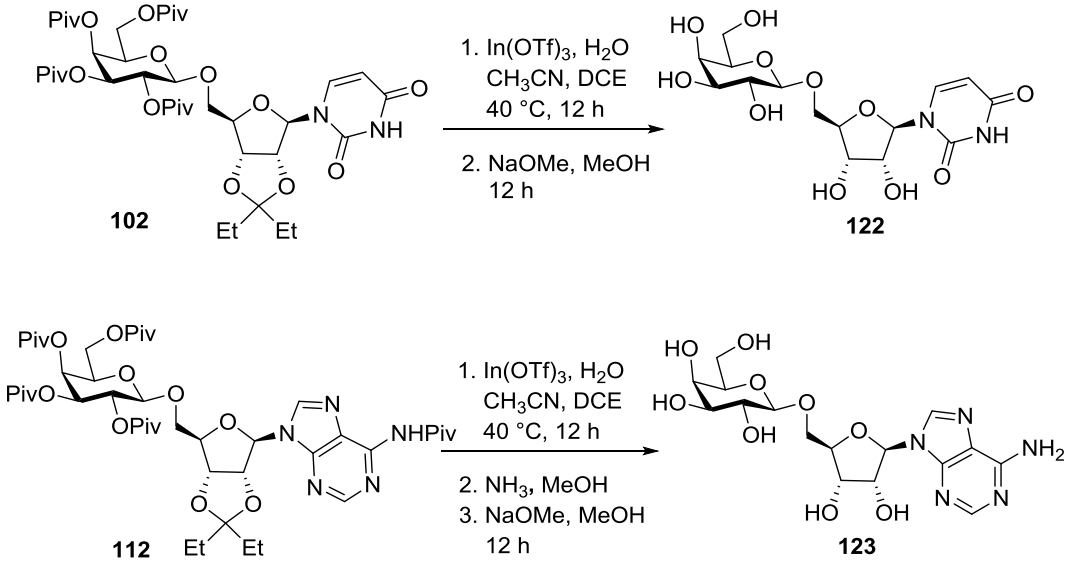
Overall, the results with Schmidt donors illustrate modest advantages over thioglycoside donors: they demonstrate somewhat greater reactivity, and embody the versatility of using the reducing sugar as the starting point for donor synthesis. As with thioglycoside donors (Table 5), indium(III) triflate-promoted migration of the donor moiety from nucleobase to hydroxyl appears to occur analogously in these examples, by way of the same probable intermediates (e. g., **99)**.

Table 6. Nucleoside *O*-Glycosylation with Schmidt Donors



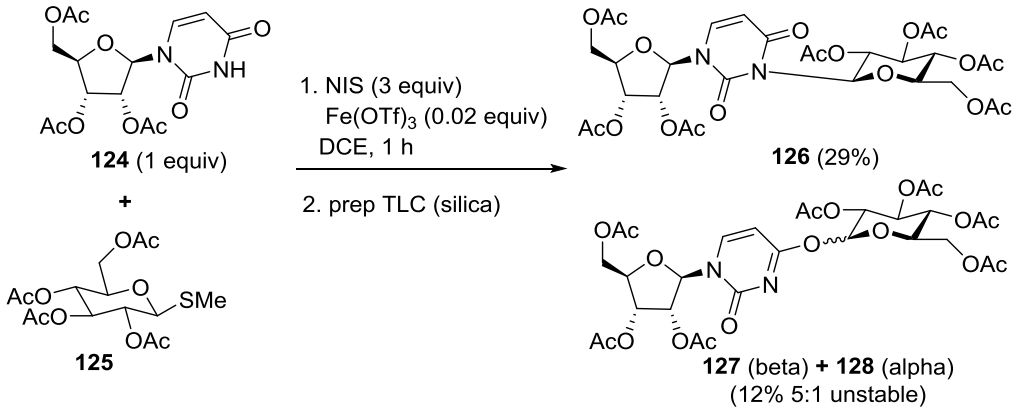
We also demonstrate the deprotection of two of the nucleoside disaccharides (Scheme 32). Purification and isolation of such highly polar compounds can be challenging, and is rarely done as part of literature reports, even though the ultimate synthetic targets must surely be the deprotected disaccharides themselves. Thus, hydrolysis of the 3-pentylidine acetal of **102**, followed by removal of the pivaloates under basic hydrolytic conditions and purification by reverse phase chromatography, with aq acetonitrile as the eluant, gave the pyrimidine disaccharide **122** in good overall yield. Indium(III) triflate was found to promote clean 3-pentylidene acetal hydrolysis in aq acetonitrile / dichloroethane solution, a reaction that was discovered during these investigations when wet rather than dry acetonitrile was inadvertently used for a glycosylation reaction. Analogous hydrolysis reactions of other carbohydrate acetals are known.[61]

Scheme 32. Deprotection of Nucleoside Disaccharides



Similarly, hydrolysis of the 3-pentylidene acetal of **112**, and then sequential removal of the (N-6)-pivaloyl by ammonolysis, and the remaining pivaloates by methanolysis, gave the deprotected purine disaccharide **123**. Purification relied on reverse phase chromatography as for **122**. The two step procedure was used because methoxide treatment of (N-6)-acylated purines does not normally lead to successful deacylation due to competing deprotonation at N-6.[62]

Scheme 33. Glycosylation of Uridine on the Pyrimidine Ring



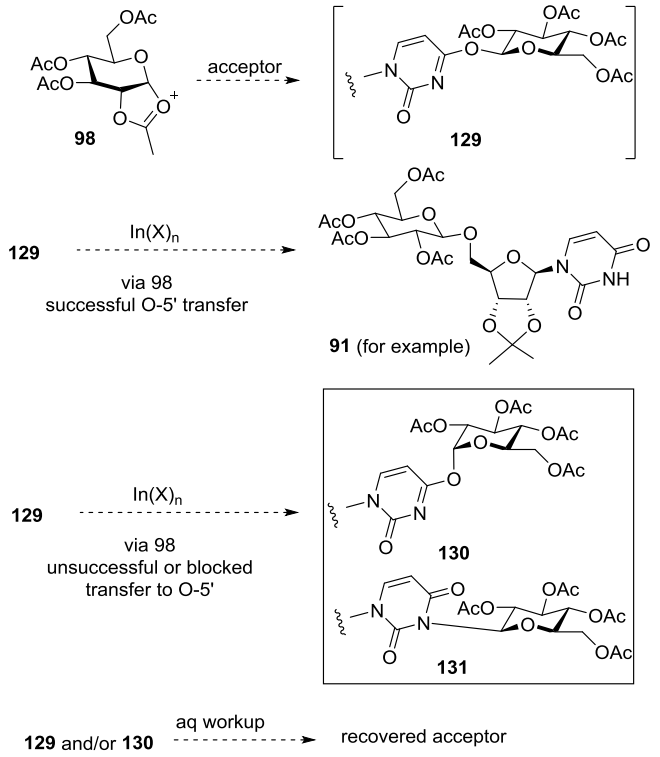
A focused effort was made to characterize possible nucleobase-glycosylated intermediates such as **99** (Scheme 31) that might serve as "ancillary donors," subject to indium(III) triflate-promoted intramolecular transfer of the glycosyl moiety to the sugar hydroxyl. Such intermediates were occasionally observed by TLC, but could not be isolated from quenched reaction mixtures because they are readily hydrolyzed to give back the original acceptor. However, an increase in the quantity of donor (**125**, Scheme 33) and NIS relative to acceptor **124**, and a supply of just 0.02 equiv of iron(III) triflate as the activator, led to the accumulation of observable intermediates. Direct preparative thin layer chromatography of the crude reaction mixture allowed the isolation of the pyrimidine ring-glycosylated compounds **126** and **127**/**128**. (N-3)-Glycosylated uridine

126 matches the known compound, previously obtained from **123** by a Mitsunobu coupling reaction.[63] It is stable to handling, and shows no spontaneous tendency to hydrolyze back to **124**. On the other hand, the *O*-glycosylated uridine products **127**/**128** were obtained as a (moisture and storage-sensitive) 5:1 mixture. Mass spectroscopic and proton and carbon NMR analysis indicates that they are a *beta*/*alpha* pair of *O*-glucopyranoside derivatives of **124**. The respective H-1" and C-1'' resonances [**127**: 6.20 ppm (J = 6.9 Hz) and 93.1 ppm; **128**: 6.76 ppm (J = 4 Hz) and 90.2 ppm] match closely the analogous *beta*/*alpha* pairs of D-glucopyranoside tetra-acetates derived from 4-nitrophenol[64] and *N*-phenyltrifluoroacetimidate,[65] and the Schmidt trichloroacetimidate donor **116**.[66] Furthermore, an (O-6)-β-D-glucopyranosyl guanosine derivatized as the hepta-acetate[67] shows H-1"/C-1" signals [6.50 ppm, (J = 8.1 Hz) and 94.1 ppm] similar to those of **127**, and a series of four O-4 alkylated uridine triacetates shows ribofuranoside H-1' and uridine H-5/6 values in line with those of **127**/**128**.[68] The upfield position of C-5 of **127** (96.3 ppm) strongly suggests that glycosylation has occurred at O-4 (expected for C-5: ~97 ppm) rather than the less reactive and more hindered O-2 (expected for C-5: ~108 ppm).[69,70]

A more complete picture of the nucleoside glycosylation process now emerges, as illustrated in Scheme 34 for the reaction of the presumed acetoxy-participated glucopyranose-derived oxonium donor species **98** with a uridine acceptor. Initial reaction of **98** with an acceptor heteroatom on the pyrimidine can be expected to provide the O-4 *beta* glucopyranoside (**129**) initially. In the presence of a suitable Lewis acid such as indium(III) triflate, **129** can transfer the donor moiety **98** to the hydroxyl accepting atom to give a disaccharide product such as **91**. Alternatively, should transfer of **98** to the

hydroxyl be slow or blocked, **129** can rearrange to the more stable *alpha* isomer, **130**. By comparison, **98** (generated from acetobromo-α-D-glucose and silver triflate) reacts with tetramethylurea on the oxygen atom to give the α-D-glucopyranosyl oxonium adduct only.[71] Acetamido *O*-glycosylations, some of them observed during attempted disaccharide formation, have also been described.[72] A β-L-fucopyranoside donor reacted on the amide oxygen with an acceptor acetamido substituent to give the *alpha* (equatorial) *O*-glycosylated product. Larger amounts of the silver(I) perchlorate activator, however, led instead to the isomeric, and presumably more stable, *beta* (axial) glycosylated product.[73] The possibility that some **130** is formed initially cannot be ruled out, but **98** is reliable for producing only the *beta* glycoside with a variety of acceptors, including the nucleoside hydroxyl acceptors described in this work, under conditions where equilbration is unlikely.

Scheme 34. The Uridine Nucleobase as "Ancillary Donor"



Indium(II) triflate-promoted rearrangement of either **129** or **130** to the (N-3)-glycosylated product **131** can occur subsequently if no other acceptor site is more reactive. The *N*-glycoside **131** is observed to be quite stable to isolation, and is presumably less reactive than **129** or **130** to serve as an activatable donor species to give **91**. The fact that **131** is obtained as only the *beta* isomer suggests that this isomer forms first and does not isomerize to *alpha* under the reaction or isolation conditions.

3.3 Conclusion

Mild and general experimental conditions have been developed for the efficient O-glycosylation of nucleoside ribofuranose hydroxyls despite competition from more Lewis basic sites on the purine or pyrimidine nucleobase. Indium(III) triflate serves both to activate the glycosyl donor, either a thioglycoside or glycosyl trichloroacetimidate, and to promote the isomerization of ancillary donor, heterocycle-glycosylated, intermediates to the desired nucleoside disaccharide. The isolation and characterization of (O-4)- and (*N*-3)-2″,3″,4″,6″-tetra-acetyl-D-glucopyranosyl derivatives of uridine 2′,3′,5′-triacetate provides evidence for the susceptibility of these sites to unintended or temporary glycosylation.

Chapter IV

Direct Glycosylation of Peptides Promoted by Catalytic Copper(I) Triflate

4.1 Introduction

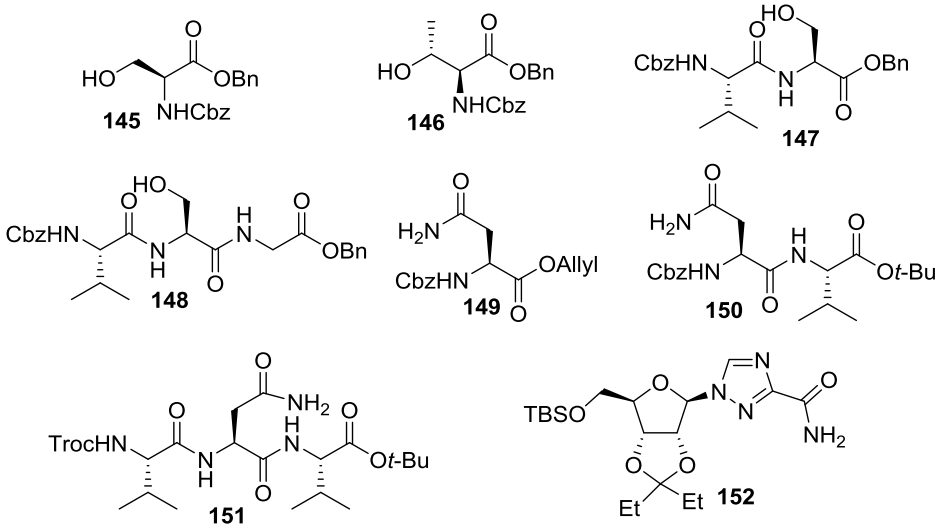
N- and *O*-glycosides attached to asparagines or serines/threonines through a *β*-glycosidic bond are found in various proteins and play significant roles in biological processes.[74] The *GlcNAc-β-Asn* bond was initially described in ovalbumin in 1961 by Johansen et al.[75] Soon thereafter, it was observed in a vast array of proteins in eukaryotes, including plasma protein, thyroglobulins, hormones, enzymes, cell surface receptors, immunoglobulins, and lectins.[76] The *GlcNAc-β-Ser/Thr* motif is distinctive in that it was found in nuclear and cytoskeletal proteins.[77] Unlike most other peptide-liked monosaccharides, the *GlcNAc-β-Ser/Thr* construct does not become further substituted by other sugars. To further understand the biological role of these glycoproteins and potential drug uses, their partial fragments, such as *N*- and *O*-glycopeptides, have served as effective biochemical probes and are attractive synthetic targets.[78]

In spite of the continual advances that have been made in carbohydrate chemistry over the centuries, efficient glycosylation still remains a challenge for chemists in many instances: 1) unreactive substrates such as hindered alcohols[79] and derivatives of phenol[80] and *N*-glycosylation of amides[81] present particular difficulties; 2) direct glycosylation of nucleosides and peptides represents another type of difficulty due to the potential interference of more reactive sites in the molecules. Recently, we have reported an example of “transient protection” that allows mild and efficient *O*-glycosylation of

nucleoside ribofuranoside hydroxyls despite competition from the more Lewis basic sites on the purine or pyrimidine nucleobase.[82] The key aspect of the procedure is to use (the inexpensive commercially available) indium (III) triflate to serve both to activate the glycosyl donor, either a thioglycoside or glycosyl trichloroacetimidate, and to promote the isomerization of heterocycle-glycosylated intermediates to the desired nucleoside disaccharide. We envisioned that the same principle can be potentially used for efficient *O* or *N*-glycosylation of peptides in a manner that has not been widely explored.

Furthermore, the underlying protecting strategies for glycosyl donors and peptides acceptors are worth addressing because the ultimate synthetic targets must surely be the deprotected glycopeptides themselves. We choose to employ readily removable carboxybenzyl (Cbz) and benzyl (Bn) groups, among the most common protecting groups for peptides in glycopeptide conjugation,[78] for the peptide acceptors and the glycosyl-donors. This allows the global deprotection of *O*-benzyl and carbobenzyloxy in a single hydrogenation step.

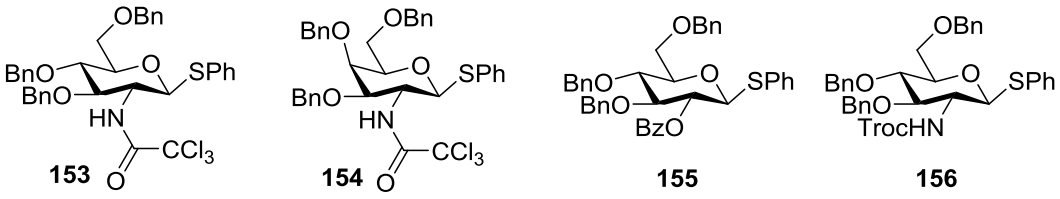
Scheme 35. Peptide Acceptors for Glycosylation



4.2 Results and discussion

We began with the synthesis of appropriately protected peptide acceptors and glycosyl donors. The *N*-carboxybenzyloxy (Cbz) amino acid benzyl ester glycosyl acceptors **145** and **146** were achieved by a one-step synthetic protocol[83] starting from commercially available *N*-Cbz amino acid. Dipeptide **147** was synthesized by coupling of commercially available *N*-Cbz *L*-valine with benzyl *L*-serinate and **147** was further extended by a peptide coupling reaction to give tripeptide acceptor **148.** The glycosyl acceptors **149**, **150** and **151** were synthesized according to the reported literature procedures.[81c] Ribavirin derivative acceptor **152** was synthesized by a two-step synthetic protocol.[52] In short, ribavirin was reacted with 3-pentanone with camphorsulfonic acid as catalyst to form the cyclic acetal followed by *O*-protection with *t*-butyldimethylsilyl chloride in moderate yield. Glycosyl donor **153**, **154**, **155** and **156** were synthesized by following the literature procedures (**Scheme 36**).[81c, 84, 85, 86]

Scheme 36. Sugar Donors for Glycosylation



The serine/threonine hydroxyls of an appropriately protected peptide are relatively inaccessible to direct glycosylation due to the interference by amide carboxyls.[87] The chemical synthesis of glycopeptides has mainly relied on solid-phase syntheses since it was first introduced by Lavielle et al. in 1981.[88] Since then, the chemistry of both carbohydrate and peptide portions has been highly optimized and various *O*- and *N*-linked glycopeptides have been prepared.[78, 89] However, the range of

chemistry available on solid phase is limited and it is difficult to monitor the progress of reaction when the substrates and products are attached to the solid phase. In order to address the general and special synthetic problems raised by the diverse natural glycosidic linkages, efforts to search for a 'better' glycosylation method have never ceased. Here we reported a relatively convergent chemical approach to synthesize glycopeptides by directly glycosylation of serine/threonine hydroxyls of appropriately peptides.

Based on the optimized reaction conditions reported for glycosylation of nucleosides, [82] we started a survey of a series of commercially available metal triflate activators for glycosylation of protected serine/thereonine. Among them, copper (I) triflate benzene complex stands out as one of the most superior activators in this case. In addition, further investigation revealed that catalytic amount (0.15 equiv) of copper triflate benzene complex is sufficient for efficient glycosylation of peptides.

As shown in Table **7**, both commercially available *N*-Cbz amino acid methyl ester and *N*-Cbz amino acid benzyl ester acceptors react with *gluco* donor **153** efficiently, with isolated yields of 90% and 91% (**157** and **159**, respectively). Sterically hindered threonine acceptors work almost as effectively as serine acceptors (86% and 87% yield). Galactopyranoside donor **154** proved to be slightly less effective (84% and 85%) than the *gluco* donor. Donor **154** was also employed successfully with *N*-*tert*-butoxycarbonyl-L-serine benzyl ester (88%).

Not only were mono-peptides glycosylated efficiently under standard reaction conditons with 2 equiv of glycosyl-donors (**Table 7**), but the dipeptide and tripeptide acceptors **147** and **148** were also glycosylated in 80% and 58% yields with gluco-donor

153, and donor **154** worked as almost as well, giving 78% and 61% yields (**Table 8**). To the best of our knowledge, there are no previous reports describing the synthesis of glycopeptides by direct glycosylation of di- or tri-peptides with thio-glycosyl donors.

Table 7. Peptide *O*-Glycosylation with Thioglycoside Donors

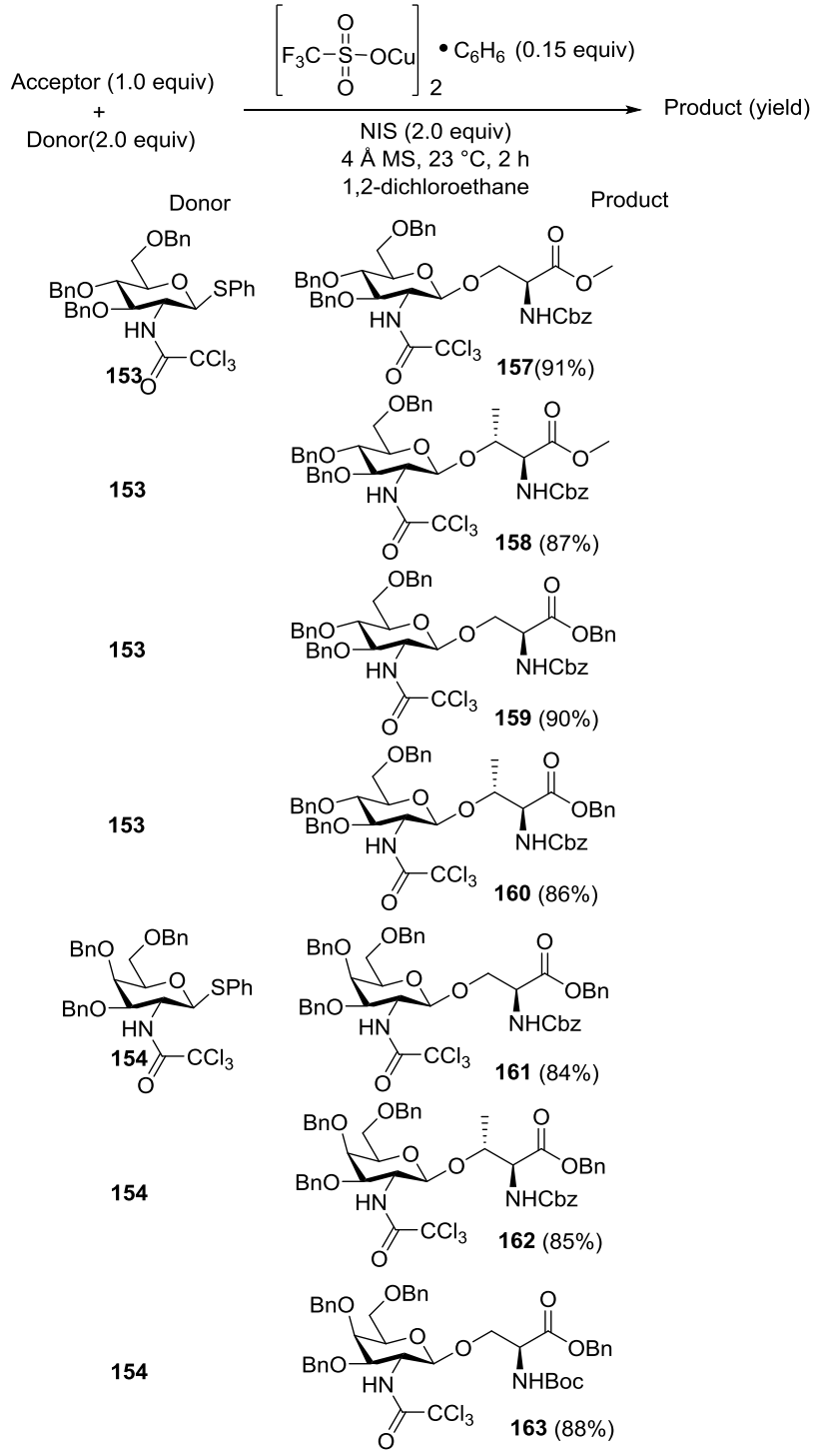
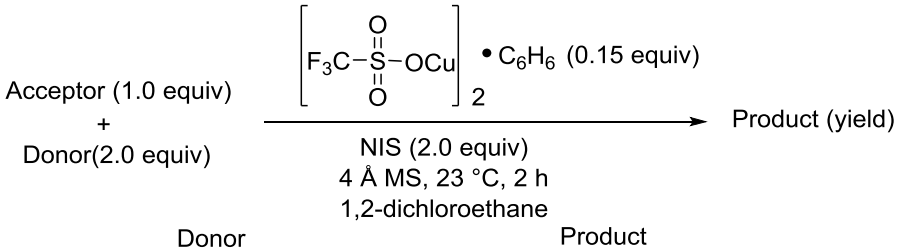
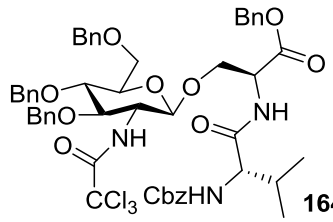
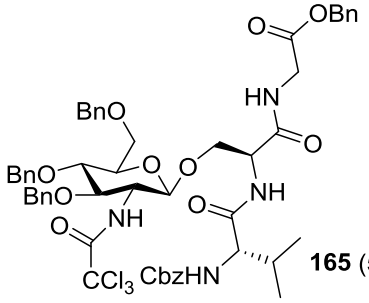
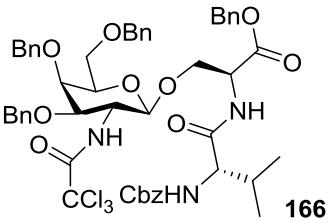
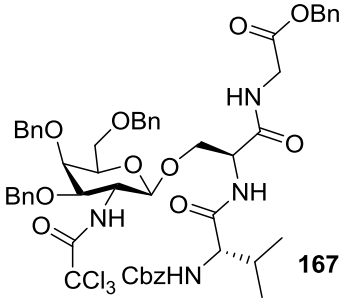


Table 8. Di- or Tri-peptides *O*-Glycosylation with Thio-glycosyl Donors



Donor	Product
153	 **164** (80%)
153	 **165** (58%)
154	 **166** (78%)
154	 **167** (61%)

The efficient synthesis of *N*-glycosides by *N*-glycosylation of asparagine-containing peptides poses a greater challenge due to the very poor nucleophilicity of the nitrogen of the amide group toward glycosylation. In addition, *O*-glycosylation of the

amides can also lead to bothersome side reactions. To address those issues, researchers have focused on identifying appropriate donors or enhancing the nucleophilicity of the primary amide nitrogen to maximize the formation of *N*-glycosides. In 1989, Kahne et al. reported that the coupling of a *N*-silyl acetamide with a perbenzyl galactosyl sulfoxide provided α-N-glycosyl acetamide as a major product.[81a] However, the scope of the reaction is limited due to the impractiality of preparing *N*-silyl asparagines. In 2005, Takahashi et al. demonstrated an efficient method to synthesize N-glycosides by *N*-glycosylation of asparagine containing peptides with glycosyl *N*-phenyltrifluoroimidates utilizing a catalytic amount of TMSOTf in nitromethane solution.[81c] The method allows for the first time the synthesis of various *N*-glycosyl amides from the primary amide derivatives. Recently, Yu et al. have demonstrated direct *N*-glycosylation of amides with glycosyl ortho-alkynyl benzoates and catalytic Au(I) complexes in moderate yields.[81d] The successful implementation of direct *O*-glycosylation of peptides catalyzed by the CuOTf benzene complex inspired us to further extend the reaction conditions for the direct *N*-glycosylation of the asparagine-containing peptides.

The mild and practical reaction conditions, namely, slight excess (2.0 equiv) each of donor, NIS, and, copper (I) triflate benzene complex at 23 °C for 1 h, was explored for the *N*-glycosylation of asparagine-containing peptides shown in **Table 9**. Mono-peptide **149** underwent *N*-glycosylation well with gluco-donor **155** providing the corresponding *β*-glycoside **168** in 82% yield. The dipeptide acceptor **150** also worked resonably well in moderate yield (56%), but tripetide acceptor **151** performed pooly (**170**, 36%), possibly due to the low solubility of **151** under the reaction conditions.

Table 9. Peptides *N*-Glycosylation with Thio-glycosyl Donors

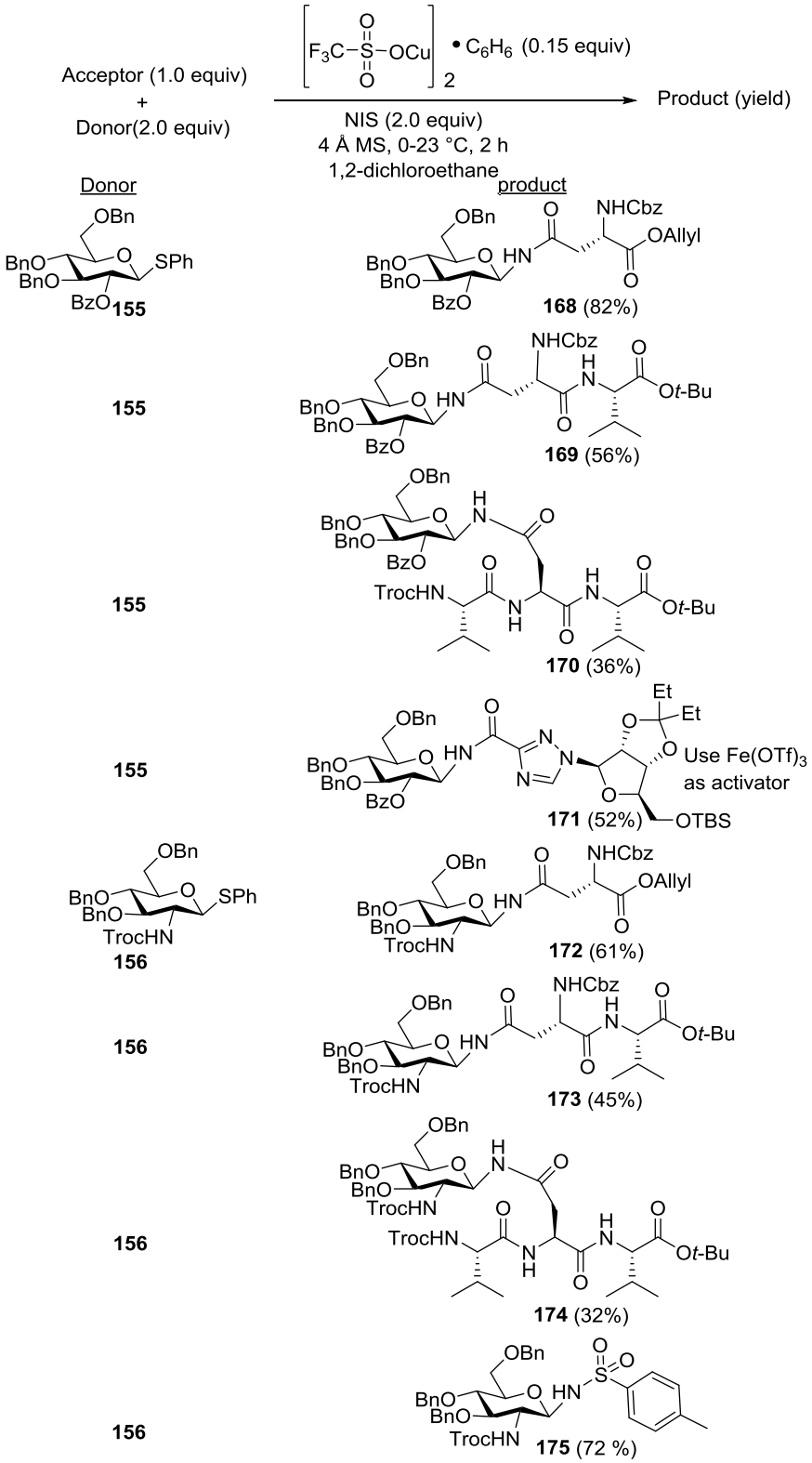
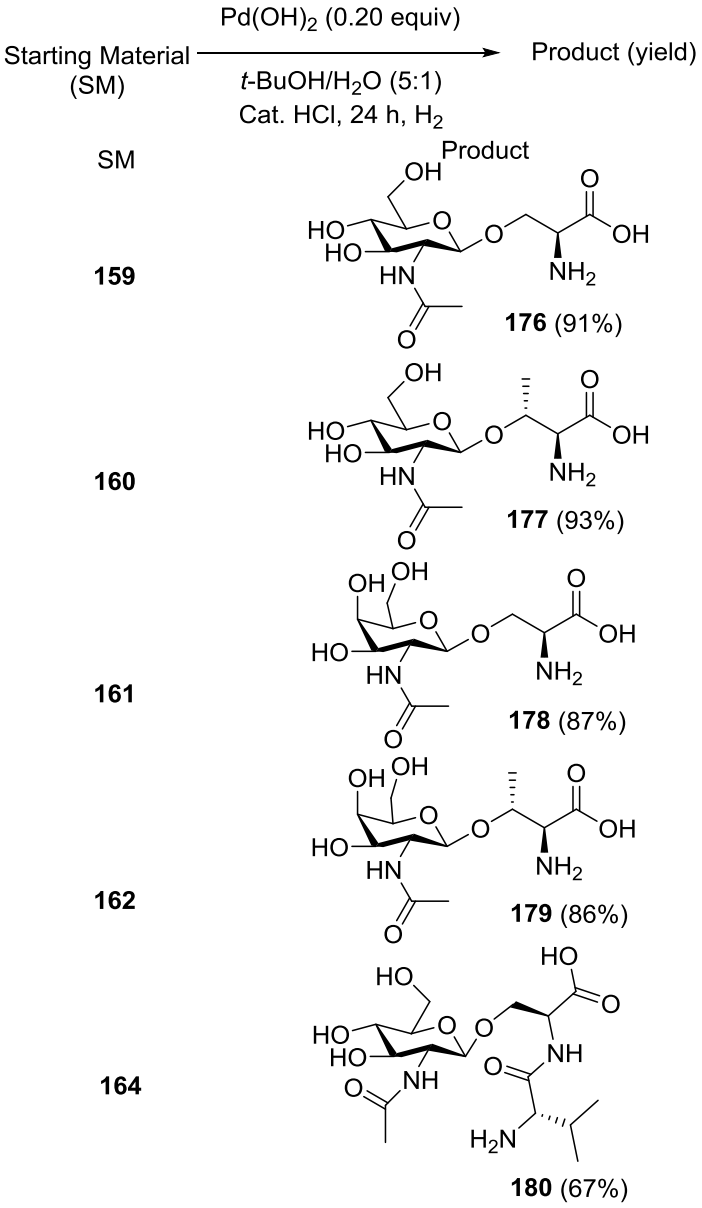


Table 10. Deprotection of Peptide Nucleosides



Most interestingly, ribavirin derivative acceptor **152** with multiple Lewis basic sites underwent direct *N*-glycosylation with *gluco* donor **155** in acceptable yield (**171**, 52%). Glycosides of drugs are larger and usually more hydrophilic than the drugs themselves. These properties tend to reduce penetration across biological membrane.[90] If an orally administered drug glycoside is not cleaved by digestive enzymes of the upper

intestine, it should pass unabsorbed into the large intestine, where bacterial glycosidases can hydrolyze the glycoside prodrug, thus achieving site-specific drug delivery.

The *N*-Troc glucosamine **156** was converted to the corresponding glycosyl amide **172** in moderate yield. However, glycosylation of di-peptides and tri-peptides resulted in reduced yields of the corresponding glycopeptides **173** (45% yield) and **174** (32% yield). The low efficiency of these reactions might have resulted from the poor solubility of the peptides in 1,2-dichloromethane. As reported in **Table 9**, we also demonstrate that t *N*-Troc glucosamine **156** reacts with half an equivalent of p-toluenesulfonamide under standard conditions to provide the corresponding *N*-glycosyl *p*-toluenesulfinamide **175** in good yield. The sulfonamide linkages have drawn wide attention due to their unusual enzyme-resistant properties.[91]

Next, we demonstrated the deprotection of a few peptides nucleosides. A brief survey of reaction conditions, including Pd catalysts, solvents, and reaction time, was conducted to optimize the sequence. In the first attempt, 10% Pd/C-catalyzed hydrogenolysis of the benzyl ethers and carboxybenzyl group of the peptide acceptor, along with concommitant reduction of trichloroacetyl into acetyl in **159** under MeOH/H_2O conditions overnight afforded fully deprotected glucopeptide **176** in low yield after RP-HPLC purification (67%). A considerable amount of decomposition was observed in the reaction. Milder conditions using $Pd(OH)_2$/C in place of Pd/C were tried in the second attempt. About 80% of fully deprotected glucopeptide **176 along** with ~20% of partial reduced chloroacetyl product was observed from LC-MS monitoring of the reaction, with almost no decomposition. Based on the initial two attempts, we adopted $Pd(OH)_2$/C as the prefered catalyst. A few more attempts allowed us to identify the

optimized condition shown in **Table 10**. Both gluco-peptides **159, 160** and galacto-peptides **161**, **162** worked efficiently with isolated yield ranging from 86% to 93%. Gluco-dipeptide **164** worked less efficiently in 67% yield, due to incompletely reduced chloroacetyl side product.

4.3 Conclusion

We have demonstrated the efficient and direct synthesis of *N*, *O*-glycopeptides by *N*- and *O*-glycosylation of asparagine or serine/threonine containing peptides with thioglycosides activated by a catalytic amount of copper triflate benzene complex in dichloroethane. This coupling method allows for the synthesis of the various *N*- and *O*-glycopetides from the primary amide or alcohol derivatives, which have potential as biochemical probes for elucidating the role of glycopeptides.

Chapter V

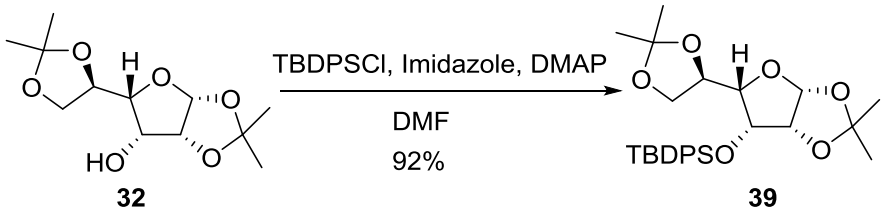
Experimental Section

5.1. General

All reagents were purchased from commercial suppliers and used without purification. ^{1}H NMR analysis was conducted at 400 MHz. Spectra are referenced to the residual solvent signal. ^{13}C NMR was conducted at 125 MHz by using a standard ^{1}H decoupled pulse sequence. Spectra are referenced to the residual solvent signal. Purification by column chromatography on silica gel refers to the use of an automated MPLC instrument using pre-packed silica gel columns. The product was eluted by using the indicated solvent gradients and was monitored at a wavelength of 260 nM. Analytical LCMS was conducted with a Waters Xterra MS C18 (2.1 x 20 mm, 3.5 μM) IS column; 10 μL injection; gradient of 10% to 100% acetonitrile (with 0.05% TFA) in water (with 0.05% TFA) over 3.75 min at 1 mL/min, 5.5 min analysis time, 7 min total run time, monitored at 254 nM; 62 to 1500 amu mass range; electrospray ionization with positive ion detection. Analytical TLC was conducted by using pre-coated Analtech plates, #21511.

5.2. Experimental Section for Chapter II

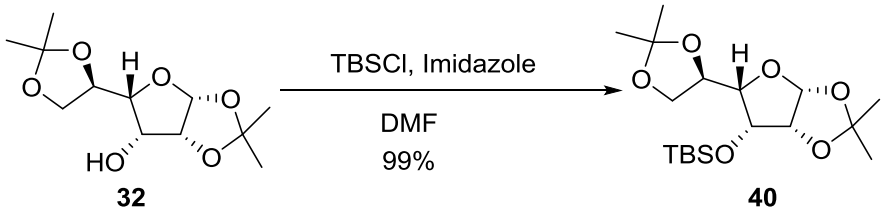
***tert*-Butyl(((3a*R*,5*S*,6*R*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)diphenylsilane (39).**



32 **39**

Furanose derivative **32** (5.0 g, 19.23 mmol) in dimethylformamide (10 mL) was added *tert*-butylphenylsilyl chloride (7.93 g, 28.85 mmol) and imidazole (2.62 g, 38.46 mmol). The mixture was allowed to stir at room temperature for 18 hours. The resulting reaction was added 100 mL water. The mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic extract was washed sequentially with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and then chromatographed with 1:9 ethyl acetate/hexane as the eluent to afford **39** (8.82 g, 17.69 mmol, 92% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 1 H, *J* = 8.0 Hz), 7.64 (d, 2 H, *J* = 7.6 Hz), 7.36-7.50 (m, 6 H), 5.50 (d, 1 H, *J* = 3.6 Hz), 4.91 (dd, 1 H, *J* = 6.0 and 6.8 Hz), 4.31 (m, 2 H), 4.07 (dd, 1 H, *J* = 7.6 and 9.6 Hz), 3.84 (dd, 1 H, *J* = 6.4 and 6.8 Hz), 3.72 (dd, 1 H, *J* = 7.6 and 8.4 Hz), 3.61 (dd, 1 H, *J* = 3.6, 4.4 Hz), 1.63 (s, 3 H), 1.48 (s, 3 H), 1.41 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 9 H); ^{13}C NMR (125MHz, $CDCl_3$) δ 136.2, 135.5, 133.1, 132.5, 130.4, 130.3, 128.1, 127.7, 112.9, 108.3, 104.5, 83.3, 78.2, 75.4, 73.5, 67.8, 27.1, 27.0, 26.7, 25.6, 25.4, 19.3; LC-ESI-MS $(M + Na)^+$ calcd for $C_{28}H_{38}O_6NaSi$ 521.23; found 521.35.

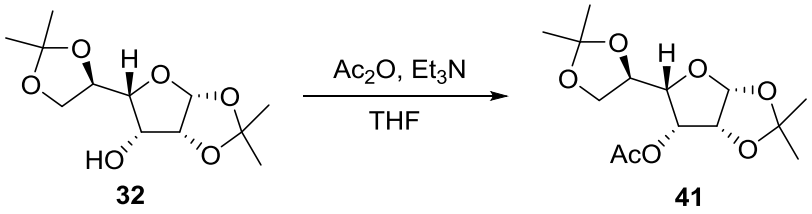
***tert*-Butyl(((3a*R*,5*S*,6*R*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)dimethylsilane (40).**



Furanose derivative **32** (5.0 g, 19.2 mmol) in dimethylformamide (20 mL) was added *tert*-butyldimethylsilyl chloride (4.3 g, 28.8 mmol) and imidazole (2.6 g, 38.2 mmol). The mixture was allowed to stir at room temperature for 16 hours. The resulting

reaction was added 100 mL water. The mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic extract was washed sequentially with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, concentrated, and then chromatographed with 1:9 ethyl acetate/hexane as the eluent to afford **40** (7.12 g, 19.00 mmol, 99% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (d, 1 H, *J* = 3.6 Hz); 4.44 (dd, 1 H, *J* = 9.6 and 6.4 Hz), 4.20 (dd, 1 H, *J* = 3.6 and 5.2 Hz) 4.11 (dd, 1 H, *J* = 5.2 and 7.2 Hz), 3.84 (dd, 1 H, *J* = 6.4 and 6.8 Hz), 3.72 (dd, 1 H, *J* = 7.2, 9.6 Hz), 3.25 (dd, 1 H, *J* = 7.6, 8.4 Hz), 1.33 (s, 3 H), 1.16 (s, 3 H), 1.08 (s, 3 H), 1.05 (s, 3 H), 0.67 (s, 9 H), -0.11 (s, 3 H), -0.13 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 113.5, 108.4, 104.9, 83.8, 79.4, 75.4, 72.9, 67.6, 27.0, 26.9, 26.2, 26.0, 25.4, 18.5, -4.6, -4.8; LC-ESI-MS $(M + Na)^+$ calcd for $C_{18}H_{34}O_6NaSi$ 397.20; found 397.42 .

(3a*R*,5*S*,6*R*,6a*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl acetate (41).

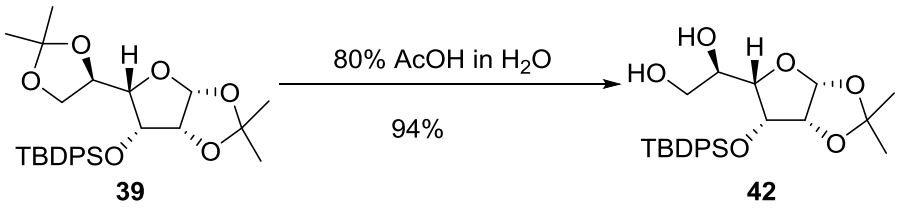


32 **41**

Acetic anhydride (2.59 g, 25.37 mmol) was added to a mixture of furanose derivative **32** (5.5 g, 21.13 mmol) and triethylamine (3.21 g, 31.70 mmol) in 200 mL tetrahyrofuran at room temperature. The mixture was allowed to stir at 50 ºC for 1 hour. The resulting reaction was concentrated in *vacuo*. The residue obtained was chromatogrpahed with 1:1 ethyl acetate/hexane as eluent to afford **41** (6.31 g 20.90 mmol, 99% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (d, 1 H, *J* = 4.0 Hz), 4.95 (dd, 1 H, *J* = 6.0 and 6.8 Hz), 4.68 (dd, 1 H, *J* = 4.0 and 6.4 Hz), 4.46 (m, 1 H),

3.95 (dd, 1 H, *J* = 6.8 and 10.2 Hz), 3.41 (dd, 1 H, *J* = 3.6 and 4.4 Hz), 2.00 (s, 3 H), 1.44 (s, 3 H), 1.29 (s, 3 H), 1.24 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 114.5, 109.3, 105.0, 81.4, 78.6, 75.2, 71.9, 66.5, 27.0, 26.9, 25.5, 20.9; LC-ESI-MS $(M + Na)^+$ calcd for $C_{14}H_{22}O_7Na$ 325.13; found 325.28.

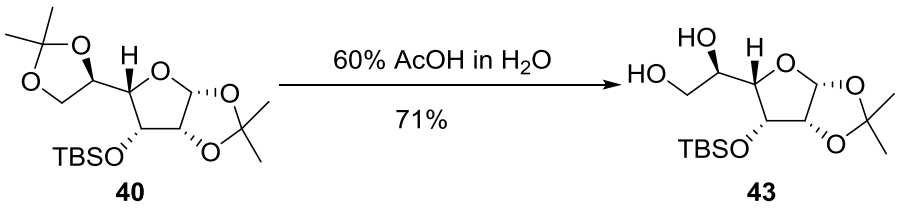
(*R*)-1-((3a*R*,5*S*,6*R*,6a*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethane-1,2-diol (42).



39 **42**

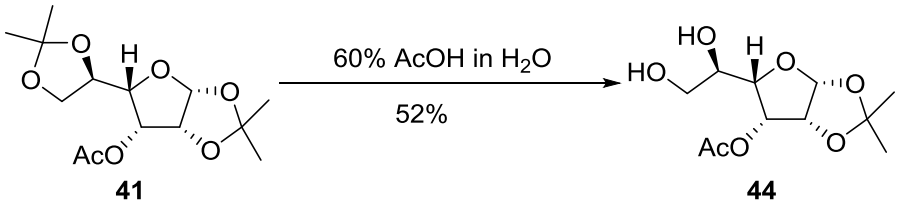
The solution of **39** (8.0 g, 16.04 mmol) in 200 mL 80% acetic acid aqueous solution was allowed to stir at room temperature for overnight. The solvent was removed azotropically by vacuum coevaporation with toluene (2 × 50 mL), and the resulting gummy crude diol was purified by chromatography with 1:1 ethyl acetate/hexane as eluent to afford diol **42** (6.9 g, 15.08 mmol, 94% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 2 H, *J* = 8.0 Hz), 7.66 (d, 2 H, *J* = 8.0 Hz), 7.37-7.50 (m, 6 H), 5.53 (d, 1 H, *J* = 3.6 Hz), 4.42 (dd, 1 H, *J* = 5.2, 7.6 Hz), 4.36 (m, 1 H), 4.15 (dd, 1 H, *J* = 6.4 and 7.6 Hz), 3.88 (dd, 1 H, *J* = 3.6 and 7.6 Hz), 3.81 (dd, 1 H, *J* = 4.0 and 5.2 Hz), 3.76 (dd, 1 H, *J* = 5.2 and 7.6 Hz), 3.23 (broad, 1 H), 2.32 (broad, 1 H), 1.66 (s, 3 H), 1.20 (s, 3 H), 1.11 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 135.7, 133.1, 132.6, 130.5, 130.4, 128.2, 127.9, 113.7, 104.6, 79.9, 78.5, 73.4, 69.2, 64.2, 27.1, 26.3, 25.6, 19.4; LC-ESI-MS $(M + Na)^+$ calcd for $C_{25}H_{34}O_6NaSi$ 481.20; found 481.35 $(M + Na)^+$.

(*R*)-1-((3a*R*,5*S*,6*R*,6a*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethane-1,2-diol (43).



The solution of furanose derivative **40** (7.0 g, 18.69 mmol) in 100 mL 60% acetic acid aqueous solution was stirred at room temperature for 3 hours. The solvent was removed azotropically by vacuum coevaporation with toluene (2 × 20 mL), and the resulting gummy crude diol was purified by chromatography with 1:3 to 1:1 ethyl acetate/hexane as eluent to afford diol **43** (4.44 g 13.27 mmol, 71% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (d, 1 H, *J* = 3.6 Hz), 4.40 (m, 2 H), 4.13 (m, 1 H), 4.01 (d, 1 H, *J* = 6.8 Hz), 3.73 (dd, 1 H, *J* = 3.6 and 7.6 Hz), 3.57 (dd, 1 H, *J* = 4.8 and 11.2 Hz), 3.15 (broad, 1 H), 2.75 (broad, 1 H), 1.54 (s, 3 H), 1.27 (s, 3 H), 0.87 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 113.6, 104.6, 79.7, 79.3, 72.9, 69.3, 63.7, 26.4, 26.2, 26.0, 18.4, -.4.5, -4.9; LC-ESI-MS $(M + Na)^+$ calcd for $C_{15}H_{30}O_6NaSi$ 357.17; found 357.29.

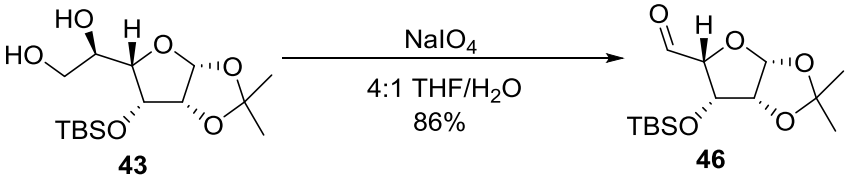
(3a*R*,5*S*,6*R*,6a*R*)-5-((*R*)-1,2-Dihydroxyethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl acetate (44).



The solution of furanose derivative **41** (5.60 g, 18.52 mmol) in 100 mL 60% acetic acid aqueous solution was stirred at room temperature for 3 hours. The solvent was removed azeotropically by vacuum coevaporation with toluene (2 × 20 mL), and the

resulting gummy crude diol was purified by chromatography with 1:2 to 2:1 ethyl acetate/hexane as eluent to afford diol **44** (2.53 g, 9.63 mmol, 52% yield) as colorless oil: ^{1}H NMR (400 Hz, $CDCl_3$) δ 5.80 (d, 1 H, *J* = 4.0 Hz), 5.12 (dd, 1 H, *J* = 6.0 Hz), 4.85 (dd, 1 H, *J* = 4.0 and 5.6 Hz), 4.18 (m, 2 H), 3.77 (dd, 1 H, *J* = 2.8 and 11.6 Hz), 3.55 (dd, 1 H, *J* = 4.4 and 11.6 Hz), 2.16 (s, 3 H), 1.57 (s, 3 H), 1.34 (s, 3 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 169.9, 114.5, 104.7, 78.4, 78.2, 72.0, 69.5, 63.5, 26.7, 26.6, 21.0; LC-ESI-MS $(M + Na)^+$ calcd for $C_{11}H_{18}O_7Na$ 285.10; found 285.28.

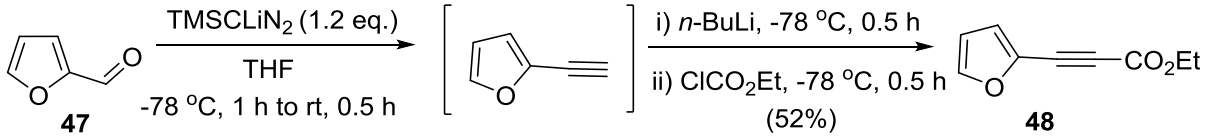
(3a*R*,5*R*,6*R*,6a*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole-5-carbaldehyde (46).



Sodium periodate (8.63 g, 40.36 mmol) was added to a solution of diol **43** (4.50 g, 13.45 mmol) in 150 mL 4:1 tetrahydrofuran/water. The mixture was allowed to stir at room temperature for 3 h. The resulting reaction was added 100 mL water. The mixture was extracted with 2 × 150 mL ethyl acetate. The combined extract was washed sequentially with sodium bisulfite saturated solution (100 mL), brine (100 mL), dried over anhydrous sodium sulfate, concentrated in *vacuo* and then chromatographed with 1:9 ethyl acetate/hexane as the eluent to afford aldehyde **46** (3.50 g, 11.57 mmol, 86% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, 1 H, *J* = 2.4 Hz), 5.79 (d, 1 H, *J* = 3.2 Hz), 4.58 (dd, 1 H, *J* = 4.4 and 8.4 Hz), 4.46 (dd, 1 H, *J* = 3.6 and 4.4 Hz), 4.17 (dd, 1 H, *J* = 2.4 and 4.4 Hz), 1.52 (s, 3 H), 1.30 (s, 3 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 114.0, 105.4, 83.9, 79.0, 74.8, 26.4, 26.0,

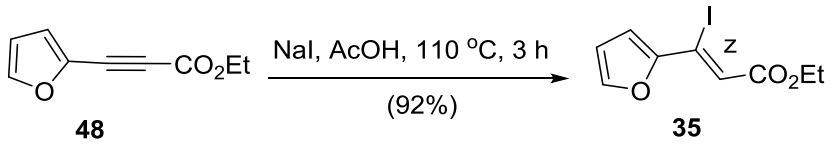
25.9, 18.3, -4.8, -5.0; LC-ESI-MS $(M + Na)^+$ calcd for $C_{14}H_{26}O_5NaSi$ 325.14; found 325.31.

Ethyl 3-(2-furyl)propiolate (48).



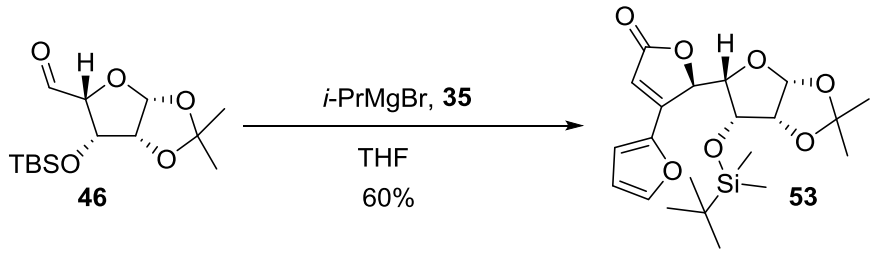
Under a nitrogen atmosphere, *n*-butyllithium (2.5 M solution in hexane, 2.4 mL, 6.0 mmol) was added dropwise to a solution of trimethylsilyldiazomethane (1.0 M in hexane, 6.0 mL, 6.0 mmol) in THF (40.0 mL) at -78 °C, and the mixture was stirred at –78 °C for 0.5 hour. A solution of 2-furylaldehyde (5.0 mmol) in tetrahydrofuran (10.0 mL) was added dropwise at –78 °C and the mixture was stirred at -78 °C for 1 hour, then at room temperature for 0.5 hour. After addition of *n*-butyllithium (2.5 M in hexane, 6.0 mL, 15.0 mmol) at –78 °C, the mixture was further stirred at –78 °C for 0.5 h. Ethyl chloroformate (25.0 mmol) was added dropwise at –78 °C, and the mixture was stirred at –78 °C for 0.5 hour. After addition of saturated aqueous ammonium chloride at –78 °C, the mixture was extracted with ethyl acetate (3 × 300 mL). The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with 1:9 ethyl acetate/hexane as the eluent to afford **48** (0.43 g, 2.6 mmol, 52% yield) as a deep brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 1 H, *J* = 1.6 Hz), 6.90 (d, 1 H, *J* = 3.2 Hz), 6.44 (dd, 1 H, *J* = 1.6 and 3.2 Hz), 4.27 (q, 2 H, *J* = 7.2 Hz), 1.31 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 146.3, 134.6, 121.1, 111.7, 85.9, 74.4, 41.7, 14.2; LC-ESI-MS $(M+H)^+$ calcd for $C_9H_8O_3$ 165.06; found 165.02.

Ethyl (*Z*)-3-(furan-2-yl)-3-iodoacrylate (35).



Sodium iodide (7.12 g, 47.52 mmol, 1.5 equiv) was added to acetylene **48** (5.25 g, 31.68 mmol) solution in 100 mL acetic acid. The mixture was allowed to stir at 80 ºC for overnight. The resulting reaction was concentrated *in vacuo*. The residue obtained was chromatographed with 1:9 ethyl acetate/hexane to afford **35** (8.51 g, 29.15 mmol, 92% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 1 H, *J* = 1.6 Hz), 7.01 (d, 1 H, *J* = 3.6 Hz), 6.98 (s, 1 H), 6.48 (dd, 1 H, *J* = 1.6 and 3.6 Hz), 4.27 (q, 2 H, *J* = 7.2 Hz), 1.33 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.20, 153.97, 145.35, 120.79, 118.57, 112.68, 98.49, 60.86, 14.47; LC-ESI-MS $(M+H)^+$ calcd for $C_9H_9IO_3$, 292.97; found, 292.88.

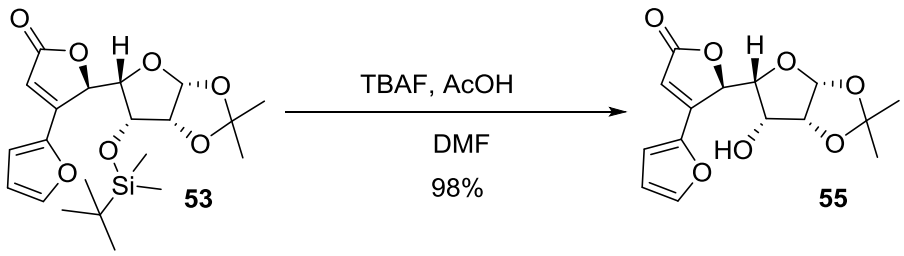
(*R*)-2'-((3a*R*,5*S*,6*R*,6a*R*)-6-((*ter*t-Butyldimethylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-[2,3'-bifuran]-5'(2'H)-one (53).



To a stirred solution of iodide **35** (2.5 g, 8.56 mmol) in 85 mL tetrahydrofuran at -20 ºC was added isopropyl magnesium bromide (3 M in tetrahydrofuran, 2.85 mL). The mixture was allowed to stir at this temperature for 2 hours before aldehyde **46** (1.29 g, 4.28 mmol) in 10 mL tetrahydrofuran was added. The mixture was then slowly warmed up to room temperature for overnight. The resulting reaction was added saturated

ammonium chloride saturated aqueous solution (100 mL). The mixture was extracted with 2×100 mL ethyl acetate. The combined extract was washed sequentially with water (100 mL), brine (100 mL), dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue obtained was chromatographed with 3:7 ethyl acetate/hexane as the eluent to afford lactone **53** (1.09 g, 2.57 mmol, 60% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, 1 H, *J* = 2.4 Hz), 5.79 (d, 1 H, *J* = 3.2 Hz), 4.58 (dd, 1 H, *J* = 4.4 and 8.4 Hz), 4.46 (dd, 1 H, *J* = 3.6 and 4.4 Hz), 4.17 (dd, 1 H, *J* = 2.4 and 4.4 Hz), 1.52 (s, 3 H), 1.30 (s, 3 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H); ^{13}C NMR (125 MHz, CDCl3) δ 173.2, 153.5, 146.4, 145.6, 115.3, 113.9, 113.4, 112.7, 105.6, 81.1, 79.8, 78.0, 72.1, 26.8, 26.1, 26.0, 18.6, -4.3, -4.9; LC-ESI-MS $(M + Na)^+$ calcd for $C_{21}H_{30}O_7NaSi$ 445.17; found 445.34.

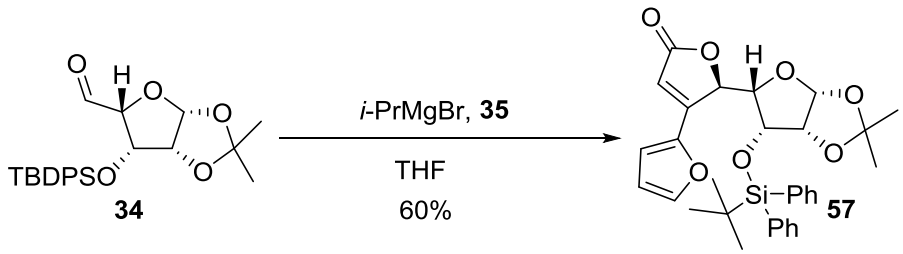
(*R*)-2'-((3a*R*,5*R*,6*R*,6a*R*)-6-Hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-[2,3'-bifuran]-5'(2'H)-one (55).



Tetrabutylammonium fluoride (1 M in tetrahyrofuran, 0.69 mL) was added to a mixture of acetic acid (0.03 g, 0.69 mmol) and lactone **53** (0.25 g, 0.46 mmol) in 5 mL dimethylformamide. The mixture was allowed to stir at room temperature for overnight, by which TLC (1:1 ethyl acetate/hexane) indicated consumption of starting material. Water (50 mL) was added and the mixture was extracted with 2×50 mL ethyl acetate. The combined extract was washed with brine, dried over anhydrous sodium sulfate and

concentrated in *vacuo*. The residue obtained was chromatographed with 1:1 ethyl acetate/hexane as eluant to afford alcohol **55** (0.14 , 0.45 mmol, 98% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ7.57 (d, 1 H, *J* = 1.2 Hz), 6.81 (d, 1 H, *J* = 3.6 Hz), 6.54(dd, 1 H, *J* = 1.6 and 3.6 Hz), 6.23 (d, 1 H, *J* = 0.8 Hz), 5.65 (d, 1 H, *J* = 3.2 Hz), 5.55 (s, 1 H), 4.63-4.66 (3 H), 3.22 (broad, 1 H), 1.71 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 145.4, 142.8, 142.0, 117.4, 114,7, 111.5, 109.8, 107.2, 104.9, 79.9, 76.4, 72.3, 27.0, 26.6; LC-ESI-MS $(M + H)^+$ calcd for $C_{15}H_{16}O_7$ 309.10; found 309.07.

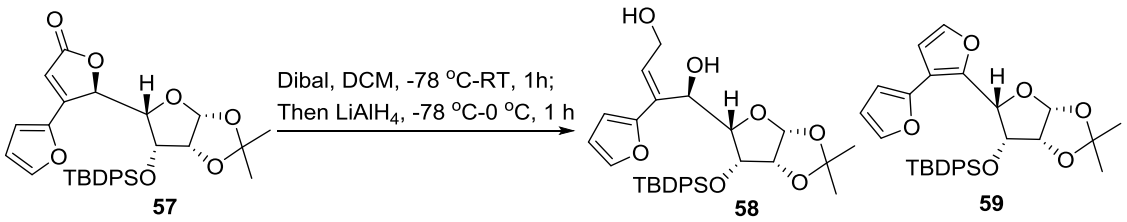
(*R*)-2'-((3a*R*,5*S*,6*R*,6a*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-[2,3'-bifuran]-5'(2'H)-one (**57**).



To a stirred solution of iodide **35** (2.5 g, 8.56 mmol) in 85 mL tetrahydrofuran at -20 ºC was added isopropyl magnesium bromide (3 M in tetrahydrofuran, 2.85 mL). The mixture was allowed to stir at this temperature for 2 hours before aldehyde **34** (1.83 g, 4.28 mmol) in 10 mL tetrahydrofuran was added. The mixture was slowly warmed up to room temperature for overnight. Saturated ammonium chloride solution (100 mL) was added to quench the reaction. The mixture was extracted with 2 ×100 mL ethyl acetate. The combined extract was washed sequentially with water (100 mL), brine (100 mL). It was dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue obtained was chromatographed with 3:7 ethyl acetate/hexane as the eluent to afford **57**

(1.40 g, 2.57 mmol, 60% yield) as a brown gel. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, 1 H, *J* = 8.0 Hz), 7.78 (d, 1 H, *J* = 8.0 Hz), 7.55 (d, 1 H, *J* = 2.0 Hz), 7.40-7.53 (m, 6 H), 6.50 (dd, 1 H, *J* = 2.0 and 3.6 Hz), 6.43 (d, 1 H, *J* = 3.6 Hz), 6.24 (d, 1 H, *J* = 1.6 Hz), 5.52 (d, 1 H, *J* = 4.0 Hz), 5.46 (s, 1 H), 4.63 (dd, 1 H, *J* = 6.0 and 8.0 Hz), 4.46 (d, 1 H, *J* = 9.2 Hz), 4.15 (dd, 1 H, *J* = 4.0 and 6.0 Hz), 1.85 (s, 3 H), 1.23 (s, 3 H), 1.18 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 153.2, 146.4, 145.5, 136.3, 135.9, 133.8, 133.2, 130.3, 128.2, 127.9, 115.0, 113.6, 113.5, 112.6, 105.4, 81.1, 79.1, 78.2, 72.4, 27.1, 26.3, 26.0, 19.6; LC-ESI-MS $(M+Na)^+$ calcd for $C_{31}H_{34}O_7NaSi$ 569.21; found, 569.41.

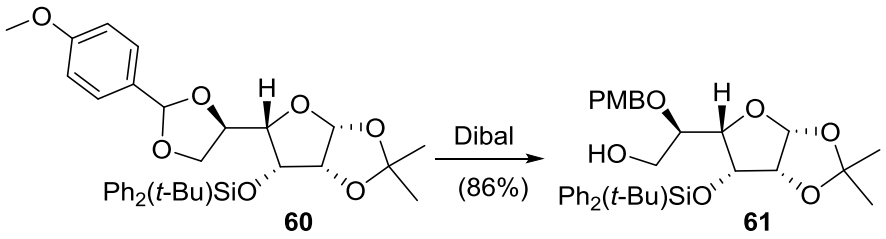
(*R*,*E*)-1-((3a*R*,5*S*,6*R*,6a*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-2-(furan-2-yl)but-2-ene-1,4-diol (58) and (((3a*R*,5*R*,6*R*,6a*R*)-5-([2,3'-bifuran]-2'-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)(*tert*-butyl)diphenylsilane (59).



Diisobutylaluminium hydride (6.86 mL, 1 M in toluene) was added to lactone **57** (2.5 g, 4.57 mmol) in 50 mL dichloromethane at 0 ºC dropwise. The mixture was allowed to stir at 0 ºC for 30 minutes and then lithium aluminium hydride (4.6 mL, 1 M in tetrahydrofuran) was added at 0 ºC. The resulting reaction was then warmed up to room temperature for 30 minutes and then quenched with 2 mL methanol at 0 ºC. It was added 50 mL saturate Rochelle salt solution and allowed to stir at room temperature for 2 h. The organic phase was separated and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic extract was washed with brine, dried over anhydrous

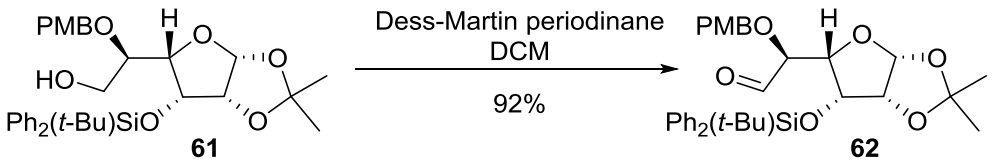
sodium sulfate and concentrated in *vacuo*. The residue obtained was chromatographed with 1:3 ethyl acetate/hexane as the eluent to afford **58** (0.70 g, 1.28 mmol, 28% yield) as colorless oil and **59** (0.80 g, 1.51 mmol, 33% yield) as an orange solid: **58:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 1 H, *J* = 8.0 Hz), 7.68 (d, 1 H, *J* = 8.0 Hz), 7.39-7.52 (m, 6 H), 7.37 (d, 1 H, *J* = 2.0 Hz), 6.60 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 6.37 (dd, 1 H, *J* = 2.0 and 3.2 Hz), 6.24 (d, 1 H, *J* = 3.2 Hz), 5.55 (d, 1 H, *J* = 3.6 Hz), 5.27 (d, 1 H, *J* = 2.8 Hz), 4.60 (m, 1 H), 4.51 (m, 2 H), 4.32 (dd, 1 H, *J* = 2.8, 4.4 Hz), 4.01 (dd, 1 H, *J* = 4.4 and 5.2 Hz), 3.75 (broad, 1 H), 2.76 (broad, 1 H), 1.80 (s, 3 H), 1.29 (s, 3 H), 1.13 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 142.0, 136.1, 135.7, 132.8, 132.3, 131.2, 130.6, 130.5, 129.3, 128.3, 128.0, 114.4, 111.4, 106.5, 104.4, 83.1, 78.9, 72.9, 70.0, 58.4, 26.9, 25.8, 25.6, 19.3; LC-ESI-MS $(M+Na)^+$ calcd for $C_{31}H_{38}O_7NaSi$ 573.23; found 573.61. **59:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1 H, *J* = 8.0 Hz), 7.40-7.47 (m, 5 H), 7.32-7.36 (m, 3 H), 7.18-7.22 (m, 2 H), 6.54 (d, 1 H, *J* = 2.0 Hz), 6.44 (dd, 1 H, *J* = 2.0 and 3.2 Hz), 6.32 (d, 1 H, *J* = 3.6 Hz), 5.67 (d, 1 H, *J* = 4.0 Hz), 5.62 (d, 1 H, *J* = 8.0 Hz), 4.55 (dd, 1 H, *J* = 5.6 and 8.0 Hz), 4.23 (dd, 1 H, *J* = 4.0 and 5.6 Hz), 1.82 (s, 3 H), 1.35 (s, 3 H), 0.90 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 146.0, 142.6, 141.6, 134.2, 135.9, 133.7, 133.1, 129.9, 129.8, 127.6, 127.6, 117.3, 114.5, 111.3, 109.3, 106.6, 105.0, 80.2, 76.5, 73.4, 26.7, 26.7, 19.3; LC-ESI-MS $(M+H)^+$.calcd for $C_{31}H_{34}O_6Si$, 531.22; found 531.25.

(*R*)-2-((3a*R*,5*S*,6*R*,6a*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-2-((4-methoxybenzyl)oxy)ethan-1-ol (61).



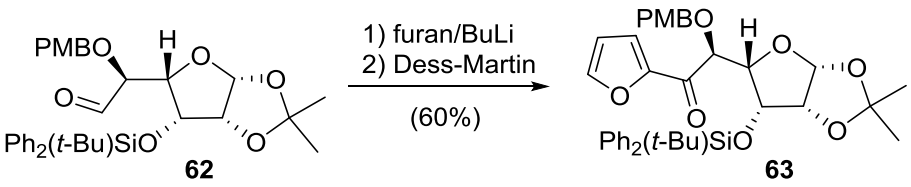
Diisobutylaluminium hydride (14.30 mL, 1 M in toluene) was added to **60** (5.50 g, 9.54 mmol) in 100 mL dichloromethane at 0 ºC dropwise. The mixture was allowed to stir at 0 ºC for 15 minutes and then warmed up to room temperature for 30 minutes. The resulting reaction was cooled back to 0 ºC and slowly quenched with 2 mL methanol. The mixture was then added 100 mL saturate Rochelle salt solution and allowed to stir at room temperature for 2 hours. The organic phase was separated and the aqueous was extracted with dichloromethane (2 × 50 mL). The combined organic extract was washed with brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue obtained was chromatographed with 1:4 ethyl acetate/hexane as the eluent to afford **61** (4.98 g, 8.20 mmol, 86% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2 H, *J* = 8.0 Hz), 7.68 (d, 2 H, *J* = 8.0 Hz), 7.26-7.47 (m, 8 H), 6.87 (d, 2 H, *J* = 8.8 Hz), 5.53 (d, 1 H, *J* = 4.0 Hz), 5.00 (d, 1 H, *J* = 10.8 Hz), 4.62 (d, 1 H, *J* = 10.8 Hz), 4.23-4.30 (m, 2 H), 4.07-4.18 (2 H), 3.80 (s, 3 H), 3.74 (dd, 1 H, *J* = 4.4 and 5.2 Hz), 2.45 (dd, 1 H, *J* = 6.0 and 6.8 Hz), 1.65 (s, 3 H), 1.19 (s, 3 H), 1.09 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 136.0,135.9, 135.4, 135.4, 132.9, 132.2, 131.1, 130.2, 130.0, 129.5, 129.1, 127.9, 127.6, 113.6, 113.6, 112.2, 104.1, 81.4, 79.8, 77.9, 73.7, 73.3, 62.3, 55.0, 26.9, 26.8, 26.2, 25.1, 19.1; LC-ESI-MS $(M+Na)^+$ calcd for $C_{33}H_{42}O_7NaSi$ 601.26; found 601.63.

(*S*)-2-((3a*R*,5*S*,6*R*,6a*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-2-((4-methoxybenzyl)oxy)acetaldehyde (62).



Dess-Martin periodinane (5.49 g, 12.96 mmol) was added to a solution of alcohol **61** (5.00 g, 8.64 mmol) in 90 mL dichloromethane. The mixture was allowed to stir at room temperature for 4 hours by which TLC (1:4 ethyl acetate/hexane) indicated consumption of starting material. The reaction was filtered through Celite. The filtrate was washed sequentially with saturated sodium carbonate aqueous solution (100 mL) and brine (100 mL). It was dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue obtained was chromatographed with 1:5 ethyl acetate/hexane as the eluent to afford aldehyde **62** (4.58 g, 7.95 mmol, 92% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (d, 1 H, *J* = 2.0 Hz), 7.76 (d, 2 H, *J* = 8.0 Hz), 7.61 (d, 2 H, *J* = 8.0 Hz), 7.31-7.47 (m, 8 H), 6.87 (d, 2 H, *J* = 14.0 Hz), 5.48 (d, 1 H, *J* = 3.6 Hz), 4.66 (d, 2 H, *J* = 11.6 Hz), 4.57 (dd, 1 H, *J* = 2.0 and 7.6 Hz), 4.43 (dd, 1 H, *J* = 7.6 Hz), 4.28 (dd, 1 H, *J* = 4.8 and 7.6 Hz), 3.78 (s, 3 H), 3.59 (dd, 1 H, *J* = 4.0 and 4.8 Hz), 1.47 (s, 3 H), 1.13 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 197.7, 159.5, 136.3, 135.7, 133.0, 132.1, 130.4, 130.3, 130.0, 129.9, 128.1, 127.8, 113.9, 112.9, 104.8, 82.5, 82.3, 77.8, 73.6, 72.1, 55.4, 26.9, 26.2, 25.3, 19.1; LC-ESI-MS $(M+Na)^+$ calcd for $C_{33}H_{40}O_7NaSi$ 599.24; found 599.48.

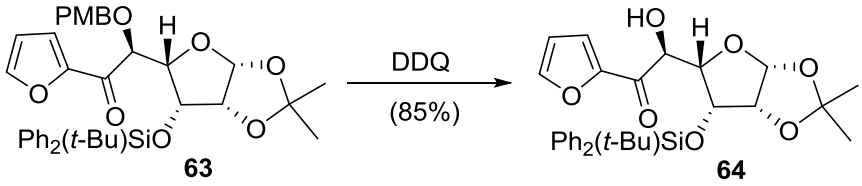
(*S*)-2-((3a*R*,5*S*,6*R*,6a*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-1-(furan-2-yl)-2-((4-methoxybenzyl)oxy)ethan-1-one (63).



A solution of furan (1.59 g, 23.41 mmol) in 200 mL tetrahydrofuran at -78 °C was added butyllithium (9.36 mL, 2.5 M in hexane). The mixture was allowed to stir at -78 °C for 5 minutes, warmed up to 0 °C for 10 minutes and then cooled back to -78 °C. A pre-prepared solution of aldehyde **62** (4.50 g, 7.80 mmol) in 10 mL tetrahydrofuran was added to above mixture dropwise. The resulting reaction was stirred at -78 °C for 15 minutes, then 0 °C for 10 minutes, quenched with 200 mL saturated ammonium chloride aqueous solution and diluted with 200 mL ethyl acetate. The organic phase was separated, washed with brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue obtained was chromatographed with 1:4 ethyl acetate/hexane as the eluant to afford 4.70 g alcohol. The above alcohol was dissolved into 100 mL dichloromethane. Dess-Martin periodinane (4.96 g, 11.70 mmol) was added. The mixture was allowed to stir at room temperature for 4 hours by which TLC (3:7 ethyl acetate/hexane) indicated consumption of starting material. The reaction was filtered through Celite. The filtrate was washed sequentially with saturated sodium carbonate solution (100 mL) and brine (100 mL). It was dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue obtained was then chromatographed with 3:7 ethyl acetate/hexane as the eluent to afford ketone **63** (3.01 g, 4.68 mmol, 60% yield over 2

steps) as a yellowish solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2 H, *J* = 9.6 Hz), 7.59 (m, 2 H), 7.36-7.43 (6 H), 7.28-7.31 (m, 2 H), 7.19-7.24 (m, 2 H), 6.76 (d, 2 H, *J* = 6.8 Hz), 6.51 (dd, 1 H, *J* = 1.6 and 3.6 Hz), 5.10 (d, 1 H, *J* = 4.4 Hz), 5.33 (d,1 H, *J* = 10.0 Hz), 4.96 (dd, 1 H, *J* = 7.6 and 10.0 Hz), 4.84 (d, 1 H, *J* = 11.2 Hz), 4.69 (d, 1 H, *J* = 11.2 Hz), 4.26 (dd, 1 H, *J* = 5.2 and 7.6 Hz), 3.78 (s, 3 H), 3.36 (dd, 1 H, *J* = 4.0 and 5.4 Hz), 1.66 (s, 3 H), 1.12 (s, 3 H), 0.77 (s, 9 H); ^{13}C (125 MHz, $CDCl_3$) δ 185.2, 159.5, 152.8, 146.6, 136.3, 135.9, 133.7, 132.3, 130.7, 130.2, 130.1, 129.7, 128.2, 127.6, 118.9, 113.7, 112.6, 112.5, 104.7, 80.6, 78.1, 76.5, 73.3, 72.5, 55.4, 26.8, 25.5, 19.4. LC-ESI-MS $(M+Na)^+$ calcd for $C_{37}H_{42}O_8NaSi$ 665.26; found 665.48.

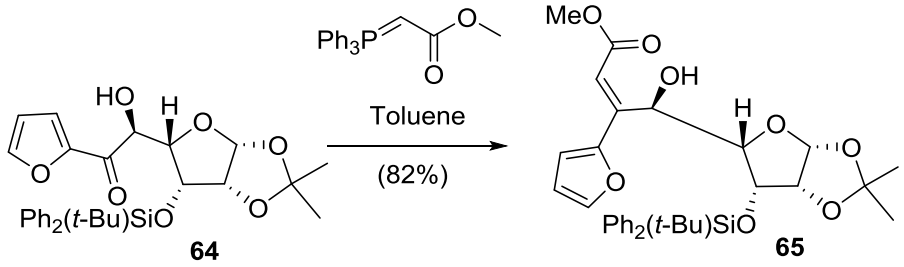
(*S*)-2-((3a*R*,5*S*,6*R*,6a*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-1-(furan-2-yl)-2-hydroxyethan-1-one (64).



To a stirred solution of ketone **63** (3.45 g, 5.37 mmol) in 50 mL 10:1 dichloromethane/water was added 2,3-dichloro-5,6-dicyanobenzoquinone (1.58 g, 6.98 mmol). The mixture was allowed to stir at room temperature for 4 hours, by which TLC (1:3 ethyl acetate/hexane) indicated consumption of starting material. Saturated sodium carbonate aqueous solution (100 mL) was added and the mixture was extracted with 2 × 200 mL dichloromethane. The combined extract was washed with brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue obtained was purified by chromatography with 3:7 ethyl acetate/hexane as eluent to afford **64** (2.39 g, 4.56

mmol, 85% yield) as a brown gel: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, 2 H, *J* = 8.0 Hz), 7.67 (d, 2 H, *J* = 8.0 Hz), 7.64 (dd, 1 H, *J* = 0.8 Hz), 7.56 (d, 1 H, *J* = 4.0 Hz), 7.36-7.48 (m, 6 H); 6.56 (dd, 1 H, *J* = 1.6 and 3.6 Hz), 5.53 (d, 1 H, *J* = 3.6 Hz), 5.26 (dd, 1 H, *J* = 2.0 and 5.6 Hz), 4.81 (dd, 1 H, *J* = 6.0 and 7.6 Hz), 4.46 (dd, 1 H, *J* = 5.2 and 8.0 Hz), 3.74 (dd, 1 H, *J* = 3.6 and 4.8 Hz), 3.48 (d, 1 H, *J* = 2.0 Hz), 1.79 (s, 3 H), 1.22 (s, 3 H), 0.96 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 147.2, 136.3, 135.8, 133.2, 132.2, 130.4, 130.4, 128.2, 127.8, 121.2, 113.7, 112.5, 104.9, 81.3, 78.5, 73.0, 72.1, 26.8, 26.4, 25.6, 19.2; LC-ESI-MS $(M+Na)^+$ calcd for $C_{29}H_{34}O_7NaSi$ 545.21; found 545.24.

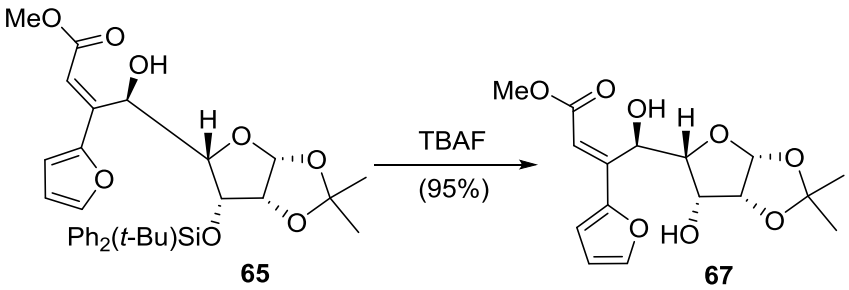
Methyl (*R*,*E*)-4-((3a*R*,5*S*,6*R*,6a*R*)-6-((*tert*-butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)-3-(furan-2-yl)-4-hydroxybut-2-enoate (65).



Methyl (triphenylphosphoranylidene)acetate (4.45 g, 13.32 mmol) was added to ketone **63** (2.32 g, 4.44 mmol) in 8 mL toluene. The mixture was heated at 90 ºC for 48 hours. The reaction was cooled down and concentrated in *vacuo*. The residue obtained was chromatographed with 2:8 ethyl acetate/hexane as eluent to afford **65** (2.10 g, 3.64 mmol, 82% yield) as a light yellow fume: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 2 H, *J* = 10.4 Hz), 7.72 (d, 2 H, *J* = 10.4 Hz), 7.36-7.52 (m, 7 H), 7.13 (d, 1 H, *J* = 3.2 Hz), 6.49 (dd, 1 H, *J* = 2.0 and 3.2 Hz), 6.41 (d, 1 H, *J* = 1.6 Hz), 5.48 (d, 1 H, *J* = 3.6 Hz), 5.28 (d, 1 H, *J* = 0.8 Hz), 4.53 (dd, 1 H, *J* = 5.2 and 8.4 Hz), 4.15 (m, 1 H), 4.10 (s, 1 H), 3.99

(dd, 1 H, *J* = 3.2 and 5.2 Hz), 3.72 (s, 3 H), 1.82 (s, 3 H), 1.30 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 149.5, 142.8, 142.7, 136.1, 135.7, 132.9, 132.4, 130.5, 130.5, 128.2, 128.0, 116.6, 114.7, 114.6, 112.0, 104.3, 82.6, 79.1, 72.8, 70.2, 51.4, 26.9, 26.4, 25.9, 19.5; LC-ESI-MS $(M + Na)^+$ calcd for $C_{32}H_{38}O_8NaSi$: 601.23; Found: 601.25.

Methyl (*R*,*E*)-3-(furan-2-yl)-4-hydroxy-4-((3a*R*,5*S*,6*R*,6a*R*)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)but-2-enoate (67).

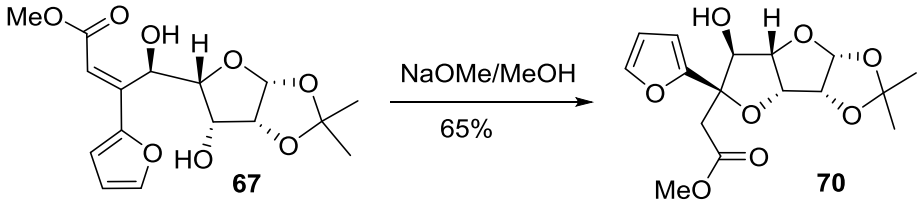


65 **67**

Acetic acid (0.33 g, 5.44 mmol) was added to a solution of alcohol **65** (2.10 g, 3.63 mmol) in 30 mL dimethylformamide, followed by adding tetrabutylammonium fluoride (5.44 mL, 1 M in tetrahydrofuran). The mixture was allowed to stir at room temperature for overnight, by which TLC (1:1 ethyl acetate/hexane) indicated consumption of starting material. Water (100 mL) was added and the mixture was extracted with 2 × 100 mL ethyl acetate. The combined extract was washed with brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue obtained was chromatographed with 4:6 ethyl acetate/hexane as eluent to afford **67** (1.17 g, 3.45 mmol, 95% yield) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, 1 H, *J* = 1.6 Hz), 7.16 (d, 1 H, *J* = 3.6 Hz), 6.46 (dd, 1 H, *J* = 1.6 and 3.6 Hz), 6.13 (d, 1 H, *J* = 1.2 Hz), 5.77 (d, 1 H, *J* = 4.4 Hz), 5.13 (d, 1 H, *J* = 7.6 Hz), 4.63 (dd, 1 H, *J* = 4.4 and 6.8 Hz), 4.41 (d, 1 H, *J* = 7.2 and 15.2 Hz), 4.15 (dd, 1 H, *J* = 2.0 and 7.2 Hz), 3.81 (d, 1 H, *J* = 8.0 Hz), 3.70 (s, 3 H), 3.21 (d, 1 H, *J* = 8.8 Hz), 1.66 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR

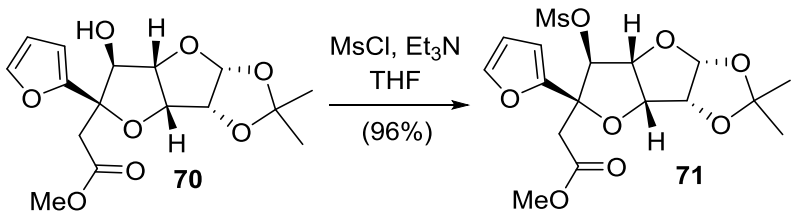
(125 MHz, $CDCl_3$) δ 166.7, 148.8, 143.1, 142.9, 115.8, 114.5, 114.0, 111.7, 104.7, 83.8, 78.9, 70.5, 69.2, 51.4, 26.2, 26.1; LC-ESI-MS $(M + Na)^+$ calcd for $C_{16}H_{20}O_8Na$ 363.13; found 363.25.

Methyl 2-((3a*R*,3b*R*,5*R*,6*S*,6a*S*,7a*R*)-5-(furan-2-yl)-6-hydroxy-2,2-dimethylhexahydrofuro[2',3':4,5]furo[2,3-*d*][1,3]dioxol-5-yl)acetate (70).



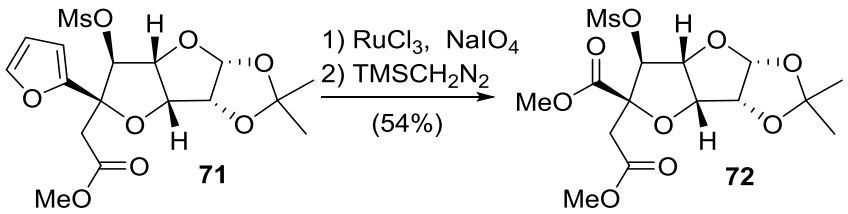
Sodium methoxide (0.71 mL, 0.71 mmol) was added to a solution of diol **67** (1.20 g, 3.53 mmol) in 34 mL methanol at room temperature. The mixture was allowed to stir for overnight. The resulting reaction was concentrated in *vacuo*. The residue obtained was added 20 mL aqueous sodium bicarbonate aqueous solution and the mixture was extracted with 3 × 20 mL ethyl acetate. The combined extract was washed with brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. The residue obtained was chromatographed with 1:1 ethyl acetate/hexane as eluent to afford (0.78 g 2.29 mmol, 65% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, 1 H, *J* = 0.8 and 1.6 Hz), 6.37 (dd, *J* = 0.8 and 3.2 Hz), 6.33 (dd, 1 H, *J* = 2.0 and 3.2 Hz), 5.91 (d, 1 H, *J* = 3.6 Hz), 5.05 (dd, 1 H, *J* = 6.8 and 7.6 Hz), 4.79 (dd, 1 H, *J* = 5.6 and 7.6 Hz), 4.70 (d, 1 H, *J* = 6.0 Hz), 4.50 (dd, 1 H, *J* = 3.6 and 6.4 Hz), 3.73 (s, 3 H), 3.39 (d, 1 H, *J* = 16.0 Hz), 3.16 (d, 1 H, *J* = 16.0 Hz), 1.67 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 152.8, 143.0, 114.1, 110.3, 109.0, 108.8, 52.6, 42.6, 27.2, 26.5; LC-ESI-MS $(M + H)^+$.calcd for $C_{16}H_{22}O_8$ 341.12; found 341.10.

Methyl 2-((3a*R*,3b*R*,5*R*,6*S*,6a*R*,7a*R*)-5-(furan-2-yl)-2,2-dimethyl-6-((methylsulfonyl)oxy)hexahydrofuro[2',3':4,5]furo[2,3-*d*][1,3]dioxol-5-yl)acetate (71).



Methanesulfonyl chloride (0.16 g, 1.10 mmol) was dropped to a mixture of triethylamine (0.22 g, 2.19 mmol) and alcohol **70** (0.25 g, 0.73 mmol) in 10 mL tetrahydrofuran at 0 °C. The mixture was allowed to stir at this temperature for 15 minutes, by which TLC (1:1 ethyl acetate/hexane) indicated consumption of starting material. Saturated ammonium chloride aqueous solution (20 mL) was added and the mixture was extracted with 2 × 50 mL ethyl acetate. The combined extract was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue obtained was chromatographed with 4:6 ethyl acetate/hexane as eluent to afford **71** (0.29 g, 0.70 mmol, 96% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, 1 H, *J* = 0.8 and 1.6 Hz), 6.35 (m, 2 H), 5.88 (d, 1 H, *J* = 3.2 Hz), 5.44 (d, 1 H, *J* = 7.2 Hz), 5.07 (dd, 1 H, *J* = 5.2 and 8.0 Hz), 5.01 (dd, 1 H, *J* = 6.4 and 8.0 Hz), 4.54 (dd, 1 H, *J* = 3.2 and 4.8 Hz), 3.64 (s, 3 H), 3.35 (d, 1 H, *J* = 11.6 Hz), 3.14 (d, 1 H, *J* = 11.6 Hz), 3.10 (s, 3 H), 1.74 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 151.5, 142.9, 114.8, 110.6, 108.8, 108.8, 85.7, 85.4, 83.7, 80.1, 78.8, 52.1, 40.7, 38.9, 31.7, 26.8, 25.2; LC-ESI-MS $(M + H)^+$calcd for $C_{12}H_{22}O_{10}S$ 419.09; found 419.12.

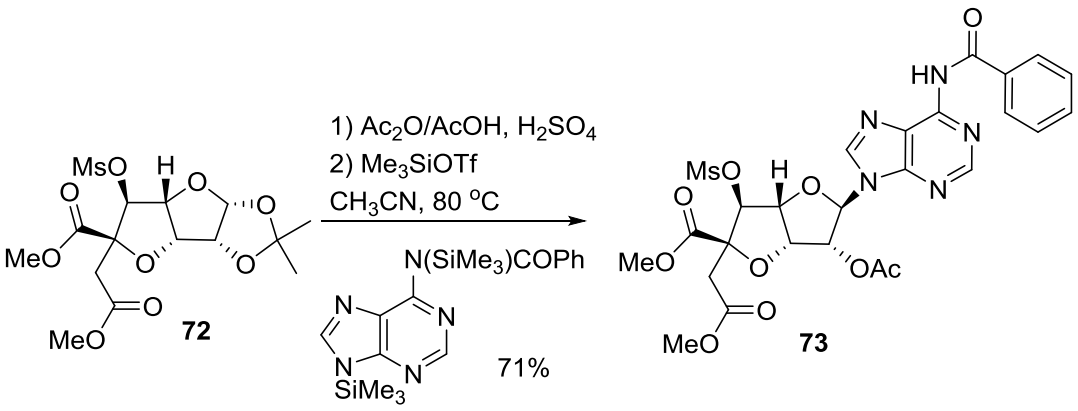
Methyl (3a*R*,3b*R*,5*R*,6*S*,6a*R*,7a*R*)-5-(2-methoxy-2-oxoethyl)-2,2-dimethyl-6-((methylsulfonyl)oxy)hexahydrofuro[2',3':4,5]furo[2,3-*d*][1,3]dioxole-5-carboxylate (72).



The mixture of ruthenium(III) chloride (15.0 mg, 0.07 mmol) and sodium periodate (1.54 g, 7.20 mmol) was stirred in 6 mL 1:1:1 acetonitrile/carbon tetrachloride/water at room temperature for 10 minutes, followed by adding furyl derivative **71** (0.30 g, 0.72 mmol) in 1 mL acetonitrile. The mixture turned into black. Additional sodium periodate was added until the reaction turned into yellowish. It was further stirred at room temperature for 5 minutes before it was added 20 mL water. The mixture was extracted with 2 ×20 mL ethyl acetate. The combined organic extract was washed with brine, dried over anhydrous sodium sulfate and concentrated in *vacuo* to afford 0.28 g crude acid. To above crude acid in 10 mL 1:5 methanol/dichloromethane was added trimethylsilyldiazomethane (2 M in hexane) dropwise until no bubbling. The resulting reaction was further stirred at room temperature for 30 minutes and concentrated in *vacuo*. The residue obtained was dissolved into 30 mL ethyl acetate. It was washed sequentially with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, concentrated and then chromatographed with 1:1 ethyl acetate/hexane as the eluent to afford ester **72** (0.16 g, 0.39 mmol, 54% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (d, 1 H, *J* = 3.2 Hz), 5.19 (d, 1 H, *J* = 6.8 Hz), 5.12 (dd, 1 H, *J* = 4.8 and 7.6 Hz), 4.89 (dd, 1 H, *J* = 7.2 and 7.6 Hz), 4.47 (dd, 1 H, *J* = 3.2 and 4.8 Hz),

3.76 (s, 3 H), 3.66 (s, 3 H), 3.40 (d, 1 H, *J* = 17.2 Hz), 3.10 (s, 3 H), 2.94 (d, 1 H, *J* = 17.2 Hz), 1.66 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 170.0, 114.6, 108.9, 86.2, 84.9, 84.9, 81.0, 78.6, 53.0, 52.2, 39.5, 39.0, 26.8, 26.1; LC-ESI-MS (M + H)$^+$calcd for $C_{15}H_{22}O_{11}S$ 410.09; found 411.11.

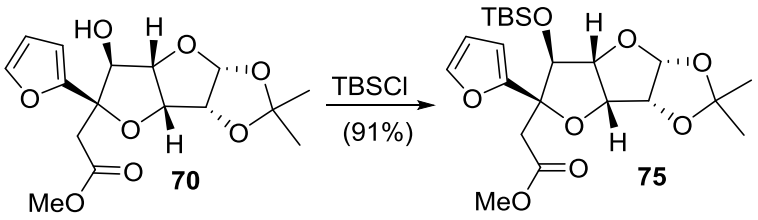
Methyl (2*R*,3*S*,3a*R*,5*R*,6*R*,6a*R*)-6-acetoxy-5-(6-benzamido-9H-purin-9-yl)-2-(2-methoxy-2-oxoethyl)-3-((methylsulfonyl)oxy)hexahydrofuro[3,2-*b*]furan-2-carboxylate (73).



A solution of ester **72** (0.16 g, 0.39 mmol) in 5 mL 1:1 Acetic acid/Acetic anhydride at 0 °C was added a catalytic amount, about 0.5 µL, of sulfuric acid. The mixture was stirred at room temperature for 6 hours. The reaction was concentrated and then dissolved into 20 mL dichloromethane. The organic was washed sequentially with saturated sodium bicarbonate aqueous solution, brine, dried over anhydrous sodium sulfate and concentrated to afford 0.18 g a mixture of anomeric acetates (α/β ~ 1:3). N^6-benzoylaminopurine (0.19 g, 0.78 mmol) in 5 ml acetonitrile was added *N*,*O*-bis(trimethylsilyl)acetamide (0.15 mL, 0.47 mmol) and the mixture was heated at 80 ºC for 15 minutes. A solution of above crude anomeric acetates in 1 mL acetonitrile and then trimethylsilyl trifluoromethanesulfonate (0.17 g, 0.78 mmol) were added. The resulting

reaction was further stirred at 80 ºC for 90 minutes. The reaction mixture was cooled down and concentrated in *vacuo*. The residue obtained was dissolved into 20 mL dichloromethane. It was washed sequentially with saturated sodium bicarbonate aqueous solution, brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. Chromatography with 5% methanol/dichloromethane as eluent afforded nucleoside **73** (0.17 g, 0.27 mmol, 71% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (broad, 1 H), 8.75 (s, 1 H), 8.11 (s, 1 H), 8.01 (d, 2 H, *J* = 8.0 Hz), 7.59 (dd, 1 H, *J* = 7.2 and 7.6 Hz),7.49 (m, 2 H), 6.23 (d, 1 H, *J* = 6.0 Hz), 6.06 (dd, 1 H, *J* = 5.2 and 5.6 Hz), 5.54 (dd, 1 H, *J* = 4.4 Hz), 5.47 (s, 1 H), 5.33 (d, 1 H, *J* = 2.8 Hz), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.27 (d, 1 H, *J* = 16.0 Hz), 3.09 (d, 1 H, *J* = 16.0 Hz), 3.07 (s, 3 H), 2.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.5, 165.0, 153.0, 151.7, 150.0, 142.4, 133.6, 133.0, 129.0, 128.9, 128.6, 128.1, 124.0, 88.5, 88.47, 87.8, 85.5, 81.4, 75.5, 53.2, 52.4, 39.8, 38.7, 20.6; LC-ESI-MS $(M + H)^+$calcd for $C_{26}H_{27}N_5O_{12}S$ 634.13; found 634.20.

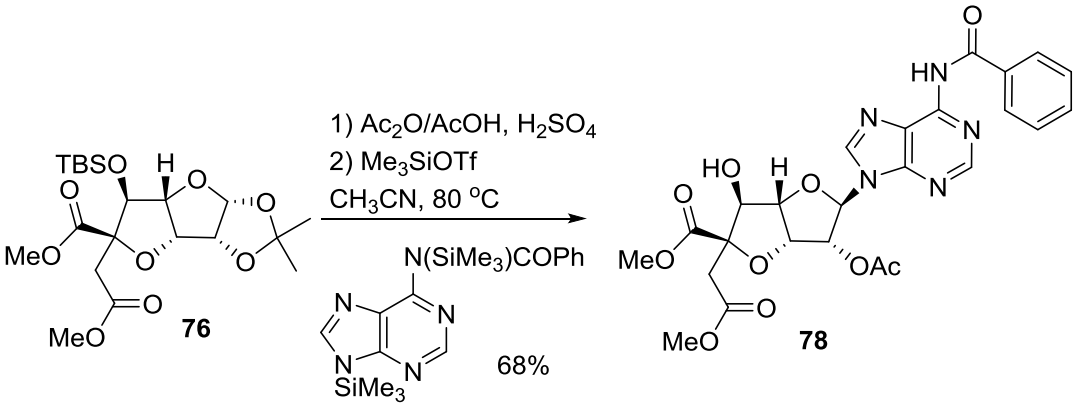
Methyl 2-((3a*R*,3b*R*,5*R*,6*S*,6a*R*,7a*R*)-6-((tert-butyldimethylsilyl)oxy)-5-(furan-2-yl)-2,2-dimethylhexahydrofuro[2',3':4,5]furo[2,3-*d*][1,3]dioxol-5-yl)acetate (75).



Alcohol **70** (1.0 g, 2.94 mmol) in dimethylformamide (10 mL) was added *tert*-butyldimethylsilyl chloride (0.66 g, 4.31 mmol, 1.5 equiv) and imidazole (0.47 g, 5.88 mmol, 2.0 equiv). The mixture was allowed to stir at room temperature for 16 hours. The resulting reaction was added 100 mL water. The mixture was extracted with ethyl acetate

(2 × 50 mL). The combined organic extract was washed sequentially with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and then chromatographed with 1:5 ethyl acetate/hexane as the eluent to afford **75** (1.22 g, 2.68 mmol, 91% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 1 H), 6.29-6.32 (m, 2 H), 5.85 (d, 1 H, *J* = 2.8 Hz), 4.94 (dd, 1 H, *J* = 4.4 and 6.4 Hz), 4.68 (dd, 1 H, *J* = 5.2 and 6.0 Hz), 4.59 (d, 1 H, *J* = 4.8 Hz), 4.48 (dd, 1 H, *J* = 2.8 and 4.4 Hz), 3.65 (s, 3 H), 3.15 (d, 1 H, *J* = 11.6 Hz), 3.00 (d, 1 H, *J* = 11.6 Hz), 1.70 (s, 3 H), 1.37 (s, 3 H), 0.79 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): 170.0, 153.9, 142.0, 114.3, 110.2, 108.7, 107.6, 89.2, 85.9, 81.1, 80.1, 79.2, 52.0, 41.3, 27.2, 26.4, 25.7, 25.7, 25.7, 17.9, -4.1, -4.9; LC-ESI-MS $(M + 1)^+$ calcd for $C_{22}H_{34}O_8Si$ 455.20; found 455.22.

methyl (2R,3S,3aS,5R,6R,6aR)-6-acetoxy-5-(6-benzamido-9H-purin-9-yl)-3-hydroxy-2-(2-methoxy-2-oxoethyl)hexahydrofuro[3,2-b]furan-2-carboxylate (78).



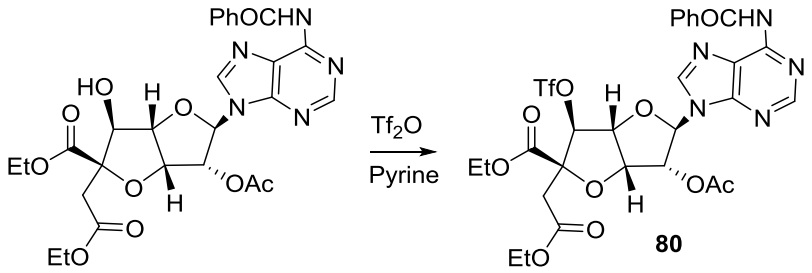
A solution of ester **76** (0.20 g, 0.45 mmol) in 5 mL 1:1 Acetic acid/Acetic anhydride at 0 °C was added a catalytic amount, about 0.5 µL, of sulfuric acid. The mixture was stirred at room temperature for 5 hours. The reaction was concentrated and then dissolved into 20 mL dichloromethane. The organic was washed sequentially with

saturated sodium bicarbonate aqueous solution, brine, dried over anhydrous sodium sulfate and concentrated to afford 0.18 g a mixture of anomeric acetates ($\alpha/\beta \sim 1{:}3$).

N^6-benzoylaminopurine (0.22 g, 0.90 mmol) in 5 ml acetonitrile was added *N*,*O*-bis(trimethylsilyl)acetamide (0.22 mL, 0.68 mmol) and the mixture was heated at 80 ºC for 15 minutes. A solution of above crude anomeric acetates in 1 mL acetonitrile and then trimethylsilyl trifluoromethanesulfonate (0.20 g, 0.90 mmol) were added. The resulting reaction was further stirred at 80 ºC for 90 minutes. The reaction mixture was cooled down and concentrated in *vacuo*. The residue obtained was dissolved into 20 mL dichloromethane. It was washed sequentially with saturated sodium bicarbonate aqueous solution, brine, dried over anhydrous sodium sulfate and concentrated in *vacuo*. Chromatography with 5% methanol/dichloromethane as eluent afforded nucleoside **77** (0.17 g, 0.23 mmol, 51% yield) as a white solid.

A solution of nucleoside **77** in 2 mL *N*,*N*-dimethylformamide was added a drop of acetic acid and 0.4 mL tetrabutylammonium fluoride (1 M solution in tetrahydrofuran). The mixture was stirred at room temperature for 12 hours. It was purified directly using Gilson eluting with 5% to 90% acetonitrile in water to afford nucleoside **78** (0.11 g 0.20 mmol, 85% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1 H), 8.86 (s, 1 H), 8.11 (d, 2 H, J = 7.5 Hz), 7.63-7.68 (m, 1 H), 6.36 (d, 1 H, J = 5.1 Hz), 5.87 (t, 1 H, J = 5.8 Hz), 5.40 (broad, 1 H), 5.30 (broad, 1 H), 4.59 (broad, 1 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 3.12 (d, 1 H, J = 15.8 Hz), 3.05 (d, 1 H, J = 15.8 Hz), 2.06 (s, 3 H). LC-ESI-MS $(M + H)^+$ calcd for $C_{25}H_{25}N_5O_{10}$ 556.51; found 556.53.

Ethyl (2R,3S,3aR,5R,6R,6aR)-6-acetoxy-5-(6-benzamido-9H-purin-9-yl)-2-(2-ethoxy-2-oxoethyl)-3-(((trifluoromethyl)sulfonyl)oxy)hexahydrofuro[3,2-b]furan-2-carboxylate (80).

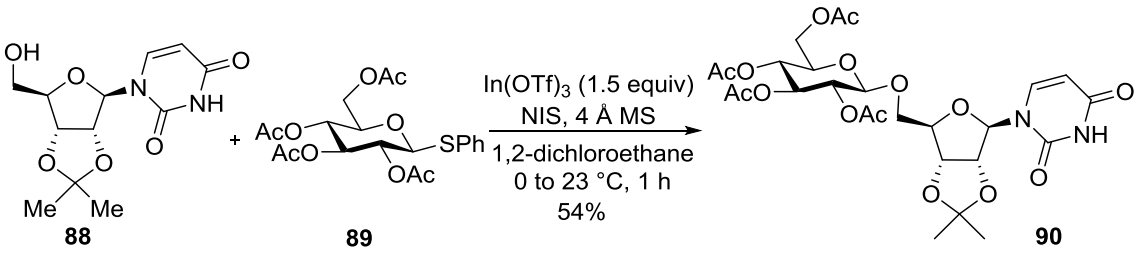


A solution of **78** (45 mg, 0.077 mmol) in 2 mL dichloromethane at -10 °C was added pyridine (12 uL 0.15 mmol) and trifluoromethanesulfonic anhydride (13 uL, 0.08 mmol). The reaction was allowed stirred at this temperature for 30 minutes before it was quenched with 2 mL saturated sodium bicarbonate aqueous solution. The aqueous was extracted with 2 × 10 mL dichloromethane. The combined organic was dried over Na_2SO_4 and concentrated. The residue was purified by prep TLC plate eluting with 2% methanol in dichloromethane to afford **80** (41 mg, 0.058 mmol, 75% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1 H), 8.12 (s, 1 H), 8.03 (d, 2 H, *J* = 5.6 Hz), 7.63 (t, 1 H, *J* = 6.0 Hz), 7.54 (t, 1 H, *J* = 6.0 Hz), 6.27 (d, 1 H, *J* = 4.8 Hz), 6.08 (dd, 1 H, *J* = 4.0 and 4.8 Hz), 5.71 (broad, 1 H), 5.65 (t, 1 H, *J* = 4.0 Hz), 5.37 (dd, 1 H, *J* = 1.2 and 3.6 Hz), 3.37-4.41 (m, 2 H), 4.23-4.30 (m, 2 H), 3.30 (d, 1 H, *J* = 13.2 Hz), 3.11(d, 1 H, *J* = 13.2 Hz), 2.00 (s, 3 H), 1.26-1.37 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.7, 168.8, 168.0, 164.9, 153.1, 151.9, 150.1, 142.4, 133.6, 133.2, 129.1, 128.1, 124.0, 119.8, 91.1, 88.1, 88.0, 87.8, 80.9, 75.2, 63.2, 61.6, 39.3, 20.6, 14.3, 14.1; LC-ESI-MS $(M + H)^+$ calcd for $C_{28}H_{28}F_3N_5O_{12}S$ 716.15; found 716.32.

5.3. Experimental Section for Chapter III

General Glycosylation Procedure. A 10 mL vial was charged with the nucleoside acceptor (0.10 mmol), indium triflate (84 mg, 0.15 mmol), activated 4 Å molecular sieves (150 mg), the glycosyl donor (0.15 mmol) and 1,2-dichloroethane (1 mL). The mixture was stirred at 0 °C or room temperature for 15 min. The reaction mixture was then treated with N-iodosuccinimide (34 mg, 0.15 mmol) and allowed to stir at 0 °C or room temperature for 45 min. The reaction mixture was filtered through a 0.45 μM PTFE syringe filter, and then rinsed with dichloromethane (2× 5 mL). The organic solution was washed with 10 mL of saturated aq sodium bisulfite, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by using a pre-packed silica gel column or preparative silica thin layer chromatography plate to afford the glycosylation product.

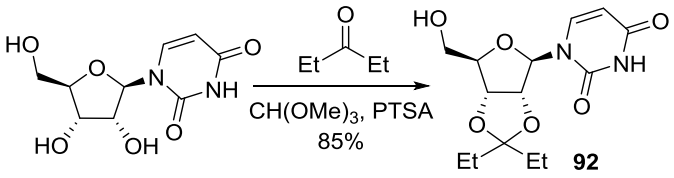
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(((3aR,4R,6R,6aR)-6-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (90).



By following the general procedure, donor **89** (66 mg, 0.15 mmol) was combined with acceptor **88** (28 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 3:2 hexane/ethylacetate as the eluant afforded **90** (33 mg, 54%) as a white solid, mp 122–142 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (br s, 1 H), 7.56 (d, 1 H, J = 6.4 Hz), 5.92 (d, 1 H, J = 2.0 Hz), 5.83 (d, 1

H, *J* = 6.4 Hz), 5.26 (d, 1 H, *J* = 7.6 Hz), 5.09 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 4.96 (dd, 1 H, *J* = 6.8 and 8.0 Hz), 4.78 (dd, 1 H, *J* = 2.0 and 4.8 Hz), 4.70 (dd, 1 H, *J* = 2.4 and 4.8 Hz), 4.56 (d, 1 H, *J* = 6.4 Hz), 4.42 (d, 1 H, *J* = 2.4 Hz), 4.32 (dd, 1 H, *J* = 3.6 and 10.0 Hz), 4.21 (dd, 1 H, *J* = 2.0 and 8.8 Hz), 4.15 (dd, 1 H, *J* = 1.6 and 10.0 Hz), 3.70–3.76 (m, 2 H), 2.13 (s, 3 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 1.60 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.4, 169.5, 164.0, 150.5, 141.8, 114.4, 102.3, 100.8, 93.1, 85.1, 84.9, 80.8, 72.4, 72.1, 71.3, 69.5, 68.4, 61.9, 27.2, 25.3, 20.8, 20.69, 20.67, 20.64; HR-ESI-MS $[M+H]^+$ calcd for $C_{26}H_{35}N_2O_{15}$ 615.2037; found 615.2029.

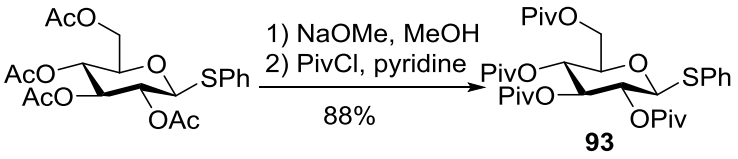
Acceptor 92 for Preparing 95, 102, 104, 118, and 120: 1-((3a*R*,4*R*,6*R*,6a*R*)-2,2-Diethyl-6-(hydroxymethyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (92).[92]



Acceptor **92** was prepared by following the literature method.[93] Trimethyl orthoformate (3.18 g, 30.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.38 g, 2.0 mmol) were added to a solution of uridine (2.44 g, 10.0 mmol) in 20 mL of 3-pentanone. The reaction was allowed to stir at room temperature for 2 h, and then was concentrated. A solution of the residue in 10 mL of dimethyl sulfoxide was chromatographed with a pre-packed C18 reverse phase column (120 g), eluting with 5% to 90% acetonitrile / water. The fractions containing product were combined and lyophilized to afford **92** (2.65 g, 85% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (broad, 1 H), 7.39 (d, 1 H, *J* = 6.4 Hz), 5.76 (d, 1 H, *J* = 6.4 Hz), 5.62 (d, 1 H, *J* = 2.0 Hz), 5.07 (dd, 1 H, *J* =

2.0 and 5.2 Hz), 4.99 (dd 1 H, *J* = 2.8 and 5.2 Hz), 4.33 (d, 1 H, *J* = 2.8 Hz), 3.94 (dd, 1 H, *J* = 2.0 and 9.6 Hz), 3.84 (dd, 1 H, *J* = 3.2, 9.6 Hz), 2.46 (br s, 1H), 1.81 (q, 2 H, *J* = 6.0 and 11.6 Hz), 1.65 (q, 2 H, *J* = 6.0 Hz), 1.01 (t, 3 H, *J* = 6.0), 0.91 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 Hz, DMSO) δ 163.4, 150.5, 142.2, 117.4, 101.9, 91.7, 86.9, 84.2, 81.1, 61.6, 29.2, 28.8, 8.4, 7.7; HR-ESI-MS $[M+H]^+$ calcd for $C_{14}H_{21}N_2O_6$ 313.1400; found 313.1390.

(2*S*,3*R*,4*S*,5*R*,6*R*)-2-(Phenylthio)-6-((pivaloyloxy)methyl)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (93).[94]



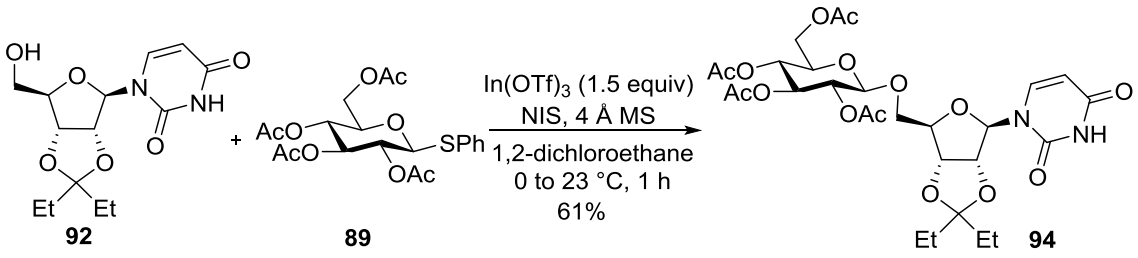
93

Sodium methoxide (122 mg, 2.27 mmol) was added to a solution of phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-*D*-glucopyranoside (2.5 g, 5.67 mmol) in methanol (50 mL). The reaction mixture was allowed to stir overnight, and then was neutralized with Dowex 50x8-100 acidic resin. The resin was filtered, and the filtrate was concentrated to afford the crude tetraol as a white residue, which was dried azeotropically with toluene (3 ×5 mL) and taken to the next step without further purification.

Pivaloyl chloride (7.5 mL, 56.7 mmol) was added by drops to a solution of the tetraol (5.67 mmol) and 4-dimethylaminopyridine (345 mg, 2.84 mmol) in pyridine (50 mL). The mixture was heated at reflux for 24 h, cooled to room temperature, and then quenched with methanol (10 mL). Concentration gave a residue that was dissolved in 150 mL of dichloromethane. The organic solution was washed sequentially with 2 N HCl (150 mL) and saturated aqueous sodium bicarbonate (3×150 mL). The organic layer was dried over sodium sulfate, concentrated, and then purified by flash chromatography,

eluting with 10% ethyl acetate in hexane, to afford the donor **93** (3.03 g, 88% over 2 steps) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.53 (m, 2 H), 7.29–7.34 (m, 3 H), 5.37 (dd, 1 H, *J* = 7.2 and 7.6 Hz), 5.11 (d, 1 H, *J* = 8.0 Hz), 5.05 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 4.75 (d, 1 H, *J* = 8.0 Hz), 4.27 (dd, 1 H, *J* = 1.6 and 10.0 Hz), 4.07 (dd, 1 H *J* = 4.8 and 9.6 Hz), 3.78 (m, 1 H), 1.24 (s, 9 H), 1.23 (s, 9 H), 1,17 (s, 9 H), 1.12 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 176.9, 176.3, 176.1, 132.7, 132.3, 128.9, 128.2, 86.4, 76.4, 73.3, 69.5, 67.6, 62.2, 38.8, 38.7, 38.6, 27.1, 27.1, 27.0; LC-ESI-MS $[M+H]^+$ calcd for $C_{32}H_{49}O_9S$, 609.31; found 609.32.

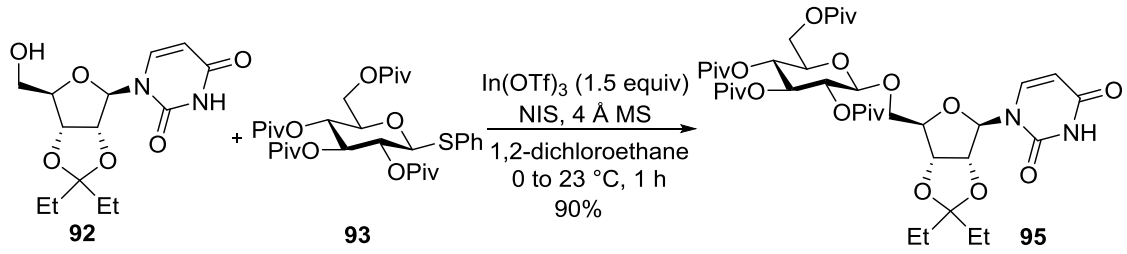
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-diethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (94).



By following the general procedure, donor **89** (66 mg, 0.15 mmol) was combined with acceptor **92** (31 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 3:2 hexane/ethyl acetate as the eluant afforded **94** (39 mg, 61%) as a white solid, mp 130–131 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (br s, 1 H), 7.54 (d, 1 H, *J* = 6.8 Hz), 5.94 (d, 1 H, *J* = 2.4 Hz), 5.82 (d, 1 H, *J* = 6.8 Hz), 5.26 (d, 1 H, *J* = 7.6 Hz), 5.10 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 4.97 (d, 1 H, *J* = 7.2 Hz), 4.79 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 4.71 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 4.55 (d, 1 H, *J* = 6.4 Hz), 4.44 (d, 1 H, *J* = 2.4 Hz), 4.32 (dd, 1 H, *J* = 3.6 and 10.0 Hz), 4.21

(dd, 1 H, *J* = 2.0 and 8.8 Hz), 4.15 (dd, 1 H, *J* = 1.6 and 10.0 Hz), 3.70–3.76 (m, 2 H), 2.13 (s, 3 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 1.81 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.63 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.01 (t, 3 H, *J* = 6.0 Hz), 0.90 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 170.4, 169.5, 169.5, 163.6, 150.7, 141.8, 118.9, 102.4, 100.9, 93.3, 85.4, 85.3, 81.2, 72.5, 72.2, 71.3, 69.7, 68.5, 61.9, 29.7, 29.6, 20.9, 20.8, 20.7, 20.7, 8.5, 8.0; HR-ESI-MS $[M+H]^+$ calcd for $C_{28}H_{39}N_2O_{15}$ 643.2350; found 643.2340.

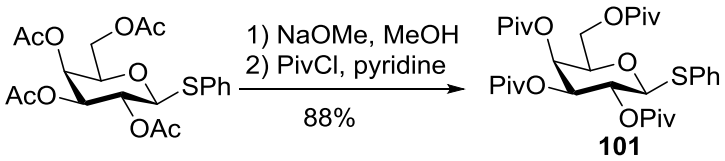
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-diethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (95).



By following the general procedure, donor **93** (91 mg, 0.15 mmol) was combined with acceptor **92** (31 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 65:35 hexane/ethyl acetate as the eluant afforded **95** (73.0 mg, 90%) as a white solid, mp 112–125 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (br s, 1 H), 7.57 (d, 1 H, *J* = 6.4 Hz), 5.97 (d, 1 H, *J* = 2.0 Hz), 5.85 (d, 1 H, *J* = 6.4 Hz), 5.36 (t, 1 H, *J* = 7.6 Hz), 5.10 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 4.96 (dd, 1 H, *J* = 6.8 and 7.6 Hz), 4.74 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 4.68 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 4.54 (d, 1 H, *J* = 6.4 Hz), 4.39 (dd, 1 H, *J* = 2.0 and 4.4 Hz), 4.22 (dd, 1 H, *J* =1.2 and

10.0 Hz), 4.18 (dd, 1 H, *J* = 2.0 and 8.4 Hz), 4.09 (dd, 1 H, *J* = 4.4 and 10.0 Hz), 3.73–3.76 (m, 1 H), 3.64 (dd, 1 H, *J* = 2.8 and 4.4 Hz), 1.79 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.58 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.23 (s, 9 H), 1.16 (s, 9 H), 1.15 (s, 9 H), 1.13 (s, 9 H), 0.99 (t, 3 H, *J* = 6.0 Hz), 0.86 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 177.3, 176.8, 176.5, 164.4, 150.4, 142.2, 118.9, 102.3, 100.9, 92.8, 85.2, 85.1, 80.8, 72.6, 71.9, 71.3, 69.2, 68.0, 61.9, 39.0, 38.8, 38.8, 38.8, 29.4, 29.3, 27.19, 27.16, 27.12, 27.10, 8.3, 7.9; HR-ESI-MS $[M+H]^+$ calcd for $C_{40}H_{63}N_2O_{15}$ 811.4228; found 811.4219.

(2*S*,3*R*,4*S*,5*S*,6*R*)-2-(Phenylthio)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (101).[95]

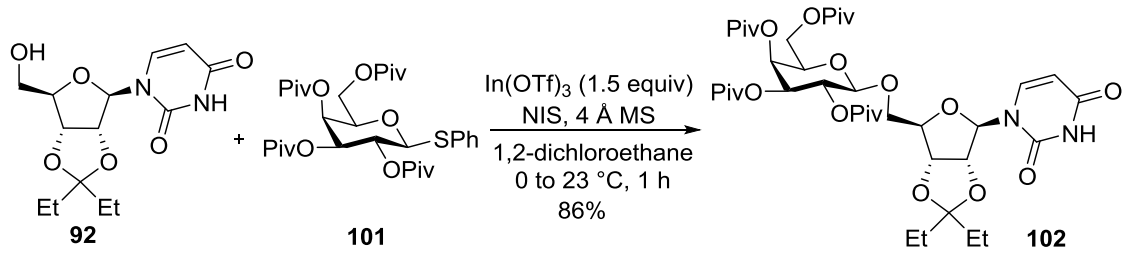


101

Donor **101** was prepared by following the procedure for **93** (83% yield overall), and was obtained as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52–7.54 (m, 2 H), 7.30–7.33 (m, 3 H), 5.42 (d, 1 H, *J* = 2.4 Hz), 5.22 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 5.13 (dd, 1 H, *J* = 2.4 and 8.0 Hz), 4.73 (d, 1 H, *J* = 8.0 Hz), 4.20 (dd, 1 H, *J* = 7.6 and 11.2 Hz), 4.01–4.05 (m, 2 H), 1.23 (s, 9 H), 1.20 (s, 9 H), 1,18 (s, 9 H), 1.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 177.4, 177.0, 176.6, 133.7, 129.0, 128.6, 86.1, 75.0, 72.4, 67.1, 66.8, 61.7, 27.3, 27.3, 27.2, 27.1; LC-ESI-MS $[M+H]^+$ calcd for $C_{32}H_{49}O_9S$ 609.31; found 609.30.

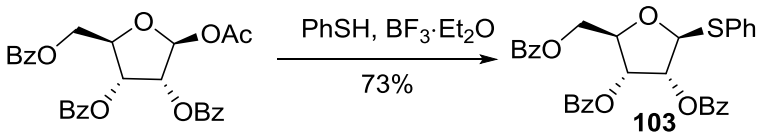
(2*R*,3*R*,4*S*,5*S*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-Dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2,2-diethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-

((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate (102).



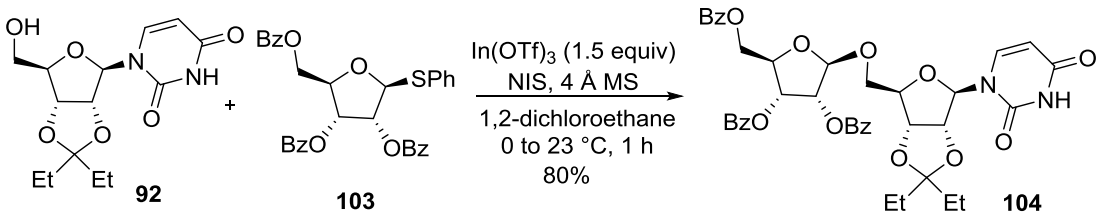
By following the general procedure, donor **101** (91 mg, 0.15 mmol) was combined with acceptor **92** (31 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 65:35 hexane/ethyl acetate as the eluant afforded **102** (70 mg, 87%) as a white solid. An analogous reaction starting with 200 mg of **92**, and with purification by flash chromatography on a prepacked silica gel column (40 g) eluting with 3:1 hexane/ethyl acetate, provided 425 mg (82%) of **102**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (br s, 1 H), 7.54 (d, 1 H, *J* = 6.4 Hz), 6.01 (d, 1 H, *J* = 2.0 Hz), 5.78 (dd, 1 H, *J* = 2.0 and 6.8 Hz), 5.41 (d, 1 H, *J* = 1.6 Hz), 5.13–5.19 (m, 2 H), 4.74 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 4.72 (dd, 1 H, *J* = 2.8 and 5.2 Hz), 4.54 (d, 1 H, *J* = 5.6 Hz), 4.36–4.38 (m, 1 H), 4.20 (dd, 1 H, *J* = 1.6 and 8.0 Hz), 4.18 (dd, 1 H, *J* = 4.8 and 8.4 Hz), 3.97–4.04 (m, 2 H), 3.65 (dd, 1 H, *J* =2.8 and 8.4 Hz), 1.79 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.58 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.28 (s, 9 H), 1.18 (s, 9 H), 1.16 (s, 9 H), 1.12 (s, 9 H), 0.99 (t, 3 H, *J* = 6.0), 0.86 (t, 3 H, *J* = 6.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 177.3, 177.0, 163.6, 150.5, 141.7, 118.9, 102.8, 101.2, 92.3, 85.97, 84.95, 80.7, 71.3, 70.7, 69.3, 69.0, 66.7, 61.1, 39.2, 38.91, 38.88, 38.82, 29.43, 29.41, 27.18, 27.28, 27.20, 8.4, 8.0; HR-ESI-MS $[M+H]^+$ calcd for $C_{40}H_{63}N_2O_{15}$ 811.4228; found 811.4213.

(2*R*,3*R*,4*R*,5*S*)-2-((Benzoyloxy)methyl)-5-(phenylthio)tetrahydrofuran-3,4-diyl dibenzoate (103).[96]



Thiophenol (0.5 mL, 4.88 mmol) was added to a stirred solution of commercial 1-*O*-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (1.01 g, 2.00 mmol) in dichloromethane (20 mL) at 0 °C. Boron trifluoride etherate (0.46 mL, 3.66 mmol) was added dropwise. After stirring at 0 °C for 3 h, the reaction was quenched by the addition of triethylamine (0.6 mL, 4.30 mmol), and then concentrated. The residue was purified by flash chromatography, eluting with 20% ethyl acetate in hexane, to afford donor **15** (815 mg, 73%) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08–8.10 (m, 2 H), 8.02–8.03 (m, 2 H), 7.93–7.94 (m, 2 H), 7.54–7.61 (m, 5 H), 7.41–7.46 (m, 4 H), 7.36–7.39 (m, 2 H), 7.24–7.31 (m, 3 H), 5.77 (dd, 1 H, *J* = 4.0 Hz), 5.72 (dd, 1 H, *J* = 4.0 Hz), 5.65 (d, 1 H, *J* = 4.0 Hz), 4.66–4.72 (m, 2 H), 4.55 (dd, 1 H, *J* = 3.2 and 5.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 165.5, 165.2, 133.9, 133.7, 133.6, 133.3, 131.4, 130.02, 129.99, 129.9, 129.7, 129.2, 129.1, 128.6, 128.6, 88.3, 80.6, 74.8, 72.5, 64.4; LC-ESI-MS $[M+H]^+$ calcd for $C_{32}H_{27}O_7S$ 555.15; found 555.12.

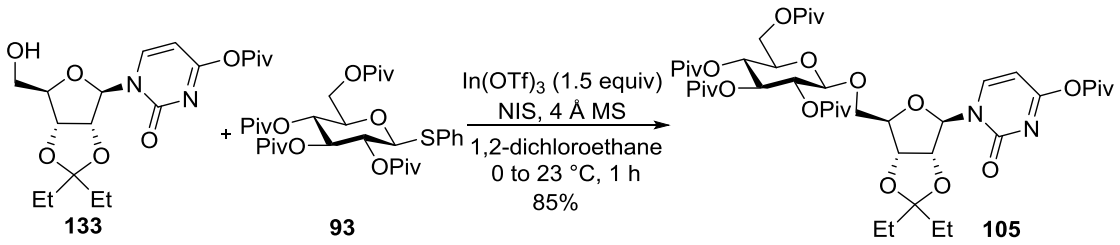
(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)tetrahydrofuran-3,4-diyl dibenzoate (104).



By following the general procedure, donor **103** (83 mg, 0.15 mmol) was combined with acceptor **92** (31 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 7:3 hexane/etyl acetate as the eluant afforded **104** (61 mg, 80%) as a white solid, mp 82–94 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1 H), 8.00–8.04 (m, 4 H), 7.90–7.92 (m, 2 H), 7.58–7.61 (m, 2 H), 7.52–7.55 (m, 2 H), 7.33–7.45 (m, 6 H), 5.80–5.85 (m, 3 H), 5.72 (d, 1 H, *J* = 3.6 Hz), 5.31 (s, 1 H), 4.90 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 4.83 (dd, 1 H, *J* = 3.2 and 5.2 Hz), 4.77 (dd, 1 H, *J* = 4.4 and 8.0 Hz), 4.66 (dd, 1 H, *J* = 3.6 and 9.6 Hz), 4.59 (dd, 1 H, *J* = 4.4 and 9.6 Hz), 4.32–4.59 (m, 1 H), 4.11 (dd, *J* = 2.8 and 9.2 Hz), 3.73 (dd, 1 H, *J* = 4.0 and 8.8 Hz), 1.77 (q, 2 H, *J* = 6.0), 1.61 (q, 2 H, *J* = 6.0 Hz), 0.98 (t, 3 H, *J* = 6.0 Hz), 0.88 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 165.4, 165.3, 163.7, 150.3, 141.9, 133.7, 133.6, 133.3, 129.89, 129.85, 129.6, 129.1, 128.9, 128.6, 128.5, 119.1, 106.1, 103.0, 93.7, 85.8, 84.8, 80.9, 79.1, 75.4, 72.2, 68.4, 64.8, 29.5, 29.3, 8.5, 7.9; HR-ESI-MS $[M+H]^+$ calcd for $C_{40}H_{41}N_2O_{13}$ 757.2609; found 757.2592.

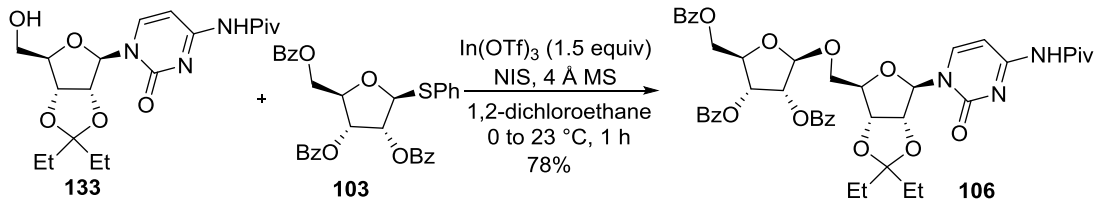
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-2,2-Diethyl-6-(2-oxo-4-pivalamidopyrimidin-1(2*H*)-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate)

(105).



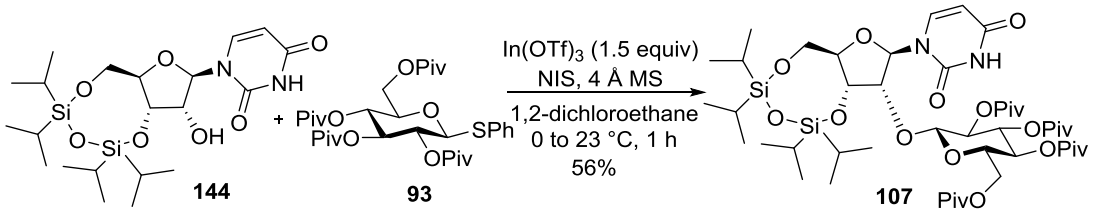
According to the general procedure, donor **93** (91.3 mg, 0.15 mmol 1.5 equiv) was reacted with acceptor **133** (40 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 94:6 dichloromethane/methanol as the eluant afforded **105** (76 mg, 85%) as a white solid, mp 113–126 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1 H, *J* = 6.0 Hz), 7.66 (d, 1 H, *J* = 6.0 Hz), 5.93 (d, 1 H, *J* = 2.0 Hz), 5.34 (d, 1 H, *J* = 7.6 Hz), 5.11 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 4.81–4.84 (m, 2 H), 4.67 (dd, 1 H, *J* = 1.6 and 4.8 Hz), 4.61 (d, 1 H, *J* = 2.0 Hz), 4.52 (d, 1 H, *J* = 6.4 Hz), 4.21–4.25 (m, 3 H), 3.75–3.79 (m, 1 H), 3.65 (dd, 1 H, *J* = 2.4 and 8.4 Hz), 3.52 (br s, 1 H), 1.79 (q, 2 H, *J* = 6.0 Hz), 1.59 (q, 2 H, *J* = 6.0 Hz), 1.36 (s, 9 H), 1.25 (s, 9 H), 1.18 (s, 9 H), 1.14 (s, 9 H), 1.11 (s, 9 H), 1.00 (t, 3 H, *J* = 6.0 Hz), 0.88 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 177.3, 177.1, 176.9, 176.35, 161.43, 148.9, 118.4, 100.8, 96.1, 96.0, 87.3, 86.3, 81.7, 73.0, 71.8, 71.0, 69.1, 68.3, 62.1, 41.3, 39.0, 38.90, 38.88, 29.4, 29.2, 27.30, 27.28, 27.25, 27.19, 27.18, 27.13, 27.11, 26.6, 8.4, 7.8; HR-ESI-MS $[M+H]^+$ calcd for $C_{45}H_{72}N_3O_{15}$ 894.4963; found 894.4951.

(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(((3a*R*,4*R*,6*R*,6a*R*)-2,2-diethyl-6-(2-oxo-4-pivalamidopyrimidin-1(2*H*)-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)tetrahydrofuran-3,4-diyl dibenzoate (106).



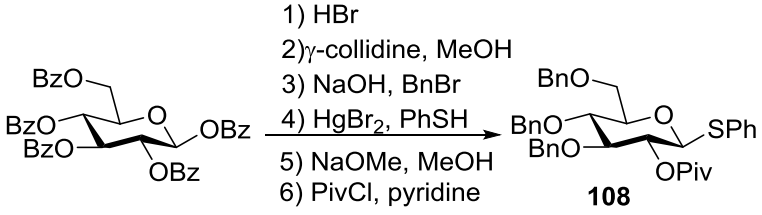
By following the general procedure, donor **103** (83 mg, 0.15 mmol) was combined with acceptor **133** (40 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 94:6 dichlorokethane/methanol as the eluant afforded the **106** (66 mg, 78%) as a white solid, mp 56–80 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–8.07 (m, 2 H), 8.01–8.03 (m, 2 H), 7.94–7.96 (m, 2 H), 7.70 (br s, 1 H), 7.54–7.61 (m, 3 H), 7.36–7.45 (m, 6 H), 5.83 (br s, 1 H), 5.78 (dd, 1 H, *J* = 4.0 and 5.2 Hz), 5.67 (d, 1 H, *J* = 3.6 Hz), 5.30 (s, 1 H), 4.99 (d, 1 H, *J* = 5.2 Hz), 4.78 (dd, 1 H, *J* = 3.2 and 4.4 Hz), 4.73 (dd, 1 H, *J* = 3.2 and 9.2 Hz), 4.60 (dd, 1 H, *J* = 4.4 and 9.6 Hz), 4.49 (m, 1 H), 4.12 (dd, 1 H, *J* = 2.4 and 9.2 Hz), 3.76 (dd, 1 H, *J* = 5.2 and 9.2 Hz), 1.78 (q, 2 H, *J* = 6.0 Hz), 1.62 (q, 2 H, *J* = 6.0 Hz), 1.31 (s, 9 H), 0.99 (t, 3 H, *J* = 6.0 Hz), 0.89 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 165.6, 165.5, 162.2, 148.1, 133.8, 133.7, 133.5, 130.02, 129.97, 129.9, 129.7, 129.2, 129.0, 128.7, 128.6, 128.62, 128.60, 119.0, 106.4, 96.5, 87.5, 85.7, 81.3, 79.4, 75.4, 72.2, 68.9, 64.7, 41.1, 29.6, 29.3, 26.7, 8.5, 7.9; HR-ESI-MS $[M+H]^+$ calcd for $C_{45}H_{50}N_3O_{13}$ 840.3344; found 840.3327.

(2*S*,3*R*,4*S*,5*R*,6*R*)-2-(((6a*R*,8*R*,9*R*,9a*R*)-8-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl)oxy)-6-((pivaloyloxy)methyl)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (107).



By following the general procedure, donor **93** (121.7 mg, 0.20 mmol, 2.0 equiv) was combined with acceptor **144** (49 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 4:1 hexane/ethyl acetate as the eluant afforded **107** (55 mg, 56%) as a white solid, mp 108–125 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1 H); 7.87 (d, *J* = 8.1 Hz, 1 H), 6.10 (s, 1 H), 5.66 (dd, 1 H, *J* = 1.5 and 8.1 Hz), 5.29 (t, 1 H, *J* = 8.9 Hz), 5.09–5.17 (m, 2 H), 4.21–4.26 (m, 3 H), 4.09 (d, 1 H, *J* = 9.2 Hz), 4.02 (dd, 1 H, *J* = 5.8 and 12.3 Hz), 3.92 (dd, 1 H, *J* = 1.5 and 13.7 Hz), 3.81 (dd, 1 H, *J* = 4.9 and 10.0 Hz), 0.83–1.17 (m, 64 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 177.3, 176.6, 176.4, 163.7, 149.8, 140.2, 101.6, 100.8, 88.8, 81.7, 81.5, 72.9, 72.4, 71.4, 68.4, 68.2, 62.2, 59.4, 38.93, 38.89, 38.85, 38.76, 27.4, 27.3, 27.2, 27.1, 17.63, 17.55, 17.5, 17.4, 17.2, 17.1, 17.0, 13.4, 13.0, 12.9; LC-ESI-MS $[M+H]^+$ calcd for $C_{47}H_{81}N_2O_{16}Si_2$ 985.5125; Found: 985.5119.

(2*S*,3*R*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-(phenylthio)tetrahydro-2*H*-pyran-3-yl pivalate (108).[97,98]



A 33% hydrobromic acid solution in acetic acid (3.18 mL, 53.1 mmol) was added by drops to a stirred solution of α-D-glucopyranose penta-benzoate (6.20 g, 8.85 mmol)

in 50 mL of dry dichloromethane. The reaction mixture was allowed to stir under argon for 16 h at room temperature, and then was diluted with 100 mL of dichloromethane. The organic solution was washed sequentially with 100 mL of water, saturated aqueous sodium bicarbonate, and water. The organic phase was dried over magnesium sulfate and concentrated, and the resulting residue was dissolved in 50 mL nitromethane. Activated molecular sieves (4 Å, 1.50 g) were added, and the resulting mixture was stirred under argon for 1 h. The flask was then covered with foil, and treated sequentially with γ-collidine (1.50 mL, 11.36 mmol), dry methanol (0.34 mL, 8.9 mmol), and *tert*-butylammonium bromide (5.0 mmol, 1.62 g). After 16 h of stirring, triethylamine (0.4 mL) was added, the solution was filtered, and the filtrate was washed with 100 mL of saturated aqueous sodium bicarbonate. The organic layer was separated, and the aqueous layer was back extracted with 2 × 50 mL of dichloromethane. The combined organic solution was washed with water, dried over magnesium sulfate, and then concentrated. The product was sequentially debenzoylated and benzylated by using the reported procedure.[99] The product was purified by column chromatography on silica gel, eluting with 20-40% ethyl acetate / hexane, to afford the known orthoester (3.57 g, 6.28 mmol, 71% yield) as a light yellow gel.

The above orthoester (1.2 g, 2.11 mmol) was stirred with activated molecular sieves (4 Å, 500 mg) and acetonitrile (10 mL) under an argon atmosphere for 1 h. Thiophenol (2.35 g, 21.3 mmol) and mercury(II) bromide (0.076 g, 0.211 mmol) were added, and the mixture was heated at reflux for 2.5 h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was dissolved in dichloromethane (20 mL). The organic solution was washed sequentially with 1% aq sodium hydroxide (30 mL) and

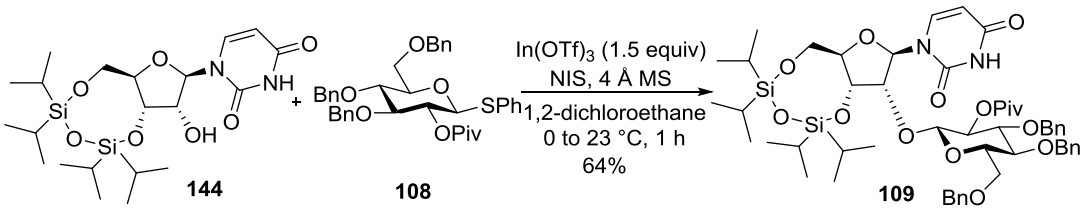
water (30 mL), dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in hexane, to afford the thioglycoside (976 mg, 71% yield) as white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–8.05 (m, 2 H), 7.61–7.80 (m, 1H), 7.44–7.50 (m, 4 H), 7.19–7.36 (m, 13 H), 7.11–7.14 (m, 5 H), 5.29 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 4.82 (d, 1 H, *J* = 9.2 Hz), 4.79 (d, 1 H *J* = 8.4 Hz), 4.73 (d, 1 H, *J* = 8.8 Hz), 4.64 (d, 1 H, *J* = 8.4 Hz), 4.56–4.61 (m, 3 H), 3.82–3.87 (m, 2 H), 3.73–3.78 (m, 2 H), 3.61–3.64 (m, 1 H, 1.56 (br s, 1 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 165.4, 138.4, 138.1, 137.8, 133.4, 133.1, 132.7, 130.1, 130.0, 129.0, 128.62, 128.60, 128.5, 128.4, 128.19, 128.16, 127.9, 127.8, 127.7, 86.3, 84.5, 79.7, 76.2, 75.2, 73.7, 72.6, 69.2; LC-ESI-MS $[M+H]^+$ calcd for $C_{40}H_{39}O_6S$ 647.25; found 646.98.

Sodium methoxide (7.5 mg, 0.14 mmol) was added to a solution of the thioglycoside (900 mg, 1.39 mmol) in methanol (15 mL), and the reaction mixture was allowed to stir for 3 h. The solution was neutralized with Dowex 50x8-100 acidic resin, the resin was filtered, and the filtrate was concentrated. The residue was dried azeotropically with toluene (2 ×5 mL) and taken to the next step without further purification.

Pivaloyl chloride (0.20 mL, 1.50 mmol) was added by drops to a solution of the crude carbinol (1.39 mmol) and 4-dimethylaminopyridine (168 mg, 1.39 mmol) in pyridine (10 mL). The mixture was heated at 60 °C for 24 h, and then cooled to room temperature and quenched with methanol (1 mL). After concentration, the residue was dissolved in 20 mL of dichloromethane, and the organic solution was washed sequentially with 2 N HCl (10 mL) and saturated aqueous sodium bicarbonate (2×10 mL). The organic layer was dried over sodium sulfate, concentrated, and purified by flash

chromatography, eluting with 10% ethyl acetate in hexane, to afford the thioglycoside donor **108** (705 mg, 81% over 2 steps) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.53 (m, 2 H), 7.21–7.31 (m, 16 H), 7.16–7.18 (m, 2 H), 5.10 (t, 1 H, *J* = 9.8 Hz), 4.75–4.78 (m, 2 H), 4.61–4.70 (m, 2 H), 4.53–4.58 (m, 2 H), 3.80 (dd, 1 H, *J* = 1.5 and 11.0 Hz), 3.66–3.75 (m, 2 H), 3.55–3.58 (m, 1 H), 1.24 (s, 9 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 176.7, 138.3, 138.1, 138.0, 133.5, 132.3, 128.9, 128.5, 128.4, 128.0, 127.9, 127.8, 127.75, 127.71, 127.6, 127.4, 86.7, 84.8, 79.5, 77.8, 75.3, 75.11; 73.6, 71.7, 69.1, 38.9, 27.3; LC-ESI-MS $[M+H]^+$ calcd for $C_{38}H_{43}O_6S$ 627.28; found 627.00.

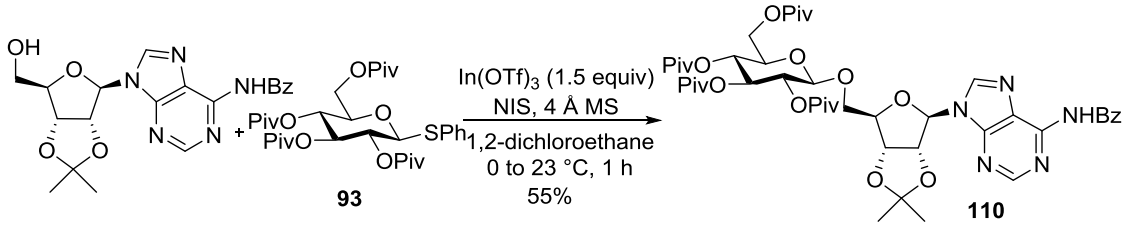
(2*S*,3*R*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-(((6a*R*,8*R*,9*R*,9a*R*)-8-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-f][1,3,5,2,4]trioxadisilocin-9-yl)oxy)tetrahydro-2*H*-pyran-3-yl pivalate (109).



By following the general procedure, donor **108** (125 mg, 0.20 mmol, 2.0 equiv) was combined with acceptor **144** (see SI, 49 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 9:1 hexane/ethyl acetate as the eluant afforded **109** (65 mg, 64%) as a white solid, mp 71–94 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 1 H), 7.78 (d, 1 H, *J* = 8.2 Hz), 7.26–7.30 (m, 13 H), 7.16–7.18 (m, 2 H), 5.93 (s, 1 H), 5.61 (d, 1 H, *J* = 8.1 Hz), 5.30 (d, 1 H, *J* = 1.2 Hz), 5.17 (t, 1 H, *J* = 8.0 Hz), 5.02 (d, 1 H, *J* = 7.9 Hz), 4.78 (d, 1 H, *J* = 11.2 Hz),

4.73 (d, 1 H, *J* = 11.1 Hz), 4.67 (d, 1 H, *J* = 11.2 Hz), 4.62 (d, 1 H, *J* = 11.2 Hz), 4.55 (d, 1 H, *J* = 10.7 Hz), 4.54 (d, 1 H, *J* = 10.8 Hz), 4.37 (d, 1 H, *J* = 4.2 Hz), 4.28 (dd, 1 H, *J* = 3.6 and 5.9 Hz), 4.21 (d, 1 H, *J* = 13.5 Hz), 4.07–4.15 (m, 1 H), 3.91 (d, 1 H, *J* = 13.6 Hz), 3.73–3.79 (m, 2 H), 3.66 (t, 1 H, *J* = 9.2 Hz), 3.55–3.57 (m, 1 H), 0.83–1.27 (m, 37 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.7, 163.2, 149.4, 140.7, 138.5, 138.3, 138.1, 128.6, 128.5, 128.4, 128.1, 128.0, 127.7, 127.4, 101.4, 100.4, 90.0, 83.7, 81.3, 79.5, 78.0, 75.4, 75.0, 74.9, 73.5, 73.1, 68.9, 68.8, 59.5, 38.9, 29.8, 27.4, 17.6, 17.6, 17.5, 17.43, 17.37, 17.2, 17.13, 17.05, 13.5, 13.3, 13.0, 12.8; LC-ESI-MS $[M+H]^+$ calcd for $C_{53}H_{75}N_2O_{13}Si_2$ 1003.4807; found 1003.4821.

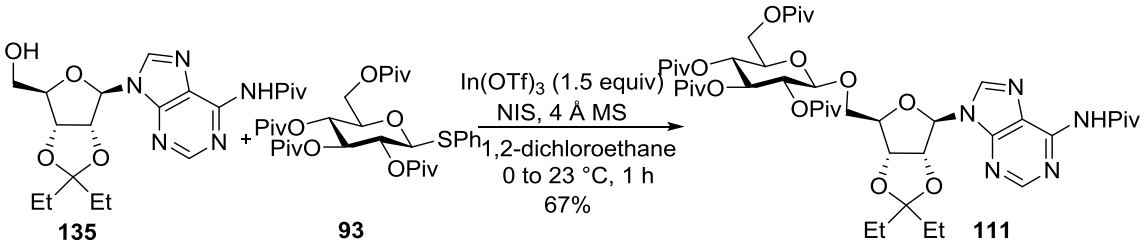
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Benzamido-9H-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (110).



By following the general procedure, donor **93** (92 mg, 0.15 mmol) was combined with commercial N^6-benzoyl-2',3'-*O*-isopropylideneadenosine (49 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After work-up, purification by thin layer chromatography with 93:7 dichloromethane/methanol as the eluant afforded **110** (50 mg, 55%) as a white solid, mp 88–122 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1 H), 8.61 (s, 1 H), 8.17 (d, 2 H, *J* = 6.0 Hz), 7.65 (dd, 1 H, *J* = 5.6 and 6.0 Hz), 7.57 (dd, 1 H, *J* =

5.6 and 6.4 Hz), 6.33 (d, 1 H, *J* = 2.0 Hz), 5.26–5.31 (m, 2 H), 5.21 (dd, 1 H, *J* = 7.6 Hz), 4.81 (dd, 1 H, *J* = 1.2 and 4.8 Hz), 4.65–4.68 (m, 2 H), 4.48 (d, 1 H, *J* = 7.2 Hz), 4.23 (dd, 1 H, *J* = 1.2 and 8.0 Hz), 4.15 (dd, 1 H, *J* = 4.8 and 9.6 Hz), 3.70–3.74 (m, 1 H), 3.63 (dd, 1 H, *J* =2.0 and 8.4 Hz), 1.68 (s, 3 H), 1.41 (s, 3 H), 1.22 (s, 9 H), 1.17 (s, 9 H), 1.10 (s, 9 H), 1.06 (s, 9 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 178.3, 177.3, 176.7, 176.5, 165.3, 151.8, 151.3, 149.0, 142.8, 133.3, 133.0, 129.0, 128.7, 122.4, 114.4, 100.5, 93.0, 86.0, 85.4, 81.9, 77.5, 72.9, 71.9, 71.1, 69.1, 68.1, 62.1, 39.0, 38.94, 38.86, 38.83, 27.3, 27.31, 27.29, 27.28, 27.21, 25.5; HR-ESI-MS $[M+H]^+$ calcd for $C_{46}H_{64}N_5O_{14}$ 910.4450; found 910.4433.

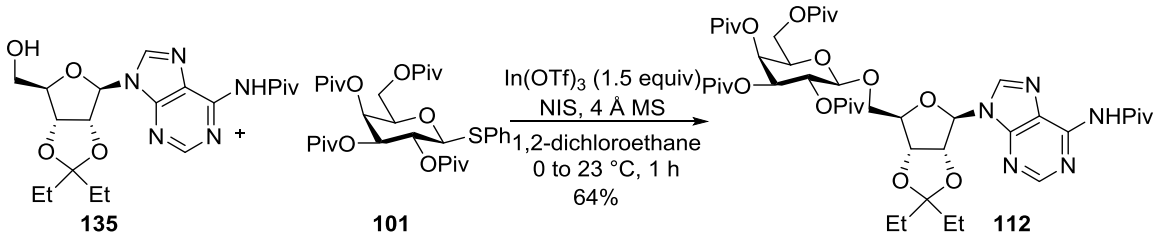
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-2,2-Diethyl-6-(6-pivalamido-9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (111).



By following the general procedure, donor **93** (91 mg, 0.15 mmol) was combined with acceptor **135** (42 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 93:7 dichloromethane/methanol as the eluant afforded **111** (62 mg, 67%) as a white solid, mp 75–89 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1 H), 8.68 (s, 1 H), 6.34 (d, 1 H, *J* = 1.2 Hz), 5.27–5.30 (m, 2 H), 5.13 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 4.82 (d, 1 H, *J* = 4.8 Hz),

4.69 (dd, 1 H, *J* = 6.4 and 7.6 Hz), 4.66 (s, 1 H), 4.45 (d, 1 H, *J* = 6.4 Hz), 4.17–4.22 (m, 2 H), 4.10 (dd, 1 H, *J* = 5.2 and 10.0 Hz), 3.69–3.72 (m, 1 H), 3.62 (dd, 1 H, *J* = 2.4 and 8.4 Hz), 1.87 (q, 2 H, *J* = 6.0 Hz), 1.66 (q, 2 H, *J* = 6.0 Hz), 1.45 (br s, 1 H), 1.22 (s, 9 H), 1.18 (s, 9 H), 1.17 (s, 9 H), 1.03 (s, 18 H), 1.06 (t, 3 H, *J* = 6.0 Hz), 0.92 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 177.3, 176.8, 176.7, 151.8, 150.7, 148.4, 143.1, 121.7, 118.9, 100.6, 92.9, 86.5, 85.5, 82.1, 72.9, 71.9, 71.1, 69.3, 68.3, 62.5, 39.04, 38.95, 38.86, 29.6, 29.4, 27.29, 27.25, 27.23, 27.20, 8.5, 7.9; HR-ESI-MS $[M+H]^+$ calcd for $C_{46}H_{72}N_5O_{14}$ 918.5076; found 918.5059.

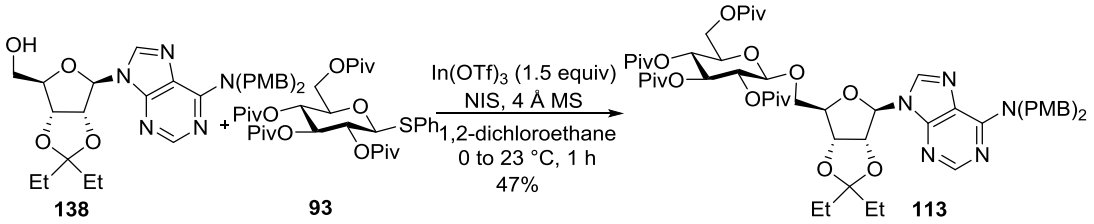
(2*R*,3*R*,4*S*,5*S*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-2,2-Diethyl-6-(6-pivalamido-9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (112).



By following the general procedure, donor **101** (92 mg, 0.15 mmol) was combined with acceptor **135** (42 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 97:3 dichloromethane/methanol as the eluant afforded **112** (59 mg, 64%) as a white solid, 86–121 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1 H), 8.56 (br s, 1 H), 8.32 (s, 1 H), 6.27 (d, 1 H, *J* = 2.0 Hz), 5.41 (d, 1 H, *J* = 2.4 Hz), 5.28 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 5.23 (dd, 1 H, *J* = 6.4 and 8.4 Hz), 5.11 (dd, 1 H, *J* = 2.4 and 8.4 Hz), 4.93 (dd, 1 H, *J* = 2.0

and 4.8 Hz), 4.51–4.52 (m, 2 H), 4.15 (dd, 1 H, *J* = 5.2 and 8.8 Hz), 4.11 (dd, 1 H, *J* = 2.4 and 8.4 Hz), 4.02 (dd, 1 H, *J* = 4.8 and 8.8 Hz), 3.95 (app t, 1 H, *J* = 5.2 Hz), 3.68 (dd, 1 H, *J* = 4.0 and 8.4 Hz), 1.85 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.64 (q, 2 H, *J* = 6.0 Hz), 1.42 (s, 9 H), 1.30 (s, 9 H), 1.28 (s, 9 H), 1.12 (s, 9 H), 1.21 (s, 9 H), 1.05 (t, 3 H, *J* = 6.0 Hz), 0.90 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 177.3, 177.0, 176.9, 175.7, 153.0, 151.3, 149.8, 142.0, 123.1, 119.0, 101.2, 91.0, 85.5, 85.0, 81.8, 71.2, 70.8, 69.5, 68.8, 66.7, 61.1, 40.7, 39.2, 38.9, 38.8, 29.5, 29.4, 27.5, 27.3, 27.20, 27.17, 27.14, 8.5, 8.0; HR-ESI-MS $[M+H]^+$ calcd for $C_{46}H_{72}N_5O_{14}$, 918.5076; found 918.5058.

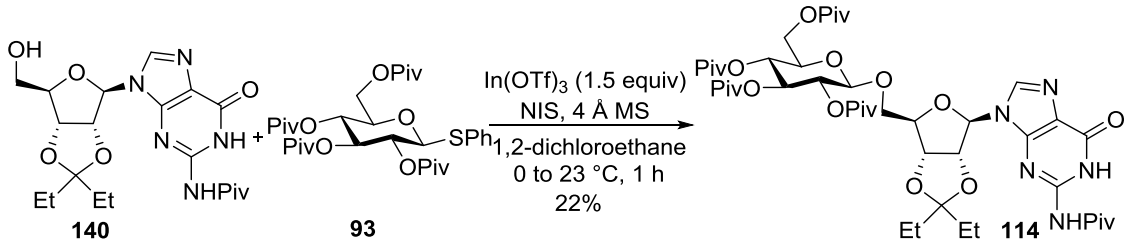
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(Bis(4-methoxybenzyl)amino)-9*H*-purin-9-yl)-2,2-diethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (113).



By following the general procedure, donor **93** (92 mg, 0.15 mmol) was reacted with acceptor **138** (58 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 95:5 dichloromethane/methanol as the eluant afforded **113** (51 mg, 47%) as a white solid, mp 58–91 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.95 (s, 1 H), 7.23 (d, 4 H, *J* = 6.8 Hz), 6.87 (d, 4 H, *J* = 6.8 Hz), 6.19 (d, 1 H, *J* = 2.0 Hz), 5.35 (dd,1 H, *J* = 2.0 and 5.2 Hz), 5.31 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 5.12 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 5.04 (dd, 1 H, *J* = 6.4 and 7.8 Hz), 4.96 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 4.52 (d, 1 H, *J* = 6.4 Hz), 4.46 (m,

1 H), 4.20 (d, 1 H, *J* = 8.8 Hz), 4.12 (dd, 1 H, *J* = 3.2 and 8.4 Hz), 4.04 (dd, 1 H, *J* = 4.4 and 9.6 Hz), 3.82 (s, 6 H), 3.73 (dd, 1 H, *J* = 4.8 and 8.4 Hz), 3.68 (dd, 1 H, *J* = 2.8 and 8.0 Hz), 1.85 (q, 2 H, *J* = 6.0 Hz), 1.65 (q, 2 H, *J* = 6.0 Hz), 1.21 (s, 9 H), 1.18 (s, 9 H), 1.12 (s, 9 H), 1.09 (s, 9 H), 1.05 (t, 3 H, *J* = 6.0 Hz), 0.91 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 177.3, 176.7, 176.5, 159.1, 155.0, 152.9, 150.7, 137.7, 129.4, 120.0, 118.9, 114.1, 101.1, 90.7, 85.5, 84.7, 81.9, 72.6, 72.2, 71.2, 69.6, 68.0, 61.9, 55.4, 29.6, 29.4, 27.3, 27.24, 27.19, 27.13, 8.5, 8.0; HR-ESI-MS $[M+H]^+$ calcd for $C_{57}H_{80}N_5O_{15}$ 1074.5651; found 1074.5646.

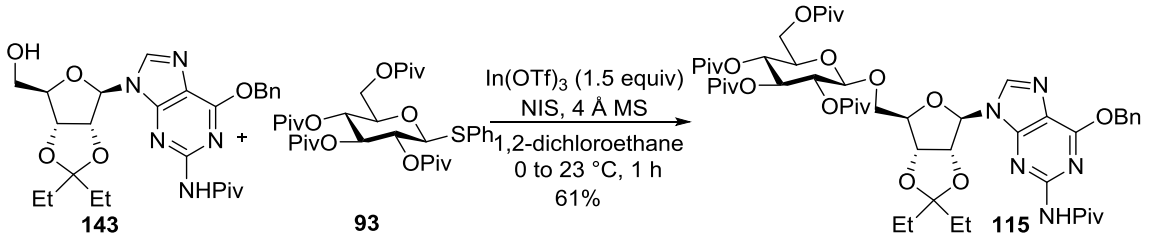
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-2,2-Diethyl-6-(6-hydroxy-2-pivalamido-9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (114).



According to the general procedure, donor **93** (92 mg, 0.15 mmol) was reacted with acceptor **140** (44 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 92:8 dichloromethane/methanol as the eluant afforded **114** (21 mg, 22%) as a white solid, 65–-89 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 8.61 (s, 1 H), 8.00 (s, 1 H), 8.17 (d, 2 H, *J* = 6.0 Hz), 6.01 (d, 1 H, *J* = 2.4 Hz), 5.36 (dd, 1 H, *J* = 7.6 Hz), 5.17 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 5.10 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 5.02 (dd, 1 H, *J* = 6.8 and 7.2 Hz), 4.85

(dd, 1 H, *J* = 2.4 and 5.2 Hz), 4.52 (d, 1 H, *J* = 6.4 Hz), 4.41 (m, 1 H), 4.27 (d, 1 H, *J* = 9.2 Hz), 4.06 (dd, 1 H, *J* = 2.8 and 8.4 Hz), 4.02 (dd, 1 H, *J* = 4.8 and 10.0 Hz), 3.72 (m, 1 H), 3.62 (dd, 1 H, *J* =2.8 and 8.4 Hz), 1.83 (q, 2 H, *J* = 6.0 Hz), 1.63 (q, 2 H, *J* = 6.0 Hz), 1.53 (s, 9 H), 1.19 (s, 9 H), 1.17 (s, 18 H), 1.14 (s, 9 H), 1.04 (t, 3 H, *J* = 6.0 Hz), 0.90 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 178.2, 177.3, 177.0, 176.5, 155.5, 148.2, 148.0, 137.6, 122.0, 119.2, 100.9, 90.2, 84.6, 84.6, 81.1, 72.8, 72.0, 71.2, 68.6, 68.1, 61.9, 40.5, 39.0, 39.99, 38.95, 38.93, 29.6, 29.4, 27.4, 27.32, 27.26, 27.24, 27.21, 8.6, 8.1; HR-ESI-MS $[M+H]^+$ calcd for $C_{46}H_{72}N_5O_{15}$ 934.5025; found 934.5007.

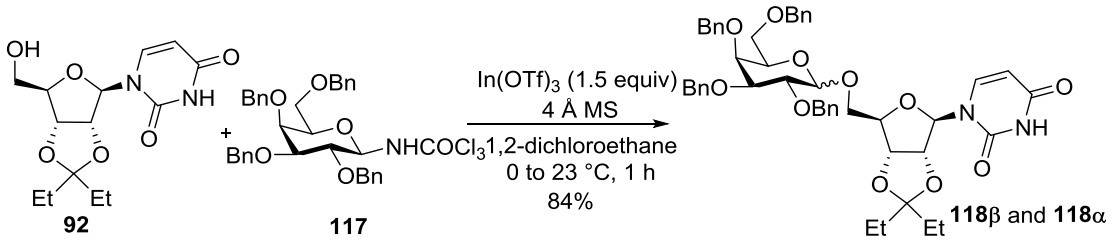
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(Benzyloxy)-2-pivalamido-9H-purin-9-yl)-2,2-diethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (115).



By following the general procedure, donor **93** (92 mg, 0.15 mmol) was combined with acceptor **143** (see SI, 53 mg, 0.10 mmol) at 0 °C for 15 min and then 23 °C for 45 min. After workup, purification by thin layer chromatography with 96:4 dichloromethane/methanol as the eluant afforded **115** (63 mg, 61%) as a white solid, mp 81–97 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1 H), 8.02 (br s, 1 H), 7.55–7.56 (m, 2 H), 7.32–7.38 (m, 3 H), 6.15 (s, 1 H), 5.66 (s, 2 H), 5.34 (d, 1 H, *J* = 5.2 Hz), 5.27 (app

t, 1 H, *J* = 7.6 Hz), 5.21 (dd, 1 H, *J* = 2.4 and 4.8 Hz), 5.10 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 4.97 (dd, 1 H, *J* = 6.8 and 7.2 Hz), 4.44–4.48 (m, 2 H), 4.14 (d, 1 H, *J* = 10.0 Hz), 4.05 (dd, 1 H, *J* = 2.0 and 8.4 Hz), 3.99 (dd, 1 H, *J* = 4.0 and 8.8 Hz), 3.73 (dd, 1 H, *J* = 4.2 and 8.4 Hz), 3.62 (dd, 1 H, *J* = 3.6 and 8.0 Hz), 1.82 (q, 2 H, *J* = 6.0 Hz), 1.65 (q, 2 H, *J* = 6.0 Hz), 1.37 (s, 9 H), 1.17 (s, 9 H), 1.14 (s, 9 H), 1.10 (s, 9 H), 1.05 (s, 9 H), 1.03 (t, 3 H, *J* = 6.0 Hz), 0.89 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 177.4, 176.7, 176.4, 175.2, 161.0, 152.5, 141.1, 136.1, 128.7, 128.6, 128.3, 118.6, 101.1, 90.6, 86.6, 84.8, 81.8, 72.4, 72.2, 71.2, 70.1, 69.1, 67.9, 61.8, 40.4, 40.0, 38.86, 38.85, 38.79, 29.49, 29.46, 27.7, 27.4, 27.3, 27.23, 27.18, 27.1, 8.5, 8.0; HR-ESI-MS $[M+H]^+$ calcd for $C_{53}H_{78}N_5O_{15}$ 1024.5494; found 1024.5484.

1-((3a*R*,4*R*,6*R*,6a*R*)-2,2-Diethyl-6-((((2R/*2S*,3*R*,4*S*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)oxy)methyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (118*α/β*).

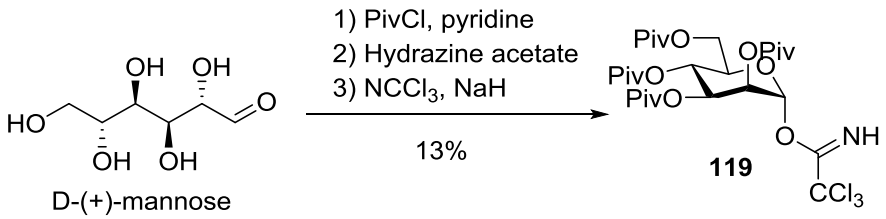


By following the general procedure, commercial available donor **117** (102.8 mg, 0.15 mmol 1.5 equiv) was combined with acceptor **92** (31.2 mg, 0.10 mmol) at 0 °C for 60 minuntes. After workup, purification by thin layer chromatography using 4:1 hexane/ethyl acetate as the eluant afforded **118*α*** (30.9 mg, 37%) as a white solid, R_f = 0.21, mp 65–93 °C, and **118*β*** (39 mg, 47%) as a white solid, R_f = 0.28, mp 62–78 °C. For

118*α*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (broad, 1 H), 7.83 (d, 1 H, *J* = 6.4 Hz), 7.29-7.41 (m, 18 H), 7.14-7.28 (m, 2 H), 6.09 (d, 1 H, *J* = 2.4 Hz), 5.53 (d, 1 H, *J* = 6.4 Hz), 4.98 (d, 1 H, *J* = 8.8 Hz), 4.85 (d, 1 H, *J* = 9.2 Hz), 4.81 (d, 1 H, *J* = 10.0 Hz), 4.78 (dd, 1 H, *J* = 2.8 and 5.2 Hz), 4.71 (d, 1 H, *J* = 2.8 Hz), 4.68 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 4.63 (d, 1 H, *J* = 5.2 Hz), 4.61 (d, 1 H, *J* = 5.2 Hz), 4.51 (d, 1 H, *J* = 1.2 Hz), 4.49 (d, 1 H, *J* = 2.4 Hz), 4.41 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 3.92 (dd, 1 H, *J* = 2.8 and 8.8 Hz), 3.87 (dd, 1 H, *J* = 6.4 and 6.8 Hz), 3.60-3.73 (overlapped, 6 H), 1.83 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.64 (q, 2 H, *J* = 6.0, 12.0 Hz), 1.04 (t, 3 H, *J* = 6.0 Hz), 0.91 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.12, 150.21, 141.67, 138.66, 138.14, 138.02, 137.95, 128.87, 128.72, 128.70, 128.68, 128.49, 128.28, 128.19, 128.15, 128.13, 128.05, 128.00, 119.35, 103.10, 97.87, 91.47, 85.16, 84.72, 82.08, 80.58, 80.07, 77.73, 75.94, 75.45, 73.93, 73.74, 70.99, 68.48, 68.07, 29.59, 8.61, 8.14; HR-ESI-MS $[M+H]^+$ calcd for $C_{48}H_{55}N_2O_{11}$ 835.3806; found 835.3790. For **118*β***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (br s, 1 H), 7.63 (d, 1 H, *J* = 6.4 Hz), 7.29–7.36 (m, 18 H), 7.18–7.20 (m, 2 H), 5.99 (d, 1 H, *J* = 1.5 Hz), 5.72 (d, 1 H, *J* = 6.5 Hz), 4.92 (d, 1 H, *J* = 8.8 Hz), 4.86 (d, 1 H, *J* = 8.6 Hz), 4.84 (d, 1 H, *J* = 8.8 Hz), 4.81 (d, 1 H, *J* = 8.8 Hz), 4.79 (d, 1 H, *J* = 8.7 Hz), 4.75 (dd, 1 H, *J* = 1.2 and 5.2 Hz), 4.63 (d, 1 H, *J* = 9.8 Hz), 4.58 (d, 1 H, *J* = 9.8 Hz), 4.56 (d, 1 H, *J* = 9.8 Hz), 4.52 (br d, 1 H, J = 2.2 Hz), 4.46 (d, 1 H, *J* = 6.3 Hz), 4.26 (dd, 1 H, *J* = 2.1 and 8.6 Hz), 3.74–3.78 (m, 2 H), 3.63–3.72 (m, 3 H), 3.48 (dd, 1 H, *J* = 3.3 and 7.3 Hz), 3.40 (t, 1 H, 6 H *J* = 6.4 Hz), 1.81 (q, 2 H, *J* = 6.0 Hz), 1.57 (q, 2 H, *J* = 6.0 Hz), 1.02 (t, 3 H, *J* = 6.0 Hz), 0.87 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 150.1, 141.7, 138.5, 138.2, 138.1, 138.0, 128.5, 128.5, 128.1, 128.04, 127.95, 127.92, 127.90, 127.84, 127.75, 118.8, 103.4, 102.0, 93.9, 86.1, 85.7, 84.8, 82.2, 81.2, 77.8, 75.8,

75.2, 75.1, 75.0, 73.6, 69.8, 68.7, 29.5, 29.3, 8.5, 7.9. HR-ESI-MS $[M+H]^+$ calcd for $C_{48}H_{54}N_2O_{11}$ 835.3809; found 835.3790.

(2*R*,3*R*,4*S*,5*S*,6*R*)-2-((Pivaloyloxy)methyl)-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (119).

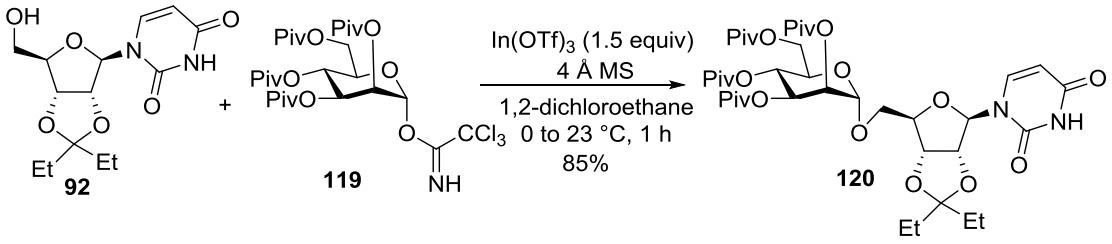


Donor119 was prepared by following the literature method.[100] A solution of pivaloyl chloride (10.65 mL, 86.50 mmol), pyridine (10.05 mL, 125 mmol), and D-(+)-mannose (2.50 g, 14.00 mmol) in 20 mL of chloroform was stirred at room temperature for 2 days, and then was transferred to a separatory funnel along with 200 mL of ethyl acetate. The organic phase was separated and washed sequentially with water (100 mL) and 1 N HCl (2× 100 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated to afford a sticky solid. The product was crystallized twice from methanol to give 3.05 g (36% yield) of the penta-pivaloate as a white solid.

A solution of the above solid (3.0 g, 4.99 mmol) and hydrazine acetate (1.07 g, 11.47 mmol) in dimethylformamide (50 mL) was heated at 50 °C under a nitrogen atmosphere for 48 h. The reaction mixture was cooled to room temperature and diluted with 200 mL of ethyl acetate. The organic was washed sequentially with water (100 mL) and brine (100 mL), dried over sodium sulfate, and then concentrated. The residue was purified by chromatography, eluting with 10-60% ethyl acetate in hexane, to afford 1.55 g (61% yield) of the reducing sugar as a light yellow oil.

A solution of the reducing sugar (1.54 g, 2.98 mmol) in dichloromethane (50 mL) was treated with trichloroacetonitrile (1.20 mL, 11.92 mmol), and then sodium hydride (0.11 g, 2.98 mmol) was added at room temperature with vigorous stirring. The reaction mixture was allowed to stir for 2 h, filtered through Celite, and then concentrated. The residue was purified by flash chromatography, eluting with 10% ethyl acetate/hexane, to afford **119** (1.20, 59% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.77 (s, 1 H), 6.20 (d, 1 H, *J* = 1.2 Hz), 5.58 (dd, 1 H, *J* = 8.0 and 8.4 Hz), 5.47 (dd, 1 H, *J* = 1.2 and 2.0 Hz), 5.43 (dd, 1 H, *J* = 2.4 and 8.0 Hz), 4.18–4.21 (m, 3 H), 1.28 (s, 9 H), 1.21 (s, 9 H), 1,17 (s, 9 H), 1.12 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.7, 177.0, 176.6, 176.5, 159.8, 94.7, 71.6, 69.3, 69.2, 67.8, 64.4, 61.5, 38.9, 38.8, 38.7, 27.1, 27.1, 27.1; HR-ESI-MS $[M–CCl_3CONH]^+$ calcd for $C_{26}H_{43}O_9^+$ 499.2902; found 498.2907.

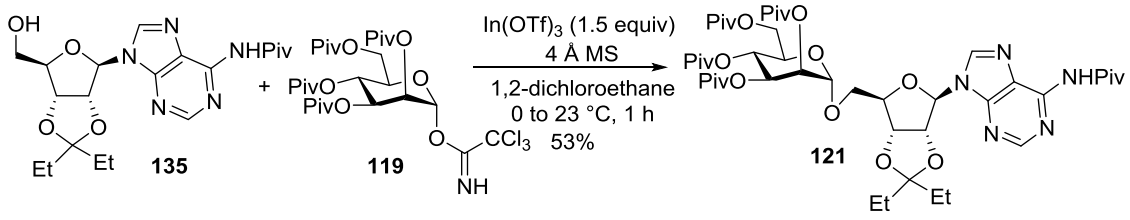
(2*S*,3*S*,4*S*,5*R*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-Dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-diethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (120).



By following the general procedure, donor **119** (99 mg, 0.15 mmol) was combined with acceptor **92** (31 mg, 0.10 mmol, mp 167–172 °C) at 0 °C for 60 min. After workup, purification by thin layer chromatography with 3:2 hexane/ethyl acetate as the eluant afforded **120** (69 mg, 85%) as a white solid, mp 97–127 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (br s, 1 H), 7.31 (d, 1 H, *J* = 6.4 Hz), 5.82–5.84 (m, 2 H), 5.49 (dd, 1

H, *J* = 8.0 Hz), 5.31 (dd, 1 H, *J* = 2.4 and 8.0 Hz), 5.26 (m, 1 H), 4.94 (dd, 1 H, *J* = 2.0 and 6.4 Hz), 4.88 (dd, 1 H, *J* = 3.6 and 5.2 Hz), 4.81 (s, 1 H), 4.29 (dd, 1 H, *J* = 3.2 and 6.0 Hz), 4.12–4.18 (m, 2 H), 4.01 (d, 1 H, *J* = 8.0 Hz), 3.91 (dd, 1 H, *J* = 3.2 and 9.2 Hz), 1.79 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.63 (q, 2 H, *J* = 6.0 and 12.0 Hz), 1.25 (s, 9 H), 1.22 (s, 9 H), 1.14 (s, 9 H), 1.11 (s, 9 H), 0.99 (t, 3 H, *J* = 6.0 Hz), 0.88 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 177.5, 177.1, 176.6, 163.8, 150.3, 141.8, 119.3, 103.2, 98.29, 93.28, 85.2, 84.7, 80.7, 69.6, 69.4, 69.1, 67.6, 64.9, 61.8, 38.9, 38.8, 29.5, 29.3, 27.18, 27.16, 27.13, 27.11, 8.5, 7.9; HR-ESI-MS $[M+H]^+$ calcd for $C_{40}H_{63}N_2O_{15}$ 811.4228; found 811.4239.

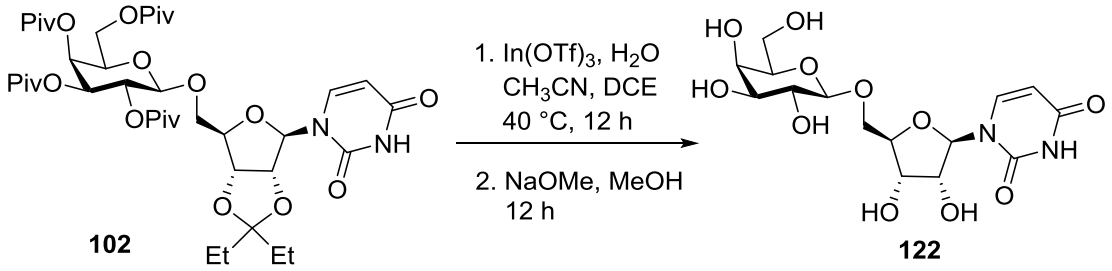
(2*S*,3*S*,4*S*,5*R*,6*R*)-2-(((3a*R*,4*R*,6*R*,6a*R*)-2,2-Diethyl-6-(6-pivalamido-9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)-6-((pivaloyloxy)methyl)tetrahydro-2*H*-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) (121).



By following the general procedure, donor **119** (99 mg, 0.15 mmol) was combined with acceptor **135** (42 mg, 0.10 mmol) at 0 °C for 60 min. After work-up, purification by thin layer chromatography with 94:6 dichloromethane/methanol as the eluant afforded **121** (49 mg, 53%) as a white solid, mp 106–131 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1 H), 8.66 (br s, 1 H), 8.08 (s, 1 H), 6.19 (d, 1 H, *J* = 1.2 Hz), 5.62 (dd, 1 H, *J* = 1.2 and 4.8 Hz), 5.42 (dd, 1 H, *J* = 8.0 and 8.4 Hz), 5.31 (s, 1 H), 5.18 (dd, 1 H, *J* = 2.4 and 8.0 Hz), 5.09 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 4.98 (dd, 1 H, *J* = 1.2 and 6.4 Hz),

4.67 (d, 1 H, *J* = 1.2), 4.57–4.59 (m, 1 H), 4.99 (dd, 1 H, *J* = 2.8 and 10.0 Hz), 3.75–3.83 (m, 3 H), 3.70 (dd, 1 H, *J* = 3.6 and 8.8 Hz), 1.85 (q, 2 H, *J* = 6.0 Hz), 1.71 (q, 2 H, *J* = 6.0 Hz), 1.41 (s, 9 H), 1.25 (s, 9 H), 1.20 (s, 9 H), 1.13 (s, 9 H), 1.09 (s, 9 H), 1.05 (t, 3 H, *J* = 6.0 Hz), 0.96 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 177.2, 177.1, 176.6, 175.9, 153.2, 151.1, 150.1, 142.0, 123.9, 119.1, 98.2, 92.0, 86.5, 84.7, 82.2, 69.4, 69.2, 69.0, 68.3, 64.9, 61.7, 40.7, 39.1, 39.0, 38.93, 38.88, 29.8, 29.3, 27.5, 27.31, 27.28, 27.24, 27.21, 8.7, 7.9; HR-ESI-MS $[M+H]^+$ calcd for $C_{46}H_{72}N_5O_{14}$ 918.5076; found 918.5066.

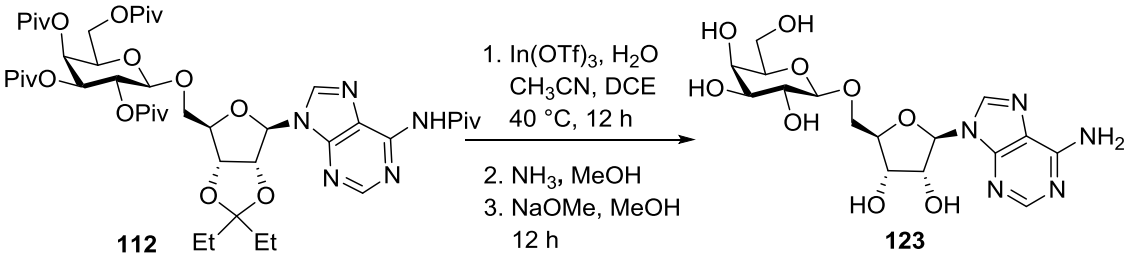
1-((2*R*,3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-((((2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)methyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (122).



A solution of nucleoside disaccharide **102** (110 mg, 0.14 mmol), indium triflate (114 mg, 0.20 mmol, and one drop of water in 1 mL of 1,2-dichloroethane and 1 mL of acetonitrile was allowed to stir at 40 °C for 12 h. Twenty mL of water was added, and the mixture was extracted with ethyl acetate (3×20 mL). The organic extract was dried over anhydrous sodium sulfate and concentrated to provide 102 mg of crude diol product. A solution of the crude product in 2 mL of methanol was treated with freshly prepared 1M sodium methoxide (methanol solution, 0.55 ml, 0.544 mmol) at 0 °C. The solution was allowed to warm to room temperature and stir at this temperature for 12 h. The pH of the

resulting solution was adjusted to approximately 7 by the addition of solid carbon dioxide. The solvent was removed and the residue obtained was dissolved 2 mL of dimethyl sulfoxide. This solution was loaded onto a C-18 reverse phase column (40 g) eluting with 0% to 60% acetonitrile/water. The desired fraction was collected and concentrated by lyophilization to afford **122** (47 mg, 0.117 mmol, 86% overall) as a white solid, mp 146–159 °C: ^{1}H NMR (400 MHz, D_2O) δ 3.49 (dd, 1 H, *J* = 6.4, 8.0 Hz), 3.58 (dd, 1 H, *J* = 2.8 and 8.0 Hz), 3.62 (dd, 1 H, *J* = 3.2 and 6.4 Hz), 3.67 (dd, 1 H, *J* = 3.6 and 9.6 Hz), 3.72 (dd, 1 H, *J* = 6.4 and 9.6 Hz), 3.81 (dd, 1 H, *J* = 2.8 and 9.2 Hz), 3.86 (d, 1 H, *J* = 2.4 Hz), 4.16 (d, 1 H, *J* = 2.0 Hz), 4.19–4.21 (m, 1 H), 4.26 (dd, 1 H, *J* = 4.0 Hz), 4.30 (dd, 1 H, *J* = 3.6 and 4.0 Hz), 4.39 (d, 1 H, *J* = 6.4 Hz), 5.83 (d, 1 H, *J* = 3.6 Hz), 5.85 (s, 1 H), 7.88 (d, 1 H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, D_2O) δ 168.8, 153.7, 144.2**,** 105.0, 104.3, 91.4, 85.2, 77.3, 75.9, 74.9, 73.0, 71.8, 70.7, 70.6, 63.2; LC-ESI-MS $[M+H]^+$ calcd for $C_{15}H_{23}N_2O_{11}$ 407.13; found 407.10.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(((2*R*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methoxy)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol (123).



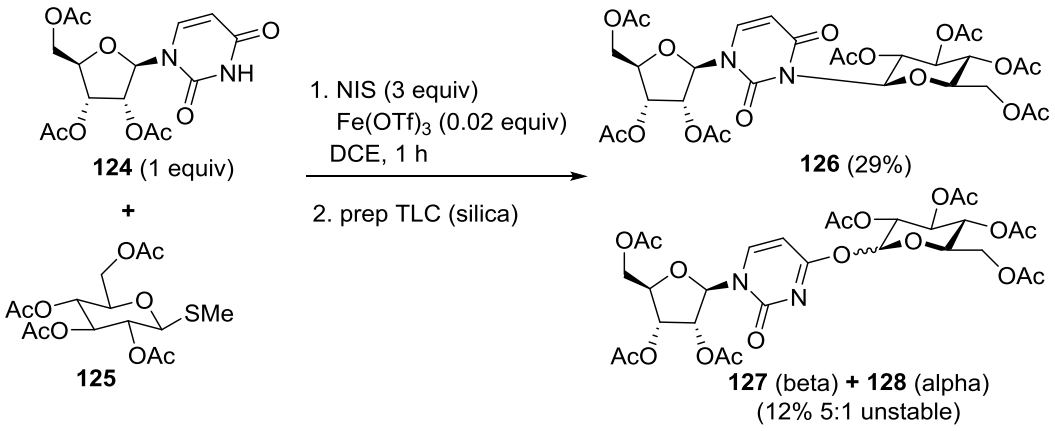
Nucleoside disaccharide **112** (92 mg, 0.10 mmol) was hydrolyzed as for **102** (above). A solution of the crude diol product in 2 mL of 7N ammonia in methanol was

allowed to stir at room temperature for 12 h. The resulting reaction was concentrated and the residue obtained was further dried with high vacuum pump for overnight to afford 81 mg of white solid.

A solution of the above product in 2 mL of methanol was treated with freshly prepared 1M methanolic sodium methoxide (0.3 ml, 0.30 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stir for 12 h. The pH of the resulting solution was adjusted to about 7 by the addition of solid carbon dioxide. The solvent was removed and the crude product was dissolved in 2 mL of dimethyl sulfoxide. This solution was chromatographed as for **122** (above) to provide **123** (31 mg, 0.07 mmol, 72% overall) as a white solid, mp 198 °C (dec.): ^{1}H NMR (400 MHz, D_2O): δ 8.39 (s, 1H), 8.18 (s, 1 H), 6.03 (d, 1 H, *J* = 4.0 Hz), 4.67 (m, 1H), 4.42 (dd, 1 H, *J* = 3.6 and 4.0 Hz), 4.37 (d, 1 H, *J* = 6.4 Hz), 4.28–4.31 (m, 1 H), 4.15 (dd, 1 H, *J* = 2.4 and 9.6 Hz), 3.85 (dd, 1 H, *J* = 3.2 and 8.8 Hz), 3.83 (d, 1 H, *J* = 3.2 Hz), 3.69 (dd, 1 H, *J* = 6.4 and 9.6 Hz), 3.65 (dd, 1 H, *J* = 3.6 and 9.6 Hz), 3.62 (dd, 1 H, *J* = 3.6 and 6.4 Hz), 3.55 (dd, 1 H, *J* = 2.8 and 8.0 Hz), 3.47 (dd, 1 H, *J* = 6.4 and 8.0 Hz); ^{13}C NMR (125 MHz, D_2O) δ 155.5, 152.0, 150.6, 143.0, 120.6, 105.3, 89.9, 85.8, 77.4, 76.3, 74.9, 73.0, 72.4, 71.1, 70.8, 63.2; LC-ESI-MS $[M+H]^+$ calcd for $C_{16}H_{24}N_5O_9$ 430.16; found: 430.12.

(2*R*,3*R*,4*S*,5*R*,6*R*)-2-(Acetoxymethyl)-6-(3-((2*R*,3*R*,4*R*,5*R*)-3,4-diacetoxy-5-(acetoxymethyl)tetrahydrofuran-2-yl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, (2*R*,3*R*,4*S*,5*R*)-2-(acetoxymethyl)-6-((1-((2*R*,3*R*,4*R*,5*R*)-3,4-diacetoxy-5-(acetoxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, and (2*R*,3*R*,4*S*,5*R*,6*R*)-2-(acetoxymethyl)-6-((1-((2*R*,3*R*,4*R*,5*R*)-3,4-diacetoxy-5-

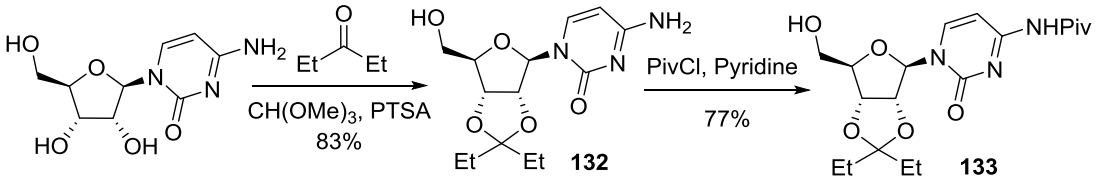
(acetoxymethyl)tetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate (126, 127, and 128, respectively).



A solution of 2',3',5'-tri-*O*-acetyluridine (37.03 mg, 0.10 mmol) and methyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranoside (113.5 mg, 0.30 mmol) in 2 mL of 1,2-dichloroethane was treated with 100 mg 3 Å molecular sieves and *N*-iodosuccinimide (67.5 mg, 0.30 mmol), and the mixture was allowed to stirred at room temperature for 15 min. Iron(III) triflate (1.0 mg, 0.002 mmol) was added, and the reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was directly applied to a thin layer chromatography plate; double elution with 95:5 dichloromethane/methanol afforded **126** (R_f = 0.37, 20.3 mg, 0.029 mmol, 29% yield) and **127**/**128** (R_f = 0.40, 8.4 mg, 0.012 mmol, 12% yield) as white solids. For **126**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 1 H, *J* = 8.2 Hz), 6.17 (d, 1 H, *J* = 5.8 Hz), 6.06 (d, 1 H, *J* = 4.8 Hz), 5.76 (d, 1 H, *J* = 8.2 Hz), 5.29–5.36 (m, 3 H), 5.17 (t, 1 H, *J* = 9.9 Hz), 4.42–4.14 (m, 5H), 3.83 (dd, 1 H, *J* = 3.0 and 8.2 Hz), 2.15 (s, 3 H), 2.13 (s, 6 H), 2.08 (s, 3 H), 2.04 (s, 3 H), 2.00 (s, 3 H), 1.91 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 170.2, 170.1, 170.0, 169.8, 169.7, 169.6, 149.2, 138.3, 101.7, 86.5, 80.2, 79.3, 77.4, 74.9, 73.7, 72.6, 70.4, 68.1, 68.0, 63.4, 62.1, 20.9, 20.9, 20.8, 20.7, 20.7, 20.6, 20.5; LC-ESI-MS $[M+H]^+$ calcd for

$C_{29}H_{36}N_2O_{18}$ 701.20; found 701.04. For **127**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, 1 H, *J* = 7.5 Hz), 7.79 (d, 1 H, *J* = 7.4 Hz), 6.22 (d, 1 H, *J* = 6.9 Hz), 6.04 (d, 1 H, *J* = 3.8 Hz), 5.99 (d, 1 H, *J* = 7.4 Hz), 5.37 (t, 1 H, *J* = 4.6 Hz), 5.28 (t, 1 H, *J* = 5.4 Hz), 5.21–5.25 (m, 1 H), 5.12–5.16 (m, 1 H), 4.36–3.38 (m, 3 H), 4.29 (dd, 1 H, *J* = 3.8 and 12.6 Hz), 4.08–4.11 (m, 2 H), 3.92 (d, 1 H, *J* = 9.7 Hz), 2.11 (s, 3 H), 2.10 (s, 3 H), 2.08 (s, 3 H), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.98 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.2, 170.1, 170.0, 169.6, 169.5, 169.5, 169.5, 154.9, 144.0, 154.9, 144.0, 96.3, 93.1, 89.6, 80.0, 73.7, 72.9, 72.6, 70.5, 69.8, 69.8, 62.9, 61.4, 20.84, 20.79, 20.67, 20.66, 20.56, 20.55; LC-ESI-MS $[M+H]^+$ calcd for $C_{29}H_{36}N_2O_{18}$ 701.20; found, 701.06. For **128**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (minor resonances identifiable in the mixture with **39**) 7.83 (d, 1 H, *J* = 7.5 Hz), 6.76 (d, 1 H, *J* = 3.2 Hz), 6.24 (obscured d), 6.05 (obscured d), 5.52 (t, 1 H, *J* = 9.8 Hz), 5.07 (t, 1 H, *J* = 10 Hz), 4.87 (dd, 1 H, *J* = 3.3 and 10 Hz), 4.24 (dd, 1 H, *J* = 4 and 10 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (minor resonances identifiable in the mixture with **39**) 154.6, 143.6, 90.2, 62.1, 60.5.

Acceptor 133 for Preparing 105 and 106: *N*-(1-((3a*R*,4*R*,6*R*,6a*R*)-2,2-Diethyl-6-(hydroxymethyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)pivalamide (133).

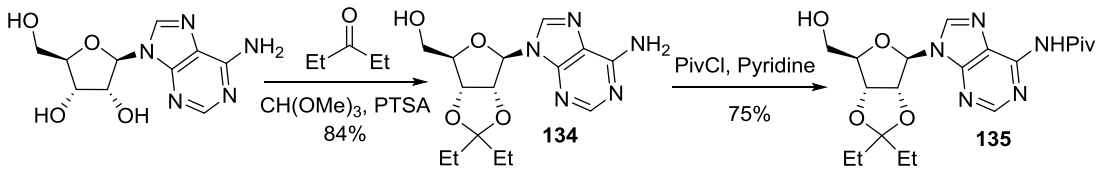


The 3-propanone acetal (**132**) was prepared from cytidine by following the procedure for **92** (622 mg, 83% yield) as a white solid, mp 146–150 °C: ^{1}H NMR (400 MHz, CD_3OD) δ 8.18 (d, 1 H, *J* = 6.4 Hz), 6.11 (d, 1 H, *J* = 6.4 Hz), 5.89 (d, 1 H, *J* = 2.0

Hz), 4.83 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 4.38 (m, 1 H), 3.80 (dd, 1 H, *J* = 2.8 and 5.2 Hz), 3.72 (dd, 1 H, *J* = 3.6 and 6.4 Hz), 1.78 (q, 2 H, *J* = 6.0 Hz), 1.64 (q, 2 H, *J* = 6.0 Hz), 1.00 (t, 3 H, *J* = 6.0), 0.89 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, DMSO) δ 160.3, 147.9, 145.4, 116.9, 93.8, 93.3, 88.1, 84.8, 81.0, 61.3, 29.0, 28.7, 8.3, 7.6; LC-ESI-MS $[M+H]^+$ calcd for $C_{14}H_{21}N_3O_5$ 312.15; found 312.11.

A solution of **132** (622 mg, 2.0 mmol) in 20 mL of pyridine was treated with trimethylacetyl chloride (2.49 mL, 20.0 mmol), added by drops at room temperature, and the mixture was allowed to stir overnight. The reaction was cooled to 0 °C, quenched with 5 mL of methanol, and then concentrated. The residue was purified by using a pre-packed C-18 reverse phase column (120 g), eluting with 5% to 90% acetonitrile / water. The fractions containing product were collected and lyophilized to afford **133** (640 mg, 77% yield) as a white solid, mp 129–165 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 1 H), 7.73 (d, 1 H, *J* = 6.0 Hz), 7.49 (d, 1 H, *J* = 6.0 Hz), 5.54 (d, 1 H, *J* = 2.0 Hz), 5.28 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 5.16 (dd, 1 H, *J* = 2.8 and 5.2 Hz), 4.41 (m, 1 H), 3.97 (dd, 1 H, *J* = 2.0 and 9.6 Hz), 3.86 (dd, 1 H, *J* = 2.8 and 9.6 Hz), 1.82 (q, 2 H, *J* = 6.0 Hz), 1.65 (q, 2 H, *J* = 6.0 Hz), 1.31 (s, 9 H), 1.03 (t, 3 H, *J* = 6.0), 0.91 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 155.3, 147.7, 118.5, 98.2, 96.6, 88.7, 84.8, 80.9, 62.8, 40.5, 29.5, 29.2, 27.7, 27.1, 8.5, 7.9; HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{30}N_3O_6$ 396.2135; found 396.2126.

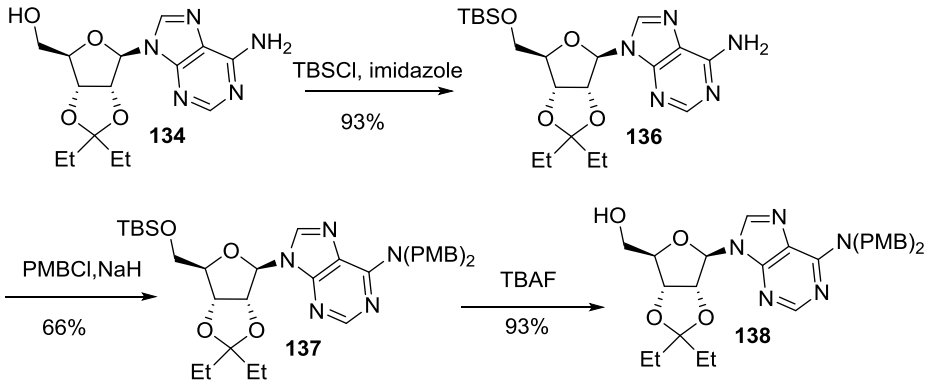
Acceptor 135 for Preparing 111 and 112: *N*-(9-((3a*R*,4*R*,6*R*,6a*R*)-2,2-diethyl-6-(hydroxymethyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)pivalamide (135).



The 3-pentanone acetal **134** was prepared from adenosine by following the procedure for **92** (84% yield) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1 H), 8.26 (s, 1 H), 6.22 (d, 1 H, *J* = 2.4 Hz), 5.33 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 5.05 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 4.39 (m, 1 H), 3.77 (dd, 1 H, *J* = 3.2 and 10.0 Hz), 3.70 (dd, 1 H, *J* = 3.6 and 9.6 Hz), 1.85 (q, 2 H, *J* = 6.0 Hz), 1.68 (q, 2 H, *J* = 6.0 Hz), 1.05 (t, 3 H, *J* = 6.0 Hz), 0.91 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, DMSO) δ 154.8, 150.9, 148.7, 140.5, 119.0, 117.3, 89.9, 87.2, 83.9, 81.7, 61.6, 28.9, 28.7, 8.3, 7.7; LC-ESI-MS $[M+H]^+$ calcd for $C_{15}H_{22}N_5O_4$ 336.16; found 336.10.

N-Pivaloyl derivative **135** was prepared from **134** by following the procedure for **133** (75% yield) as a white solid, mp 90–118 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (br s, 1 H), 8.72 (s, 1 H), 8.11 (s, 1 H), 6.11 (d, 1 H, *J* = 3.2 Hz), 5.21 (dd, 1 H, *J* = 3.6 and 4.8 Hz), 5.13 (dd, 1 H, *J* = 1.2 and 5.2 Hz), 4.53 (s, 1 H), 3.96 (dd, 1 H, *J* = 1.2 and 6.0 Hz), 3.81 (dd, 1 H, *J* = 2.0 and 6.0 Hz), 1.86 (q, 2 H, *J* = 6.0 Hz), 1.65 (q, 2 H, *J* = 6.0 Hz), 1.40 (s, 9 H), 1.24 (s, 1 H), 1.05 (t, 3 H, *J* = 6.0), 0.89 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 152.4, 150.7, 150.5, 142.6, 124.2, 118.9, 93.8, 86.9, 83.8, 81.6, 63.3, 40.7, 29.5, 29.2, 27.5, 27.3, 8.7, 8.2; HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{30}N_5O_5$ 420.2247; found 420.2237.

Acceptor 138 for Preparing 113: ((3aR,4*R*,6*R*,6a*R*)-6-(6-(Bis(4-methoxybenzyl)amino)-9*H*-purin-9-yl)-2,2-diethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (138).[101]



A solution of adenosine 3-propanone acetal **134** (1.20 g, 3.58 mmol) in 35 mL of dimethylformamide was treated with *tert*-butyldimethylsilyl chloride (1.08 g, 7.06 mmol) and imidazole (0.73 g, 10.74 mmol). The reaction was allowed to stir at room temperature overnight. The reaction mixture was diluted with 100 mL of water, and extracted with ethyl acetate (3×100 mL). The combined organic solution was dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography, eluting with 1:1 ethyl acetate/hexane to afford the O-5' silyl ether **136** (1.57 g, 97% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 8.06 (s, 1 H), 6.21 (d, 1 H, *J* = 2.0 Hz), 5.58 (br s, 1 H), 5.38 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 5.01 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 4.46 (m, 1 H), 3.88 (dd, 1 H, *J* = 3.6 and 8.8 Hz), 3.78 (dd, 1 H, *J* = 3.6 and 8.8 Hz), 1.87 (q, 2 H, *J* = 6.0 Hz), 1.71 (q, 2 H, *J* = 12.0 Hz), 1.08 (t, 3 H, *J* = 6.0), 0.95 (t, 3 H, *J* = 6.0 Hz), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 153.4, 149.7, 139.7, 120.3, 118.7, 91.7, 88.0, 85.3, 82.0, 63.8, 29.8, 29.5, 26.1, 18.5, 8.6, 8.0, -5.2, -5.3; LC-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{36}N_5O_4Si$ 450.25; found 450.21.

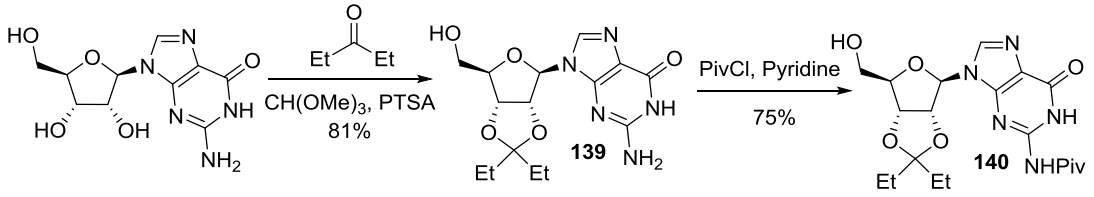
Sodium hydride (0.30 g, 7.40 mmol) was added to a stirred solution of **136** (1.57 g, 3.50 mmol) in 35 mL of tetrahydrofuran at 0 °C, followed by 4-methoxybenzyl chloride (1.16 g, 7.4 0 mmol). The mixture was stirred at room temperature overnight,

and then quenched with 100 mL of saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate (3×100 mL), and the combined organic solution was dried over anhydrous sodium sulfate and then concentrated. The residue was purified by flash chromatography, eluting with 15% ethyl acetate/hexane to afford the *N*,*N*-*bis*(*p*-methoxybenzyl ether **137** (1.62 g, 66% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1 H), 7.93 (s, 1 H), 7.23 (d, 4 H, *J* = 6.8 Hz), 6.86 (d, 4 H, *J* = 6.8 Hz), 6.21 (d, 1 H, *J* = 1.6 Hz), 5.42 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 5.03 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 4.43 (m, 1 H), 3.88 (dd, 1 H, *J* = 3.6 and 8.8 Hz), 3.83 (s, 6 H), 3.78 (dd, 1 H, *J* = 4.8 and 8.8 Hz), 1.87 (q, 2 H, *J* = 6.0 Hz), 1.71 (q, 2 H, *J* = 6.0 Hz), 1.07 (t, 3 H, *J* = 6.0 Hz), 0.95 (t, 3 H, *J* = 6.0 Hz), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 155.0, 152.9, 150.7, 137.6, 129.4, 120.4, 118.6, 114.2, 91.5, 87.9, 85.1, 82.1, 63.8, 55.5, 29.8, 29.5, 26.2, 26.1, 18.6, 8.6, 8.0, -5.2, -5.3; LC-ESI-MS $[M+H]^+$ calcd for $C_{37}H_{52}N_5O_6Si$ 690.93; found 690.87.

A tetrabutylammonium fluoride solution in tetrahydrofuran (2.50 mL, 2.50 mmol) was added to a solution of **137 (**1.62 g, 2.35 mmol) in 20 mL of THF. The mixture was allowed to stir at room temperature for 30 min, concentrated, and then purified by flash chromatography, eluting with 60% ethyl acetate/hexane, to afford **138** (1.26 g, 93% yield) as a white foam, mp 69–90 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.77 (s, 1 H), 7.22 (d, 4 H, *J* = 6.8 Hz), 6.87 (d, 4 H, *J* = 6.8 Hz), 5.92 (d, 1 H, *J* = 3.6 Hz), 5.31 (dd, 1 H, *J* = 3.6 and 5.2 Hz), 5.21 (dd, 1 H, *J* =1.2 and 5.2 Hz), 4.58 (m, 1 H), 4.02 (d, 1 H, *J* = 10.4 Hz), 3.86 (dd, 1 H, *J* =1.2 and 10.4 Hz), 3.83 (s, 6 H), 1.89 (q, 2 H, *J* = 6.0 Hz), 1.71 (q, 2 H, *J* = 6.0 Hz), 1.09 (t, 3 H, *J* = 6.0 Hz), 0.93 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 156.8, 152.0, 150.7, 140.6, 131.5, 131.0, 121.9, 120.4,

115.7, 93.3, 89.0, 86.3, 83.7, 64.3, 56.4, 31.0, 30.8, 9.5, 9.0; HR-ESI-MS $[M+H]^+$ calcd for $C_{31}H_{38}N_5O_6$ 576.2822; found 576.2809.

Acceptor 140 for Preparing 114: *N*-(9-((3a*R*,4*R*,6*R*,6a*R*)-2,2-Diethyl-6-(hydroxymethyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)pivalamide (140).

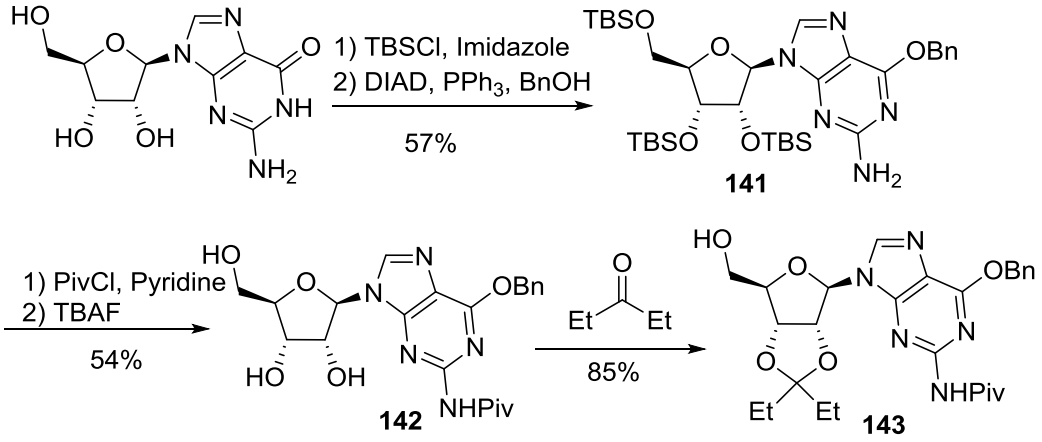


The 3-pentanone acetal of guanosine (**139**) was prepared by following the procedure for **92** (81% yield), and was obtained as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (s, 1 H), 6.05 (d, 1 H, *J* = 2.0 Hz), 5.27 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 5.05 (dd, 1 H, *J* = 2.4 and 5.2 Hz), 4.32 (m, 1 H), 3.76 (dd, 1 H, *J* = 3.6 and 9.6 Hz), 3.70 (dd, 1 H, *J* = 3.6 and 9.6 Hz), 1.83 (q, 2 H, *J* = 6.0 Hz), 1.68 (q, 2 H, *J* = 6.0 Hz), 1.05 (t, 3 H, *J* = 6.0 Hz), 0.91 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, DMSO) δ 156.7, 153.7, 150.7, 136.0, 117.2, 116.5, 88.6, 87.2, 84.0, 81.5, 61.7, 28.9, 28.6, 8.3, 7.7; LC-ESI-MS $[M+H]^+$ calcd for $C_{15}H_{22}N_5O_5$ 352.16; found 352.07.

Acceptor **140** was prepared from **139** by following the procedure for **133** (45% yield) and was obtained as a white solid, mp 111–128 °C: ^{1}H NMR (400 MHz, CD_3OD) δ 8.41 (s, 1 H), 8.11 (s, 1 H), 6.14 (d, 1 H, *J* = 1.6 Hz), 5.26 (dd, 1 H, *J* = 1.6 and 5.2 Hz), 5.01 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 4.44 (m, 1 H), 3.77 (dd, 1 H, *J* = 2.8 and 9.6 Hz), 3.71 (dd, 1 H, *J* = 3.6, 9.6 Hz), 1.82 (q, 2 H, *J* = 6.0 Hz), 1.69 (q, 2 H, *J* = 6.0 Hz), 1.33 (s, 9 H), 1.03 (t, 3 H, *J* = 6.0 Hz), 0.92 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ

183.8, 157.3, 151.2, 140.2, 120.6, 120.0, 93.9, 90.2, 87.5, 83.9, 63.8, 42.2, 31.0, 30.8, 27.7, 9.4, 8.7; HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{30}N_5O_6$ 436.2196; found 436.2188.

Acceptor 143 for Preparing 115: *N*-(6-(Benzyloxy)-9-((3a*R*,4*R*,6*R*,6a*R*)-2,2-diethyl-6-(hydroxymethyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9H-purin-2-yl)pivalamide (143).[102]



A stirred solution of guanosine (1.45 g, 5.0 mmol) in dry dimethylformamide (20 mL) was treated with imidazole (2.7 g, 40.0 mmol) and *tert*-butyldimethylsilyl chloride (4.5 g, 30.0 mmol). The reaction mixture was allowed to stir at room temperature overnight, diluted with ethyl acetate (150 mL), and then was washed sequentially with water (3 ×50 mL), saturated aqueous ammonium chloride, and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to afford the *tris*(silyl ether) as a white solid (3.0 g). This product was further dried overnight under high vacuum and then was dissolved in anhydrous tetrahydrofuran (40 mL). Triphenylphosphine (1.97 g, 7.5 mmol) was added, followed by benzyl alcohol (1.03 mL, 10 mmol). The mixture was cooled to 0 °C, and diisopropyl azodicarboxylate (1.48 mL, 7.5 mmol) was added dropwise. The solution was allowed to stir at room temperature for 4 h, and then concentrated. The residue was purified by flash column chromatography,

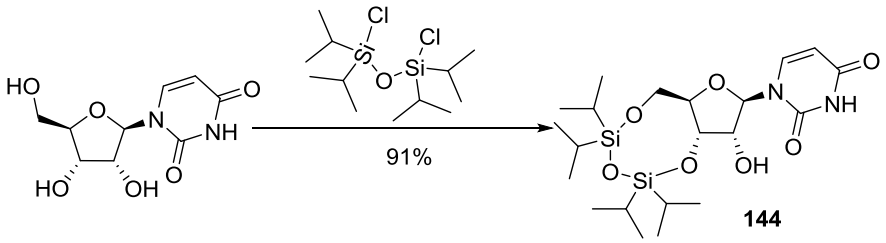
eluting with 5% ethyl acetate/hexane, to afford the O-benzyl derivative (**141**, 2.0 g, 57% over 2 steps) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1 H), 7.51–7.49 (m, 2 H), 7.38–7.26 (m, 3 H), 5.92 (d, 1 H, *J* = 4.0 Hz), 5.56 (s, 2 H), 5.96 (br s, 2 H), 4.52 (dd, 1 H, *J* = 3.6 and 4.0 Hz), 4.30 (d, 1 H, *J* = 3.2 Hz), 4.01 (m, 1 H), 3.98 (dd, 1 H, *J* = 3.2 and 9.2 Hz), 3.78 (dd, 1 H, *J* = 2.0 and 8.8 Hz), 0.95 (s, 9 H), 0.94 (s, 9 H), 0.83 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H), 0.12 (s, 6 H), -0.02 (s, 3 H), -0.14 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 159.7, 154.1, 137.7, 136.7, 128.7, 128.48, 128.46, 128.4, 128.4, 128.3, 128.0, 115.7, 87.4, 85.6, 76.7, 72.5, 68.0, 62.9, 26.0, 25.8, 25.6, 18.7, 18.3, 18.0, -4.1, -4.55, -4.57, -4.9, -5.2, -5.3; LC-ESI-MS $[M+H]^+$ calcd for $C_{35}H_{62}N_5O_5Si_3$ 716.40; found 716.40.

A solution of **141** (2.0 g, 2.80 mmol) in pyridine (20 mL) was treated with pivaloyl chloride (1.01 g, 8.40 mmol) and 4-dimethylaminopyridine (0.17 g, 1.40 mmol) at room temperature. The mixture was allowed to stir at room temperature for 5 h, and then was concentrated. The residue was diluted with ethyl acetate (100 mL), and the organic solution was washed sequentially with 0.2 N HCl (3×50 mL) and brine. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated to provide the *N*-pivaloyl derivative as a white solid (2.1 g). The white solid was dissolved in 20 mL tetrahydrofuran, and the solution was treated with tetra-*n*-butylammonium fluoride tetrahydrofuran solution (9.0 mL, 9.00 mmol). The reaction mixture was allowed to stir at room temperature for 30 min, then was concentrated. The residue was purified by flash column chromatography, eluting with ehtyl acetate, to afford triol **142** (680 mg, 54% over 2 steps) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1 H), 7.81 (s, 1 H), 7.49–7.47 (m, 2 H), 7.36–7.29 (m, 3 H), 5.76 (d, 1 H, *J* = 5.2 Hz), 5.67 (d, 2 H, *J* =

9.6 Hz), 5.46 (d, 2 H, *J* = 9.6 Hz), 4.83 (dd, 1 H, *J* = 4.0 and 5.2 Hz), 4.34 (t, 1 H, *J* = 4.4 Hz), 3.85 (dd, 1 H, *J* = 2.0 Hz and 10.0 Hz), 3.70 (dd, 1 H, *J* = 2.4 Hz and 10.0 Hz), 1.35 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 160.3, 151.7, 151.2, 141.6, 135.6, 128.8, 128.6, 128.5, 118.5, 91.4, 87.7, 74.5, 72.9, 69.2, 62.9, 40.4, 27.6; LC-ESI-MS $[M+H]^+$ calcd for $C_{22}H_{28}N_5O_6$ 458.20; found 458.03.

The 3-pentanone acetal of **142** was prepared by following the procedure for **92** (85% yield), affording acceptor **143** as a white solid, mp 92–121 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (br s, 1 H), 7.84 (s, 1 H), 7.55–7.57 (m, 2 H), 7.32–7.38 (m, 3 H), 5.95 (d, 1 H, *J* = 2.8 Hz), 5.65–5.71 (m, 2 H), 5.37 (dd, 1 H, *J* = 2.0 and 5.2 Hz), 5.21 (dd, 1 H, *J* = 2.8 and 5.2 Hz), 4.90 (dd, 1 H, *J* = 2.8 and 8.0 Hz), 4.48 (m, 1 H), 3.94–3.97(m, 1 H), 3.77–3.82 (m, 1 H), 1.85 (q, 2 H, *J* = 6.0 Hz), 1.66 (q, 2 H, *J* = 6.0 Hz), 1.37 (s, 9 H), 1.05 (t, 3 H, *J* = 6.0 Hz), 0.90 (t, 3 H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 161.2, 151.9, 151.7, 141.5, 135.9, 128.8, 128.5, 128.3, 119.6, 118.5, 92.5, 87.5, 81.4, 69.2, 62.8, 40.4, 29.4, 29.3, 27.5, 8.5, 8.1; HR-ESI-MS $[M+H]^+$ calcd for $C_{27}H_{36}N_5O_6$ 526.2666; found 526.2656.

Acceptor 144 for Preparing 107 and 109: 1-((6a*R*,8*R*,9*R*,9a*S*)-9-Hydroxy-2,2,4,4-tetraisopropyltetrahydro-6*H*-furo[3,2-*f*][1,3,5,2,4]trioxadisilocin-8-yl)pyrimidine-2,4(1*H*,3*H*)-dione (144).[103]



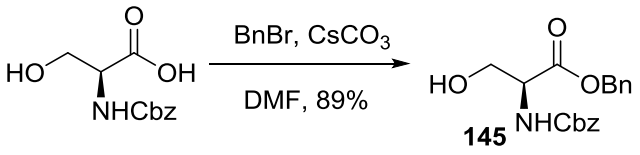
1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (3.52 mL, 11.00 mmol) was added by drops and with vigorous stirring to a solution of uridine (2.5 g, 10.25 mmol) in

pyridine (100 mL) at 0 °C. The mixture was allowed to warm to room temperature and stir overnight. The pyridine was removed and the residue was partitioned between dichloromethane and water. The organic layer was washed with brine, and then dried over anhydrous sodium sulfate. Concentration gave a residue that was purified by silica gel chromatography, eluting with 40% ethyl acetate / hexanes to afford acceptor **144** (4.50 g, 9.23 mmol, 91%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1 H), 7.68 (d, 1 H, *J* = 8.16 Hz), 5.73 (s, 1 H), 5.69 (dd, 1 H, *J* = 1.6 and 8.0 Hz), 4.37 (dd, 1 H, *J* = 5.0 and 8.7 Hz), 4.17–4.21 (m, 2 H), 4.09–4.11 (m, 1 H), 3.99 (dd, 1 H, *J* = 2.6 and 13.1 Hz), 3.06 (br s, 1 H), 1.02–1.11 (28 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 150.3, 140.1, 102.1, 91.1, 82.1, 75.3, 69.0, 60.4, 17.6, 17.5, 17.4, 17.4, 17.2, 17.09, 17.05, 17.0, 13.5, 13.09, 13.06, 12.7; LC-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{39}N_2O_7Si_2$ 487.23; found 487.24.

5.4. Experimental Section for Chapter IV

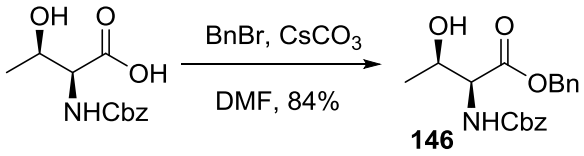
General Glycosylation Procedure: A 10 mL vial was charged with the peptide acceptor (0.10 mmol), copper triflate benzene complex (5.8 mg, 0.02 mmol), activated 4 Å molecular sieves (150 mg), the glycosyl donor (0.20 mmol) and 1,2-dichloroethane (1 mL). The mixture was stirred at 0 °C or room temperature for 15 min. The reaction mixture was then treated with *N*-iodosuccinimide (44 mg, 0.20 mmol) and allowed to stir at 0 °C or room temperature for 105 min. The reaction mixture was filtered through a 0.45 μM PTFE syringe filter, and then rinsed with dichloromethane (2× 5 mL). The organic solution was dried over anhydrous sodium sulfate, and concentrated. The residue was purified by using a pre-packed silica gel column or preparative silica thin layer chromatography plate to afford the glycosylation product.

Benzyl ((benzyloxy)carbonyl)-*L*-serinate (145). [104]



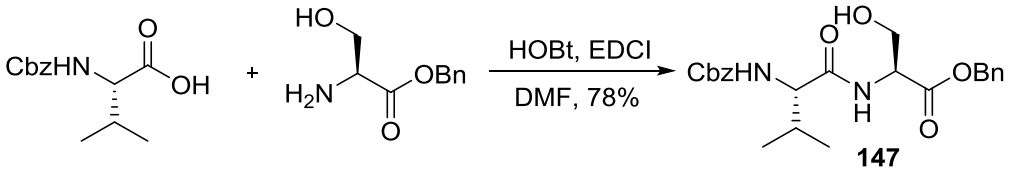
((Benzyloxy)carbonyl)-L-serine (1.0 g, 4.18 mmol) was dissolved in *N*, *N*-dimethylformamide (15.0 mL) and deionized water (5.0 mL), cesium carbonate (405 mg, 2.10 mmol) was added. After 30 minutes the reaction was concentrated, co-evaporated with toluene (3×10 mL), benzyl bromide (0.71 mL, 5.9 mmol) dissolved in *N*, *N*-dimethylformamide (10.0 mL) was then added. After 24 hours, water (15 .00 mL) was added, the mixture was extracted with ethyl acetate (2×30 mL). The combined extract was dried over anhydrous sodium sulfate and concentrated. The residue obtained was purified by flash column chromatography eluting with 1:3 ethyl acetate/hexane to afford **145** (1.23 g, 3.72 mmol, 89% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.35 (m, 10 H), 5.73 (d, 1 H, *J* = 6.3 Hz), 5.22 (s, 2 H), 5.12 (s, 2 H), 4.48-4.50 (m, 1 H), 3.95-4.00 (broad, 2 H), 2.17 (broad, 1 H), 1.62 (broad, 1 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 170.5, 156.4, 136.2, 135.2, 128.7, 128.6, 128.6, 128.3, 128.3, 128.2, 67.6, 67.3, 63.3, 56.3; LC-ESI-MS $[M+H]^+$ calcd for $C_{18}H_{19}NO_5$ 330.35; found 330.36.

Benzyl ((benzyloxy)carbonyl)-*L*-threoninate (146).[105]



Compound **146** was prepared by following the same procedure as compound **146** (84% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.35 (m, 10 H), 5.60 (d, 1 H, *J* = 8.7 Hz), 5.17-5.24 (m, 2 H), 5.13 (s, 2 H), 4.37-4.39 (m, 2 H), 1.97 (broad, 1 H), 1.63 (broad, 1 H), 1.23 (d, 1 H, *J* = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 156.9, 136.2, 135.3, 128.6, 128.5, 128.5, 128.2, 128.0, 68.0, 67.4, 67.2, 59.5, 19.9; LC-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{21}NO_5$ 344.14; found 344.03.

Benzyl ((benzyloxy)carbonyl)-*L*-valyl-*L*-serinate (147).

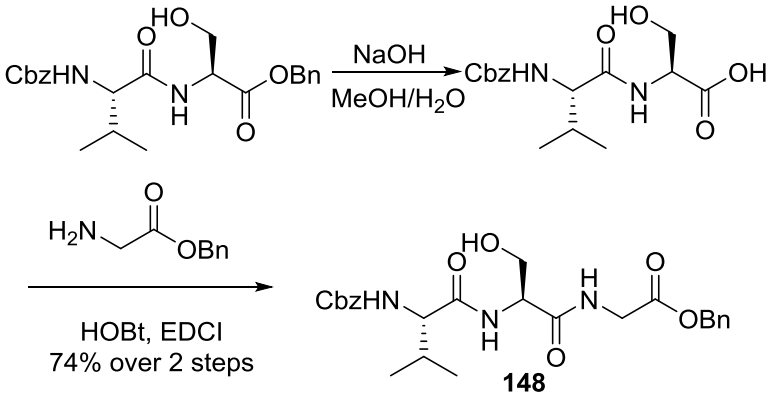


147

To a solution of *N*-(benzyloxycarbonyl)-*L*-valine (2.51 g, 10.0 mmol) and benzyl *L*-serinate (1.95 g, 10.0 mmol) in dry dichloromethane and dry dimethylformamide (10:1, 100 mL) was added 1-hydroxybenzotriazole (1.61 g, 12.0 mmol), *N*,*N*-diisopropylethylamine (3.80 mL, 24.0 mmol) and 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (2.29 g, 12.0 mmol) at 0 °C. After being stirred at the same temperature for 3 hours, the reaction mixture was poured into dichloromethane (100 mL) and 1.2 M aqueous hydrochloric acid (150 mL). The organic layer was separated and the aqueous layer was extracted with two portions of dichloromethane (50 mL). The combined extract was washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by flash chromatography on silica gel column eluting with 3:97 methanol/dichloromethane to afford compound **147 (**3.35 g, 78% yield) as a white solid:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.35 (m, 10 H), 6.87 (d, 1 H, *J* = 7.2 Hz),5.44 (d, 1 H, *J* = 8.1 Hz), 5.18-5.24 (m, 2 H), 5.10 (d, 1 H, *J* = 12.0 Hz), 5.04 (d, 1 H, *J* = 12.0 Hz), 4.70-4.72 (m, 1 H), 3.90-4.02 (m, 3 H), 2.04-2.13 (m, 1 H), 1.69 (broad, 2 H), 0.97 (d, 3 H, *J* = 6.6 Hz), 0.93 (d, 3 H, *J* = 6.6 Hz); ^{13}C NMR (125 Hz, $CDCl_3$) δ 171.9, 170.3, 157.0, 136.2, 135.2, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 67.6, 67.3, 62.9, 60.7, 54.8, 31.3, 19.3, 18.1; LC-ESI-MS $[M+H]^+$ calcd for $C_{23}H_{28}N_2O_6$ 428.19; found 429.28.

Benzyl ((benzyloxy)carbonyl)-*L*-valyl-*L*-serylglycinate (148).

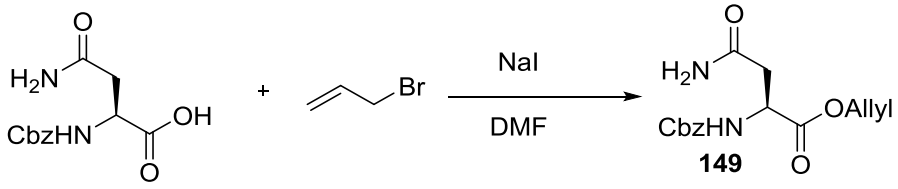


The solution of **147** (1.2 g, 2.80 mmol) in methanol (30 mL) was added 2 N sodium hydroxide (2.8 mL, 5.60 mmol) at room temperature. The mixture was allowed to stir at this temperature for 5 hours. The resulting reaction was concentrated in *vacuo* and the residue obtained was added 50 mL EtOAc and 50 mL 2 N aqueous hydrochloric acid solution. The organic layer was separated, dried over Na_2SO_4 and concentrated to afford 1.1 g crude acid as a white solid.

To a solution of above crude acid (1.1 g, 2.80 mmol) and benzyl glycinate hydrochloride (564 mg, 2.80 mmol) in dry dichloromethane and dry dimethylformamide

(10:1, 30 mL) was added 1-hydroxybenzotriazole (402 mg, 3.0 mmol), *N*,*N*-diisopropylethylamine (1.0 mL, 6.0 mmol) and 1-(3-dimethyl aminopropyl)-3-ethylcarbodiimide hydrochloride (763 mg, 3.0 mmol) at 0 °C. After being stirred at the same temperature for 3 hours, the reaction mixture was poured into dichloromethane (100 mL) and 1.2 M aqueous hydrochloric acid (100 mL). The organic layer was separated and the aqueous layer was extracted with two portions of dichloromethane (2×50 mL). The combined extract was washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by flash chromatography on silica gel column eluting with 4:96 methanol/dichloromethane to afford compound **148 (**1.0 g, 74% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO) δ 8.30 (t, 1 H, *J* = 5.4 Hz), 7.89 (d, 1 H, *J* = 7.8 Hz), 7.27-7.34 (m, 10 H), 5.20 (s, 2 H), 4.98-5.05 (m, 2 H), 4.86 (t, 1 H, *J* = 5.6 Hz), 4.33-4.38 (m, 1 H), 3.89-3.95 (m, 3 H), 3.55 (t, 2 H, *J* = 5.4 Hz), 1.96-2.01 (m, 1 H), 0.84 (d, 3 H, *J* = 6.7 Hz), 0.79 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR (125 Hz, DMSO) δ 171.1, 170.4, 169.6, 156.2, 137.1, 135.9, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6, 65.9, 65.5, 61.8, 60.1, 64.8, 40.8, 30.4, 19.2, 17.9; LC-ESI-MS $[M+H]^+$ calcd for $C_{25}H_{31}N_3O_7$ 485.22; found: 486.05.

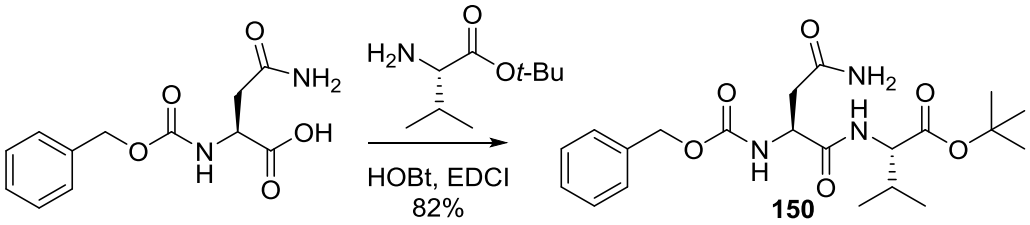
Allyl ((benzyloxy)carbonyl)-*L*-asparaginate (149).[81c]



To a solution of *N*-(benzyloxycarbonyl)-*L*-asparagine (2.0 g, 7.51 mmol) in 35 mL *N*, *N*-dimethylformamide was added allyl bromide (0.78 mL, 9.01 mmol) and sodium

iodide (1.64 g, 11.0 mmol) and sodium bicarbonate (630 mg, 7.51 mmol). After being stirred at room temperature for 24 hours, the reaction mixture was poured into ethyl acetate (150 mL) and water (150 mL). The organic layer was separated and the aqueous layer was extracted with two portions of ethyl acetate (2×50 mL). The combined extract was washed with 1.2 M aqueous hydrochloric acid solution (100 mL), saturated sodium bicarbonate aqueous solution (100 mL), and brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue obtained was purified by chromatography on silica gel column eluting with 1:3 ethyl acetate/hexane to afford **149** (1.79 g, 78%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5 H), 6.03 (d, 1 H, *J* = 4.0 Hz), 5.94-5.86 (m, 1 H), 5.57 (broad, 1 H), 5.45 (broad, 1 H), 5.32 (d, 1 H, *J* = 16.0 Hz), 5.25 (d, 1 H, *J* = 4.0 Hz), 5.13 (s, 2 H), 4.66 (d, 2 H, *J* = 4.0 Hz), 4.64-4.62 (m, 1 H), 3.00 (dd, 1 H, *J* = 4.0 and 16.0 Hz), 2.78 (dd, 1 H, *J* = 4.0 and 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.5, 171.1, 156.4, 136.4, 131.7, 128.7, 128.3, 128.2, 118.8, 67.2, 66.4, 50.9, 37.2; LC-ESI-MS $[M+H]^+$ calcd for $C_{15}H_{18}N_2O_5$ 307.12; found 306.93.

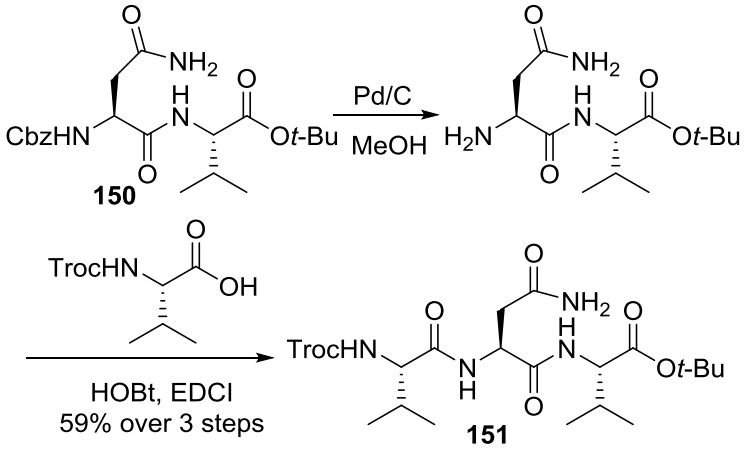
***tert*-Butyl ((benzyloxy)carbonyl)-*L*-asparaginyl-*L*-valinate (150).**[81c]



To a solution of *N*-(benzyloxycarbonyl)-*L*-asparagine (1.88 g, 7.06 mmol) and *L*-valine *tert*-butyl ester hydrochloride (1.48 g, 7.06 mmol) in dry dichloromethane and dry dimethylformamide (10:1, 70 mL) was added 1-hydroxybenzotriazole (1.14 g, 8.48 mmol), *N*, *N*-diisopropylethylamine (2.24 mL, 14.12 mmol) and 1-(3-dimethyl

aminopropyl)-3-ethylcarbodiimide hydrochloride (1.62 g, 8.48 mmol) at 0 °C. After being stirred at the same temperature for 3 hours, the reaction mixture was poured into dichloromethane (50 mL) and washed with 1.2 M aqueous hydrochloric acid (100 mL). The aqueous layer was extracted with two portions of dichloromethane (2×50 mL). The combined extract was washed with saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by silica gel flash chromatography eluting with 4:96 methanol/dichloromethane to afford **150** (2.40 g, 82% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.42 (m, 5H), 6.42 (d, 1 H, *J* = 7.2 Hz), 5.91 (s, 1 H), 5.47 (s, 1 H), 5.14 (s, 2 H), 4.58 (m, 1 H), 4.35 (dd, 1 H, *J* = 4.3 and 8.7 Hz), 2.96 (dd, 1 H, *J* = 3.4 and 16.0 Hz), 2.62 (dd, 1 H, *J* = 6.8 and 16.0 Hz), 2.17 (m, 1 H), 1.46 (s, 9 H), 0.91 (d, 3 H, *J* = 6.8 Hz), 0.89 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7 171.2, 170.5, 156.3, 136.2, 128.4, 128.1, 128.0, 81.8, 66.9, 57.9, 51.6, 37.0, 31.1, 28.0, 18.9, 17.5; LC-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{31}N_3O_6$ 423.22; found 421.98.

***tert*-Butyl ((2,2,2-trichloroethoxy)carbonyl)-*L*-valyl-*L*-asparaginyl-*L*-valinate (151).**[81c]

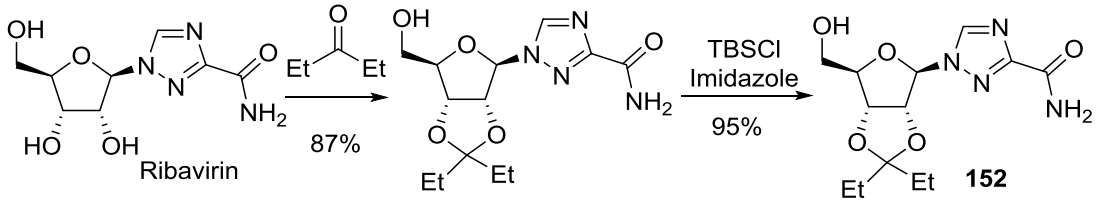


Palladium on carbon (0.30 g, 10 wt% on activated carbon) was added to a solution of *N*-(benzyloxycarbonyl)-*L*-asparaginyl-*L*-valine **150** (3.00 g, 7.63 mmol) in methanol (76.0 mL). The reaction mixture was exposed with hydrogen balloon for 3 hours. The resulting reaction was filtered through a pad of Celite and concentrated. The residue obtained was used for the next reaction without further purification.

To a solution of the above residue (7.63 mmol) and ((2,2,2-trichloroethoxy)carbonyl)-*L*-valine (2.67 g, 9.16 mmol) in dry dichloromethane and dry dimethylformamide (10:1, 76.0 mL) was added 1-hydroxybenzotriazole (1.45 g, 10.7 mmol), *N*,*N*-diisopropylethylamine (2.24 mL, 15.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.05 g, 10.7 mmol) at 0 °C. After being stirred at room temperature for 13 hours, the reaction mixture was poured into dichloromethane (100 mL) and washed with 1 M aqueous hydrochloric acid (100 mL). The aqueous layer was extracted with two portions of dichloromethane (50 mL). The combined extract was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated. The residue obtained was purified by C18 reverse-phase column eluting with 5% to 100% acetonitrile/water. The desired fraction was collected and dried by lypholizer to afford **151** (2.55 g, 59% yield over 2 steps) as a white solid: ^{1}H NMR (500 MHz, DMSO) δ 8.16 (d, 1 H, *J* = 9.5 Hz), 7.79 (d, 1 H, *J* = 10.4 Hz), 7.74 (d, 1 H, *J* = 11.0 Hz), 7.33 (s, 1 H), 6.93 (s, 1 H), 4.82 (d, 1 H, *J* = 15.5 Hz), 4.72 (d, 1 H, *J* = 15.5 Hz), 4.62 (m, 1 H), 3.99 (dd, 1 H, *J* = 7.0 and 10.3 Hz), 3.88 (dd, 1 H, *J* = 9.0 and 10.7 Hz), 2.49 (dd, 1 H, *J* = 6.7 and 19.4 Hz), 2.40 (dd, 1 H, *J* = 9.4 Hz and 19.9), 1.99 (m, 1 H), 1.37 (s, 9 H), 0.81-0.89 (m, 12 H); ^{13}C NMR (125 MHz, DMSO) δ 171.4, 170.9, 170.6, 170.2, 154.6, 96.1, 80.6, 73.5, 60.5,

60.0, 57.9, 51.7, 49.3, 37.1, 30.3, 30.0, 27.6, 19.1, 18.8, 18.1, 17.8; LC-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{35}Cl_3N_4O_7$ 561.16; found 561.12.

1-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2-diethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1*H*-1,2,4-triazole-3-carboxamide (152).

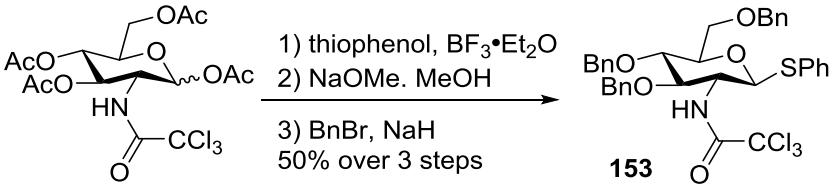


Trimethyl orthoformate (3.18 g, 30.0 mmol) and 4-methylbenzenesulfonic acid monohydrate (0.38 g, 2.00 mmol) was added to a stirred solution of Ribavirin (2.44 g, 10.0 mmol) in 3-pentanone (20 mL). The reaction was stirred at 50 °C for 2 hours and concentrated. A solution of the residue in 10 mL of dimethyl sulfoxide was chromatographed with a pre-packed C18 reverse phase column (120 g), eluting with 5% to 90% acetonitrile/water. The fractions containing product were combined and lyophilized to afford alcohol (2.72 g, 87% yield) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1 H), 6.21 (d, 1 H, *J* = 1.5 Hz), 5.28 (dd, 1 H, *J* = 1.5 and 6.3 Hz), 4.96 (dd, 1 H, *J* = 2.0 and 6.3 Hz), 4.39 (m, 1 H), 3.62 (dd, 1 H, *J* = 5.4 and 11.7 Hz), 3.56 (dd, 1 H, *J* = 5.4 and 11.7 Hz), 1.78 (q, 2 H, *J* = 7.8 and 15.1 Hz), 1.65 (q, 2 H, *J* = 7.3 and 15.1 Hz), 0.98 (t, 3 H, *J* = 7.3 Hz), 0.89 (t, 3 H, *J* = 7.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 163.2, 158.3, 146.7, 118.9, 95.3, 90.7, 86.5, 83.6, 63.3, 30.2, 30.1, 8.7, 8.0; LC-ESI-MS $[M+H]^+$ calcd for 313.14; found 313.00.

Imidazole (1.19 g, 17.42 mmol) and *tert*-butyldimethylsilyl chloride (1.97 g, 13.06 mmol) were added to a stirred solution of above alcohol (2.72 g, 8.71 mmol) in 10

mL *N*, *N*-dimethylformamide. The mixture was stirred at room temperature for overnight and diluted with ethyl acetate (100 mL). The mixture was washed successively with water (100 mL), brine (100 mL), dried over magnesium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 1:4 ethyl acetate/hexane to give **152** (3.53 g, 95% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.02 (s, 1 H), 6.55 (broad, 1 H), 6.05 (s, 1 H), 5.32 (d, 1 H, *J* = 5.8 Hz), 4.83 (d, 1 H, *J* = 6.3 Hz), 4.51 (dd, 1 H, *J* = 4.4 and 4.9 Hz), 3.74 (dd, 1 H, *J* = 4.4 and 11.2 Hz), 3.64 (dd, 1 H. *J* = 4.9 and 11.2 Hz), 1.78 (q, 2 H, *J* = 7.3 and 14.6 Hz), 1.63 (q, 2 H, *J* = 7.3 and 14.6 Hz), 0.97 (t, 3 H, *J* = 7.3 Hz), 0.89 (t, 3 H, *J* = 7.3 Hz), 0.82 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 157.2, 144.0, 118.2, 95.4, 89.5, 85.7, 82.0, 63.7, 29.5, 29.2, 26.0, 18.4, 8.6, 7.8, 5.4, 5.4; LC-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{34}N_4O_5Si$ 427.23; found 427.06.

_N_-((2_S_,3_R_,4_R_,5_S_,6_R_)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-(phenylthio)tetrahydro-2_H_-pyran-3-yl)-2,2,2-trichloroacetamide (153).[106]



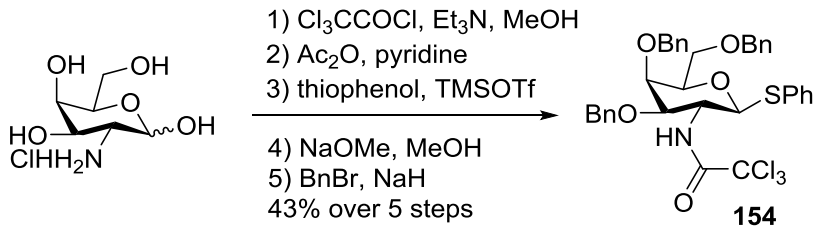
Thiophenol (2.3 mL, 22.4 mmol) and boron trifluoroboron etherate (4.3 mL, 33.6 mmol) were added at room temperature to a solution of commercial available 1,3,4,6-tetra –O-acetyl-2-deoxyl-2-(trichloroactyl)amino]-*β*-D-glucopyranose (5.5 g, 11.2 mmol) in anhydrous dichloromethane (100 mL). The mixture was stirred at room temperature for 15 hours and quenched with saturated sodium bicarbonate aqueous solution (100 mL).

The organic phase was separated, dried over magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography eluting with 4:6 ethyl acetate/hexane to give thioglycoside (4.1 g, 68% yield) as a white solid.

A solution of above thioglycoside (4.0 g, 7.37 mmol) in anhydrous methanol (80 mL) was treated with sodium methoxide (40 mg, 0.74 mmol). The solution was stirred at room temperature under nitrogen for 2 hours and quenched with Dowex-H^+ resin. The resin was filtered, and the filtrate was concentrated to give 3.07 g white solid. This residue was dissolved in anhydrous dimethylformamide (40 mL), the solution was cooled to –10 °C, and benzyl bromide (5.2 mL, 43.92 mmol) and sodium hydride (60% in oil, 1.77 g, 43.92 mmol) were successively added. The mixture was stirred under nitrogen keeping the temperature below 0 °C for 2 hours. The reaction was quenched with 5 mL methanol, diluted with ethyl acetate (150 mL), and washed with water (100 mL) and brine (100 mL). The organic phase was dried with anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with dichloromethane to give 4.1 g crude **153**. It was recrystallized in 7% ethyl acetate in hexane to afford **153** (3.62 g, 72% yield) as a white solid: ^{1}H NMR (400 Hz, $CDCl_3$) δ 7.56 (d, 2 H, *J* = 1.7 Hz), 7.20–7.54 (m, 18 H), 6.89 (d, 1 H, *J* = 10.5 Hz), 5.13 (d, 1 H, *J* = 12.5 Hz), 4.78 (dd, 1 H, *J* = 6.6 and 13.4 Hz), 4.68 (d, 1 H, *J* = 13.4 Hz), 4.64 (d, 1 H, *J* = 11.1 Hz), 4.60 (d, 1 H, *J* = 9.9 Hz), 4.56 (d, 1 H, *J* = 14.9 Hz), 4.10 (dd, 1 H, *J* = 10.3 and 11.9 Hz), 3.82 (dd, 1 H, *J* = 2.9 and 13.5 Hz), 3.77 (dd, 1 H, *J* = 4.9 and 13.5 Hz), 3.57-3.70 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 138.3, 137.9, 137.7, 133.2, 132.2, 129.2, 128.7, 128.6, 128.5, 128.4, 128.1, 128.05; 128.0, 127.9, 127.8, 127.7, 92.6,

84.7, 81.5, 79.4, 78.4, 75.5, 74.9, 73.6, 69.0, 56.9; LC-ESI-MS $[M+Na]^+$ calcd for $C_{35}H_{34}Cl_3NO_5S$ 709.11; found 709.28.

_N_-((2_S_,3_R_,4_R_,5_R_,6_R_)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-(phenylthio)tetrahydro-2_H_-pyran-3-yl)-2,2,2-trichloroacetamide (154).[106]



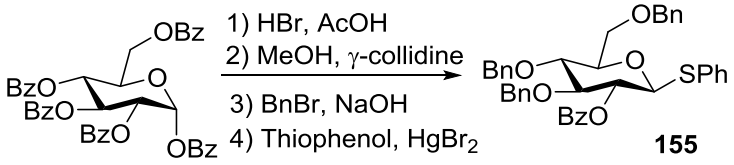
Triethylamine (16.5 mL, 116.0 mmol) was added to a suspension of D-(+)-galactosamine hydrochloride (12.5 g, 58.0 mmol) in MeOH (100 mL) at 0 °C. Trichloroacetyl chloride (6.5 mL, 58.0 mmol) was then added by drops. The suspension was warmed to room temperature and stirred for 48 hours. The reaction was filtered through a plug of Celite, washed with methanol, and the solvent was removed in *vacuo*. The crude residue was dissolved in pyridine (100 mL) and cooled to 0 °C. Acetic anhydride (50 mL) was added by drops, and the solution was allowed to warm to room temperature and stirred for 16 h. The reaction was filtered through a Celite plug, and solvent removed in *vacuo*. The crude material was taken in ethyl acetate (150 mL) and the organic washed with 1 M hydrochloric acid (3×50 mL), saturated aqueous sodium bicarbonate (3 ×50 mL), brine (100 mL), dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography eluting with 1:3 ethyl acetate/hexane to provide 15.0 g 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranose.

To above 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-trichloroacetamido-*β*-D-galactopyranose (15.0 g, 30.4 mmol) dissolved in dry dichloromethane (100 mL) at room temperature under nitrogen was added thiophenol (4.1 mL, 39.6 mmol) and trimethylsilyl trifluoromethanesulfonate (5.5 mL, 30.4 mmol) by drops. The resulting dark red solution was stirred at room temperature for 18 hours and then poured onto a vigorously stirred solution of aqueous sodium bicarbonate (10.0 g in 30 mL water) and stirred for 30 minutes. The layers were separated, and the aqueous extracted with dichloromethane (100 mL). The organic was combined, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography eluting with 1:4 ethyl acetate/hexane to provide 9.0 g glycoside as a brown solid.

A solution of thioglycoside (9.0 g, 16.58 mmol) in anhydrous methanol (100 mL) was treated with sodium methoxide (0.5 M in methanol, 830 μL, 1.66 mmol). The reaction was stirred at room temperature under nitrogen for 2 hours and quenched with Dowex-H^+ resin. The resin was filtered, and the filtrate was concentrated. This residue was dissolved in anhydrous dimethylformamide (100 mL), and cooled to –10 °C. Benzyl bromide (3.3 mL, 27.6 mmol) and sodium hydride (60% in mineral oil, 1.11 g, 27.6 mmol) were successively added. The mixture was stirred under nitrogen for 2 hours and quenched with 1 mL methanol. The reaction mixture was diluted with ethyl acetate (150 mL), and washed with water (2×100 mL), brine (100 mL), dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash chromatography eluting with dichloromethane to give 5.4 g crude **154**. It was recrystallized in 7% ethyl acetate in hexane to afford **154** (4.9 g, 43%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.53 (m, 2 H), 7.18–7.37 (m, 18 H), 6.82 (d, 1 H, *J* = 7.4 Hz), 5.28 (d, 1 H, *J* = 10.2 Hz),

4.88 (d, 1 H, *J* = 11.4 Hz), 4.67 (d, 1 H, *J* = 11.2 Hz), 4.56 (d, 1 H, *J* = 11.2 Hz), 4.52 (d, 1 H, *J* = 11.2 Hz), 4.51 (d, 1 H, *J* = 11.2 Hz), 4.45 (d, 1 H, *J* = 11.2 Hz), 4.26 (dd, 1 H, *J* = 2.7 and 10.5 Hz), 4.06 (d, 1 H, *J* = 2.1 Hz), 3.88-3.95 (m, 1 H), 3.67–3.76 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 138.5, 137.9, 137.4, 132.8, 132.4, 129.0, 128.8, 128.7, 128.5, 128.3, 128.2, 128.17, 128.02, 128.0, 127.9, 127.8, 127.6, 92.6, 84.5, 78.5, 74.6, 73.7, 72.7, 72.5, 68.6, 53.8; LC-ESI-MS $[M+Na]^+$ calcd for $C_{35}H_{34}Cl_3NO_5SNa$ 708.11; found 708.29.

(2*S*,3*R*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-(phenylthio)tetrahydro-2*H*-pyran-3-yl benzoate (155).[107]



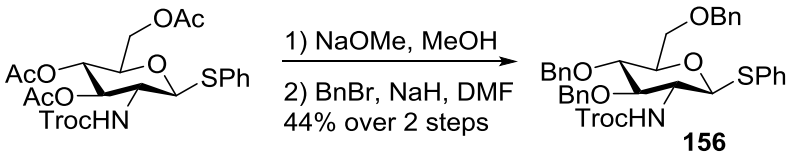
A solution of α-D-glucopyranose pentabenzoate (6.20 g, 8.85 mmol) in dry 50 mL dichloromethane was added dropwise 33% hydrogen bromide solution in acetic acid (3.18 mL, 53.1 mmol). The reaction mixture was stirred under nitrogen for 16 hours at room temperature, and then diluted with 100 mL dichloromethane, washed with 100 mL water, saturated aqueous sodium bicarbonate and water. The organic phase was separated, dried over anhydrous magnesium sulfate and concentrated. The resulting residue was then dissolved in 50 mL nitromethane, to which molecular sieves (4Å, 1.50 g) were added and the resulting mixture was stirred under nitrogen for 1 hour. The flask was then covered with foil, added sequentially with γ-collidine (1.50 mL, 11.36 mmol), dry methanol (0.34 mL, 8.9 mmol), and *tert*-butylammonium bromide (5.0 mmol, 1.62

g). After stirring for 16 hours, triethylamine (0.4 mL) was added, the solid was filtered off and the filtrate was washed with 100 mL saturated aqueous sodium bicarbonate. The organic layer was separated, and the remaining aqueous layer was extracted with 2 × 50 mL dichloromethane. The combined organic fraction was washed with water, then dried over magnesium sulfate and concentrated. The crude mixture was simultaneously debenzoylated and benzylated by a previously reported procedure.[108] The compound was purified by column chromatography on silica gel eluting with 3:7 ethyl acetate/hexane to give known compound orthoester (3.57 g, 71% yield) as light yellow gel.

The above orthoester (3.57 g, 6.28 mmol) was mixed with molecular sieves (4 Å, 1.5 g), dry acetonitrile (40 mL), and the resulting mixture was stirred under mitogen for 30 minutes. Thiophenol (2.35 g, 21.3 mmol) and mercuric(II) bromide (0.076 g, 0.211 mmol) were added, and the mixture was refluxed for 2.5 hours. The resulting reaction was filtered and the filtrate was concentrated. The residue was diluted with dichloromethane (20 mL) and washed successively with 1% aqueous sodium hydroxide (30 mL), water (2 × 30 mL), dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give donor **155** (3.04 g, 75% yield) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.05 (m, 2 H), 7.61-7.8 (m, 1H), 7.44-7.50 (m, 4 H), 7.19-7.36 (m, 13 H), 7.11-7.14 (m, 5 H), 5.29 (dd, 1 H, *J* = 7.6 and 8.0 Hz), 4.82 (d, 1 H, *J* = 9.2 Hz), 4.79 (d, 1 H, *J* = 8.4 Hz), 4.73 (d, 1 H, *J* = 8.8 Hz), 4.64 (d, 1 H, *J* = 8.4 Hz), 4.56-4.61 (m, 3 H), 3.82-3.87 (m, 2 H), 3.73-3.78 (m, 2 H), 3.61-3.64 (m, 1 H), 1.56 (broad, 1 H); ^{13}C NMR(125 MHz, $CDCl_3$) δ 165.4, 138.4,138.1, 137.8, 133.4, 133.1, 132.7, 130.1, 130.0, 129.0, 128.6, 128.6, 128.5, 128.4, 128.2, 128.2, 127.9, 127.9, 127.8, 86.3, 84.5,

79.7, 75.5, 75.3, 73.7, 72.6, 69.2; LC-ESI-MS $[M+Na]^+$ calcd for $C_{40}H_{38}O_6S$ 669.23; found: 669.19.

2,2,2-Trichloroethyl ((2*S*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-2-(phenylthio)tetrahydro-2*H*-pyran-3-yl)carbamate (156).[81c]

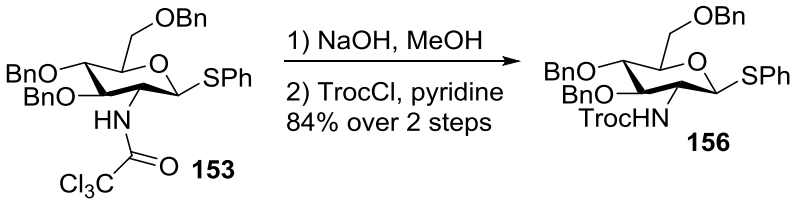


Method 1:

Sodium methoxide (24 mg, 0.44 mmol) was added to a solution of commercial available *(*2*R*,3*S*,4*R*,5*R*,6*S)*-2-(acetoxymethyl)-6-(phenylthio)-5-(((2,2,2-trichloroethoxy)carbonyl)amino)tetrahydro-*2H*-pyran-3,4-diyl diacetate (2.50 g, 4.36 mmol) in methanol (50 mL). The reaction mixture was allowed to stir overnight, and then was neutralized with Dowex50x8-100 acidic resin. The resin was filtered, and the filtrate was concentrated to afford the crude triol as a white solid, which was dried azeotropically with toluene (3 ×5 mL) and taken to the next step without further purification.

The above triol (4.36 mmol) in dimethylformamide (20 mL) was added 60% sodium hydride in mineral oil (697 mg, 17.44 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 30 minutes. Benzyl bromide (2.6 mL, 21.80 mmol) was added, and the mixture was stirred at room temperature for 24 hours. The resulting reaction was added 100 mL saturated aqueous ammonium chloride and extracted with ethyl acetate (3 × 50 mL). The combined extract was dried over magnesium sulfate and concentrated.

The residue was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate/hexane to give donor **156** (1.37 g, 1.92 mmol, 44% yield) as a white solid.



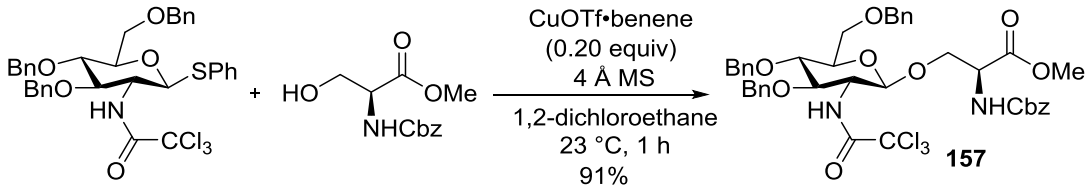
Method 2:

Potassium hydroxide (163 mg, 2.91 mmol) was added to a solution of **153** (2.0 g, 2.91 mmol) in methanol (30 mL)/water (5 mL). The reaction mixture was allowed to stir at 90 °C overnight. It was concentrated to remove most of solvent. The residue was purified by column chromatography eluting with 10% MeOH/DCM to give 1.50 g thioglycoside as white solid.

The above thioglycoside (1.50 g, 2.77 mmol) in 25 mL dichloromethane at 0 °C was added pyridine (0.45 mL, 5.54 mmol) and 2,2,2-trichlorethoxycarbonyl chloride (0.42 mL, 3.05 mmol). The mixture was stirred at this temperature for 1 hour before it was added 50 mL saturated sodium bicarbonate aqueous solution. The organic was separated and the aqueous was extracted with 50 mL dichloromethane. The combined organic was dried over anhydrous sodium sulfate and concentrated. The residue was crystallized from 5% Ethyl acetate/hexane to give **156** (1.75 g, 2.44 mmol) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.54 (m, 2H), 7.21–7.35 (m, 18 H), 5.09 (d, 1 H, *J* = 8.5 Hz), 4.95 (d, 1 H, *J* = 10.5 Hz), 4.70-4.84 (m, 5 H), 4.61-4.63 (m, 2 H), 4.55 (d, 1 H, *J* = 12.0 Hz), 3.89 (t, 1 H, *J* = 8.5 Hz), 3.79 (d, 1 H, *J* = 11.0 Hz), 3.75 (dd, 1 H, *J* = 4.0 and 11.5 Hz), 3.66 (t, 1 H, *J* = 9.0 Hz), 3.58 (broad, 1 H), 3.45-3.48 (m, 1 H); ^{13}C

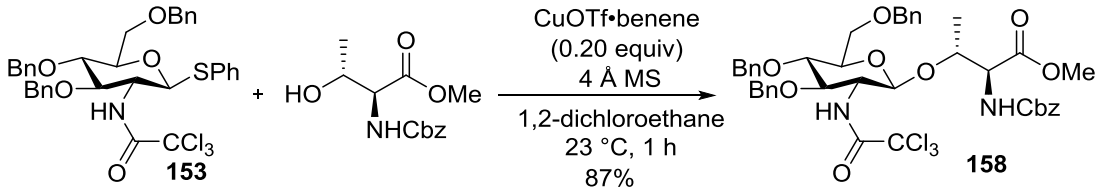
NMR (125 MHz, $CDCl_3$) δ 153.9, 138.4, 138.1, 132.2, 129.1, 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.95, 127.8, 127.7, 85.9, 82.4, 79.4, 78.6, 77.4, 75.4, 75.0, 74.6, 73.6, 69.1, 56.8; LC-ESI-MS $[M+Na]^+$ calcd for $C_{36}H_{36}Cl_3NO_6SNa$ 738.12; found 738.29.

Methyl *N*-((benzyloxy)carbonyl)-*O*-((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-L-serinate (157).



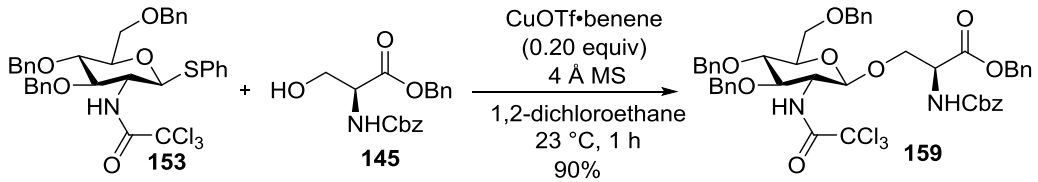
By following the general procedure, donor **153** (103.1 mg, 0.15 mmol) was reacted with commercial available methyl ((benzyloxy)carbonyl)-*L*-serinate (25.3 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **157** (75.5 mg, 91%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.35 (m 18 H), 7.18-7.20 (m, 2 H), 6.98 (d, 1 H, *J* = 7.6 Hz), 5.70 (d, 1 H, *J* = 8.2 Hz), 5.07-5.13 (m, 2 H), 4.84 (d, 1 H, *J* = 7.6 Hz), 4.77 (d, 1 H, *J* = 10.3 Hz), 4.75 (d, 1 H, *J* = 10.1 Hz), 4.68 (d, 1 H, *J* = 11.2 Hz), 4.50-4.60 (m, 4 H), 4.30 (dd, 1 H, *J* = 3.0 and 10.4 Hz), 4.05 (t, 1 H, *J* = 8.9 Hz), 3.80 (dd, 1 H, *J* = 2.9 and 10.0 Hz), 3.69-3.74 (m, 6 H), 3.57-3.60 (m, 2 H), 1.85 (broad, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 161.9, 156.1, 137.9, 137.7, 136.2, 128.5, 128.44, 128.42, 128.2, 128.1, 127.9, 127.8, 127.7, 99.4, 92.4, 79.5, 77.9, 75.0, 74.8, 74.6, 73.5, 69.1, 68.6, 67.1, 57.5, 54.2, 52.7; LC-ESI-MS $[M+H]^+$ calcd for $C_{41}H_{43}Cl_3N_2O_{10}$ 829.20; found 829.37.

Methyl *N*-((benzyloxy)carbonyl)-*O*-((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-L-threoninate (158).



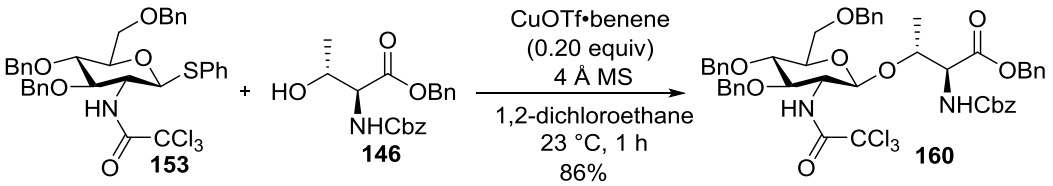
By following the general procedure, donor **153** (103.1 mg, 0.15 mmol) was reacted with commercial available methyl ((benzyloxy)carbonyl)-*L*-threoninate (26.7 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 7:3 hexane/ethyl acetate as eluant afforded **158** (73.4 mg, 87%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.35 (m 18 H), 7.19-7.21 (m, 2 H), 7.04 (d, 1 H, J = 7.6 Hz), 5.75 (d, 1 H, J = 8.7 Hz), 5.09-5.16 (m, 2 H), 4.91 (d, 1 H, J = 8.2 Hz), 4.78-4.83 (m, 2 H), 4.69 (d, 1 H, J = 10.1 Hz), 4.60 (d, 1 H, J = 10.1 Hz), 4.55 (d, 1 H, J = 12.0 Hz), 4.48 (d, 1 H, J = 12.1 Hz), 4.40-4.42 (m, 1 H), 4.35 (dd, 1 H, J = 2.6 and 8.8 Hz), 4.14 (t, 1 H, J = 9.2 Hz), 3.71-3.76 (m, 2 H), 3.68 (s, 3 H), 3.42-3.52 (m, 2 H), 2.17 (broad, 1 H), 1.22 (d, 3 H, J = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 161.9, 156.8, 138.0, 138.0, 137.9, 136.4, 128.59, 128.56, 128.5, 128.48, 128.2, 128.1, 128.0, 127.9, 127.86, 127.8, 127.78, 97.3, 92.5, 79.7, 78.4, 75.0, 74.8, 74.5, 73.7, 68.7, 67.1, 57.8, 58.6, 52.5, 17.4; LC-ESI-MS $[M+H]^+$ calcd for $C_{42}H_{45}Cl_3N_2O_{10}$ 843.21; found: 843.14.

Benzyl *N*-((benzyloxy)carbonyl)-*O*-((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-*L*-serinate (159).



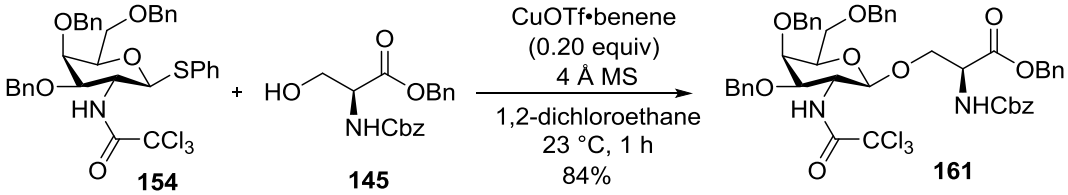
By following the general procedure, donor **153** (103.1 mg, 0.15 mmol) was reacted with acceptor **145** (32.9 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 7:3 hexane/ethyl acetate as eluant afforded **159** (81.6 mg, 90%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.33 (m, 23 H), 7.18-7.20 (m, 2 H), 6.93 (d, 1 H, *J* =7.6 Hz), 5.71 (d, 1 H, *J* = 8.3 Hz), 5.16-5.18 (m, 2 H), 5.06-5.12 (m, 2 H), 4.84 (d, 1 H, *J* = 7.7 Hz), 4.78 (d, 1 H, *J* = 5.0 Hz), 4.75 (d, 1 H, *J* = 5.0 Hz), 4.67 (d, 1 H, *J* = 11.0 Hz), 4.58 (d, 1 H, *J* = 11.4 Hz), 4.54 (d, 1 H, *J* = 11.4 Hz), 4.47 (d, 1 H, *J* = 12.1 Hz), 4.35 (dd, 1 H, *J* = 2.9 and 10.1 Hz), 4.06 (t, 1 H, *J* = 9.0 Hz), 3.81 (dd, 1 H, *J* = 3.0 and 10.1 Hz), 3.68-3.72 (m, 2 H), 3.46-3.55 (m, 2 H), 1.64 (broad, 1 H), 1.26 (broad, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 162.0, 156.1, 138.0, 137.9, 137.8, 136.3, 135.5, 128.7, 128.6, 128.58, 128.5, 128.49, 128.4, 128.2, 128.19, 128.1, 128.0, 127.97, 127.94, 127.9, 127.88, 127.8, 99.4, 92.5, 79.6, 78.1, 77.5, 75.1, 75.0, 74.7, 73.7, 69.3, 68.7, 67.4, 67.2, 57.9, 54.4, 29.8; LC-ESI-MS $[M+H]^+$ calcd for $C_{47}H_{47}Cl_3N_2O_{10}$ 905.23; found 905.14.

Benzyl *N*-((benzyloxy)carbonyl)-*O*-((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-*L*-threoninate (160).



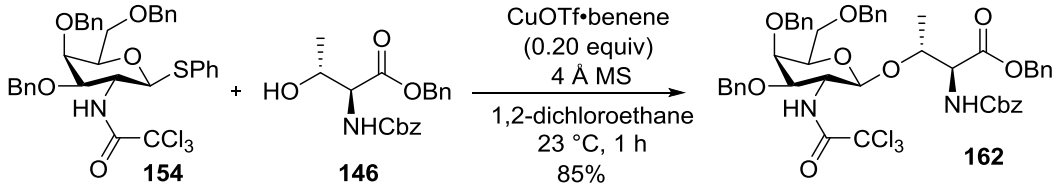
By following the general procedure, donor **153** (103.1 mg, 0.15 mmol) was reacted with acceptor **146** (34.3 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 7:3 hexane/ethyl acetate as eluant afforded **160** (79.1 mg, 86%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.35 (m, 23 H), 7.17-7.20 (m, 2 H), 6.89 (d, 1 H, *J* =7.5 Hz), 5.73 (d, 1 H, *J* = 8.9 Hz), 5.19 (d, 1 H, *J* = 12.4 Hz), 5.11-5.14 (m, 2 H), 4.89 (d, 1 H, *J* = 8.1 Hz), 4.79 (t, 2 H, *J* = 10.6 Hz), 4.66 (d, 1 H, *J* = 11.0 Hz), 4.57 (d, 1 H, *J* = 11.0 Hz), 4.45-4.48 (m, 2 H), 4.36-4.40 (m, 1 H), 4.10 (t, 1 H, *J* = 9.9 Hz), 3.63-3.70 (m, 2 H), 3.33-3.39 (m, 2 H), 1.71 (broad, 1 H), 1.27 (broad, 1 H),1.21 (d, 3 H, *J* = 6.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 161.9, 156.8, 138.0, 138.0, 137.9, 136.4, 135.6, 128.6, 128.59, 128.55, 128.5, 128.4, 128.39, 128.2, 128.16, 128.1, 128.0, 127.94, 127.9, 127.8, 127.78, 127.7, 97.1, 92.5, 79.6, 78.4, 75.1, 75.0, 74.8, 74.5, 73.6, 68.6, 67.3, 67.1, 58.9, 58.7, 17.4; LC-ESI-MS $[M+H]^+$ calcd for $C_{48}H_{49}Cl_3N_2O_{10}$ 919.25; found 919.13.

Benzyl *N*-((benzyloxy)carbonyl)-*O*-((2*R*,3*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-*L*-serinate (161).



By following the general procedure, donor **154** (103.1 mg, 0.15 mmol) was reacted with acceptor **145** (32.9 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 7:3 hexane/ethyl acetate as eluant afforded **161** (76.1 mg, 84%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.37 (m, 23 H), 7.16-7.18 (m, 2 H), 6.82 (d, 1 H, *J* = 7.0 Hz), 5.66 (d, 1 H, *J* = 8.3 Hz), 5.20 (d, 1 H, *J* = 12.5 Hz), 5.14 (d, 1 H, *J* = 12.6 Hz), 5.10 (d, 1 H, *J* = 12.4 Hz), 5.05 (d, 1 H, *J* = 12.3 Hz), 4.87-4.91 (m, 2 H), 4.65 (d, 1 H, *J* = 11.3 Hz), 4.57 (d, 1 H, *J* = 11.3 Hz), 4.47-4.52 (m, 2 H), 4.43 (d, 1 H, *J* = 11.5 Hz), 4.42 (d, 1 H, *J* = 11.5 Hz), 4.33 (dd, 1 H, *J* = 2.7 and 10.1 Hz), 4.17 (dd, 1 H, *J* = 2.5 and 11.0 Hz), 4.02 (d, 1 H, *J* = 2.3 Hz), 3.73-3.78 (m, 2 H), 3.56-3.64 (m, 3 H), 1.61 (broad, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 162.1, 156.1, 138.3, 137.8, 137.5, 136.2, 135.4, 128.6, 128.57, 128.53, 128.5, 128.4, 128.3, 128.2, 128.1, 128.09, 128.0, 127.9, 127.8, 127.79, 127.6, 99.4, 92.5, 77.3, 74.9, 73.7, 73.6, 72.5, 72.4, 69.2, 68.3, 67.3, 67.1, 55.7, 54.3; LC-ESI-MS $[M+H]^+$ calcd for $C_{47}H_{47}Cl_3N_2O_{10}$ 905.23; found 905.14.

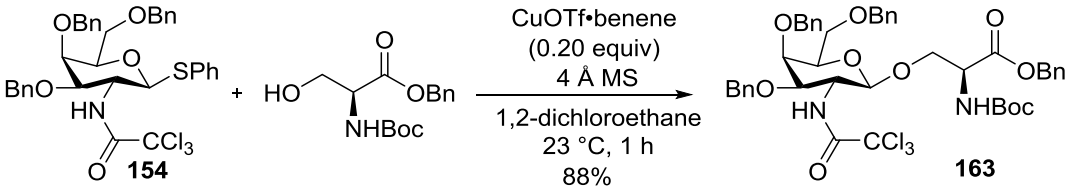
Benzyl *N*-((benzyloxy)carbonyl)-*O*-((2*R*,3*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-*L*-threoninate (162).



By following the general procedure, donor **154** (103.1 mg, 0.15 mmol) was reacted with acceptor **146** (34.3 mg, 0.10 mmol) at room temperature for 2 hours. After

work-up, purification by thin-layer chromatography with 7:3 hexane/ethyl acetate as eluant afforded **162** (78.2 mg, 85%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.35 (m, 25 H), 6.84 (d, 1 H, *J* = 7.1 Hz, 1 H); 5.68 (d, *J* = 8.7 Hz, 1 H); 5.06-5.15 (m, 3 H); 4.93 (d, *J* = 8.2 Hz, 1 H); 4.85 (d, *J* = 11.3 Hz), 4.63 (d, 1 H, *J* = 11.3 Hz), 4.54 (d, 1 H, *J* = 11.3 Hz), 4.49 (d, 1 H, *J* = 11.3 Hz), 4.38-4.42 (m, 1 H), 4.34 (d, 1 H, *J* = 11.3 Hz), 4.33 (d, 1 H, *J* = 11.3 Hz), 4.16 (dd, 1 H, *J* = 2.6 and 11.0 Hz), 3.99 (d, 1 H, *J* = 2.2 Hz), 3.57-3.70 (m, 2 H), 3.66-3.53 (m, 2 H), 1.61 (broad, 1 H), 1.18 (d, 1 H, *J* = 6.3 Hz); ^{13}C NMR (125 Hz, $CDCl_3$): 170.1, 161.9, 156.8, 138.4, 137.9, 137.5, 136.4, 135.5, 128.7, 128.6, 128.5, 128.3, 128.26, 128.2, 128.14, 128.1, 128.02, 128.0, 127.89, 127.8, 127.7, 97.1, 92.6, 77.0, 74.9, 74.4, 73.5, 73.5, 72.6, 72.3, 68.1, 67.2, 67.0, 58.9, 55.9, 17.2; LC-ESI-MS $[M+H]^+$ calcd for $C_{48}H_{49}Cl_3N_2O_{10}$ 919.25; found 919.24.

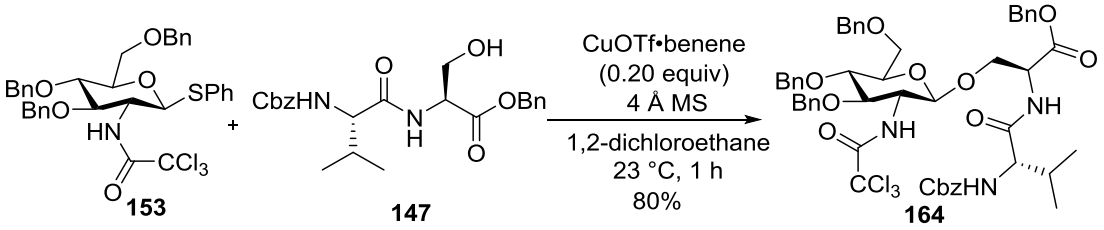
Benzyl *O*-((2*R*,3*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-*N*-(tert-butoxycarbonyl)-L-serinate (163).



By following the general procedure, donor **154** (103.1 mg, 0.15 mmol) was reacted with commercial available benzyl (tert-butoxycarbonyl)-*L*-serinate (29.5 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 7:3 hexane/ethyl acetate as eluant afforded **163** (76.8 mg, 88%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24- 7.38 (m, 24 H), 7.12-7.16 (m, 1 H), 6.87

(d, 1 H, *J* = 7.0 Hz), 5.38 (d, 1 H, *J* = 8.6 Hz), 5.23 (d, 1 H, *J* = 12.6 Hz), 5.11 (d, 1 H, *J* = 12.6 Hz), 4.91 (d, 1 H, *J* = 11.2 Hz), 4.89 (d, 1 H, *J* = 11.2 Hz), 4.66 (d, 1 H, *J* = 11.3 Hz), 4.58 (d, 1 H, *J* = 11.2 Hz), 4.52 (d, 1 H, *J* = 11.3 Hz), 4.43-4.47 (m, 2 H), 4.36 (dd, 1 H, *J* = 2.5 and 9.8 Hz), 4.22 (dd, 1 H, *J* = 2.2 and 11.0 Hz), 4.03 (d, 1 H, *J* = 2.0 Hz), 3.57-3.75 (m, 6 H), 1.41(s, 9 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 170.1, 162.1, 155.5, 138.4, 137.8, 137.5, 135.6, 128.7, 128.6, 128.41, 128.37, 128.13, 128.12, 128.1, 128.0, 127.9, 127.8, 99.4, 92.6, 80.1, 77.3, 75.0, 73.7, 72.6, 72.4, 69.6, 68.3, 67.2, 55.9, 53.9, 28.4; LC-ESI-MS $[M+H]^+$ calcd for $C_{44}H_{49}Cl_3N_2O_{10}$ 871.25; found 871.22.

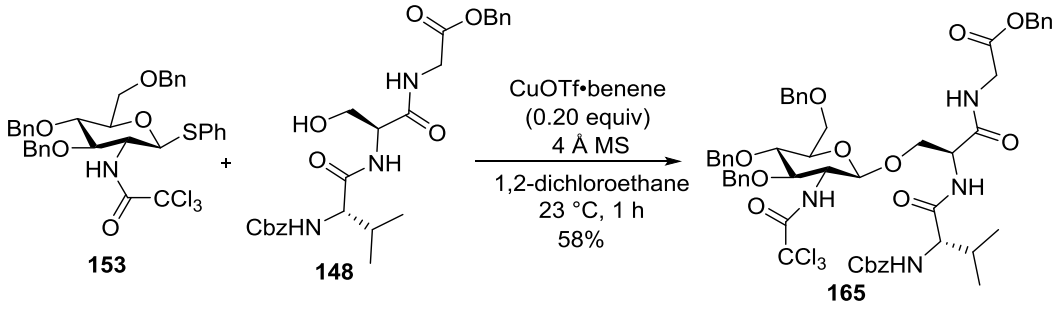
Benzyl *N*-(((benzyloxy)carbonyl)-*L*-valyl)-*O*-((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-*L*-serinate (164).



By following the general procedure, donor **153** (103.1 mg, 0.15 mmol) was reacted with acceptor **147** (42.8 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **164** (80.4 mg, 80%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 1 H, *J* = 8.8 Hz), 7.14-7.37 (m, 23 H), 7.14-7.16 (m, 2 H), 6.75 (d, 1 H, *J* = 7.4 Hz), 5.37 (d, 1 H, *J* = 8.1 Hz), 5.18 (s, 2 H), 5.11 (d, 1 H, *J* = 12.5 Hz), 5.05 (d, 1 H, *J* = 12.5 Hz), 4.19-4.77 (m, 2 H), 4.66 (d, 1 H, *J* = 10.7 Hz), 4.59 (d, 1 H, *J* = 12.1 Hz), 4.52 (d, 1 H, *J* = 12.1 Hz), 4.49 (d, 1 H, *J* = 12.1 Hz), 4.36 (dd, 1 H, *J* = 1.4 and 11.3 Hz), 3.98 (dd,

1 H, *J* = 9.1 and 18.0 Hz), 3.87-3.90 (m, 2 H), 3.76 (t, 1 H, *J* = 8.6 Hz), 3.66-3.71 (m, 2 H), 3.24-3.27 (d, 1 H, *J* = 9.1 Hz), 2.00-2.05 (m, 1 H), 0.98 (d, 3 H, *J* = 6.7 Hz), 0.97 (d, 3 H, *J* = 6.7 Hz); ^{13}C NMR (125 Hz, $CDCl_3$) δ 171.2, 169.0, 162.0, 156.8, 138.1, 138.0, 137.8, 136.0, 135.1, 128.8, 128.7, 128.6, 128.5, 128.44, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.3, 101.9, 93.1, 81.9, 78.0, 75.2, 75.1, 74.6, 73.5, 68.9, 68.6, 67.8, 67.2, 61.5, 57.1, 53.1, 30.5, 19.4, 18.7; LC-ESI-MS $[M+H]^+$ calcd for $C_{53}H_{56}Cl_3N_3O_{11}$ 1004.30; found 1004.39.

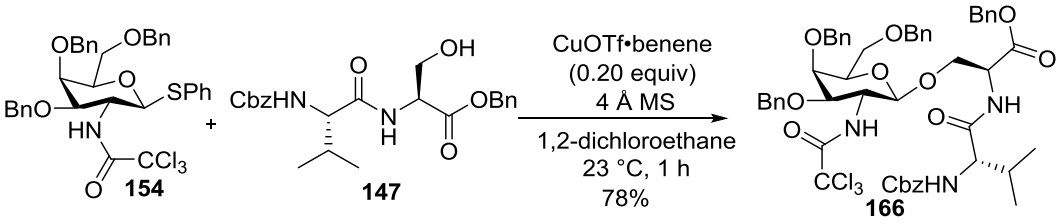
Benzyl *N*-(((benzyloxy)carbonyl)-*L*-valyl)-*O*-((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-*L*-serylglycinate (165).



By following the general procedure, donor **153** (103.1 mg, 0.15 mmol) was reacted with acceptor **148** (48.5 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded the title compound **165** (61.6 mg, 58%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.34 (m, 23 H), 7.19-7.20 (m, 2 H), 7.09 (m, 1 H), 6.78 (d, 1 H, *J* = 5.3 Hz), 5.43 (d, 1 H, *J* = 6.3 Hz), 5.14 (s, 2 H), 5.08-5.11 (m, 2 H), 4.77-4.81 (m, 4 H), 4.68-4.70 (m, 2 H), 4.55-4.57 (m, 2 H), 4.46 (d, 1 H, *J* = 9.4 Hz), 3.48-4.07 (m, 5 H),

3.89 (dd, 1 H, *J* =3.5 and 14.7 Hz), 3.70-3.81 (m, 6 H), 3.55 (d, 1 H, *J* = 6.5 Hz), 2.05-2.09 (m, 1 H), 1.86 (broad, 1 H), 0.84-0.91 (m, 6 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 171.7, 169.6, 169.5, 162.2, 156.7, 137.9, 137.8, 136.2, 135.3, 128.8, 128.7, 128.64, 128.6, 128.5, 128.4, 128.1, 128.04, 128.0, 127.97, 127,9, 100.6, 92.7, 80.4, 78.1, 75.2, 74.9, 74.8, 73.6, 68.9, 68.6, 67.3, 61.0, 57.8,52.6, 41.5, 30.8, 19.4, 18.0; LC-ESI-MS $[M+H]^+$ calcd for $C_{54}H_{59}Cl_3N_4O_{12}$ 1061.32; found 1061.45.

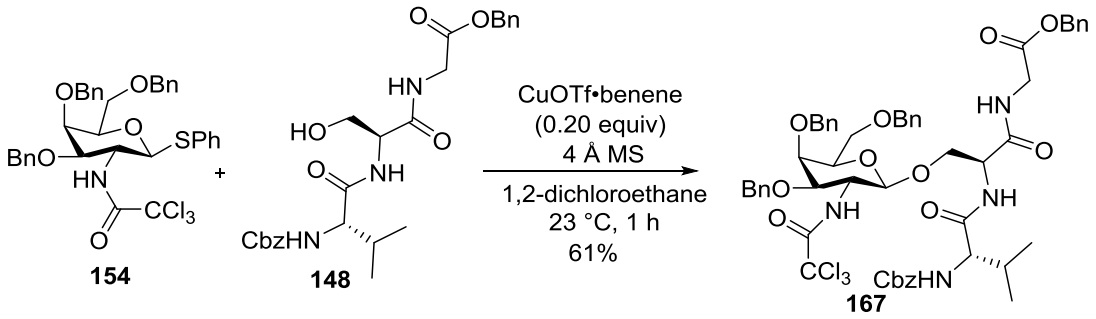
Benzyl *N*-(((benzyloxy)carbonyl)-*L*-valyl)-*O*-((2*R*,3*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-*L*-serinate (166).



By following the general procedure, donor **154** (103.1 mg, 0.15 mmol) was reacted with acceptor **147** (42.8 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **166** (78.4 mg, 78%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1 H, *J* = 8.4 Hz), 7.26- 7.37 (m, 25 H), 6.75 (d, 1 H, *J* = 7.4 Hz), 5.39 (d, 1 H, *J* = 8.2 Hz), 5.16 (s, 2 H), 4.96 (s, 1 H), 4.90 (d, 1 H, *J* = 11.4 Hz), 4.64 (d, 1 H, *J* = 11.5 Hz), 4.56-4.60 (m, 2 H), 4.48 (d, 1 H, *J* = 11.6 Hz), 4.40-4.46 (m, 2 H), 4.32 (d, 1 H, *J* = 10.8 Hz), 4.21 (dd, 1 H, *J* = 8.8 and 18.8 Hz), 3.97 (t, 1 H, *J* = 7.2 Hz), 3.93 (s, 1 H), 3.85 (dd, 1 H, *J* =2.0 and 10.7 Hz), 3.69 (dd, 1 H, *J* =2.0 and 10.8 Hz), 3.60 (t, 1 H, *J* = 8.4 Hz), 3.53 (t, 1 H, *J* = 5.3 Hz), 3.36 (t, 1 H, *J* = 6.1 Hz), 2.64 (broad, 1 H), 2.03-2.08 (m, 1 H),

1.27 (broad, 1 H), 0.95-0.98 (d, *J* = 6.7 Hz, 6 H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 171.2, 169.1, 162.2, 156.6, 138.4, 137.9, 137.6, 136.1, 135.2, 128.7, 128.62, 128.6, 128.5, 128.4, 128.35, 128.3, 128.24, 128.2, 128.0, 127.9, 127.8, 127.5, 101.4, 93.1, 74.7, 73.6, 73.55, 72.2, 71.8, 68.6, 68.4, 67.6, 66.9, 61.1, 54.7, 53.0, 30.8, 19.4, 18.4; LC-ESI-MS $[M+H]^+$ calcd for $C_{53}H_{56}Cl_3N_3O_{11}$ 1004.30; found 1004.39.

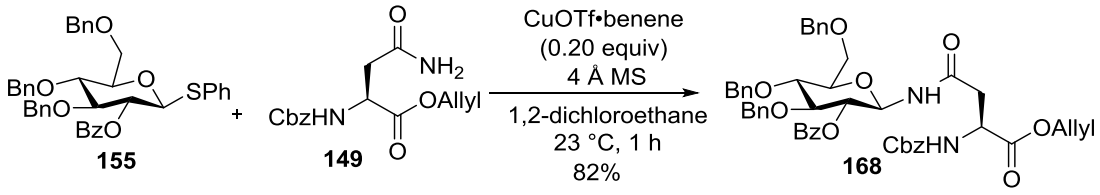
Benzyl *N*-(((benzyloxy)carbonyl)-*L*-valyl)-*O*-((2*R*,3*R*,4*R*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(2,2,2-trichloroacetamido)tetrahydro-2*H*-pyran-2-yl)-*L*-serylglycinate (167).



By following the general procedure, donor **154** (103.1 mg, 0.15 mmol) was reacted with acceptor **148** (48.5 mg, 0.10 mmol) at room temperature for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **167** (64.8 mg, 61%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.37 (m, 25 H), 7.11 (d, 1 H, *J* = 4.4 Hz), 6.99 (t, 1 H, *J* = 4.2 Hz), 6.73 (d, 1 H, *J* = 5.4 Hz), 5.28 (d, 1 H, *J* = 6.4 Hz), 5.14 (s, 2 H), 5.09 (d, 1 H, *J* = 9.7 Hz), 5.04 (d, 1 H, *J* = 9.6 Hz), 4.89 (d, 1 H, *J* = 9.1 Hz), 4.81 (d, 1 H, *J* = 5.6 Hz), 4.66 (d, 1 H, *J* = 9.2 Hz), 4.58 (d, 1 H, *J* = 9.1 Hz), 4.51 (d, 1 H, *J* = 9.2 Hz), 4.49 (d, 1 H, *J* = 9.1 Hz), 4.44 (d, 1 H, *J* = 9.4 Hz), 4.12 (dd, 1 H, *J* =3.7 and 8.1 Hz), 4.01-4.08 (m, 5 H), 3.96 (dd, 1 H, *J* =4.2

and 15.9 Hz), 3.64-3.71 (m, 4 H), 2.07-2.13 (m, 1 H), 1.69 (broad, 1 H), 0.95 (d, 3 H, *J* = 5.3 Hz), 0.89 (d, 3 H, *J* = 5.3 Hz); ^{13}C NMR (125 Hz, $CDCl_3$) δ 171.5, 169.6, 169.5, 162,4, 156.6, 138.4, 137.8, 137.5, 136.3, 135.3, 128.8, 128.7, 128.68, 128.63, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 100.5, 92.8, 78.0, 77.4, 74.8, 73.7, 73.7, 72.3, 72.0, 68.3, 67.3, 67.2, 60.7, 55.3, 52.6, 41.6, 31.1, 19.4, 17.9; LC-ESI-MS $[M+H]^+$ calcd for $C_{54}H_{59}Cl_3N_4O_{12}$ 1061.32; found 1061.42.

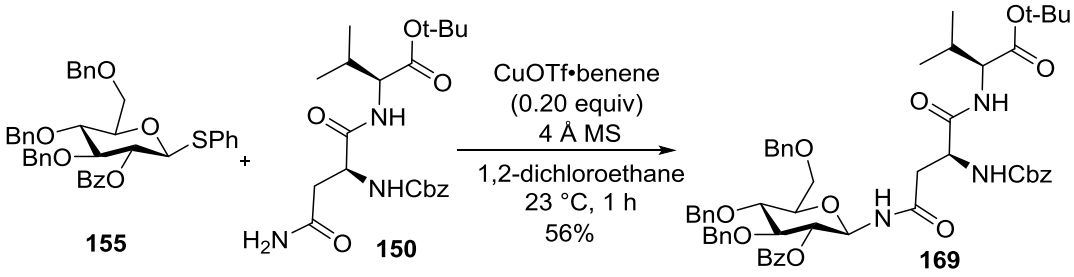
(2*R*,3*R*,4*S*,5*R*,6*R*)-2-((*S*)-4-(allyloxy)-3-(((benzyloxy)carbonyl)amino)-4-oxobutanamido)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-3-yl benzoate (168).



By following the general procedure, donor **155** (97.0 mg, 0.15 mmol) was reacted with acceptor **149** (30.6 mg, 0.10 mmol) at 0 °C for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **168** (70.95 mg, 82%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 2 H, *J* = 7.2 Hz), 7.58 (t, 1 H, *J* = 7.2 Hz), 7.42-7.45 (m, 2 H), 7.27-7.34 (m, 15 H), 7.10-7.17 (m, 5 H), 6.49 (d, 1 H, *J* = 9.2 Hz), 5.90 (d, 1 H, *J* = 9.2 Hz), 5.54-5.61 (m, 1H), 5.22 (t, 1 H, *J* = 9.2 Hz), 5.13 (t, 1 H, *J* = 9.2 Hz), 5.05-5.08 (m, 3H), 5.00 (d, 1 H, *J* = 10.6 Hz), 4.80 (d, 1 H, *J* = 4.5Hz), 4.77 (d, 1 H, *J* = 4.5Hz), 4.72 (d, 1 H, *J* = 10.5), 4.65 (d, 1 H, *J* = 10.5 Hz),4.47-4.55 (m, 4 H), 4.35 (dd, 1 H, *J* = 5.8 and 13.1 Hz), 4.20 (dd, 1 H, *J*= 5.8 and 13.5 Hz), 3.90 (t, 1 H, *J* = 9.5 Hz), 3.86 (t, 1 H, *J* = 9.5 Hz), 3.74-3.79 (m, 2 H), 2.85 (dd, 1 H, *J* =

4.3 and 16.9 Hz), 2.69 (dd, 1 H, *J* = 4.3 and 16.9 Hz), 1.64 (broad, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.4, 167.0, 156.2, 138.0, 137.8, 137.78, 136.4, 133.8, 131.5, 130.0, 129.1, 128.7, 128.6, 128.57, 128.56, 128.5, 128.2, 128.17, 128.21, 128.1, 128.06, 128.0, 127.94, 127.9, 118.4, 83.1, 78.5, 77.7, 77.4, 76.8, 75.7, 75.3, 73.8, 73.6, 68.1, 67.1, 66.1, 50.5, 37.8; LC-ESI-MS $[M+H]^+$ calcd for $C_{49}H_{50}N_2O_{11}$ 843.34; found 843.28.

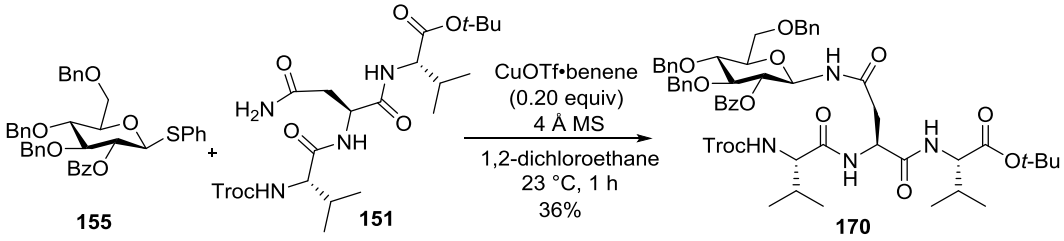
(2*R*,3*R*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-2-((*S*)-3-(((benzyloxy)carbonyl)amino)-4-(((*S*)-1-(tert-butoxy)-3-methyl-1-oxobutan-2-yl)amino)-4-oxobutanamido)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-3-yl benzoate (169).



By following the general procedure, donor **155** (97.0 mg, 0.15 mmol) was reacted with acceptor **150** (42.1 mg, 0.10 mmol) at 0 °C for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **169** (53.7mg, 56%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 2 H, *J* = 7.8 Hz), 7.56 (t, 1 H, *J* = 7.3 Hz), 7.42 (t, 2 H, *J* = 7.8 Hz), 7.11-7.35 (m, 20 H), 6.99 (d, 1 H, *J* = 8.7 Hz), 6.78 (d, 1 H, *J* = 9.2 Hz), 6.26 (d, 1 H, *J* = 7.3 Hz), 5.23 (t, 1 H, *J* = 9.2 Hz), 5.16 (t, 1 H, *J* = 9.2 Hz), 5.07 (d, 1 H, *J* = 12.0 Hz), 5.02 (d, 1 H, *J* = 12.0 Hz), 4.80 (d, 1 H, *J* = 10.6 Hz), 4.79 (d, 1 H, *J* = 11.1Hz), 4.74 (d, 1 H, *J* = 11.1 Hz), 4.65 (d, 1 H, *J* = 12.1 Hz), 4.53 (d, 1 H, *J* = 10.6 Hz), 4.48 (d, 1 H, *J* = 12.1 Hz), 4.43 (m, 1H), 4.05 (m, 1H), 3.92 (dd, 1 H, *J* = 8.6 and 9.2 Hz), 3.85 (dd, 1 H, *J* = 8.6 and 9.2 Hz), 3.77 (dd, 1 H, *J* = 2.4 and 10.6 Hz), 3.73 (d, 1 H, *J* = 10.6 Hz), 3.61(d, 1 H, *J* = 9.6 Hz), 2.79 (dd, 1 H, *J* =

3.9 and 16.0 Hz), 2.60 (dd, 1 H, *J* = 5.8 and 16.0), 1.95-1.99 (m, 1H), 1.67 (broad, 1 H), 1.43 (s, 9H), 0.76 (d, 3 H, *J* = 7.3 Hz), 0.73 (d, 3 H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 170.5, 170.2, 167.0, 156.3, 138.0, 137.83, 137.8, 136.2, 133.6, 130.1, 129.3, 128.6, 128.5, 128.4, 128.2, 128.15, 128.1, 128.0, 127.99, 127.95, 127.9, 127.86, 83.3, 81.9, 78.5, 77.4, 76.7, 75.6, 75.2, 73.7, 73.6, 68.2, 67.2, 57.7, 51.4, 37.4, 31.2, 28.1, 18.8, 17.6; LC-ESI-MS $[M+H]^+$ calcd for $C_{55}H_{63}N_3O_{12}$ 958.44; found 958. 23.

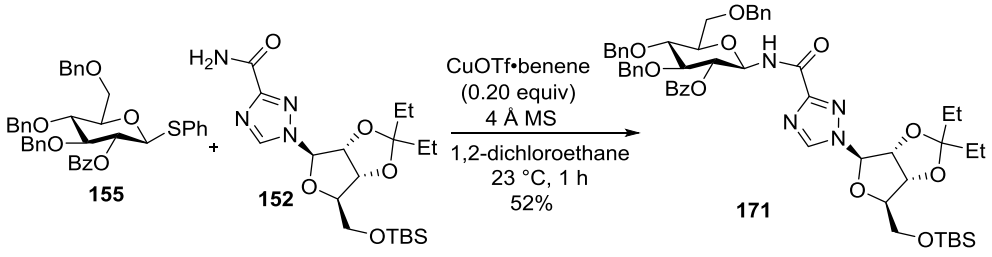
***tert*-Butyl (6*S*,9*S*,12*S*)-9-(2-(((2*R*,3*R*,4*S*,5*R*,6*R*)-3-(benzoyloxy)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)amino)-2-oxoethyl)-1,1,1-trichloro-6,12-diisopropyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oate (170).**



By following the general procedure, donor **155** (97.0 mg, 0.15 mmol) was reacted with acceptor **151** (56.2 mg, 0.10 mmol) at 0 °C for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **170** (39.6 mg, 36%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, 2 H, *J* = 9.6 Hz), 7.56-7.63 (m, 2 H), 7.43 (t, 2 H, *J* = 9.5 Hz), 7.26-7.33 (m, 7 H), 6.94-7.16 (m, 7 H), 6.95 (d, 1 H, *J* = 10.5 Hz), 5.17-5.23 (m, 2 H), 4.72-4.80 (m, 3 H), 4.67 (d, 1 H, *J* = 9.9 Hz), 4.64 (d, 1 H, *J* = 10.0 Hz), 4.52 (d, 1 H, *J* = 13.8 Hz), 4.48 (d, 1 H, *J* = 15.2 Hz), 4.05 (dd, 1 H, *J* = 6.8 and 10.0 Hz), 3.90-3.97 (m, 2 H), 3.82 (t, 1 H, *J* = 11.7 Hz), 3.75 (broad, 1 H), 3.63 (d, 1 H, *J* = 12.0 Hz), 2.70 (dd, 1 H, *J* = 3.6 and 16.0 Hz), 2.54 (dd, 1 H, *J* = 7.4 and

16.0), 2.43 (broad, 2 H), 2.06-2.10 (m, 1H), 1.93-1.98 (m, 1 H), 1.43 (s, 9 H), 0.93 (d, 3 H, *J* = 8.4 Hz), 0.87 (d, 3 H, *J* = 8.4 Hz), 0.77 (d, 3 H, *J* = 8.6 Hz), 0.74 (d, 3 H, *J* = 8.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 170.9, 170.3, 169.7, 167.1, 154.8, 138.0, 137.8, 133.6, 130.2, 129.5, 128.6, 128.57, 128.5, 128.2, 128.1, 128.0, 127.96, 127.9, 95.6, 83.2, 81.9, 78.5, 77.7, 77.4, 76.7, 75.7, 75.2, 74.8, 73.8, 73.8, 73.6, 68.3, 60.5, 57.9, 49.9, 37.2, 31.4, 31.1, 28.2, 19.3, 18.8, 17.7, 17.6; LC-ESI-MS $[M+H]^+$ calcd for $C_{55}H_{67}Cl_3N_4O_{13}$ 1097.38; found 1097.55.

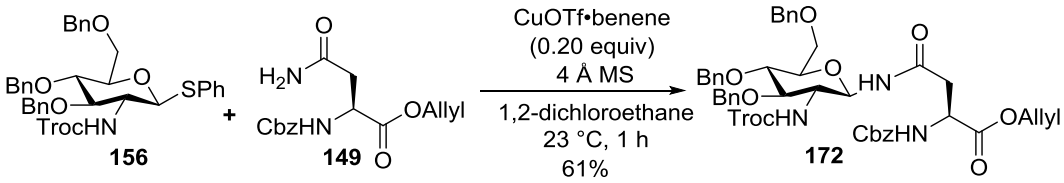
(2*R*,3*R*,4*S*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-(1-((3a*R*,4*R*,6*R*,6a*R*)-6-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-diethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-1*H*-1,2,4-triazole-3-carboxamido)tetrahydro-2*H*-pyran-3-yl benzoate (171).



By following the general procedure, donor **155** (97.0 mg, 0.15 mmol 1.5 equiv) was reacted with acceptor **152** (42.6 mg, 0.10 mmol) at 0 °C for 2 hours. After work-up, purification by thin-layer chromatography with 8:2 hexane/ethyl acetate as eluant afforded **171** (50.1 mg, 52%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 2 H, *J* = 7.8 Hz), 7.87 (d, 1 H, *J* = 9.3 Hz), 7.55 (t, 1 H, *J* = 7.3 Hz), 7.39-7.42 (m, 2 H), 7.27-7.37 (m, 10 H), 7.11-7.19 (m, 8 H), 6.09 (s, 1 H), 5.51 (t, 1 H, *J* = 9.8 Hz), 5.39 (d, 1 H, *J* = 6.4 Hz), 5.31 (d, 1 H, *J* = 9.3 Hz), 4.96 (d, 1 H, *J* = 5.7 Hz), 4.84 (d, 1 H, *J* = 10.7 Hz), 4.80 (d, 1 H, *J* = 10.7 Hz), 4.72 (d, 1 H, *J* = 11.2 Hz), 4.66 (d, 1 H, *J* = 12.2 Hz),

4.58 (d, 1 H, *J* = 10.7 Hz), 4.51 (d, 1 H, *J* = 12.2 Hz), 4.37 (t, 1 H, *J* = 6.8 Hz), 3.97 (t, 1 H, *J* = 8.8 Hz), 3.92 (t, 1 H, *J* = 9.3 Hz), 3.82 (dd, 1 H, *J* = 2.4 and 10.7 Hz), 3.77 (d, 1 H, *J* = 10.7 Hz), 3.71 (d, 1 H, *J* = 9.3 Hz), 3.57 (dd, 1 H, *J* = 7.3 and 10.7 Hz), 3.43 (dd, 1 H, *J* = 7.3 and 10.7 Hz), 1.79 (q, 2 H, *J* = 7.3 and 15.1 Hz), 1.73 (broad, 1 H), 1.65 (q, 2 H, *J* = 7.3 and 15.1 Hz), 1.01 (t, 3 H, *J* = 7.3 Hz), 0.90 (t, 3 H, *J* = 7.3 Hz), 0.81 (s, 9 H), -0.09 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 158.7, 158.0, 138.1, 137.9, 137.8, 133.5, 130.0, 129.3, 128.6, 128.55, 128.5, 128.4, 128.1, 128.07, 128.0, 127.96, 127.9, 127.8, 118.0, 101.9, 93.6, 89.8, 84.6, 83.3, 82.5, 78.2, 77.7, 77.4, 77.0, 75.6, 75.2, 73.8, 73.4, 68.3, 63.4, 29.5, 29.2, 25.9, 18.3, 8.5, 7.8, 0.1, -5.3; LC-ESI-MS $[M+H]^+$ calcd for 963.45; found: 963.21.

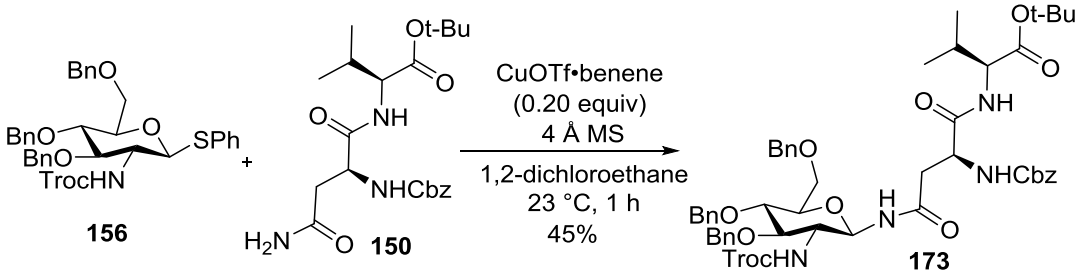
Allyl N^2-((benzyloxy)carbonyl)-N^4-((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(((2,2,2-trichloroethoxy)carbonyl)amino)tetrahydro-2*H*-pyran-2-yl)-*L*-asparaginate (172).



By following the general procedure, donor **156** (107.5 mg, 0.15 mmol) was reacted with acceptor **149** (30.6 mg, 0.10 mmol) at 0 °C for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **172** (55.7 mg, 61%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.17 (m, 20 H), 6.89 (d, 1 H, *J* = 8.3 Hz), 5.98 (d, 1 H, *J* = 9.2 Hz), 5.87-5.79 (m, 1 H), 5.26 (dd, 1 H, *J* =1.5 and 16.9 Hz), 5.18 (dd, 1 H, *J* = 1.5 and 10.7 Hz), 5.13 (d, 1 H, *J* = 12.1

Hz), 5.08 (d, 1 H, *J* = 12.1 Hz), 4.84-4.89 (m, 2 H), 4.79 (d, 1 H, *J* = 10.6 Hz), 4.76 (d, 1 H, *J* = 12.1 Hz), 4.64-4.70 (m, 3 H), 4.57-4.59 (m, 2 H), 4.55 (d, 1 H, *J* = 10.6 Hz), 4.47 (d, 1 H, *J* = 7.6 Hz), 3.81 (t, 1 H, *J* = 9.2 Hz), 3.69-3.76 (m, 2 H), 3.59 (dd, 1 H, *J* = 7.2 and 9.2 Hz), 3.41-3.48 (m, 2 H), 2.86 (dd, 1 H, *J* = 4.3 and 16.9 Hz), 2.68 (dd, 1 H, *J* = 4.4 and 16.9 Hz), 1.87 (broad, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 156.2, 156.0, 137.8, 137.5, 136.4, 131.7, 129.1, 128.8, 128.6, 128.55, 128.23, 128.2, 128.1, 127.9, 118.6, 95.4, 80.12, 80.1, 78.4, 77.4, 76.7, 75.1, 74.9, 74.6, 73.8, 68.1, 67.2, 66.3, 55.8, 50.6, 37.8; LC-ESI-MS $[M+H]^+$ calcd for $C_{45}H_{48}Cl_3N_3O_{11}$ 912.24; found 912. 33.

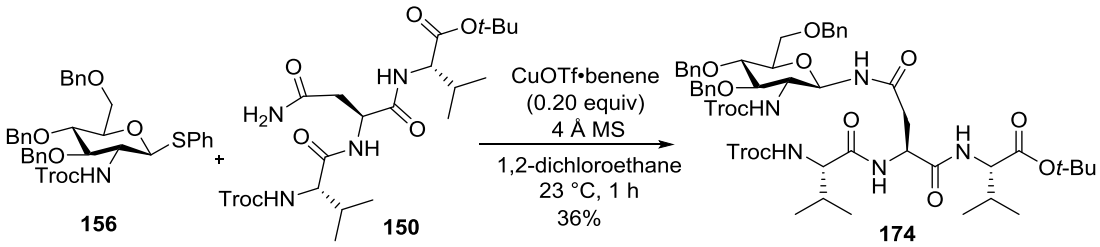
***tert*-Butyl N^2-((benzyloxy)carbonyl)-N^4-((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(((2,2,2-trichloroethoxy)carbonyl)amino)tetrahydro-2*H*-pyran-2-yl)-*L*-asparaginyl-*L*-valinate (173).**



By following the general procedure, donor **156** (107.5 mg, 0.15 mmol) was reacted with acceptor **150** (42.1 mg, 0.10 mmol) at 0 °C for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **173** (46.3 mg, 45%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.40 (m, 18 H), 7.18-7.19 (m, 2 H), 7.02 (d, 1 H, *J* = 8.2 Hz), 6.43 (d, 1 H, *J* = 7.3 Hz), 5.13 (d, 1 H, *J* = 12.0 Hz), 5.09 (d, 1 H, *J* = 12.0 Hz), 4.90 (d, 1 H, *J* = 12.1 Hz), 4.86 (dd, 1 H, *J* = 8.2 and 9.2 Hz), 4.85 (d, 1 H, *J* = 12.0 Hz), 4.80 (d, 1 H, *J* = 11.1 Hz), 4.62-4.70 (m, 4 H), 4.57 (d, 1 H, *J* = 11.1 Hz), 4.48 (broad, 1H), 4.47 (d, 1 H, *J* = 12.1 Hz), 4.28 (dd, 1

H, *J* = 4.9 and 8.7 Hz), 3.80 (t, 1 H, *J* = 9.2 Hz), 3.67-3.76 (m, 2 H), 3.60 (m, 1 H), 3.47-3.49 (m, 2 H), 2.78 (dd, 1 H, *J* = 3.4 and 16.4 Hz), 2.58 (dd, 1 H, *J* = 5.8 and 16.4 Hz), 2.05-2.10 (m, 1 H), 1.44 (s, 9 H), 0.82 (d, 6 H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 170.6, 170.4, 156.1, 137.9, 137.8, 137.5, 136.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.17, 128.1, 127.9, 95.5, 82.0, 80.0, 78.5, 77.4, 76.7, 75.14, 75.1, 74.6, 73.8, 68.2, 67.3, 58.0, 55.9, 51.4, 37.6, 31.3, 28.2, 19.0, 17.7; LC-ESI-MS $[M+H]^+$ calcd for $C_{51}H_{61}Cl_3N_4O_{12}$ 1027.34; found 1027.37.

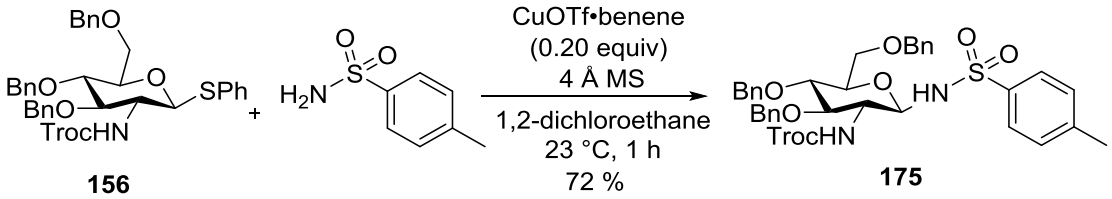
***tert*-Butyl N^4-((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3-(((2,2,2-trichloroethoxy)carbonyl)amino)tetrahydro-2*H*-pyran-2-yl)-N^2-(((2,2,2-trichloroethoxy)carbonyl)-*L*-valyl)-*L*-asparaginyl-*L*-valinate (174).**



By following the general procedure, donor **156** (107.5 mg, 0.15 mmol) was reacted with acceptor **150** (42.1 mg, 0.10 mmol) at 0 °C for 2 hours. After work-up, purification by thin-layer chromatography with 6:4 hexane/ethyl acetate as eluant afforded **174** (37.4 mg, 32%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, 1 H, *J* = 8.7 Hz), 7.18-7.40 (m, 15 H), 5.66 (d, 1 H, *J* = 10.1 Hz), 4.79-4.91 (m, 4 H), 4.63-4.71 (m, 4 H), 4.56 (d, 1 H, *J* = 13.5 Hz), 4.48 (d, 1 H, *J* = 15.1 Hz), 4.24 (dd, 1 H, *J* = 5.8 and 10.5 Hz), 4.09 (t, 1 H, *J* = 7.1 Hz), 3.60-3.81 (m, 4 H), 3.46 (d, 1 H, *J* = 11.3 Hz), 2.72 (dd, 1 H, *J* = 3.8 and 20.0 Hz), 2.54 (dd, 1 H, *J* = 7.5 and 19.8 Hz), 2.06-2.18 (m, 2 H), 1.85 (broad, 2 H), 1.44 (s, 9 H), 0.98 (d, 3 H, *J* = 8.4 Hz), 0.93 (d, 3 H, *J* = 8.4

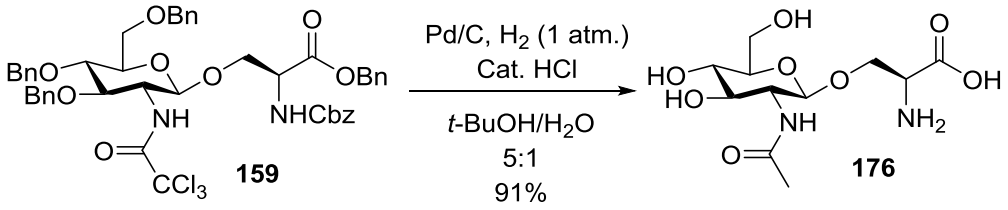
Hz), 0.85-0.86 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 170.9, 170.4, 170.0, 156.1, 137.9, 137.8, 137.5, 129.1, 128.8, 128.6, 128.58, 128.2, 128.1, 128.0, 95.5, 82.0, 80.1, 80.0, 78.5, 77.4, 76.7, 75.3, 75.1, 74.8, 74.6, 73.8, 68.2, 60.6, 58.2, 55.8, 49.9, 37.1, 31.4, 31.2, 28.2, 19.4, 19.0, 17.9, 17.7; LC-ESI-MS $[M+H]^+$ calcd for $C_{51}H_{65}Cl_6N_5O_{13}$ 1166.27; found 1166.37.

2,2,2-Trichloroethyl ((2*R*,3*R*,4*R*,5*S*,6*R*)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methylphenyl)sulfonamido)tetrahydro-2H-pyran-3-yl)carbamate (175).[91]



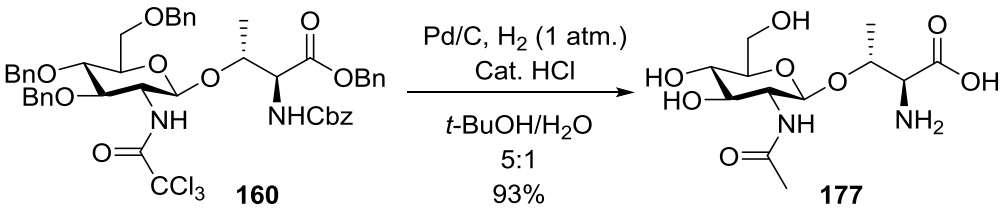
By following the general procedure, donor **156** (107.5 mg, 0.15 mmol) was reacted with 4-methylbenzenesulfonamide (17.1 mg, 0.10 mmol) at 0 °C for 2 hours. After work-up, purification by thin-layer chromatography with 4:1 hexane/ethyl acetate as eluant afforded **175** (56.0 mg, 72%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (m 2 H), 7.17-7.39 (m, 17 H), 6.03 (d, 1 H, *J* = 8.9 Hz), 4.87 (d, 1 H, *J* = 7.8 Hz), 4.83 (d, 1 H, *J* = 11.6 Hz), 4.79 (d, 1 H, *J* = 10.9 Hz), 4.75 (d, 1 H, *J* = 12.0 Hz), 4.63-4.70 (m, 3 H), 4.58 (d, 1 H, *J* = 11.0 Hz), 4.43 (d, 1 H, *J* = 12.1 Hz), 4.31 (d, 1 H, *J* = 12.1 Hz), 3.63-3.69 (m, 2 H), 3.51-3.61 (m, 2 H), 3.38-3.43 (m, 2 H), 2.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 143.4, 138.9, 138.0, 137.8, 137.5, 129.4, 128.9, 128.6, 128.54, 128.5, 128.1, 127.9, 127.8, 127.3, 95.3, 84.4, 80.5, 78.3, 76.5, 75.1, 74.9, 74.8, 73.8, 68.4, 56.1, 40.5, 21.6; LC-ESI-MS $[M+H]^+$ calcd for $C_{37}H_{39}Cl_3N_2O_8S$ 777.15; found 777.13.

***O*-((2*R*,3*R*,4*R*,5*S*,6*R*)-3-Acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-L-serine (176).**[109]



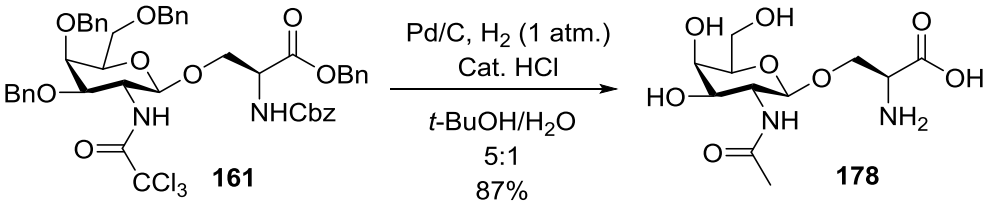
A solution of 81.5 mg (0.090 mmol) of **159** in 3.0 mL of a 5:1 *t*-butanol/water mixture was treated with 40.0 mg of palladium hydroxide (20 wt % on activated carbon) and 20 μL of 1 N aqueous hydrochloric acid. The reaction was purged 3 times with a balloon filled with hydrogen gas, and then stirred under positive hydrogen pressure for 12 hours. The reaction was then filtered through Celite and concentrated to give **176** (28.0 mg, 91% yield) as a white solid: ^{1}H NMR (400 MHz, DMSO) δ 8.34 (t, 2 H, *J* = 19.4 Hz), 7.92 (d, 1 H, *J* = 6.3 Hz), 4.43 (d, 1 H, *J* = 6.6 Hz), 4.16 (s, 1 H), 4.05 (dd, 1 H, *J* = 2.9 and 9.1 Hz), 3.48-3.96 (broad, 4 H), 3.95 (d, 1 H, *J* = 8.4 Hz), 3.68 (d, 1 H, *J* = 9.5 Hz), 3.47 (dd, 1 H, *J* = 3.6 and 9.1 Hz), 3.39 (t, 1 H, *J* = 7.4 Hz), 3.30 (t, 1 H, *J* = 6.8 Hz), 3.07-3.11 (m, 2 H), 1.84 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 167.3 102.2, 78.1, 75.6, 71.8, 66.9, 62.4, 56.7, 54.2, 23.0; LC-ESI-MS $[M+H]^+$ calcd for $C_{11}H_{20}N_2O_8$ 309.12; found 309.07.

***O*-((2*R*,3*R*,4*R*,5*S*,6*R*)-3-Acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-*L*-threonine (177).**[110]



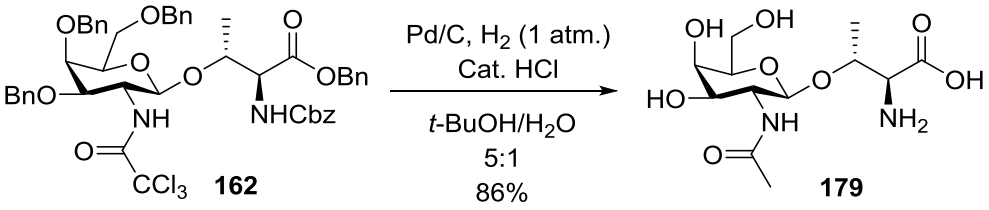
Compound **177** was prepared by following the same procedure as compound **176** (93% yield) as a white solid: ^{1}H NMR (400 MHz, CD_3OD) δ 4.45 (d, 1 H, *J* = 8.2 Hz), 4.25 (t, 1 H, *J* = 6.0 Hz), 3.92 (d, 1 H, *J* = 11.8 Hz), 3.83 (d, 1 H, *J* = 5.0 Hz), 3.62-3.69 (m, 2 H), 3.44-3.47 (m, 1 H), 3.30 (overlap with CD_3OD, 2 H), 2.00 (s, 3 H), 1.35 (d, *J* = 5.8 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.6, 101.0, 77.8, 75.2, 74.1, 71.8, 62.3, 58.5, 57.1, 22.9, 18.4; LC-ESI-MS $[M+H]^+$ calcd for $C_{12}H_{22}N_2O_8$ 323.14; found 323.08.

***O*-((2*R*,3*R*,4*R*,5*R*,6*R*)-3-Acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-*L*-serine (178).[111]**



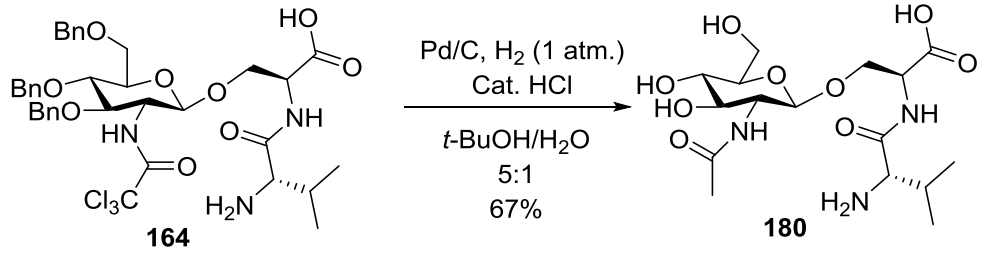
Compound **178** was prepared by following the same procedure as compound **176** (87% yield) as a white solid after purified by Gilson: ^{1}H NMR (400 MHz, CD_3OD) δ 4.41 (d, 1 H, *J* = 8.4 Hz), 4.09-4.13 (m, 2 H), 3.96-4.01 (m, 3 H), 3.71 - 3.84 (m, 2H), 3.58 (dd, 1 H, *J* = 2.9 and 10.6 Hz), 3.54 (dd, 1 H, *J* = 4.6 and 6.9 Hz), 2.00 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.1, 168.3, 102.5, 77.0, 72.8, 69.6, 66.8, 62.6, 60.7, 53.5, 23.1; LC-ESI-MS $[M+H]^+$ calcd for 309.12; found 309.05.

***O*-((2*R*,3*R*,4*R*,5*R*,6*R*)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-*L*-threonine (179).** [112]



Compound **179** was prepared by following essentially the same procedure as compound **176** (86% yield) as a white solid after purified by Gilson: ^{1}H NMR (400 MHz, CD_3OD) δ 4.40 (d, 1H, *J* = 8.3 Hz), 4.20 (t, 1 H, *J* = 6.3 Hz), 3.91 (dd, 1 H, *J* = 8.6 and 10.0 Hz), 3.70 - 3.81 (m, 4 H), 3.57 (dd, 1 H, *J* = 2.3 and 10.8 Hz), 3.50 - 3.53 (m, 1 H), 1.98 (s, 3 H), 1.32 (d, 1 H, *J* = 5.3 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 174.6, 169.5, 101.4, 76.9, 73.9, 72.4, 69.6, 62.6, 58.7, 54.0, 22.9, 18.4; LC-ESI-MS $[M+H]^+$ calcd for $C_{12}H_{22}N_2O_8$ 323.14; found 323.11.

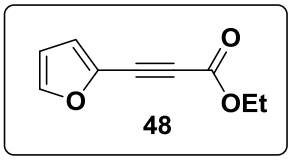
***N*-(*L*-valyl)-O-((2*R*,3*R*,4*R*,5*S*,6*R*)-3-acetamido-4,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)-*L*-serine (180).**



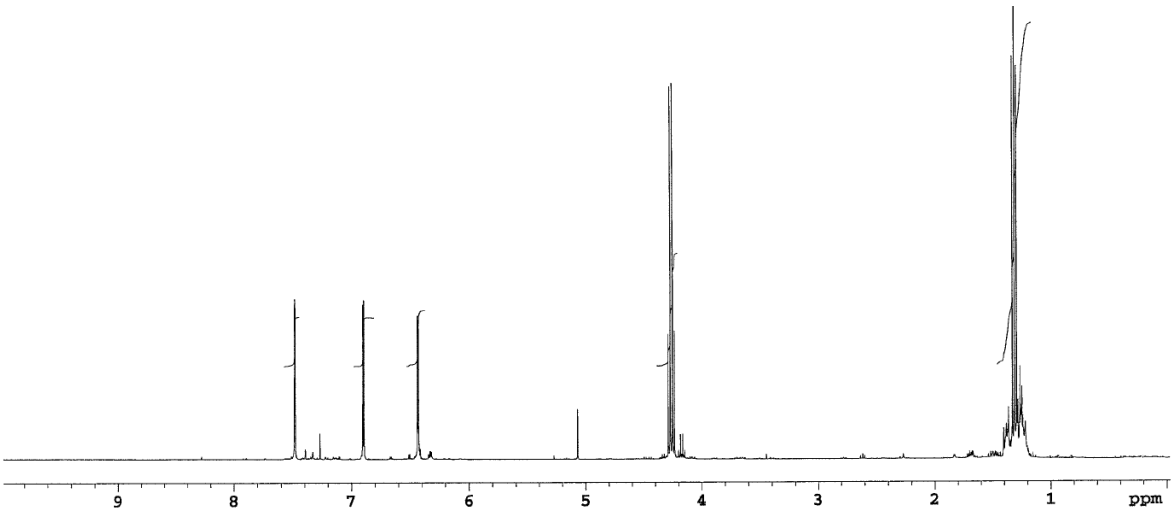
Compound **180** was prepared by following essentially the same procedure as compound **176** (67% yield) as a white solid after purified by Gilson: ^{1}H NMR (400 MHz, CD_3OD) δ 5.47 (d, 1 H, *J* = 0.8 Hz), 4.65 (t, 1 H, *J* = 4.6 Hz), 4.44 (d, 1H, *J* = 8.4 Hz),

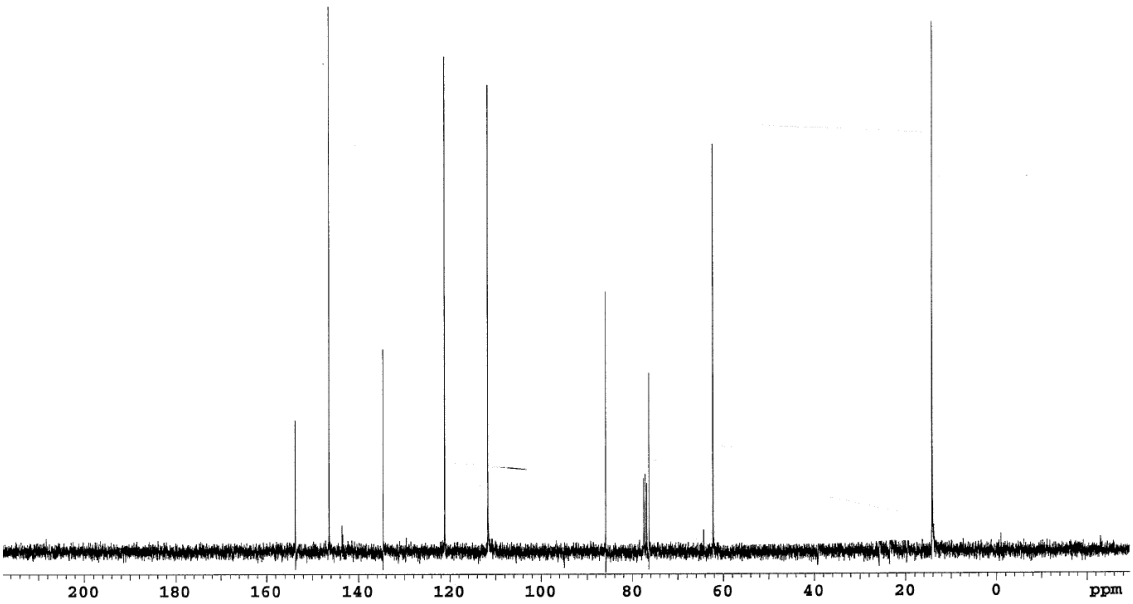
4.10 (dd, 1 H, *J* = 6.8 and 10.6 Hz), 3.90 (dd, 1 H, *J* = 4.3 and 9.2 Hz), 3.87 (d, 1 H, *J* = 12.4 Hz), 3.74 (d, 1 H, *J* = 6.0 Hz), 3.60 - 3.68 (m, 2 H), 3.40-3.44 (m, 1 H), 3.32 (d, 1 H, *J* = 0.9 Hz), 2.16-2.24 (m, 1 H), 1.99 (s, 3 H), 1.08 (t, 3 H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, CD_3OD) δ 174.4, 172.2, 169.6, 102.9, 78.1, 75.6, 72.0, 69.1, 62.6, 59.8, 57.1, 54.0, 31.6, 23.1, 18.8, 18.0; LC-ESI-MS $[M+H]^+$ calcd for $C_{16}H_{29}N_3O_9$ 408.19; found 408.22.

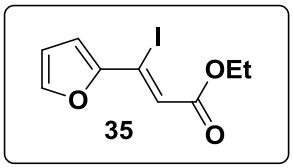
5.5. Spectrum



48







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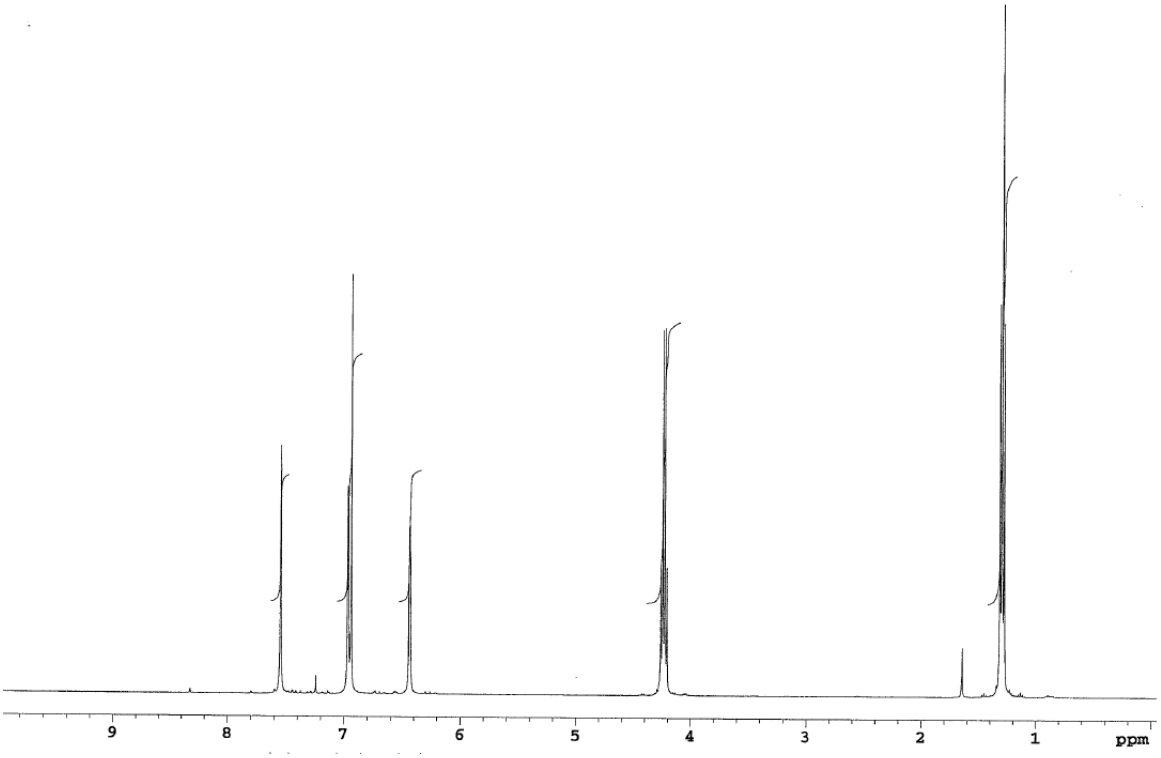

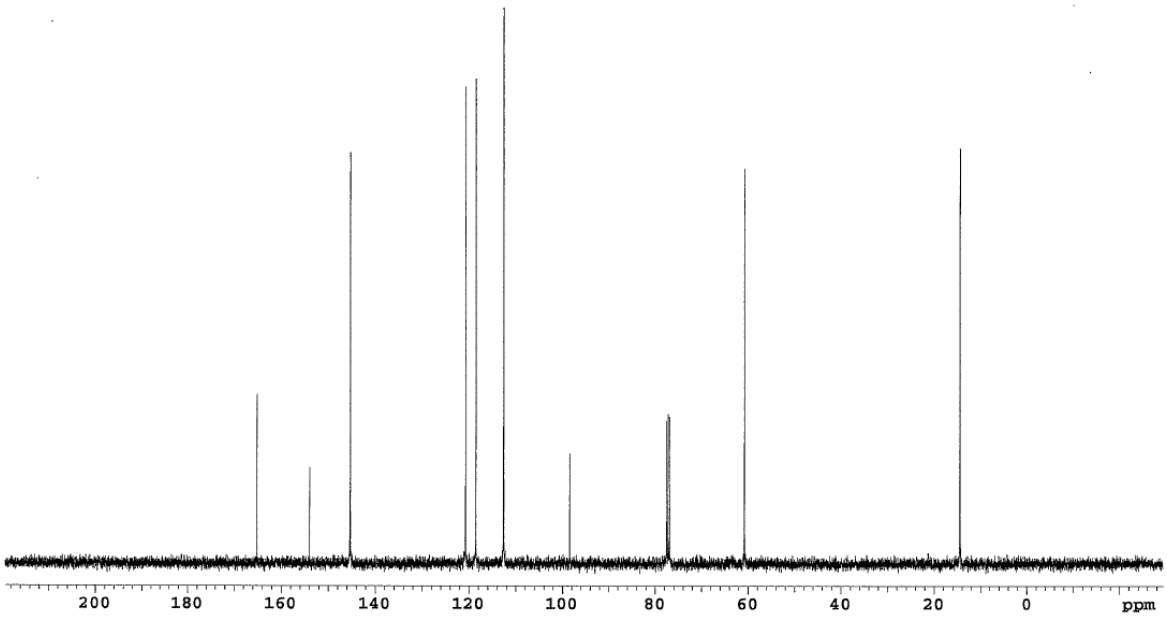

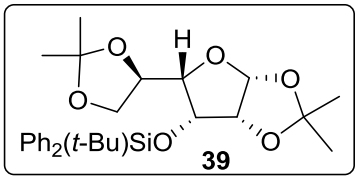
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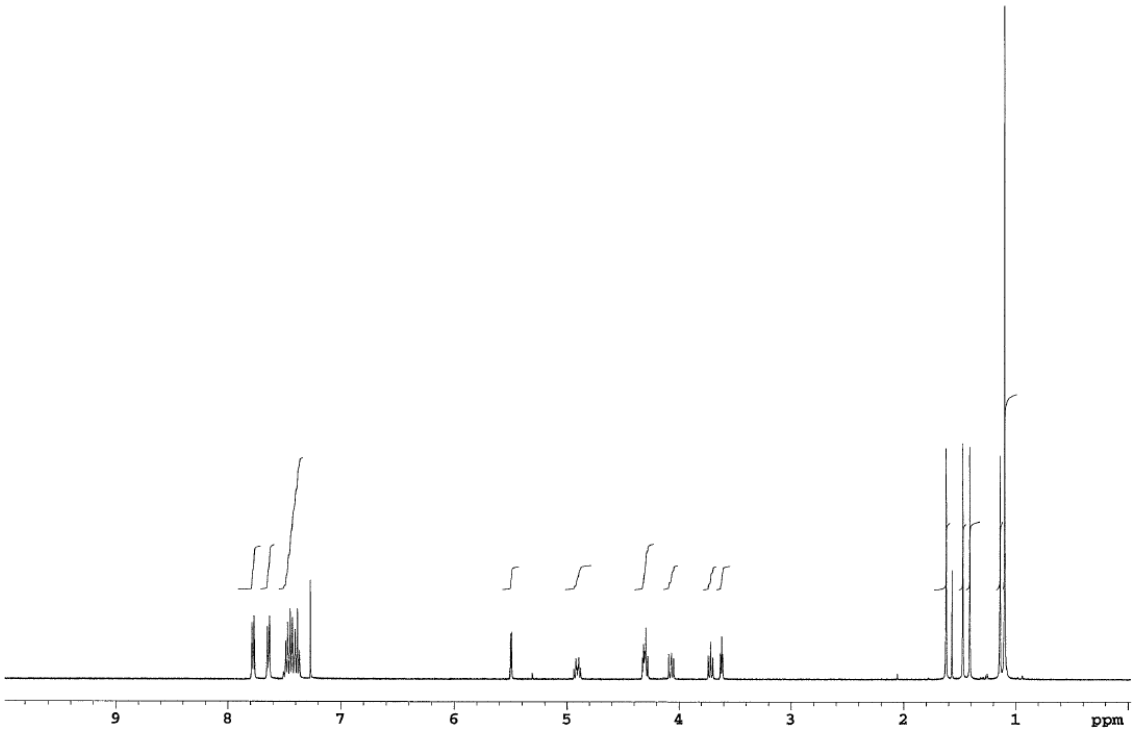
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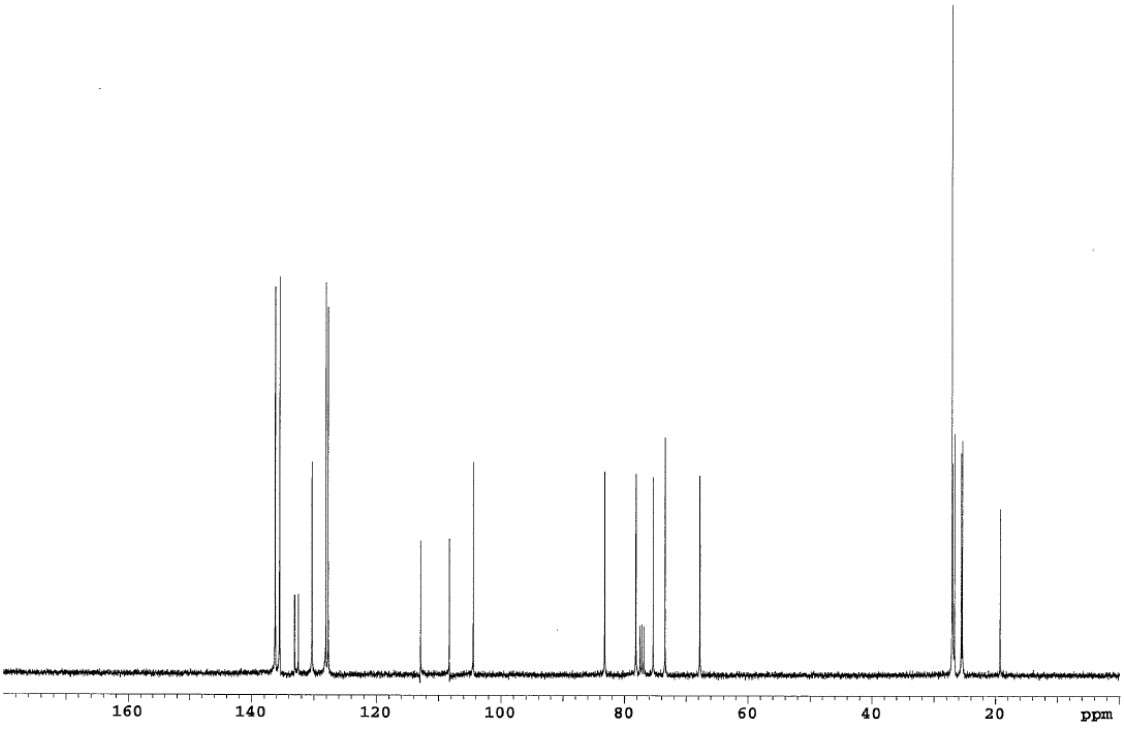
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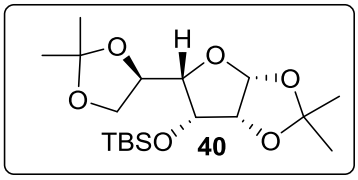
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TBSO
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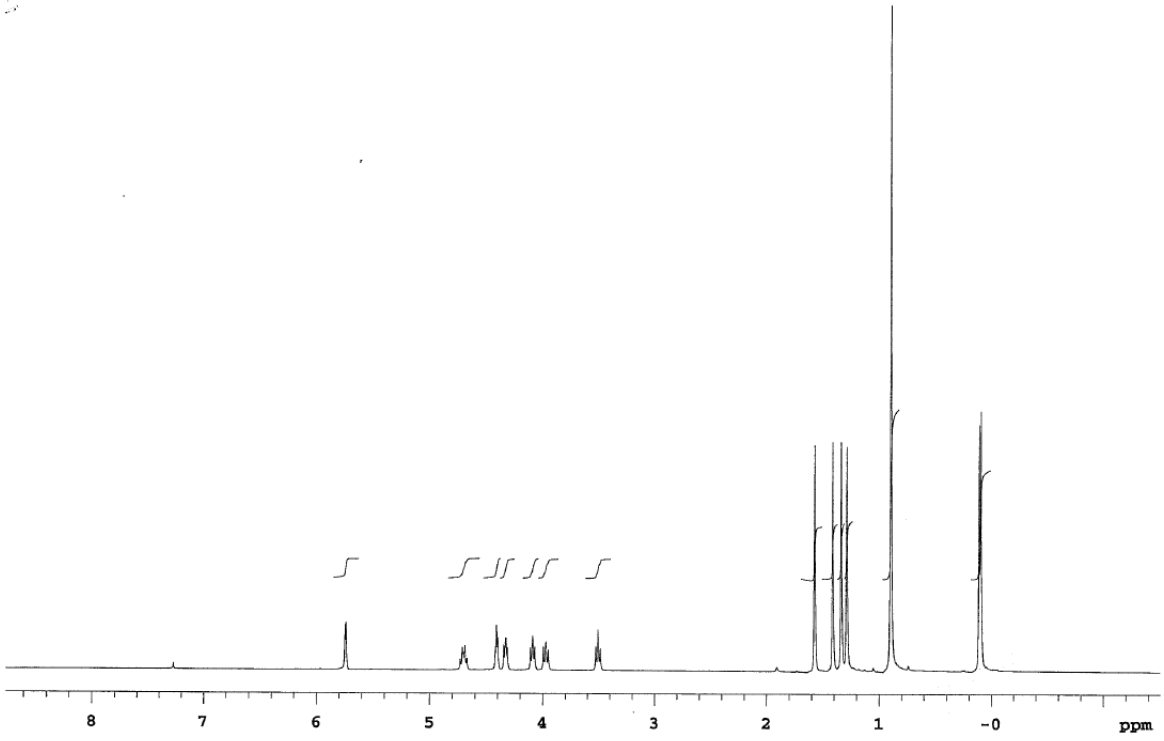
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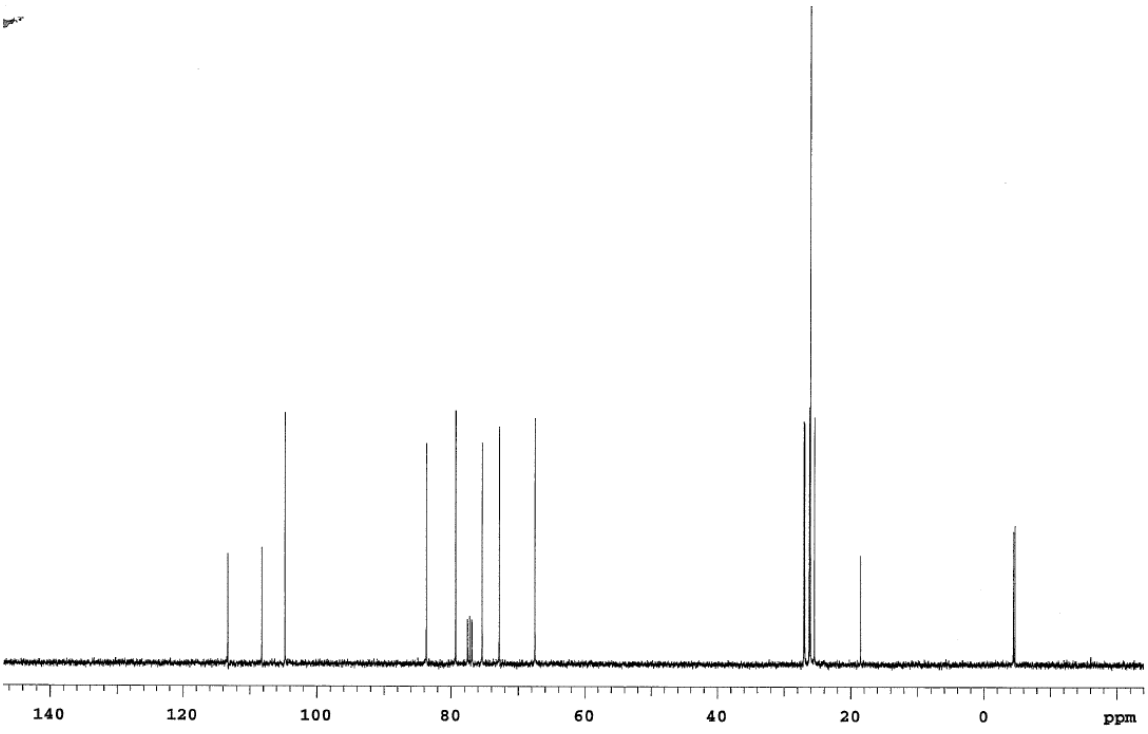
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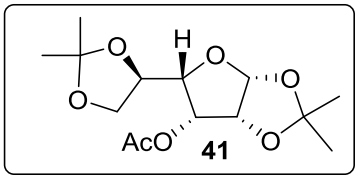
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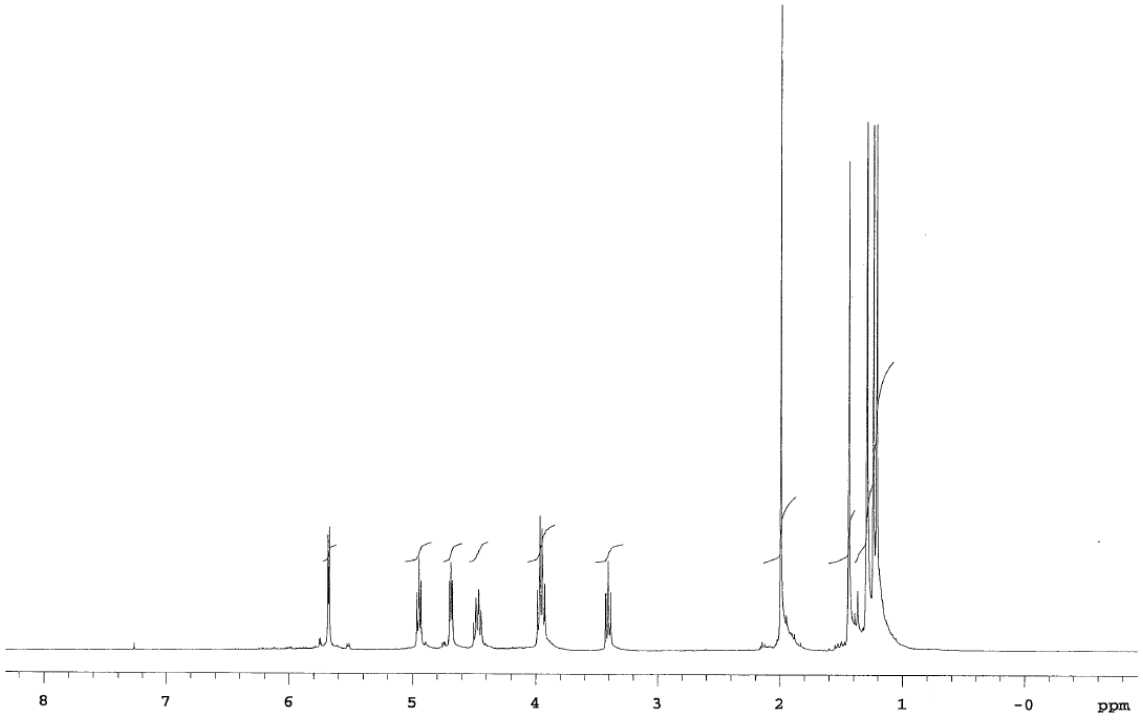
41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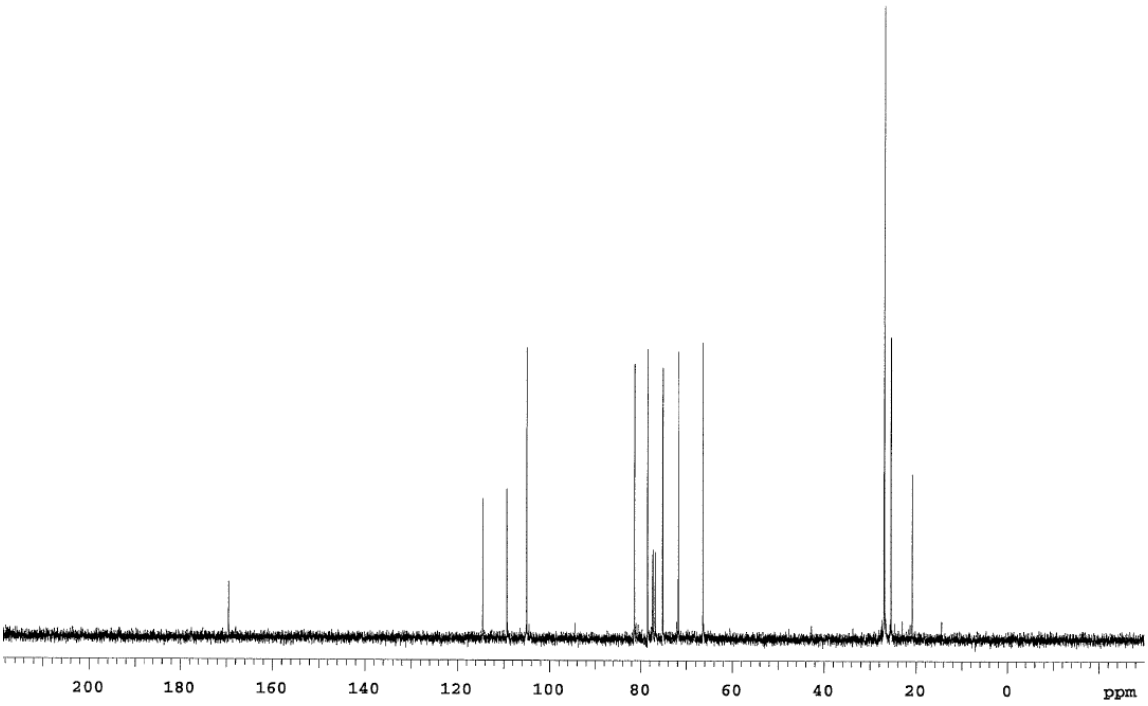
5
4
3
2
1
-0
ppm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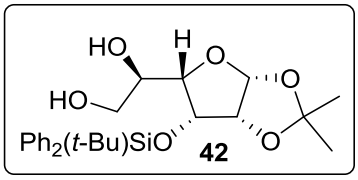
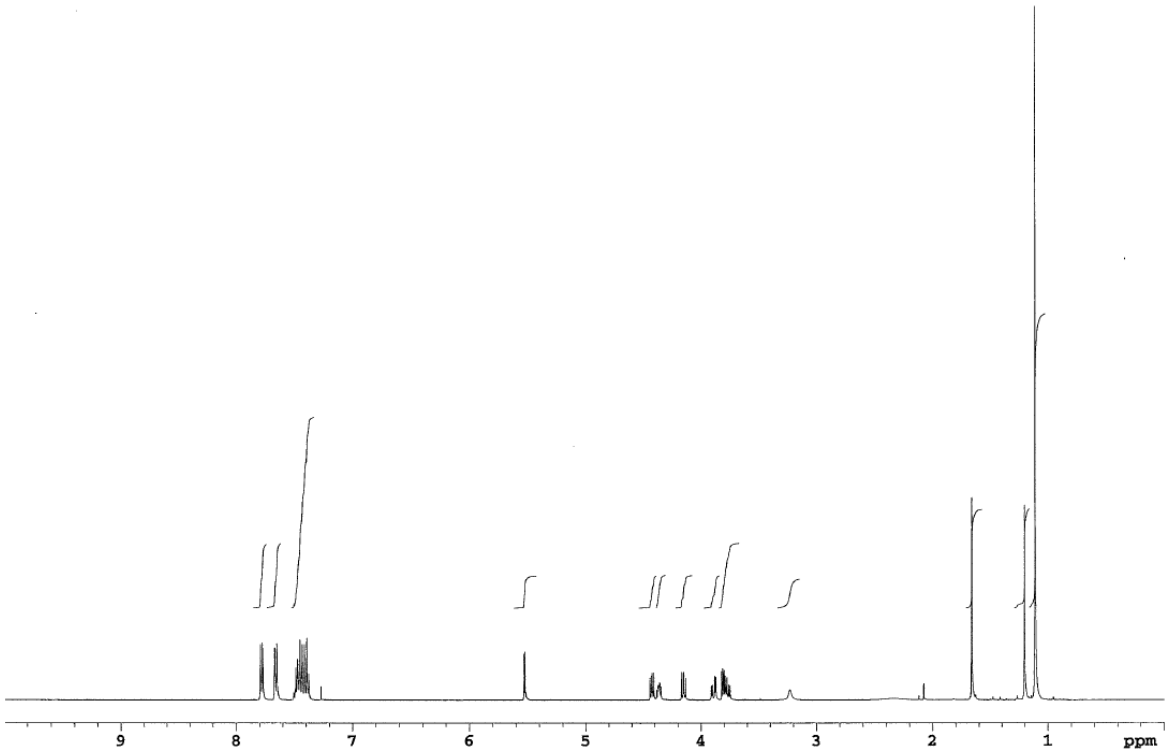
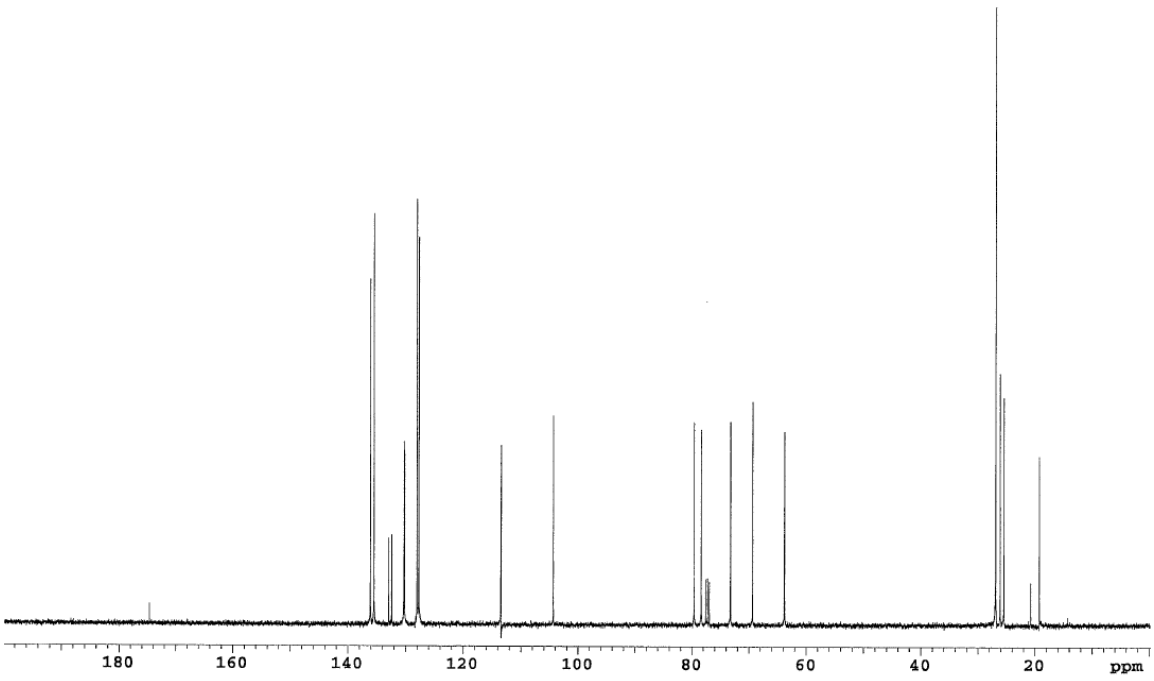
120
100
80
60
40
20
0
ppm


HO
H
O
O
HO
Ph2(t-Bu)SiO
O
42


9
8
7
6
5
4
3
2
1
ppm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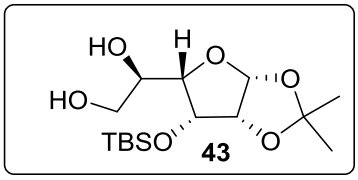
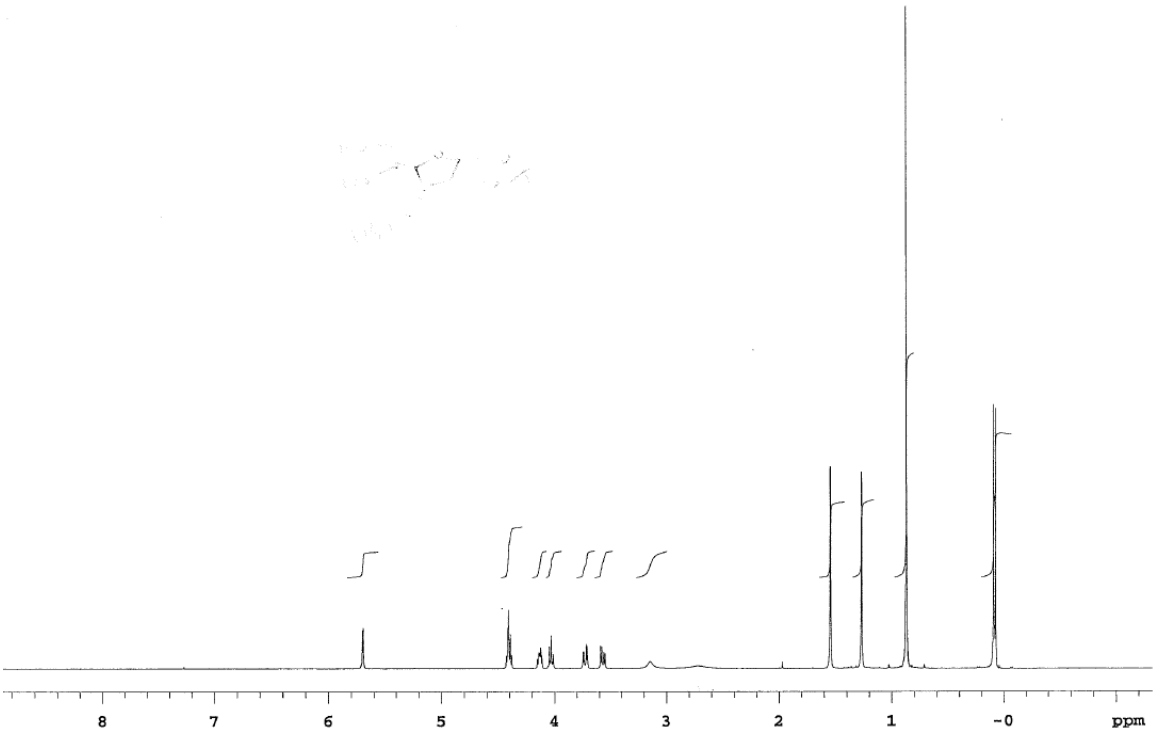
140
120
100
80
60
40
20
ppm


HO
H
O
O
HO
TBSO
O

43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7
6
5
4
3
2
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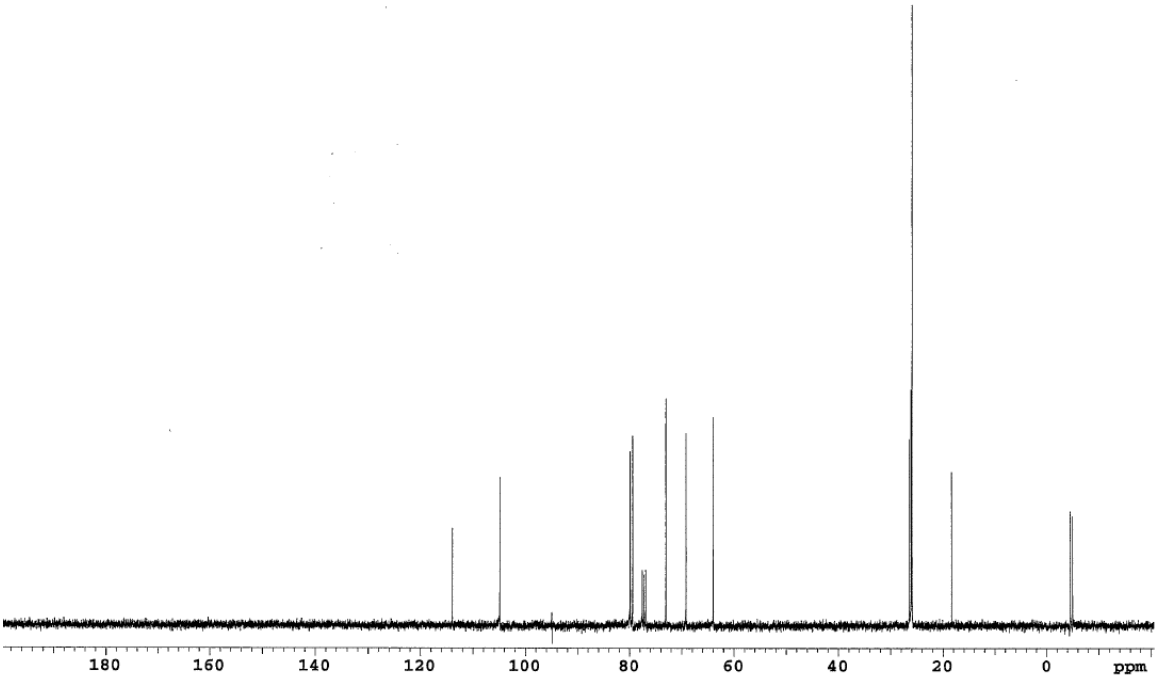
-0
ppm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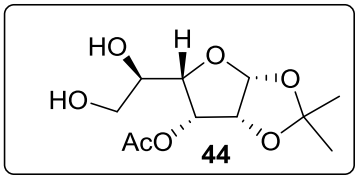
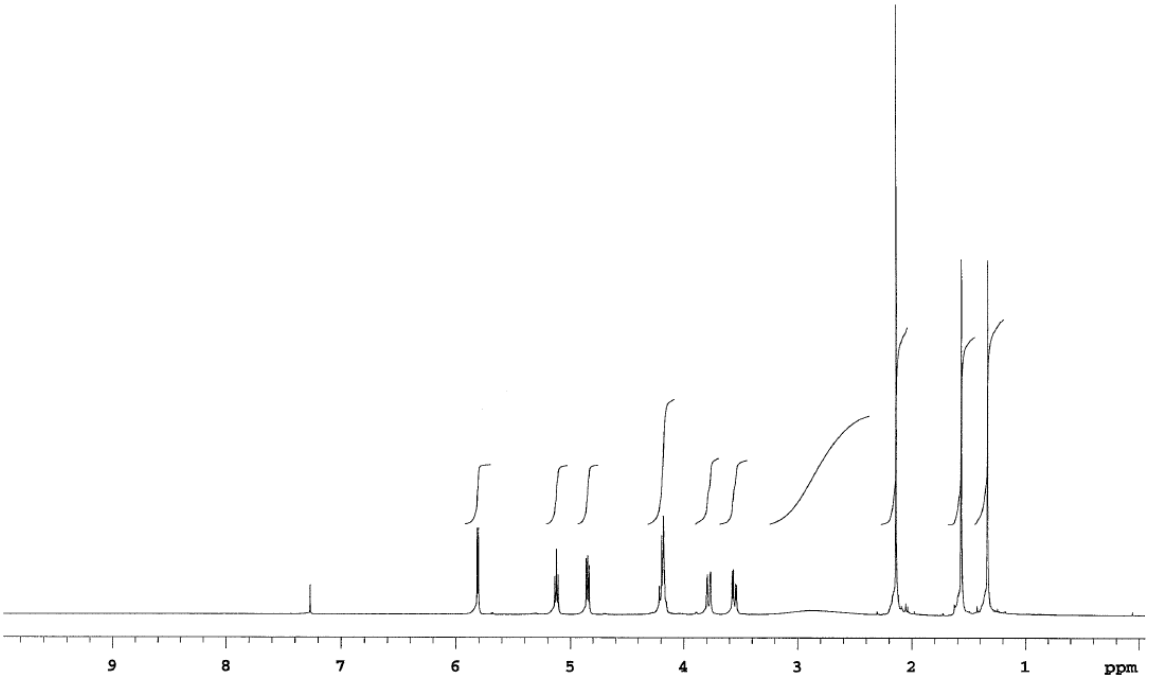
160
140
120
100
80
60
40
20
0
ppm


HO
H
O
HO
O
AcO
O
44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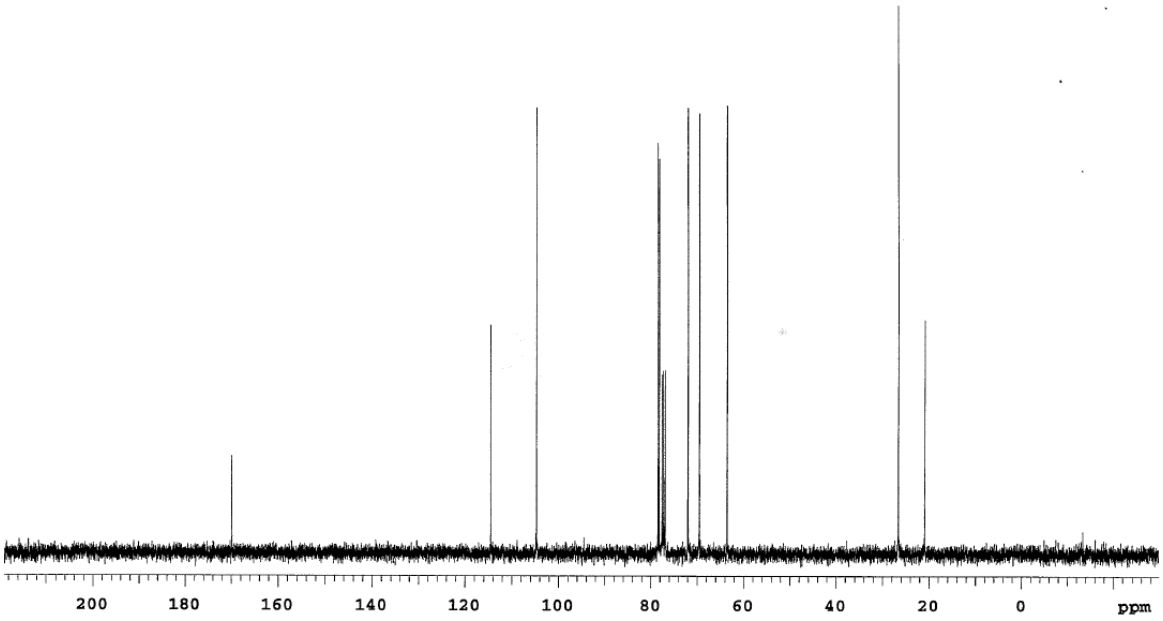
8
7
6
5
4
3
2
1
ppm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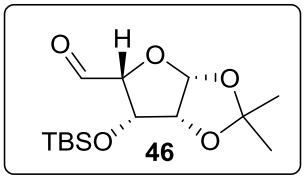
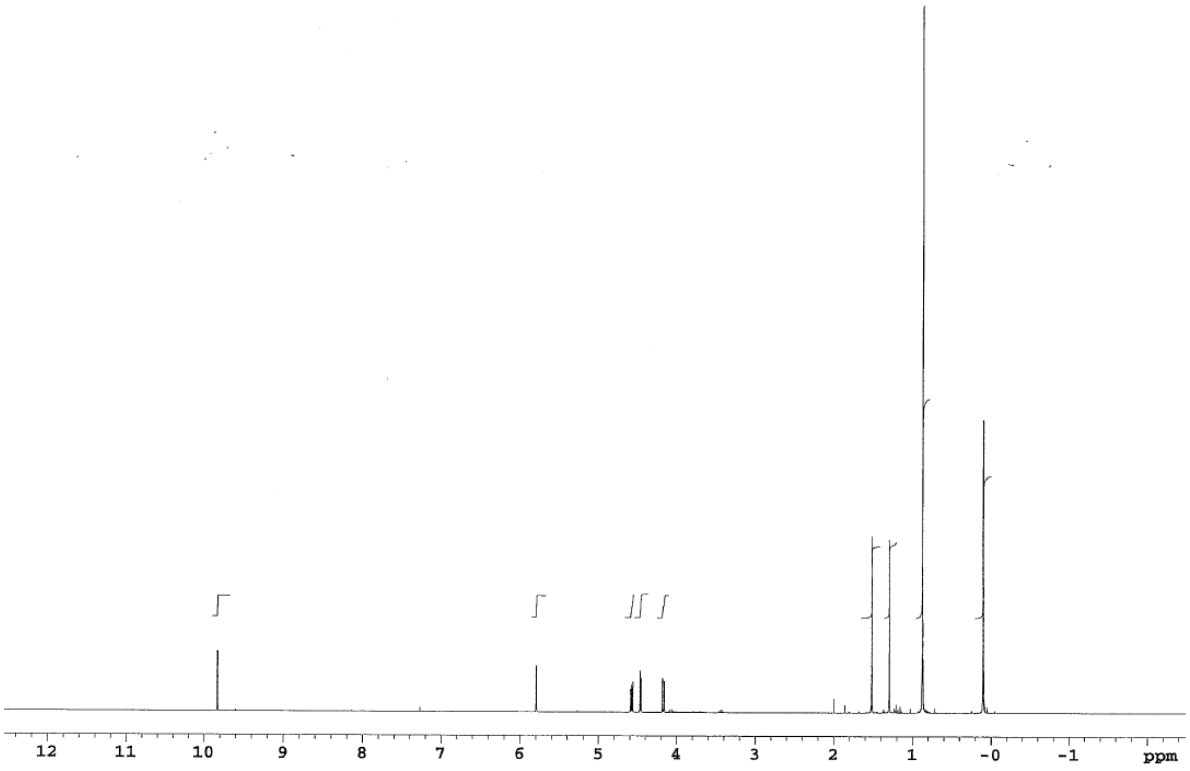
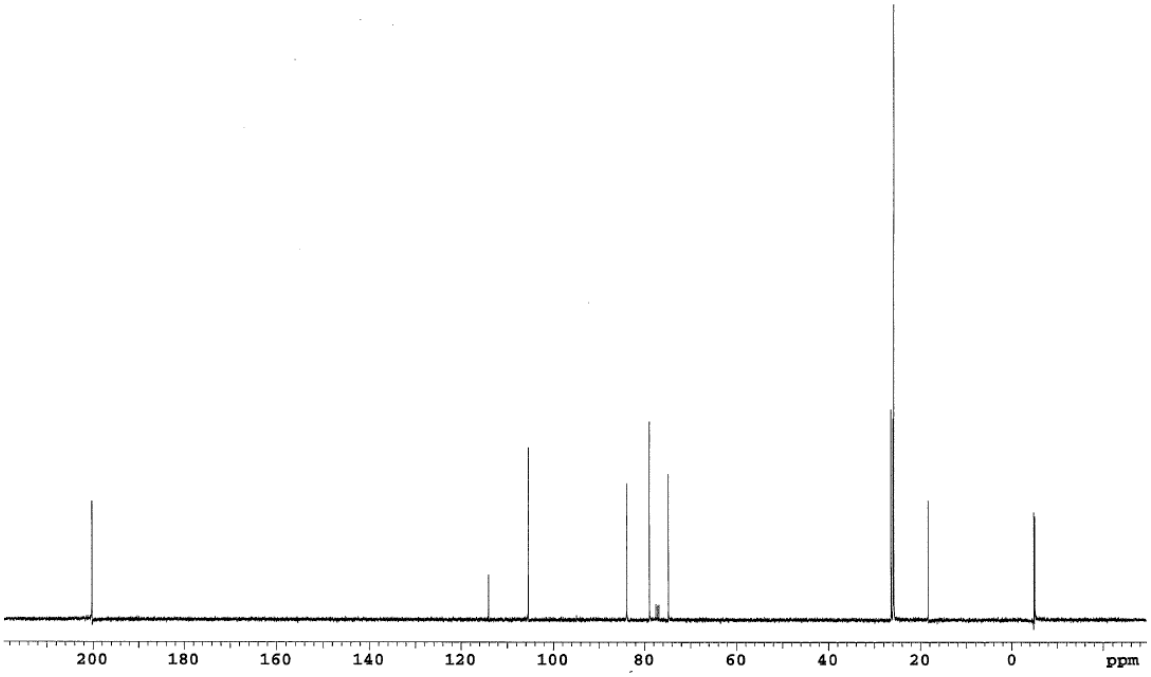
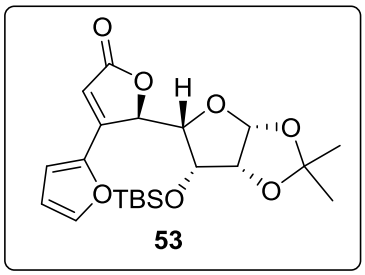
180
160
140
120
100
80
60
40
20
0
ppm


O
H
O
O
TBSO
O

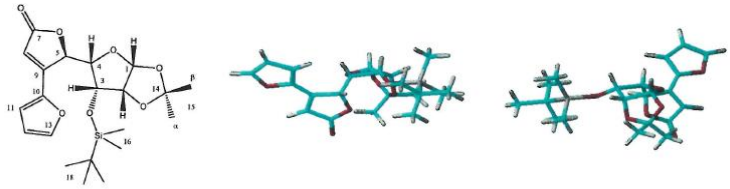
46


12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm



53

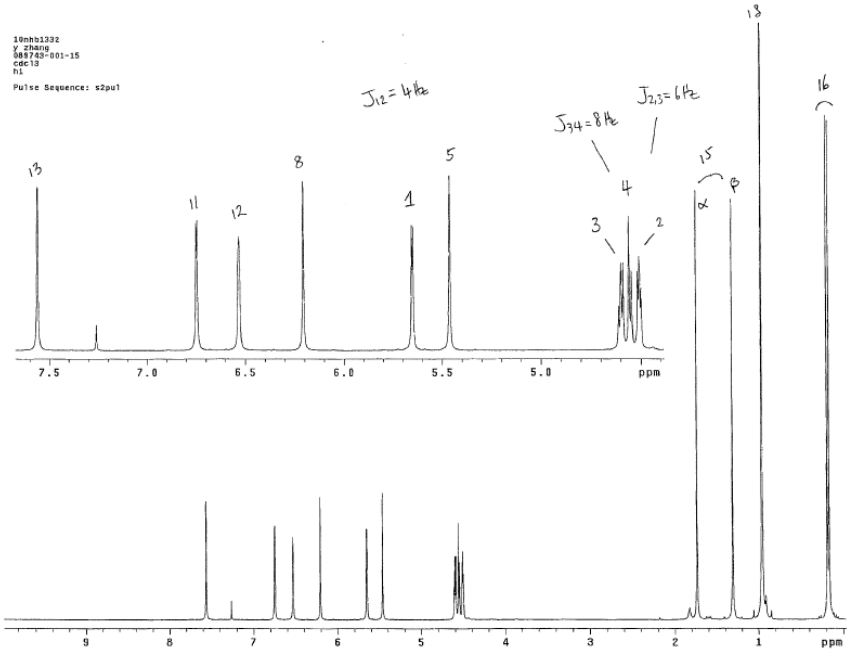


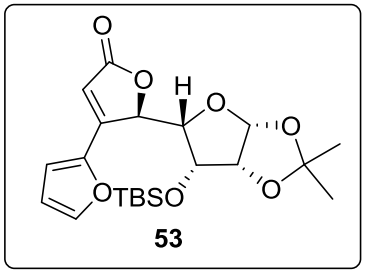
NMR spectra were taken in $CDCl_3$ on a 600 MHz spectrometer. Proton, carbon, HSQC, HMBC and NOESY spectra were obtained. The spectra are consistent with the structure.

The coupling constants observed: $J_{1,2}$ = 4 Hz, $J_{2,3}$ = 6 Hz, $J_{3,4}$ = 8 Hz, are consistent with the structure and conformation of the sugar ring.

$J_{4,5}$ ~ 1 Hz and the large NOE observed between H4 and H5 mean that H4 and H5 are gauche to each other (dihedral angle 60 or -60 deg). NOEs H5/H3 and H5/H18 are observed, which mean that H5 is pointing towards C3.

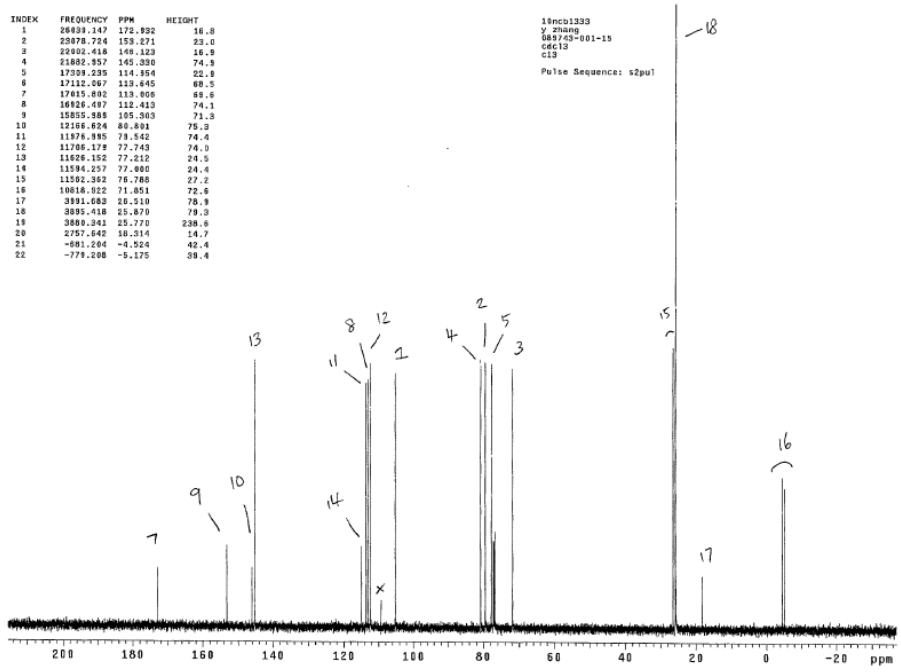
The stereochemistry at C5 is determined as R (as shown above). A large NOE is observed between H11 and H4 which is only possible for the R isomer and not possible for the S isomer (below).

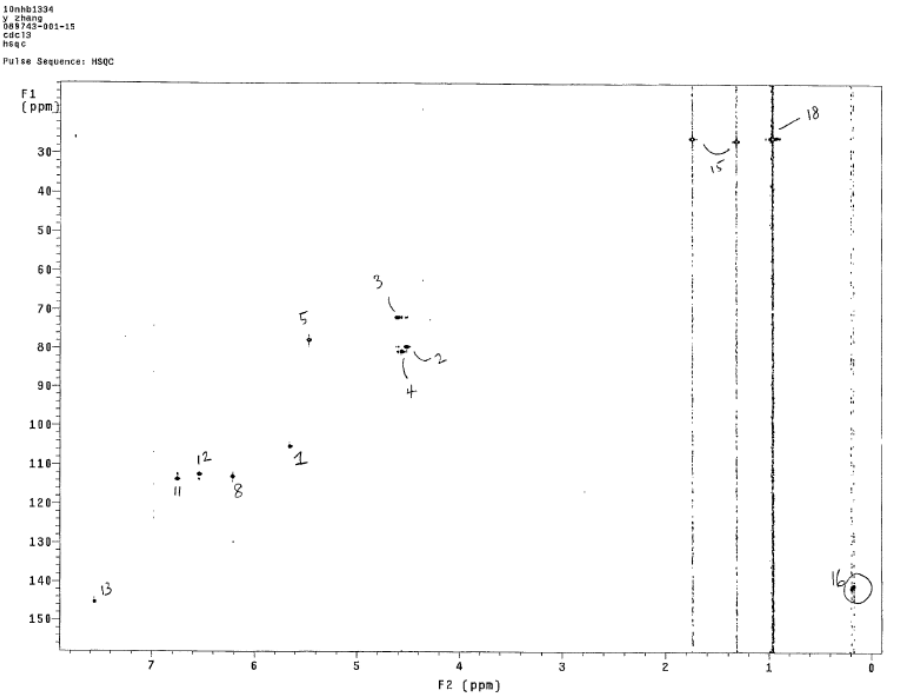


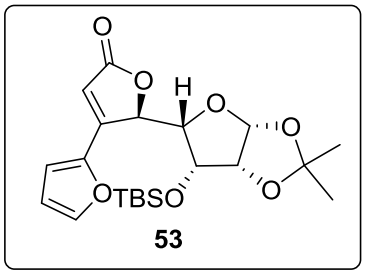


53

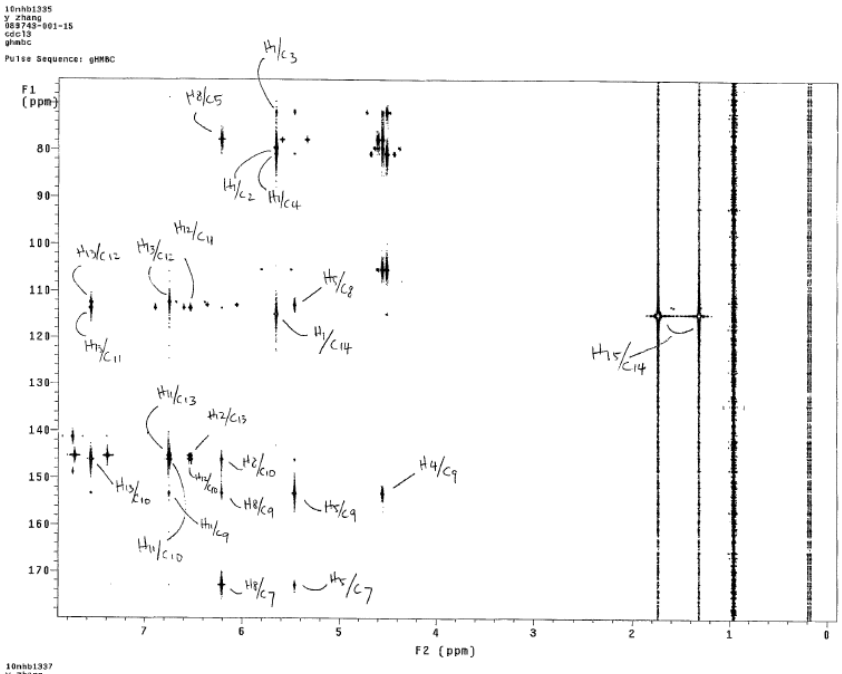
INDEX	FREQUENCY	PPM	HEIGHT
1	26839.147	172.932	16.8
2	23878.724	153.271	23.0
3	22002.418	148.123	16.9
4	21682.957	145.330	74.9
5	17738.235	114.354	22.6
6	17112.067	113.645	68.5
7	17015.802	113.606	68.6
8	16926.497	112.413	74.1
9	15855.585	105.303	71.3
10	12166.624	80.891	75.3
11	11976.995	78.542	74.4
12	11786.179	77.743	74.0
13	11626.152	77.212	24.5
14	11594.257	77.000	24.4
15	11582.362	76.788	27.2
16	10818.022	71.851	72.6
17	3891.683	26.510	78.9
18	3895.418	25.870	79.3
19	3880.341	25.770	238.6
20	2757.642	18.314	14.7
21	-681.204	-4.524	42.4
22	-779.208	-5.175	38.4

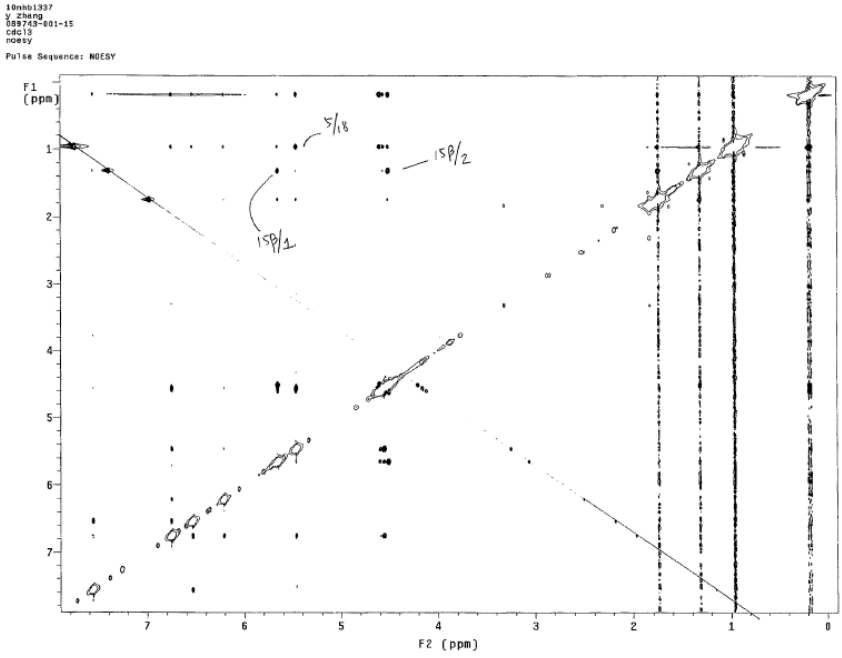


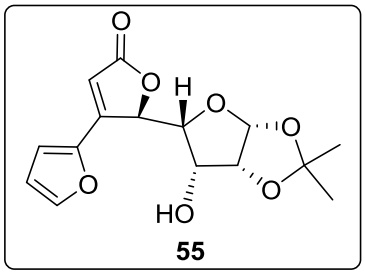



O
O
H
O
O
O
OTBSO

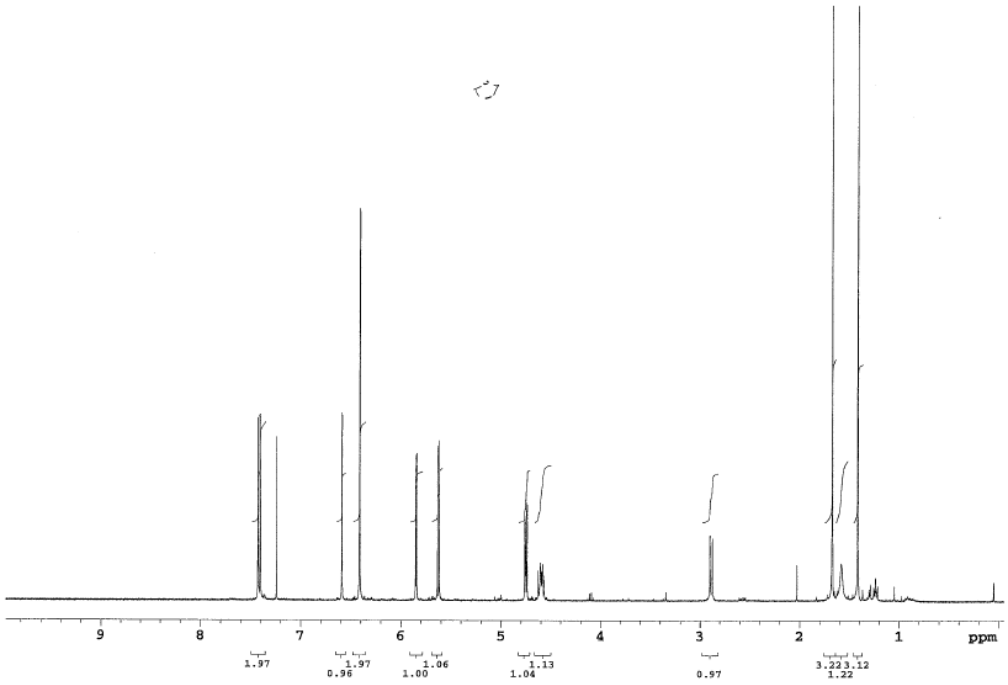
53

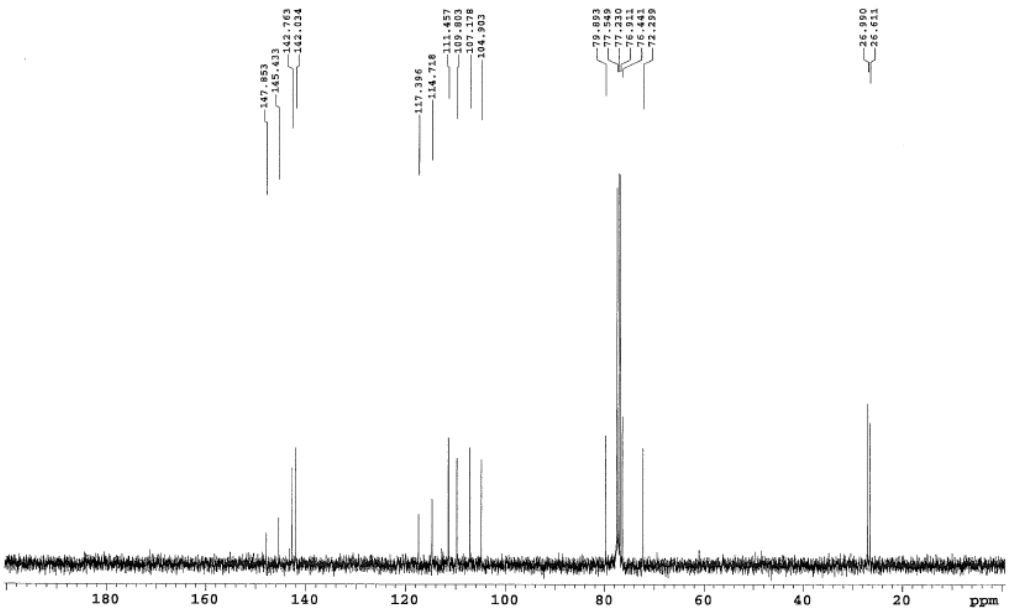

10nhb1335
y zhang
089743-001-15
cdcl3
ghmbc
Pulse Sequence: gHMBC
F1 (ppm)
F2 (ppm)


10nhb1337
y zhang
089743-001-15
cdcl3
noesy
Pulse Sequence: NOESY
F1 (ppm)
F2 (ppm)


O
O
H
O
O
O
HO

55


9
8
7
6
5
4
3
2
1
ppm
1.97
0.96
1.97
1.00
1.06
1.04
1.13
0.97
3.22
1.22
3.12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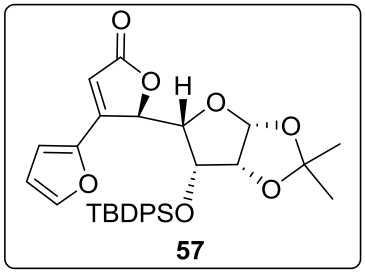
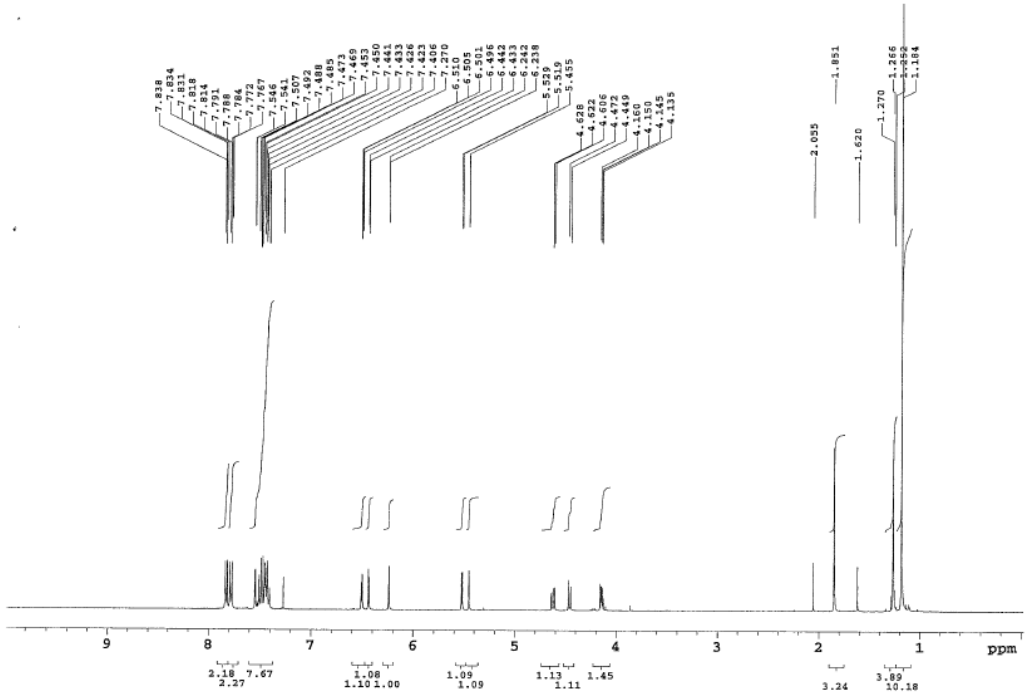
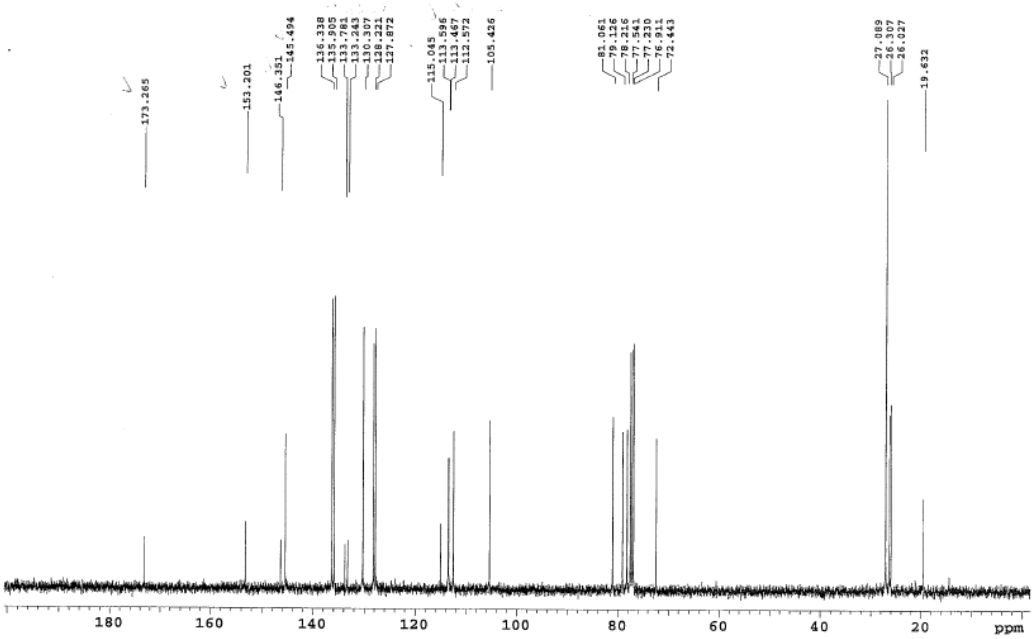
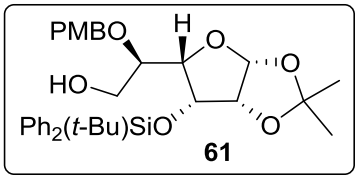
145.433
143.763
142.034
117.396
114.718
111.457
109.803
107.178
104.903
79.803
77.580
77.330
76.911
76.441
72.299
26.900
26.611
180
160
140
120
100
80
60
40
20
ppm


O
O
H
O
O
O
O
TBDPSO

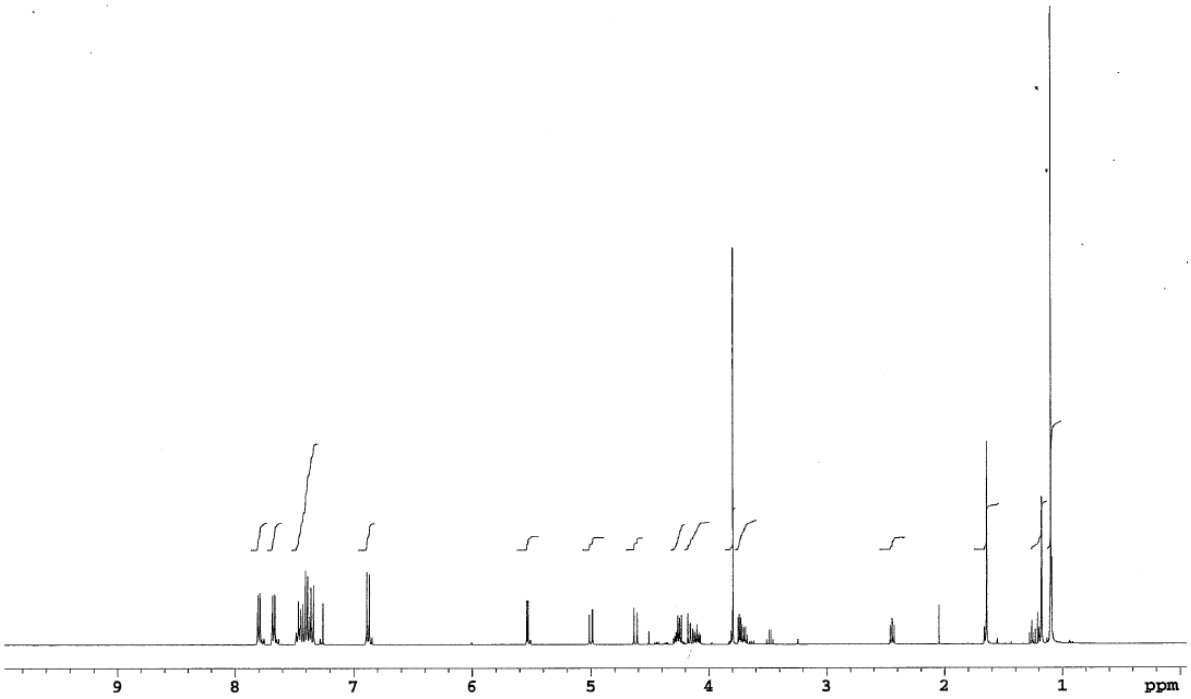
57

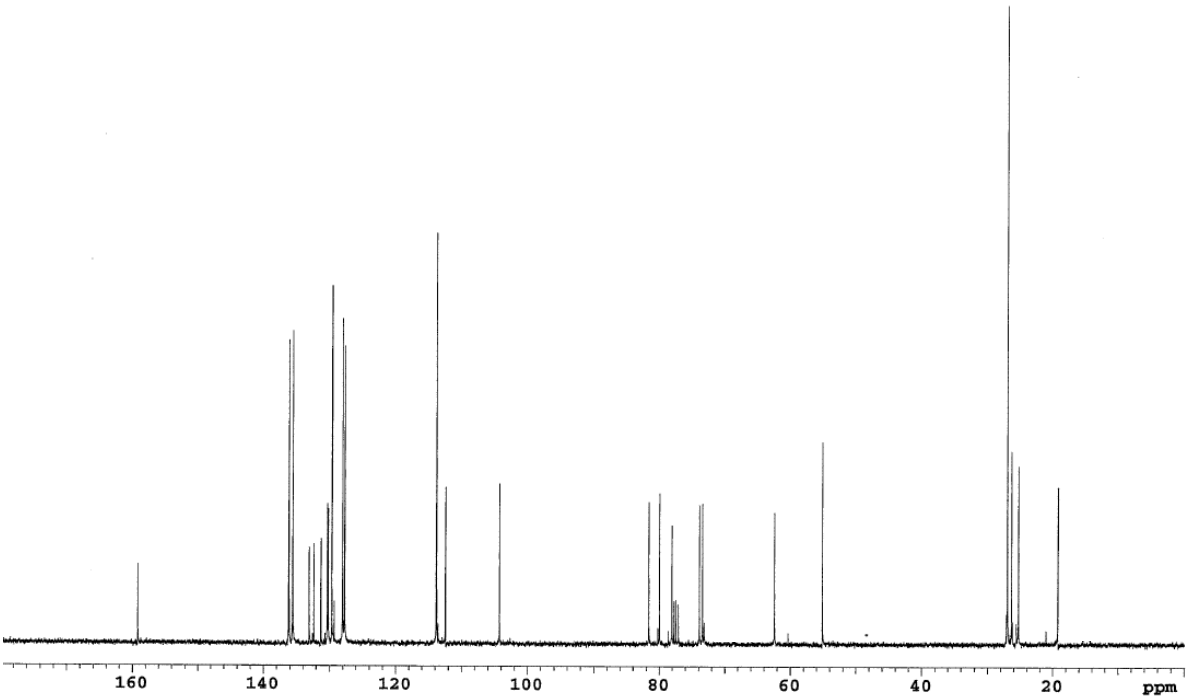

7.838
7.834
7.831
7.818
7.814
7.791
7.788
7.784
7.772
7.767
7.546
7.541
7.507
7.492
7.488
7.485
7.473
7.469
7.453
7.450
7.441
7.433
7.426
7.423
7.406
7.270
6.505
6.501
6.496
6.442
6.433
6.242
6.238
5.529
5.519
5.455
4.638
4.622
4.606
4.472
4.449
4.165
4.150
4.145
4.135
2.055
1.851
1.620
1.270
1.266
1.184
9
8
7
6
5
4
3
2
1
ppm
2.18
2.27
7.67
1.08
1.10
1.00
1.09
1.09
1.13
1.11
1.45
3.24
3.09
10.18

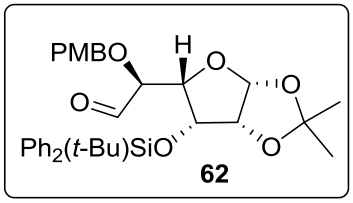

173.265
153.201
146.351
145.494
136.338
135.905
133.381
133.243
130.307
128.221
127.872
115.045
113.586
113.467
112.572
105.426
82.061
79.126
78.256
77.543
77.230
76.911
72.443
27.089
26.397
26.027
19.632
180
160
140
120
100
80
60
40
20
ppm


PMBO
H
O
HO
O
Ph2(t-Bu)SiO
O

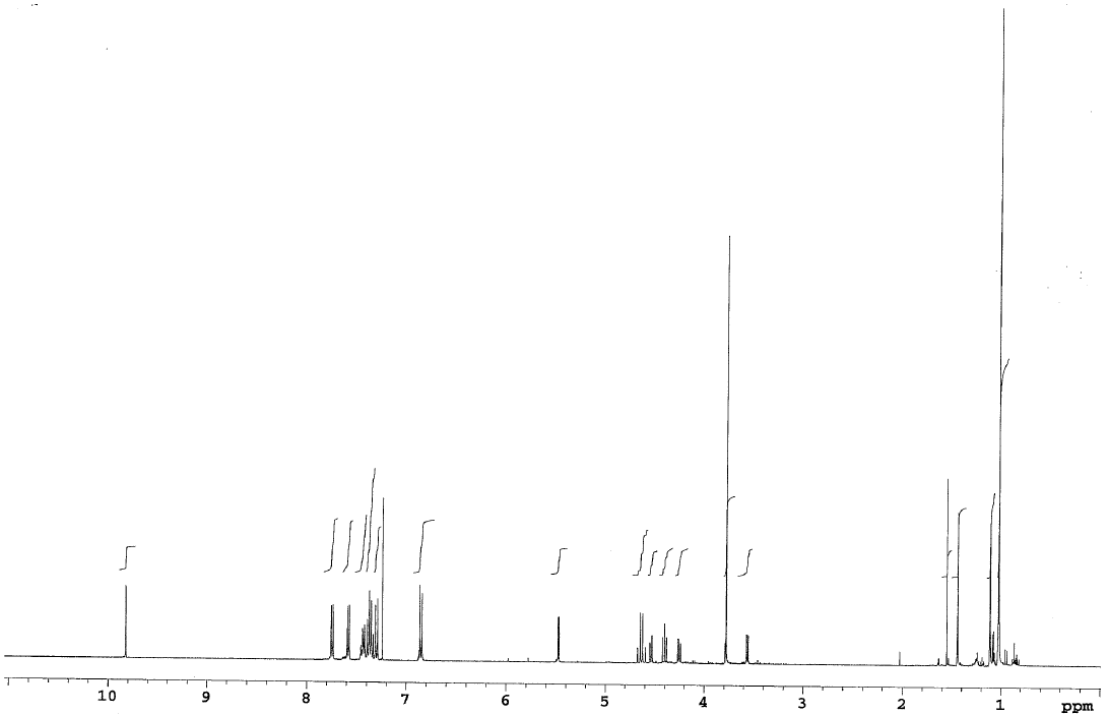
61

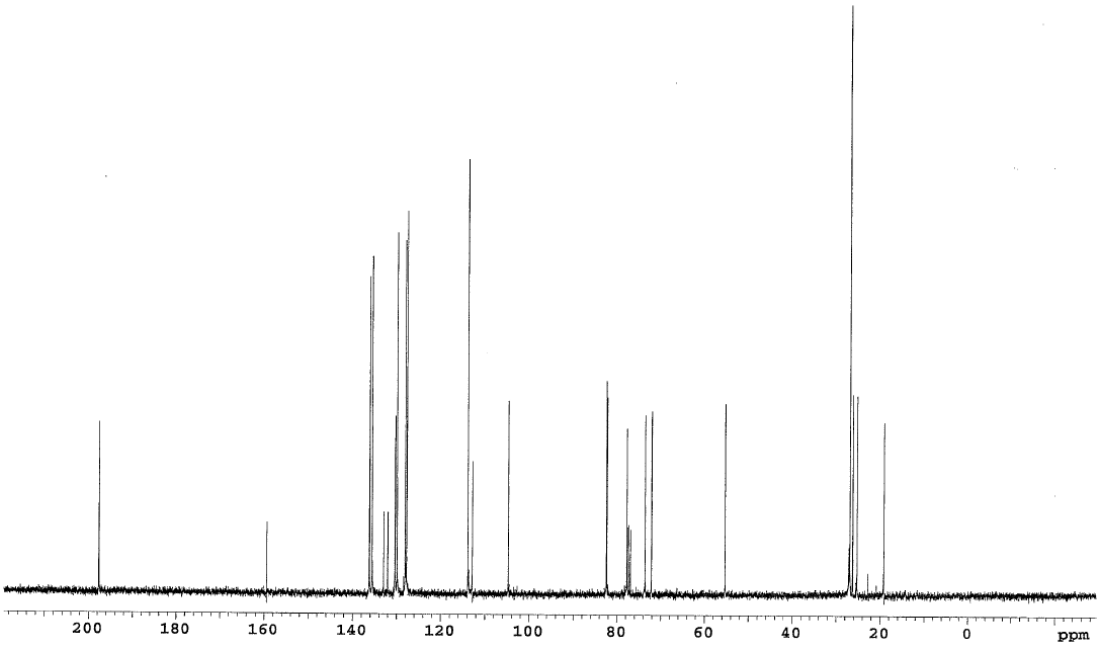

9
8
7
6
5
4
3
2
1
ppm


160
140
120
100
80
60
40
20
ppm


PMBO
H
O
O
O
Ph2(t-Bu)SiO
O

62


10
9
8
7
6
5
4
3
2
1
ppm


200
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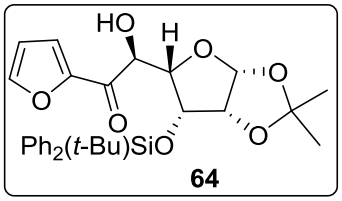
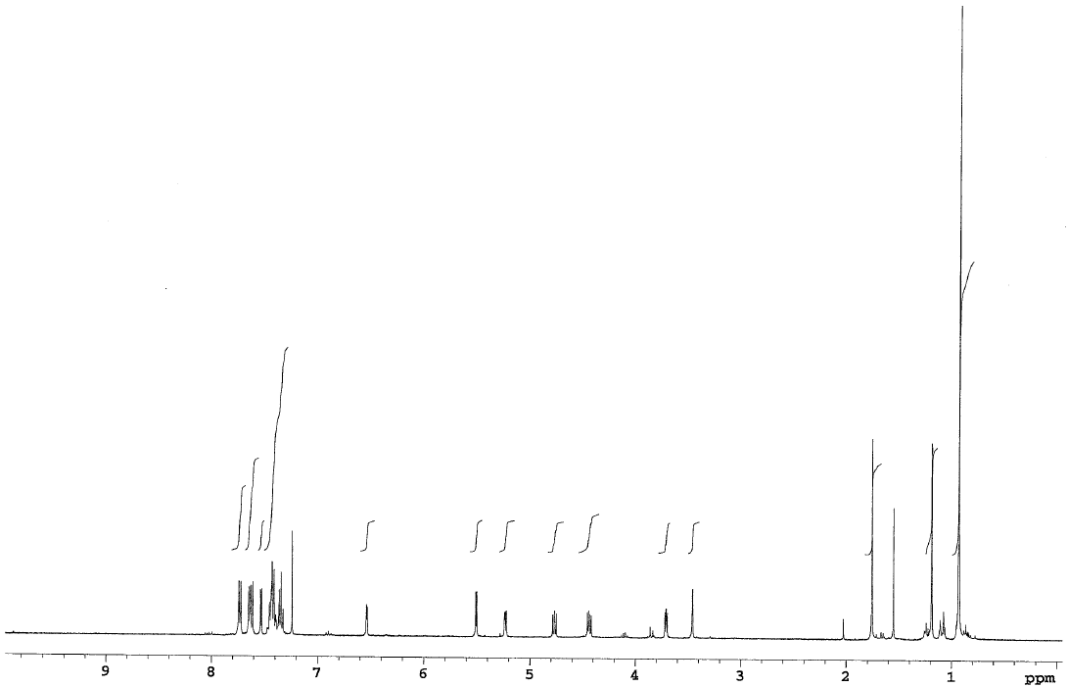
160
140
120
100
80
60
40
20
0
ppm


HO
H
O
O
O
O
O
Ph2(t-Bu)SiO

64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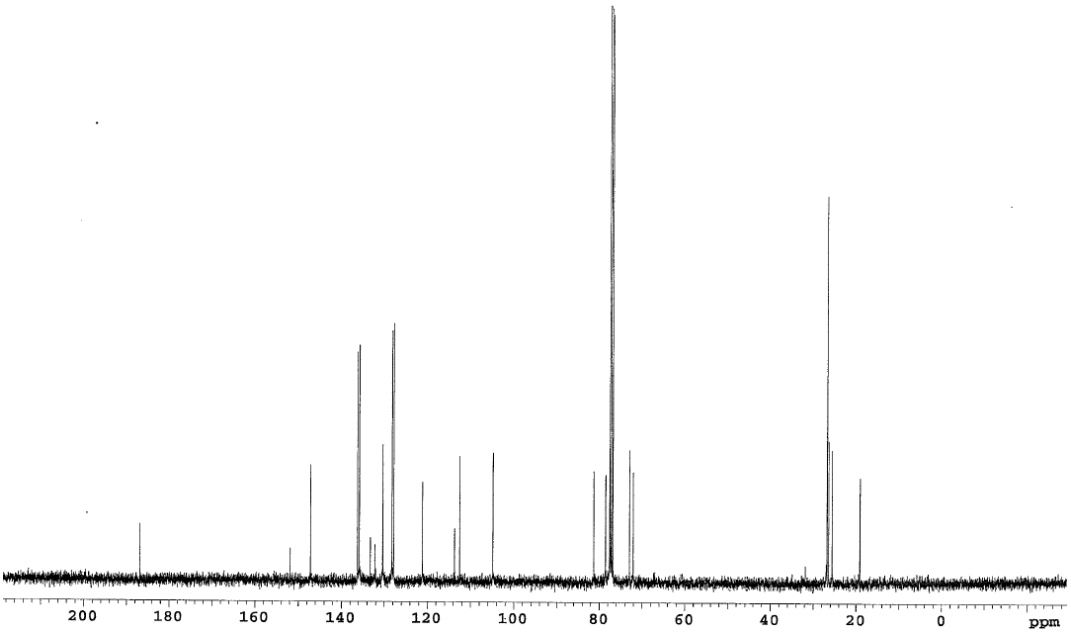
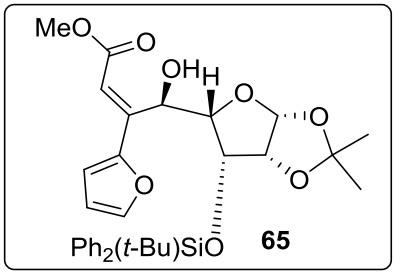
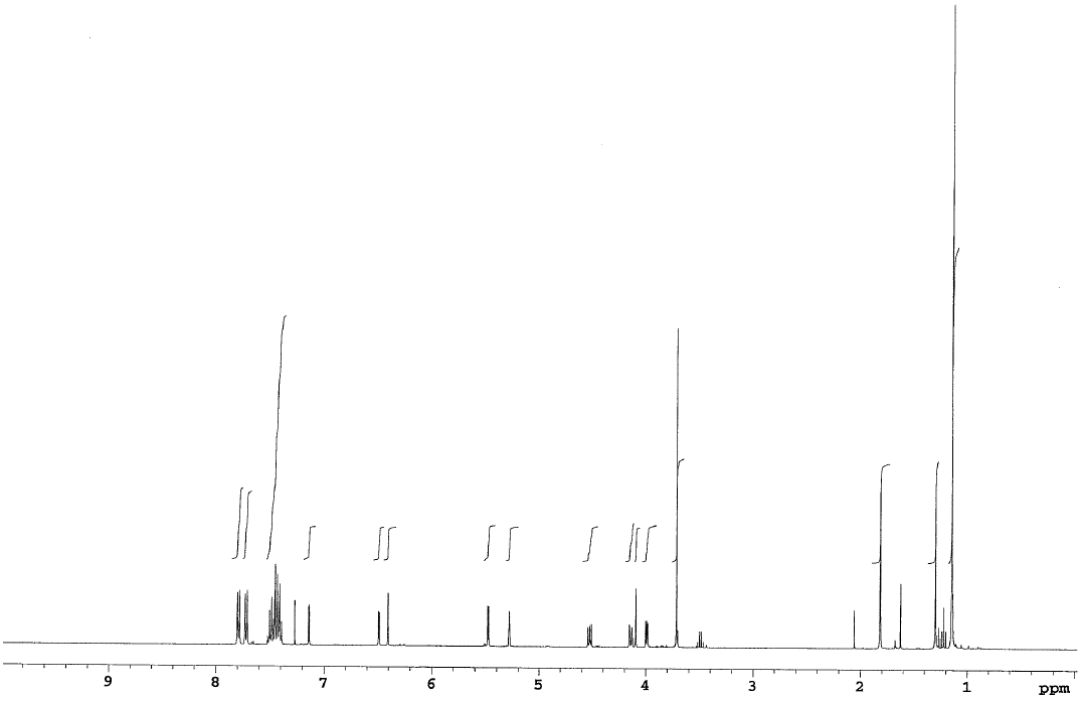
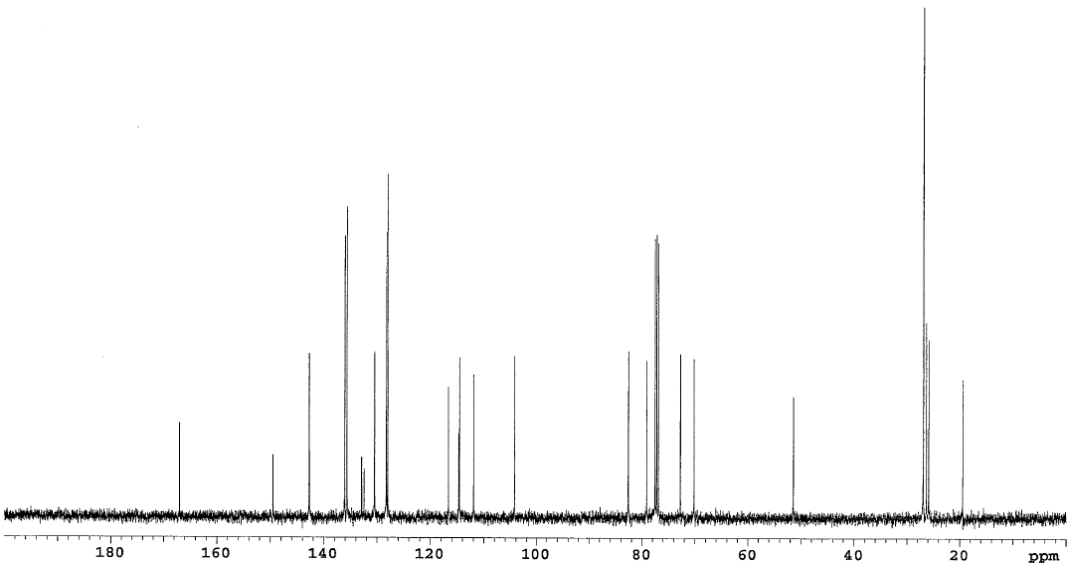
7
6
5
4
3
2
1
ppm

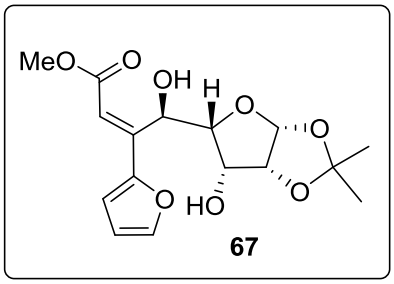

200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
O
OH
H
O
O
O
O
Ph2(t-Bu)SiO

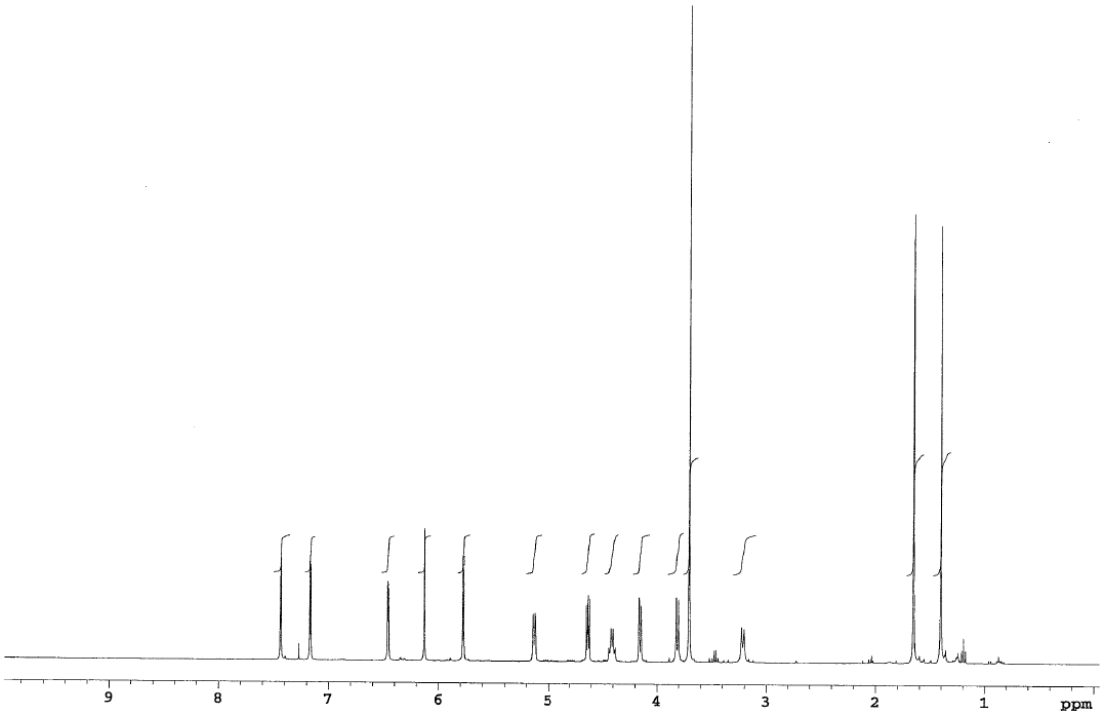
65

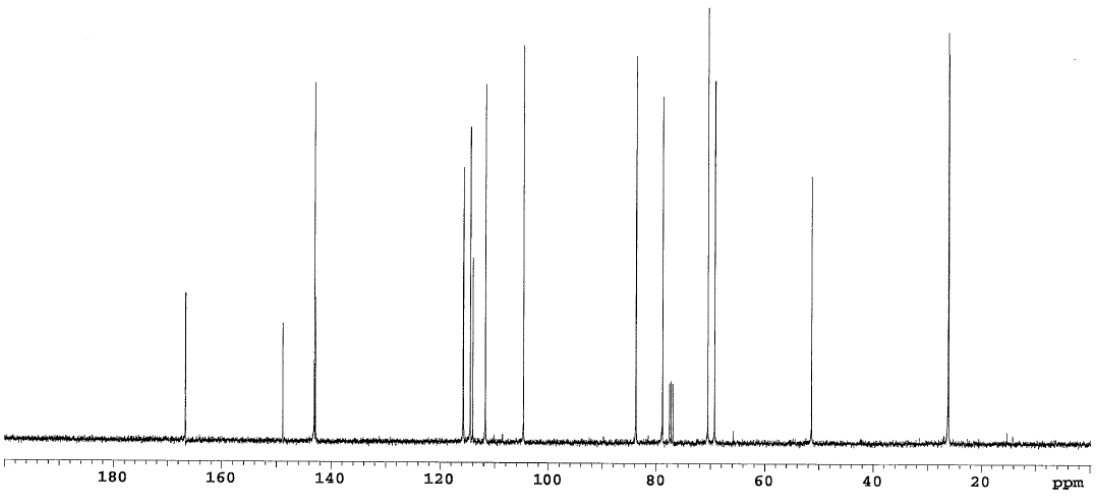

9
8
7
6
5
4
3
2
1
ppm

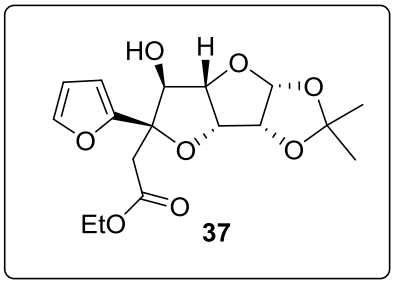

180
160
140
120
100
80
60
40
20
ppm


MeO
O
OH
H
O
O
O
O
HO

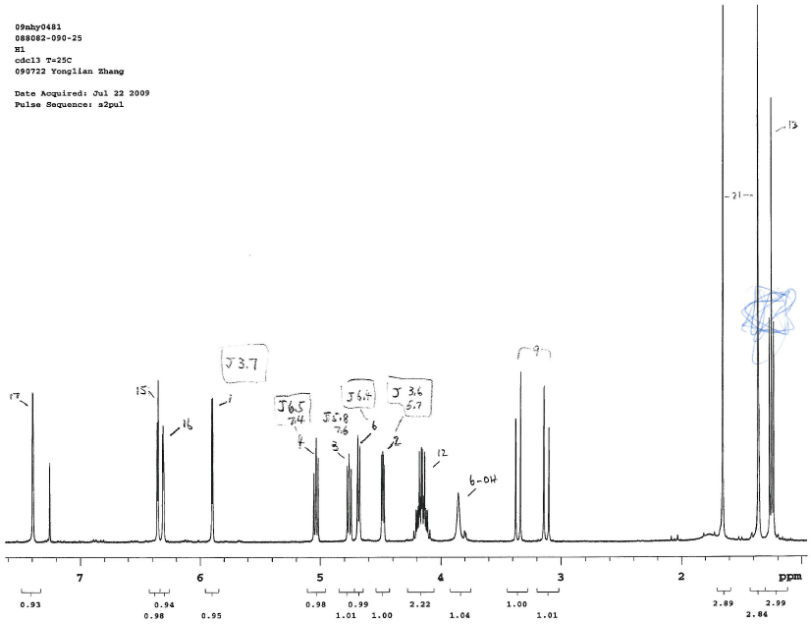
67

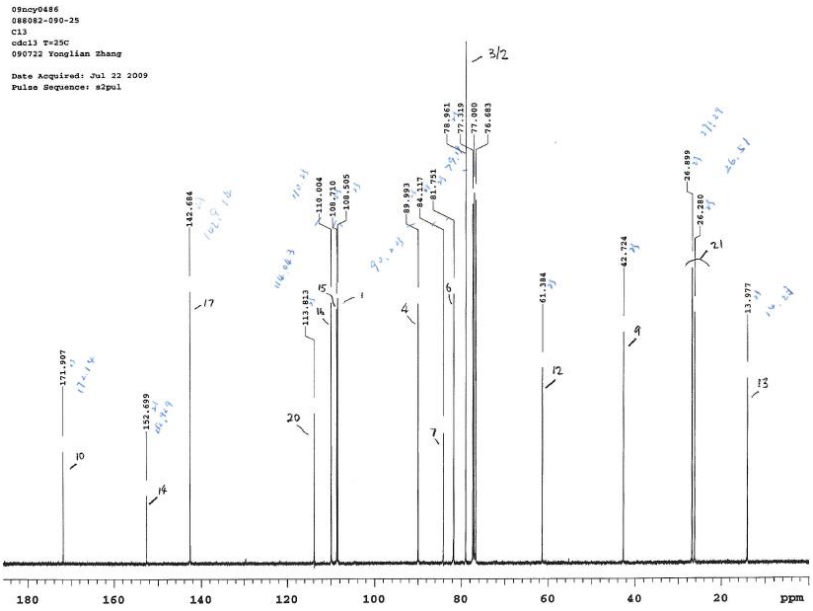

9
8
7
6
5
4
3
2
1
ppm

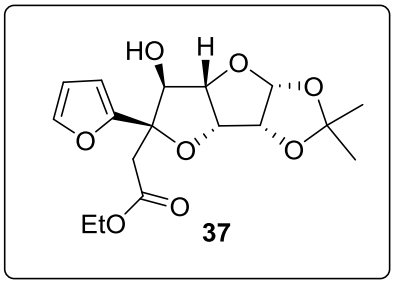

180
160
140
120
100
80
60
40
20
ppm

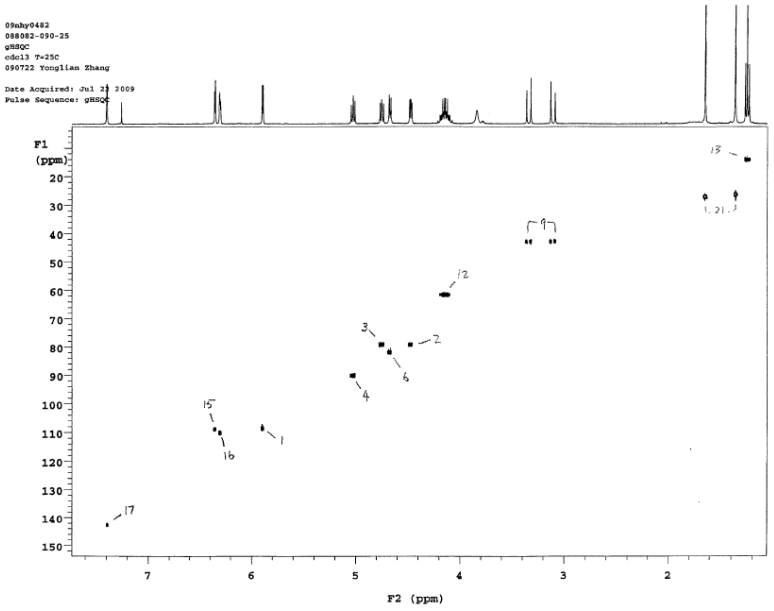

HO
H
O
O
O
O
O
O
EtO
O

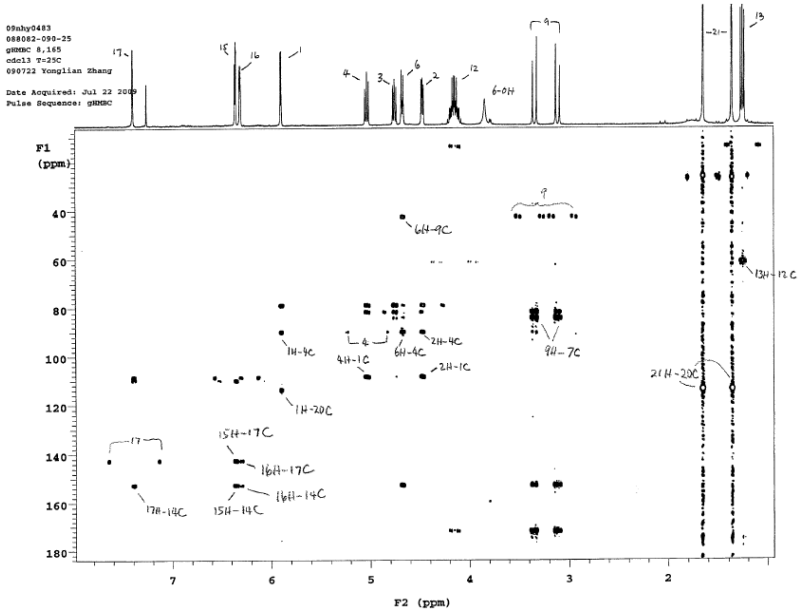
37

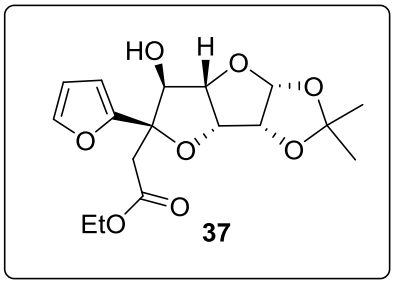

09mhy0481
088082-090-25
H1
cdcl3 T=25C
090722 Yonglian Zhang
Date Acquired: Jul 22 2009
Pulse Sequence: s2pul
ppm


09ncy0486
088082-090-25
C13
cdcl3 T=25C
090722 Yonglian Zhang
Date Acquired: Jul 22 2009
Pulse Sequence: s2pul
ppm

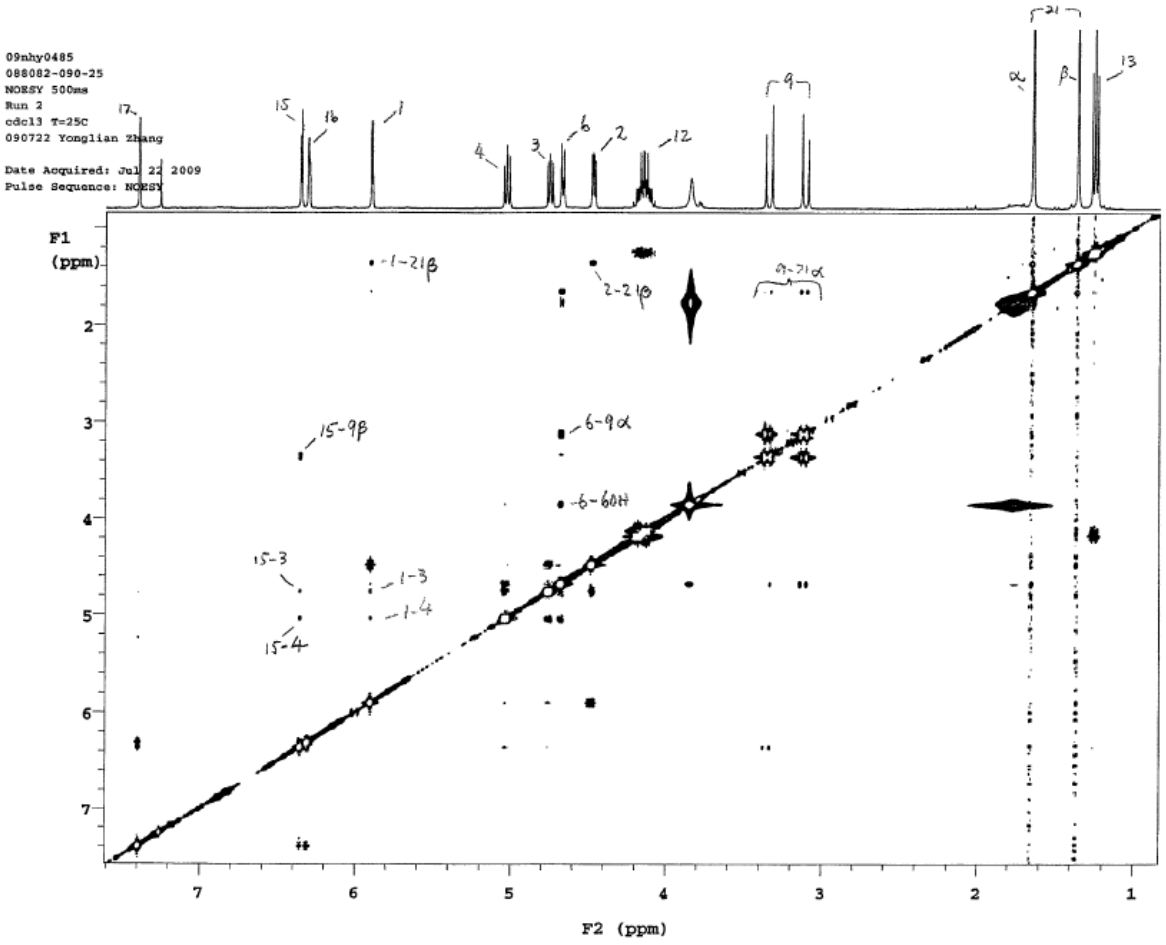

HO
H
O
O
O
O
O
O
EtO
37

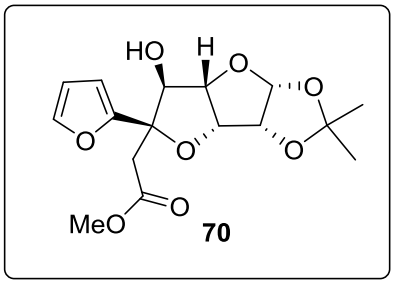

09nhy0482
088082-090-25
gHSQC
cdcl3 T=25C
090722 Yonglian Zhang
Date Acquired: Jul 23 2009
Pulse Sequence: gHSQC
F1 (ppm)
F2 (ppm)


09nhy0483
088082-090-25
gHMBC 8,165
cdcl3 T=25C
090722 Yonglian Zhang
Date Acquired: Jul 22 2009
Pulse Sequence: gHMBC
F1 (ppm)
F2 (ppm)

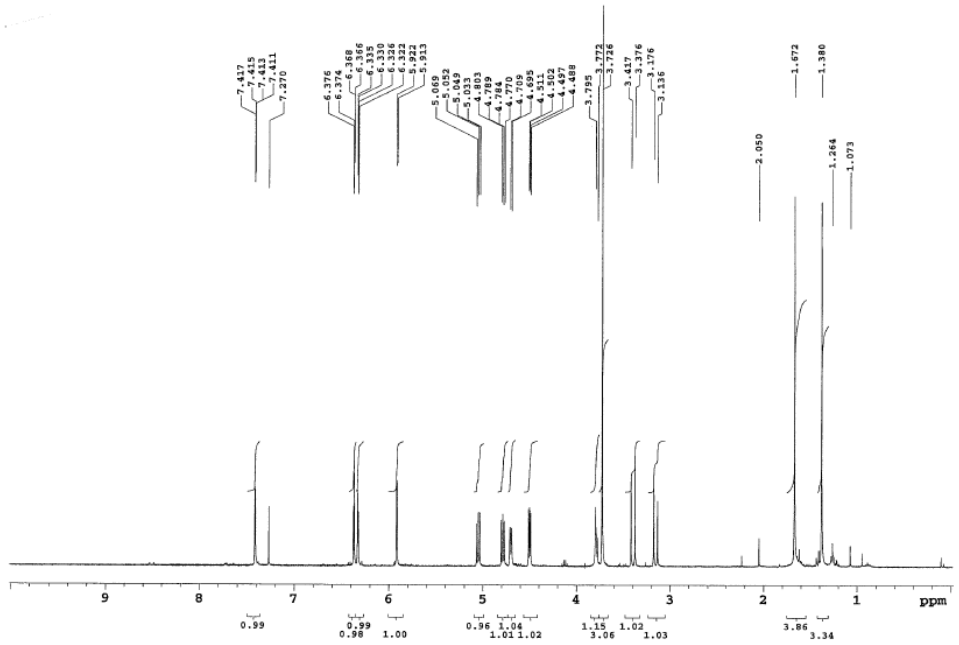

HO
H
O
O
O
O
O
EtO
O

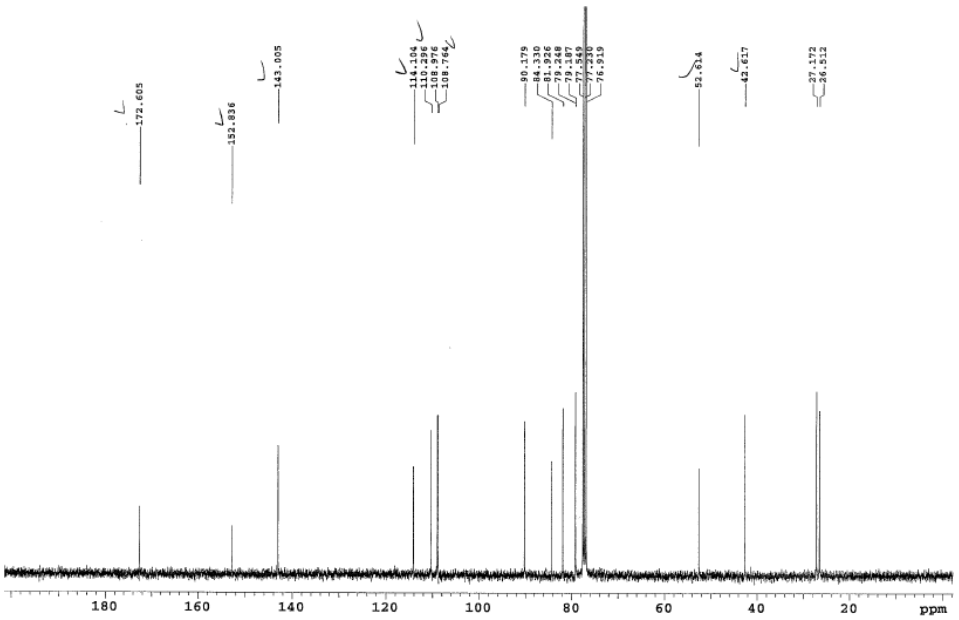
37

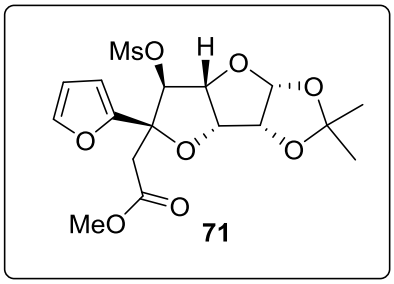

09nhy0485
088082-090-25
NOESY 500ms
Run 2
cdcl3 T=25C
090722 Yonglian Zhang
Date Acquired: Jul 22 2009
Pulse Sequence: NOESY
F1 (ppm)
F2 (ppm)
1-21β
2-21β
9-21α
15-9β
6-9α
6-6OH
15-3
1-3
1-4
15-4

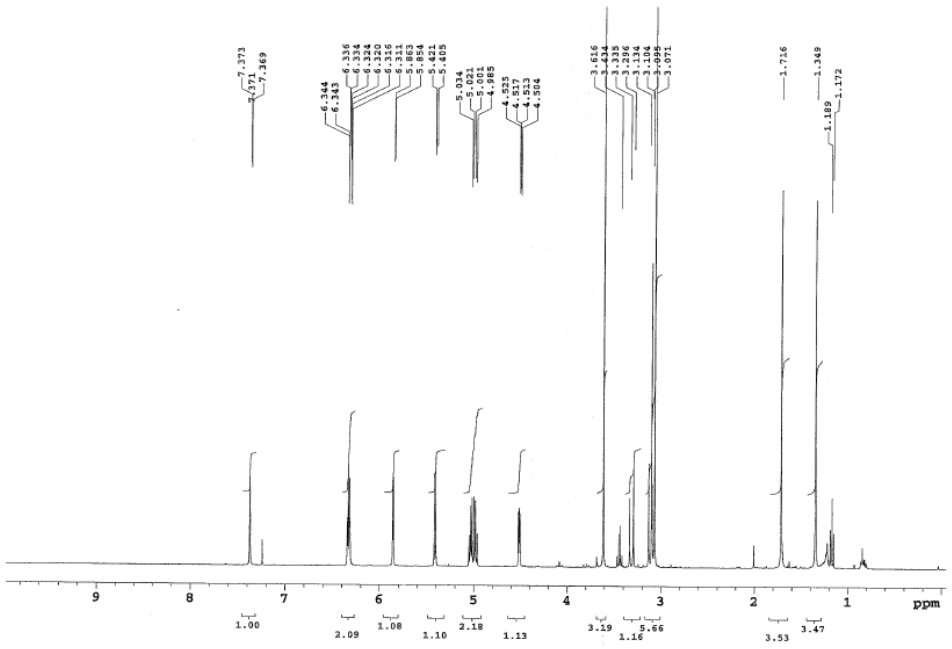

HO
H
O
O
O
O
O
O
MeO
O

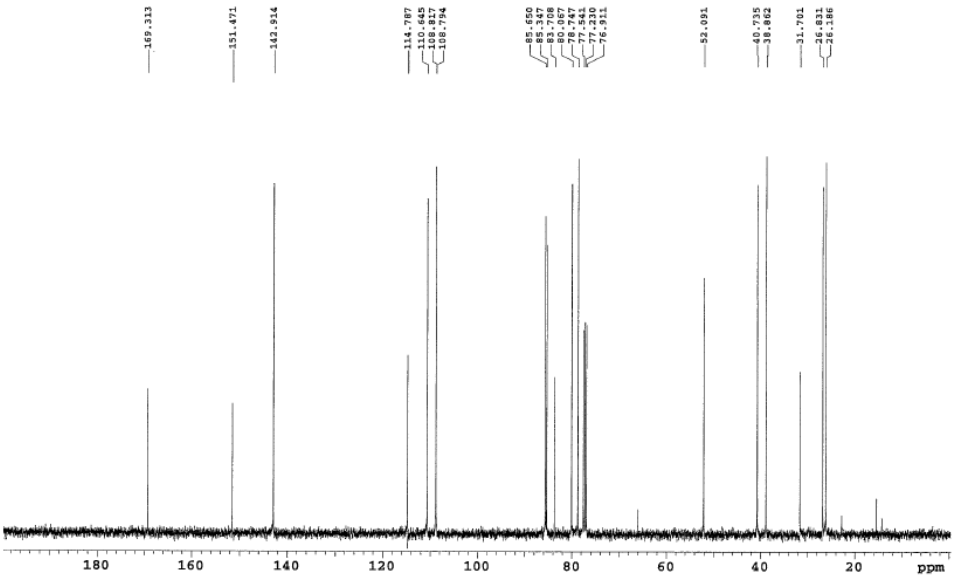
70

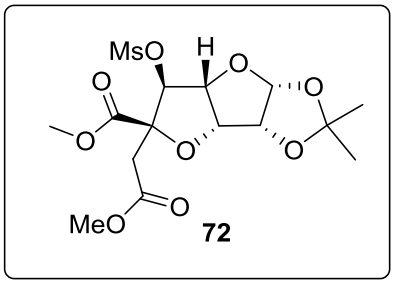

7.417
7.415
7.411
7.270
6.376
6.374
6.368
6.335
6.330
6.326
6.322
5.913
5.069
5.052
5.049
5.033
4.803
4.789
4.786
4.770
4.709
4.695
4.502
4.497
4.488
3.795
3.772
3.768
3.417
3.176
3.136
2.050
1.672
1.380
1.264
1.073
ppm


172.605
152.836
143.005
114.104
110.296
108.976
108.764
90.179
84.330
81.926
79.248
79.187
77.549
77.230
76.919
52.614
42.617
27.172
26.512
ppm

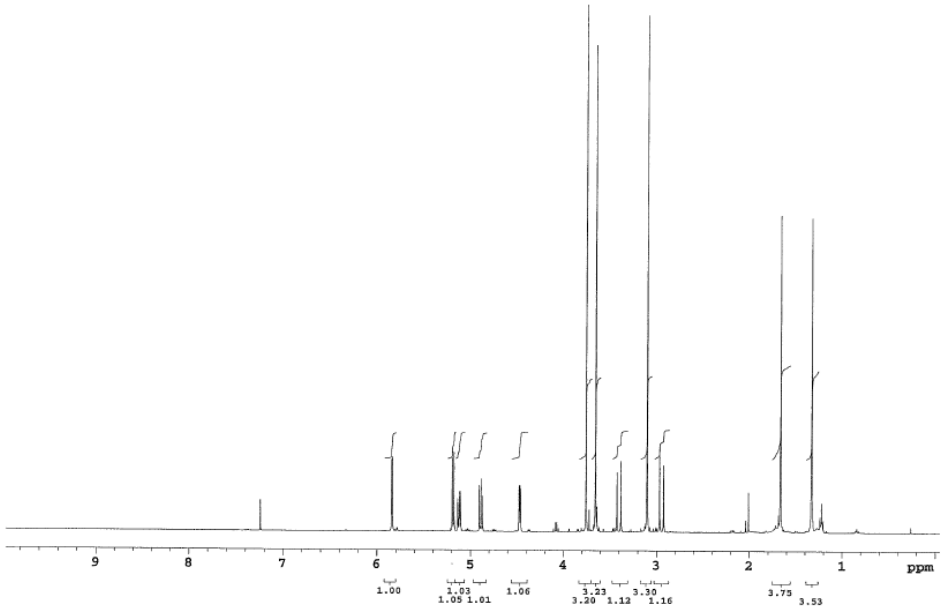

MsO
H
O
O
O
O
O
O
MeO
71

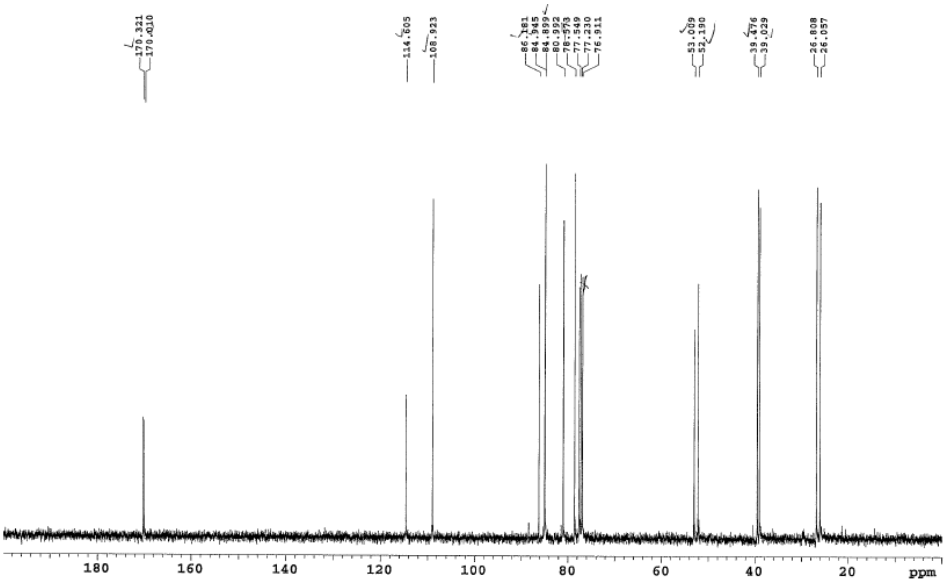

7.373
7.371
7.369
6.344
6.343
6.336
6.334
6.324
6.320
6.316
6.311
5.863
5.854
5.421
5.405
5.034
5.031
5.008
4.985
4.525
4.517
4.513
4.504
3.616
3.434
3.335
3.296
3.134
3.104
3.095
3.071
1.716
1.349
1.189
1.172
ppm
1.00
2.09
1.08
1.10
2.18
1.13
3.19
1.16
5.66
3.53
3.47

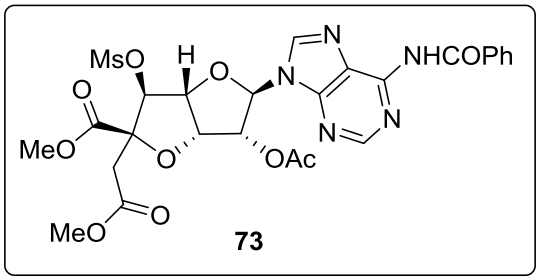

169.313
151.471
142.914
114.787
110.645
108.817
108.794
85.650
85.547
83.708
80.067
78.747
77.441
77.330
76.911
52.091
40.735
30.862
31.701
26.831
26.186
ppm


MsO
H
O
O
O
O
O
O
O
MeO

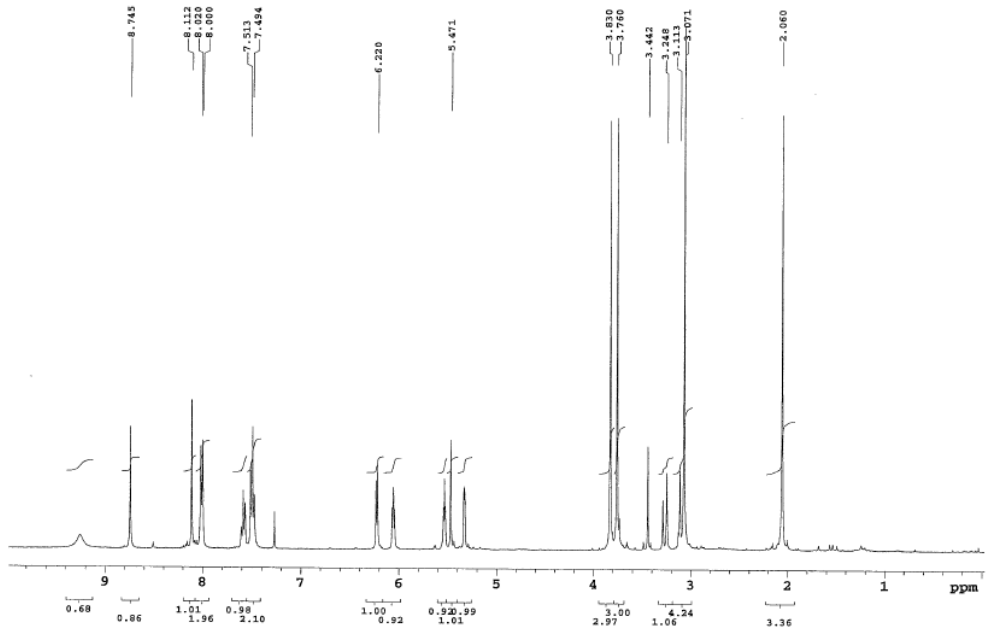
72

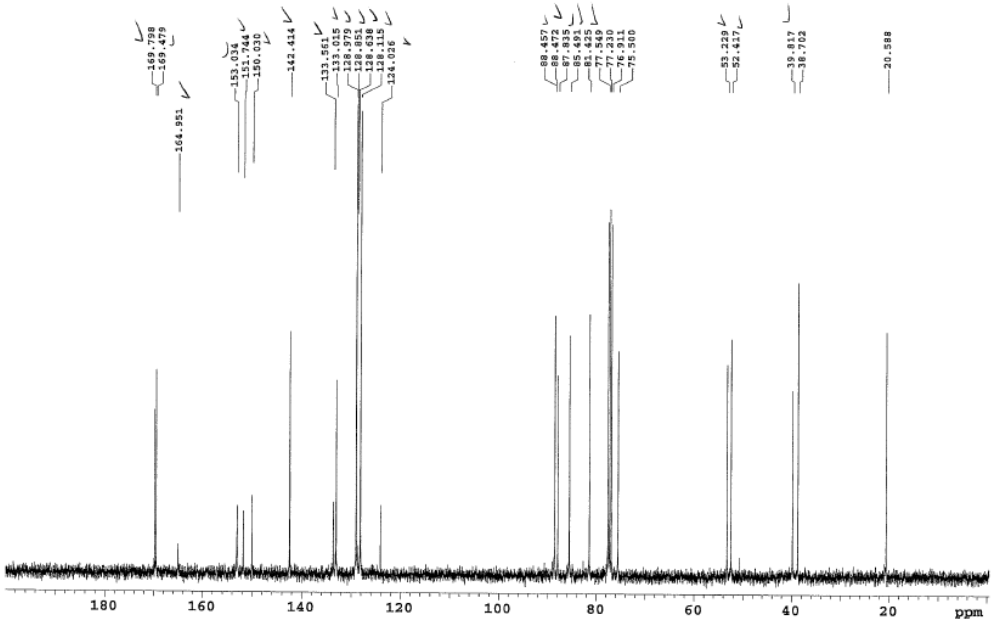

9
8
7
6
5
4
3
2
1
ppm
1.00
1.03
1.05
1.01
1.06
1.23
3.20
1.12
3.30
1.16
3.75
3.53

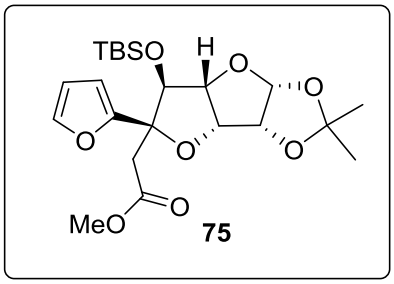

170.321
170.010
114.605
108.923
84.781
84.045
84.899
80.992
77.549
77.230
76.911
53.009
52.190
39.476
39.029
26.808
26.057
180
160
140
120
100
80
60
40
20
ppm

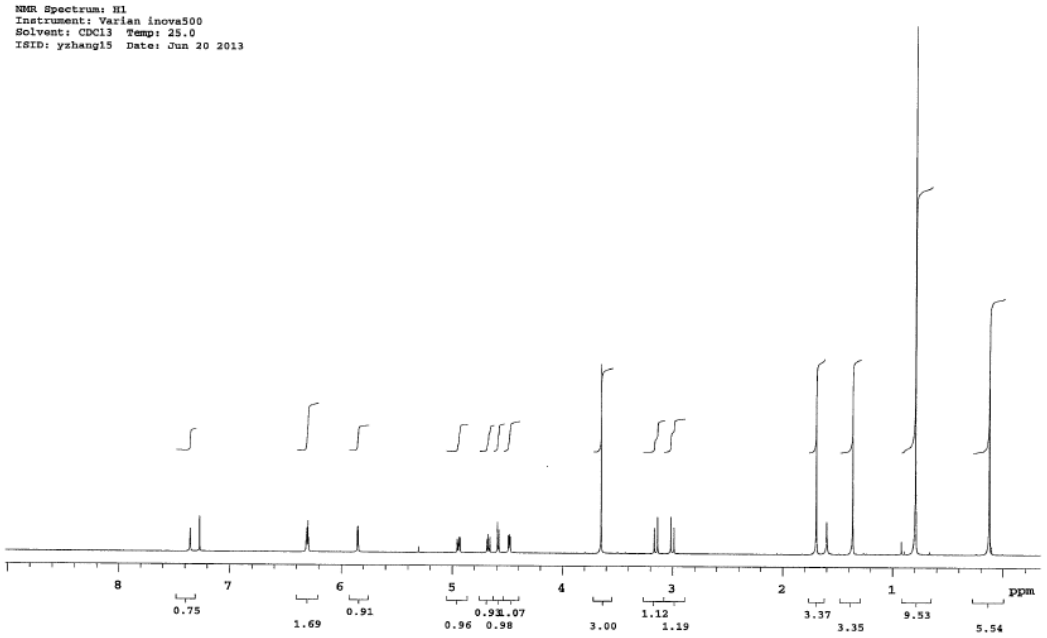

MsO
H
O
N
N
NHCOPh
O
MeO
O
N
N
OAc
O
MeO
O

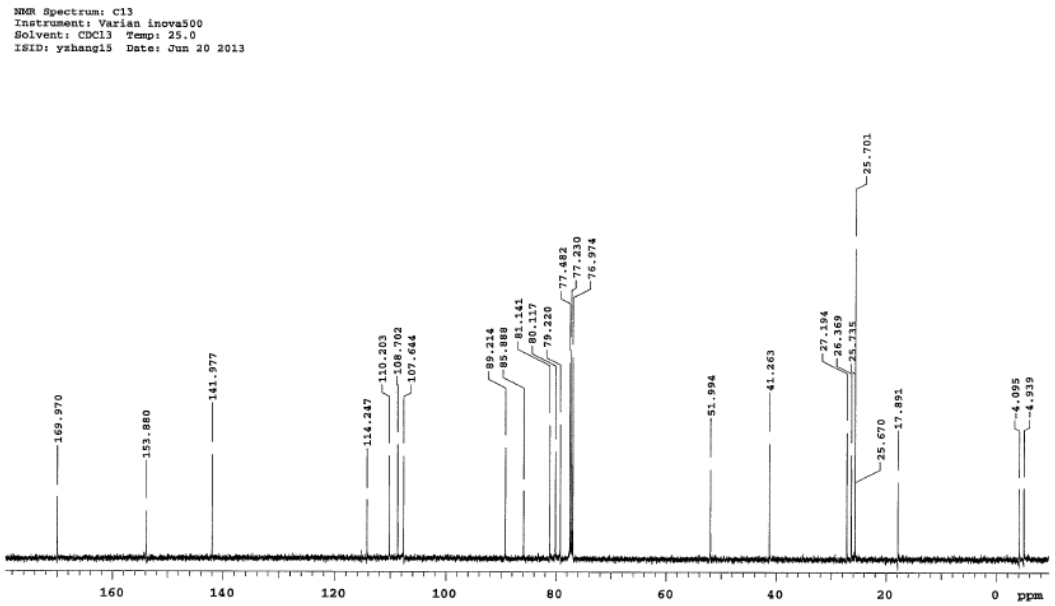
73

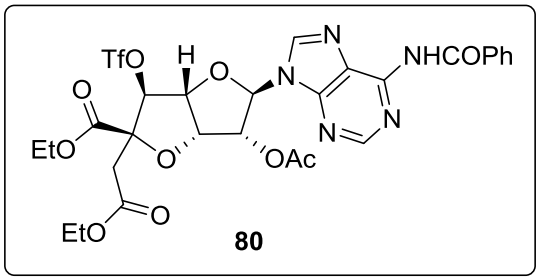

8.745
8.112
8.020
8.000
7.513
7.494
6.220
5.471
3.830
3.760
3.442
3.248
3.113
3.071
2.060
ppm


169.798
169.479
164.951
153.034
151.744
150.030
142.414
133.561
133.015
128.979
128.851
128.808
128.115
124.026
88.457
88.472
85.735
85.493
81.425
77.548
77.330
77.011
75.500
53.229
52.437
38.817
38.702
20.588
ppm

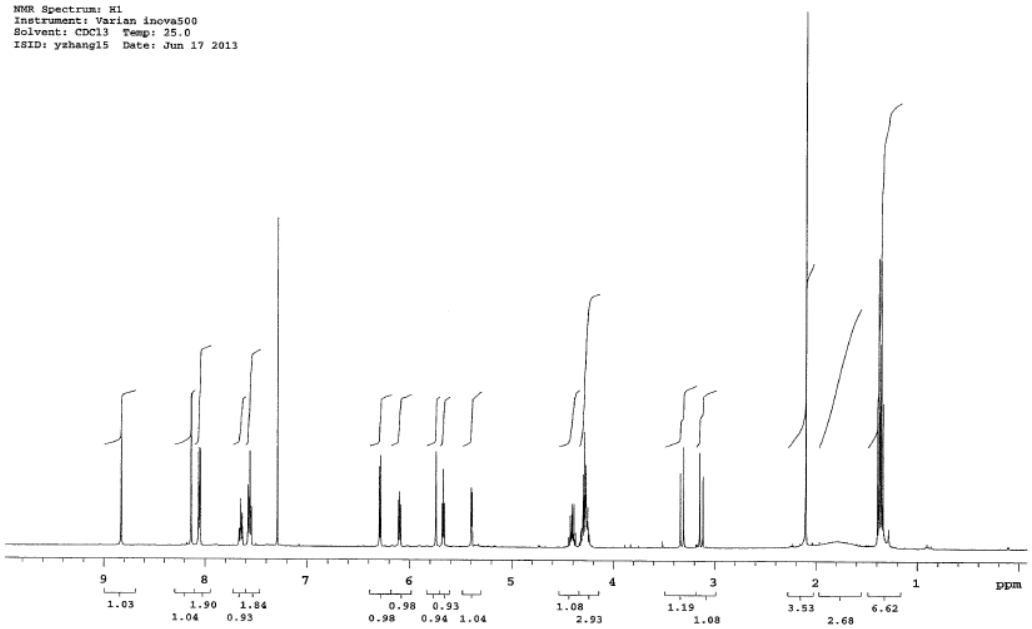

TBSO
H
O
O
O
O
O
O
MeO
75

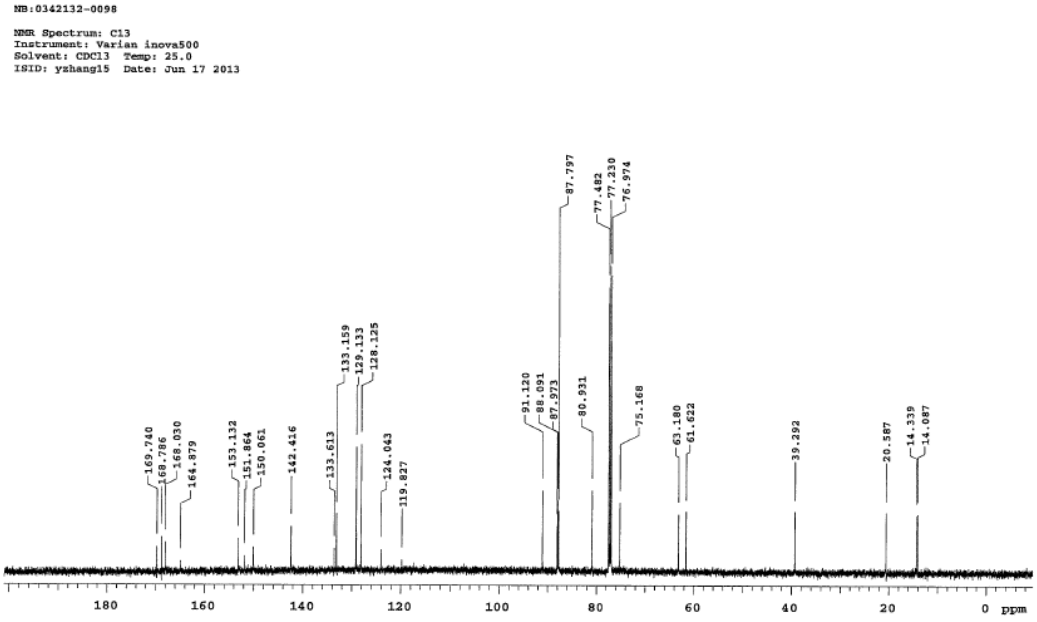

NMR Spectrum: H1
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Jun 20 2013
8
7
6
5
4
3
2
1
ppm
0.75
1.69
0.91
0.96
0.98
1.07
3.00
1.12
1.19
3.37
3.35
9.53
5.54

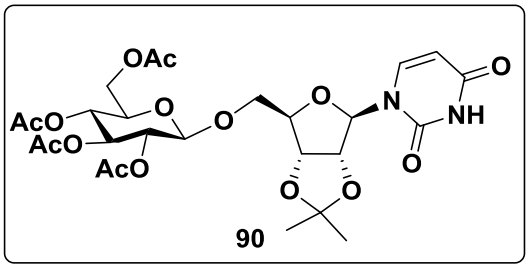

NMR Spectrum: C13
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Jun 20 2013
169.970
153.880
141.977
114.247
110.203
108.702
107.644
89.214
85.888
81.141
80.117
79.220
77.482
77.230
76.974
51.994
41.263
27.194
26.369
25.735
25.701
25.670
17.891
4.095
4.939
160
140
120
100
80
60
40
20
0
ppm


TfO
H
O
N
N
NHCOPh
O
EtO
O
OAc
N
N
EtO
O

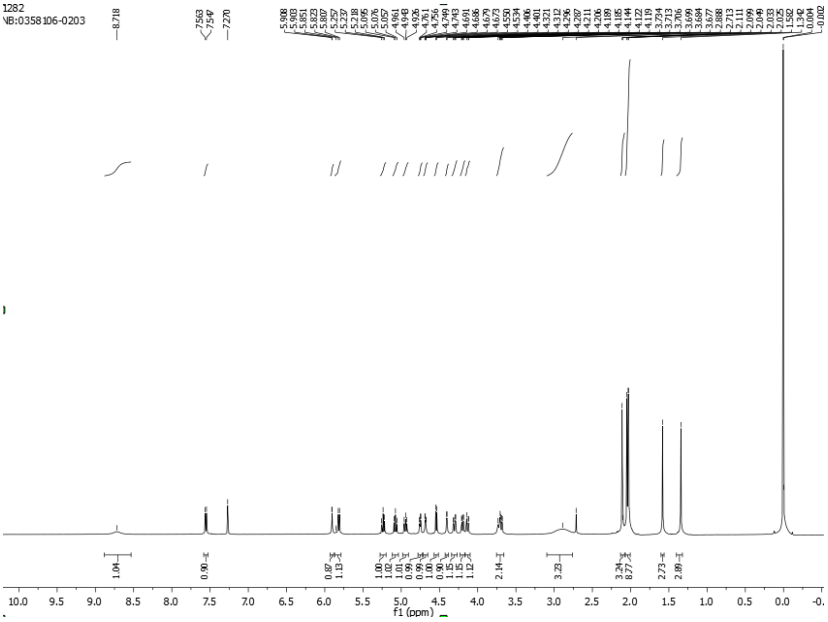
80

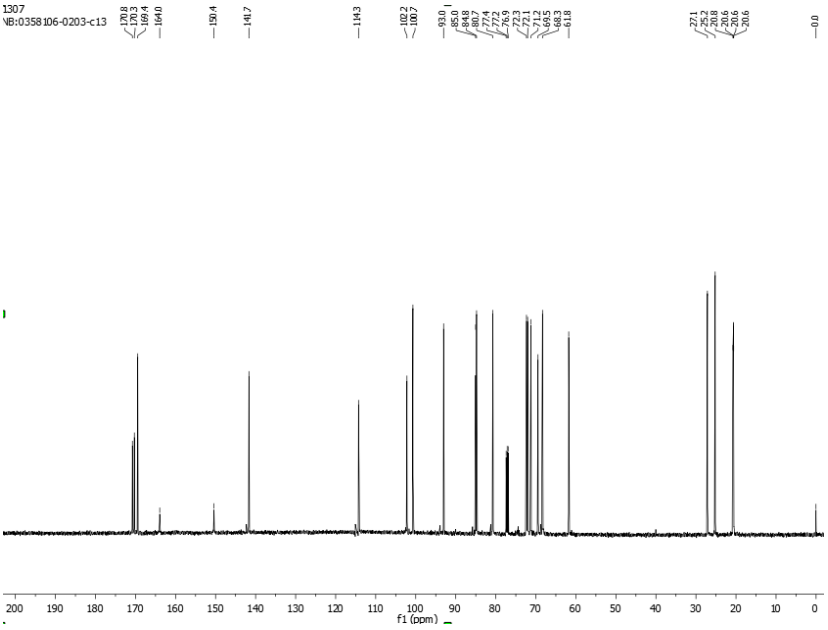

NMR Spectrum: H1
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Jun 17 2013
9
8
7
6
5
4
3
2
1
ppm
1.03
1.90
1.84
1.04
0.93
0.98
0.93
0.98
0.94
1.04
1.08
2.93
1.19
1.08
3.53
6.62
2.68

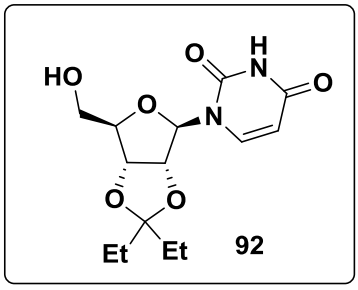

NB:0342132-0098
NMR Spectrum: C13
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Jun 17 2013
169.740
168.786
168.030
164.879
153.132
151.864
150.061
142.416
133.613
133.159
129.133
128.125
124.043
119.827
91.120
88.091
87.973
87.797
80.931
77.482
77.230
76.974
75.168
63.180
61.622
39.292
20.587
14.339
14.087
180
160
140
120
100
80
60
40
20
0
ppm

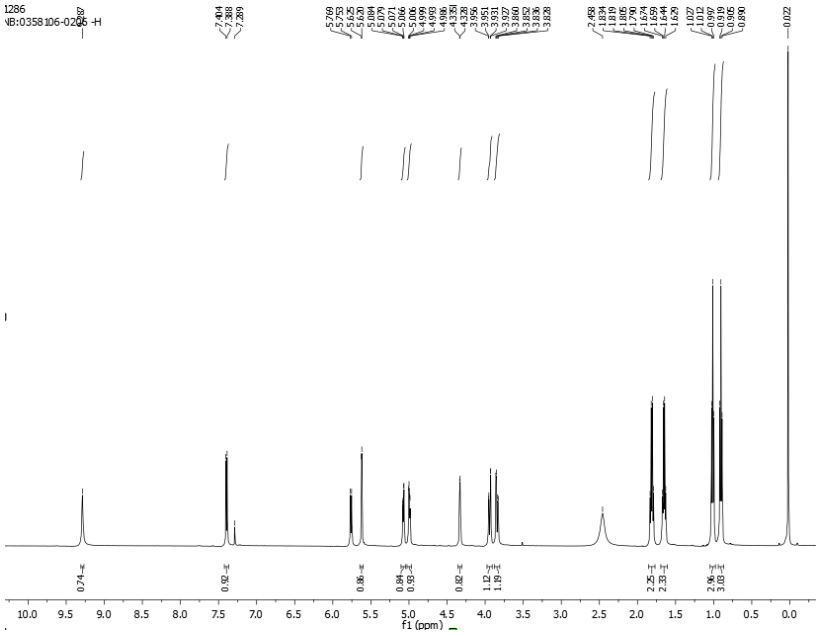


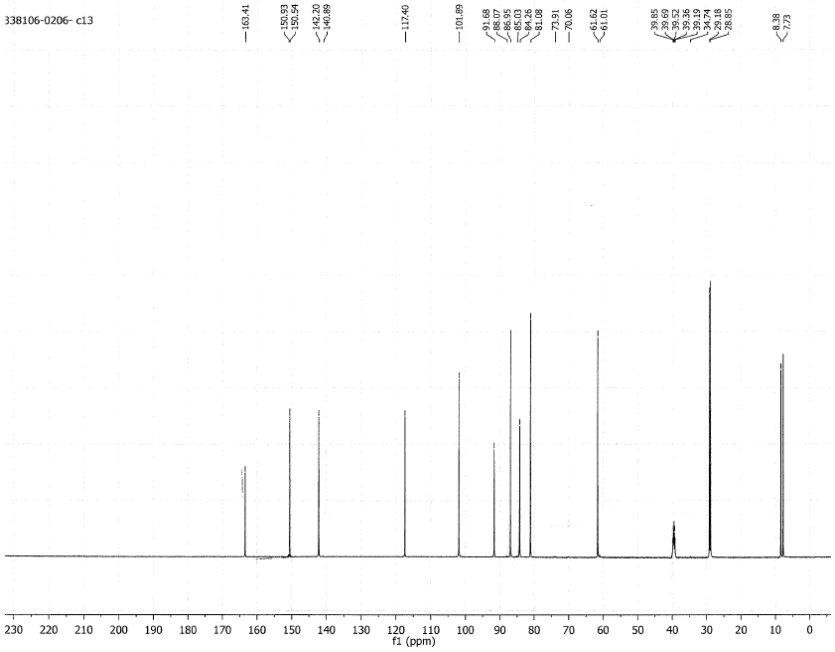
90

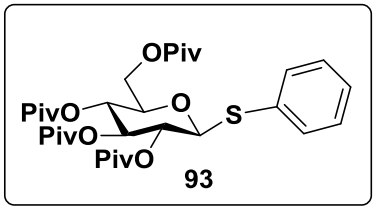




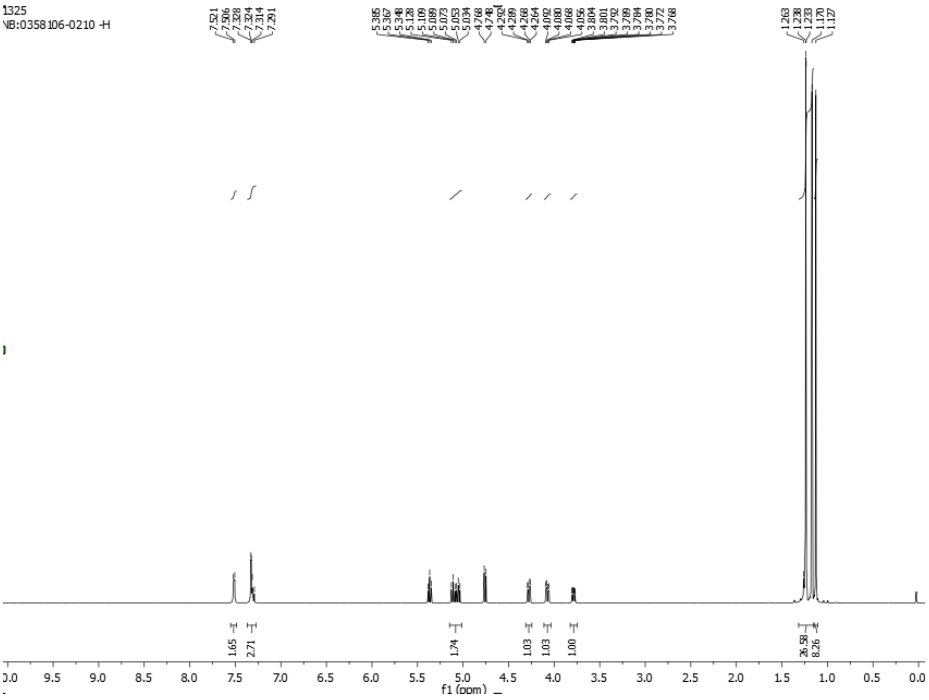

HO
O
N
H
N
O
O
O
Et
Et
92

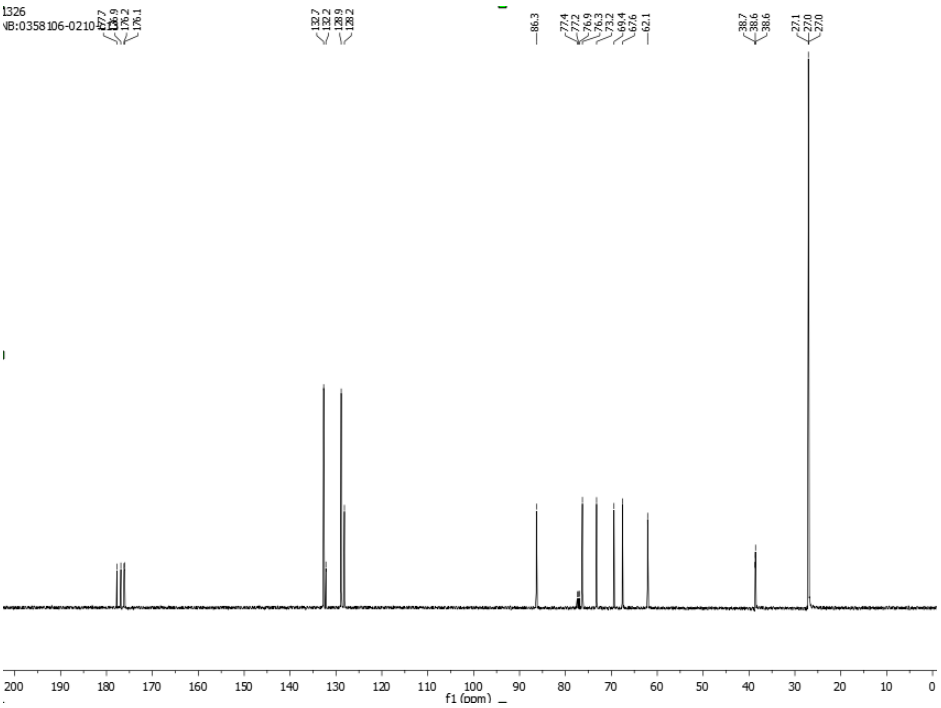

f1 (ppm)

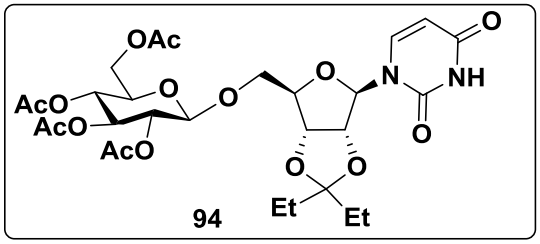

f1 (ppm)



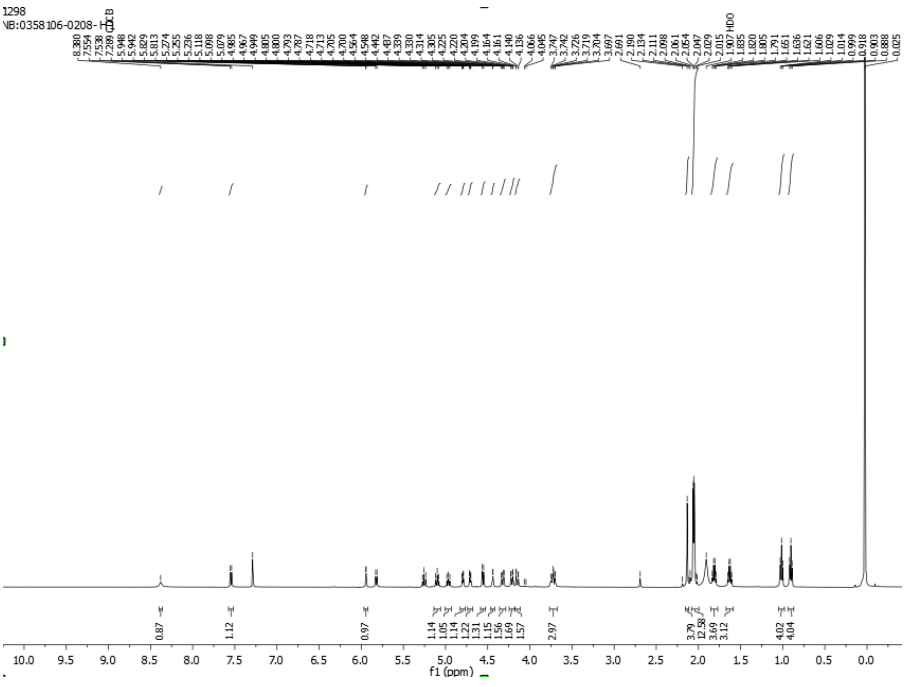
93

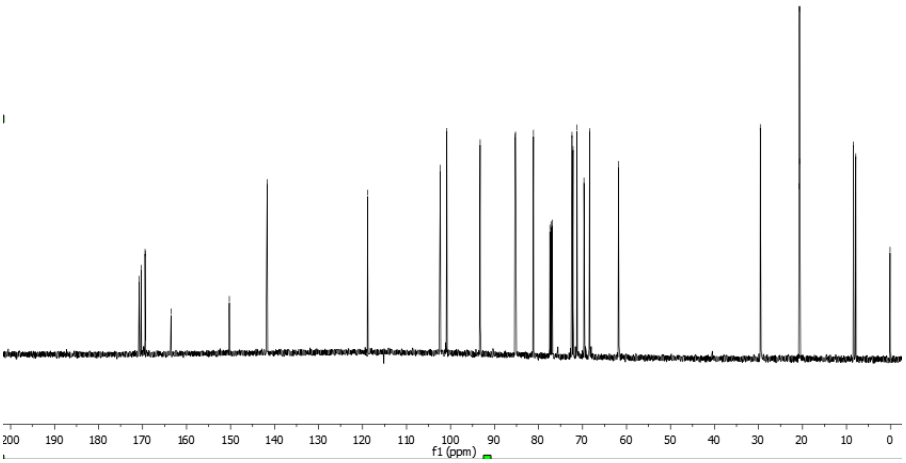


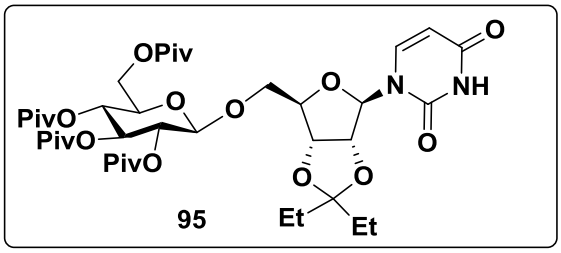




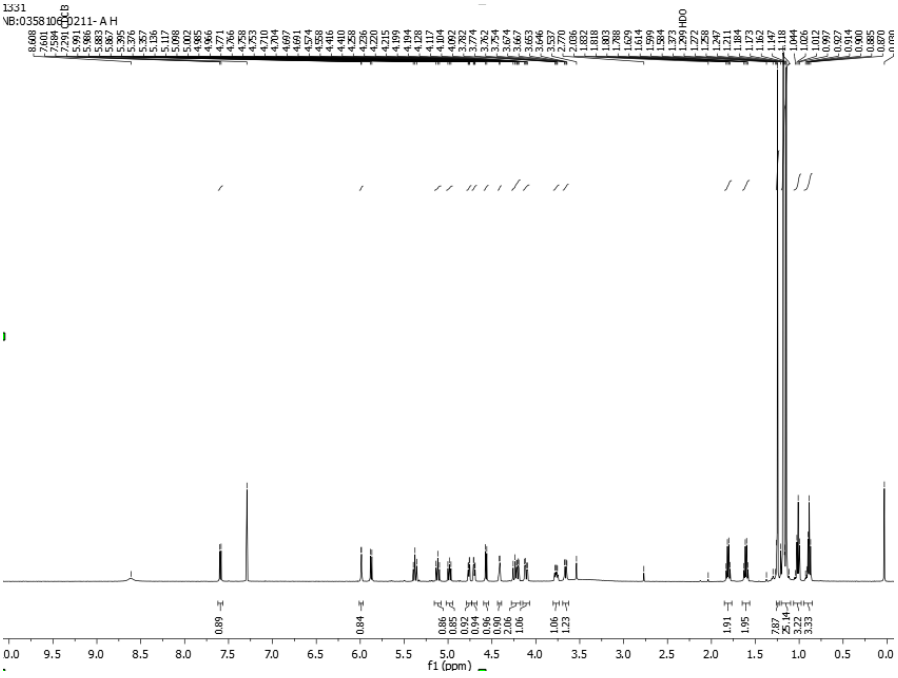
94

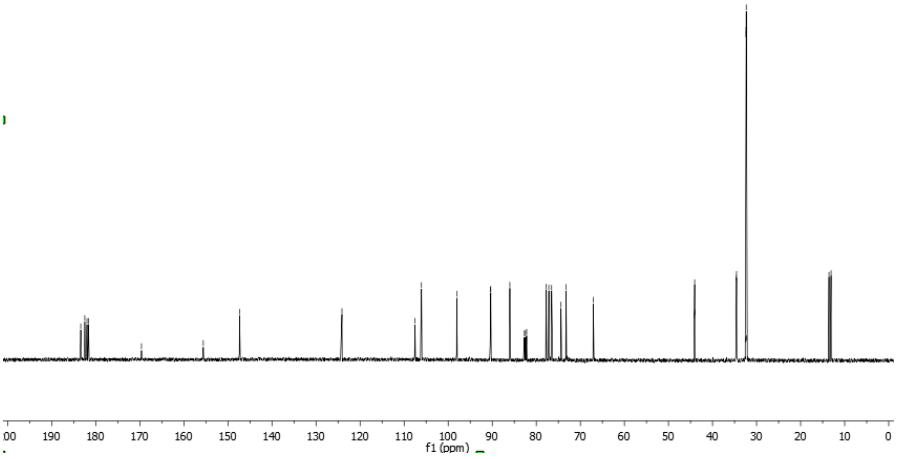


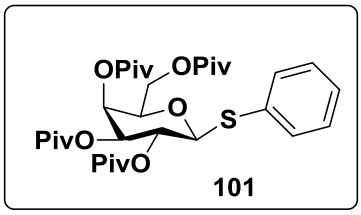




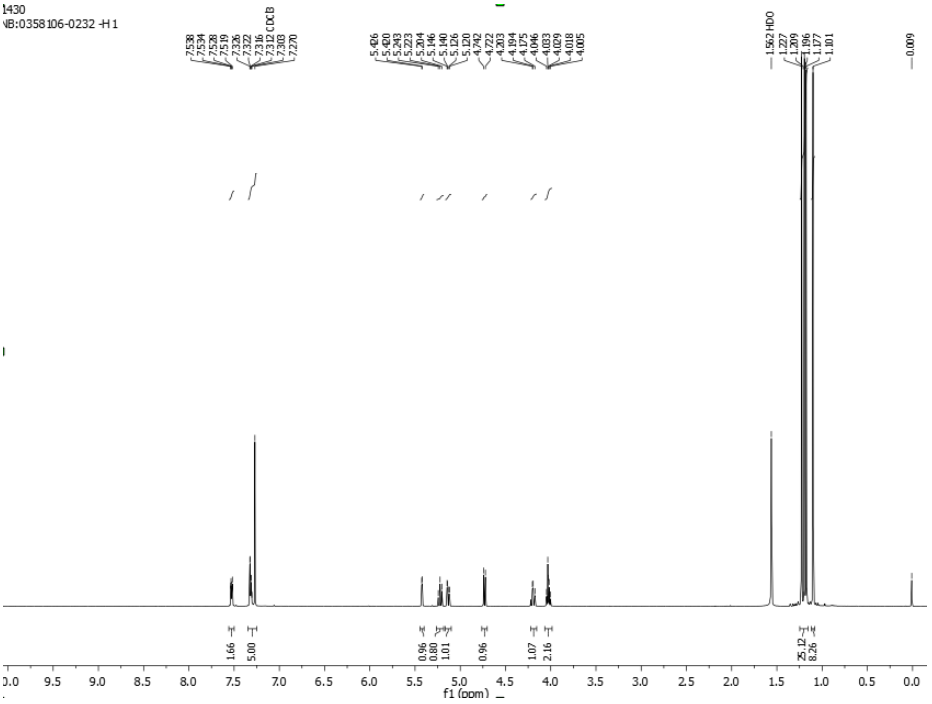
95

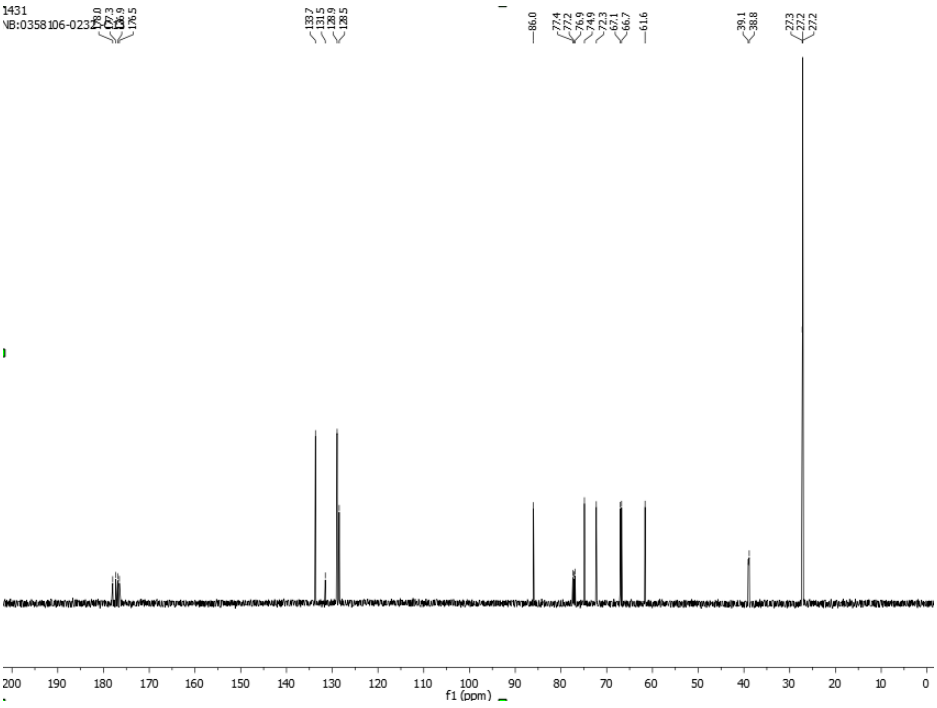


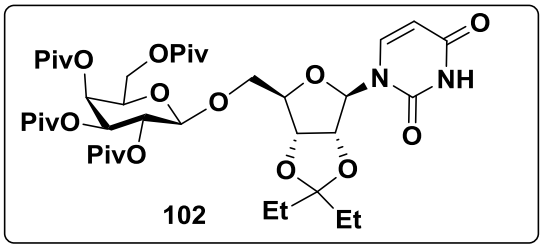




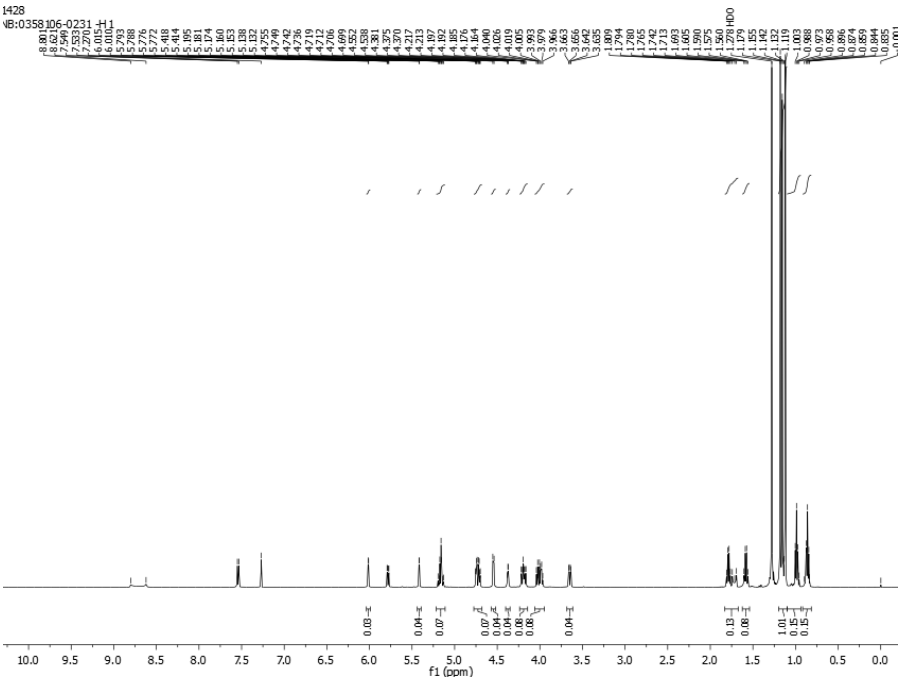
101

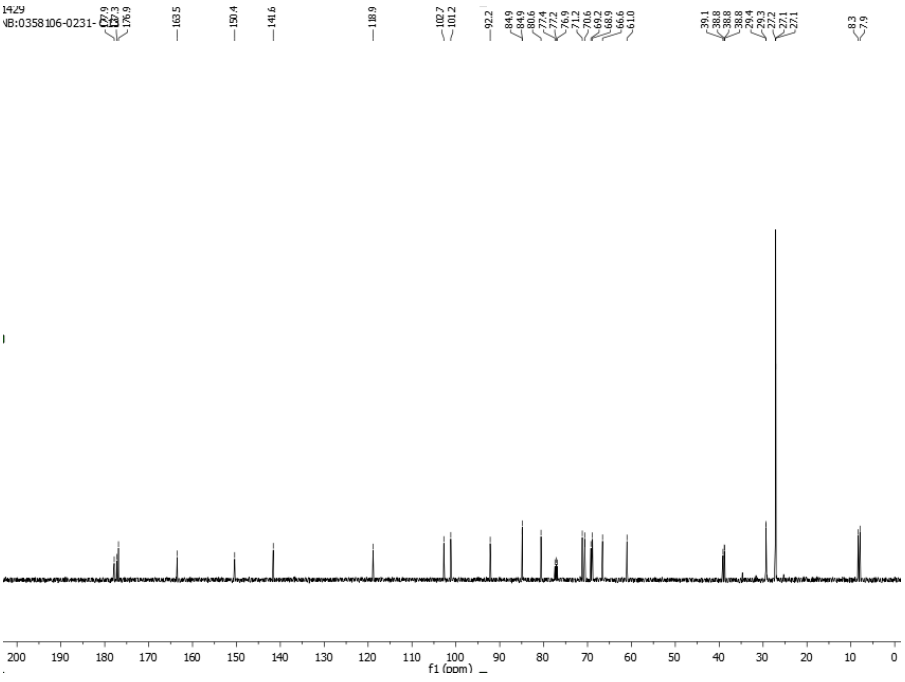


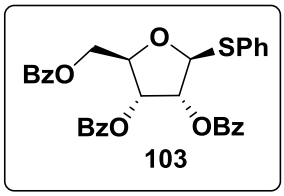




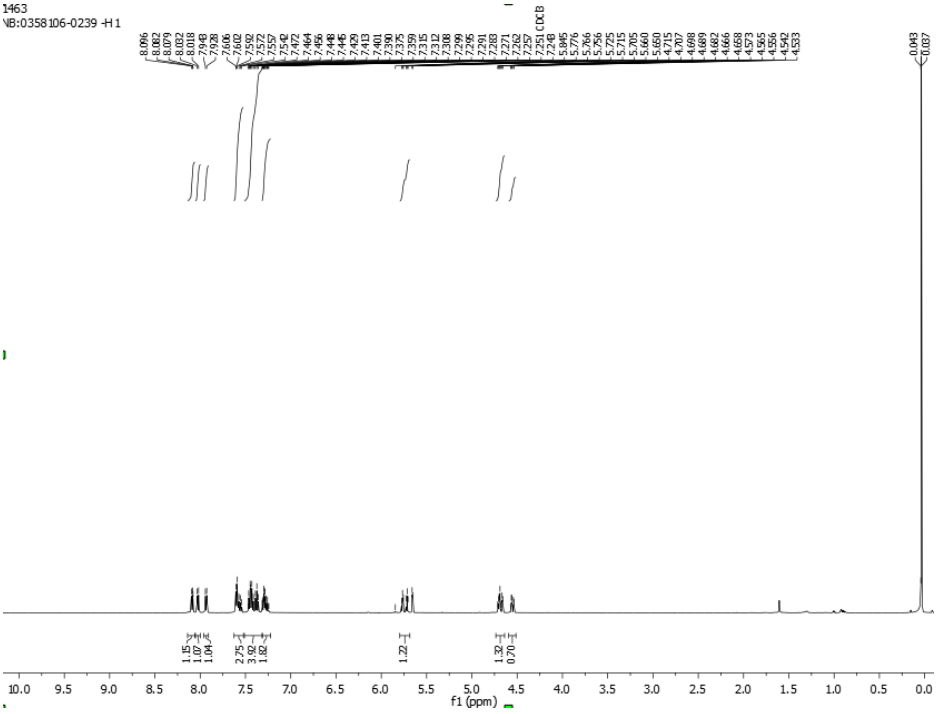
102

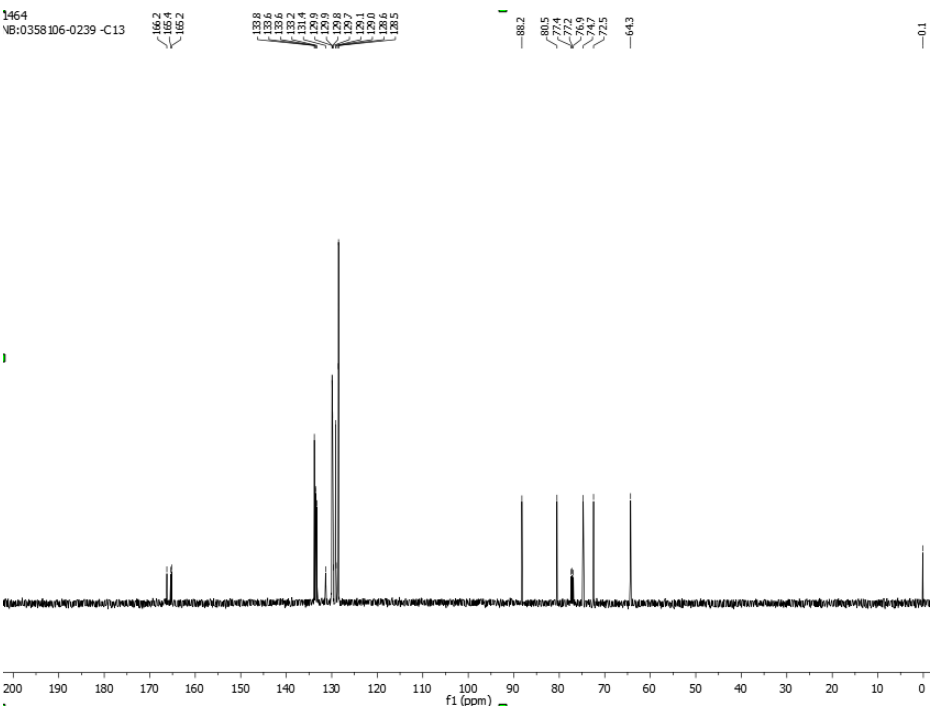


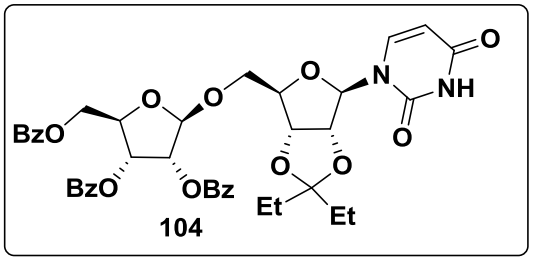



O
SPh
BzO
BzO
OBz

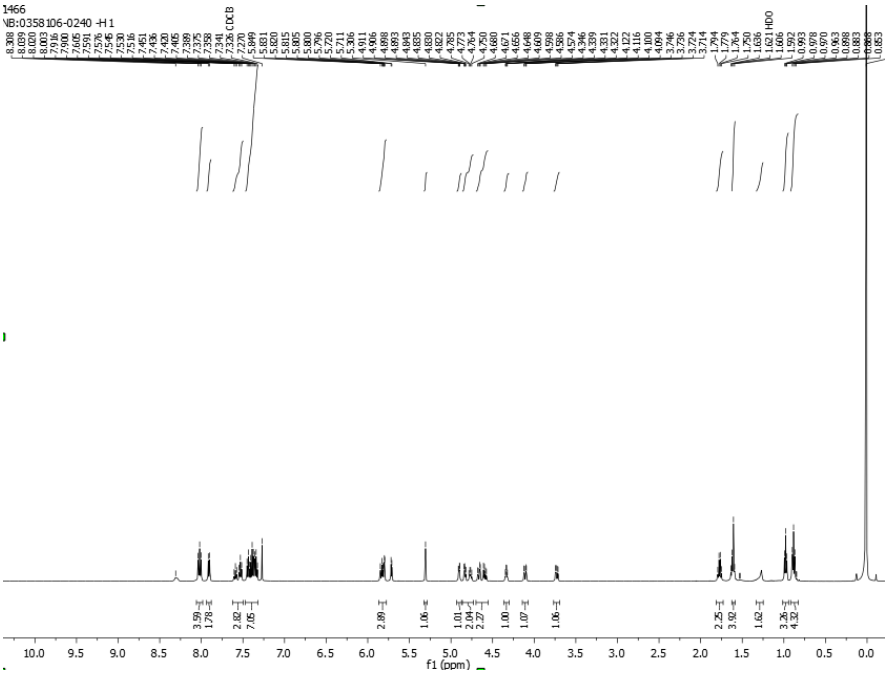
103

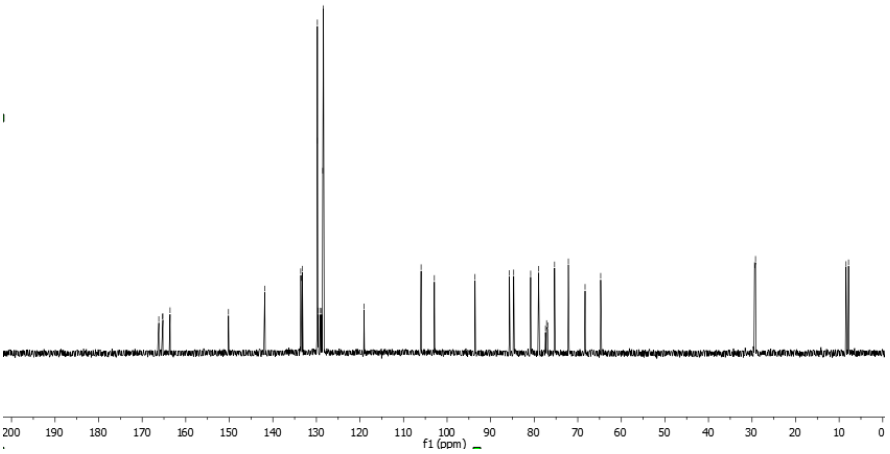

1463
NB:0358106-0239 -H 1
f1 (ppm)

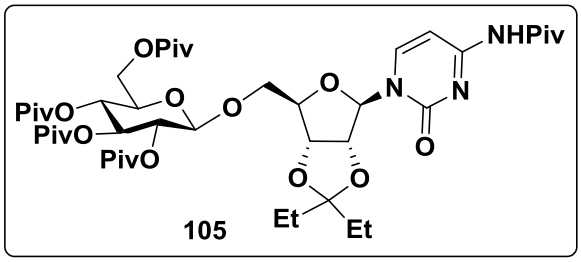

1464
NB:0358106-0239 -C13
f1 (ppm)



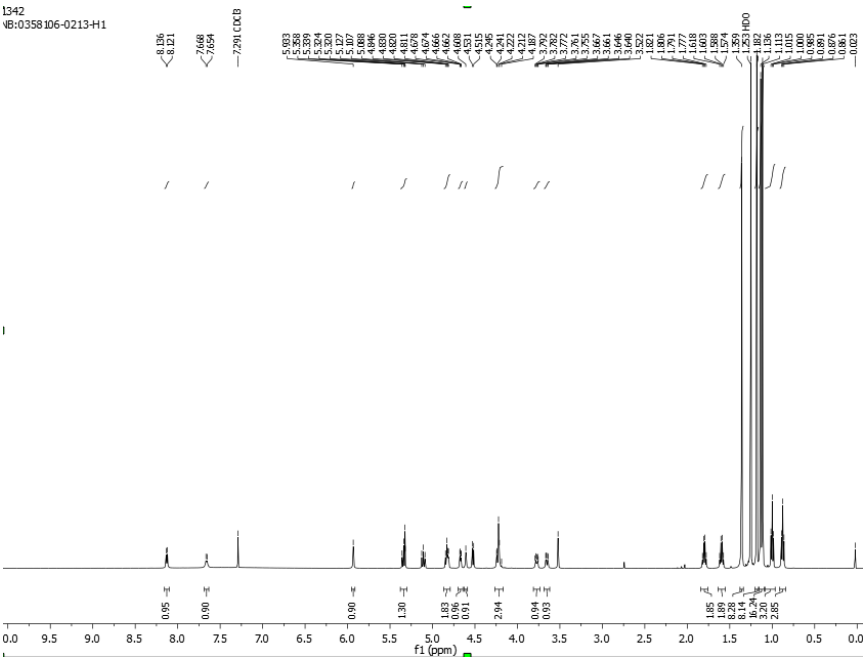
104

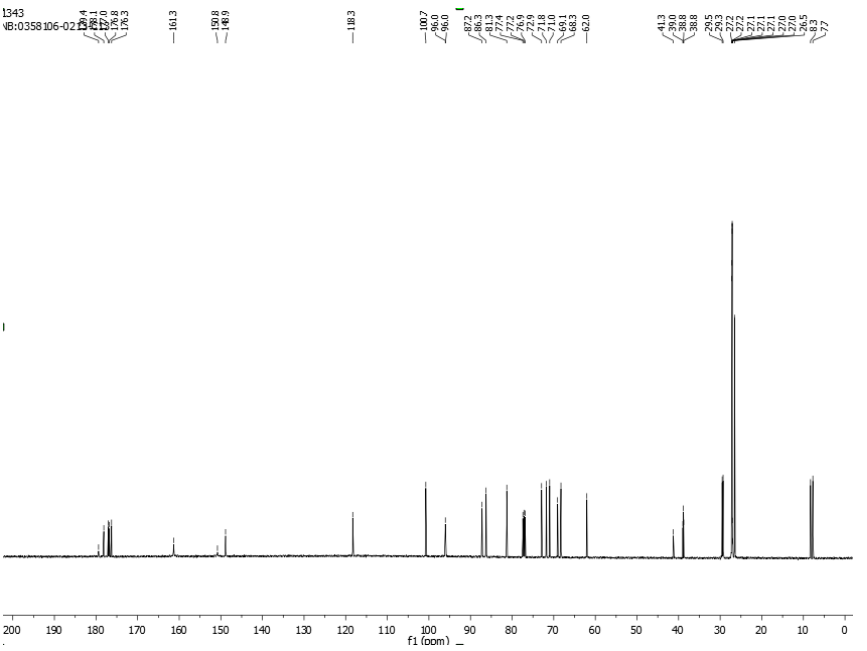


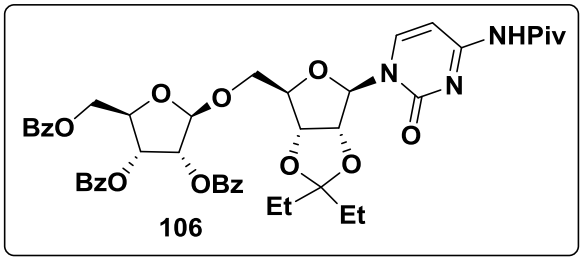




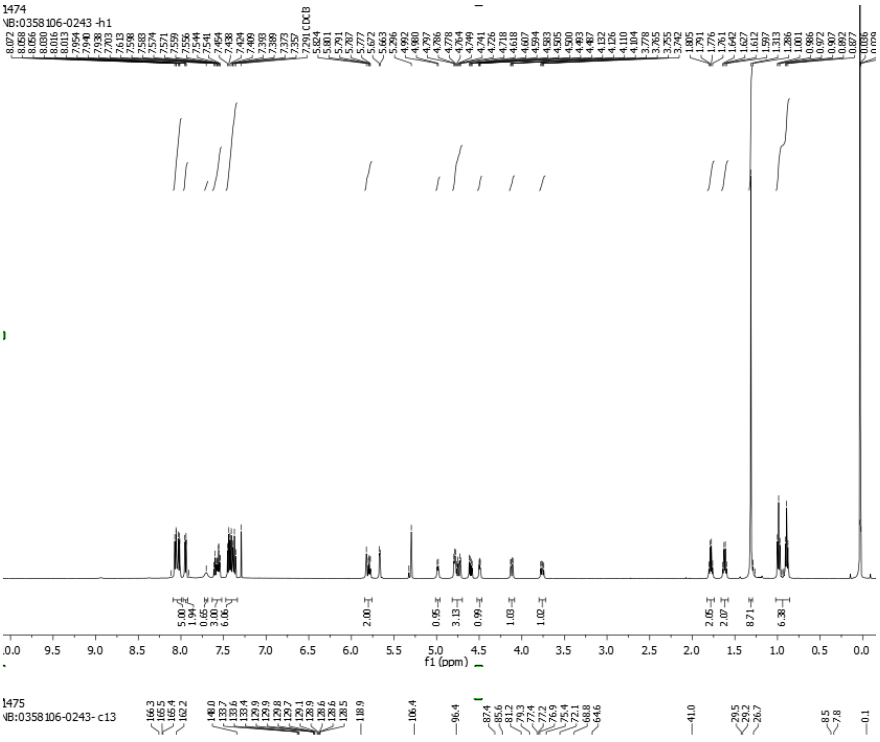
105

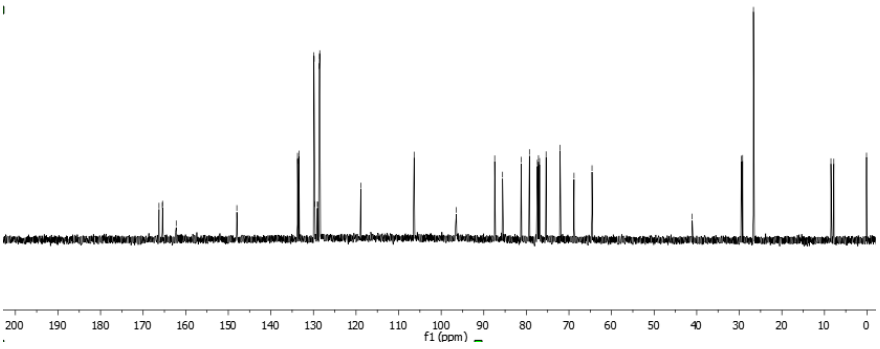


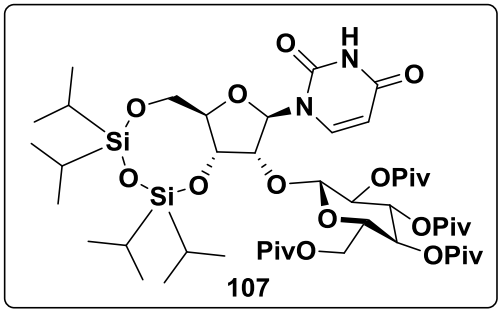




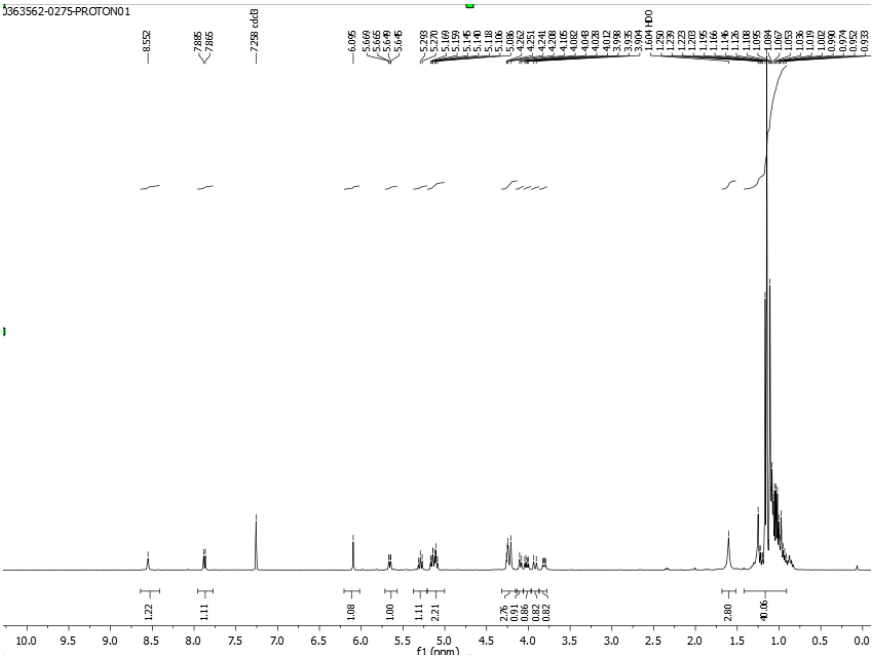
106

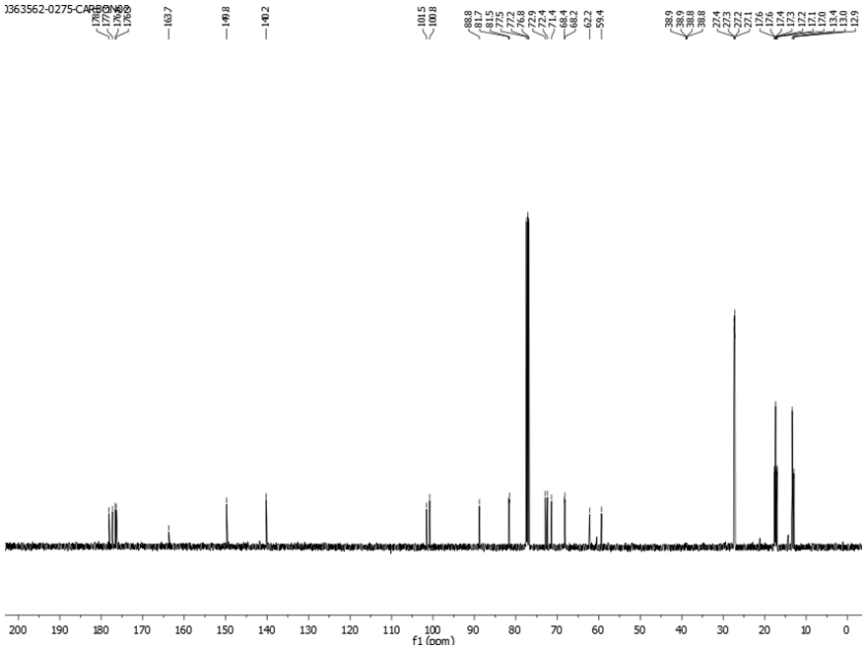


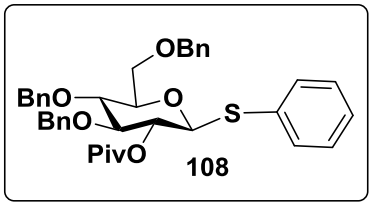


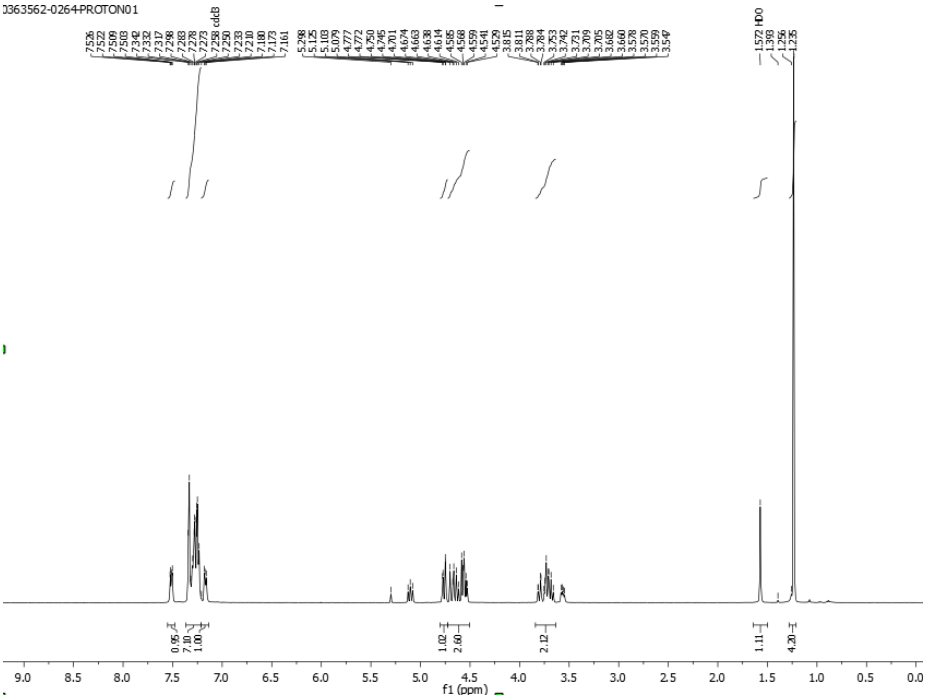

O
H
N
O
N
O
O
Si
O
Si
O
O
OPiv
O
OPiv
PivO
OPiv

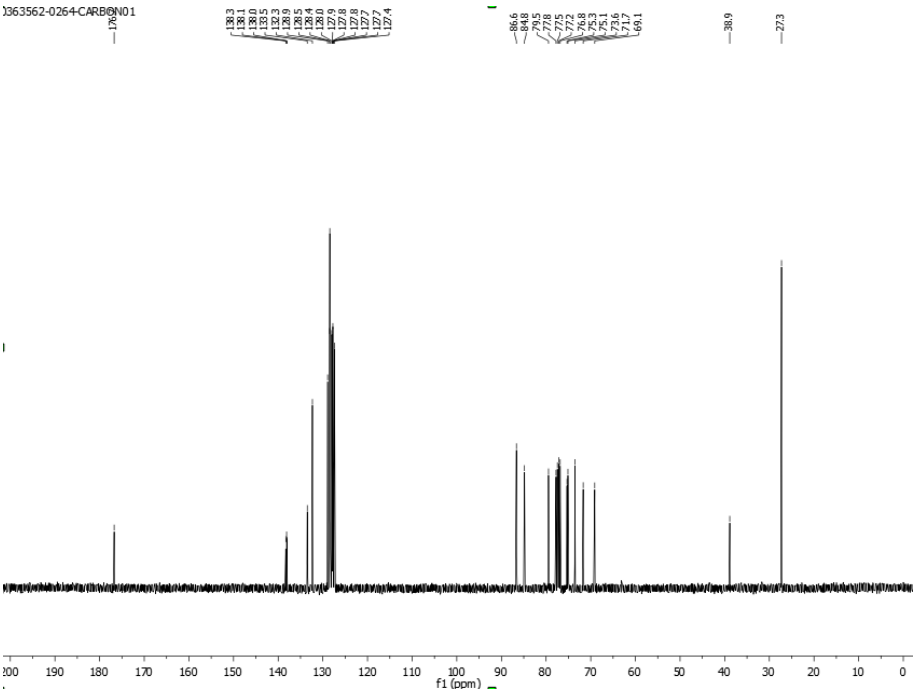
107

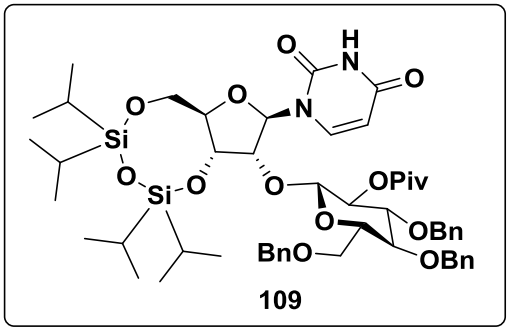

0363562-0275-PROTON01
8.552
7.885
7.865
7.298
6.095
5.669
5.665
5.648
5.646
5.293
5.270
5.169
5.159
5.145
5.140
5.118
5.106
5.086
4.262
4.251
4.234
4.208
4.105
4.082
4.048
4.028
4.012
3.998
3.935
3.904
1.604
H2O
1.230
1.239
1.223
1.203
1.195
1.166
1.146
1.126
1.108
1.095
1.084
1.057
1.053
1.036
1.019
1.003
0.990
0.974
0.952
0.933
1.22
1.11
1.08
1.00
1.11
2.21
2.76
0.91
0.98
0.82
0.82
2.80
10.06
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)


0363562-0275-CARBON
163.7
149.8
140.2
101.5
100.8
88.8
81.7
81.5
77.5
77.2
76.8
72.9
72.4
71.4
68.4
68.2
62.2
59.4
38.9
38.8
38.8
38.8
27.4
27.3
27.2
27.1
17.6
17.6
17.4
17.3
17.2
17.2
17.1
17.0
13.5
13.4
13.0
12.9
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

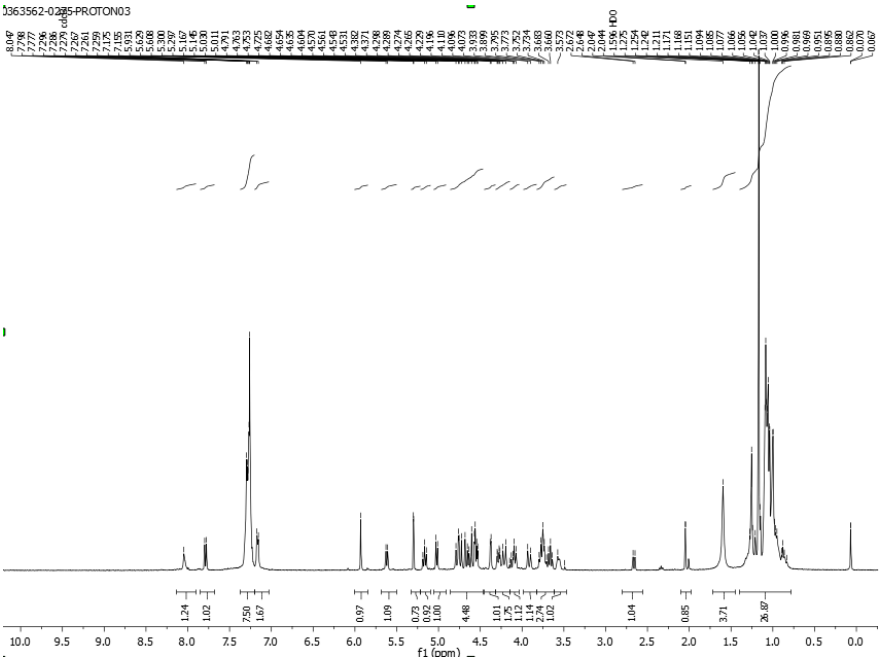

OBn
BnO
O
S
BnO
PivO
108

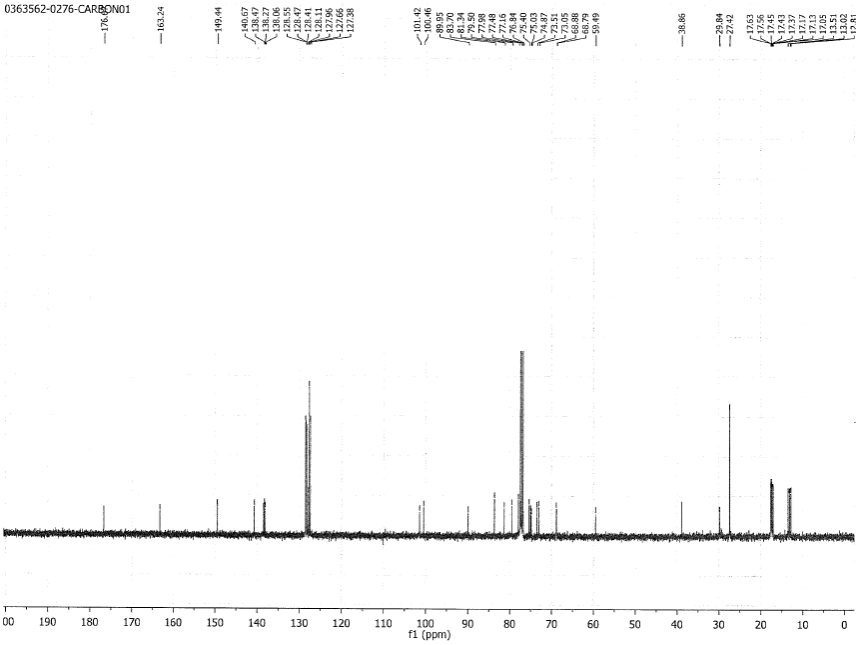

0363562-0264-PROTON01
f1 (ppm)

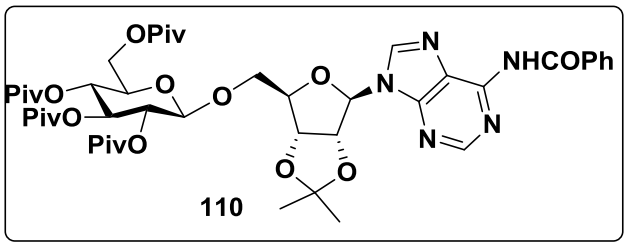

0363562-0264-CARBON01
f1 (ppm)


O
H
N
O
N
O
O
Si
O
Si
O
O
OPiv
O
OBn
BnO
OBn

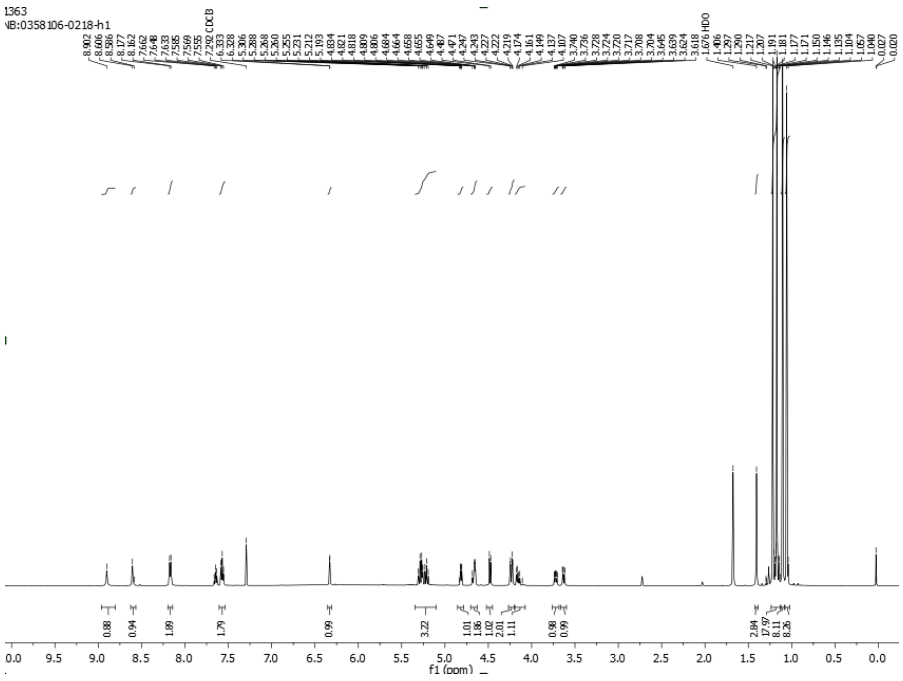
109

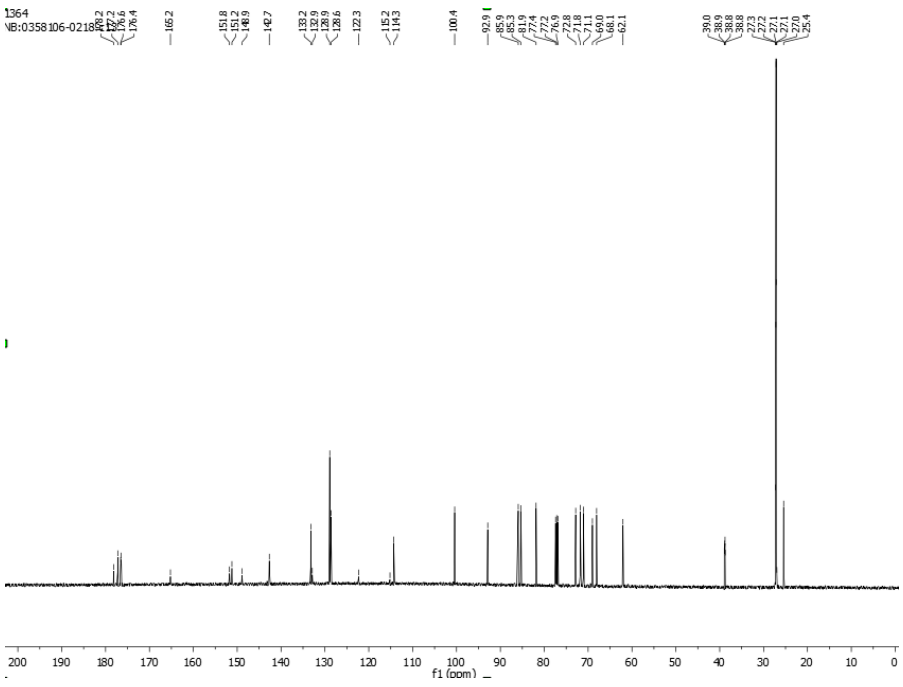

0363562-0275-PROTON03
f1 (ppm)

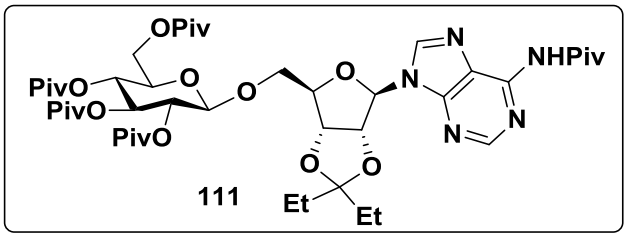

0363562-0276-CARBON01
f1 (ppm)



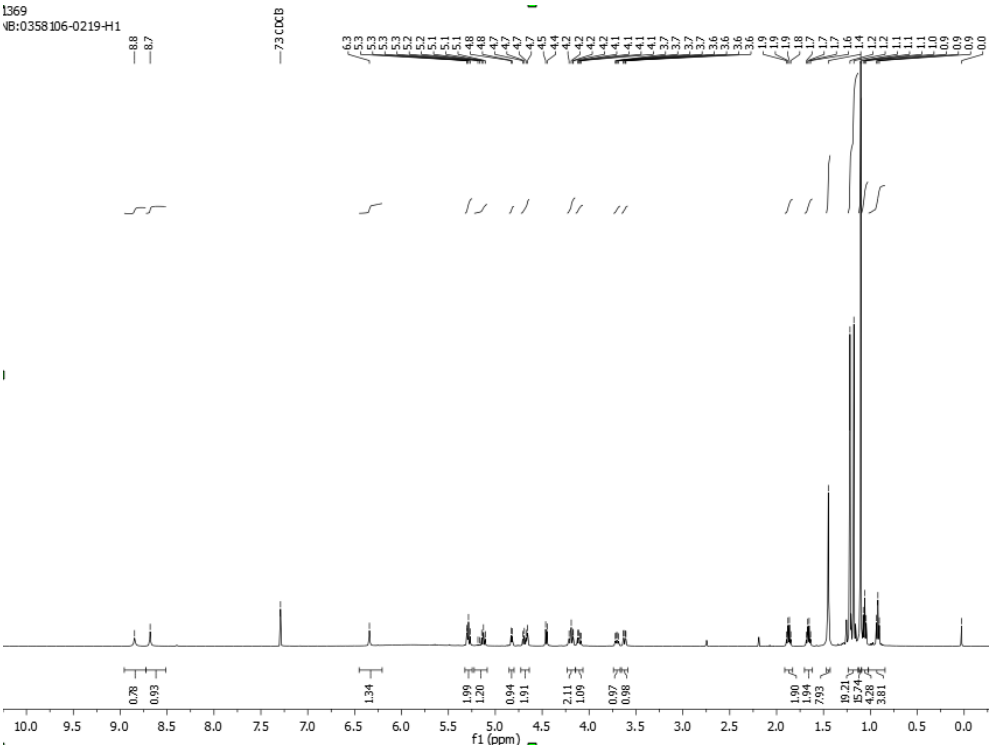
110

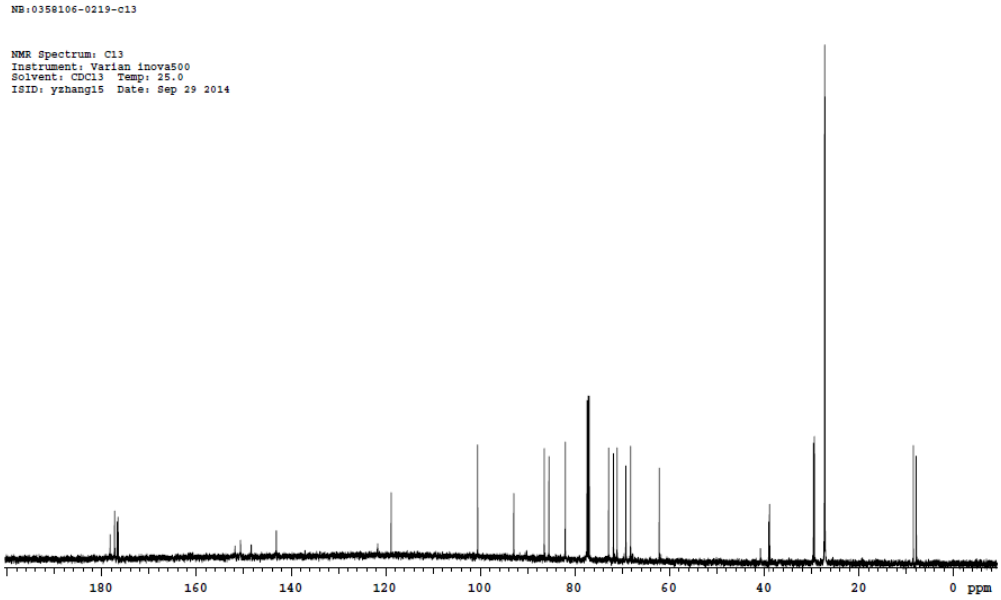


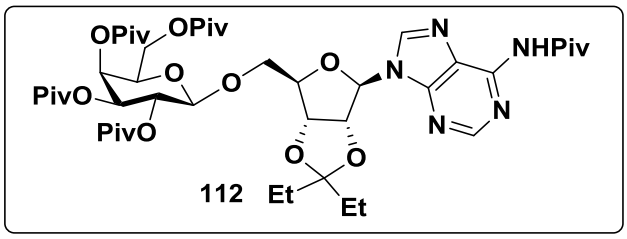


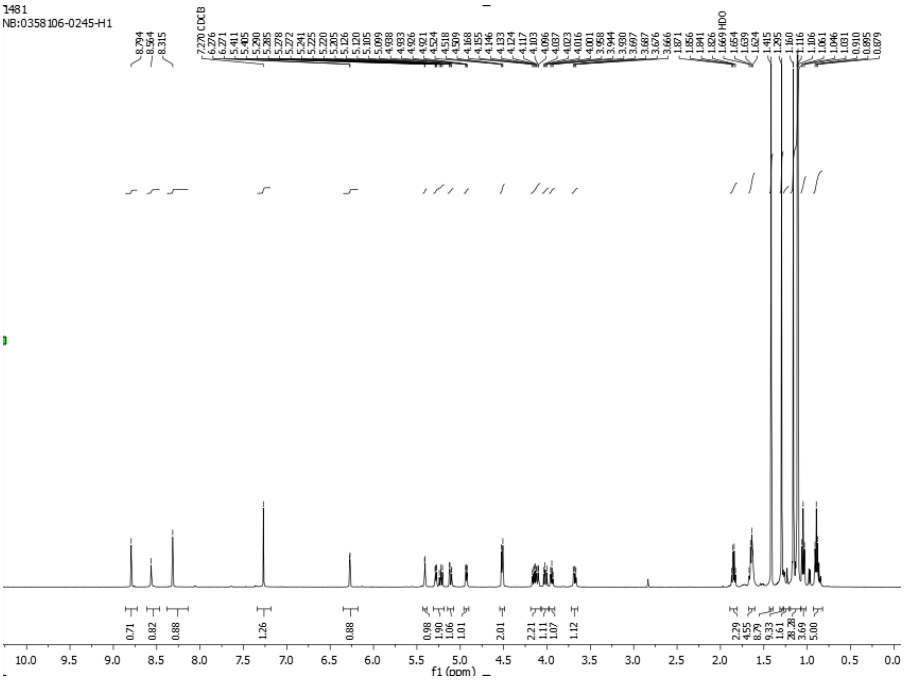

OPiv
PivO
PivO
PivO
O
O
O
N
N
N
N
NHPiv
O
O
Et
Et

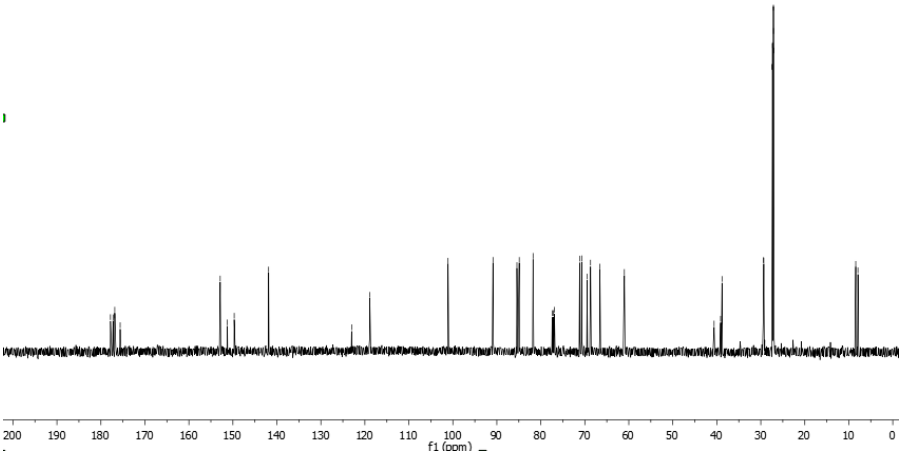
111

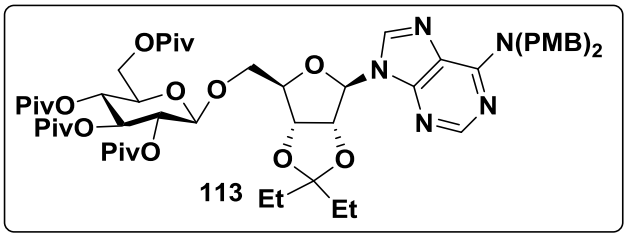

1369
NB:0358106-0219-H1
f1 (ppm)

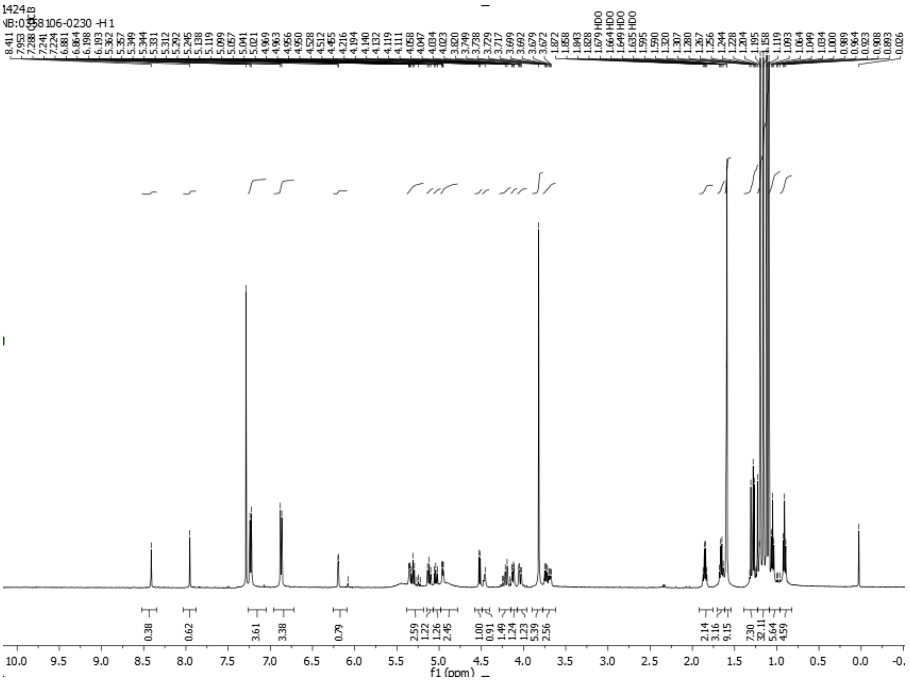

NB:0358106-0219-c13
NMR Spectrum: C13
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Sep 29 2014
ppm

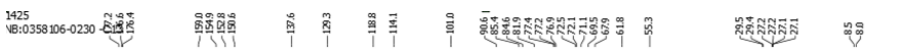

OPiv
OPiv
O
O
PivO
PivO
O
O
O
N
N
N
N
NHPiv
112
Et
Et

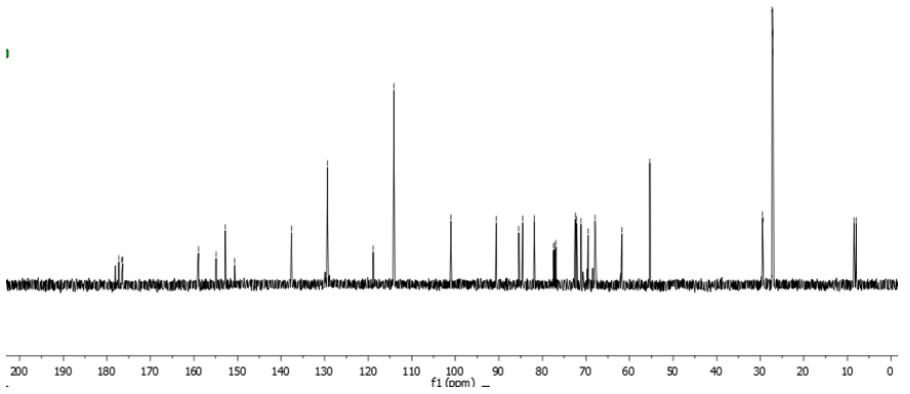


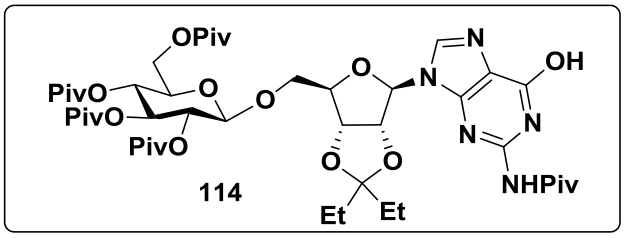



OPiv
PivO
PivO
PivO
O
O
N
N
N
N
N(PMB)2
O
O
O
113
Et
Et

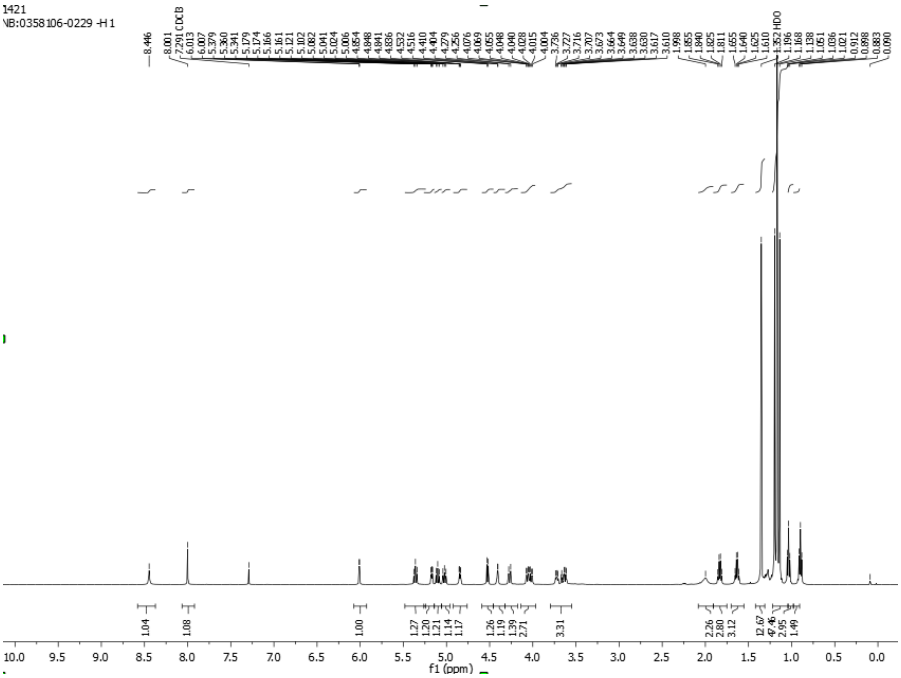


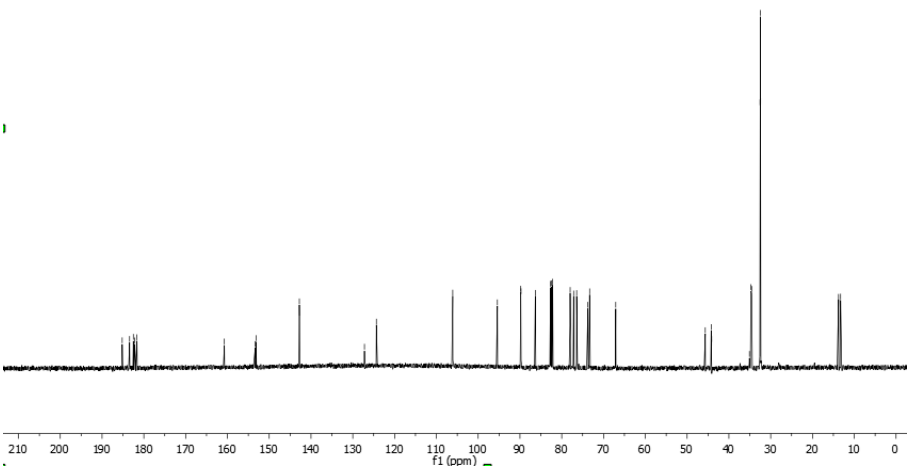


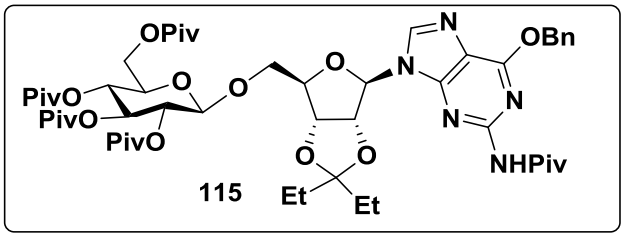


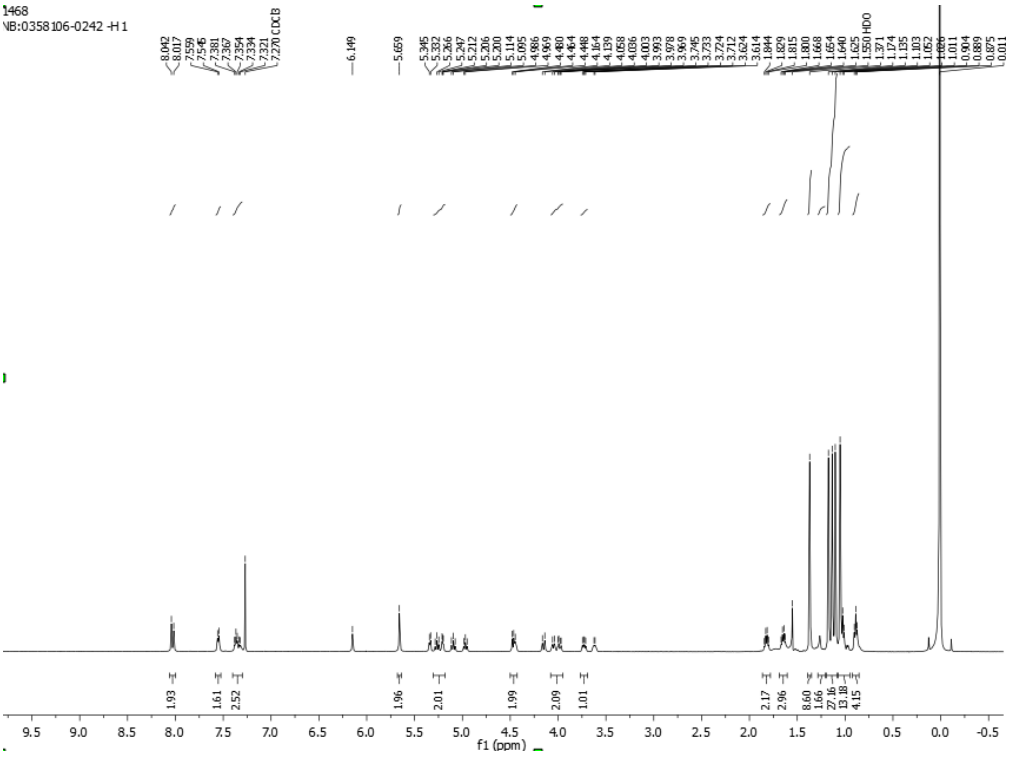


114



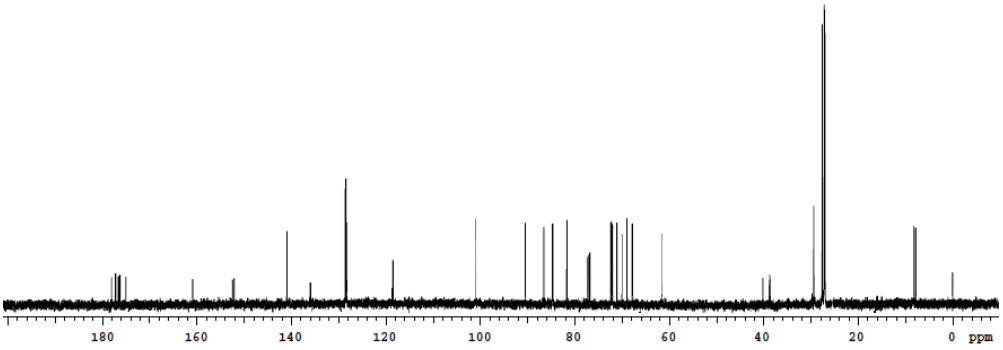


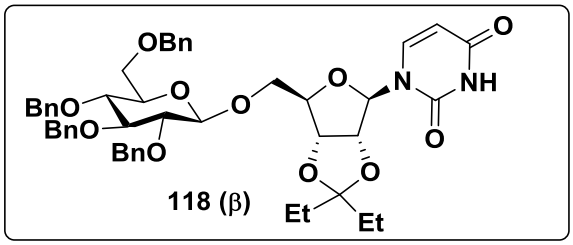


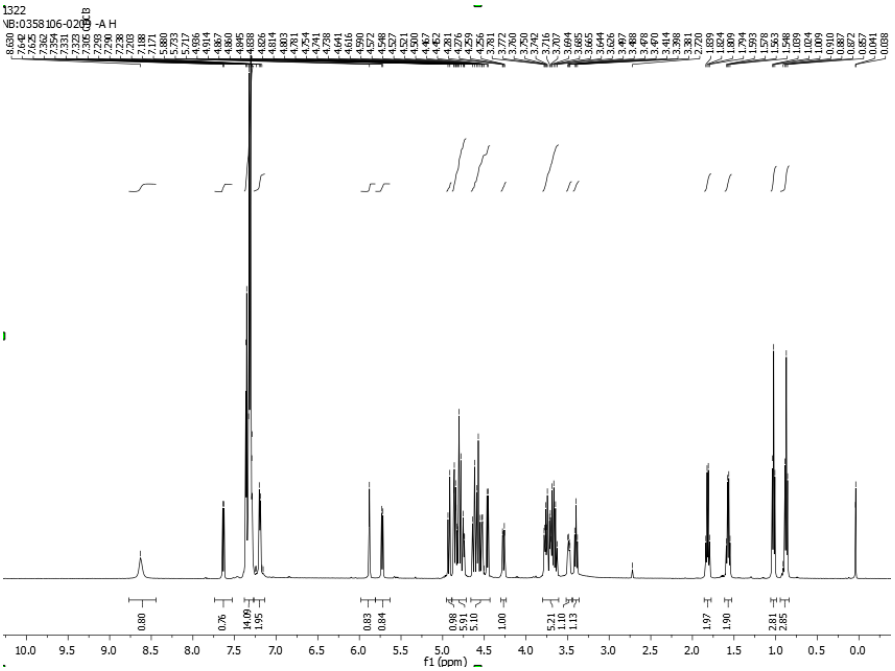


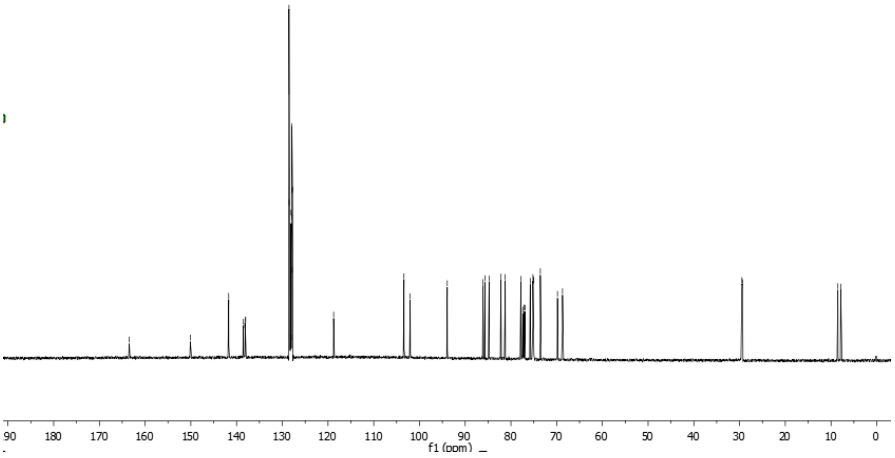
NB:0358106-0242-C13

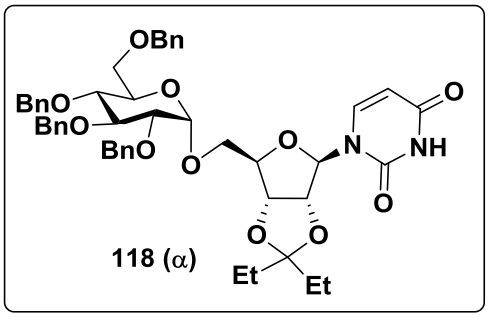
NMR Spectrum: C13
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Nov 2 2014



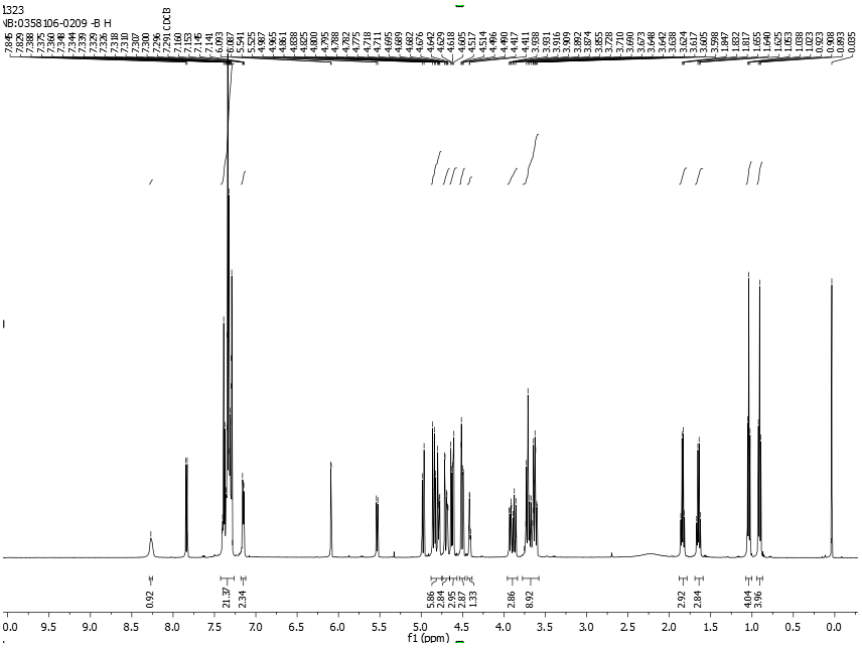

OBn
BnO
BnO
BnO
O
O
N
NH
O
O
O
O
Et
Et
118 (β)

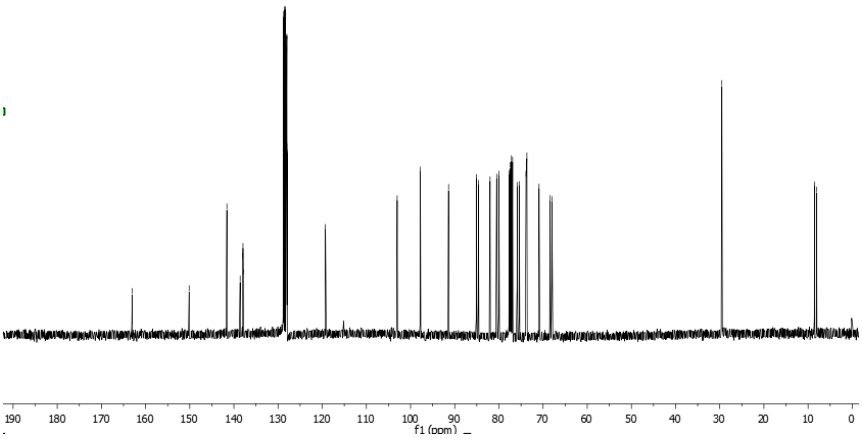


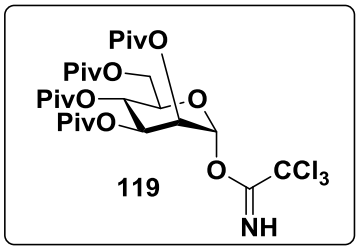




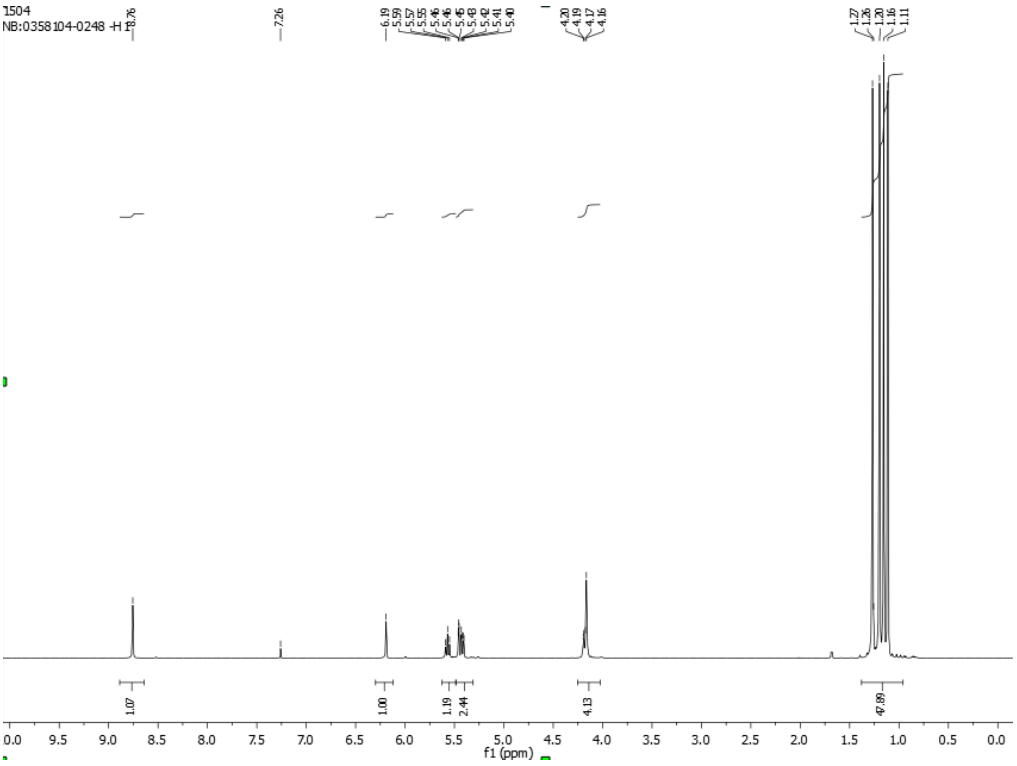
118 (α)

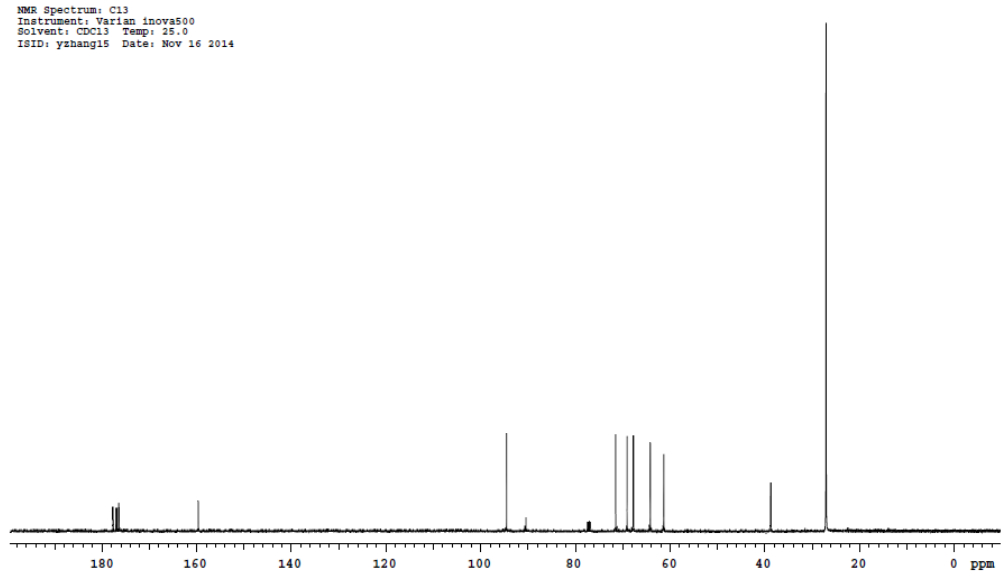


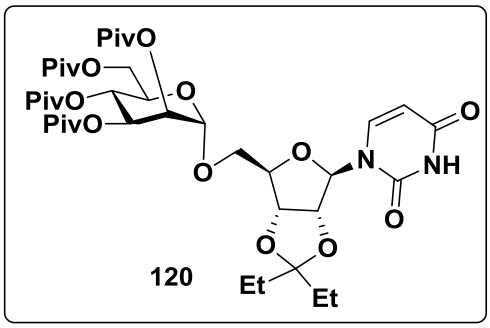



PivO
PivO
PivO
PivO
O
O
CCl3
NH

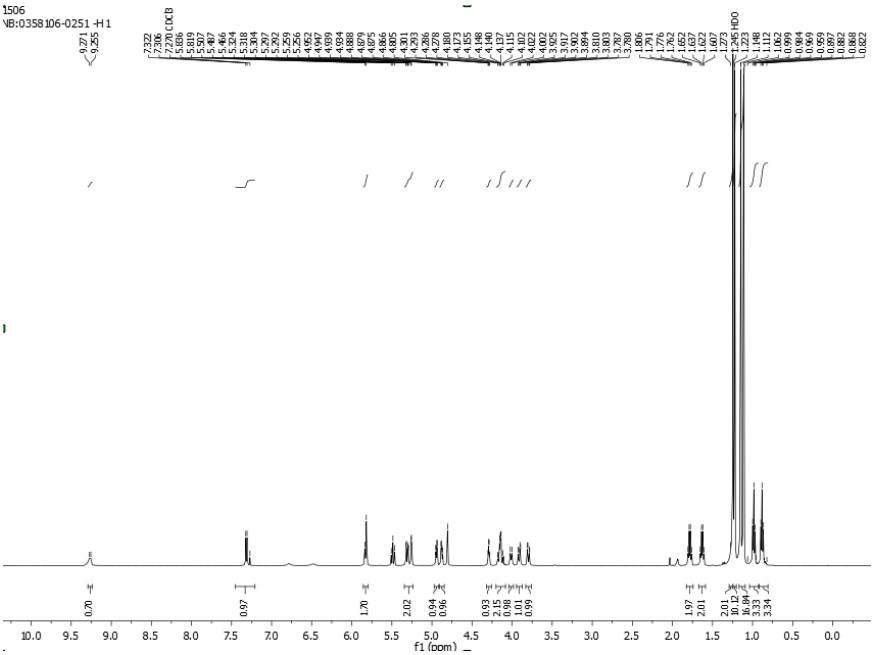
119

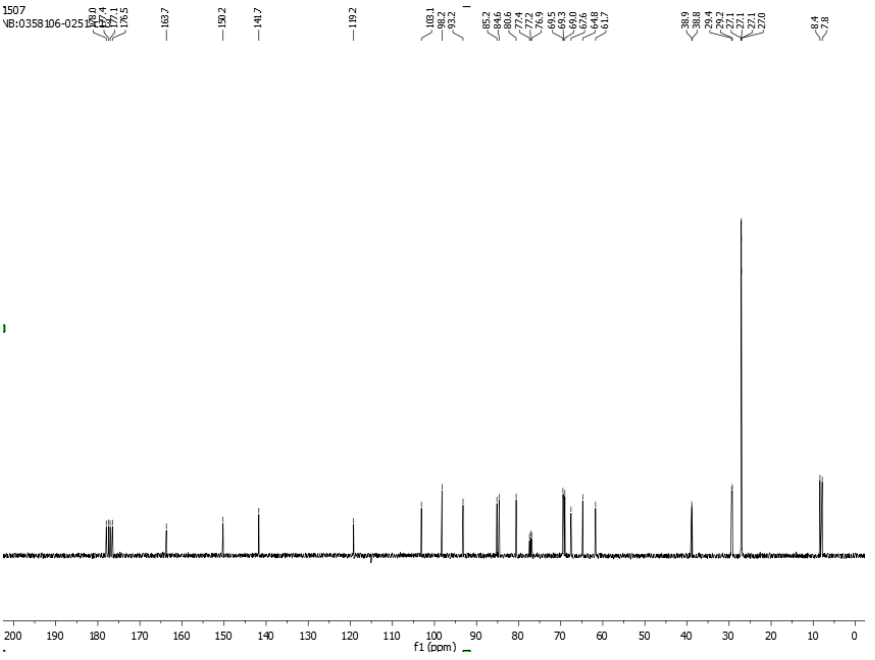

1504
NB:0358104-0248 -H
8.76
7.26
6.19
5.59
5.57
5.55
5.46
5.45
5.43
5.42
5.41
5.40
4.20
4.19
4.17
4.16
1.27
1.26
1.20
1.16
1.11
1.07
1.00
1.19
2.44
4.13
47.89
f1 (ppm)

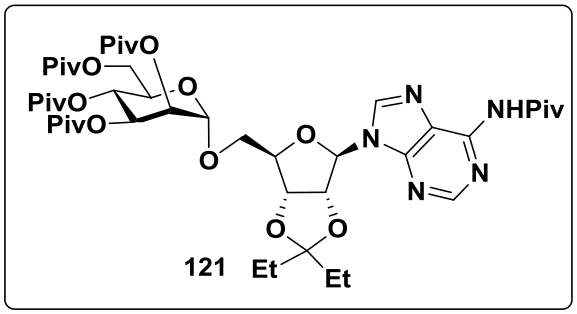

NMR Spectrum: C13
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Nov 16 2014
ppm

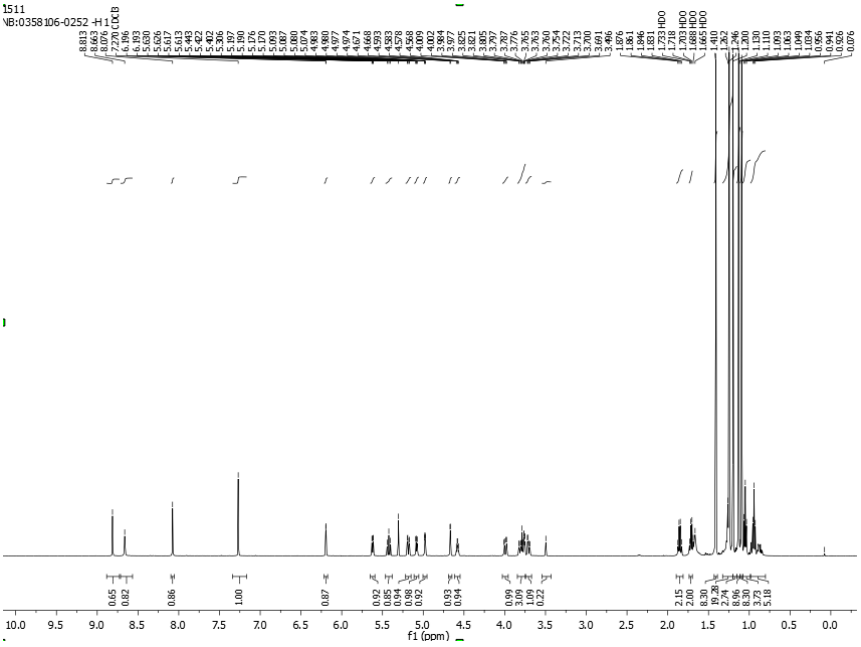


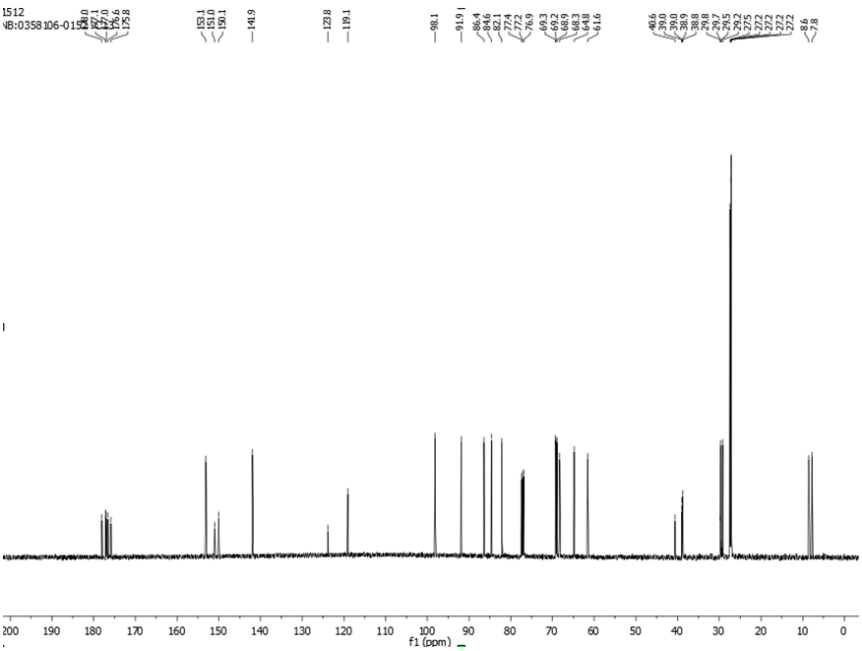
120

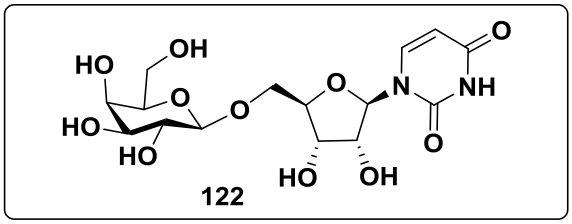




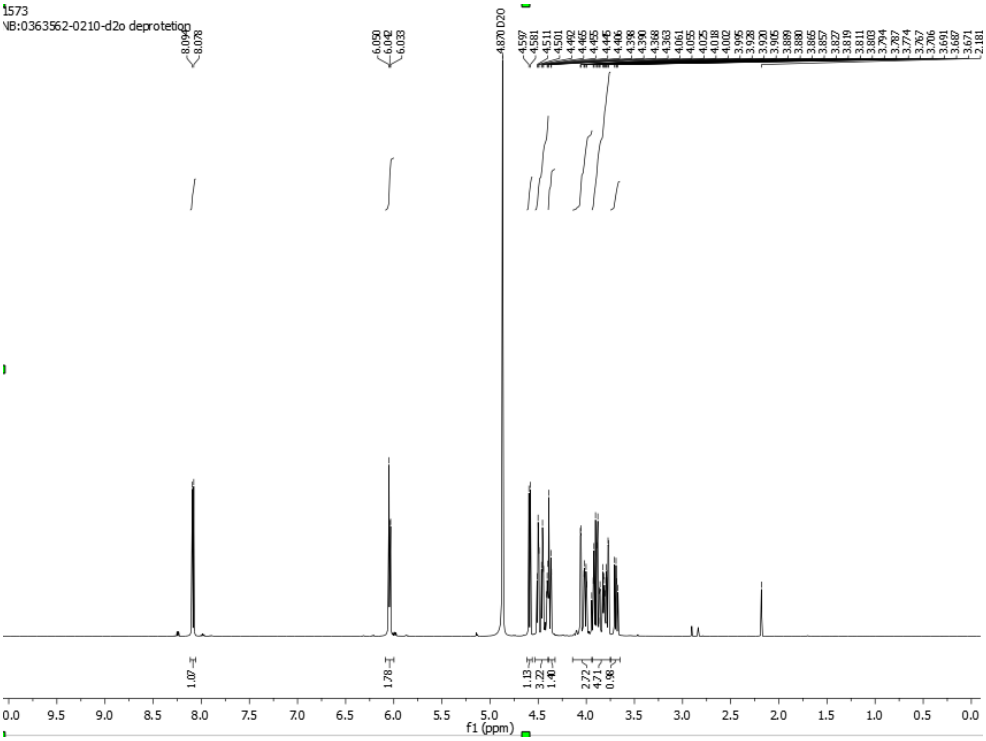

PivO
PivO
PivO
PivO
O
O
O
N
N
N
N
NHPiv
O
O
121
Et
Et

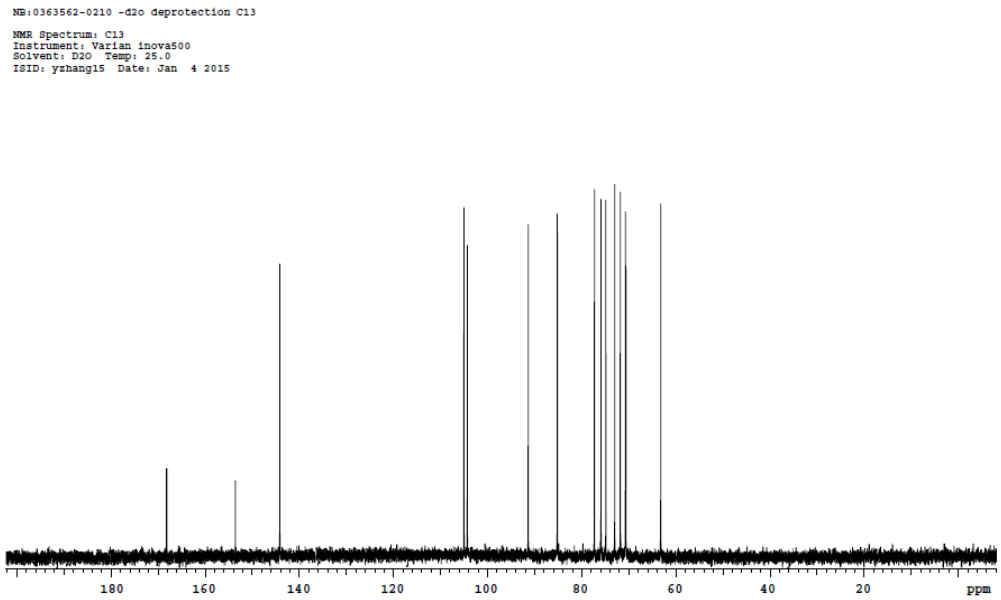

f1 (ppm)

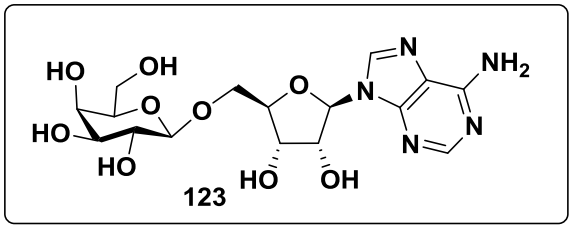

f1 (ppm)


HO
OH
O
HO
HO
O
O
N
NH
O
O
HO
OH

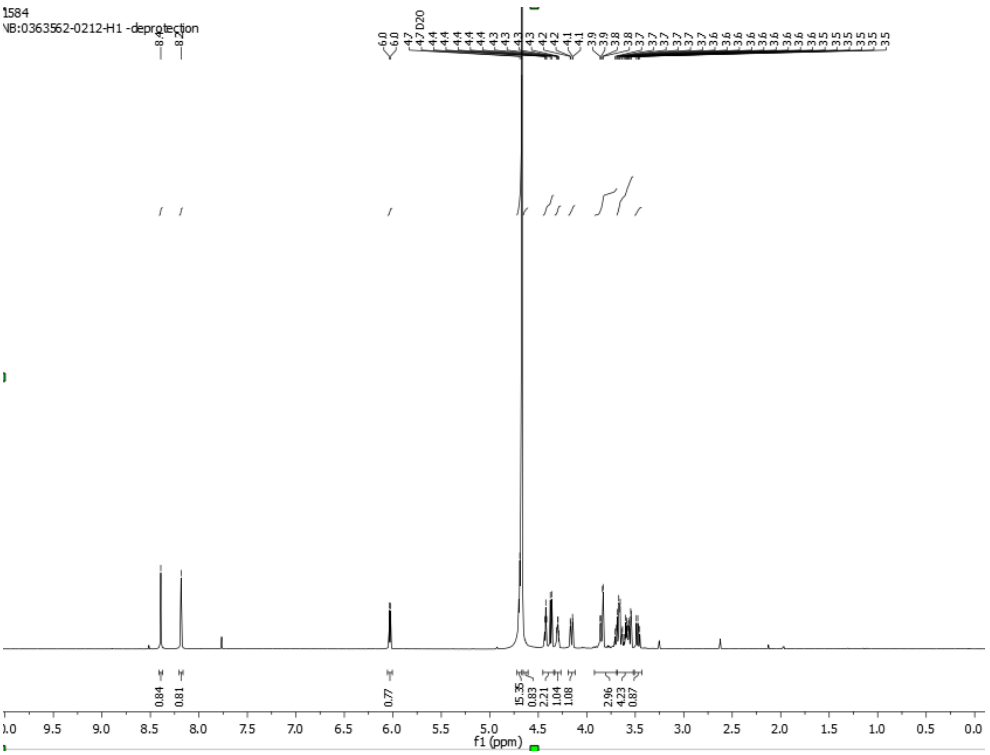
122

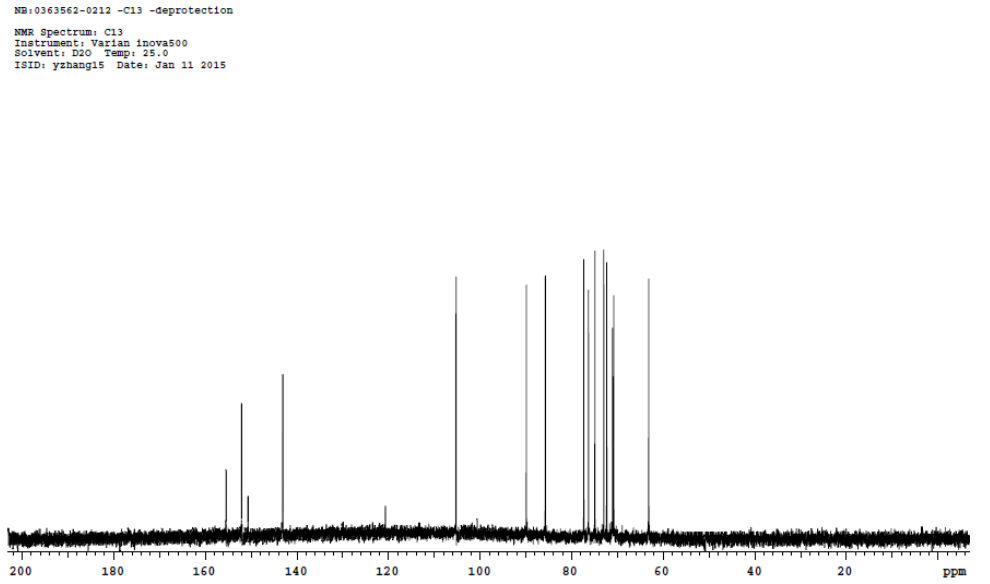

1573
NB:0363562-0210-d2o deprotetion
4.670 D2O
f1 (ppm)

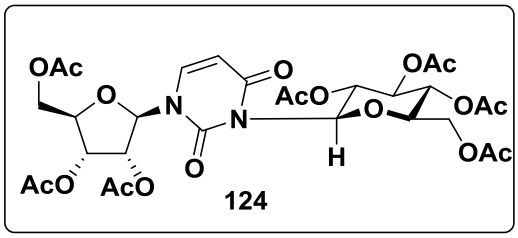

NB:0363562-0210 -d2o deprotection C13
NMR Spectrum: C13
Instrument: Varian inova500
Solvent: D2O Temp: 25.0
ISID: yzhang15 Date: Jan 4 2015
ppm


HO
OH
O
O
HO
HO
O
N
N
N
N
NH2
HO
OH

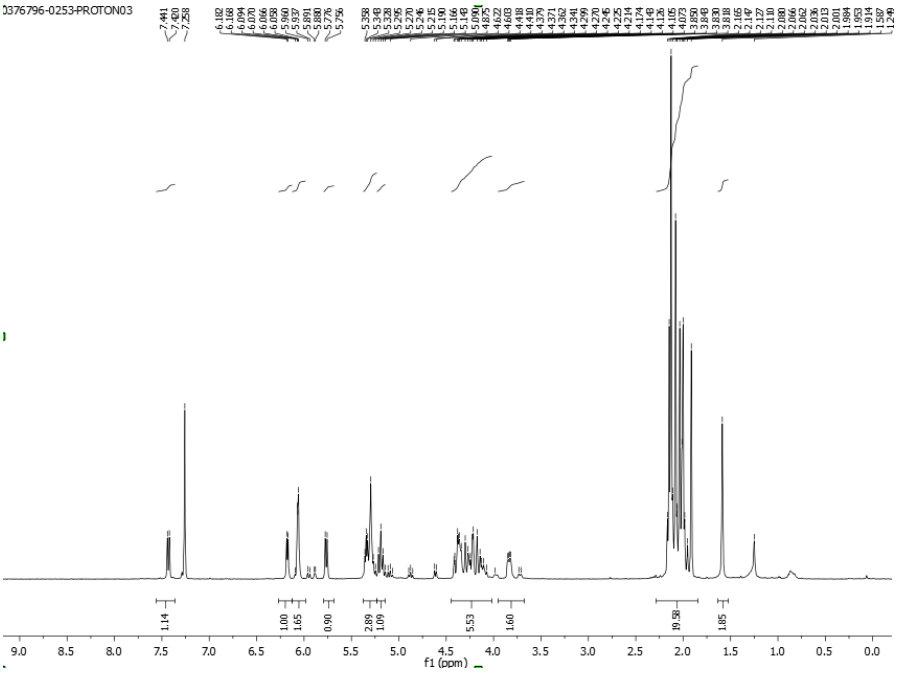
123

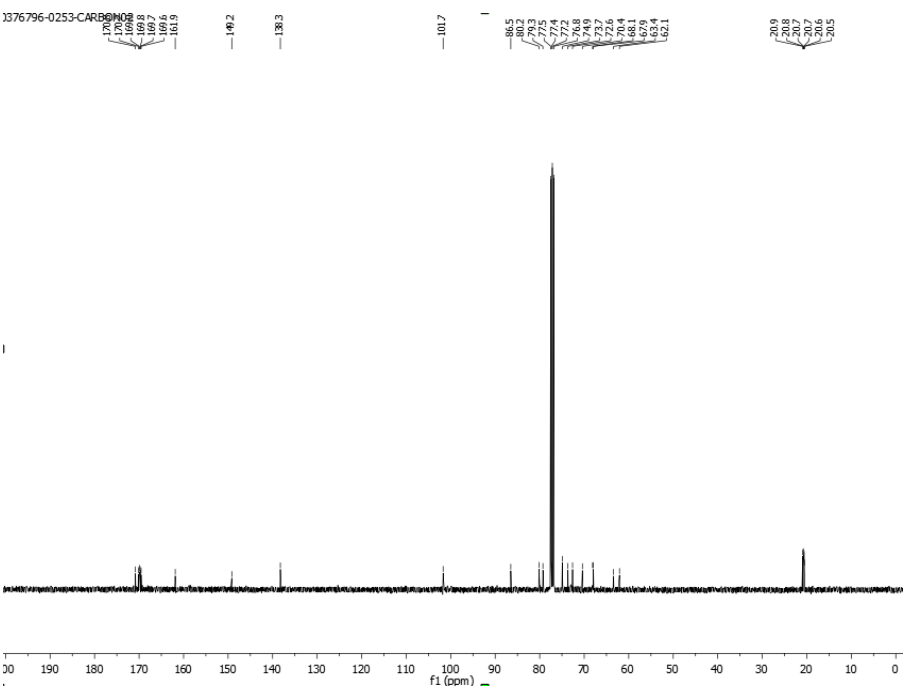

1584
NB:0363562-0212-H1 -deprotection
f1 (ppm)

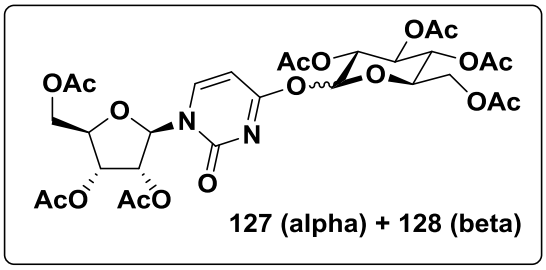

NB:0363562-0212 -C13 -deprotection
NMR Spectrum: C13
Instrument: Varian inova500
Solvent: D2O Temp: 25.0
ISID: yzhang15 Date: Jan 11 2015
ppm

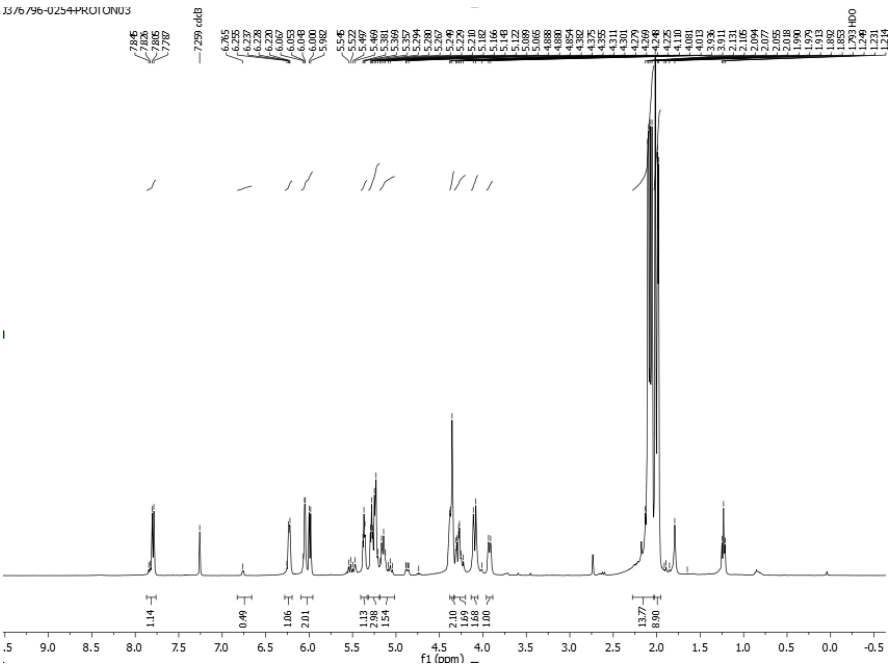

OAc
O
N
O
AcO
OAc
O
N
OAc
AcO
AcO
O
H
OAc

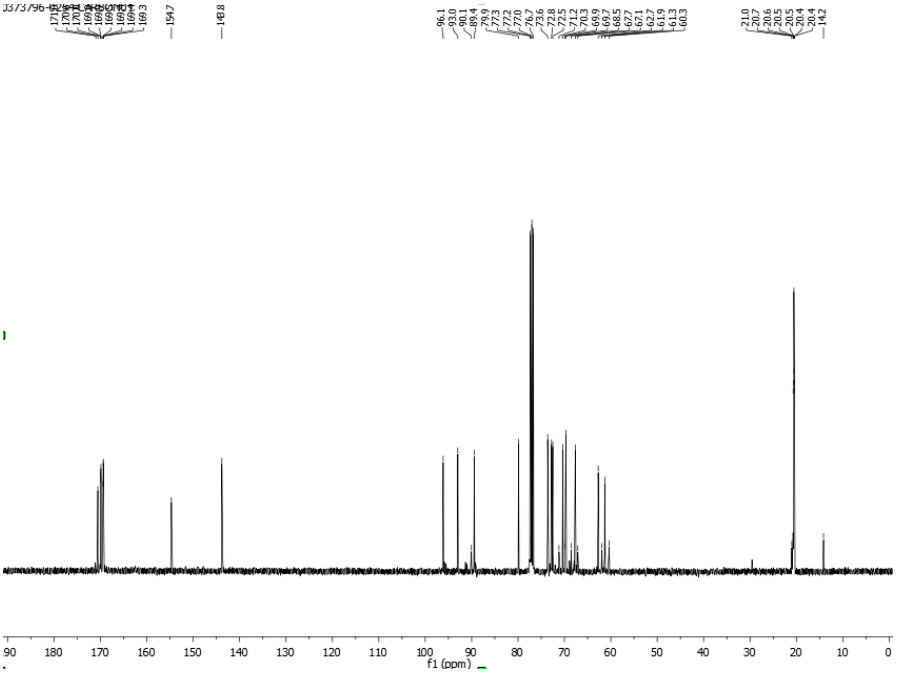
124

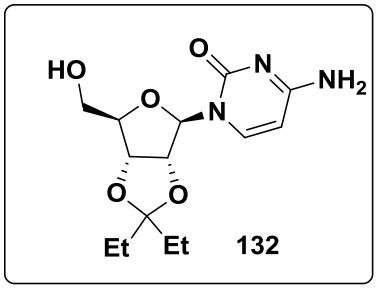

0376796-0253-PROTON03
1.14
1.00
1.65
0.90
2.89
1.09
5.53
1.60
19.58
1.85
f1 (ppm)

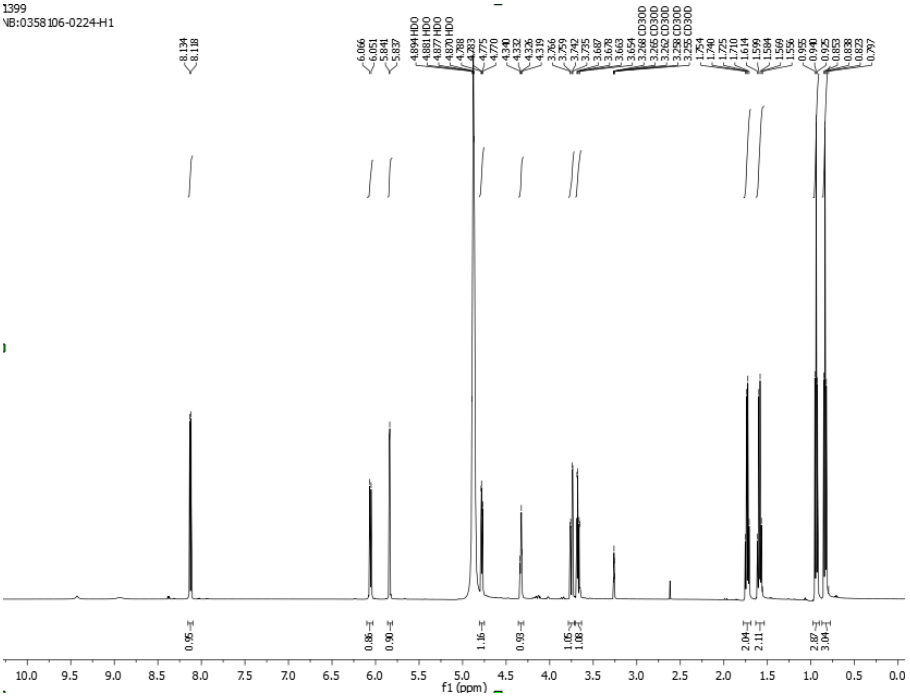

0376796-0253-CARBON03
f1 (ppm)

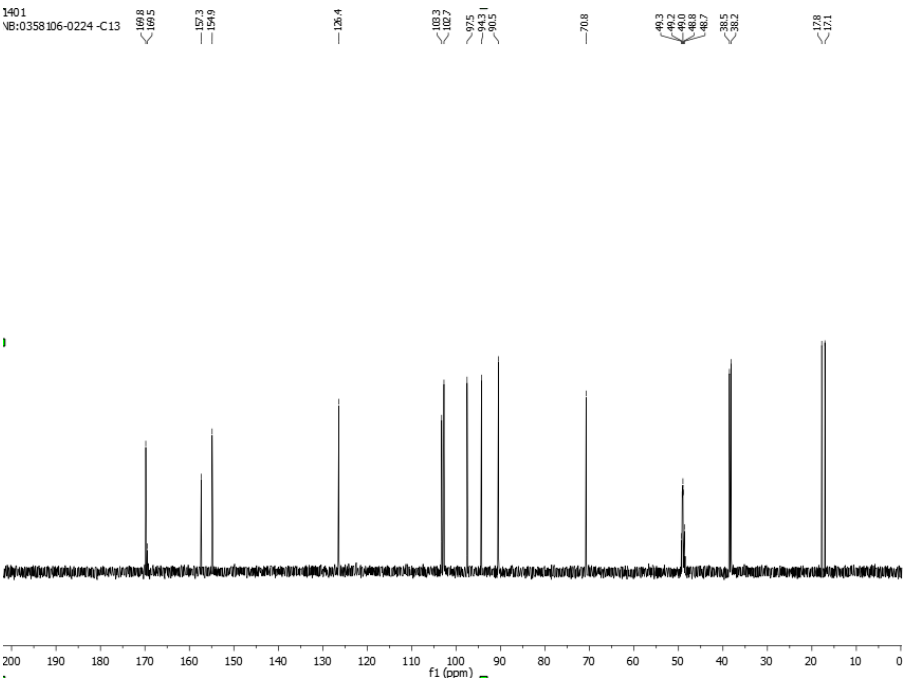

OAc
AcO
OAc
OAc
OAc
O
O
N
N
O
AcO
AcO
127 (alpha) + 128 (beta)

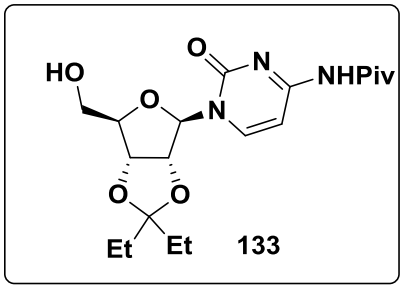

f1 (ppm)

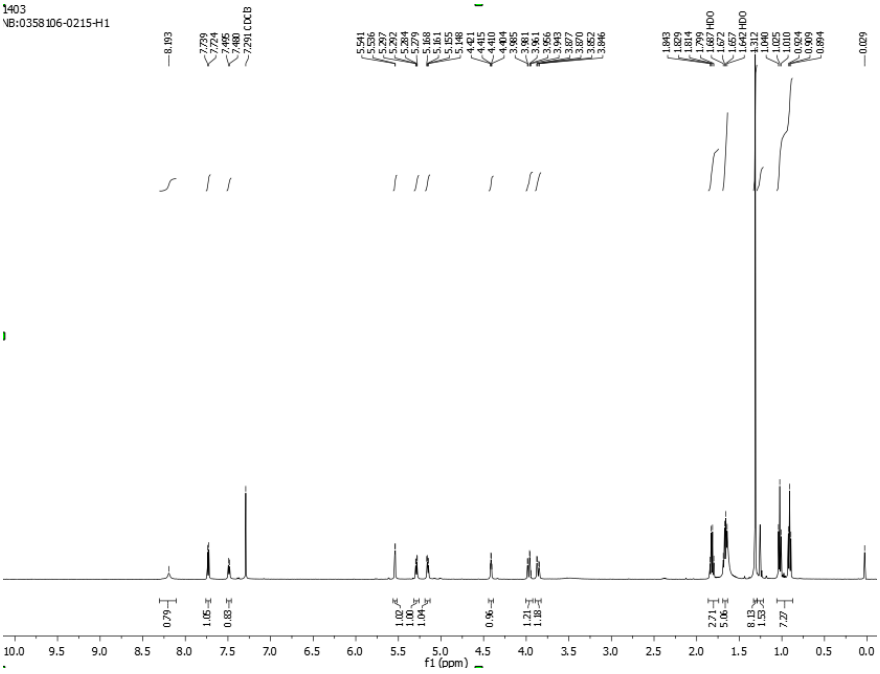

f1 (ppm)

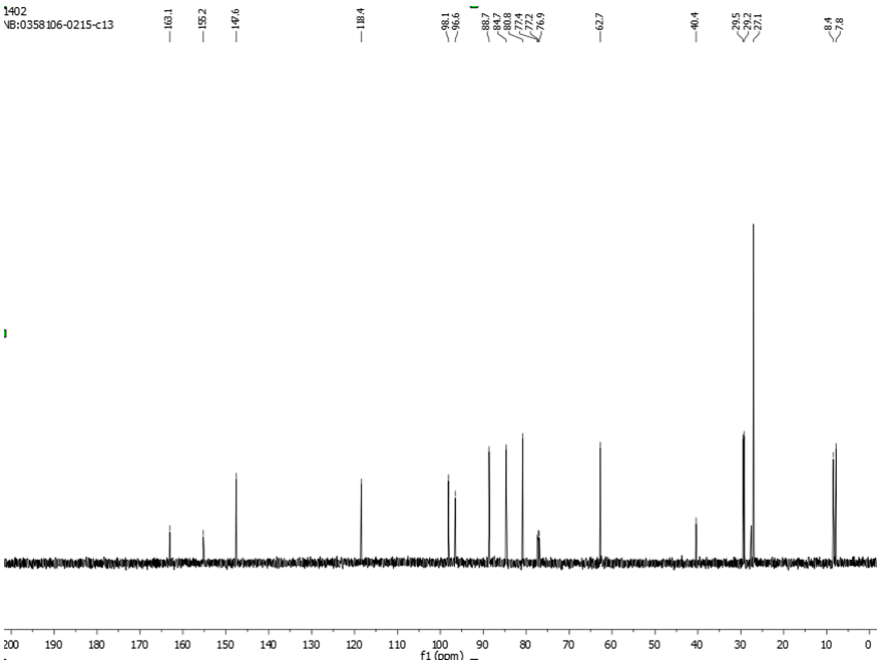

HO
O
N
NH2
O
N
O
O
Et
Et
132

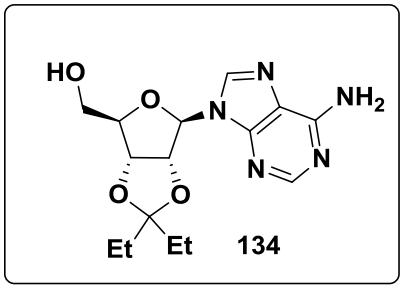

1399
NB:0358106-0224-H1
f1 (ppm)


1401
NB:0358106-0224 -C13
f1 (ppm)

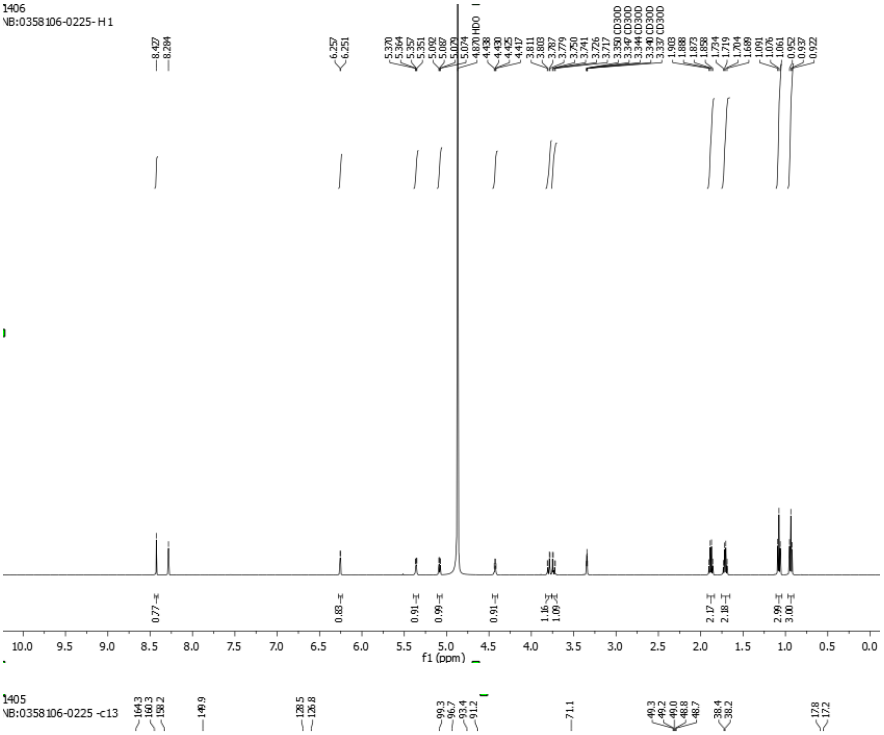

HO
O
N
NHPiv
O
N
O
O
Et
Et
133

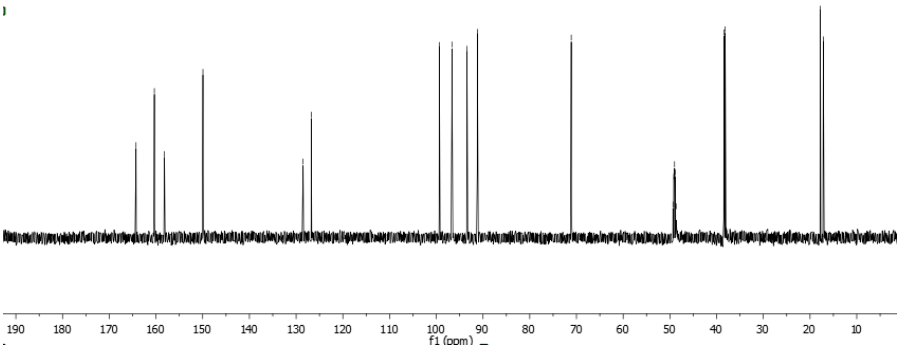


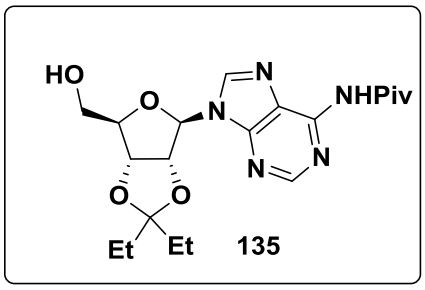


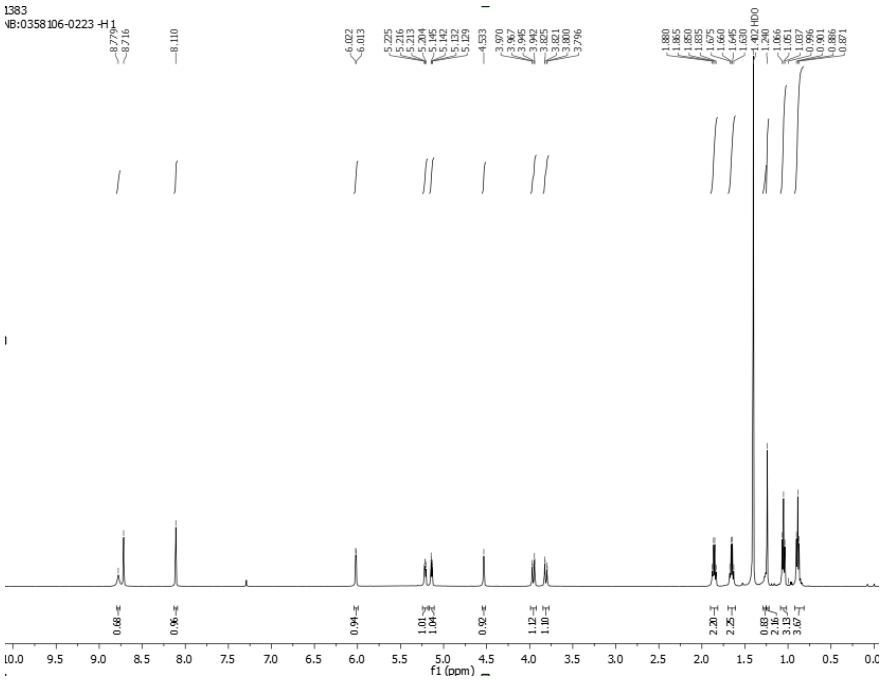


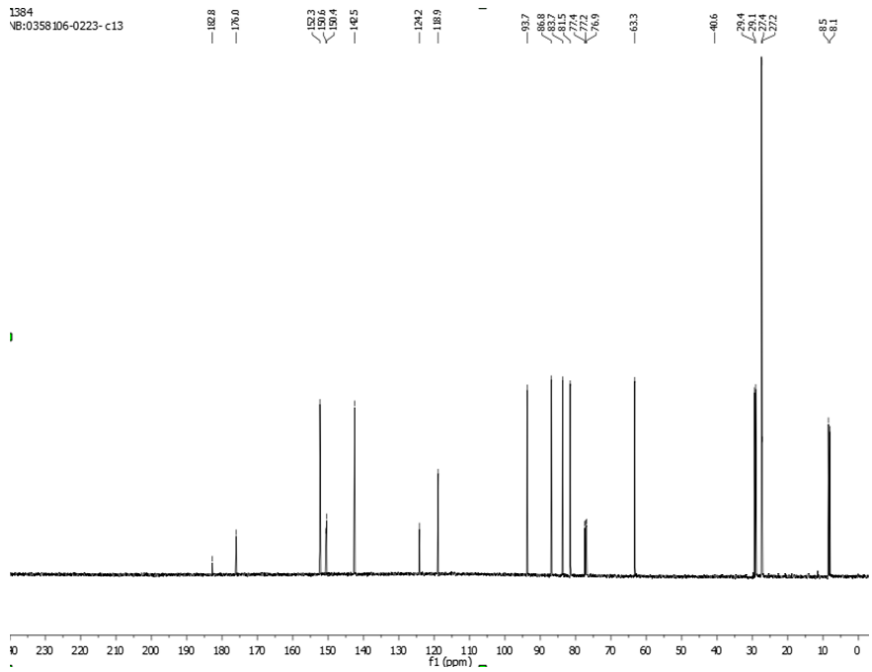
134

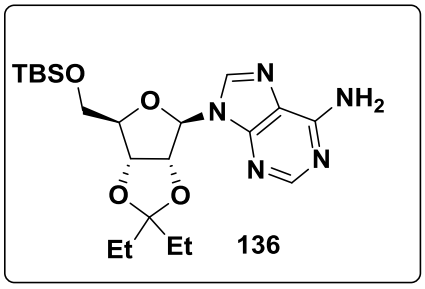




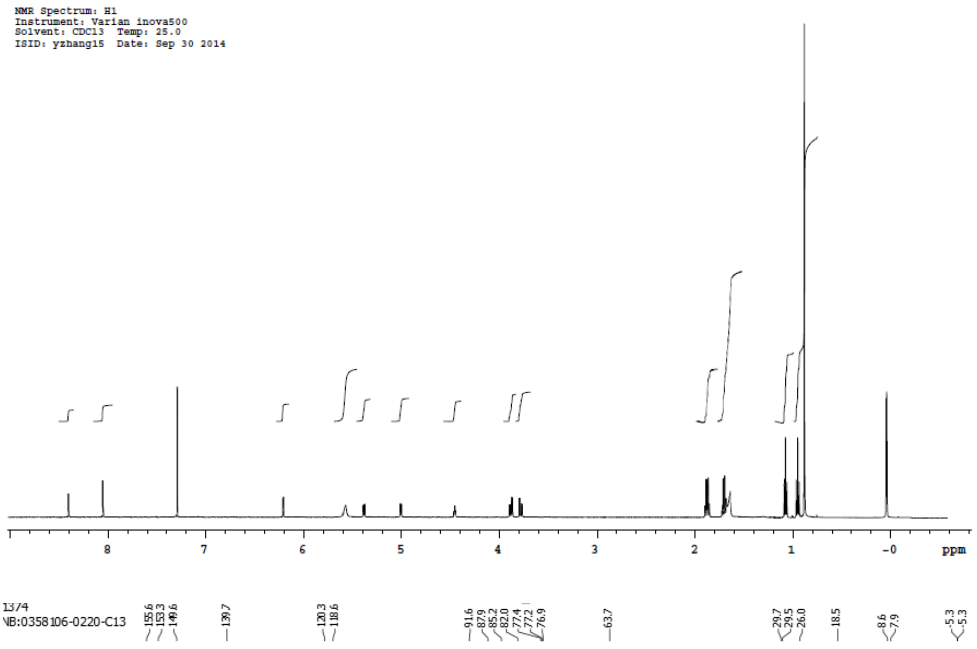

HO
O
N
N
N
N
NHPiv
O
O
Et
Et
135


f1 (ppm)

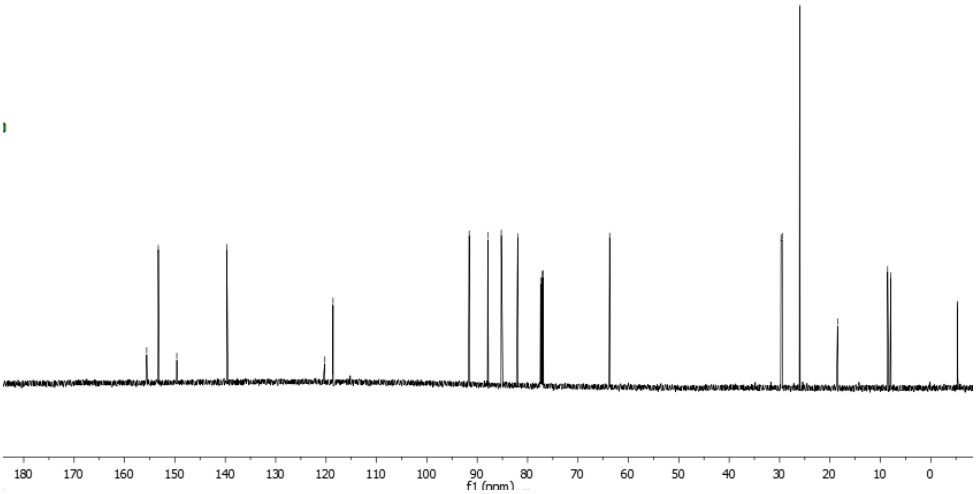

f1 (ppm)

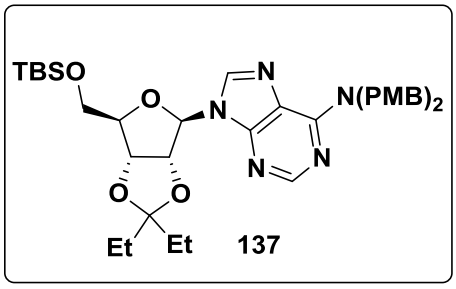

TBSO
O
N
N
N
N
NH2
O
O
Et
Et

136

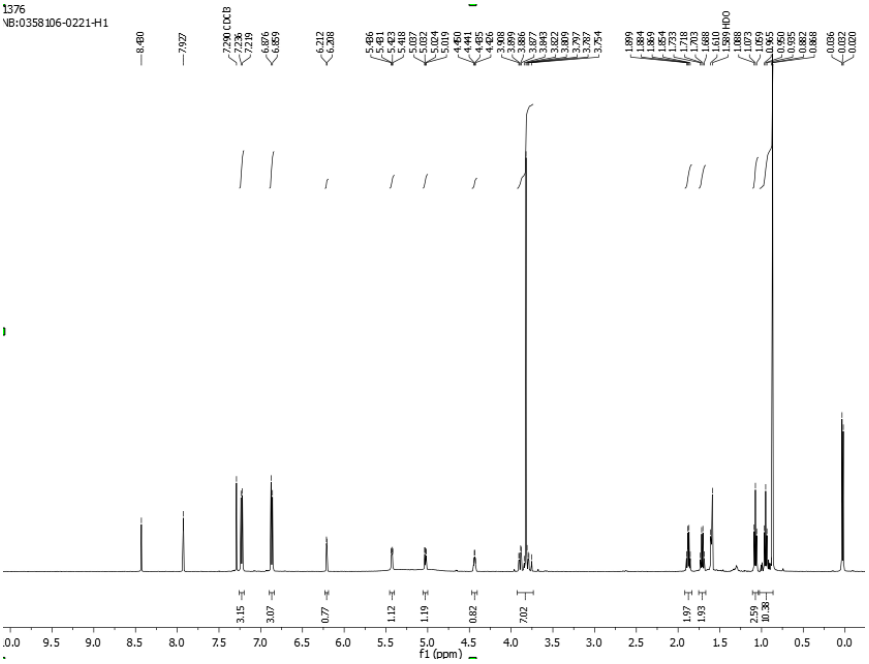

NMR Spectrum: H1
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Sep 30 2014
8
7
6
5
4
3
2
1
-0
ppm

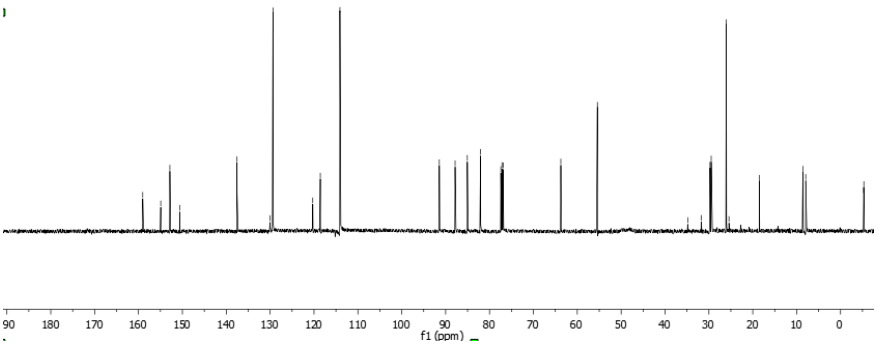
1374
NB:0358106-0220-C13
155.6
153.3
149.6
139.7
120.3
118.6
91.6
87.9
85.2
82.0
77.4
77.2
76.9
63.7
29.7
29.5
26.0
18.5
8.6
7.9
-5.3
-5.3

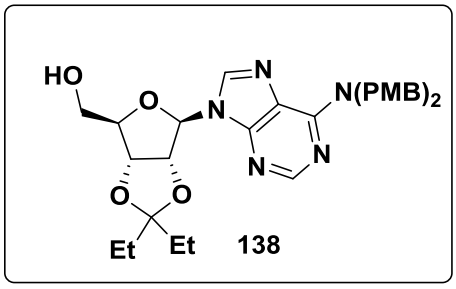

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



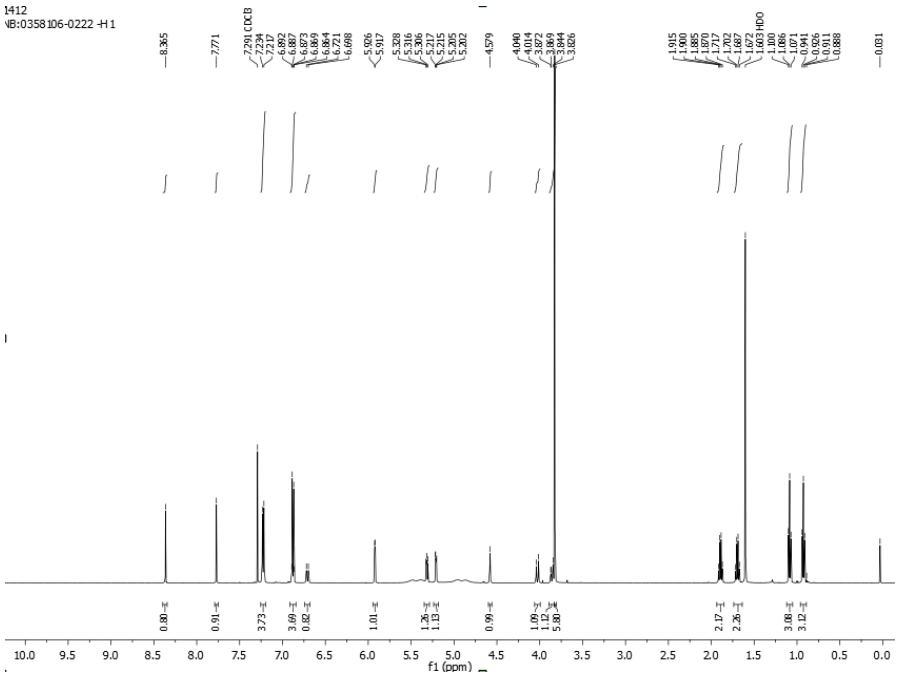
137

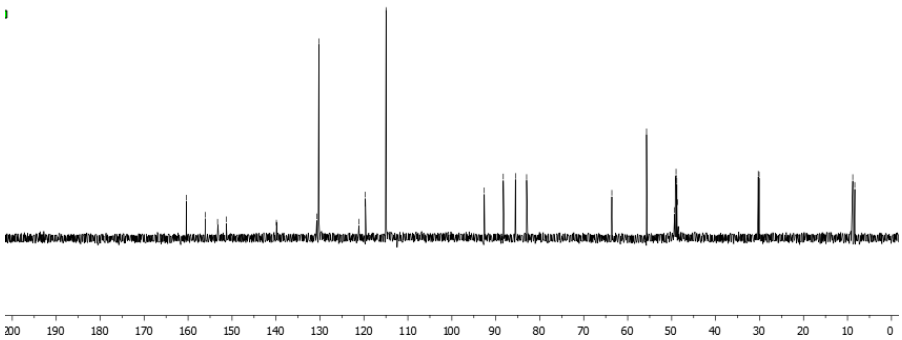


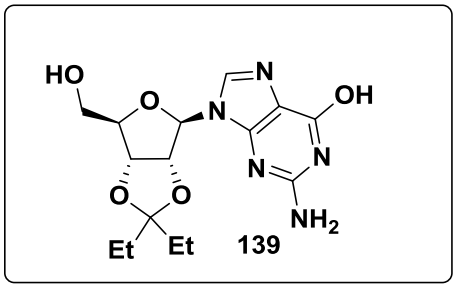




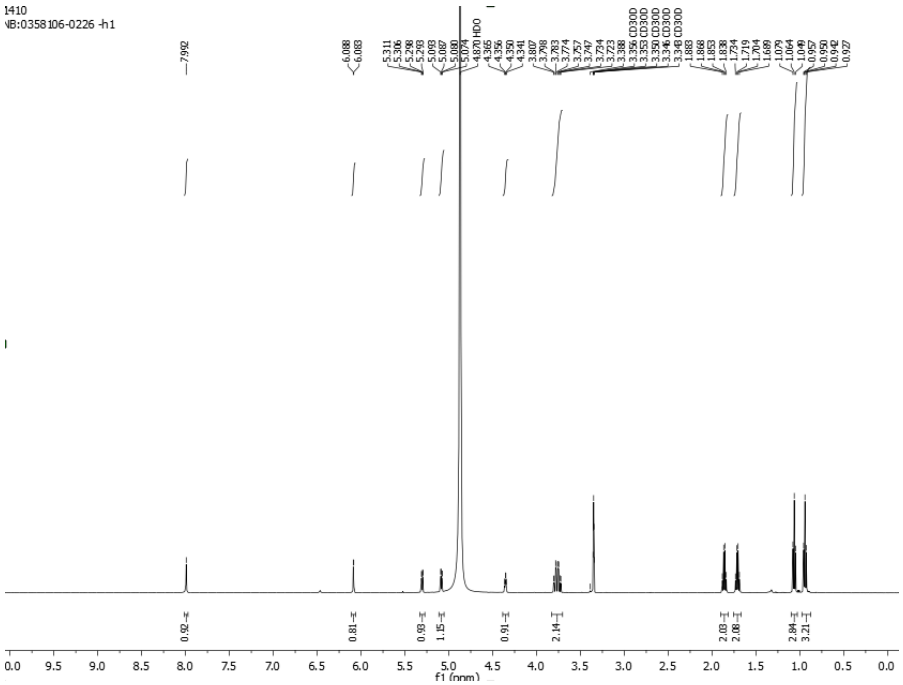
138

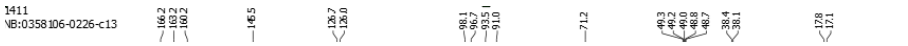


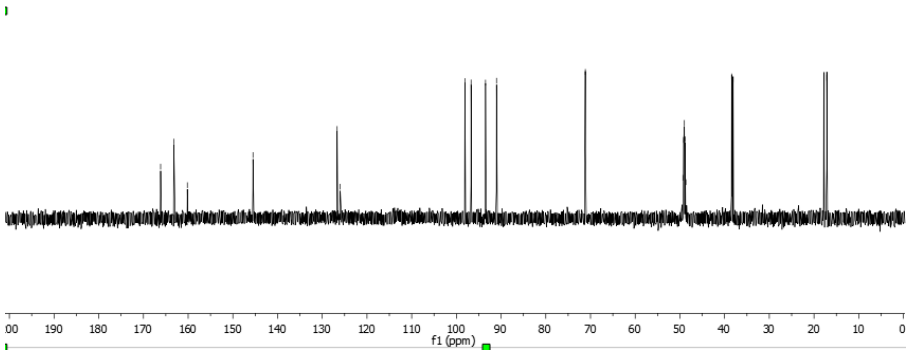


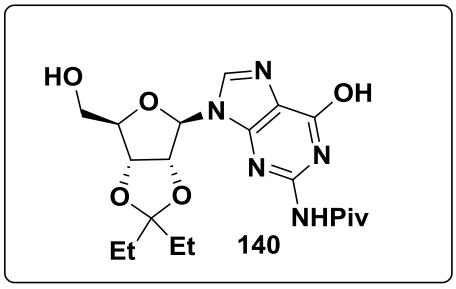


139

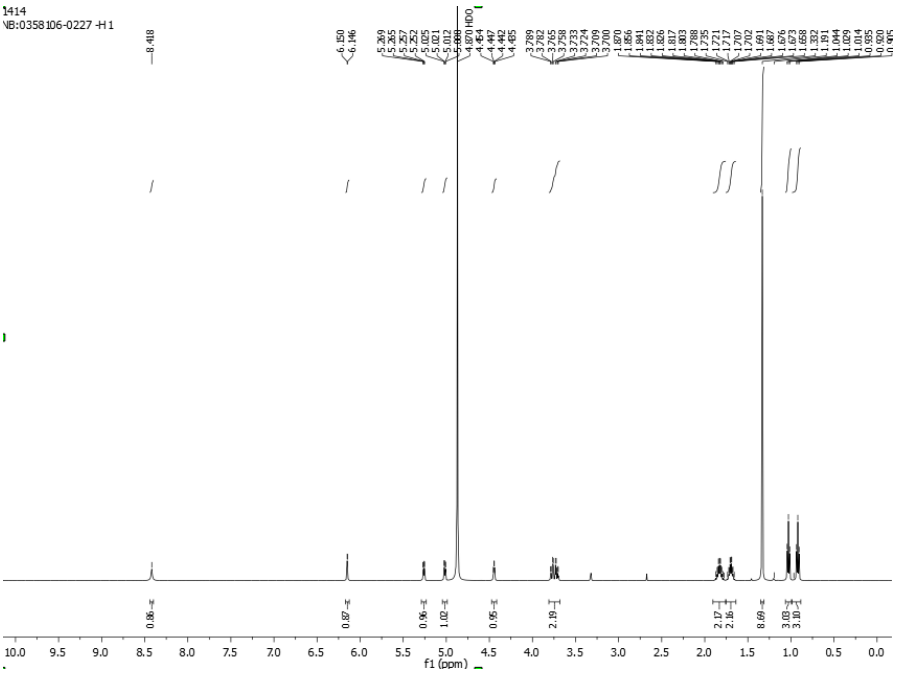


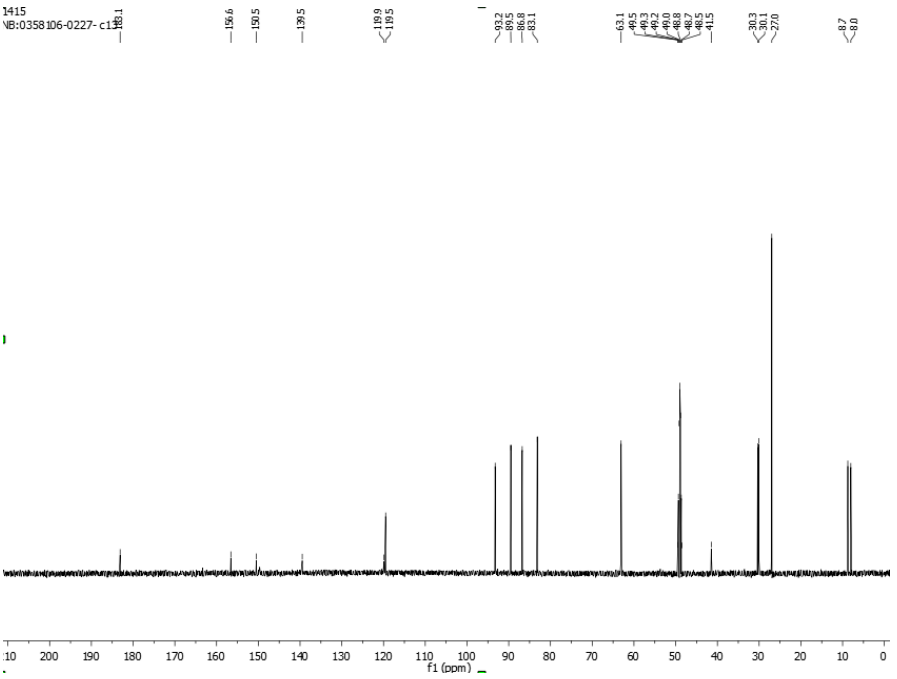


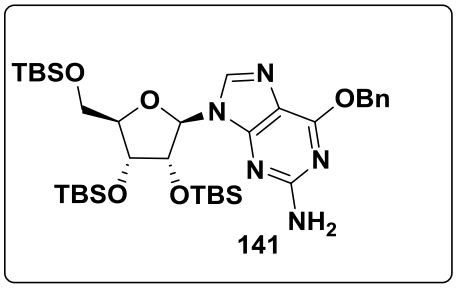




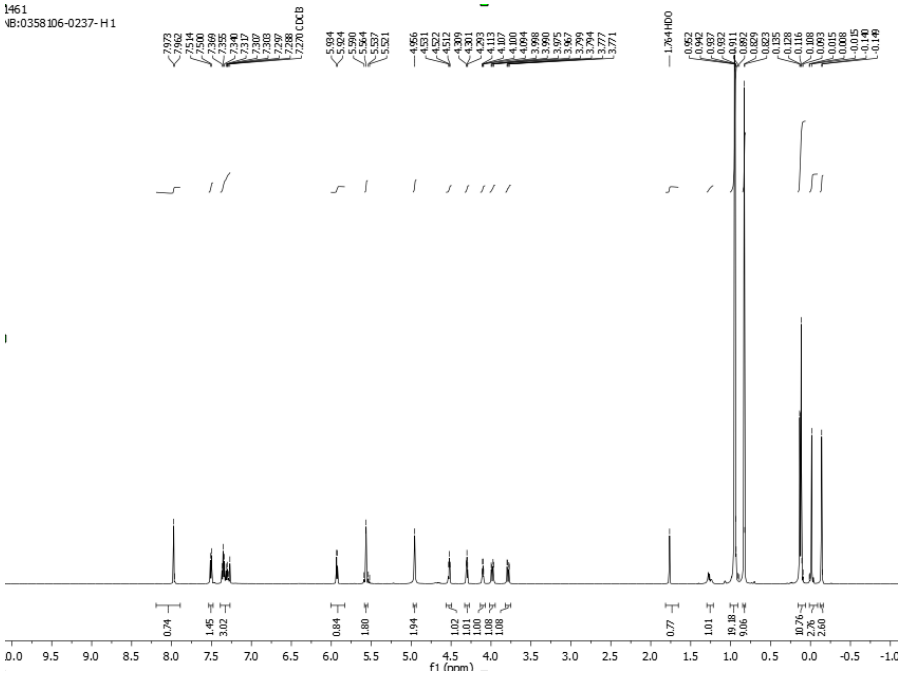
140

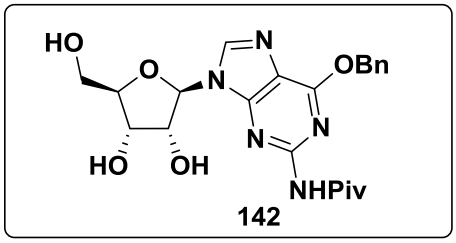




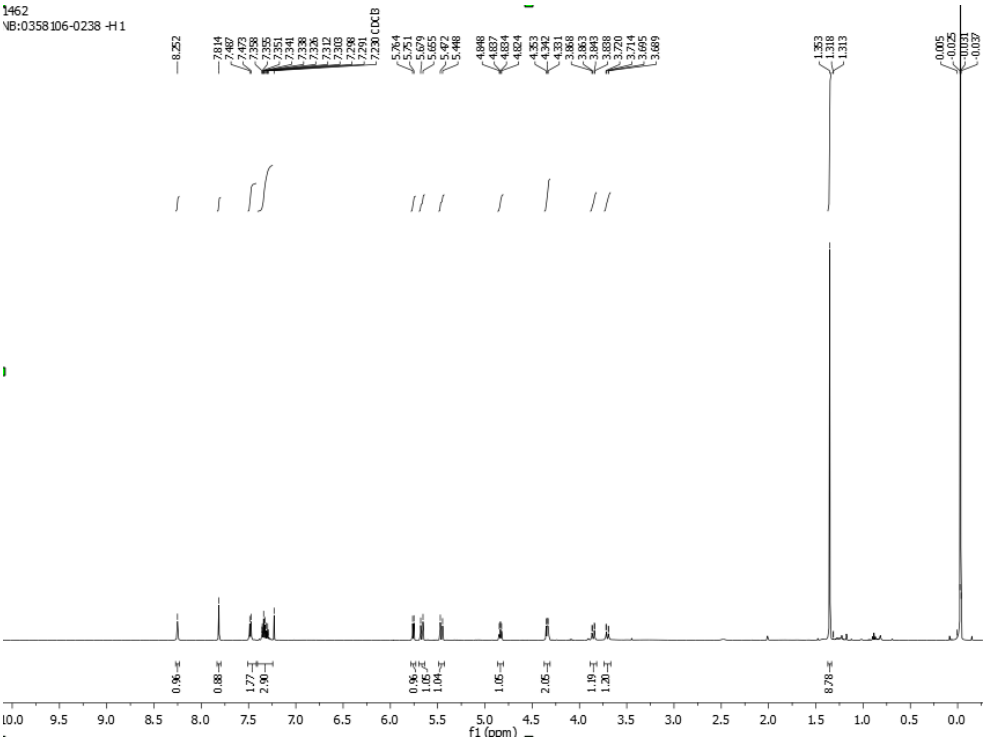

TBSO
O
N
N
OBn
N
N
TBSO
OTBS
NH2

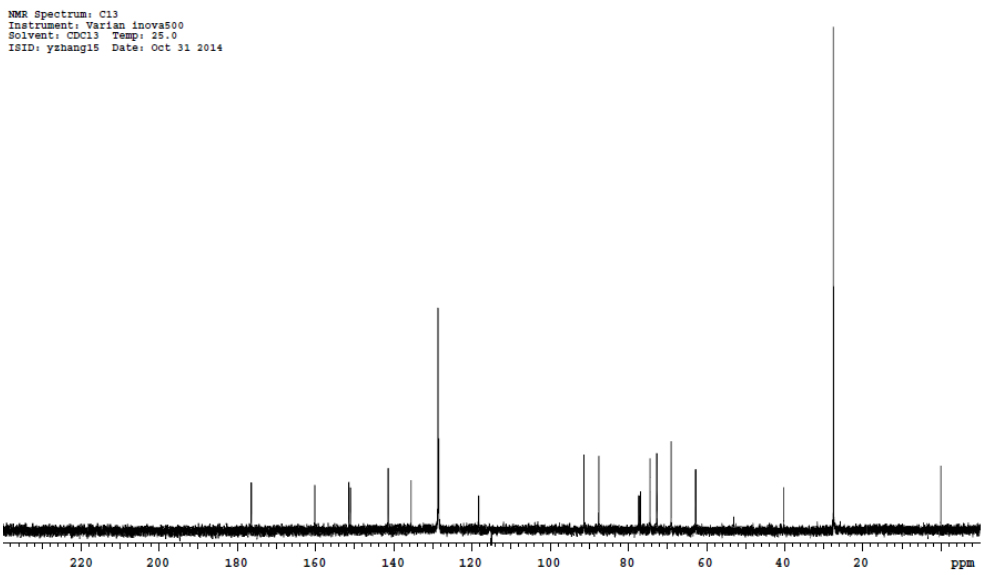
141

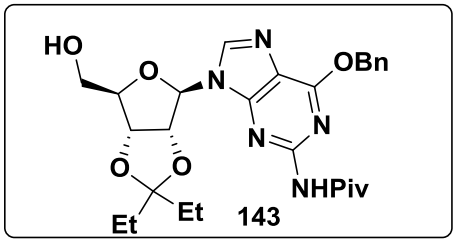

1461
NB:0358106-0237-H1
1460
NB:0358106-0237-C13
f1 (ppm)

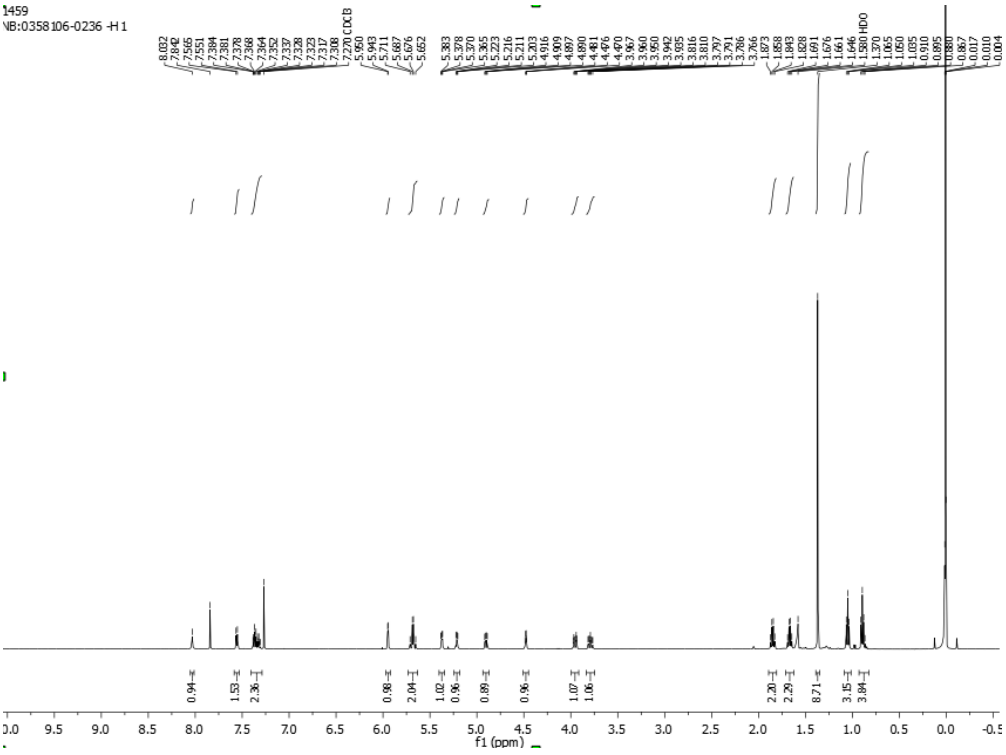

HO
O
N
N
OBn
N
N
HO
OH
NHPiv

142


1462
NB:0358106-0238 -H 1
f1 (ppm)

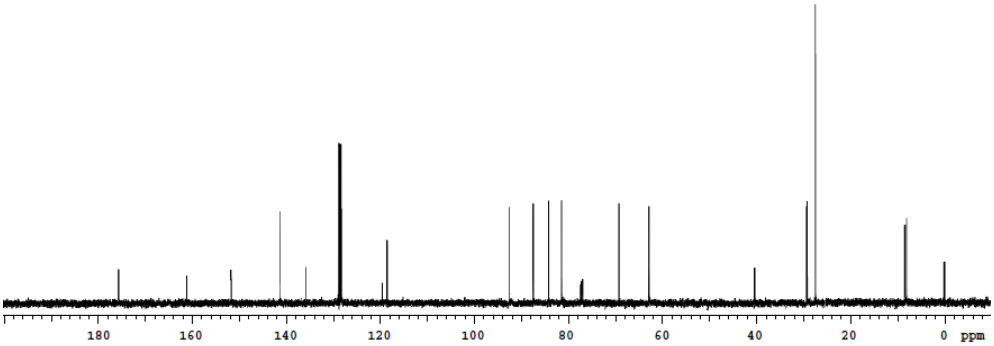

NMR Spectrum: C13
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Oct 31 2014
ppm

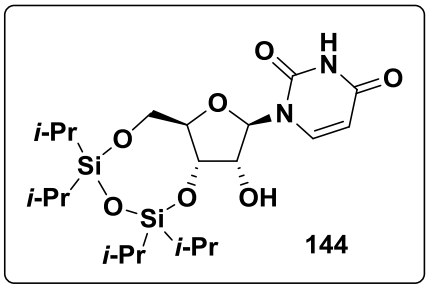




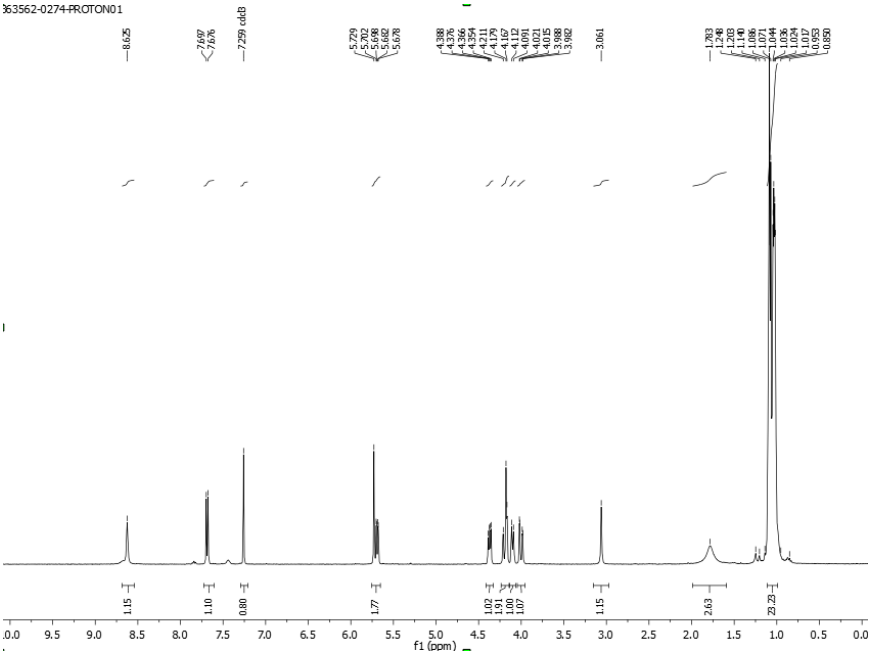
NB:0358106-0236 -C13

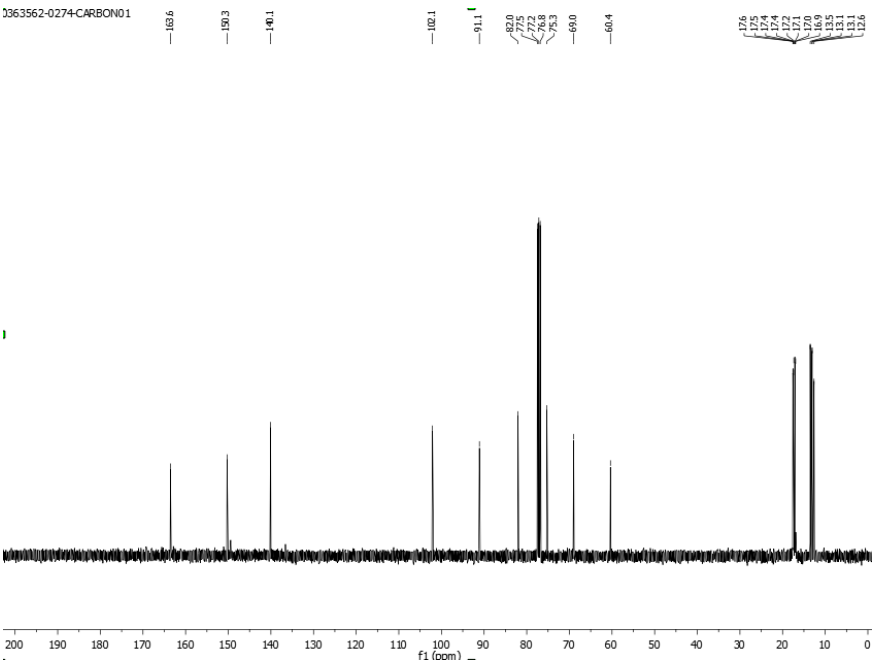
NMR Spectrum: C13
Instrument: Varian inova500
Solvent: CDCl3 Temp: 25.0
ISID: yzhang15 Date: Oct 31 2014

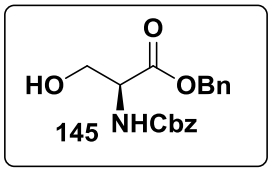



O
H
N
O
N
O
i-Pr
O
Si
i-Pr
O
Si
O
OH
i-Pr
i-Pr

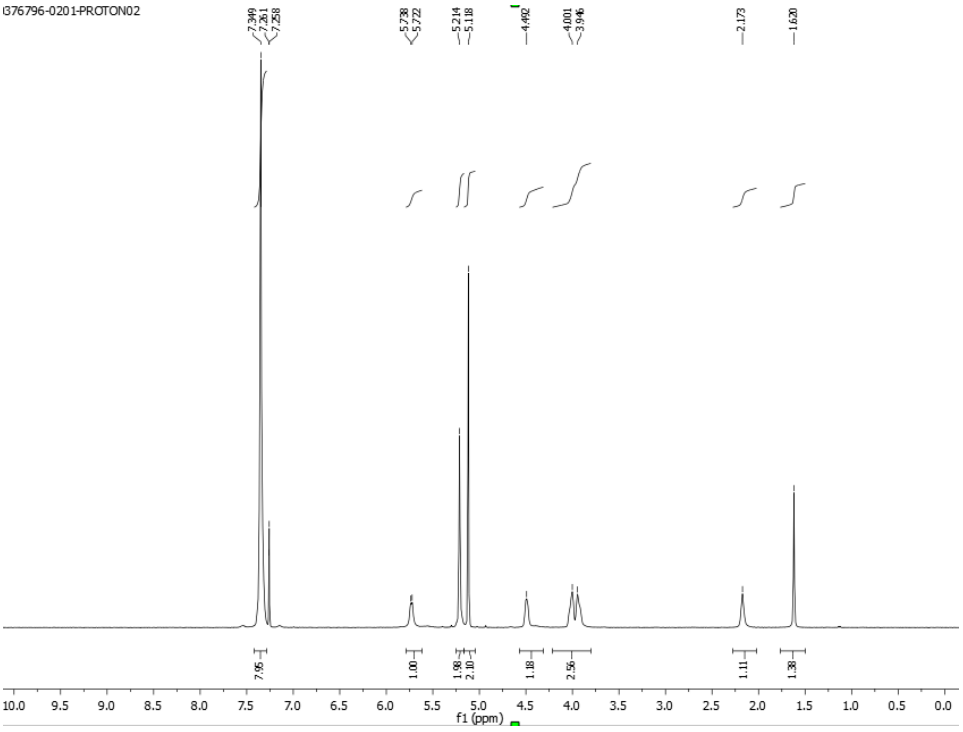
144

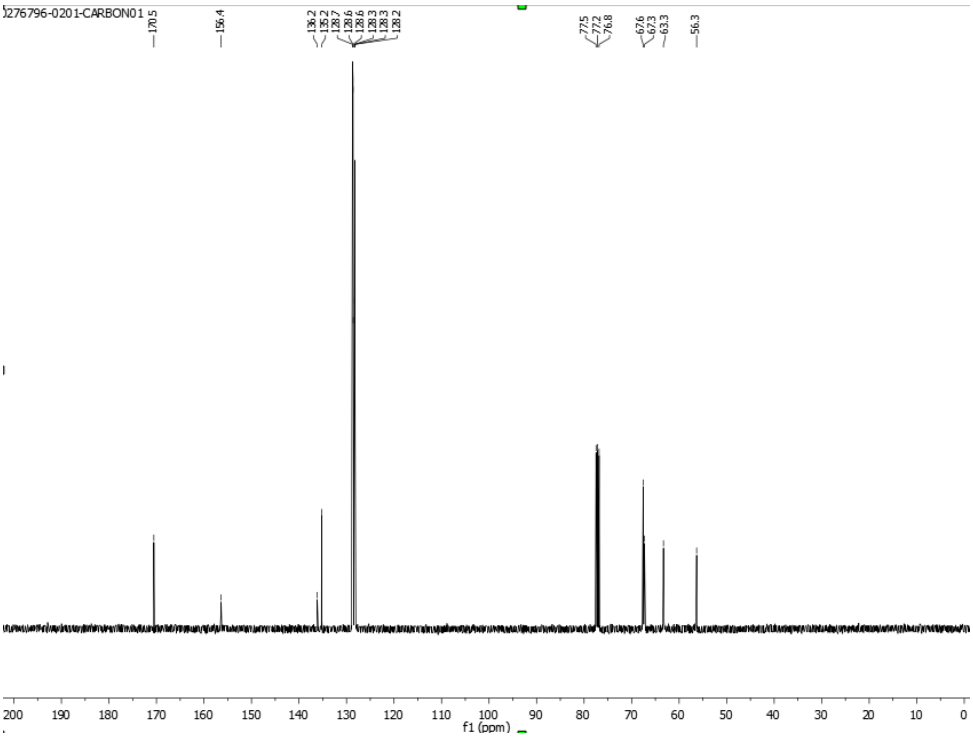

363562-0274-PROTON01
f1 (ppm)

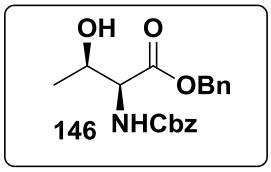

0363562-0274-CARBON01
f1 (ppm)



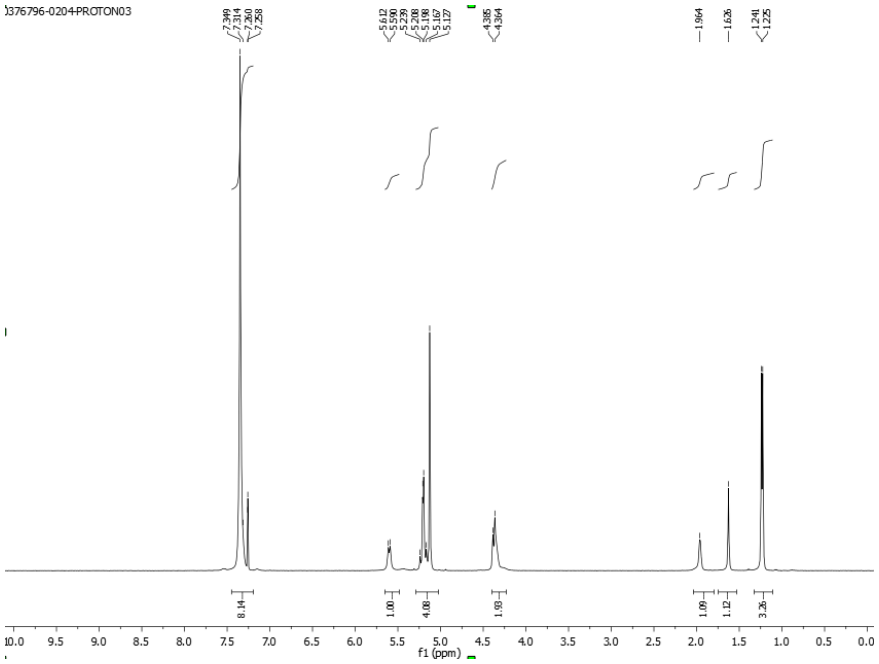
145

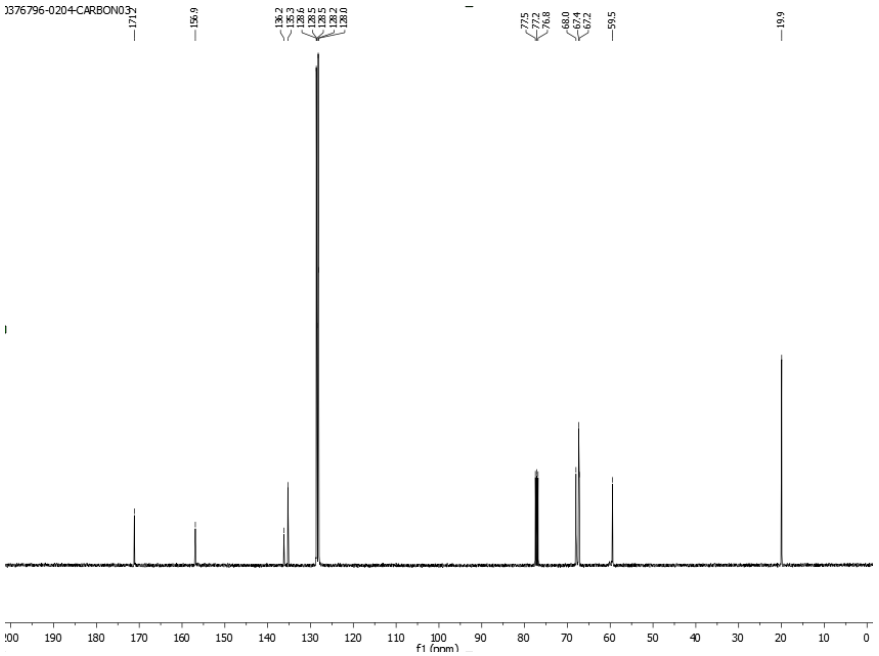


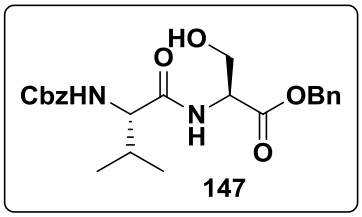



OH
O
OBn
NHCbz

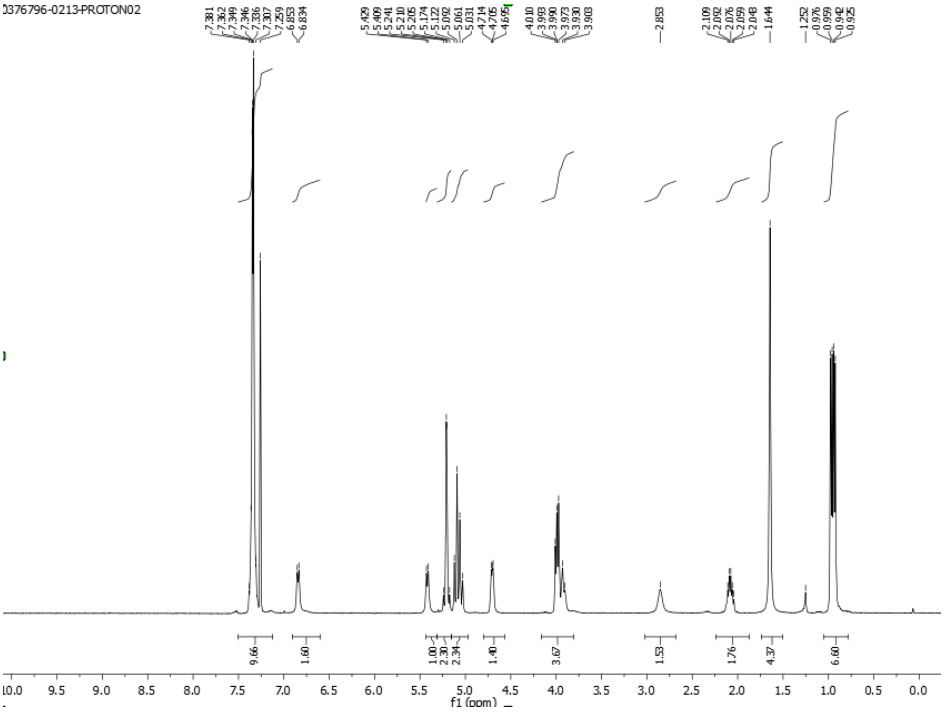
146

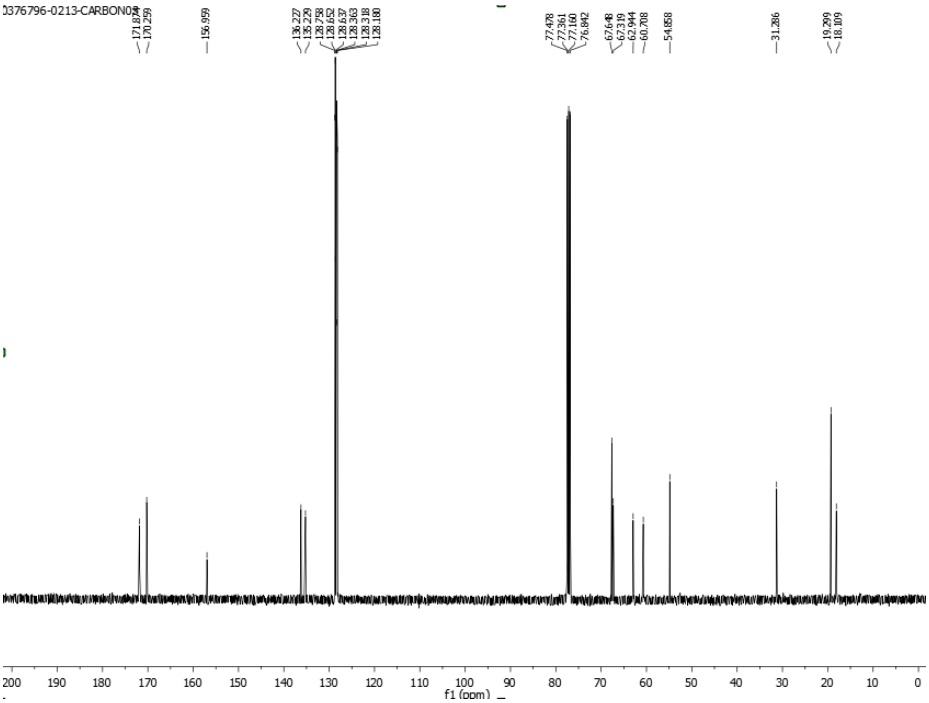

0376796-0204-PROTON03
f1 (ppm)

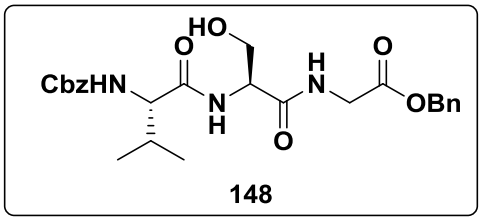

0376796-0204-CARBON03
f1 (ppm)


HO
O
CbzHN
N
H
OBn
O

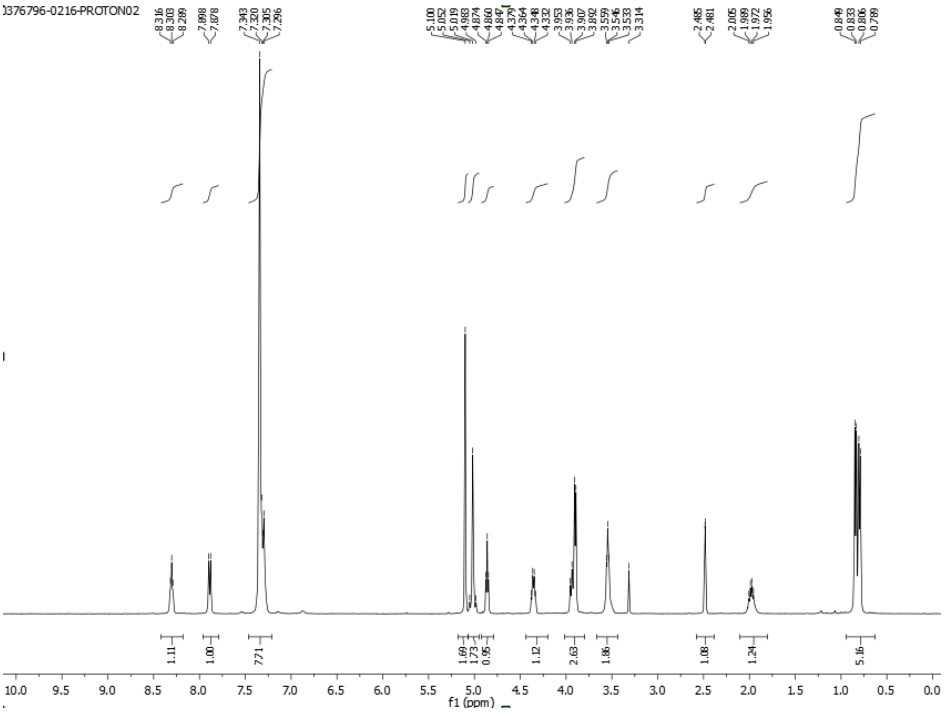
147

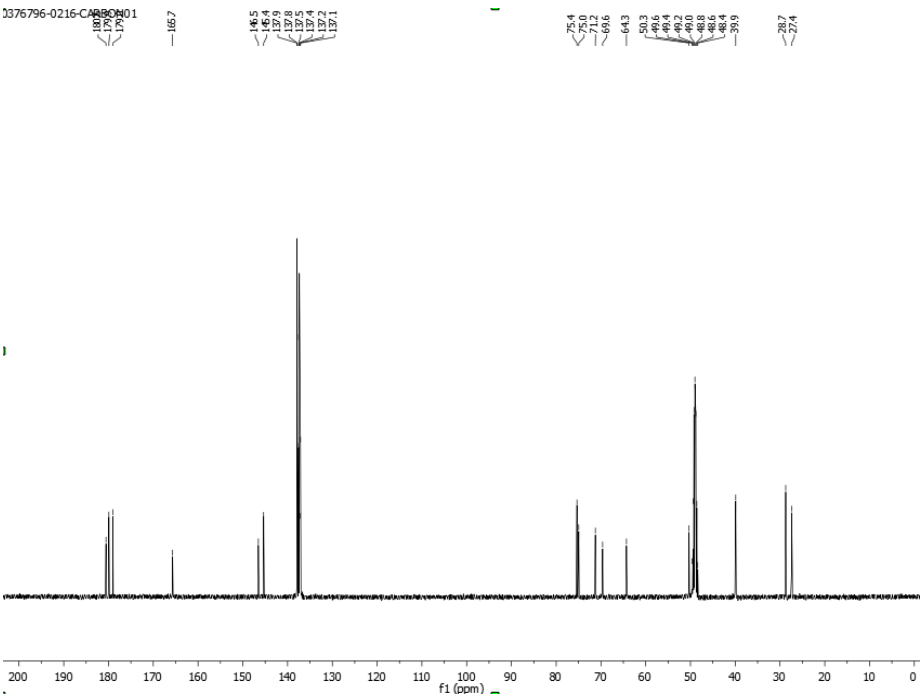

0376796-0213-PROTON02
f1 (ppm)

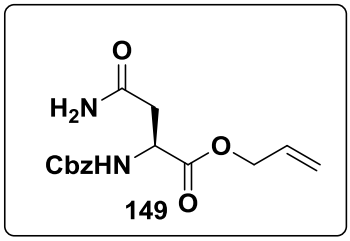

0376796-0213-CARBON02
f1 (ppm)

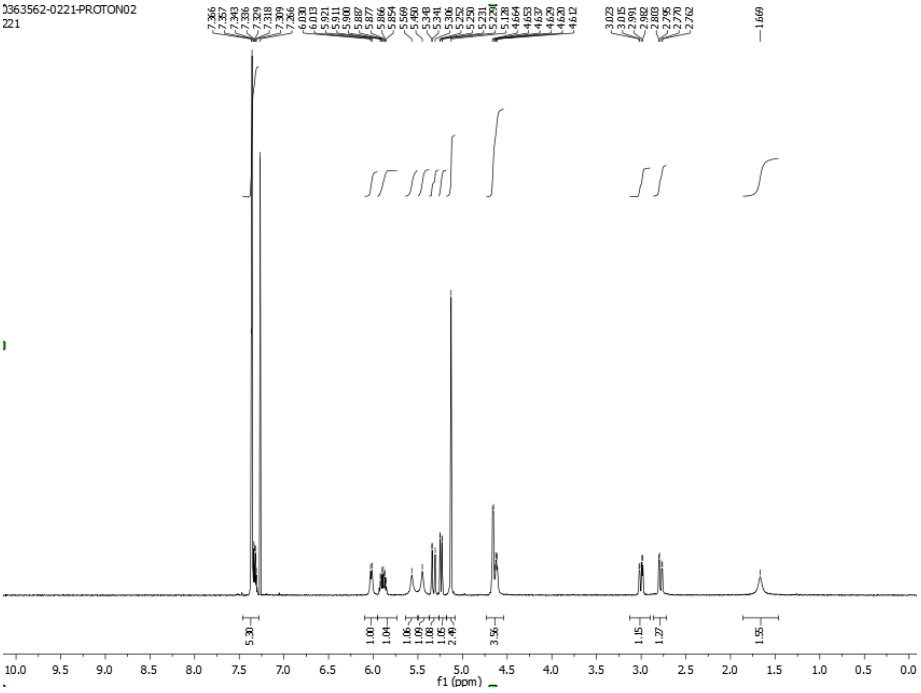

HO
O
CbzHN
N
H
H
N
O
O
OBn
O

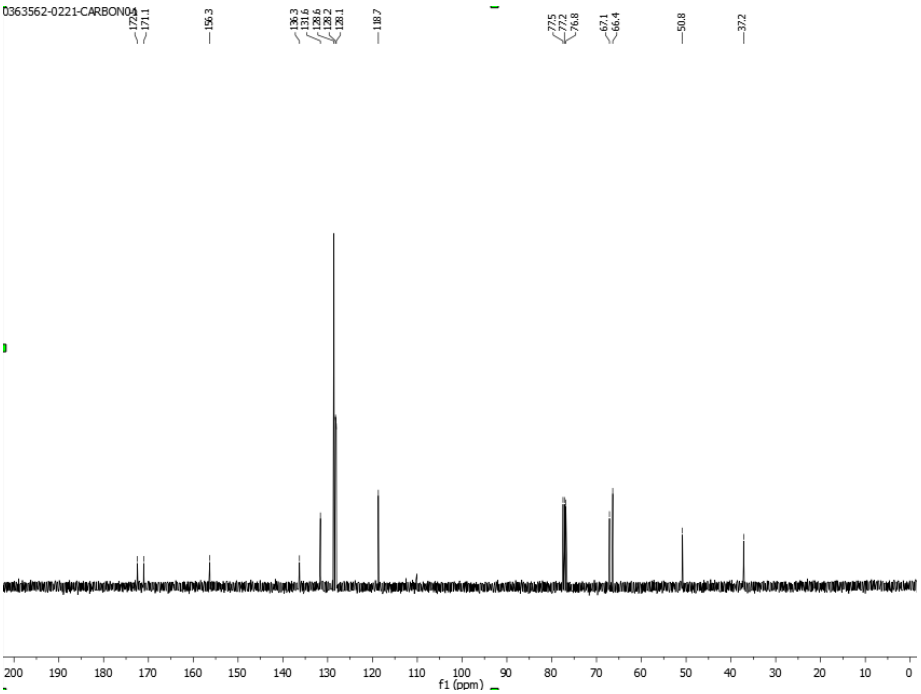
148

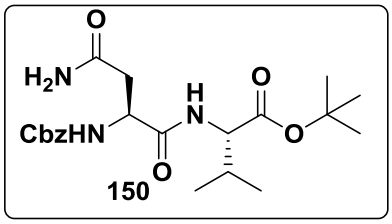

0376796-0216-PROTON02
f1 (ppm)

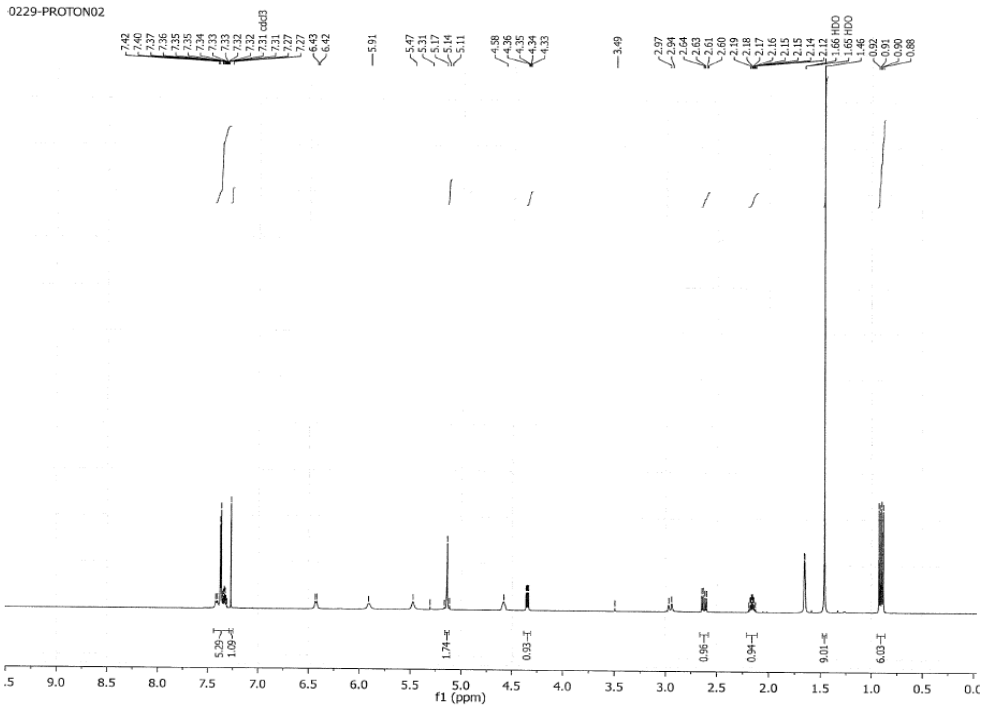

0376796-0216-CARBON01
f1 (ppm)

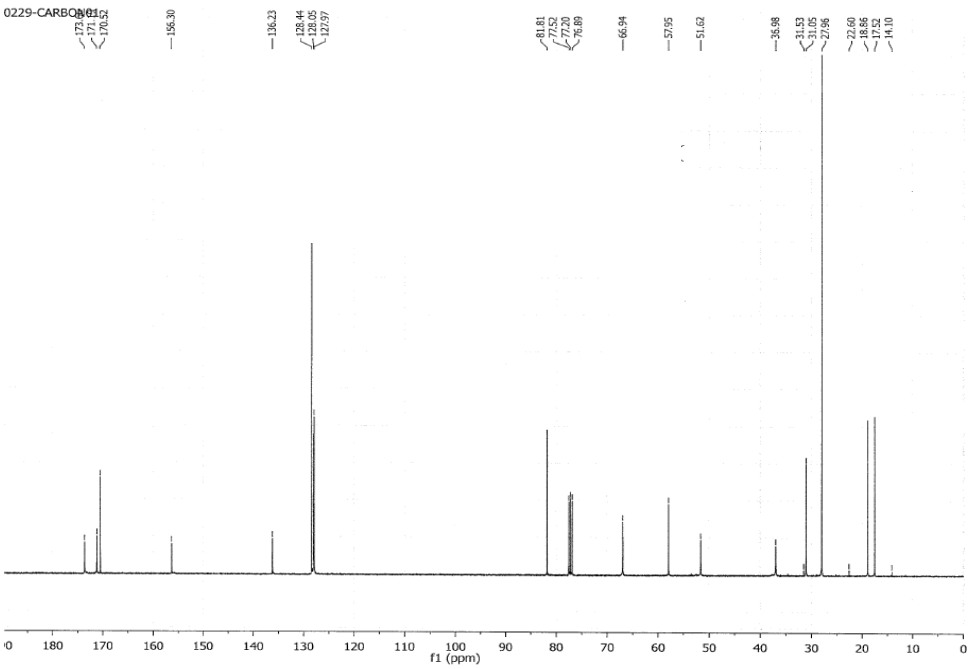

O
H2N
CbzHN
O
O
149

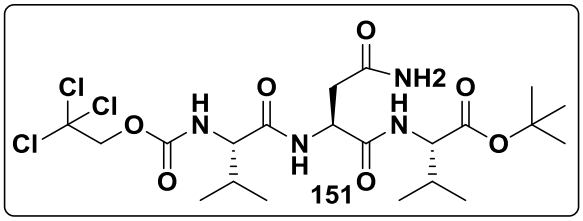

0363562-0221-PROTON02
221
f1 (ppm)

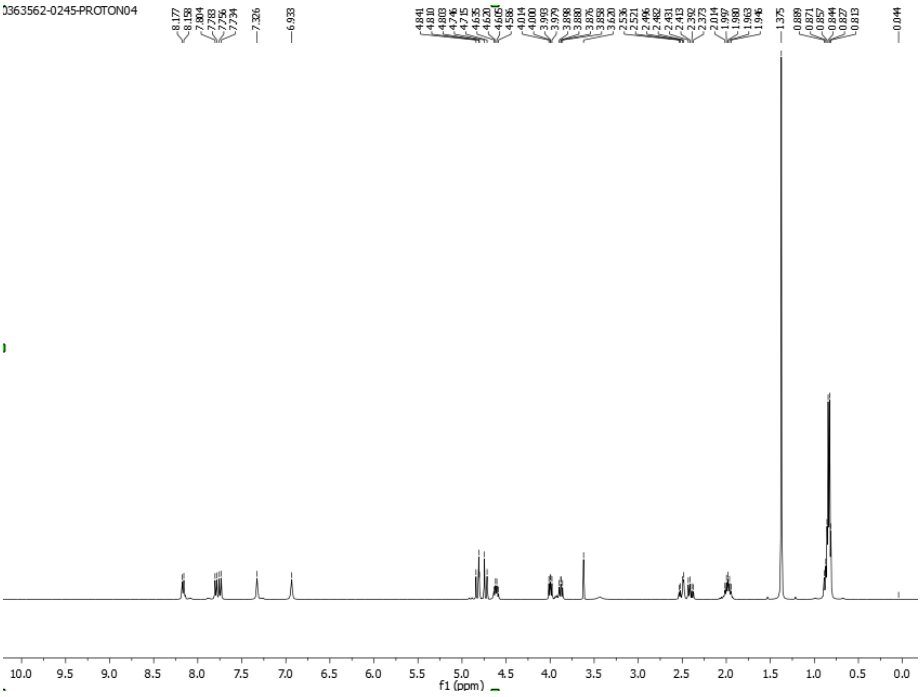

0363562-0221-CARBON04
f1 (ppm)

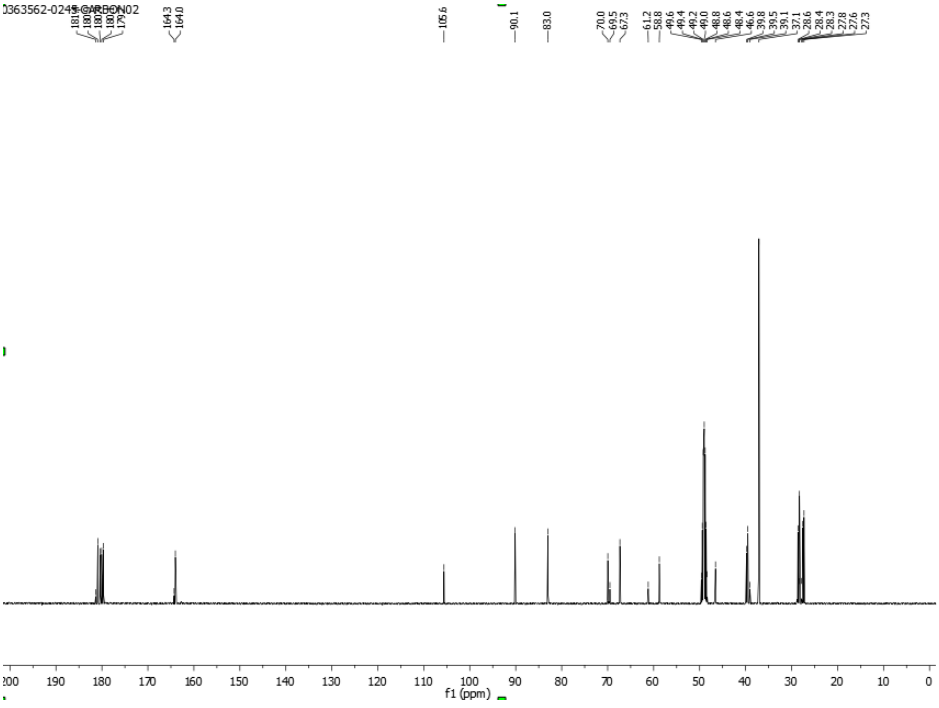

O
H2N
CbzHN
H
N
O
O
O
O
150

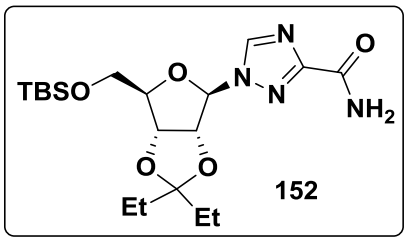

0229-PROTON02
f1 (ppm)

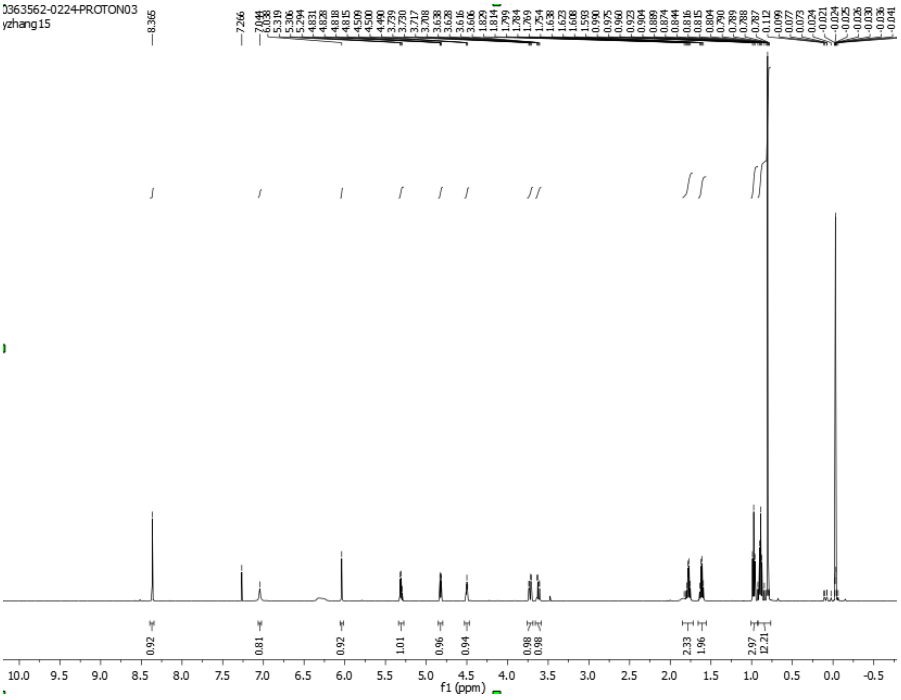

0229-CARBON01
f1 (ppm)

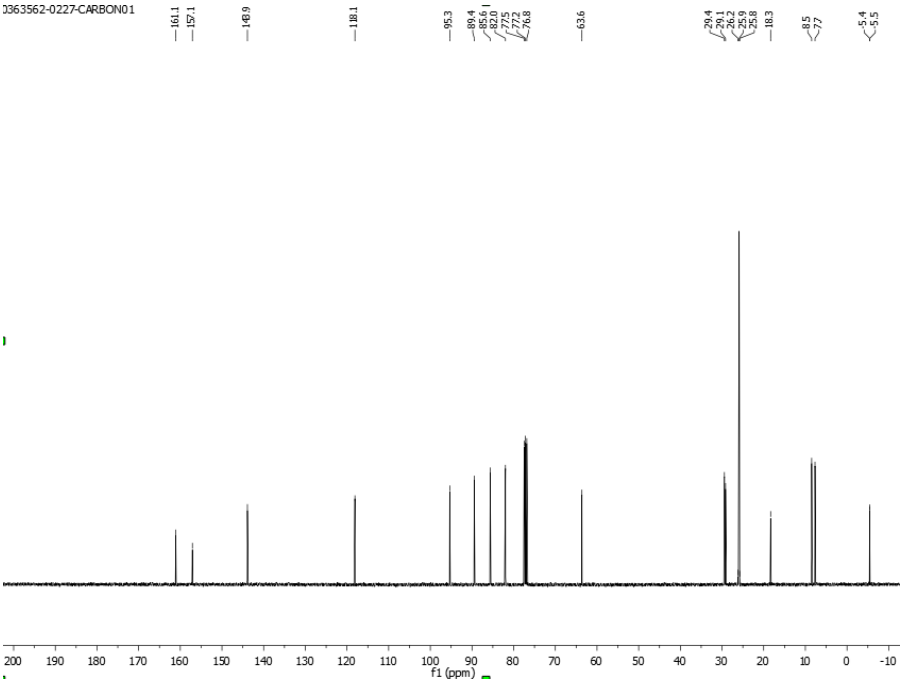

Cl
Cl
Cl
O
O
H
N
O
N
H
O
NH2
H
N
O
O
O
O
151

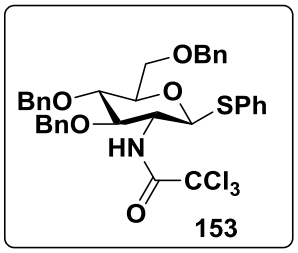

0363562-0245-PROTON04
f1 (ppm)

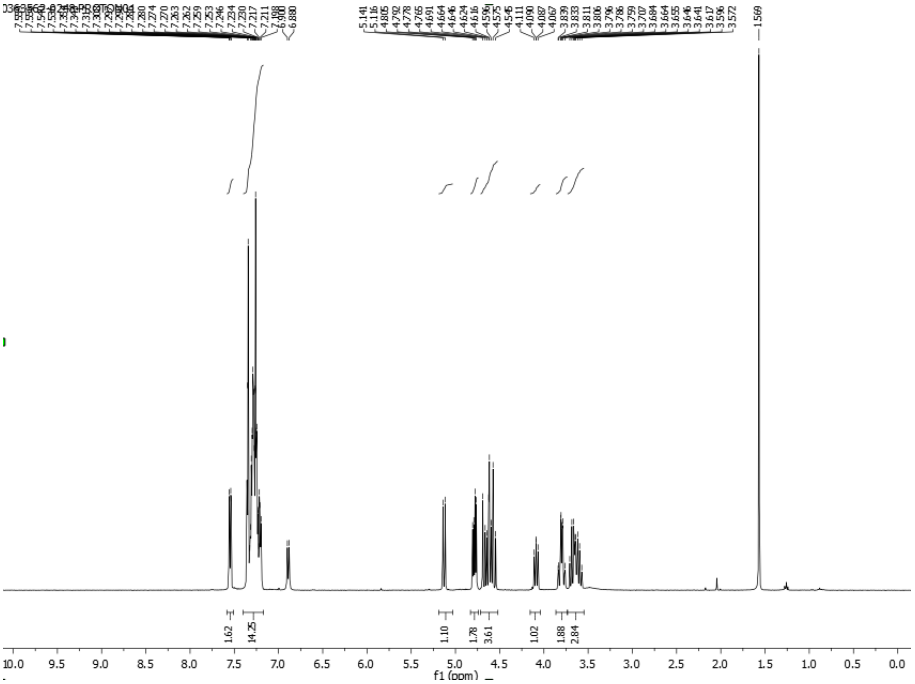

0363562-0245-CARBON02
f1 (ppm)

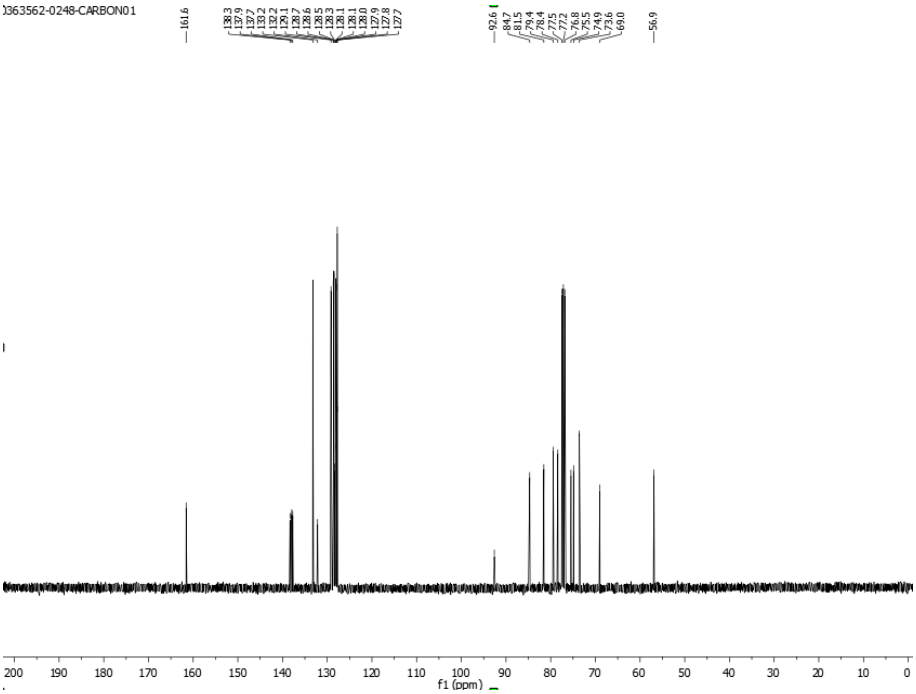

TBSO
O
N
N
N
O
NH2
O
O
Et
Et
152

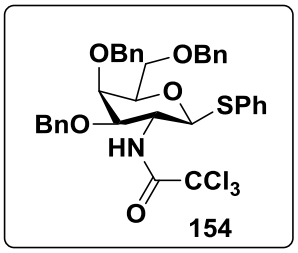

0363562-0224-PROTON03
yzhang15
f1 (ppm)


0363562-0227-CARBON01
f1 (ppm)

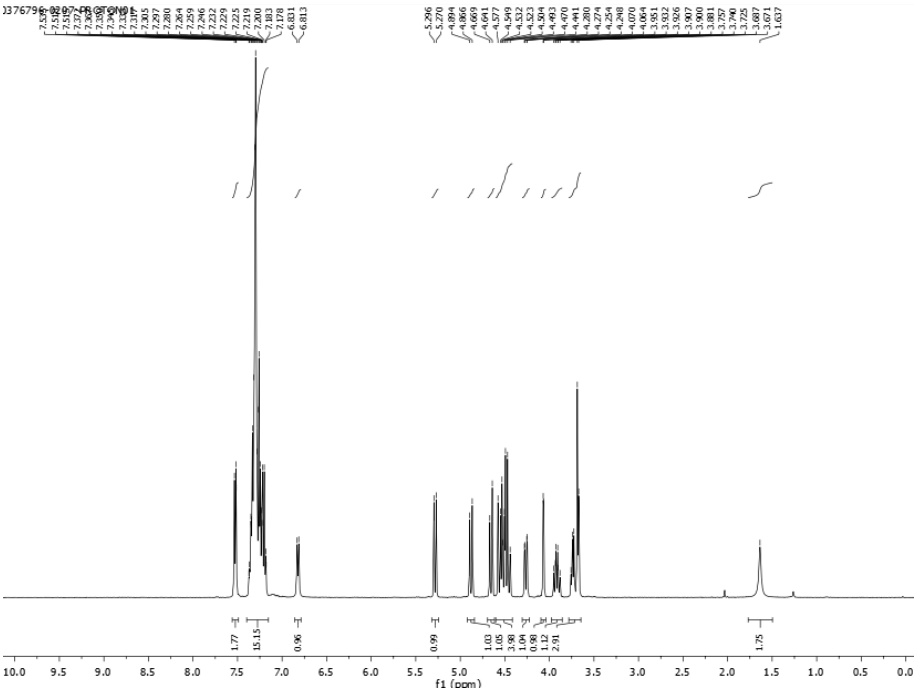

OBn
O
BnO
SPh
BnO
HN
CCl3
O
153

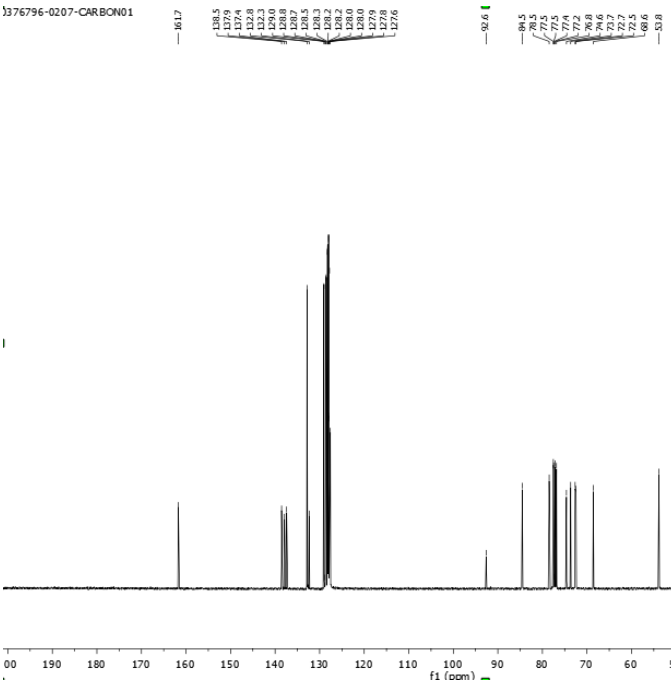


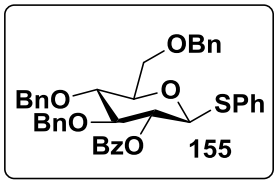


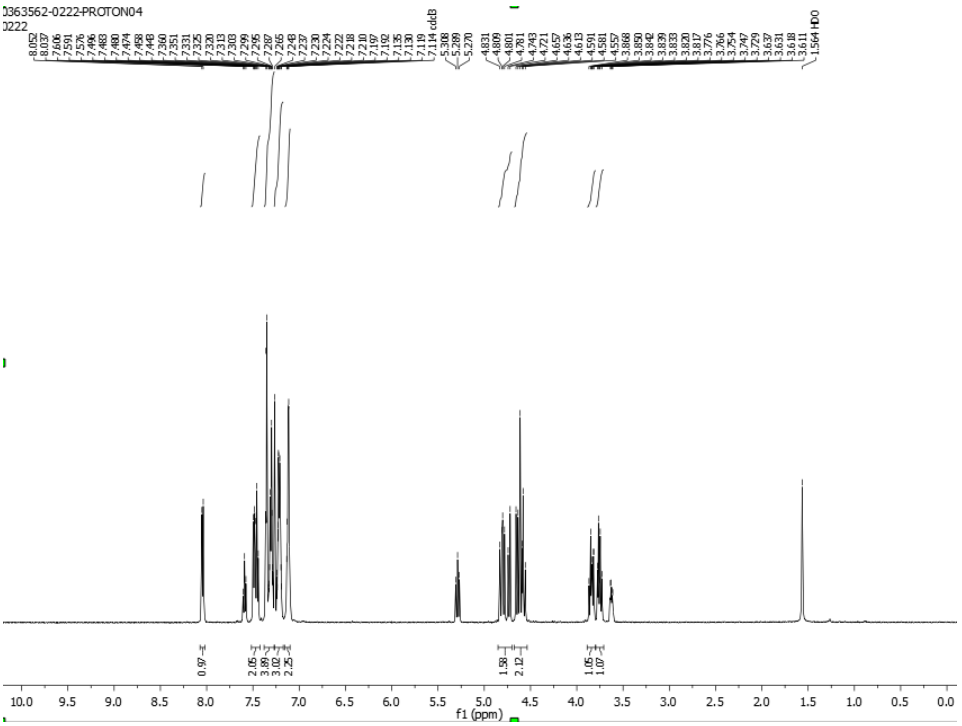


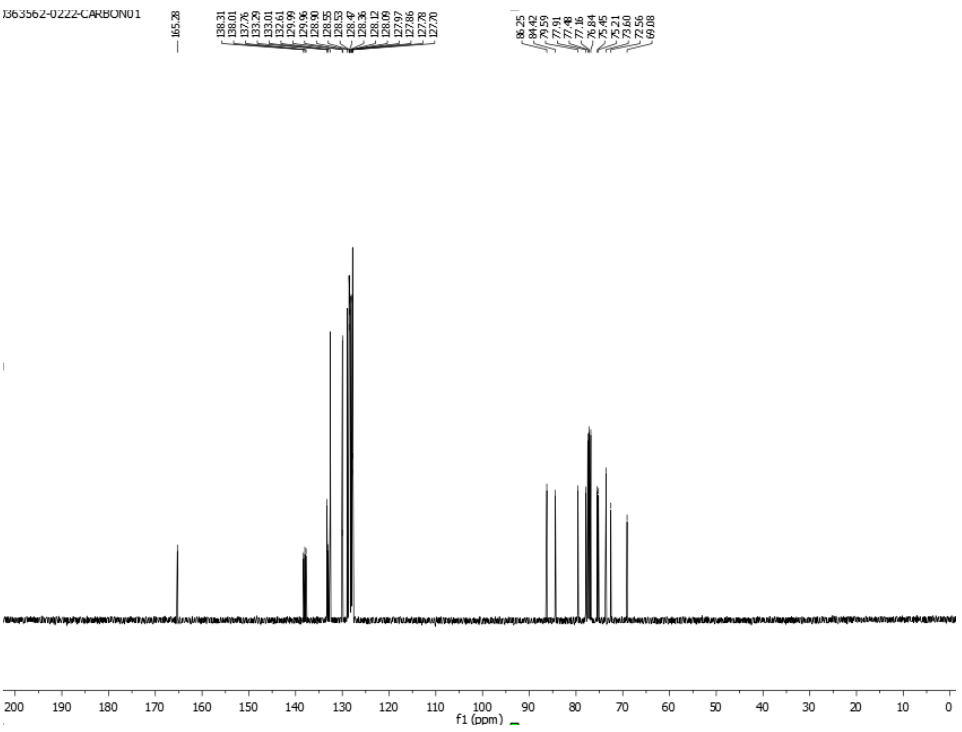
154

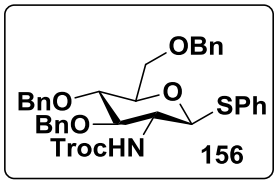


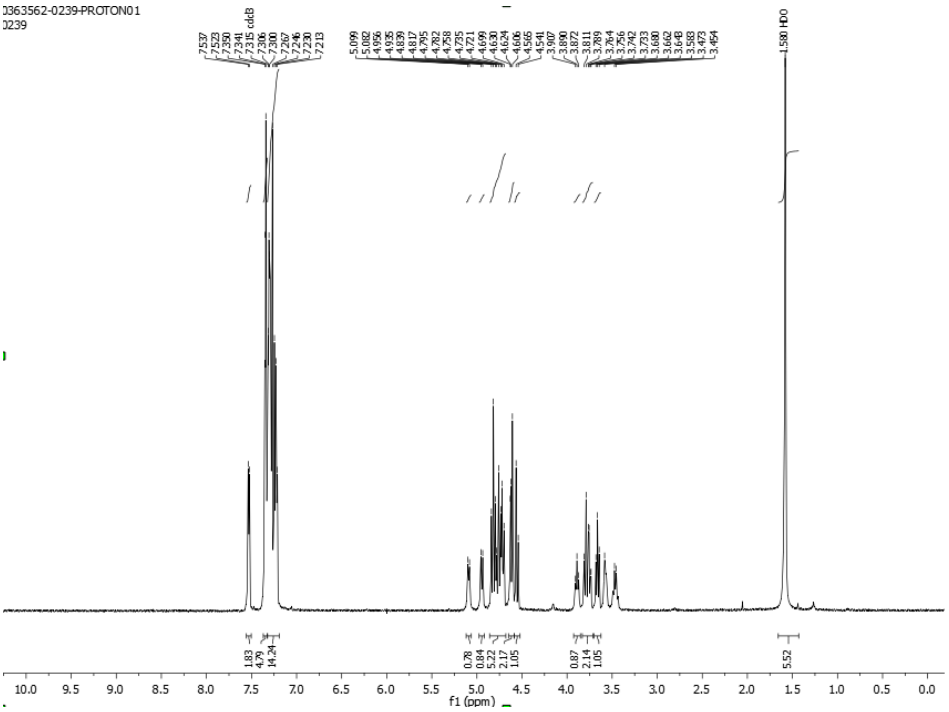


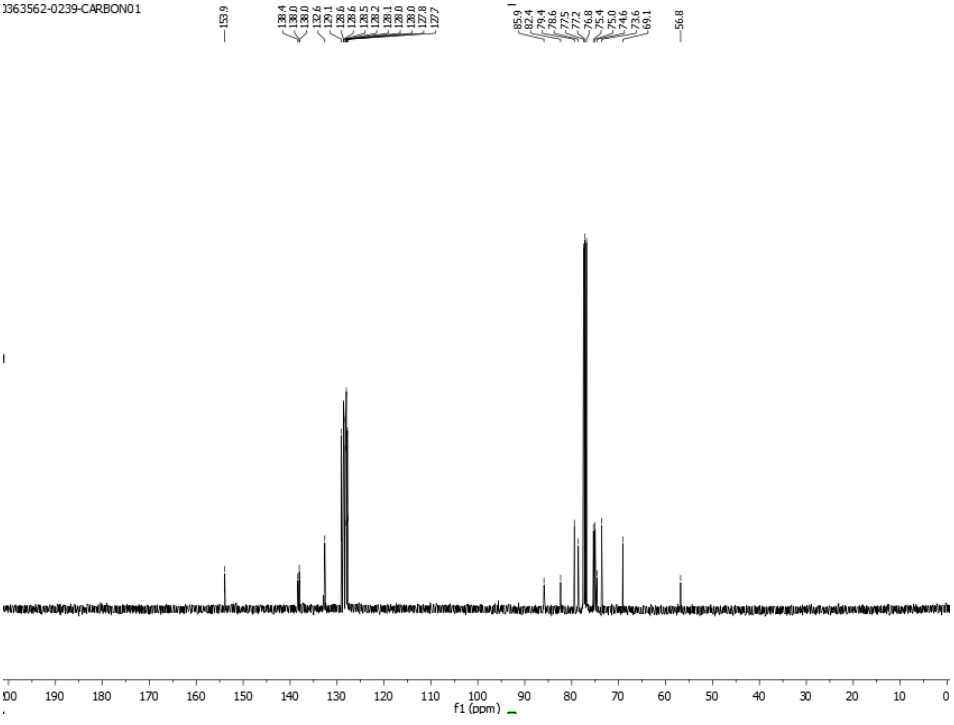

OBn
BnO
O
SPh
BnO
BzO
155

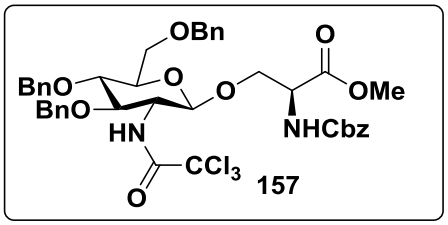

0363562-0222-PROTON04
0222
f1 (ppm)

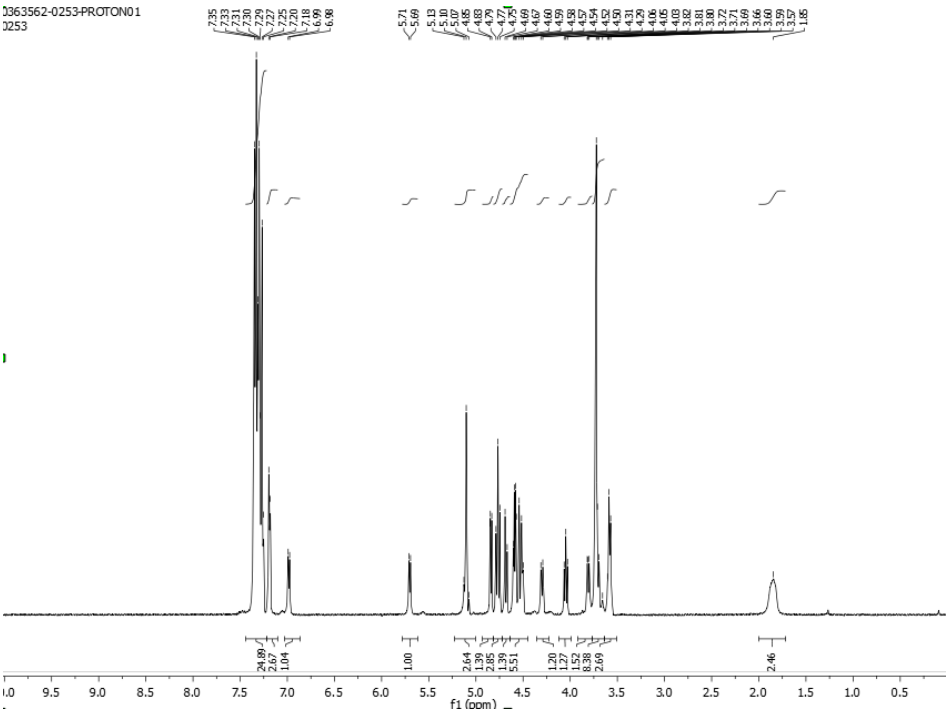

0363562-0222-CARBON01
f1 (ppm)

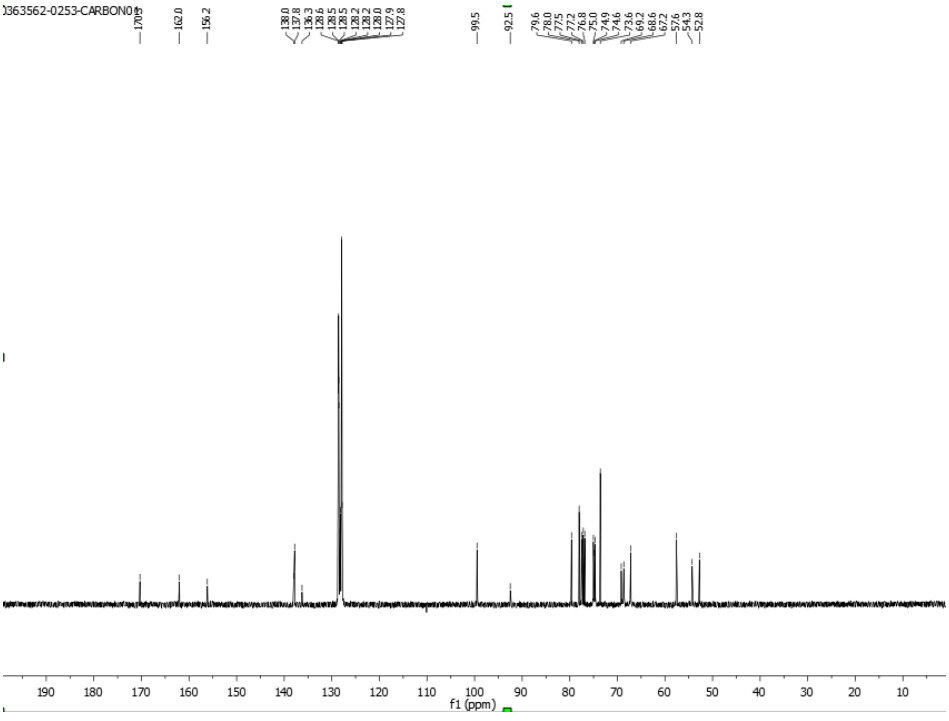

OBn
BnO
O
SPh
BnO
TrocHN
156

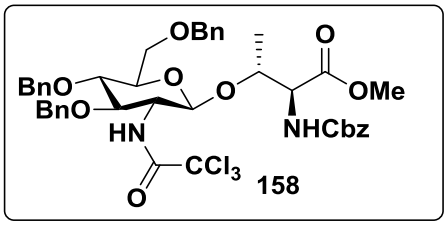

0363562-0239-PROTON01
0239
f1 (ppm)

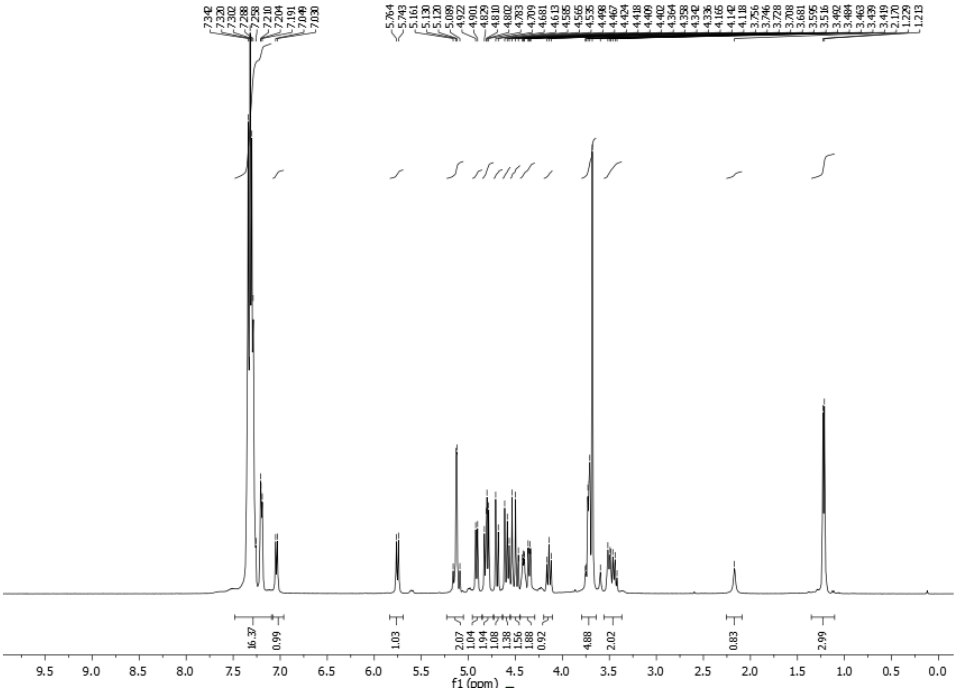

0363562-0239-CARBON01
f1 (ppm)

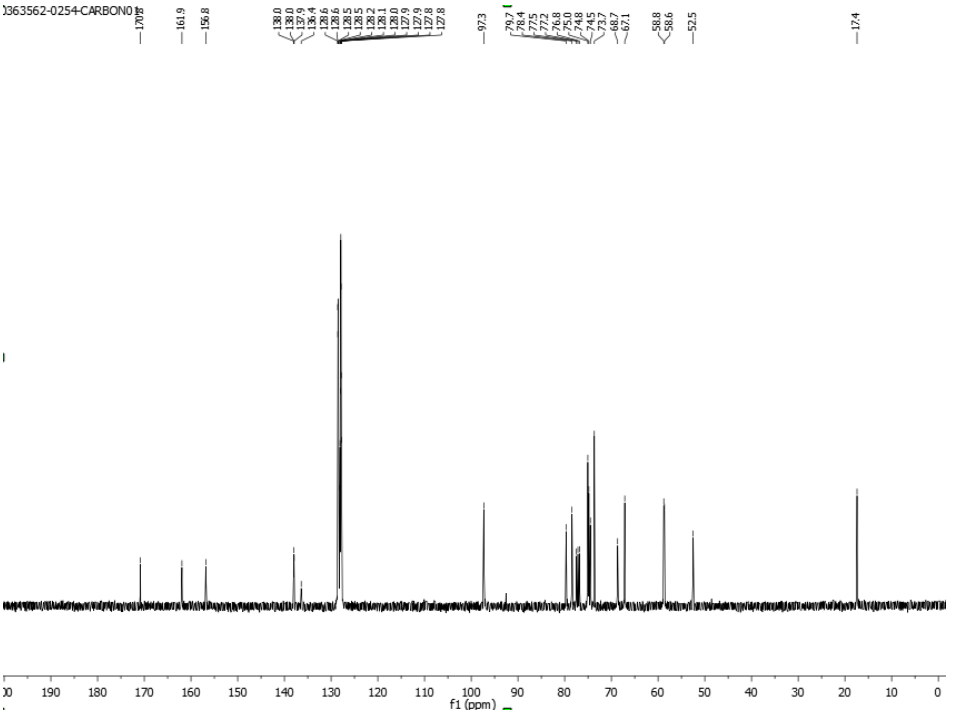

OBn
O
BnO
O
O
OMe
BnO
HN
NHCbz
CCl3
O
157

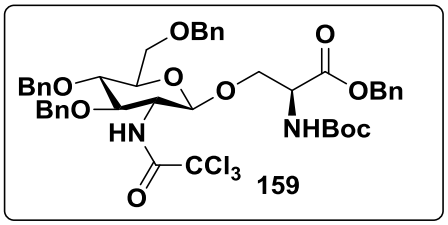

0363562-0253-PROTON01
0253
f1 (ppm)

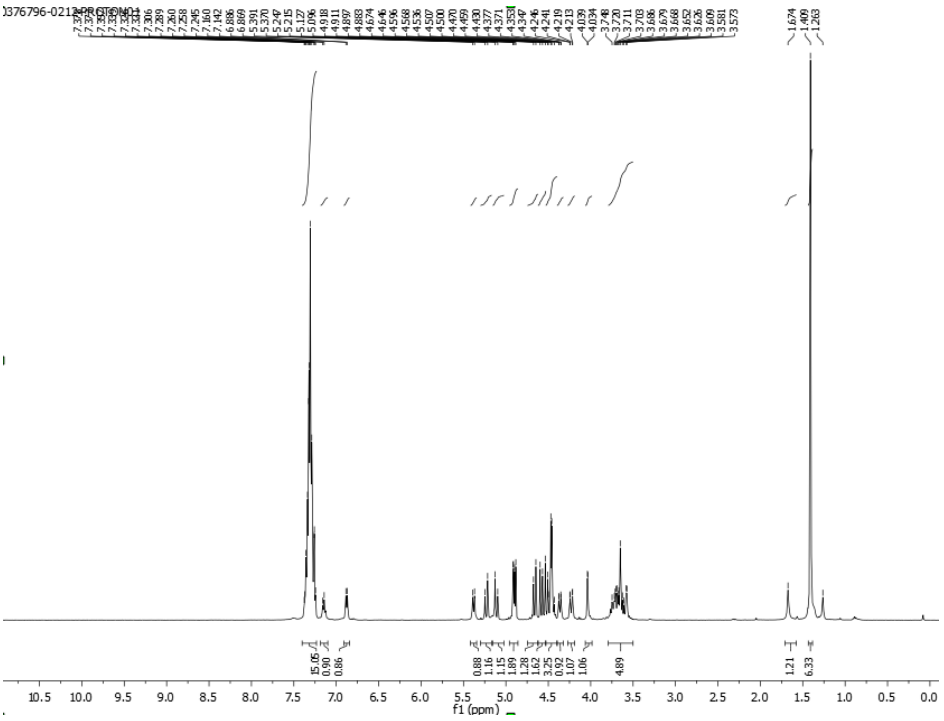

0363562-0253-CARBON01
f1 (ppm)

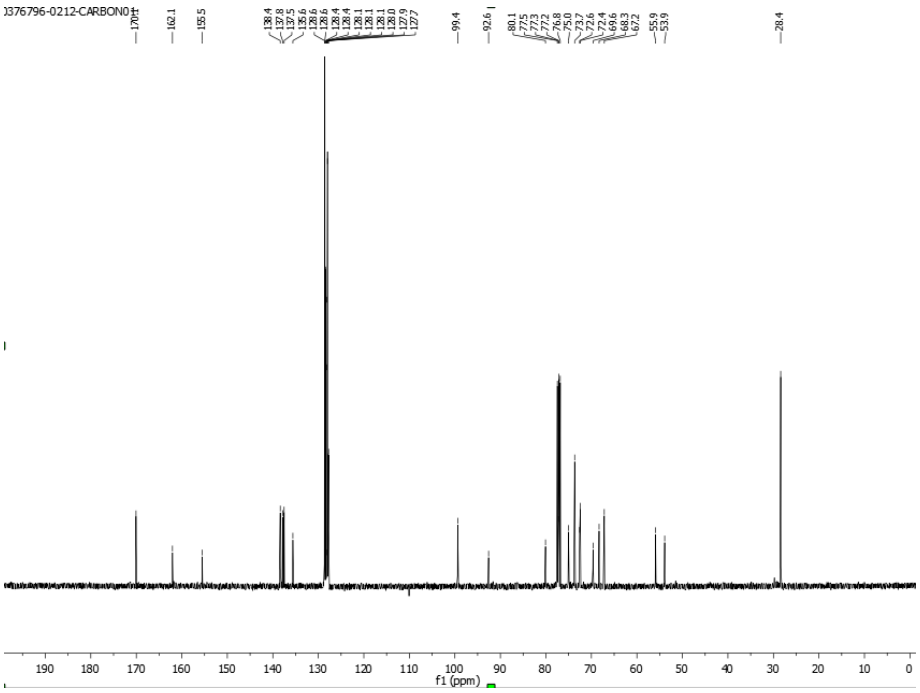

OBn
O
BnO
O
O
OMe
BnO
HN
NHCbz
CCl3
O
158

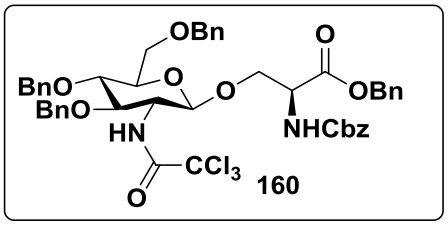


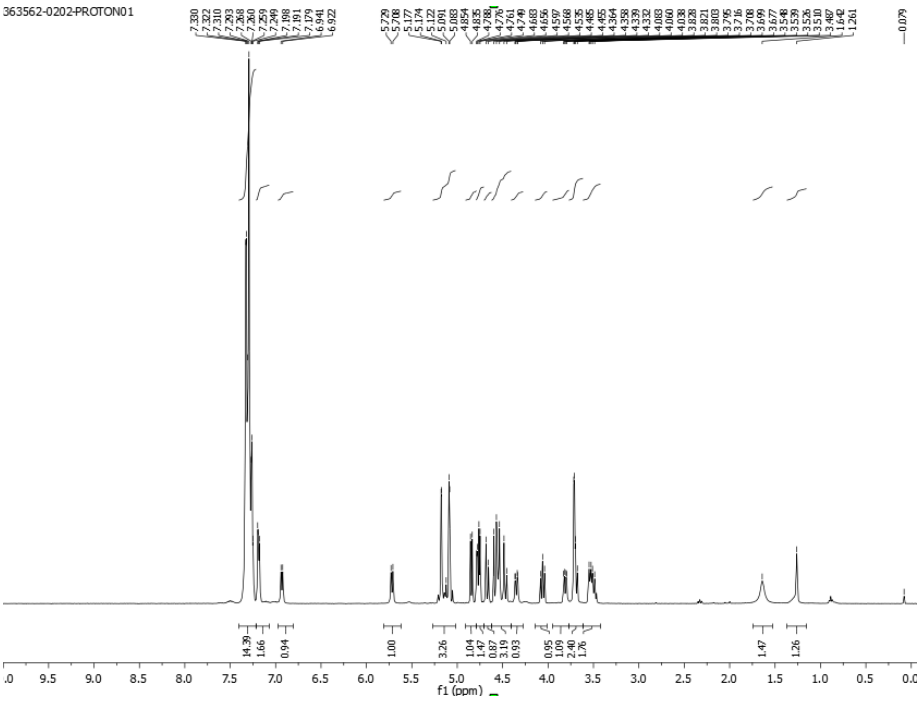


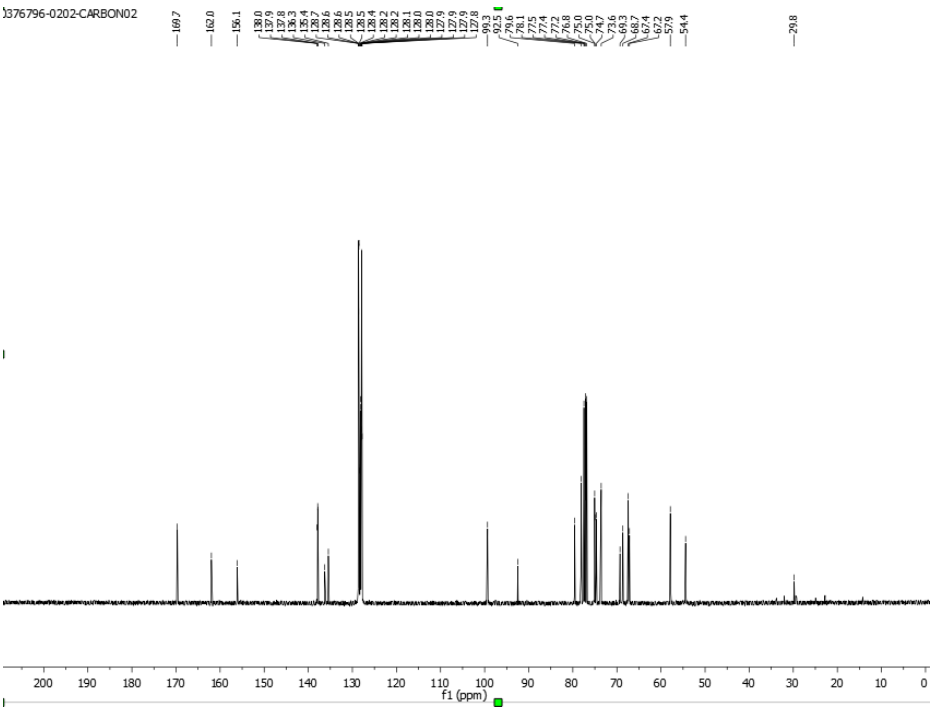

OBn
O
BnO
O
O
OBn
BnO
HN
NHBoc
CCl3
O
159

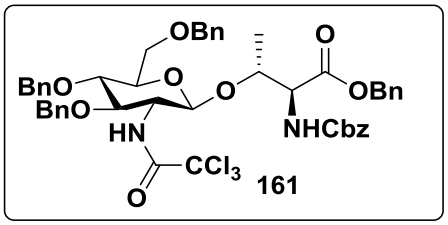

f1 (ppm)

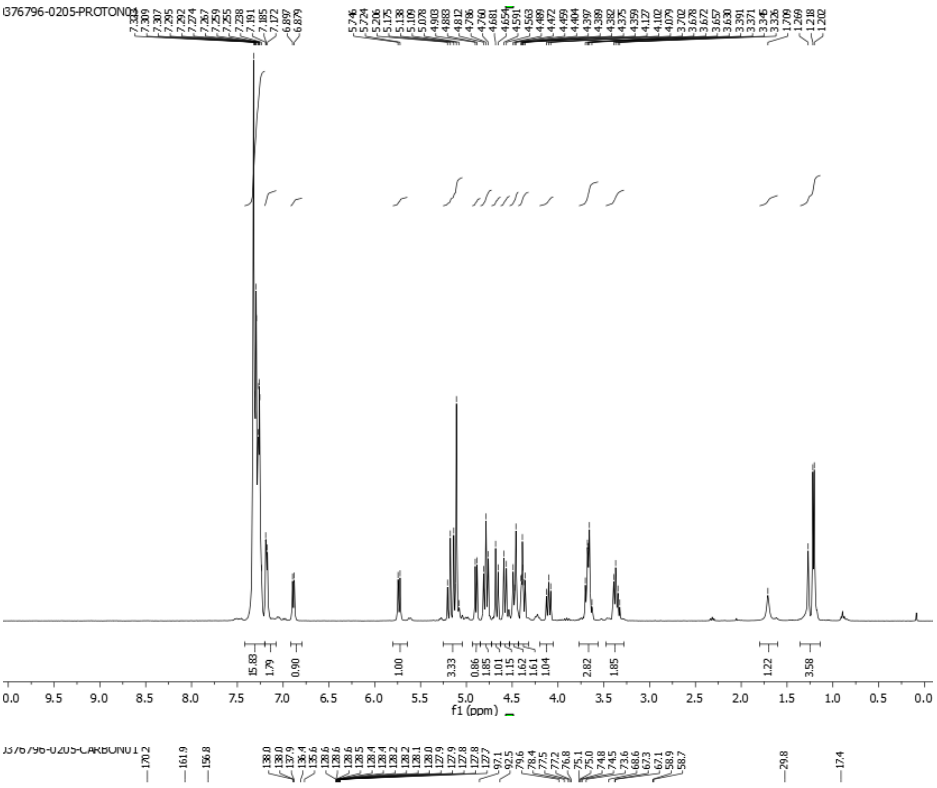

f1 (ppm)

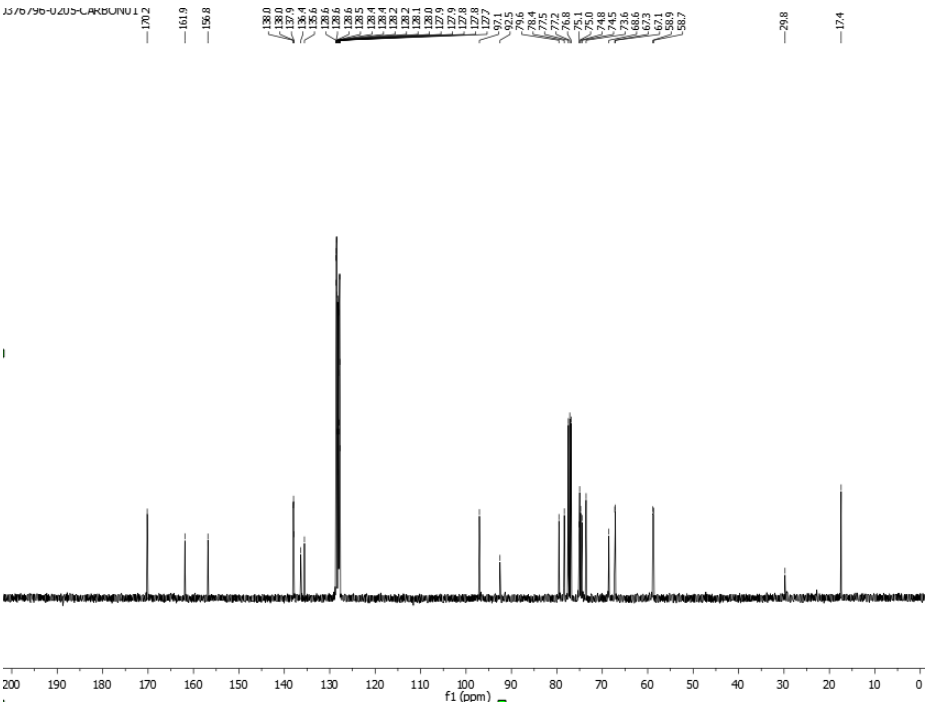

OBn
O
BnO
O
O
OBn
BnO
HN
NHCbz
CCl3
O
160

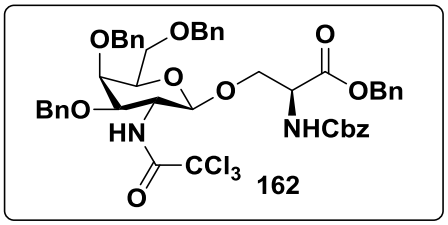

363562-0202-PROTON01
f1 (ppm)

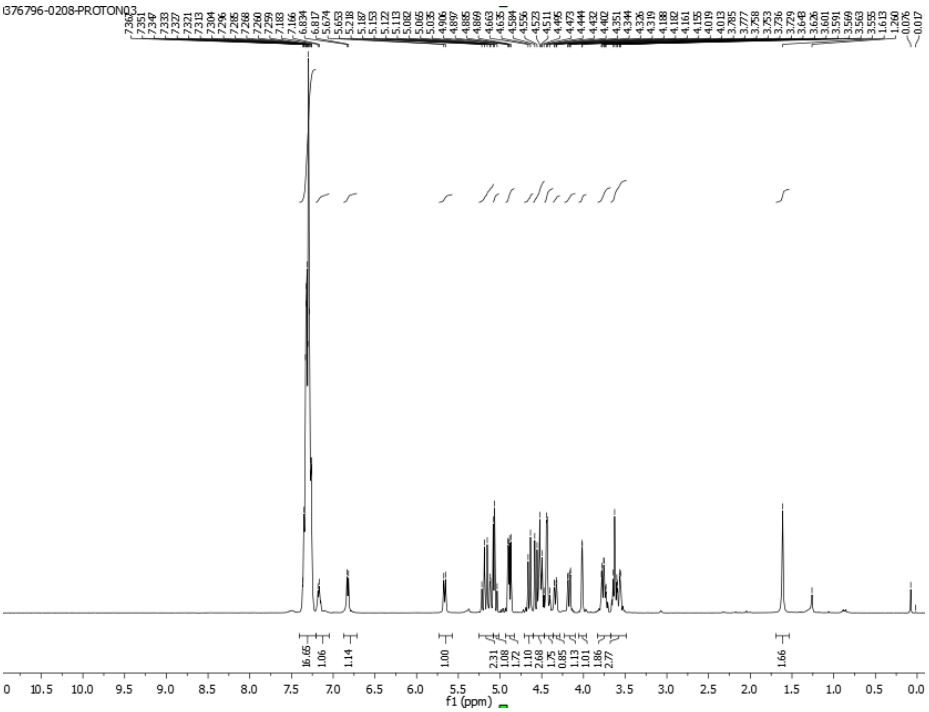

376796-0202-CARBON02
f1 (ppm)

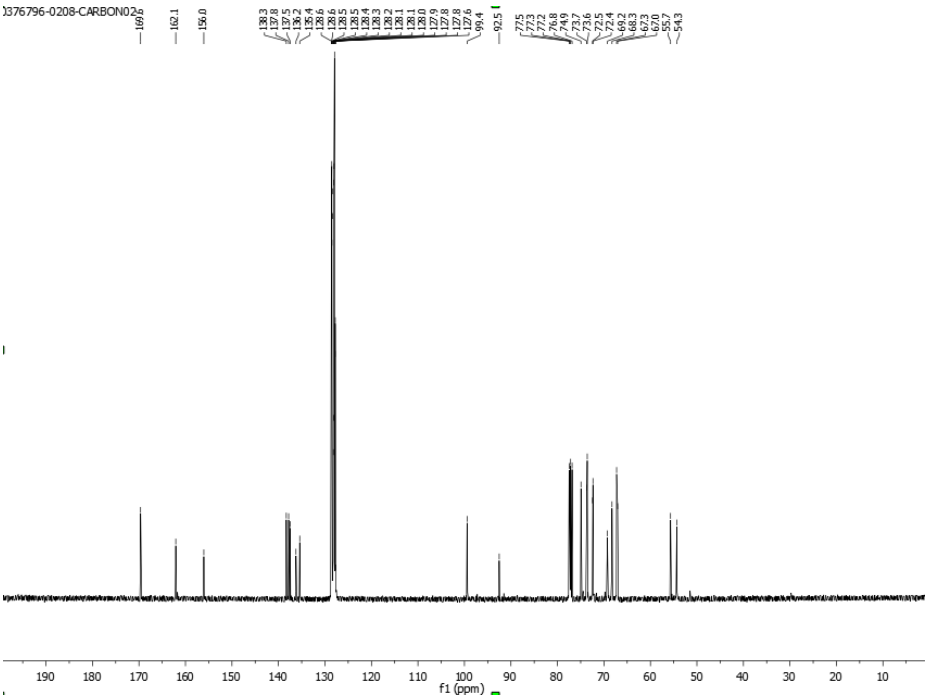

OBn
O
BnO
O
O
OBn
BnO
HN
NHCbz
CCl3
O
161

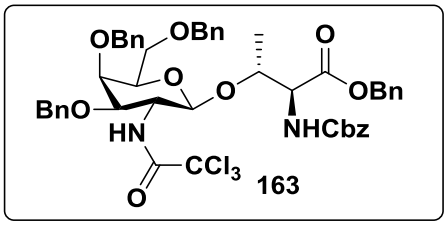

f1 (ppm)

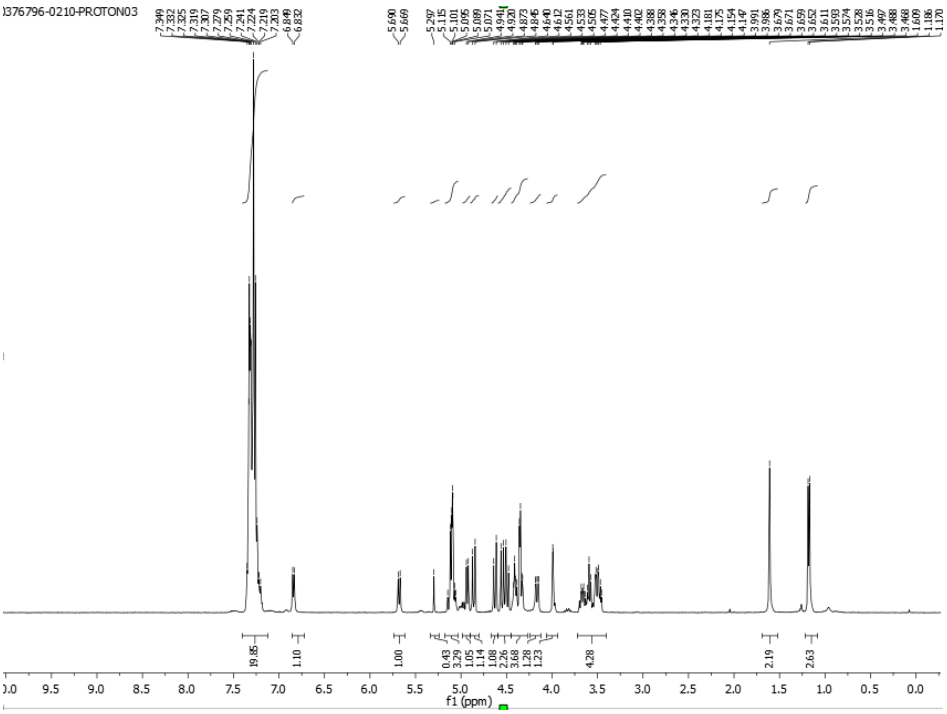

f1 (ppm)

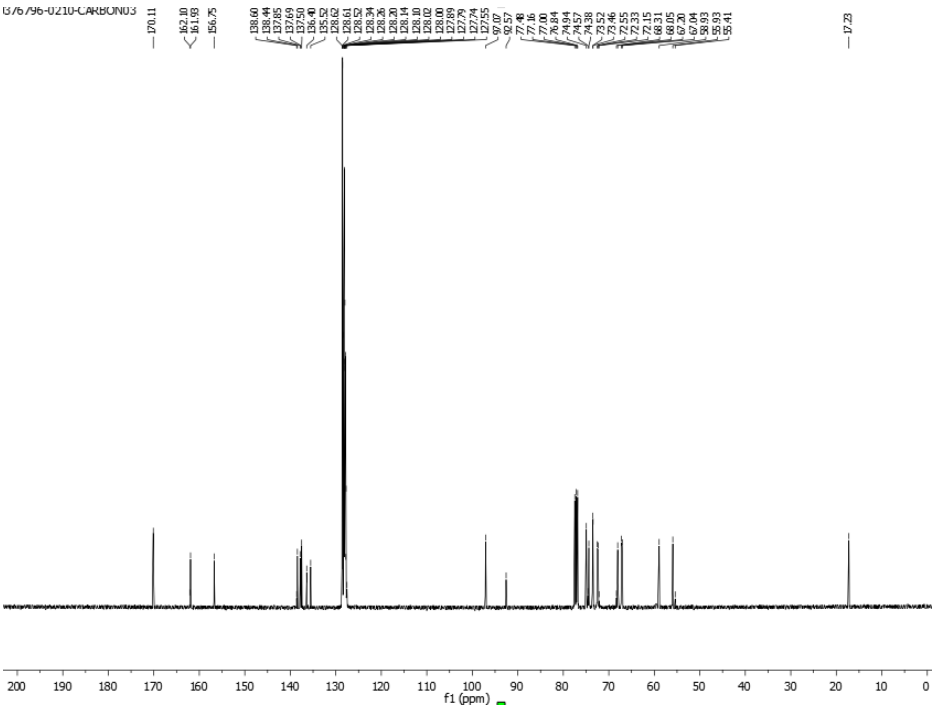

OBn
OBn
O
O
O
OBn
BnO
HN
NHCbz
CCl3
O
162

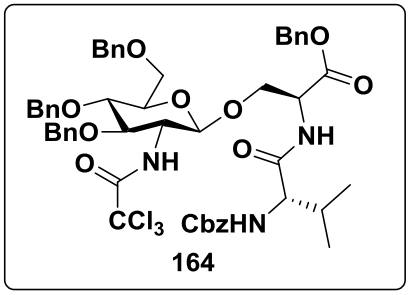

f1 (ppm)


f1 (ppm)

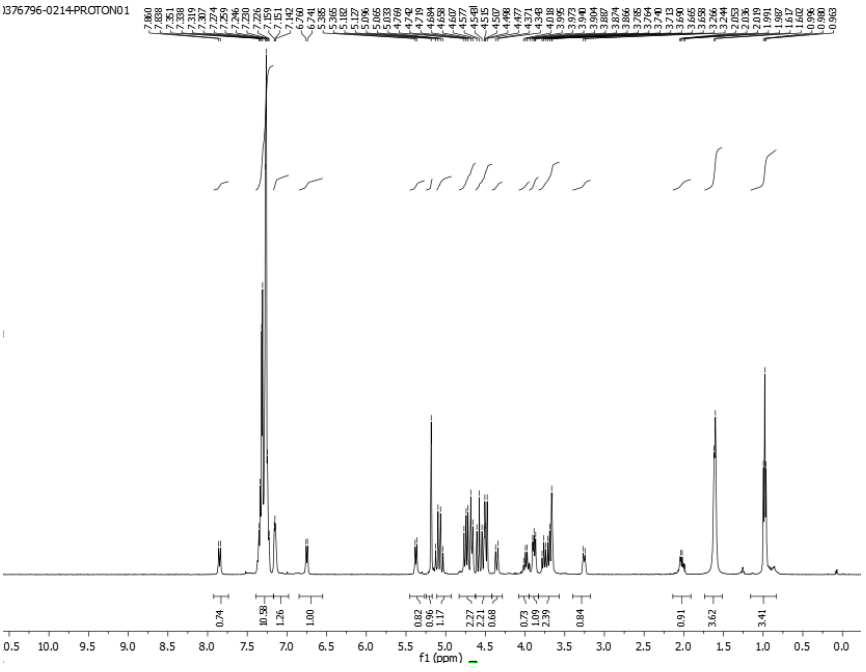

OBn
OBn
O
O
O
OBn
BnO
HN
NHCbz
CCl3
O
163

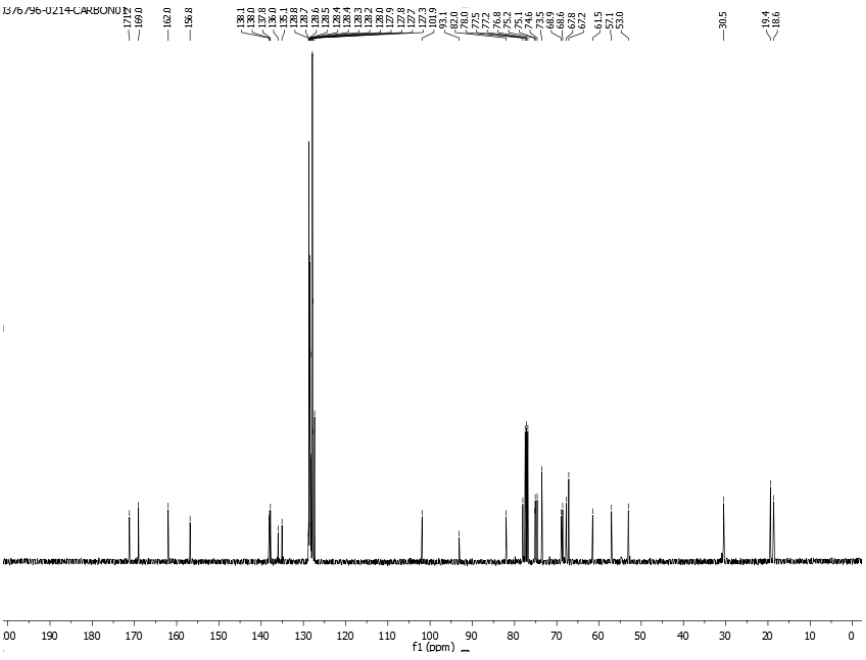

f1 (ppm)

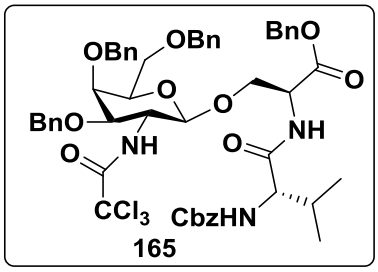

f1 (ppm)



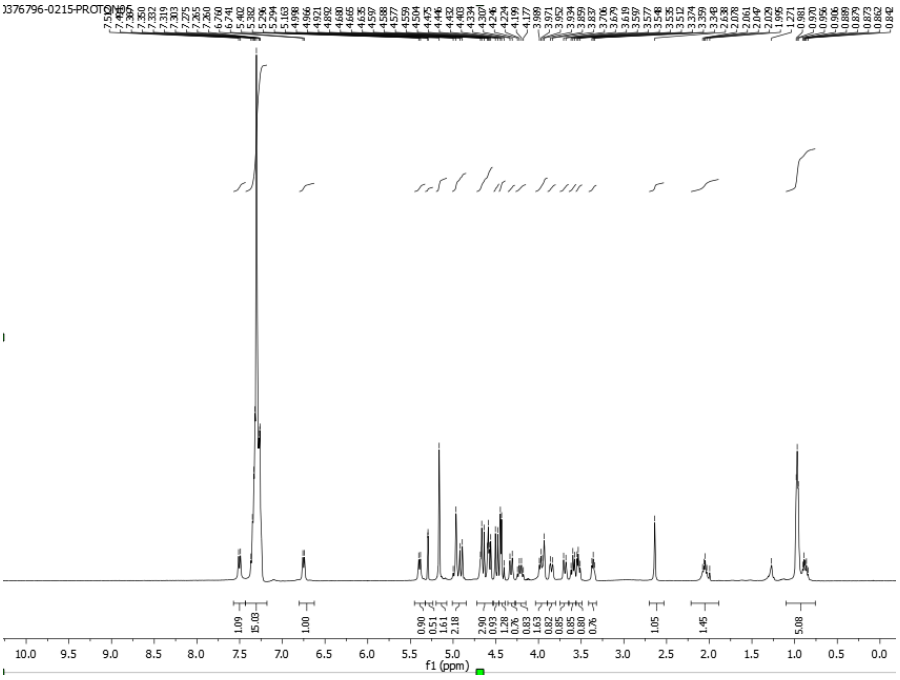
164

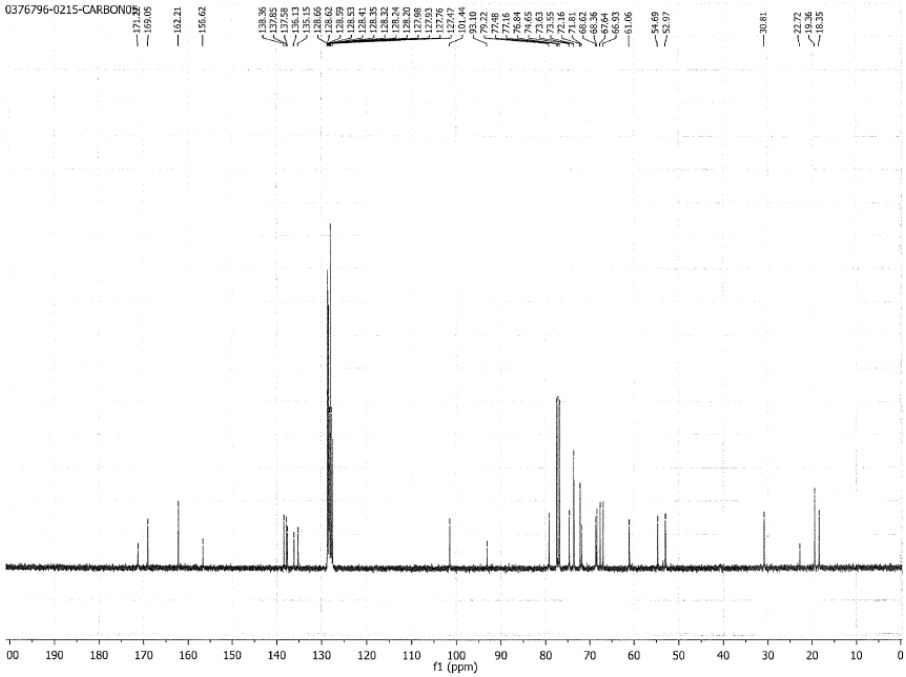


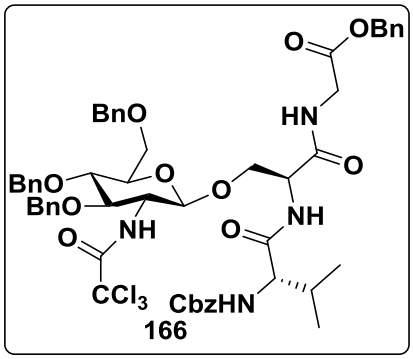



OBn
OBn
BnO
O
O
BnO
NH
O
O
NH
O
CCl3
CbzHN

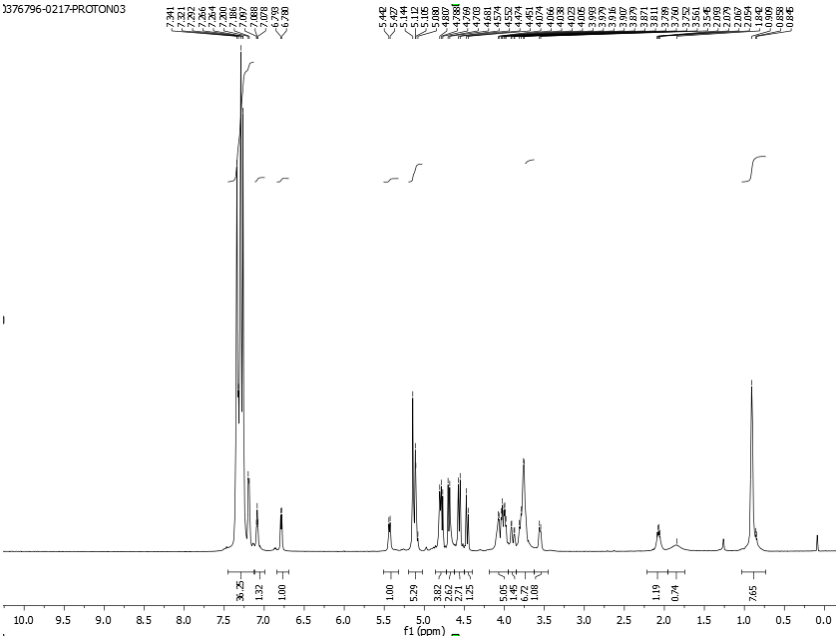
165

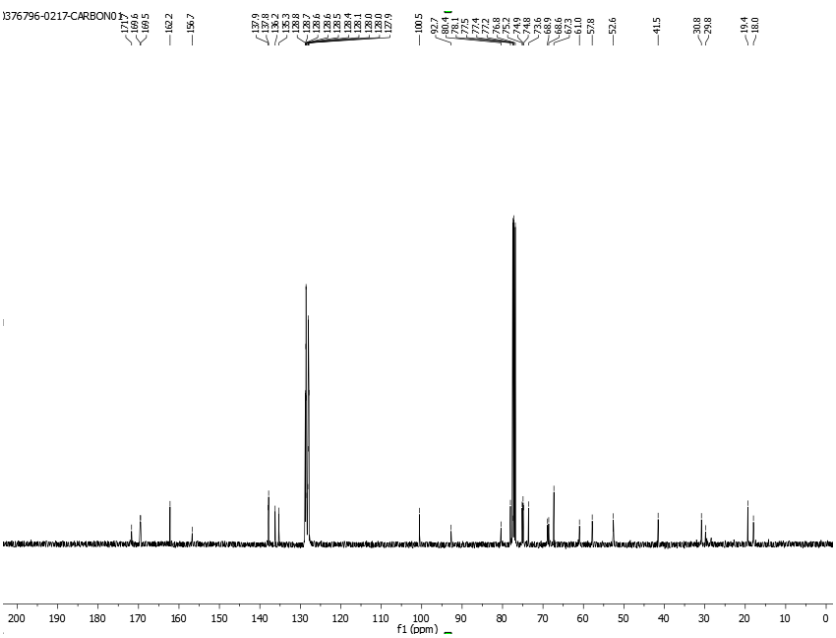

0376796-0215-PROTON05
1.09
15.03
1.00
0.90
0.51
1.14
2.18
2.90
0.93
1.28
0.76
0.82
1.63
0.82
0.85
0.85
0.80
0.76
1.05
1.45
5.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

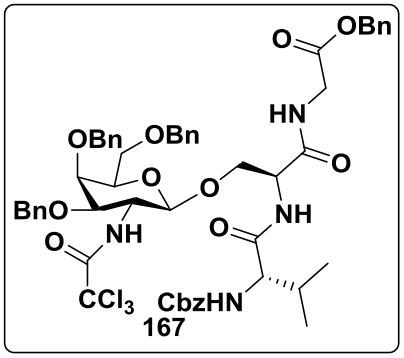

0376796-0215-CARBON05
171.28
169.05
162.21
156.62
138.36
137.85
137.58
136.13
135.15
128.62
128.59
128.53
128.41
128.35
128.32
128.24
128.20
127.98
127.93
127.76
127.47
101.44
80.10
79.22
77.48
77.16
76.84
74.45
73.63
73.55
72.16
71.61
68.67
68.36
67.64
66.93
61.06
54.69
52.97
30.81
22.72
19.36
18.35
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



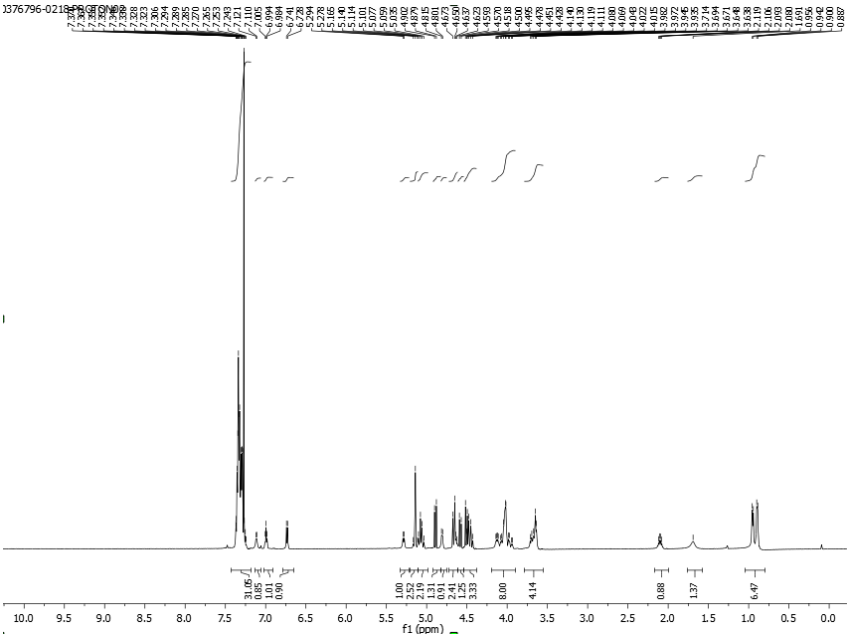
166

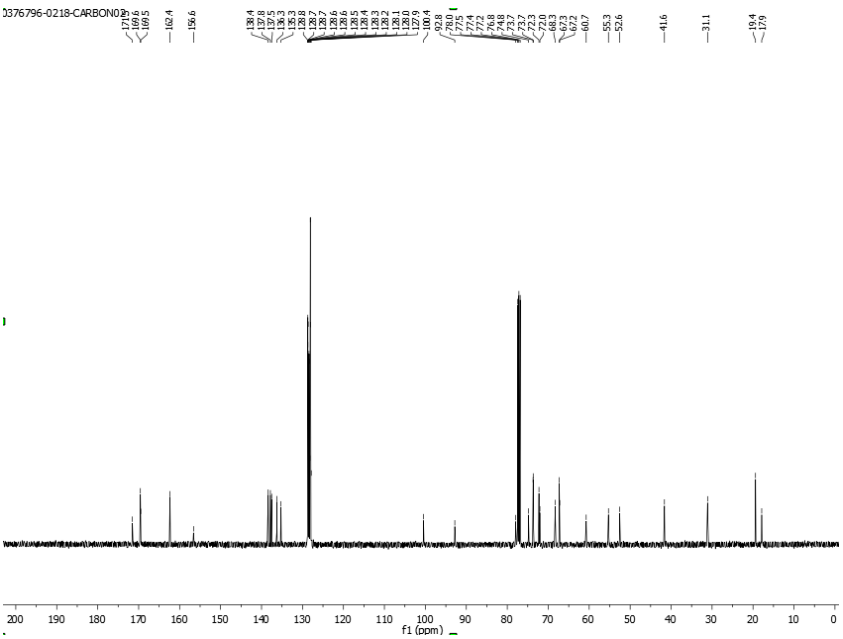


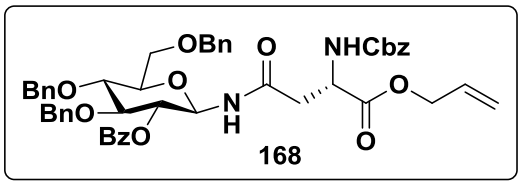


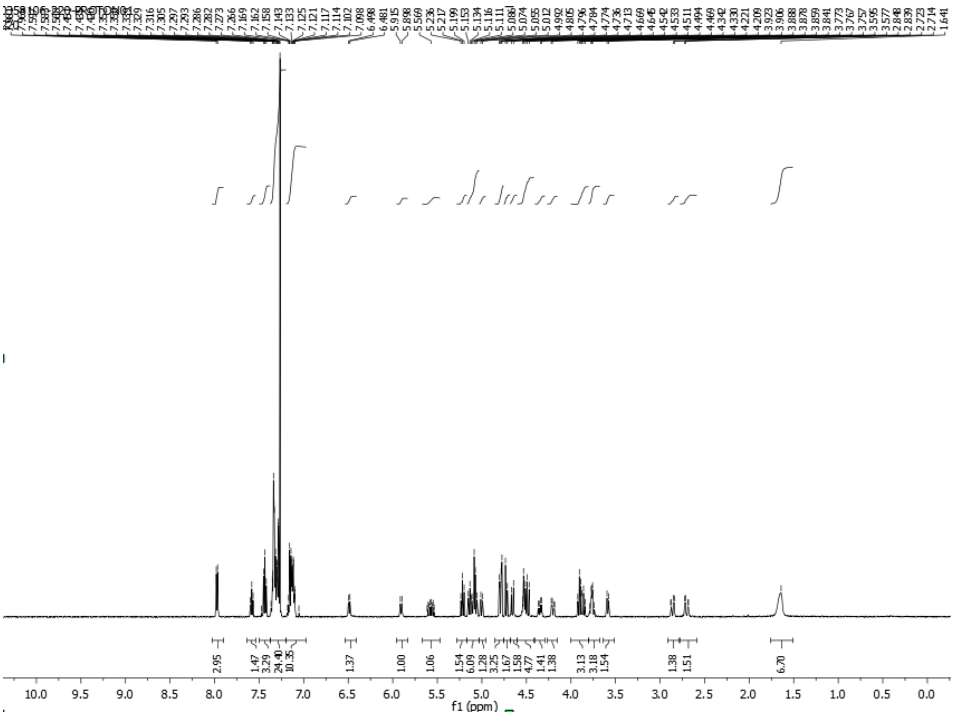

OBn
O
HN
OBn
OBn
O
O
O
BnO
NH
NH
O
O
CCl3
CbzHN

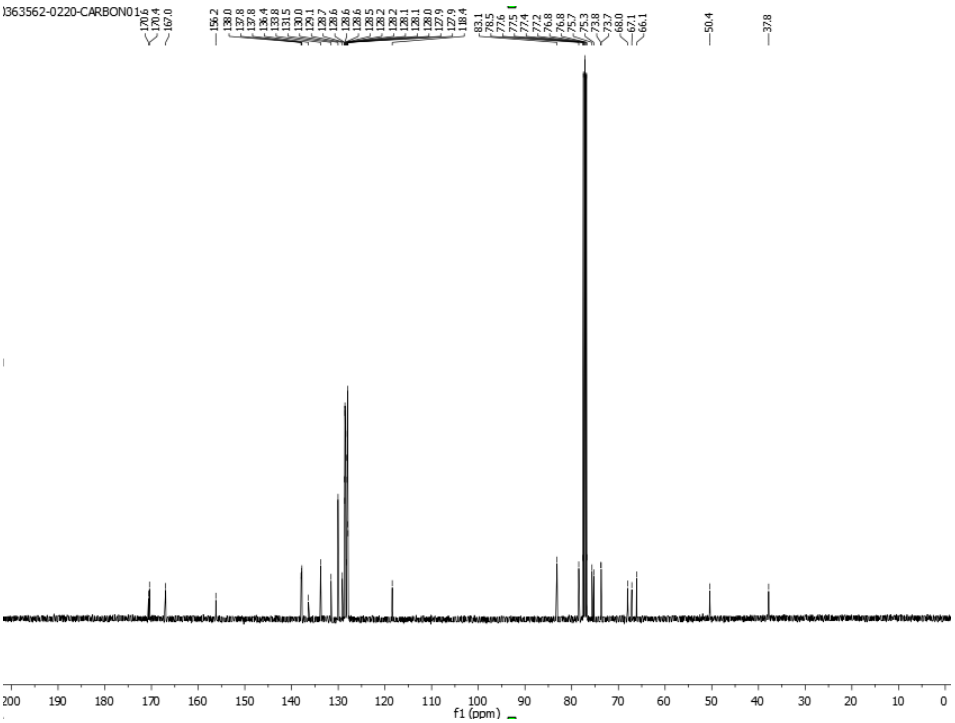
167

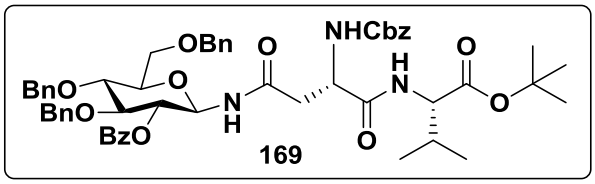

0376796-0218-PROTON01
f1 (ppm)

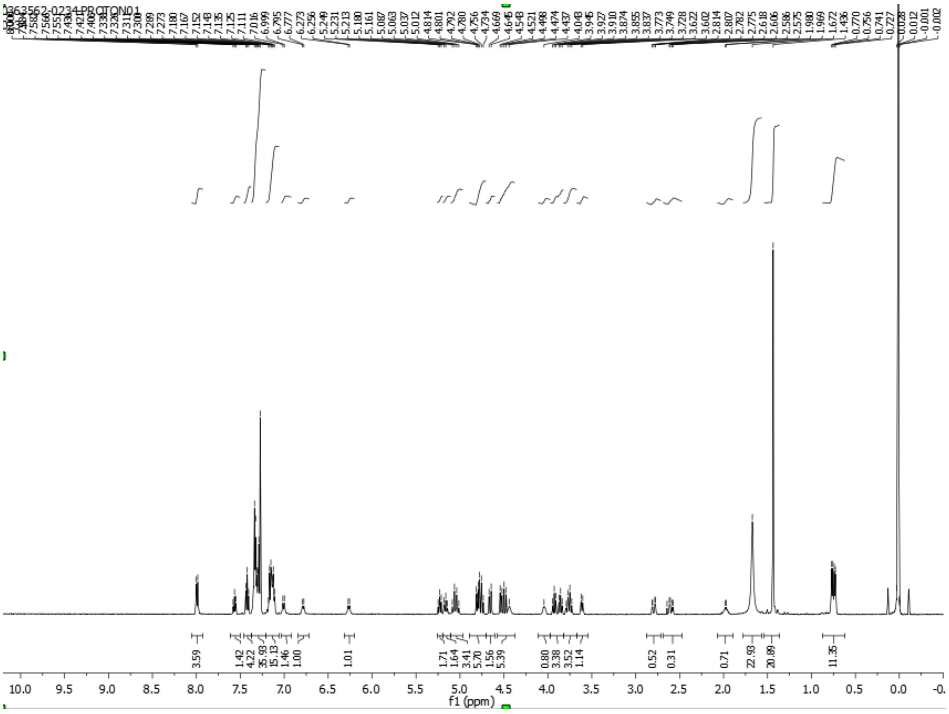

0376796-0218-CARBON01
f1 (ppm)

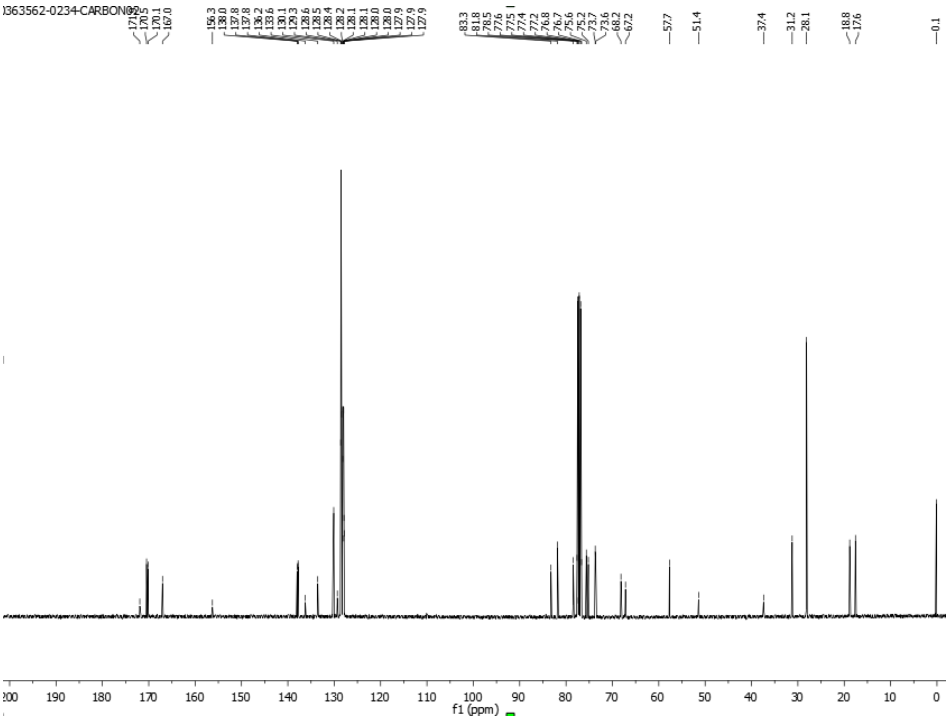

OBn
O
NHCbz
BnO
O
N
H
O
BnO
BzO
O
168

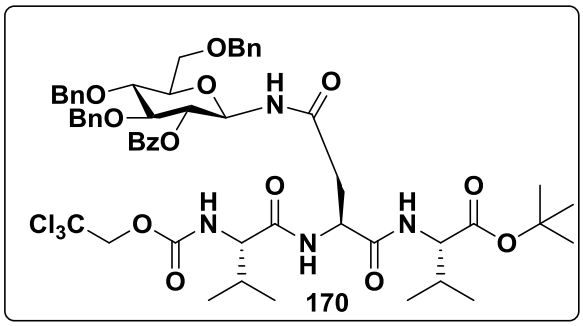

2.95
1.47
3.29
24.40
10.35
1.37
1.00
1.06
1.54
1.68
1.28
3.25
1.67
1.58
4.77
4.47
1.38
3.13
3.18
1.54
1.38
1.51
6.70
f1 (ppm)

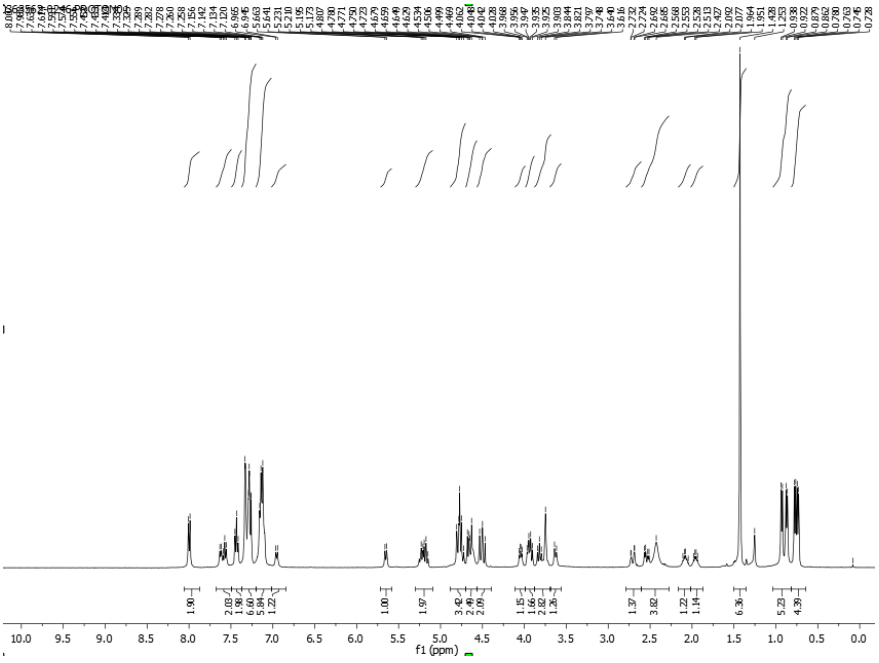

170.6
170.4
167.0
156.2
138.0
137.8
137.8
136.4
135.8
131.5
130.0
129.1
128.7
128.6
128.6
128.6
128.5
128.2
128.2
128.1
128.1
128.0
127.9
127.9
118.4
83.1
78.5
77.6
77.5
77.4
77.2
76.8
76.8
75.7
75.3
73.8
73.7
68.0
67.1
66.1
50.4
37.8
f1 (ppm)

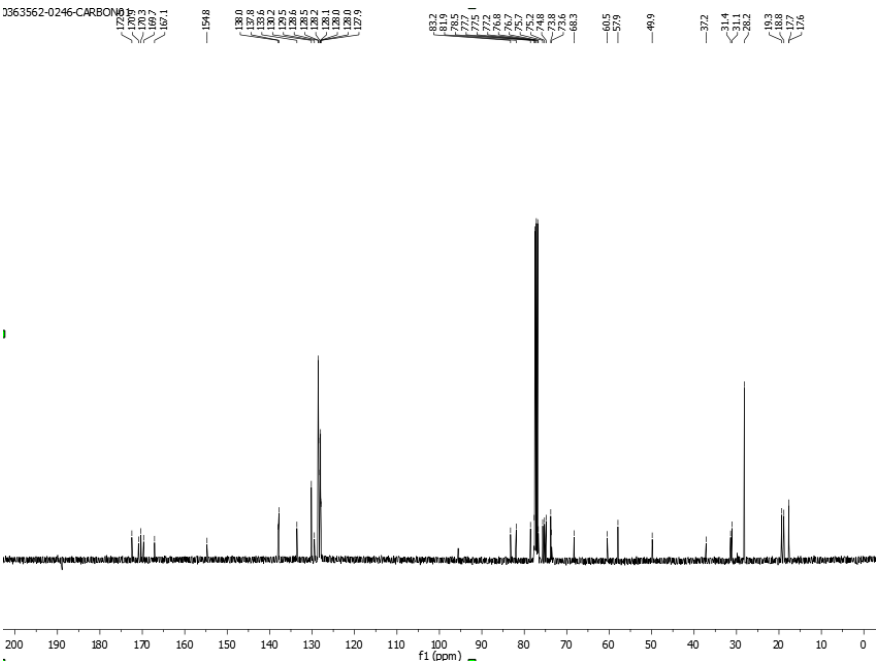

OBn
O
NHCbz
H
N
O
BnO
O
N
H
O
BnO
O
BzO
169

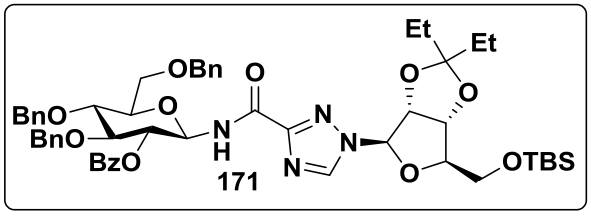

f1 (ppm)


f1 (ppm)

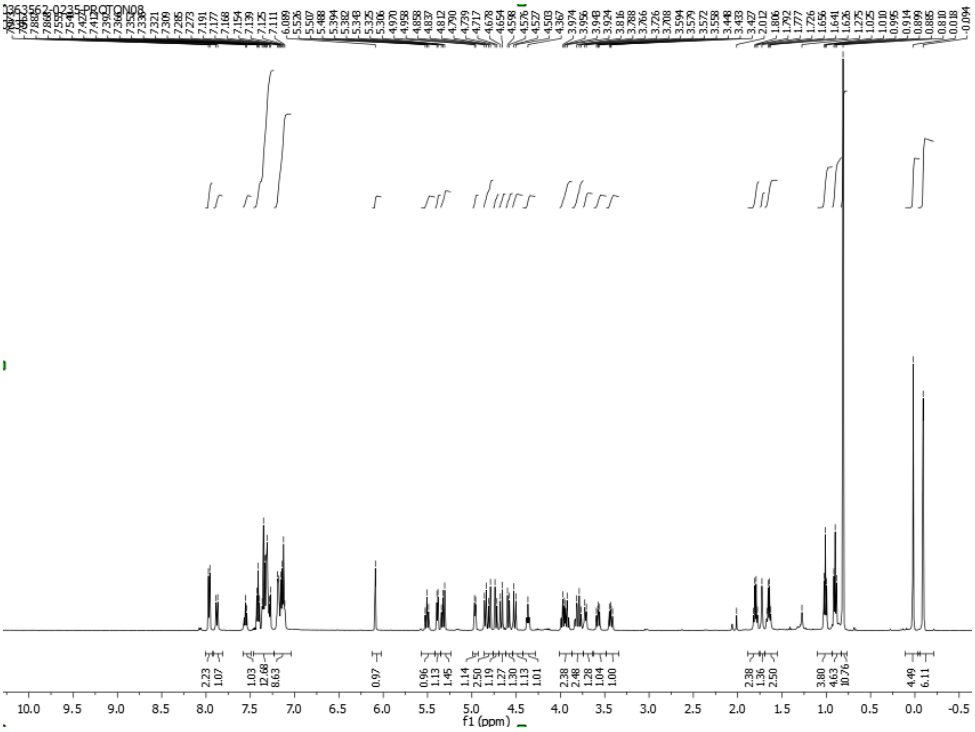

OBn
BnO
BnO
BzO
O
H
N
O
Cl3C
O
O
H
N
O
N
H
O
H
N
O
O
O
O
170

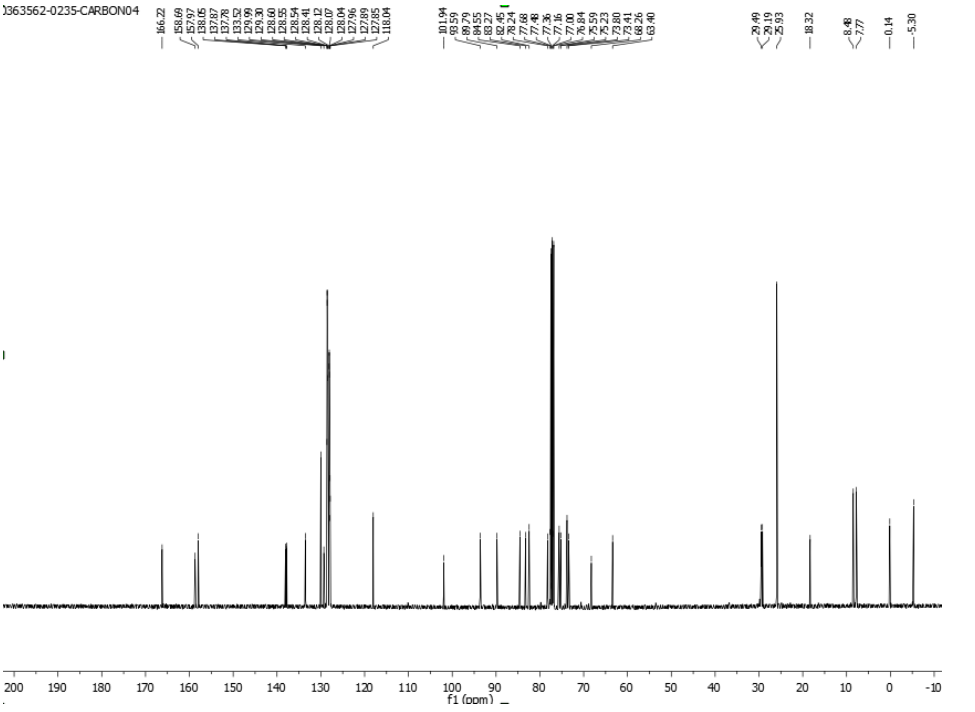

f1 (ppm)

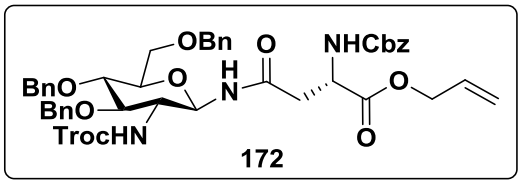

f1 (ppm)

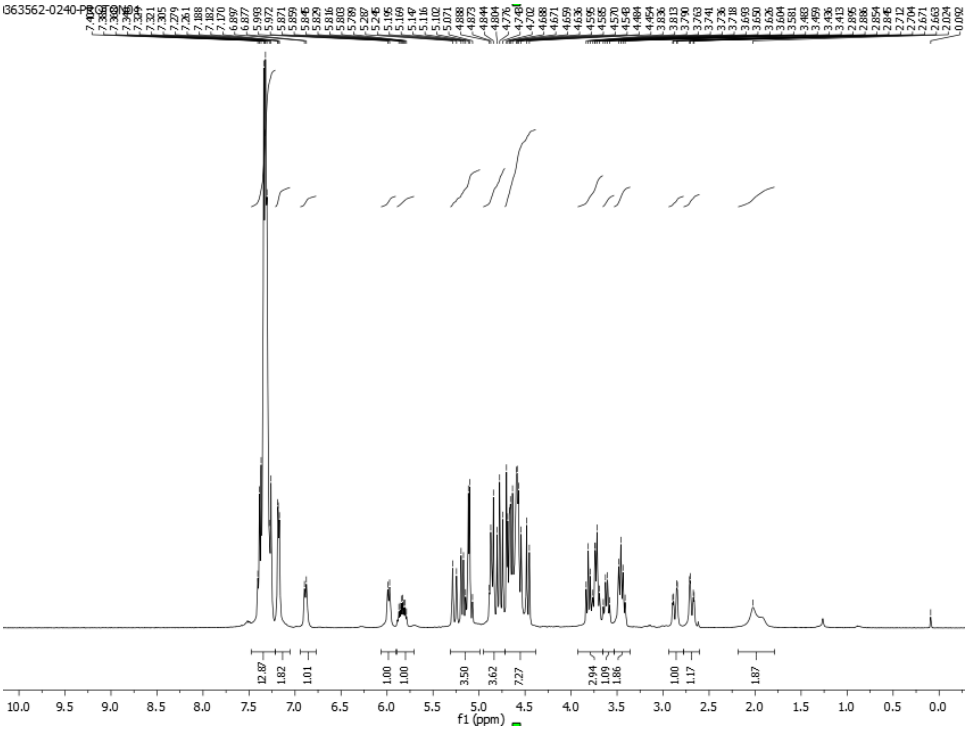


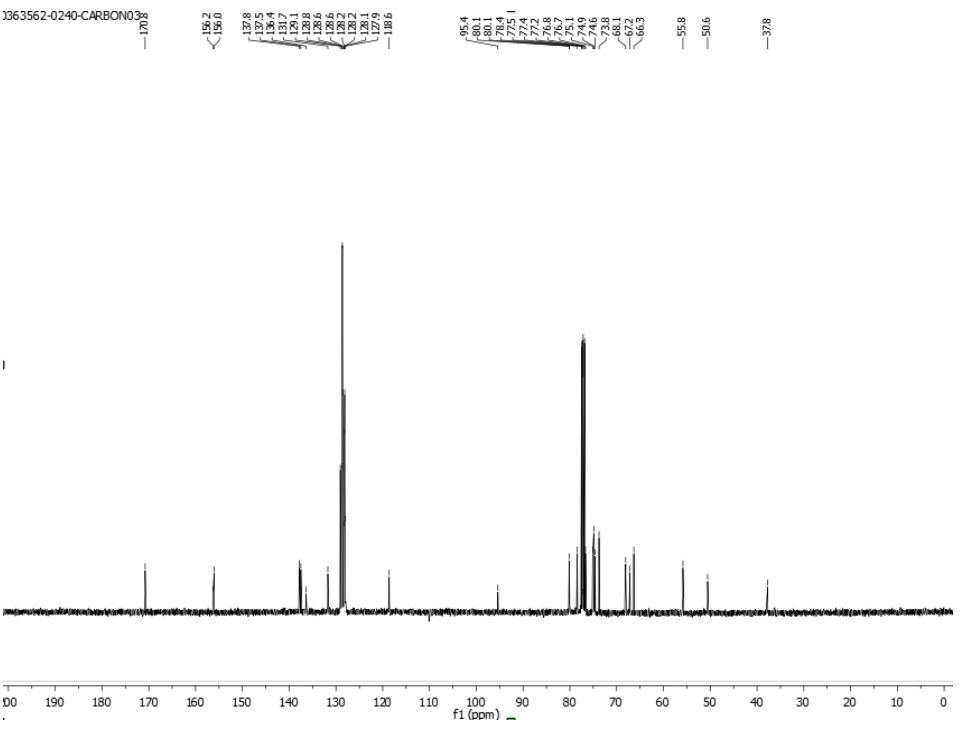
171

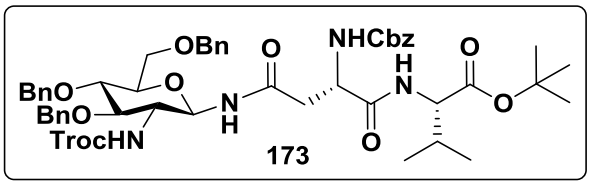


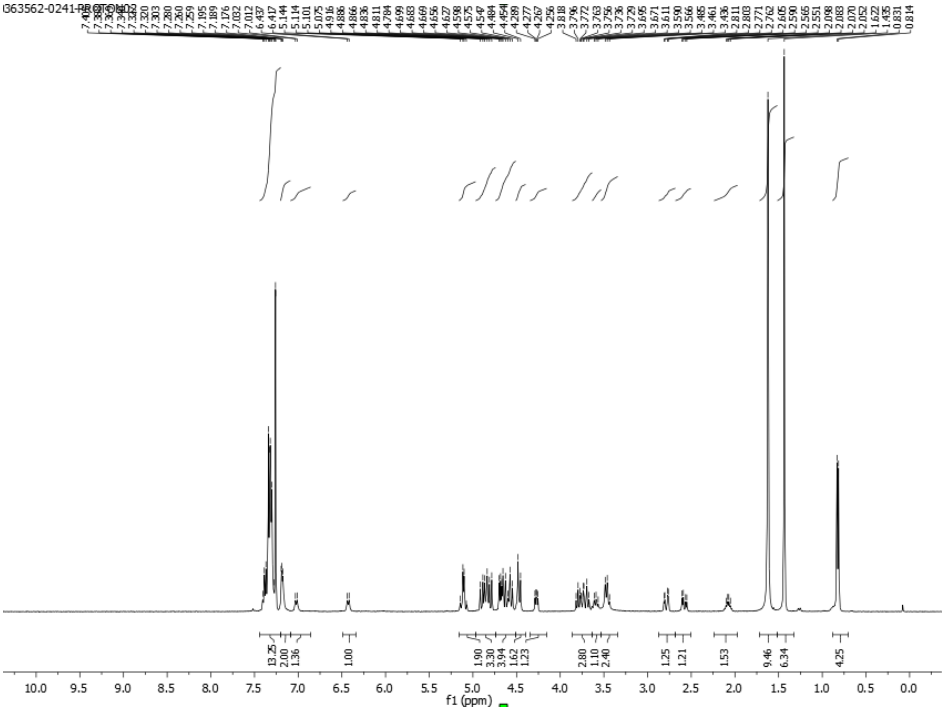


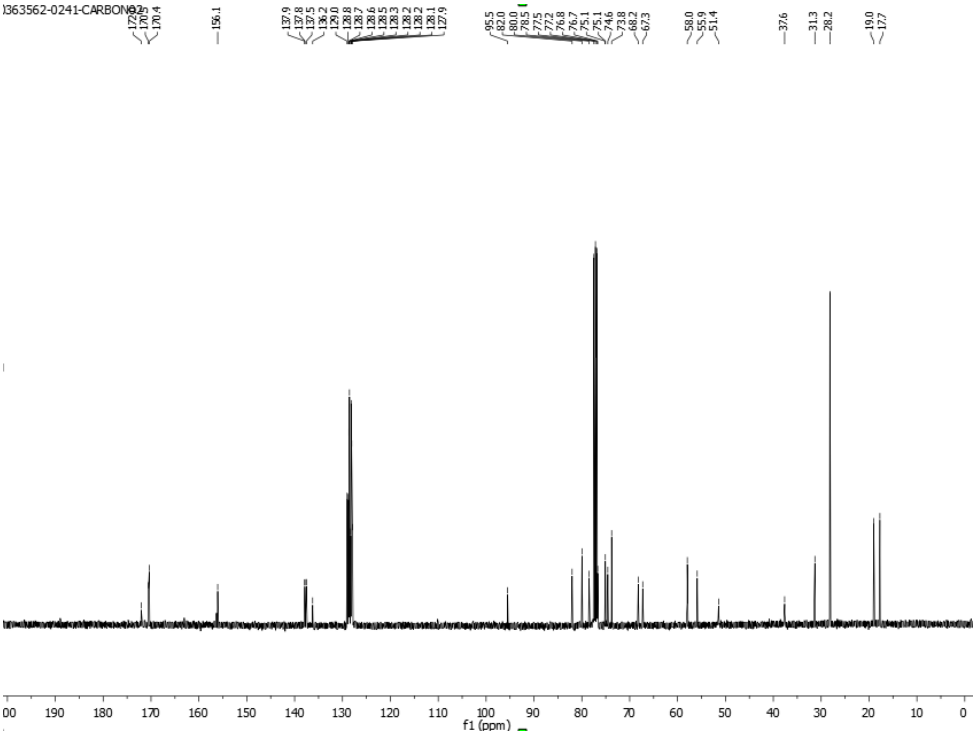

OBn
O
NHCbz
BnO
O
H
N
O
BnO
TrocHN
O
172

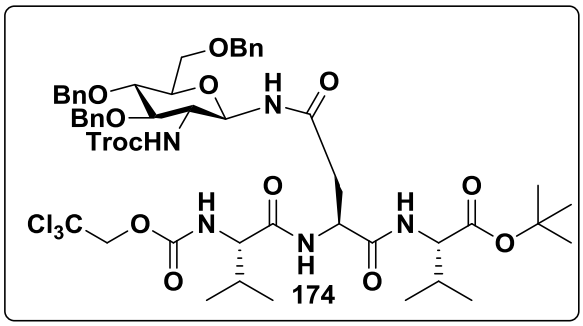

f1 (ppm)

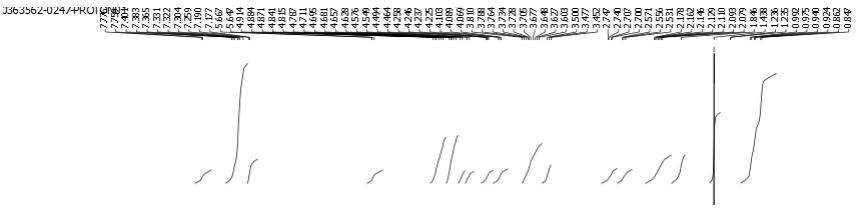

f1 (ppm)

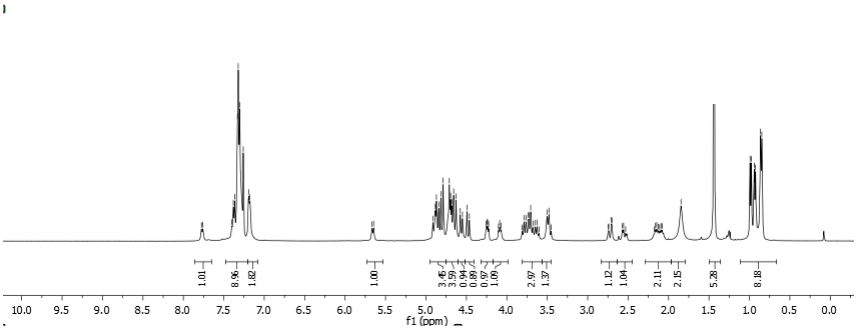

OBn
O
NHCbz
H
N
O
BnO
O
N
H
N
O
BnO
TrocHN
O
O
173

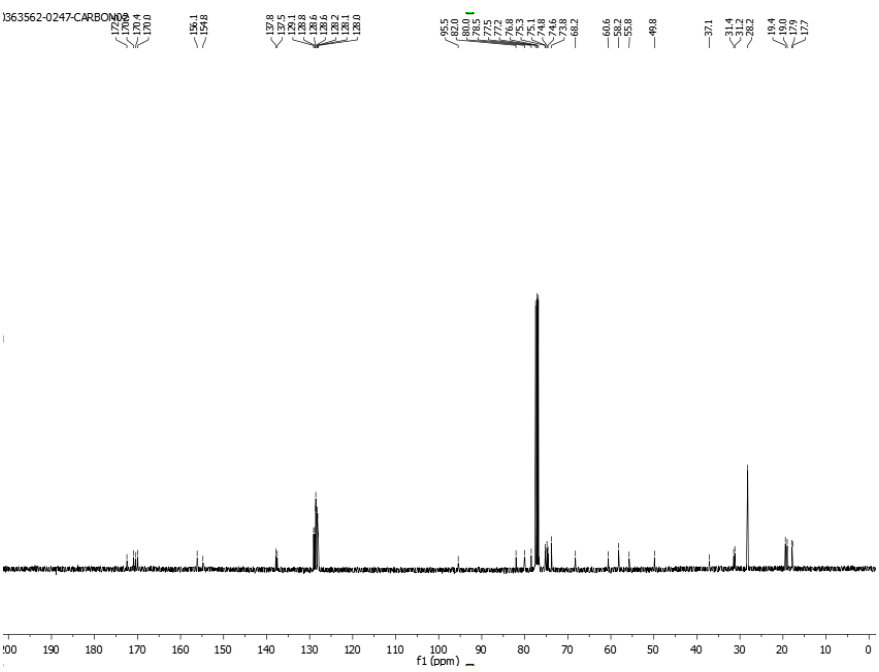

f1 (ppm)

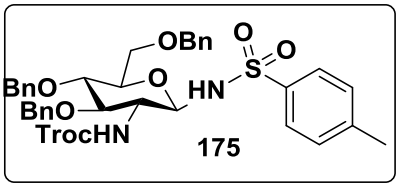

f1 (ppm)

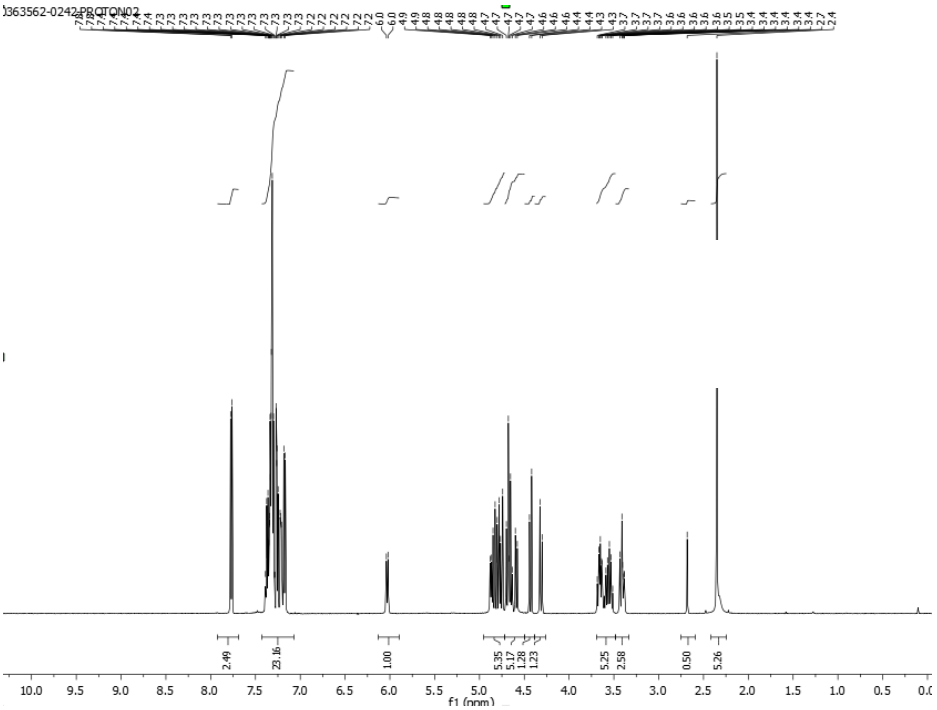

OBn
BnO
BnO
TrocHN
O
H
N
O
Cl3C
O
H
N
O
N
H
O
H
N
O
O
O
O
O
174

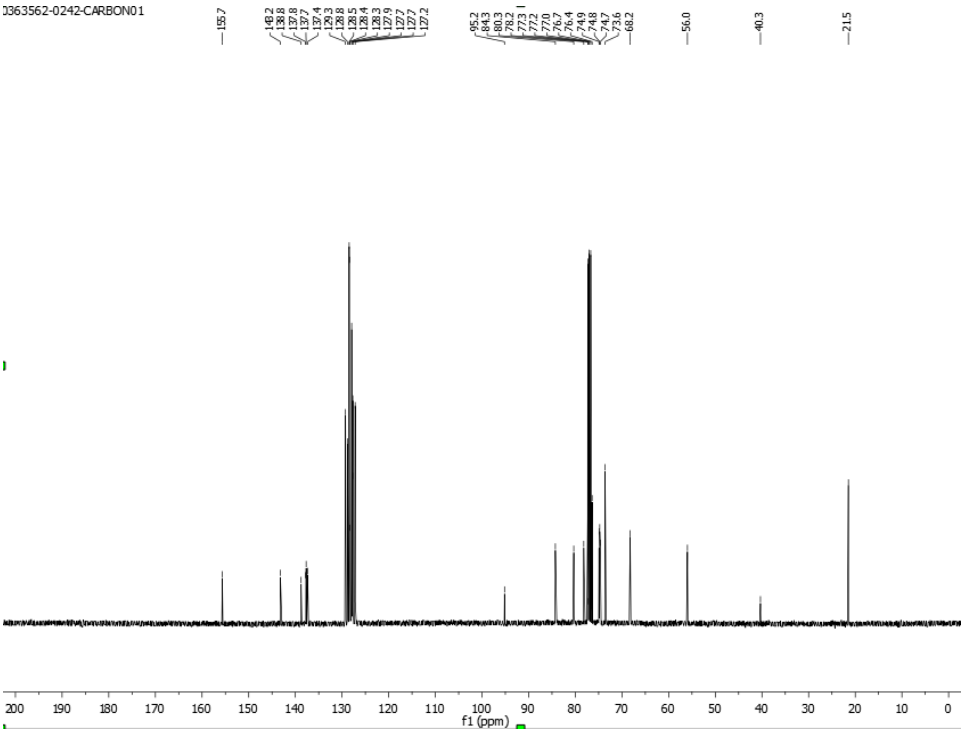


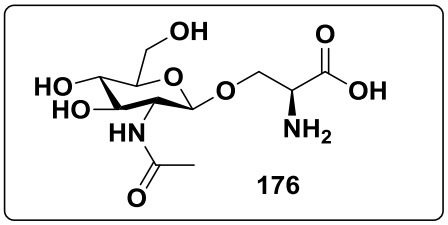

1.01
8.06
1.02
1.00
3.45
3.39
0.94
0.69
0.72
1.09
2.07
1.37
1.12
1.04
2.11
2.15
5.28
8.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


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

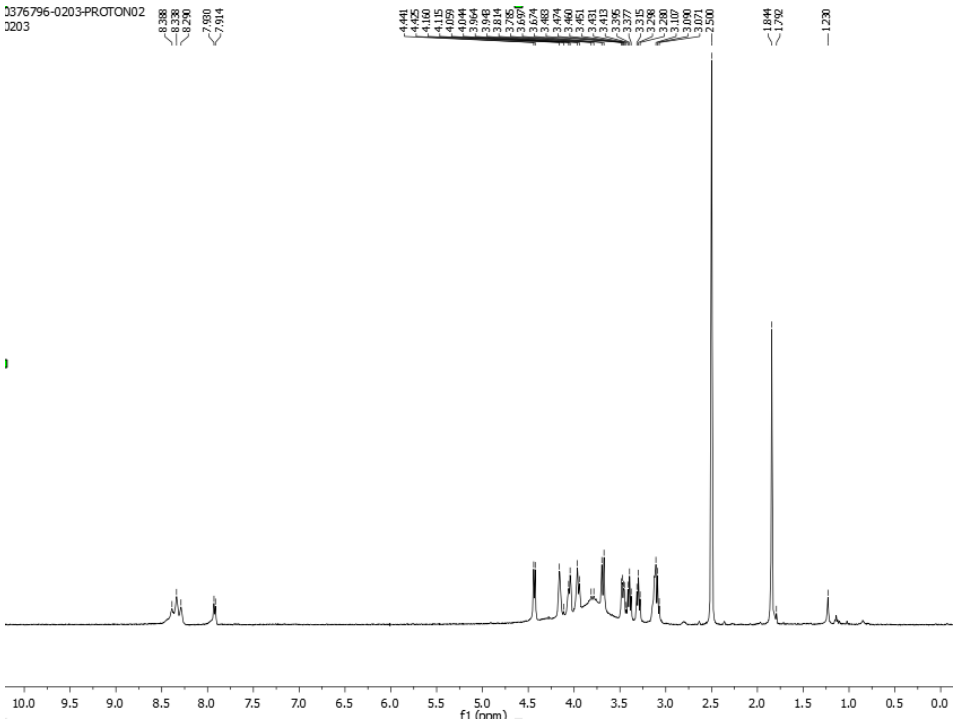

OBn
O
S
O
BnO
O
HN
BnO
TrocHN
175

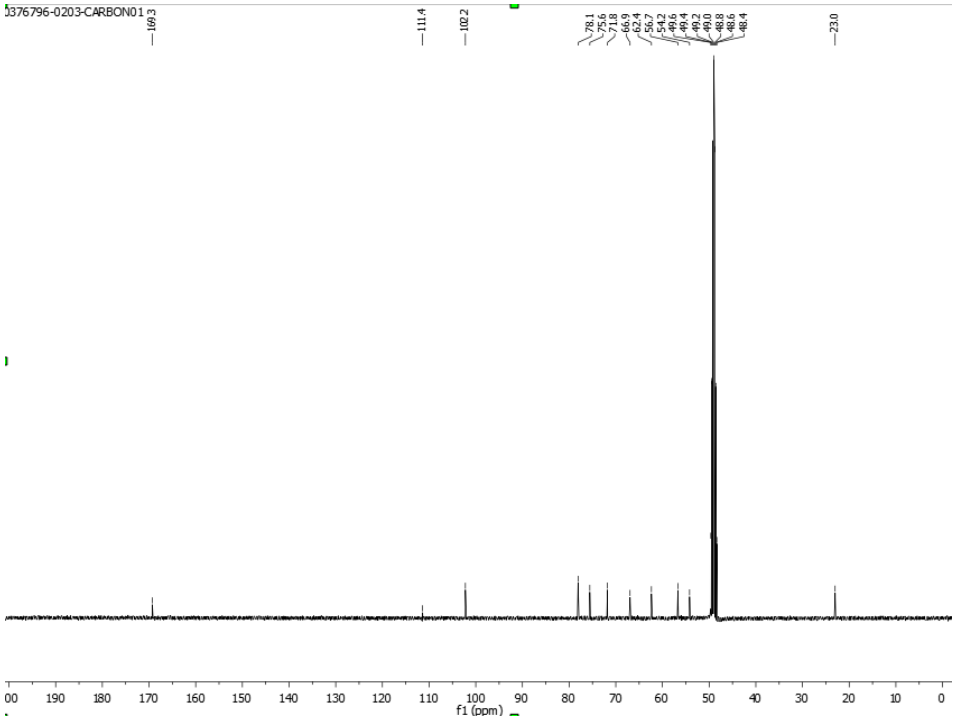

0363562-0242-PROTON02
2.49
23.16
1.00
5.35
5.17
1.28
1.23
5.25
2.58
0.50
5.26
f1 (ppm)

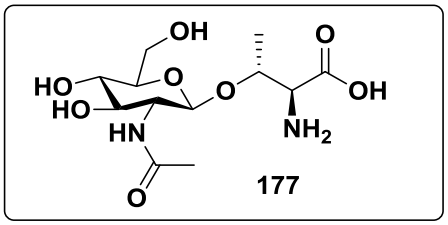

0363562-0242-CARBON01
155.7
56.0
40.3
21.5
f1 (ppm)


OH
O
HO
O
O
OH
HO
HN
NH2
O

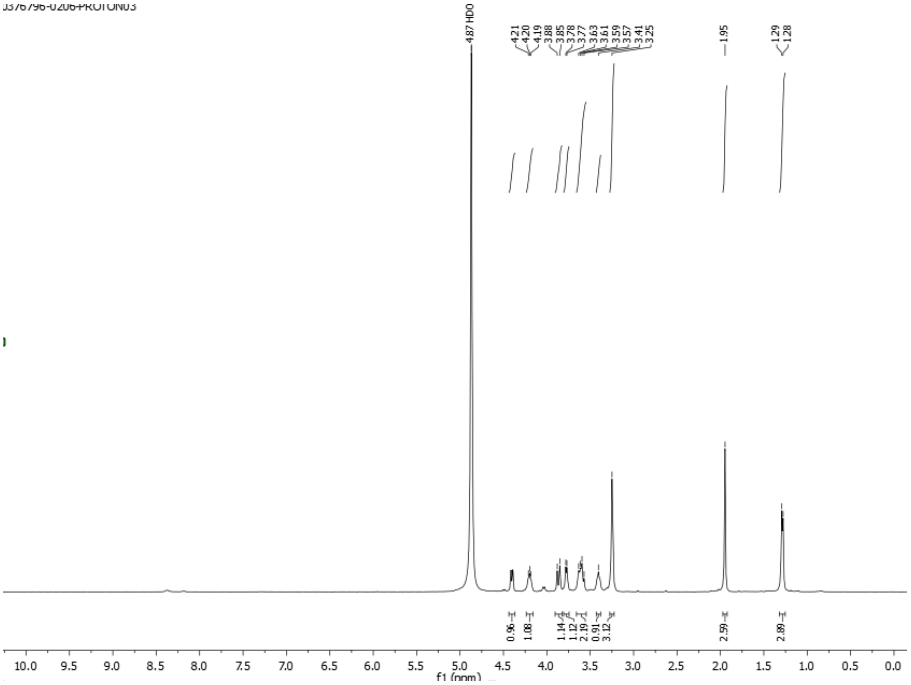
176

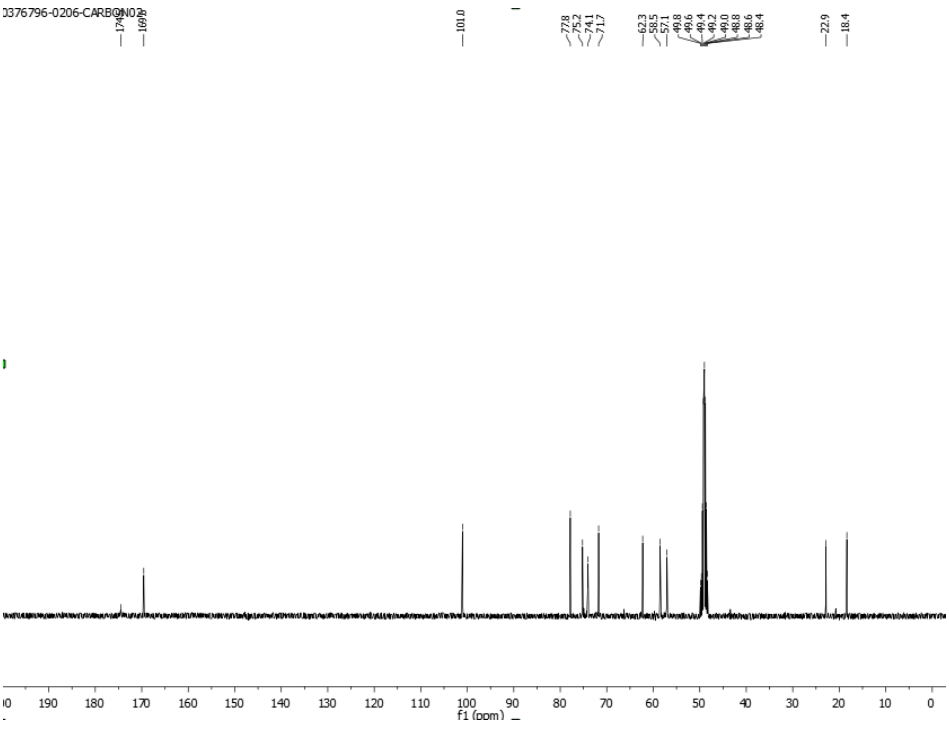

0376796-0203-PROTON02
0203
f1 (ppm)

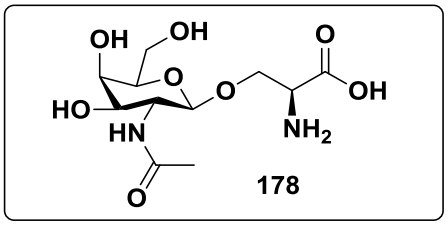

0376796-0203-CARBON01
f1 (ppm)


OH
O
HO
O
O
OH
HO
HN
NH2
O

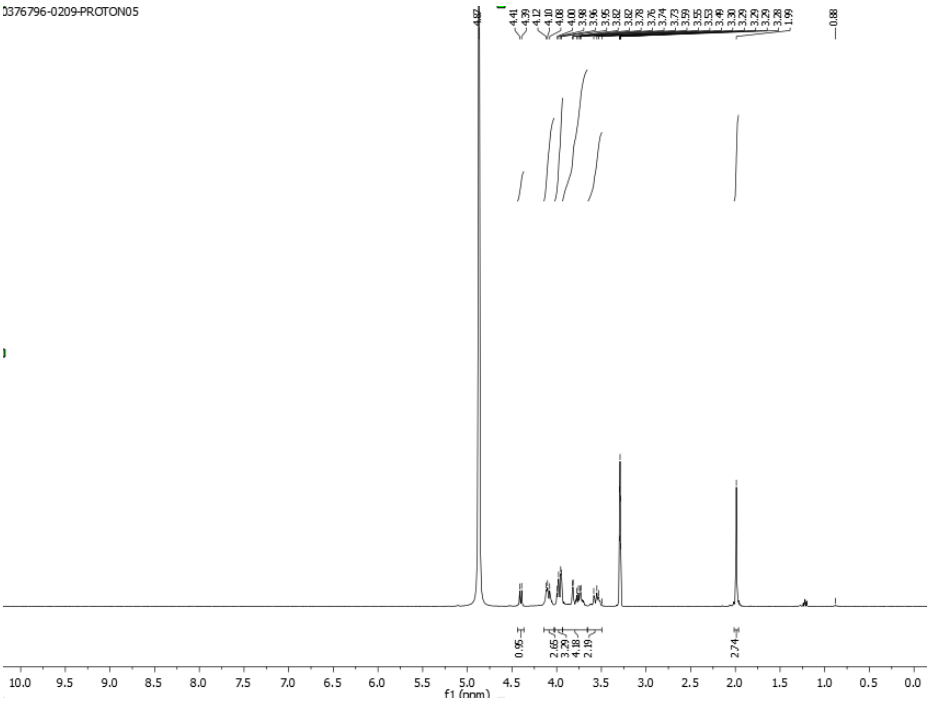
177

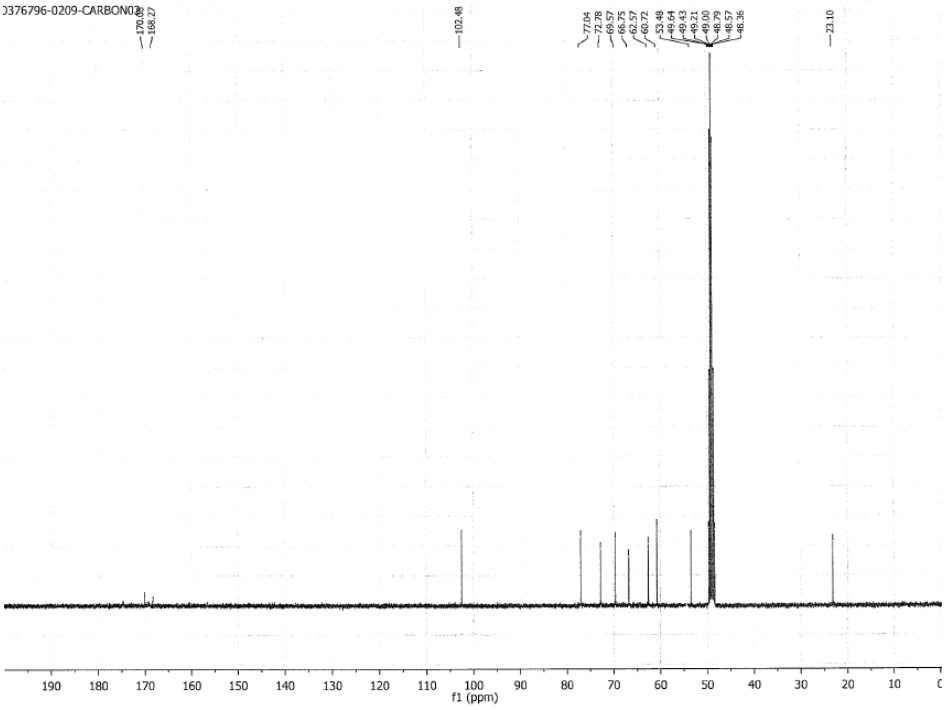

4.87 HDO
4.21
4.20
4.19
3.88
3.85
3.78
3.77
3.63
3.61
3.59
3.57
3.41
3.25
1.95
1.29
1.28
0.96
1.88
1.14
1.12
2.89
0.95
3.12
2.59
2.89
f1 (ppm)

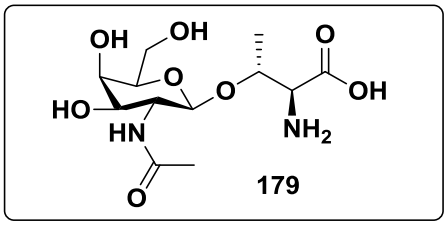

101.0
77.8
75.2
74.1
71.7
62.3
59.5
57.1
49.8
49.6
49.4
49.2
49.0
48.8
48.6
48.4
22.9
18.4
f1 (ppm)


OH
OH
O
HO
O
O
OH
HN
NH2
O

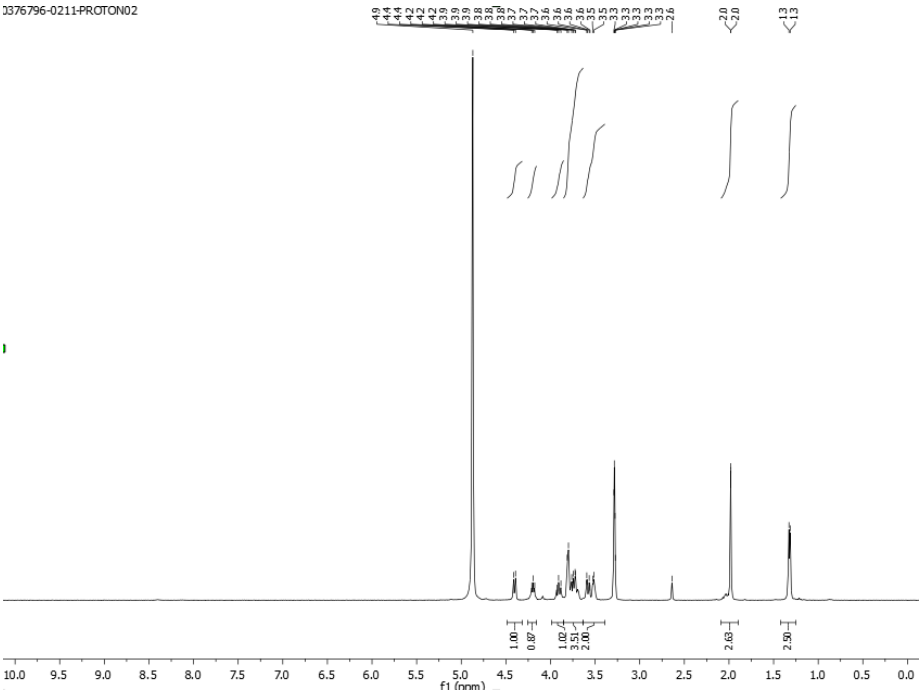
178

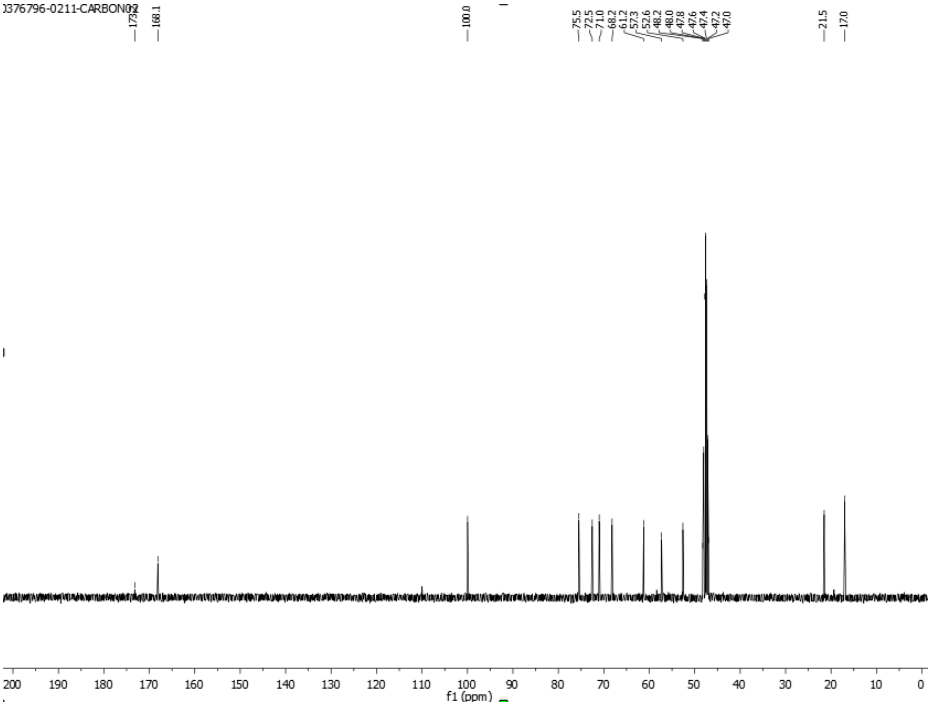

0376796-0209-PROTON05
f1 (ppm)

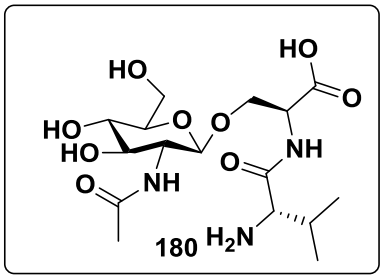

0376796-0209-CARBON02
f1 (ppm)

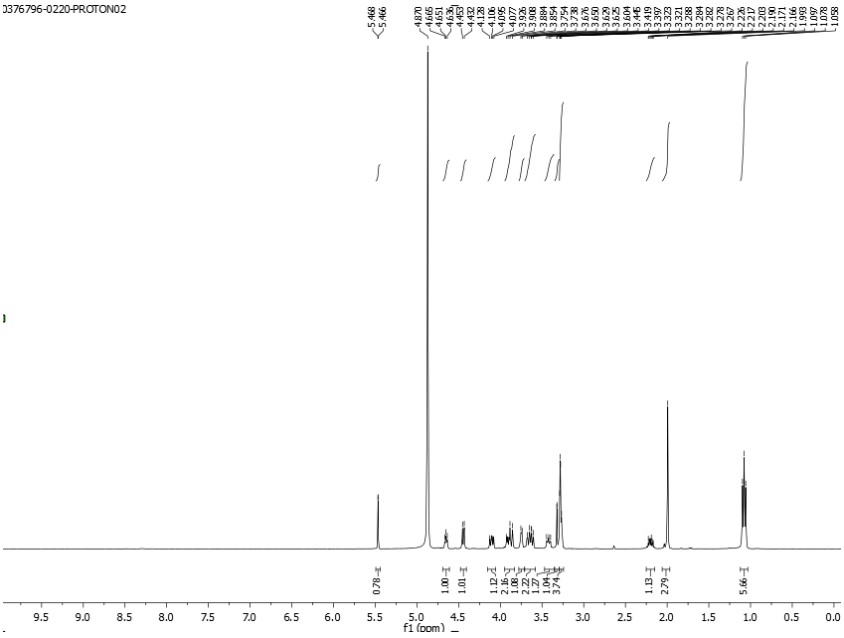

OH
OH
O
O
O
OH
HO
HN
NH2
O

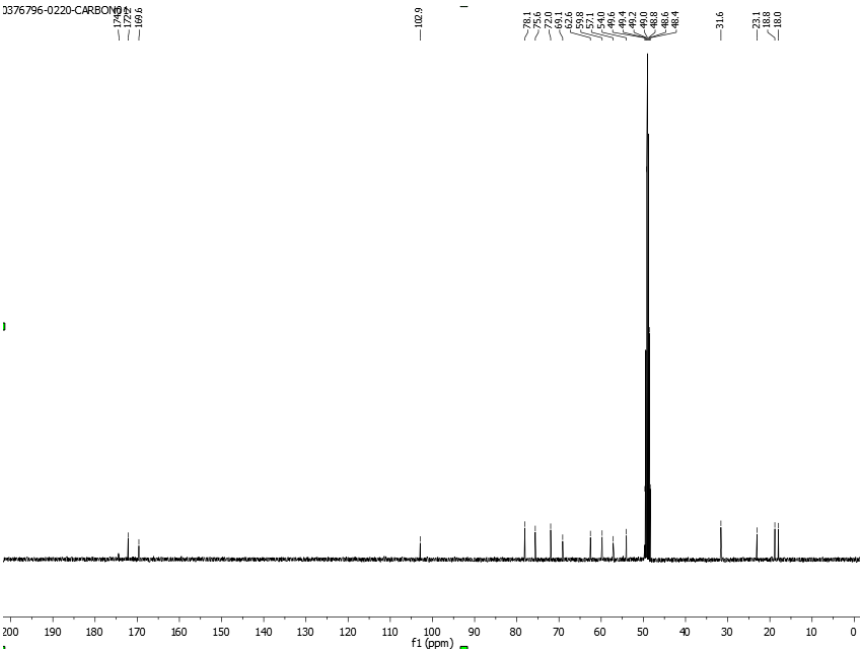
179


0376796-0211-PROTON02
1.00
0.87
1.02
3.51
2.00
2.63
2.50
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)


0376796-0211-CARBON02
173.2
168.1
100.0
75.5
72.5
71.0
68.2
61.2
57.3
52.6
48.2
48.0
47.8
47.6
47.4
47.2
47.0
21.5
17.0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HO
HO
HO
O
O
NH
O
HO
O
NH
O
180
H2N


0376796-0220-PROTON02
f1 (ppm)


0376796-0220-CARBON01
f1 (ppm)

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