Universidade do Minho
Escola de Ciências

Jennifer Martins Noro

Synthesis of polyhydroxylated compounds from Derythrose. Enzymatic inhibition studies

outubro de 2015

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Synthesis of polyhydroxylated compounds from Derythrose. Enzymatic inhibition studies

Dissertação de Mestrado
Mestrado em Química Medicinal

Trabalho efetuado sob a orientação da
Professora Doutora Maria José Chão Alves
e da
Doutora Vera Cristiana Moreira Duarte

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTA DISSERTAÇÃO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE

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Assinatura:_____

“Life is not easy for any of us.

But what of that?

We must have perseverance and

above all confidence in ourselves.

We must believe that we are gifted

for something and that this thing,

must be attained”

Marie Curie

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O término de um trabalho desta escala demonstrou ser desafiante, possibilitando aprender que uma vitória aparece após mil derrotas. Obrigada a todos!

Abstract

This thesis is divided into two parts. At first, two starting synthon compounds were obtained: the benzylidene acetal D-erythrose aldehyde and the unsaturated lactone derived from this aldehyde. Both compounds were obtained following methods reported in the literature.

The first part of the work focuses on aldehyde reactions with different primary aliphatic amines, yielding the respective imines. These were reduced to afford the respective secondary amines in low to good yields. The cleavage of the benzylidene acetal group was conducted in an acid medium, leading to the synthesis of amino-polyols also in good yields. Carbon nucleophiles were added to imines, but without success; either the starting material was recovered or complex mixtures obtained. In the second part, the unsaturated lactone was studied regarding to its reactivity and selectivity. Epoxidation, bromination and aziridination reactions do not led to the expected products. The osmilation led to a single product, which after cleavage of the acetal in acidic medium gave the allonic acid. Reactions with carbon, sulfur and nitrogen nucleophiles also led to pure products. Nitromethane, benzyl mercaptan, ethanethiol and hydroxylamine gave substituted lactones at position 4 in good yields. Hydrazine, 2-aminoethanol, benzylamine and propylamine led to amides in yields that vary from good to quantitative. The acetal group in these compounds was also removed under acidic conditions to give polyhydroxylated 4-substituted-lactones in good to excellent yields; amides undergo intramolecular cyclization yielding L-hydroxylated lactams 4- and *N*-substituted in quantitative yield. Hydrogenation of the lactam with two benzyl groups, was found to be chemo-selective, cleaving the benzyl at the amine function, and retaining the benzyl at the amide function. Both lactones and lactams were subjected to enzymatic assays. One of the lactams showed excellent activity and selectivity for α-glucosidase, which makes it a potentially powerful anticancer agent.

Resumo

O presente trabalho encontra-se dividido em duas partes. Numa primeira abordagem foram sintetizados dois sintões de partida, um aldeído da D-eritrose, e uma δ-lactona insaturada, derivada do aldeído anterior. Os dois compostos foram obtidos seguindo metodologias reportadas na literatura.

A primeira parte do trabalho debruça-se sobre reações do aldeído com diferentes aminas primárias alifáticas, obtendo-se as respetivas iminas, que foram reduzidas obtendo-se as respetivas aminas secundárias com rendimentos variados. A clivagem do grupo benzilideno acetal foi realizada em meio ácido, levando à síntese de amino-polióis, com bons rendimentos. Às iminas foram também adicionados nucleófilos de carbono, todavia sem sucesso, levando sempre à recuperação do reagente de partida ou à obtenção de misturas complexas. Na segunda parte do trabalho, a lactona obtida foi sujeita a estudos de reatividade e seletividade. Reações de epoxidação, bromação e aziridinação não levaram à obtenção do produto esperado. Por osmilação obteve-se um único produto, que após clivagem do acetal em meio ácido deu origem ao ácido alónico. Reações com nucleófilos de carbono, enxofre e azoto levaram também à obtenção de um produto puro. O nitrometano, o benzilmercaptano, o etanotiol e a hidroxilamina originaram lactonas substituídas na posição 4, com bons rendimentos. A hidrazina, o 2-aminoetanol, a benzilamina e a propilamina levaram à obtenção de uma amida com rendimentos entre bons e quantitativos. Após a remoção do acetal, em meio ácido, obtiveram-se δ-lactonas polihidroxiladas 4-substituídas com bons a excelentes rendimentos; as amidas sofreram um processo de ciclização intramolecular, originando L-lactamas polihidroxiladas *N*- e 4-substituídas com rendimento quantitativo. Foi possível encontrar um método de hidrogenação quimio-seletivo de um dos dois grupos benzilo contidos na lactama; apenas é removido o grupo benzilo da função amina. Tanto as lactonas finais como as lactamas foram submetidas a ensaios enzimáticos. Os resultados mostraram excelente atividade e seletividade de uma lactama para a α-glucosidase, o que a torna um potencial agente anticancerígeno.

Abbreviation and symbols table

δ	Chemical shift
Abs	Absolute
Ac	Acyl group
Bn	Benzyl group
Boc	*Tert*-butyloxycarbonyl group
CAN	Cerium Ammonium Nitrate
C_q	Quaternary carbon in NMR spectra
Co(TPP)	5,10,15,20-Tetrakis(4-methoxyphenyl)-21*H*,23*H*-prophine cobalt(II)
Comp.	Compound
m-CPBA	3-Chloroperbenzoic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
$DppONH_2$	*O*-(diphenylphosphinyl)hydroxylamine
Eq.	Equivalents
Et	Ethyl group
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Coherence
IBX	2-Iodoxybenzoic acid
IC_{50}	Half Maximal Inhibitory Concentration
IR	Infrared
Ki	Inhibitory constant
LDA	Lithium di-isopropyl amide
LHMDS	Lithium bis(trimethylsilyl)amide
MCT-7	Michigan Cancer Foundation-7

Me	Methyl group
M.p.	Melting point
MOMCl	Methyl chloromethyl ether
MS	Molecular sieves
MsCl	Methanesulfonyl chloride
p-NBA	*p*-nitrobenzoic acid
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NH_2Pht	*N*-aminophthalimide
NOE	Nuclear Overhauser Effect
ov	overnight
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl group
PivCl	Pivaloyl chloride
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl group
Py	Pyridine
rt	Room temperature
S_N2	Bimolecular nucleophilic substitution
TBACN	Tetrabutylammonium cyanide
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutyl ammonium iodide
TBDMS	*Tert*-butyldimethylsilyl
^tBu	*Tert*-butyl group
TEA	Triethanolamine
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl group
Ts	*p*-toluenesulfonyl group
p-TSA	*p*-toluenesulfonic acid
UV	Ultraviolet

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CHAPTER 1

INTRODUCTION

1. General aspects

The extensive need of new pharmacological drugs to increase the survival rate in some diseases is necessary, looking for the increase of the population's average life expectancy. The work of a medicinal chemist is the search of new lines of study, to help the general population having a better life.

Since carbohydrates are essential for all the good operations of our organisms, they can be classified as one of the most important classes of nutrients. Sugars are present in all organisms, and are the key to many metabolisms processes in life. Many diseases are connected to the irregular behaviour processes in which these molecules are involved. Diabetes[1], Gaucher's[2] and Krabbe's[3] disease, as well as some types of cancer[4], etc., are caused by the malfunction of enzymatic metabolic mechanisms. The key for the treatment of some of these diseases involve the selective linkage of molecules that mimics sugar units, to certain enzymes. For example, Gaucher's disease is one of the most predominant lyssomal storage disorders. Is caused by a deficient activity of the β-glucocerebrosidase enzyme, causing an accumulation of glucosylceramide[5].

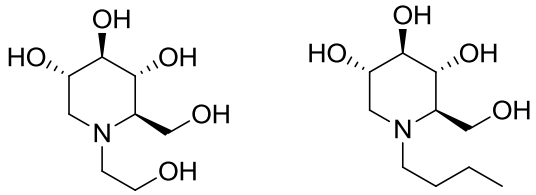


Figure 1 Structure of miglitol **1** and *N*-butyl-deoxynojirimycin **2**.

In the market, there are two imino-sugars compounds, whose therapeutic targets are glycosidases. Miglitol **1** (**figure 1**) named as Glyset® introduced in 1996 for the treatment of type II diabetes as an inhibitor of α-glucosidase[1] (**figure 2**), and *N*-butyl-deoxynojirimycin **2** as Zavesca® in 2003 for the treatment of Gaucher's disease, as an inhibitor of glucosylceramide[6].

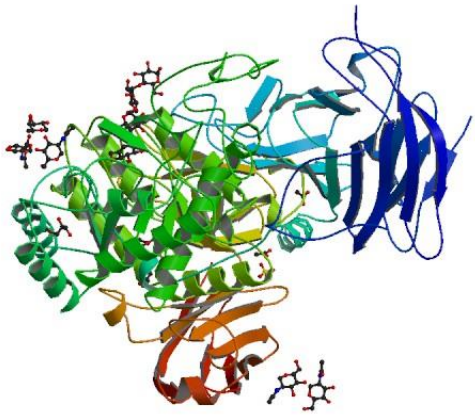
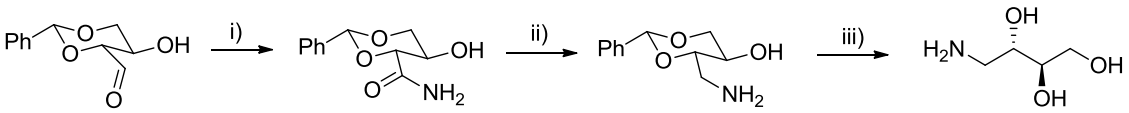


Figure 2 Sugar beet alpha-glucosidase[7].

2. Synthetic strategies for amino-alcohols from tetroses

Amino-alcohols provide an interesting scaffold for many applications, including for the synthesis of imino-sugars. Isomerically pure aminopolyols can be reacted with halopurines, and then applied in oligonucleotides sequences, to be used as mutagenic in microorganisms[8]. Dunlap *et al*[9], have synthesised (2*R*,3*S*)-4-amino-1,2,3-triol **6** from aldehyde **3** (**scheme 1**). Direct conversion of the aldehyde into the amide **4** is obtained in 86 % by treatment of aldehyde **3** with iodine, aq. ammonia and hydrogen peroxide at rt. Reduction of the amide to amine **5** (η= 85 %) is achieved by treatment with $LiAlH_4$. The final cleavage of the acetal protecting group was obtained in BCl_3 at -78 ºC giving the amino-polyols **6** with 75 % yield.

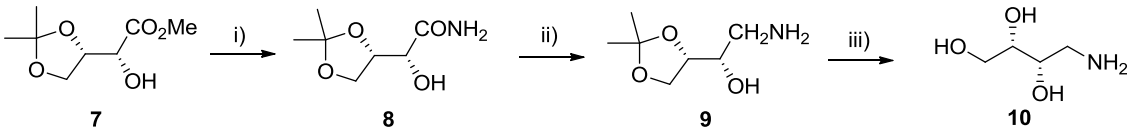


3 **4** **5** **6**

Scheme 1

Reagents and conditions[9]: i) I_2, NH_4OH, H_2O_2, THF, rt, 4 h, 86 %; ii) $LiAlH_4$, THF, 0 ºC to reflux, 6 h, 77 %, iii) BCl_3, DCM, -78 ºC, 1.5 h, 75 %.

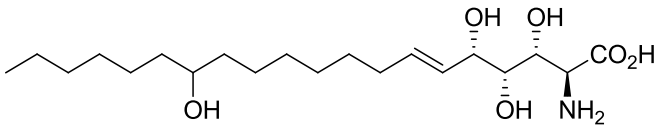
Nechev *et al*[8b] have synthesised the aminotriol **10** a diastereomer of **6**, in three steps, from ester **7** (**scheme 2**). After bubbling NH_3 for 4 h, amide **8** was obtained with excellent yield (η= 97 %). Reduction of the amide with $LiAlH_4$ afforded the amine **9**. Final cleavage of the isopropylidene acetal under acidic medium with HCl gave the aminotriol **10** with 90 % yield.



Scheme 2

Reagents and conditions[8b]: i) NH_3, MeOH, rt, 4 h, 97 %; ii) $LiAlH_4$, THF, rt, to reflux, 6 h, 89 %; iii) HCl 1 M, THF, rt, 20 h, 90 %.

Sphingofungin[10] **11** and Myriocin[11] **12** (**figure 3**) are relevant amino alcohol compounds found in nature. They are biologically active with antifungical and immunosuppressive abilities, respectively.



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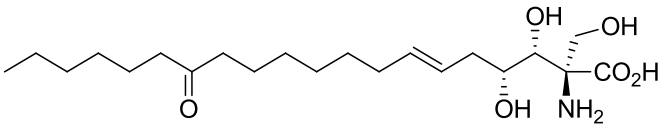

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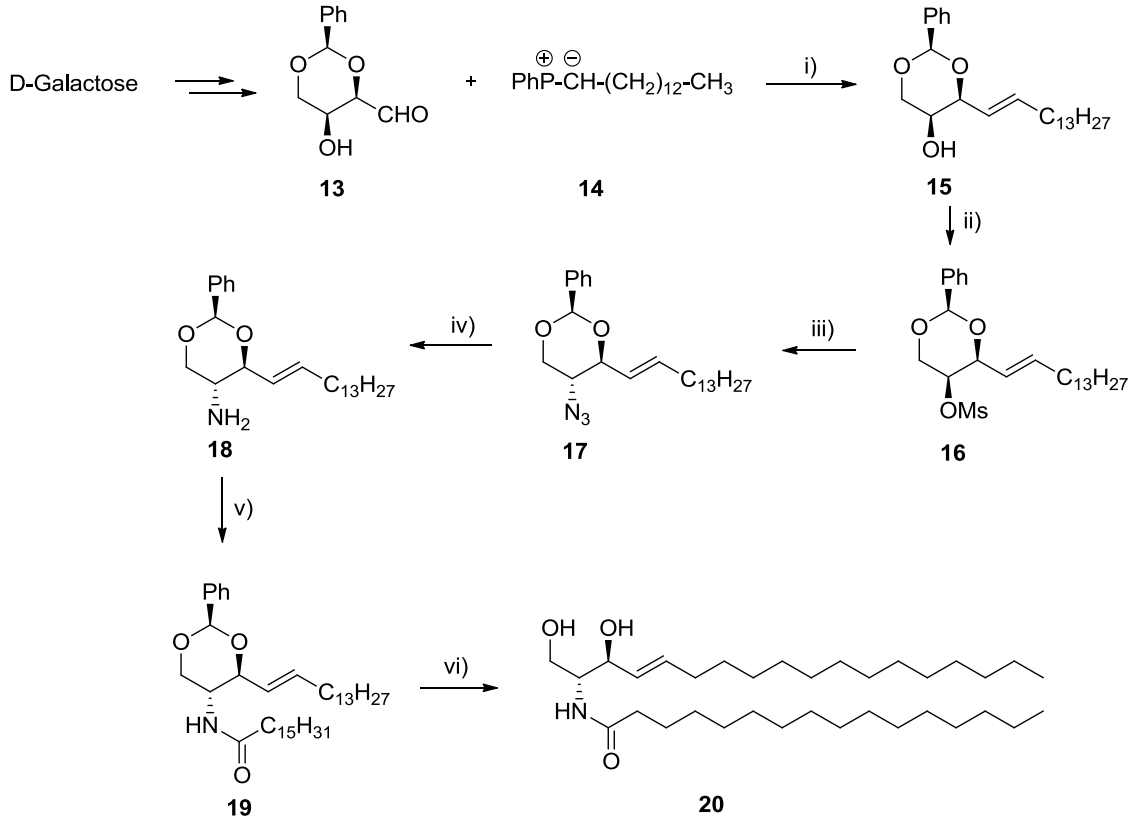
Figure 3 Sphingofungin **11** and Myriocin **12**.

Ceramides and his analogues contain amino alcohol chains, attached to lipophilic chains. The synthesis of ceramides and derivatives has been speeded up by

their potential in the treatment of Gaucher's disease, as inhibitors of glucosylceramidase[12].

Duclos[13] had reported a total synthesis of ceramide **20** from D-galactose (**scheme 3**). The aldehyde **13** was reacted with the ylide **14** generated *in situ* with phenyllithium to give the alkene **15** in moderate yield (η= 44 %). After the alcohol function mesylation, compound **16** was obtained in 86 % yield, and the mesyl group substituted by the azido unit (**17**) with poor yield η= 21 %. Reduction of the azido group to amine **18** was carried out by refluxing compound **17** in isopropanol with sodium borohydride. Product **18** was isolated in quantitative yield. Acetylation of the amine with palmitoyl chloride provides compound **19** in η= 95 %. After cleavage of the benzylidene group obtained in presence of catalytic amount of *p*-toluenesulphonic acid monohydrate ceramide **20** was formed with good yield (η= 80 %).

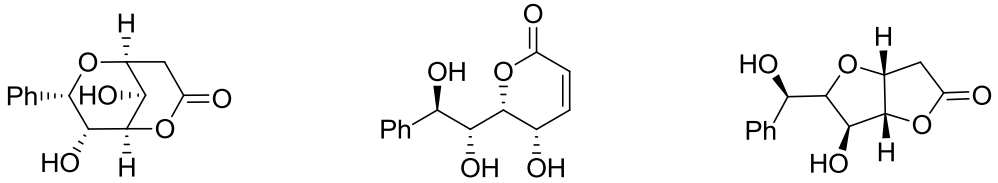


Scheme 3

Reagents and conditions[13]: i) PhMe, PhLi in Et_2O, -30 ºC, 16 h, 44 %; ii) TEA, MsCl, DCM, -30 to 0 ºC, 45 min, 86 %; iii) NaN_3, DMSO, 95 ºC, 3 days, 21 %; iv) $NaBH_4$, isopropanol, reflux, 48 h, 100 %; v) DIPEA, Palmitoyl chloride, DCM, -19 ºC to rt, 2 h, 95 %; vi) *p*-TSA·H_2O, DCM/MeOH, rt, 14 h, 80 %.

3. Synthetic strategies for the synthesis of hydroxylated lactones

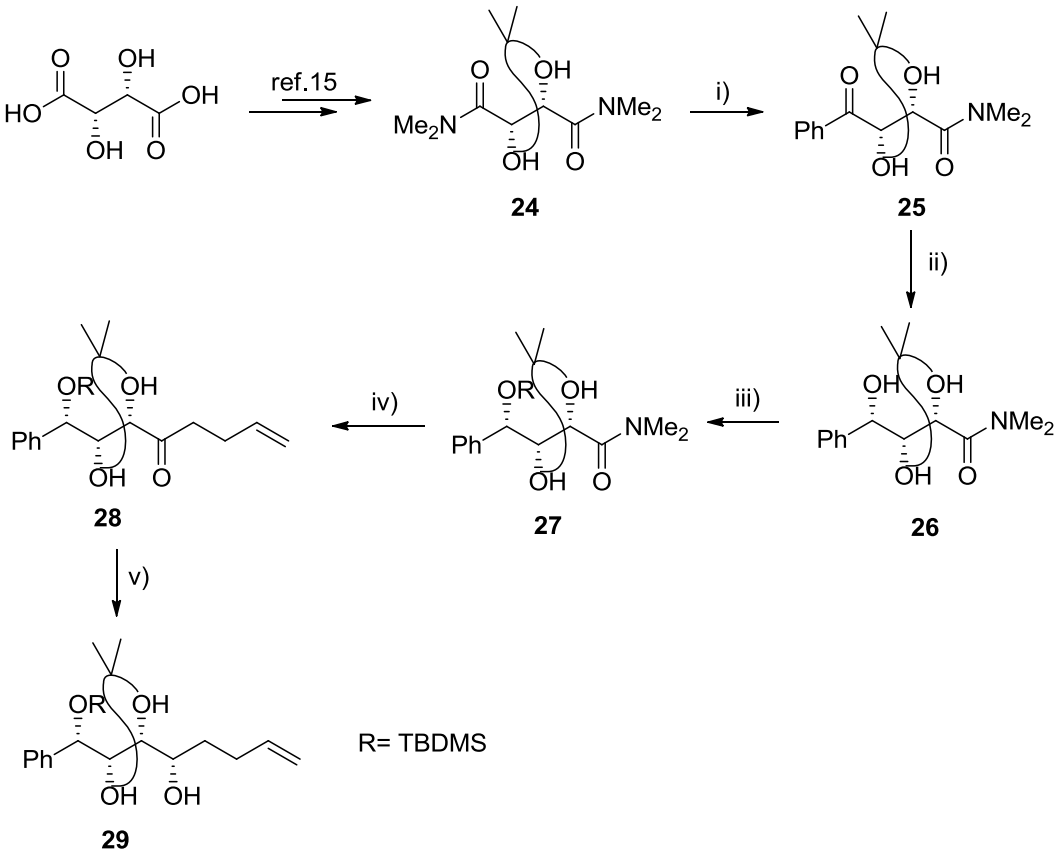
Lactones are one of the most common functional group inserted in the complex structures isolated from natural sources. They also present a large range of biological activities. Are examples, the lactones extracted from *Goniothalamus* genus: Goniopypyrone **21** and Goniotriol **22**. In particular the 6-member ring lactone **22**, had demonstrated higher anti-tumour activity that the 5-member ring Goniofufurone **23** also extracted from *Goniothalamus* plant[14] (**figure 4**).



21 **22** **23**

Figure 4 Structure of Goniopypyrone **21**, Goniotriol **22**, and Goniofufurone **23**.

Prasad and Gholap[14] reported different approaches for the synthesis of some lactones extracted from this plant, using a common scaffold **29** synthesised from D-(−)-tartaric acid, as described in **scheme 4**. After the synthesis of dimethyl amide **24**[15], this compound was treated with phenylmagnesium bromide, to give **25** with excellent yield (92 %). Ketone reduction with a mixture of sodium borohydride and $CeCl_3$ at -78 ºC, gave compound **26** (η= 86 %). Alcohol protection with TBDMS group, in presence of imidazol/DMAP provided **27** (η= 98 %). 3-Butenylmagnesium bromide was added to the amide, to afford ketone **28** with excellent yield (93 %). In the final step L-selectride led to alcohol **29**, isolated in η= 96 %.

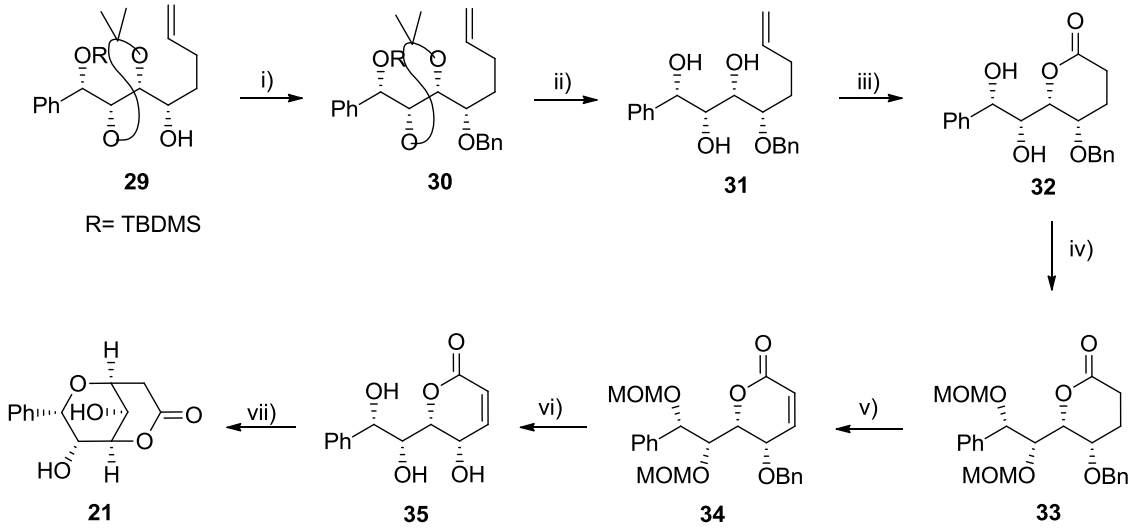


Scheme 4

Reagents and conditions[14]: i) PhMgBr, THF, -10 ºC, 30 min, 92 %; ii) $NaBH_4/CeCl_3$, MeOH, -78 ºC, 2 h, 86 %; iii) TBDMSCl, imidazole/DMAP, DMF, rt, 6 h, 98 %; iv) 3-butenylmagnesium bromide, THF, -10 ºC, 30 min, 93 %; v) L-selectride, THF, -78 ºC, 1 h, 96 %.

(+)-Goniopypyrone **21** was synthesised from compound **29** (**scheme 5**). First, the alcohol function was protected with benzyl group to give compound **30** with 91 % yield. The acetal cleavage occurred in HCl at room temperature furnishing polyol **31**. Ozonolysis of the double bond at -78 ºC to 0 ºC, followed by treatment with Ag_2CO_3 impregnated on Celite in reflux of toluene, provided the formation of lactone **32** (η= 78 % for 2 steps). Protection of the alcohol functions with methyl chloromethyl ether in the presence of base at room temperature afford the product **33** with good yield (80 %). Oxidation of compound **33** with lithium bis(trimethylsilyl)amide followed by the addition of phenylselenyl bromide at -78 ºC provided compound **34** (η= 69 %). Treatment with titanium tetrachloride at 0 ºC deprotected the alcohol function to give

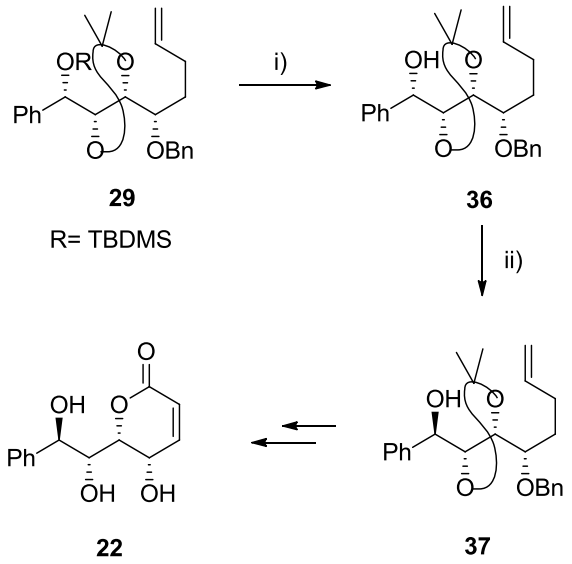
35, which after DBU treatment at room temperature, gave by intramolecular Michael addition (+)-Goniopypyrone **21** with 75 % yield.



Scheme 5

Reagents and conditions[17]: i) NaH, BnBr, DMF, 0 ºC to rt, 2 h, 91 %; ii) 4N HCl:THF (1:1), rt, 6 h, 84 %; iii) (a) O_3/Me_2S, DCM:MeOH, -78 ºC to 0 ºC, 6 h, (b) $AgCO_3$/Celite, toluene, reflux, 30 min, 78 %; iv) MOMCl, DIPEA, cat. DMAP, DCM, reflux, 6 h, 80 %; v) (a) LHMDS, PhSeBr, THF, -78 ºC, 1 h; (b) 30 % H_2O_2, DCM, 0 ºC, 30 min, 69 %; vi) $TiCl_4$, DCM, 0 ºC, 1.5 h, 78 %; vii) DBU, THF, rt, 4 h, 75 %.

(+)-Goniotriol **22** was obtained by the same authors by a similar methodology. This time, an inversion of a chiral centre was included in the process, as represented in **scheme 6**. The removal of TBDMS protecting group by TBAF at 0 ºC to rt gave the free alcohol **36** with 94 % yield. The inversion of the chiral centre, was achieved by Mitsunobu approach, using triphenylphosphine and diisopropyl azodicarboxylate, followed by treatment with potassium carbonate to give the product **37** in 86 % yield. The following steps followed the synthesis of compound **21**.



29

R= TBDMS

36

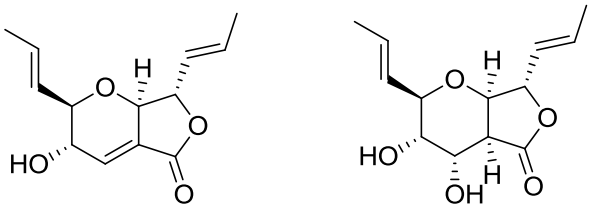
22

37

Scheme 6

Reagents and conditions[14]: i) TBAF, THF, 0 ºC to rt, 1.5 h, 94 %; ii) (a) Ph_3P, PMBA, DIAD, THF, 0 ºC to rt, 1 h, (b) K_2CO_3, MeOH, 0 ºC to rt, 30 min, 86 %.

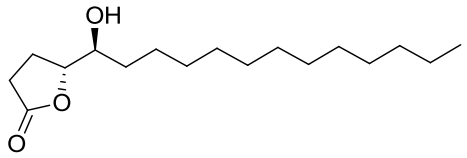
Adames *et al*[16], have isolated γ-lactones **38** and **39** from the fungus *Libertella blepharis F2644*, having tested them against different cancer cells and parasites. Compound **38** showed to be moderately active against parasite *Trypanosoma cruzi* and against breast MCF-7 cancer cell line. Also was considerably active against lung H460 cancer cell lines. However, lactone **39** showed no activity (**figure 5**).



38 **39**

Figure 5 Lactones extracted from *Libertella blepharis F2644.*

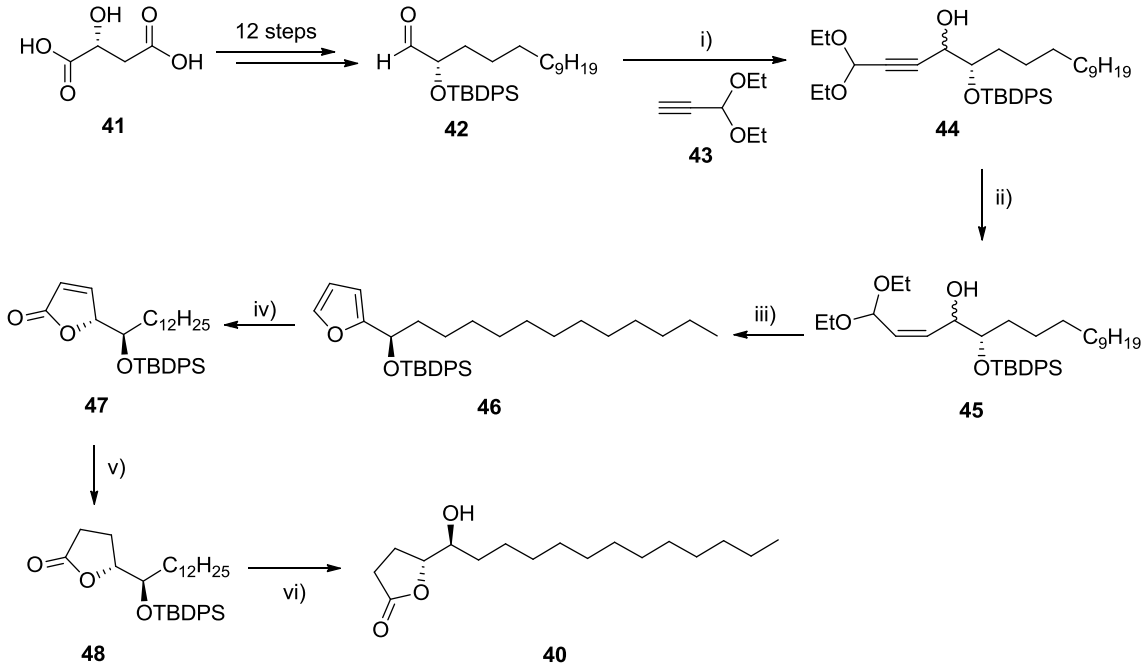
(-)-Muricatacin **40** (**figure 6**) extracted from *Annona muricata L.* showed a growing interest since the discovery of its high cytotoxicity towards several human tumour cell lines, in both enantiomeric forms[17].



40

Figure 6 Structure of (−)-Muricatacin.

González *et al*[18] reported a total synthesis of compound **40** (**scheme 7**) starting from D-malic acid (**41**). The intermediate aldehyde **42** was obtained in 13 steps with 72.9 % overall yield. The synthetic sequence represented **in scheme 7** starts from compound **42**. Initially compound **42** was submitted to nucleophilic attack of acetylene anion generated from **43** by reaction with butyl lithium to give **44**. Reduction of C≡C using Lindlar methodology gave the *cis* olefin **45**. Reaction in acidic medium provided an intramolecular cyclization furnishing furan **46** (η= 71 %) which afforded the lactone **47** with good yield (η= 71 %) in one pot reaction. Reduction of the double bond with palladium on carbon and hydrogen delivered compound **48**. In the final step the alcohol function was deprotected to give lactone **40** with good yield η= 80 %.

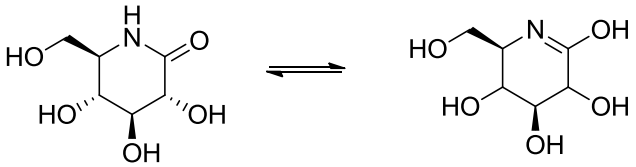


Scheme 7

Reagents and conditions[18]: i) *n*-BuLi, THF, -78 ºC to 0 ºC, 2 h, 89 %; ii) H_2, Lindlar catalyst, hexane, rt, 1 h; iii) HCl, 71 % for 2 steps; iv) (a) O_2, MeOH, rose Bengal, DIPEA, $h\nu$, 3 h, (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 2 h, (c) HCl, MeOH, rt, 15 h, 71 % for 3 steps; v) H_2, Pd/C, MeOH, rt, 4 days, 99 %; vi) TBAF, THF, rt, 22 h, 80 %.

4. Synthetic strategies for the synthesis of hydroxylated lactams

The importance of lactams is well recognized in the medicinal chemistry, for example, in the antibiotic class of compounds. Its importance in carbohydrate chemistry field has grown exponentially on the last decades, with the discovery of glucono-δ-lactam **49** (**figure 7**), as a selective glycosidase inhibitor[19]. An explanation for its activity is supposed to be connected with the possibility of tautomerism within the amide function, which can also act as imine/hydroxyl moiety, enabling hydrogen bonding[20].



49

Figure 7 Glucono-δ-lactam **49**.

Nishimura *et al*[21] synthesised lactam derivatives of all known hexoses. These are represented in **figure 8**: D-glucono-δ-lactam **49**, D-mannono-δ-lactam **50**, D-galactono-δ-lactam **51**, D-gulono-δ-lactam **52**, D-allono-δ-lactam **53**, D-talono-δ-lactam **54**, D-altrono-δ-lactam **55** and D-idono-δ-lactam **56**. These compounds were tested as inhibitors of α and β of three types of enzymes: glucosidase (Baker's yeast and almonds), mannosidase (Jack beans and Snail) and galactosidase (*Aspergillus nier* and *Aspergillus niger*).

Lactam with the glucose configuration showed to be selective for β-glucosidase (IC_{50}= 6.2x10^{-5} M). Lactam **50** showed to be more active against β-mannosidase (IC_{50}= 1.1x10^{-5} M) than to α-mannosidase (IC_{50}= 1.0x10^{-4} M), and is also very potent against β-glucosidase (IC_{50}= 7.9x10^{-7} M).

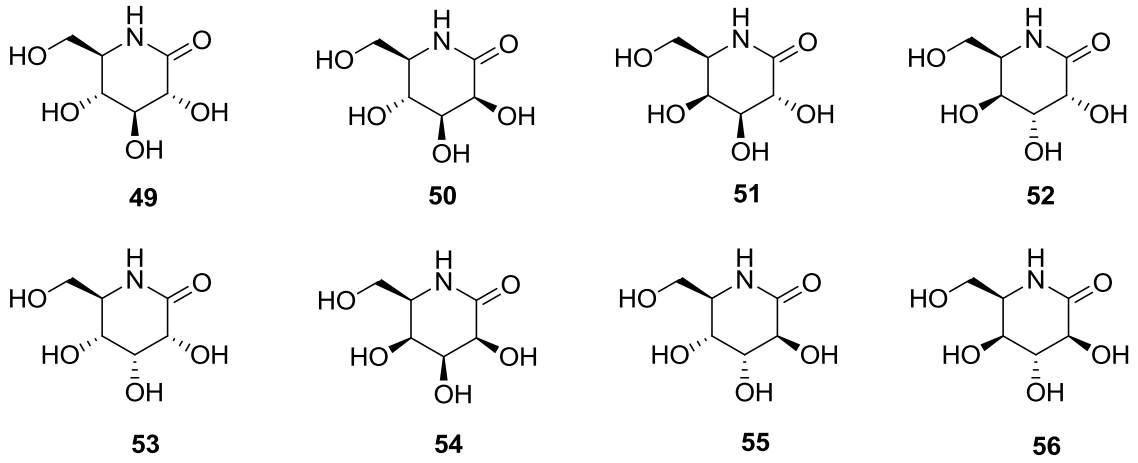
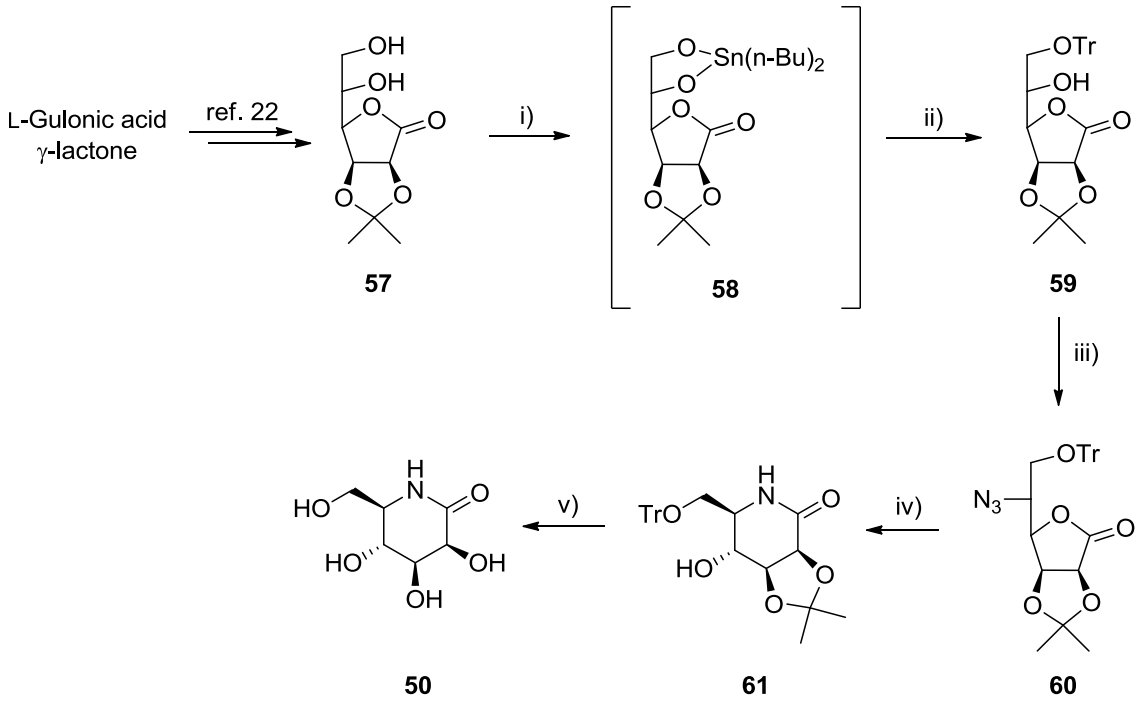


Figure 8 δ-lactams derivatives of hexoses.

The galacto isomer **51** and talono isomer **54** are non-selective compounds: **51** is active against β-glucosidase (IC_{50} = 1.6x10^{-4} M) and β-galactosidase (IC_{50}= 1.7x10^{-5} M); **54** is active against the same enzymes with IC_{50}= 1.8x10^{-4} M in β-glucosidase and with IC_{50}= 6.2x10^{-5} M in β-galactosidase. Lactams **52**, **53** and **55** do not showed inhibitory activity at 5.6x10^{-2} M in any of the enzymes tested. Compound **56** is selective for β-glucosidase (IC_{50}= 7.0x10^{-5} M).

An example of the synthetic methodology applied for these lactams is presented in **scheme 8**; it is related to compound **50**.

Starting with L-gulonic acid γ-lactone, was obtained 2,3-*O*-isopropylidene-L-gulonic acid γ-lactone **57**[22]. This compound was transformed *in situ*, by dibutyltin oxide into the cyclic stannoxane **58**. Treatment with trityl chloride in the presence of DIPEA, afforded **59** with excellent yield (η= 97 %). Activation of the remaining free alcohol with triflic anhydride, followed by substitution of the trifluorosulfonic group by azide gave **60** in 80 % yield. Raney Nickel methodology reduce the azido group, and an intramolecular cyclization was followed to obtain **61** in good yield (η= 65 %). Treatment of compound **61** with 4 M HCl removed simultaneously the isopropylidene and trityl group, to provide the pure lactam **50** (η= 68 %).

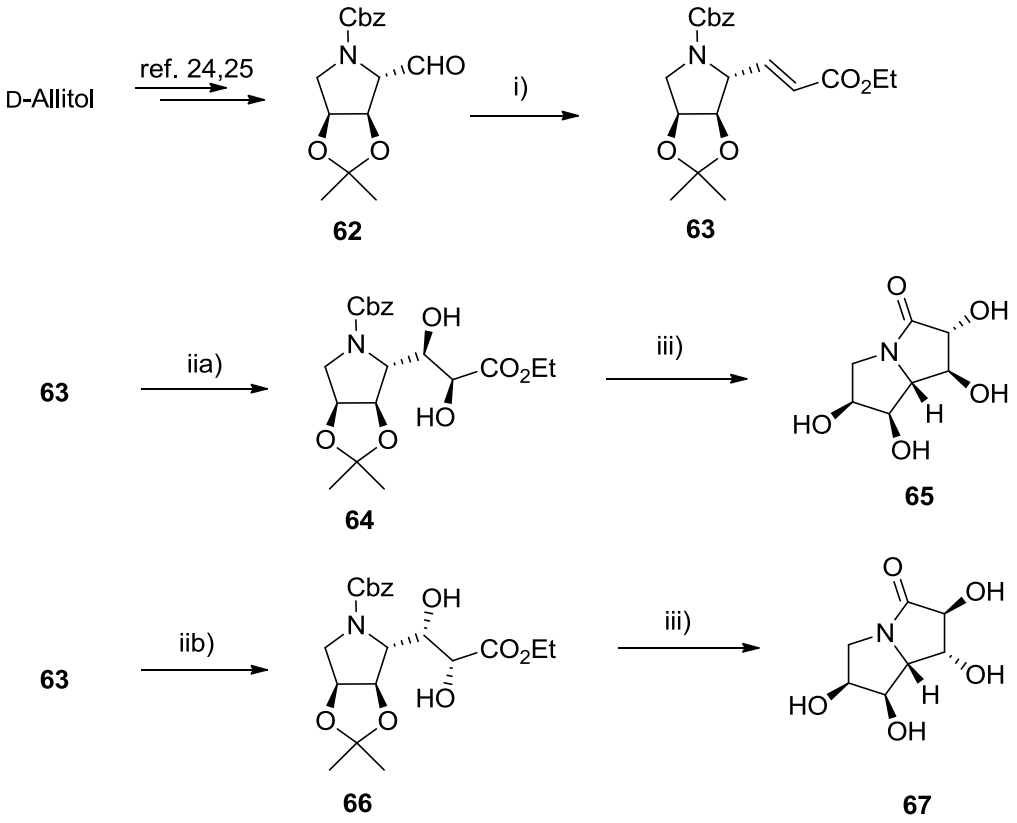


Scheme 8

Reagents and conditions[21]**:** i) $(n\text{-Bu})_2SnO$, benzene, MS 4Å, 85 ºC, ov; ii) Ph_3CCl, DIPEA, DMF, rt, 3 h 97 % (for 2 steps); iii) (a) $(CF_3SO_2)_2O$, py, DCM, -40 ºC, 2 h, (b) NaN_3, DMF, rt, ov, 80 %; iv) Raney Ni, H_2, MeOH/AcOEt, rt, 4 h, 65 %; v) 4 M HCl, dioxane, rt, 6 h, 68 %.

Carmona *et al*[23] synthesised novel tetrahydroxypyrrolizidines (**scheme 9**) from D-allitol[24,25]. After the synthesis of aldehyde **62**, Wittig elongation, provided a mixture of isomers *trans/cis* in a 10:1 ratio, respectively. *Trans* isomer **63** was isolated and submitted to Sharpless asymmetric dihydroxylation with AD-mixα and AD-mixβ giving the respective products **64** and **66**, both in 61 % yield. Cleavage of the protecting groups with aq. trifluoroacetic acid and H_2/Pd lead to an intramolecular cyclization giving lactams **65** (η= 52 %) and **67** (η= 68 %).

Either compound **65** and **67** were tested against β-galactosidase from bovine liver, revealing weak inhibition.

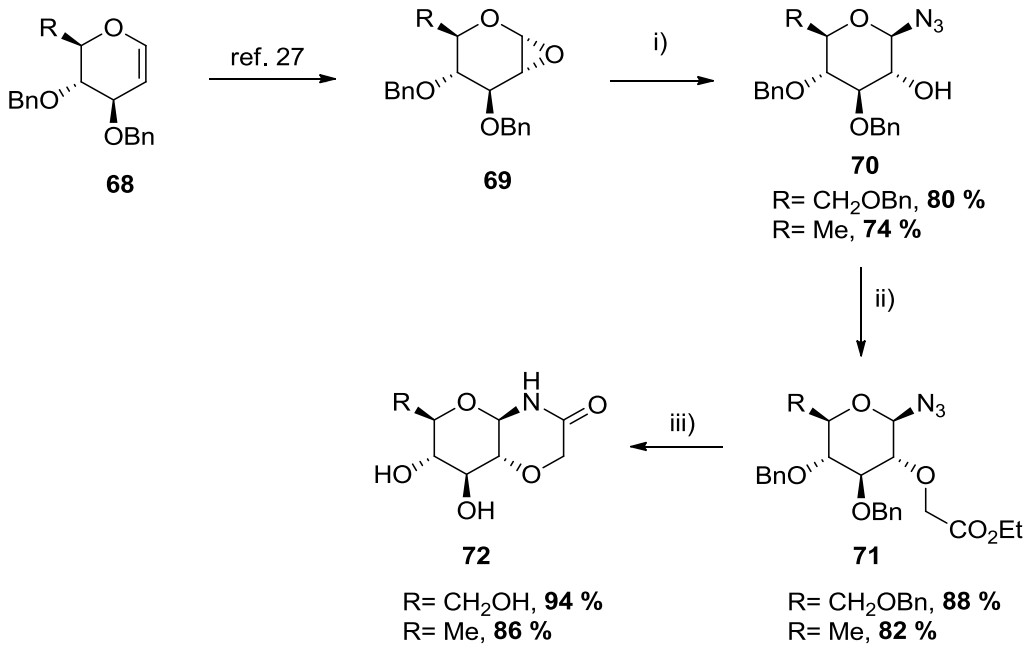


Scheme 9

Reagents and conditions[23]: i) Ph_3P=CHCOOEt, DCM, reflux, 2 h, 90 %; iia) AD-mixα, *t*-BuOH/H_2O, $MeSO_2NH_2$, rt, 16 h; iib) AD-mixβ, *t*-BuOH/H_2O, $MeSO_2NH_2$, rt, 20 h; iii) (a) 80 % TFA aq. 25 ºC, 2 h, (b) H_2, 10 % Pd/C, abs EtOH, 4 h, (c) Reflux EtOH, 24 h.

Reddy and co-workers[26] synthesised morpholine fused sugar-derivatives, starting with the corresponding D-glycals **68**. Reaction of **68** with dimethyl dioxirane generated *in situ*, provided the epoxides **69** following the procedure in the lit[27] (**scheme 10**). Opening the epoxides with azide in the presence of CAN showed to be an efficient methodology, giving the respective azido-alcohol **70** in 5 min with good yields (η= 74-80 %). Alkylation of the alcohol with ethyl bromoacetate in the presence of sodium hydride provided the product **71**. Hydrogenolysis of the azido group afforded the amino group, which immediately get involved in an intramolecular cyclization to give lactams **72** in one pot.

These lactams **72** showed no activity against α-glucosidase and α-galactosidase.



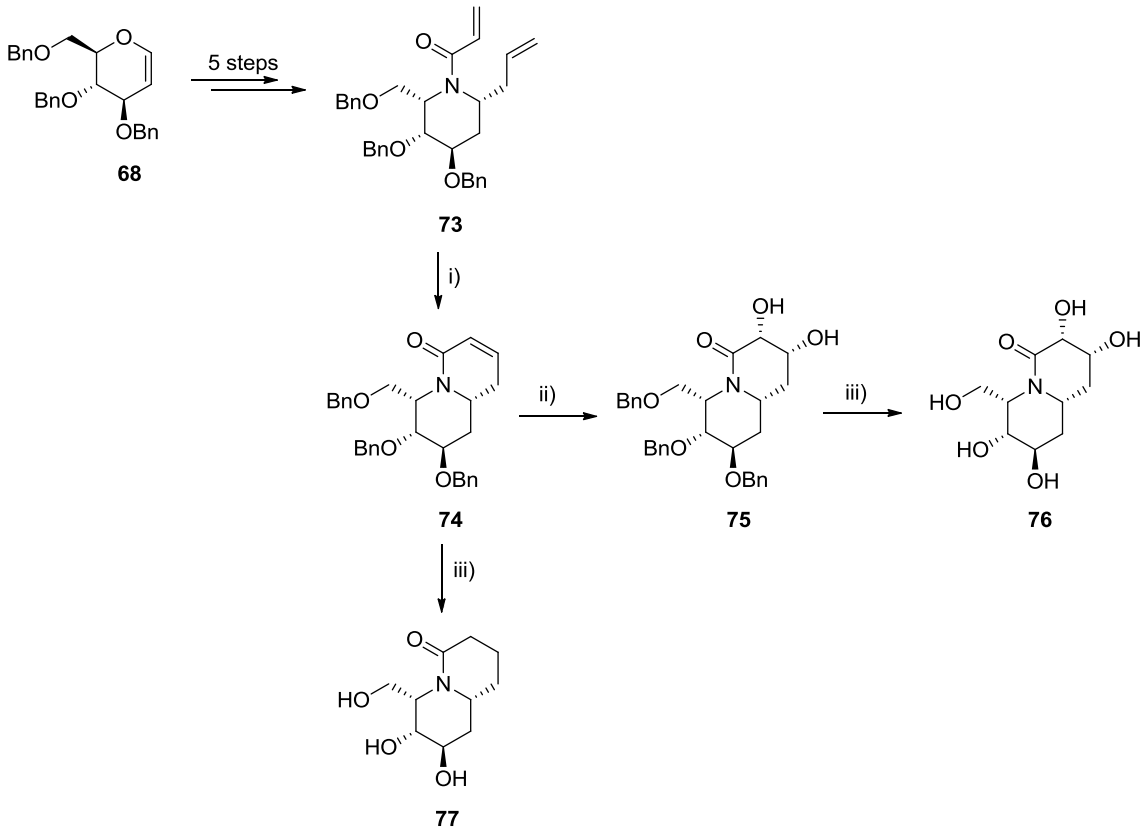
Scheme 10

Reagents and conditions[26]: i) CAN, NaN_3, CH_3CN/H_2O, rt, 5 min; ii) $BrCH_2COOEt$, NaH, DMF, 0 ºC to rt, 30 min; iii) $Pd(OH)_2/C$, MeOH, H_2 (5 atm), 30-34 h.

Starting from the commercial available D-glucal **68**, Kumari and Vankar[28], have reported the synthesis of new quinolizidines (**scheme 11**) and tested their activity

against some glycosidases. The intermediate **73** was obtained after 5 reaction steps in 68.3 % overall yield. Reflux of compound **73** in DCM in the presence of Grubbs' catalyst gave compound **74** isolated in good yield (η= 80 %). Dihydroxylation of the C=C bond with osmium tetroxide gave the alcohol **75** with excellent yield (η= 98 %). Hydrogenolysis with palladium hydroxide, deprotected the alcohols affording pure product **76** (η= 80 %). The double bond of **74** was also reduced to give product **77** (η= 80 %).

Quinolizidines **76** and **77** were submitted to enzymatic assays. Compound **76** demonstrated to be active but not selective. Assays against α-glucosidase gave IC_{50}= $1.58x10^{-3}$ M, against β-glucosidase IC_{50}= $1.98x10^{-3}$ M, and toward α-mannosidase IC_{50}= $2.50x10^{-3}$ M. Nevertheless, **77** showed to be active against β-galactosidase IC_{50}= $1.40x10^{-3}$ M, and selective.

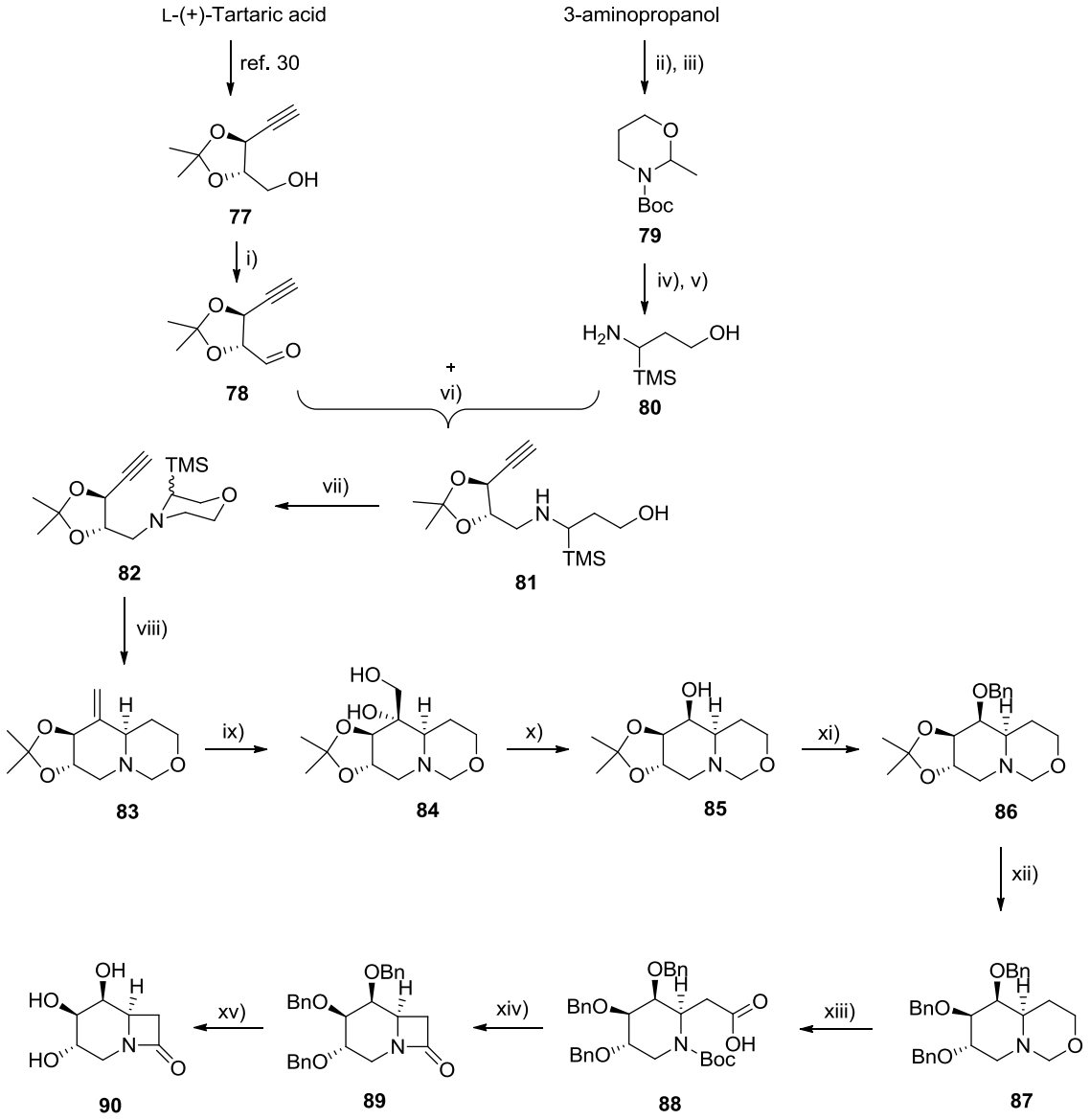


Scheme 11

Reagents and conditions[28]: i) 5 mol% Grubbs' catalyst, DCM, reflux, 7 h, 80 %; ii) cat. OsO_4, NMO, ^{t}BuOH-acetone-water (1:2:2), rt, 12 h, 98 %; iii) $Pd(OH)_2$, MeOH, 50 psi H_2, rt, 24 h, 80 %.

Pandey and co-workers[29] reported an approach for the synthesis of β-lactam-azasugar **90** (**scheme 12**). Starting from L-(+)-tartaric acid, compound **77** was obtained following the procedure on the lit[30]. The alcohol function in compound **77** was oxidized to give the respective aldehyde **78** (η= 85 %). On the other hand, 3-aminopropanol was used to provide cyclic compound **79**, which was further α-methylated, affording amino-alcohol **80** (η= 88 %). The combination of **78** and **80** gave the secondary amine **81**, which upon treatment with paraformaldehyde in a Dean-Stark apparatus provided **82** in excellent yield (95 %). At 450 W **82** cyclised affording **83**. Dihydroxylation of the C=C bond occurred with osmium tetroxide in the presence of a hexacyano iron complex to afford **84** in excellent yield (η= 90 %). Oxidative cleavage of the vicinal diol with sodium periodate followed by reduction with sodium borohydride gave the alcohol **85** (η= 82 % for 2 steps) as single diastereomer. Benzyl protection of the formed alcohol function provided compound **86**. Cleavage of the acetal protection with aq. HCl followed by the protection with the benzyl groups, gave **87** (η= 78 %). Treatment of **87** in strong acidic medium (HCl 6 M) removed the methylene group between the nitrogen and oxygen atoms. Then, with $(Boc)_2O$, the nitrogen atom is protected, and finally the alcohol was oxidized to carboxylic acid **88** using PDC (η= 57 % for 3 steps). The removal of the Boc was carried out with TFA, then, a coupling agent, Mukaiyama reagent, provided the closure of 4-membered ring, forming the β-lactam **89** (η= 53 %). Lactam **90** was isolated in excellent yield (η= 95 %) after hydrogenolysis of **89**.

This bicycle azasugar **90**, had demonstrated inhibitory activity, against α-galactosidase (K_i= 900 μM) and β-galactosidase (K_i= 172 μM).



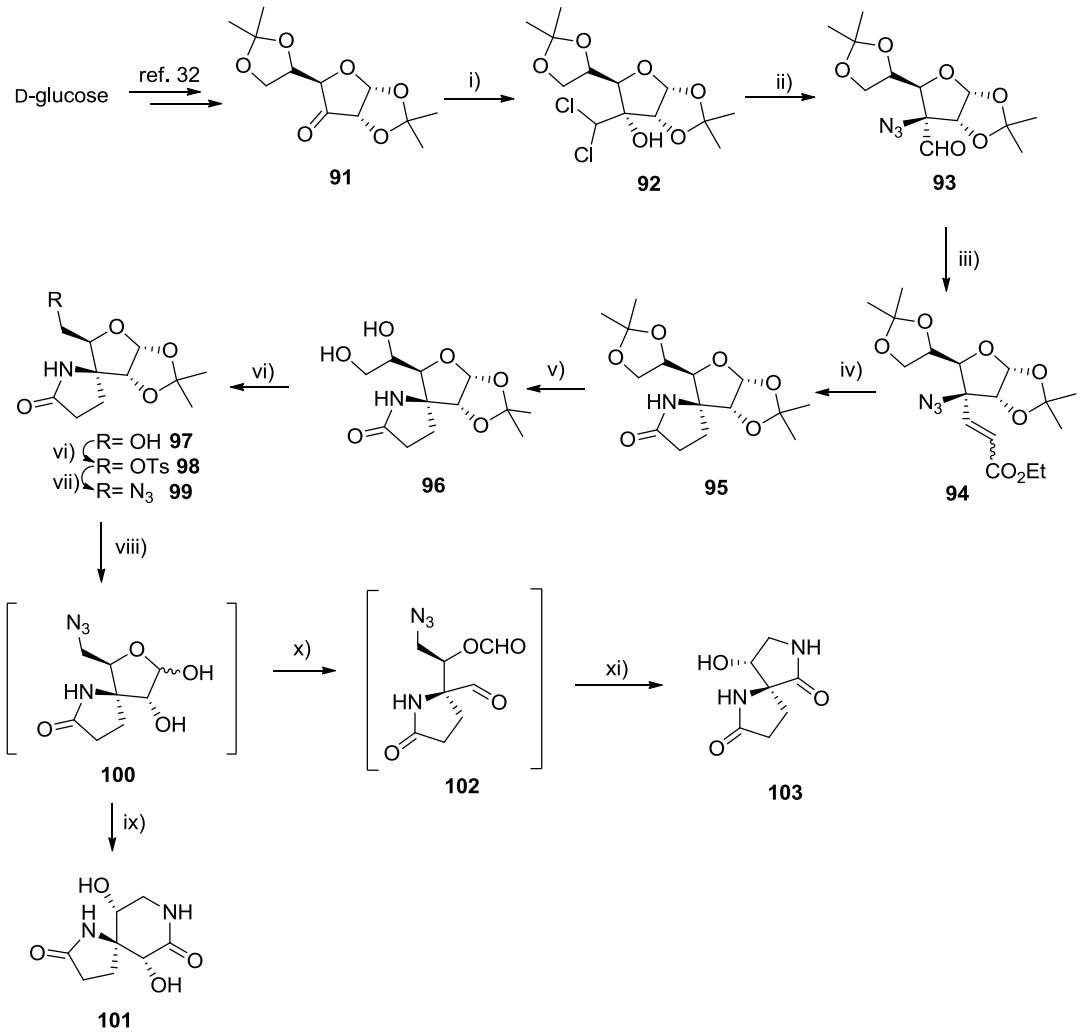
Scheme 12

Reagents and conditions[29]: i) IBX, EtOAc, reflux, 9 h, 85 %; ii) $(Boc)_2O$, TEA, 18 h; iii) $CH_3CH(OEt)_2$, PPTS, benzene, reflux, 24 h, 77 % for 2 steps; iv) *s*-BuLi, TMEDA, - 78 ºC, 3 h, then TMSCl, -78 ºC to rt, 3 h; v) 2 N HCl, dioxane, 80 ºC, 45 min, 88 % for 2 steps; vi) $NaBH(OAc)_3$, 1,2-dichloroethane, 12 h, then 2 N NaOH, 2 h, 71 %; vii) $(CH_2O)_n$, benzene, Dean-Stark, 4 h, 95 %; viii) hν, 450 W, lamp, CH_3CN, *i*-PrOH (3:1), 4 h, 60 %; ix) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, py, *t*-BuOH/H_2O (1:1), rt, 16 h, 90 %; x) (a) $NaIO_4$, silica gel, 15 min, (b) $NaBH_4$, MeOH, rt, 4 h, 82 %; xi) BnBr, NaH, THF, reflux, 12 h, 86 %; xii) (a) 1 N HCl, MeOH, rt, 4 h, (b) BnBr, NaH, TBAI, THF, reflux, 24 h, 78 %; xiii) (a) 6 N HCl, dioxane-MeOH, reflux, 48 h, (b) $(Boc)_2O$, TEA, rt, DCM, 8 h, (c) PDC, DMF, rt, 8 h, 57 %; xiv) (a) TFA, DCM, 0 ºC, 3 h, (b) 2-chloro-1-methylpyridinium iodine, TEA, CH_3CN, 60 ºC to rt, 32 h, 53 %; xv) H_2, Pd/C, 60 psi, MeOH, 6 h, 95 %.

Recently, Parihar *et al*[31], reported the synthesis of the first two hydroxylated spiro-bislactam **101** and **103** (**scheme 13**), as selective and potent glycosidase inhibitors.

Compound **91** was synthesised from D-glucose following a procedure reported in the lit[32]. Treatment of **91** with lithium diisopropylamide in DCM provided the adduct obtained from addition of a dichloromethane unit to the ketone function giving **92** with moderate yield (η= 60 %). Heating **92** in presence of catalytic amount of TBAI, provide the formation of a chlorooxirane intermediate, that was further attacked by sodium azide, opening the oxirane ring with formation of compound **93** (η= 82 %). Elongation by Wittig reaction gave **94**, which after hydrogenolysis of the azido group, afforded the free amine. An intramolecular cyclization occurred spontaneously by the attack of the amine to the ester function, providing compound **95** with η= 86 %. Selective removal of the exocyclic isopropylidene group was obtained with aqueous acetic acid giving diol **96**. Which was submitted to oxidative cleavage, followed by reduction to afford **97** (η= 87 %). Tosylation of the free alcohol function in pyridine and catalytic DMAP followed by substitution of the *O*-tosyl group by azide furnished compound **99**. Treatment of **99** with TFA led to the removal of the last isopropylidene group, giving the intermediate **100** which upon treatement with TFA/H_2O for longer time gave compound **101** which was isolated in 87 % yield. If **100** was treated first with sodium periodate, was isolated intermediate **102**, which upon TFA treatment gave the 5-member ring lactam **103** with good yield (η= 73 %).

Spiro-lactam **101** demonstrated a very good inhibitory activity against α-mannosidase (IC_{50}= $1.07x10^{-7}$ M) and α-galactosidase (IC_{50}= $1.27x10^{-7}$ M). However, **103** showed to be more potent that **101** against α-mannosidase (IC_{50}= $8x10^{-8}$ M) and α-glucosidase (IC_{50}= $1.77x10^{-7}$ M).



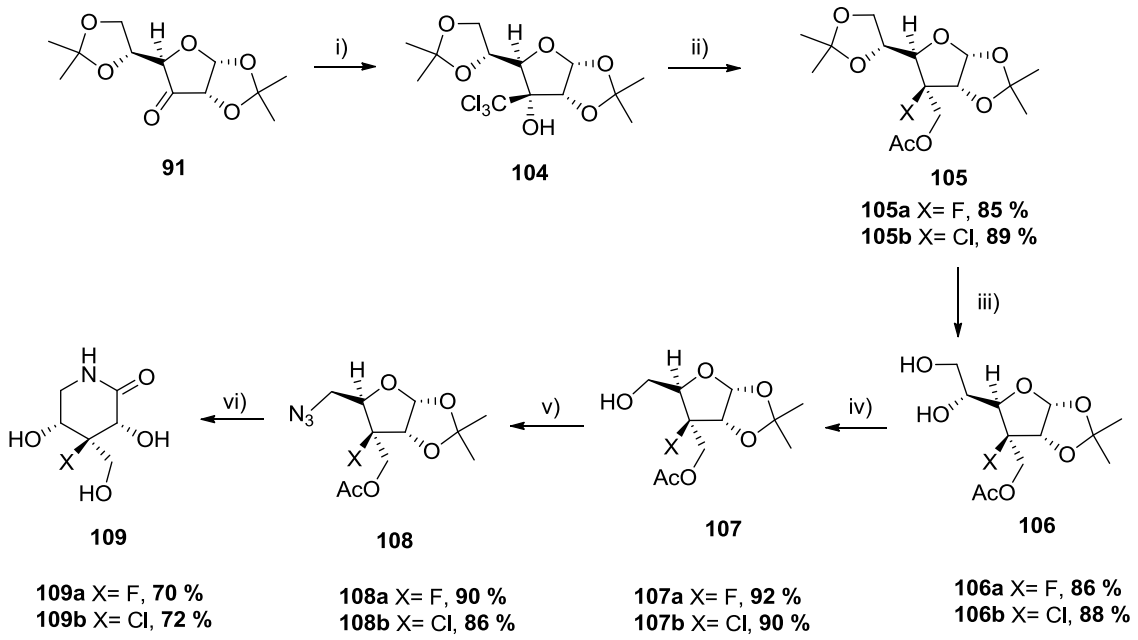
Scheme 13

Reagents and conditions[31]: i) LDA, THF, DCM, -78 ºC to rt, 60 %; ii) NaN_3, cat. TBAI, DMF, 60 ºC, 8 h, 82 %; iii) PPh_3=CH-CO_2Et, DCM, reflux, 2 h, 92 %; iv) H_2, Pd/C, MeOH, rt, 12 h, 86 %; v) (a) $NaIO_4$, acetone-water, 0 ºC to rt, 4 h, (b) $NaBH_4$, MeOH-H_2O, 0 ºC, 4 h, 87 %; vi) TsCl, py, cat. DMAP, 0 ºC to rt, 12 h, 92 %; vii) NaN_3, dry DMF, 100 ºC, 6 h, 93 %; viii) TFA-H_2O (3:1), 0 ºC to rt; ix) TFA-H_2O (5:1), 0 ºC to rt, 24 h, 87 %; x) $NaIO_4$, acetone-water, 0 ºC to rt, 4 h; xi) TFA-H_2O (5:1), 0 ºC to rt, 24 h, 73 %.

Bhuma and co-workers[20] synthesised lactams with D-xylose configuration, bearing a halogen (fluoride or chloride) at position 4 (**scheme 14**). Starting from compound **91**, a CCl_3 unit was selectively added to the ketone function providing alcohol **104** (η= 65 %). A dichloroepoxide was formed *in situ* in the presence of DBU; this was further opened by nucleophilic attack of a chloride ion, affording compound **105b**. The fluoro compound **105a** was obtained through the same procedure, but using

CsF as the nucleophile source. Selective removal of the exocyclic isopropylidene group, was carried out by acetic acid 65 % giving compounds **106**, isolated in good yields (η= 86-88 %). Oxidative cleavage with sodium periodate gave the corresponding aldehyde, that was reduced with sodium borohydride providing the respective alcohols **107** (η= 90-92 %). Activation of the hydroxyl group with triflic anhydride, followed by substitution with azide affording compounds **108** (η= 86-90 %). Treatment with TFA allowed the isolation of lactams **109** in good yields (η= 70-72 %).

The glycosidase inhibitory activity of these lactams were tested against α-glucosidase (baker's yeast and rice), β-galactosidase (bovine liver and almond), α-mannosidase (almond and jack bean), α-fucosidase (bovine kidney) and *N*-acetyl-β-D-glucosaminidase (jack bean and bovine kidney). None showed to be potent inhibitors at 10 mM.



Scheme 14

Reagents and conditions[20]: i) LHMDS, $CHCl_3$, -78 ºC, 65 %; ii) (a) for **105a**: CsF, DBU, *t*-BuOH, MeOH, rt, 2 h, for **105b**: DBU, MeOH, rt, 2 h, (b) Ac_2O, py, DCM; iii) 65 % AcOH/H_2O, 50 ºC, 3.5 h; iv) (a) $NaIO_4$, THF/H_2O, 0 ºC to rt, 2.5 h, (b) $NaBH_4$, MeOH, 0 ºC, 20 min; v) (a) Tf_2O, pyridine, DCM, -10 ºC, 1 h, (b) cat. TBAI, NaN_3, DMF, rt, 1 h; vi) (a) TFA/H_2O (5:1), 0 ºC to rt, 14.5 h, (b) TFA, 0 ºC to rt, 12 h.

Wang and co-workers[33] reported new *N*-substituted glucose-type δ-lactams, bearing aliphatic or aromatic substituents. The octyl chain showed to be the most promising lactam synthesised for the treatment of Gaucher's disease. Using it in chaperone therapy revealed a significative increase in the activation of mutant N370S β-glucocerebrosidase (**figure 9**).

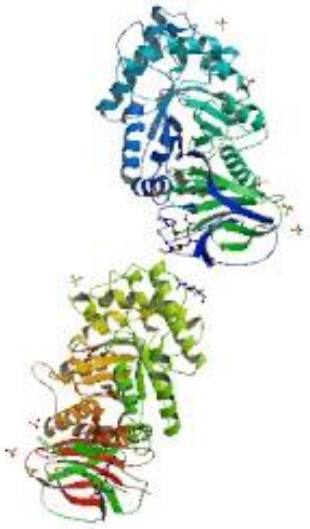
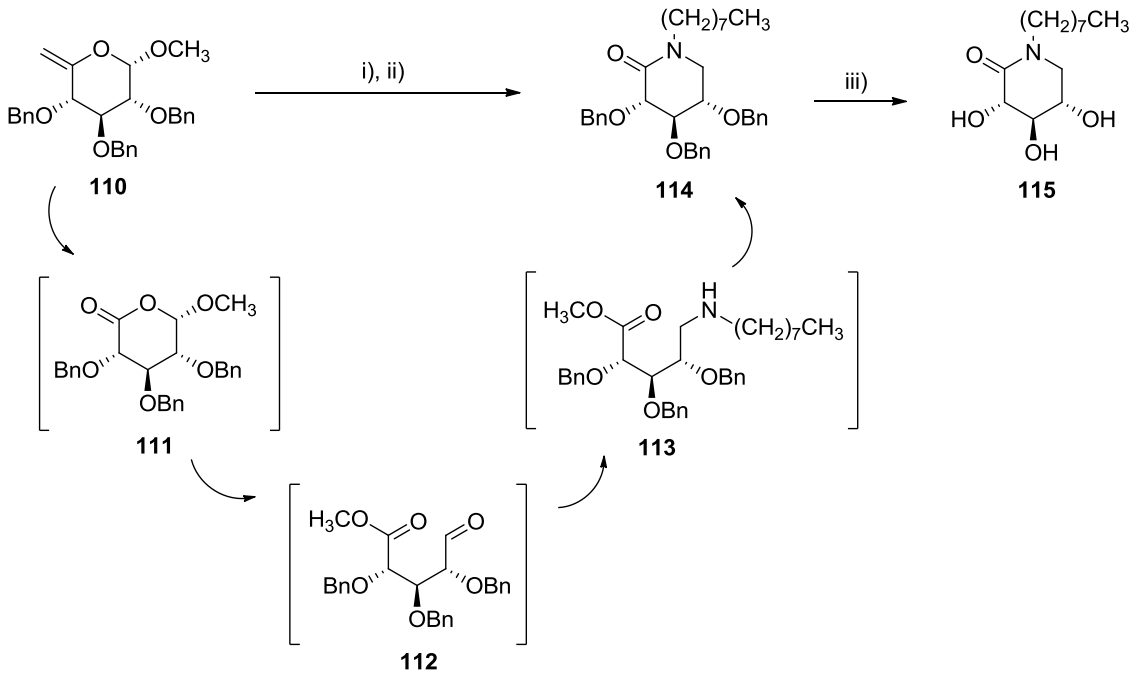


Figure 9 Structure of N370S β-glucocerebrosidase[34].

The synthesis of lactam **115** is presented in **scheme 15**. First, compound **110** was submitted to ozonolysis giving lactam **111**. This lactam was not isolated; the crude material was treated instead with $NaCNBH_3$, $ZnCl_2$ and the amine, leading through a cascade of reactions to lactam **114** with good yield (η= 82 %). The authors propose the formation of intermediate **112** by methanolysis under action of $ZnCl_2$, followed by reductive amination to give **113** which spontaneously cyclize[33]. The final step consisted in the removal of benzyl groups leading to the formation of lactam **115** in excellent yield (η= 98 %).



Scheme 15

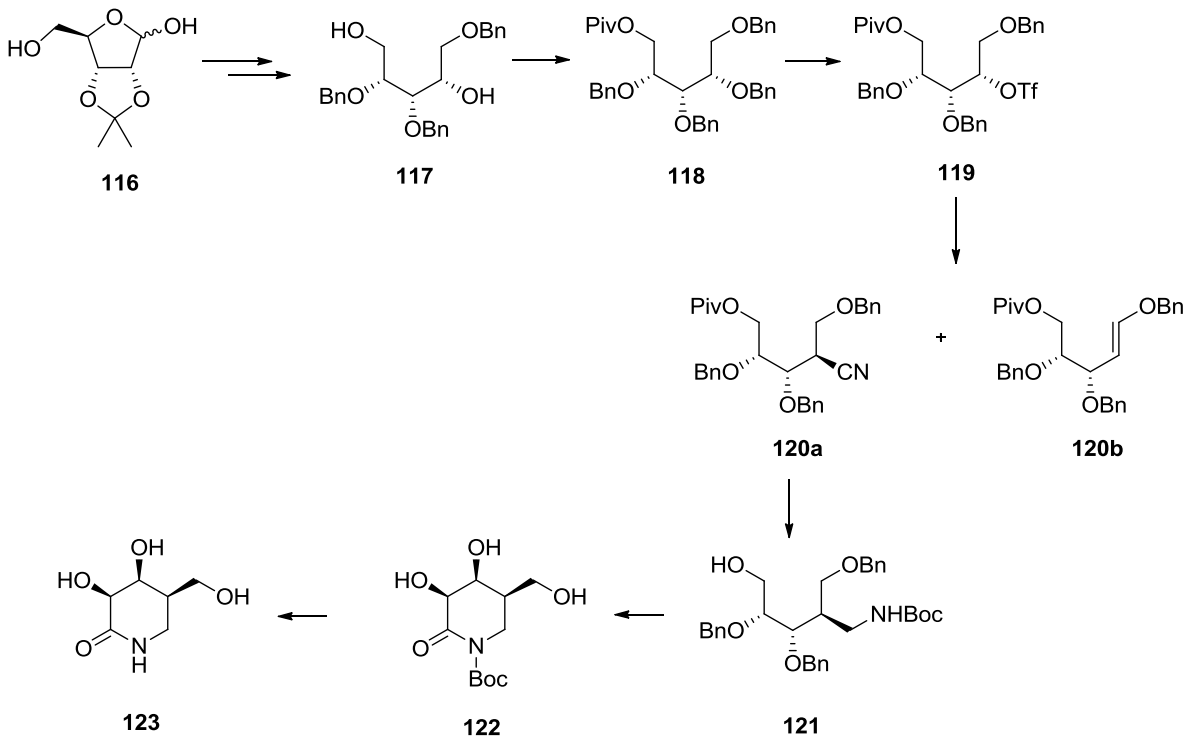
Reagents and conditions[33]: i) O_3, Me_2S, MeOH, -78 ºC, 3 min; ii) Amine, $NaCNBH_3$, $ZnCl_2$, reflux, 2 h, 82 %; iii) 10 % Pd/C, H_2, AcOH, H_2O, THF (4:2:1), 24 h, 98 %.

Chris H. Hill *et al*[3] synthesised many imino-sugars from a common intermediate **117**, starting with 2,3-*O*-isopropylidene-D-ribofuranose **116** which gave **117** in 9 steps with 80.4 % overall yield. The synthesis of iso-*galacto*-fagomine lactam **123** is represented in **scheme 16**.

The starting material is reacted with pivaloyl chloride in the presence of pyridine leading to selective protection of the primary alcohol with formation of **118** in good yield (η= 83 %). The remaining alcohol function was activated with triflic anhydride (**119**), substituted by cyanide to give **120a** (η= 49 %). In the process, the elimination product **120b** is also formed in 18 % yield. Reduction of cyano group using nickel chloride with sodium borohydride, led to the amine, which was not isolated, but the reaction mixture treated with Boc_2O providing the protected amine **121** (η= 51 %). Oxidation of **121** by treatment with TEMPO and *m*-CPBA in presence of TBAB afford the lactam **122** instantly in good yield (η= 74 %). Hydrogenolysis under Pearlman's

catalyst deprotected the alcohol functions, and addition of TFA removed the Boc group leading to the desire lactam **123** (η= 68 %).

This lactam **123** had shown to be a promissory scaffold for potential treatment of Krabbe's disease, a devastating neurodegenerative disorder[3], acting as chaperone. The authors proved that lactam **123** is more active than the fagomine analogue.



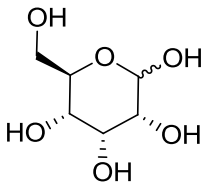
Scheme 16

Reagents and conditions[3]: i) PivCl, py, 0 ºC, 3.5 h, 83 %; ii) Tf_2O, py, DCM, 20 min; iii) TBACN, THF, 0 ºC, 1.15 h, **120a** 49 %, **120b** 18 %, (for 2 steps); iv) (a) $NiCl_2 \cdot 6H_2O/NaBH_4$, Boc_2O, MeOH, 0 ºC to rt, ov; (b) Boc_2O, K_2CO_3, MeOH, 40 ºC, 44 h, 51 %; v) TEMPO, *m*-CPBA, TBAB, DCM, rt, instantaneous, 74 %; vi) (a) H_2, $Pd(OH)_2/C$, AcOEt/MeOH, 1.5 h, (b) TFA, 15 min, 68 %.

5. D-Allose scaffold

5.1. Biological relevance

Allose **124** (**figure 10**) is a rare sugar, a C3 epimer of glucose, which belong to the aldohexose family. Therapeutically, is used as an inhibitor of sporocarp formation, a multicellular structure, and of sporulation of *Myxococcus Xanthus*[35].



124

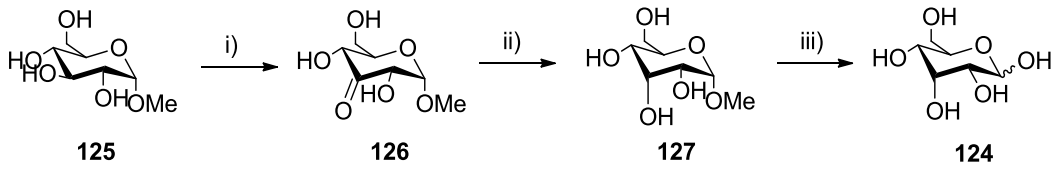
Figure 10 D-allose.

Besides this application, D-allose had demonstrated activity as antitumor, anti-inflammatory, antihypertensive, immunosuppressant[36]. It inhibits proliferation of cancer cells[37], is an anti-oxidante[38], and display protective properties in ischemia-reperfusion injuries[39-41].

5.2. Synthetic strategies

There are no many synthetic strategies for the synthesis of allose and precursors. It can be extracted from *Prontea Rubropilosa* as 6-*O*-cinnamyl glycoside, or from the alga *Ochromas malhamensis*[42]. One strategy reported in the literature is the conversion of D-ribose by pyranose oxidase enzyme. This methodology is in one hand expensive due to the high price of the enzyme, and on the other hand, presents low selectivity, giving different allose derivatives[43], and also other sugars. Other reported methodology for the synthesis of D-allose starts from D-glucose.

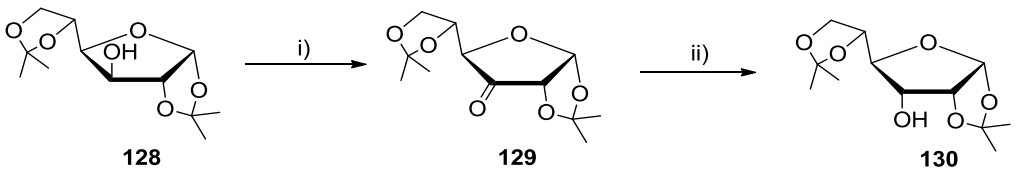
Minnaard *et al*[44] developed a selective method to oxidise C_3 of 1-methoxy-glucose **125** with palladium catalyst and benzoquinone to give the ketone **126** (**scheme 17**). Reduction of the ketone function with sodium borohydride gave the inverse configuration at C_3. Compound **127** was obtained in excellent yield (η= 95 %). D-Allose was isolated after treatment with TFA.



Scheme 17

Reagents and conditions[44]: i) 2.5 % palladium complex, benzoquinone, CH_3OH/H_2O, 98 %; ii) $NaBH_4$, MeOH, 0 ºC, 95 %; iii) TFA (yield not show).

Diacetone allose **130** can be obtained from glucose diacetonide **128** by a similar approach[45] (**scheme 18**).



Scheme 18

Reagents and conditions[45]: i) Tetrabutylammonium bromide, KBr, tetramethylpiperidine, nitrogen oxide, H_2O_2, DCM, 10-15 ºC, 2 h; ii) $NaBH_4$, isopropanol, 10 ºC, 50 min, 74.7 %.

CHAPTER 2

RESULTS AND DISCUSSION

Introduction

In this work, the D-erythrose moiety was tested as chiral inductor in the synthesis of amine, lactone and lactam derivatives of this sugar unit. The work is divided in part A and part B; part A is relative to amines synthesis and part B is relative to lactones and lactams synthesis.

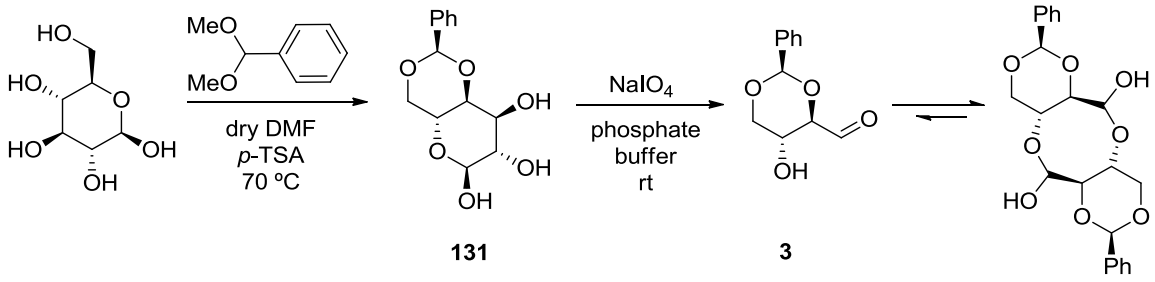
In part A, imines were obtained in the first instance, by the reaction of the aldehyde **3** with aliphatic amines. The crude products were analysed by ^{1}H NMR spectroscopy to access whether the reaction is complete. The imines were not isolated, but reacted further with hydride and carbon nucleophiles. Reductive reactions with $NaBH_4$ gave secondary amines in good yields. With carbon nucleophiles, the imines either gave mixture of products or showed no reactivity.

In part B of the work, was obtained an erythrose δ-lactone derivative **133** which was tested as reagent in epoxidation, osmilation, aziridination and bromination of the C=C incorporated in the lactone, and in Michael addition. Osmilation gave the target product; epoxidation and aziridination fail to occur. Bromination attempts gave complex mixtures. Very interesting results were obtained by Michael addition to the unsaturated δ-lactone **133** with C-, S- and N-nucleophiles. These adducts were the key step to the synthesis of new chiral polyhydroxylated lactones, lactams and open-chain products. The stereo-selectivity was found to be complete in every case, and the products were obtained pure by simple work-up. The new compounds were tested against glycosidases to judge their inhibitory potency and selectivity.

2.1. Synthesis of the precursors: aldehyde 3 and lactone 133

2.1.1. Synthesis of aldehyde 3

An efficient methodology for the synthesis of aldehyde **3** has been reported in two steps[46], starting with D-glucose, a cheap chiral material. D-glucose was reacted with benzaldehyde dimethyl acetal in the presence of a catalytic amount of *p*-toluenesulphonic acid to obtain 4,6-*O*-benzylidene-D-glucopyranose **131** formed in 58.3 %, as a white solid obtained by precipitation (**scheme 19**).



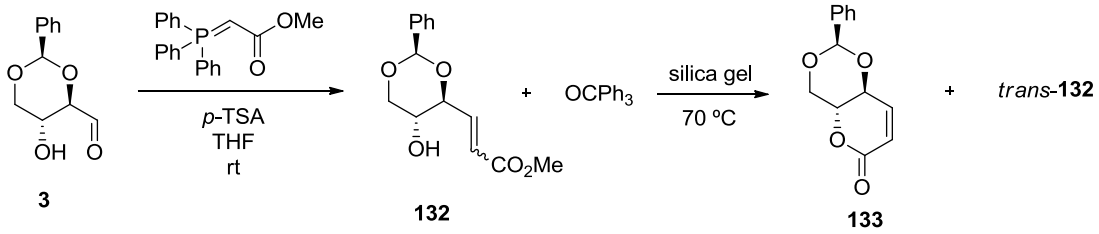
Scheme 19

Oxidative cleavage of **131** occurred with sodium periodate in phosphate buffer at pH= 7.8. The product, compound **3**, was obtained in quantitative yield, without purification, as an yellow oil. ^{1}H NMR spectroscopy analysis of the aldehyde **3** shows a complex pattern probably due to the equilibrium with the dimeric structure shown in **scheme 19**. In D_2O the spectrum shows a single pattern probably of the dimer. The equilibrium is shifted to the aldehyde monomer in the presence of acid catalysis, which allows the Wittig reaction in the next step.

2.1.2. Synthesis of lactone 133

Wittig reaction[47] is the preferred method for the synthesis of a C=C bond. It occurs by reaction of an aldehyde or ketone with a phosphin ylide. The geometry of the double bond depends on the reaction conditions and on the nature of the ylide used. Generally, a stabilized ylide generates the *E* isomer, and a non-stabilized the *Z* isomer.

Aldehyde **3** was reacted with methyl 2-(triphenylphosphoranylidene)acetate in the presence of catalytic amount of *p*-toluenesulphonic acid as described in the lit[48] (**scheme 20**). After flash chromatography, isomers **132** were isolated (η= 92.9 %), in 2.3:1 ratio, with preference to the *Z* compound.



Scheme 20

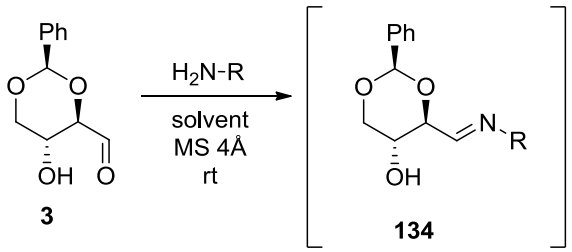
An intramolecular cyclization of the *Z* isomer **132** occurs at 70 ºC[48], after several hours at 500 mbar. This constitutes an upgrade of the synthesis of δ-lactone **133**, obtained in large scale from 4 g of compound **132**. Compound **133** was obtained in 60.3 % yield. The reactivity and selectivity of lactone **133** to nucleophiles is the object of study of this work.

Part A. Reactions with aldehyde 3

2.2. Synthesis of amines 135a-e

2.2.1. Synthesis of imines 134a-f

The syntheses of the imines were performed in dry solvent under N_2 atmosphere and under freshly activated molecular sieves 4 Å. The end of the imines synthesis (**scheme 21**) was observed by ^{1}H NMR ($CDCl_3$), where the characteristic peak C*H*=N appeared between δ_H 7.82-8.73 ppm. All the imines could not be isolated, except in the case of phthalimide derivative **134f**.



134a R= Pr
134b R= ^{t}Bu
134c R= CH_2Ph
134d R= (*S*)-CH_3CHPh
134e R= (*R*)-CH_3CHPh
134f R= Phthalimide

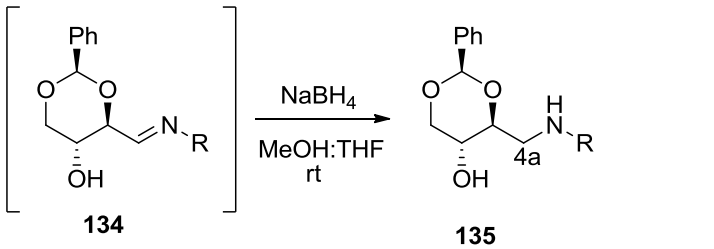
Scheme 21

Table 1 Synthesis of imines **134**: starting amine, reaction time and chemical shifts of the C*H* imine function.

Entry	Amine	Time	δ_H of imine peak (ppm)
1	NH_2Pr	30 min	7.87
2	$NH_2{}^tBu$	1 h	7.82
3	NH_2Bn	2 h	7.98
4	(*R*)-(+)-α-NH_2CHCH_3Ph	45 min	7.95
5	(*S*)-(−)-α-NH_2CHCH_3Ph	45 min	7.95
6	NH_2Pht	12 h	8.73

2.2.2. Reduction of the imines 134a-c,e

After the imine synthesis, the reductive process is followed immediately. First was added a mixture of MeOH:THF (1:1), then 2 eq. of $NaBH_4$. The mixture was stirred at rt for different periods of time, to afford the respective amines **135a-e** as pure products in low to good yields η= 37.1-87.2 % (**scheme 22**). By ^{1}H NMR spectroscopy is possible to visualize the disappearance of the imine peak, and the appearance of a doublet of doublets between δ_H 2.75-3.17 ppm, corresponding to *H*-4a, with a geminal constant *J*= 11.6-12.2 Hz. In the ^{13}C NMR spectra of C_{4a} showed up its signal at the aliphatic region (δ_C 46.9-53.2 ppm) as expected. All the other signals appeared at a lower field due to the direct attachment to an oxygen atom. In the case of C_2 the peak showed up at ≈100 ppm due attachment to two oxygen atoms.

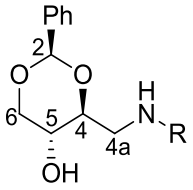


134 **135**

135a R= Pr
135b R= ^{t}Bu
135c R= CH_2Ph
135d R= (*S*)-CH_3CHPh
135e R= (*R*)-CH_3CHPh

Scheme 22

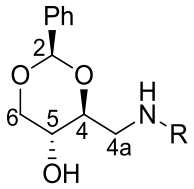
Table 2 ^{1}H NMR spectroscopic data of amines **135a-e** (400 MHz, $CDCl_3$, ppm).



Comp.	*H*-2	*H*-4	*H*-4a	*H*-5	*H*-6
135a	5.52 (s)	3.69 (td, *J*= 8.4, 4.0 Hz)	2.97 (dd, *J*= 12.0, 8.8 Hz); 3.14 (dd, *J*= 12.2, 4.8 Hz)	3.82 (td, *J*= 10.0, 5.2 Hz)	3.62 (t, *J*= 10.8 Hz); 4.31 (dd, *J*= 10.8, 5.2 Hz)
135b	5.52 (s)	3.59 (td, *J*= 9.6, 4.0 Hz)	2.87 (dd, *J*= 11.6, 10.0 Hz); 3.17 (dd, *J*= 11.6, 4.4 Hz)	3.82 (td, *J*= 10.0, 5.2 Hz)	3.62 (t, *J*= 10.4 Hz); 4.31 (dd, *J*= 10.4, 5.2 Hz)
135c	5.51 (s)	3.70 (td, *J*= 8.8, 4.4 Hz)	2.98 (dd, *J*= 12.0, 8.8 Hz); 3.17 (dd, *J*= 12.0, 4.4 Hz)	3.84 (td, *J*= 9.6, 5.2 Hz)	3.63 (t, *J*= 10.4 Hz); 4.31 (dd, *J*= 10.8, 5.2 Hz)
135d	5.47 (s)	3.58 (td, *J*= 8.4, 4.4 Hz)	2.86 (dd, *J*= 12.0, 8.4 Hz); 2.97 (dd, *J*= 12.0, 4.8 Hz)	3.86 (td, *J*= 10.0, 5.2 Hz)	3.61 (t, *J*= 10.4 Hz); 4.31 (dd, *J*= 10.4, 5.2 Hz)
135e	5.46 (s)	3.59-3.70 (m)*	2.75 (dd, *J*= 12.0, 8.4 Hz); 2.98 (dd, *J*= 12.0, 4.4 Hz)	3.59-3.70 (m)*	3.58 (t, *J*= 10.4 Hz); 4.25 (dd, *J*= 10.4, 4.4 Hz)

*indistinguishable

Table 3 ^{13}C NMR spectroscopic data of amines **135a-e** (100 MHz, $CDCl_3$, ppm).



Comp.	C_2	C_4	C_{4a}	C_5	C_6
135a	101.3	78.2	53.2	67.7	70.9
135b	101.3	79.0	46.9	64.7	70.9
135c	101.3	78.4	52.6	67.5	70.9
135d	101.2	79.1	51.1	67.3	70.8
135e	101.1	78.7	50.6	67.0	70.7

2.3. Attempts of pyrrolidine synthesis

Polyhydroxylated pyrrolidines bearing hydrophobic groups (**136**) proved to be potent inhibitors of α-D-galactosidase and α-L-fucosidase with values of K_i between 0.25-9.0 μM[49]. Also, compounds like **137**, proved to be excellent inhibitors of mannosidases, which can be considered as alternative lead of swainsonine[50] (**figure 11**).

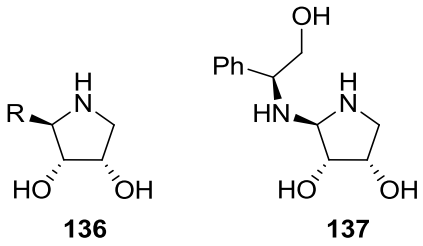
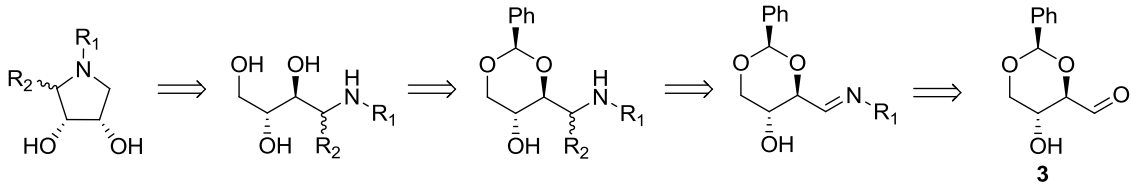


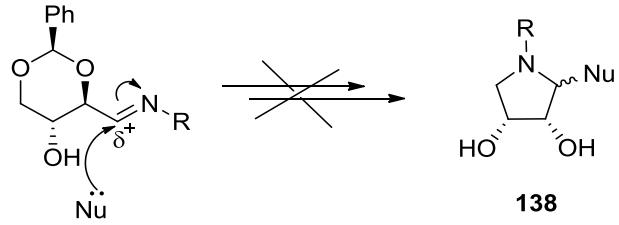
Figure 11

The synthesis of this type of compounds can be rationalized from aldehyde **3**. A retro-synthetic plan is shown in **scheme 23**. Imines will be first synthesized and then its reactivity tested to carbon nucleophiles, acetal cleavage and finally, ring closure to afford the polyhydroxylated pyrrolidines.



Scheme 23

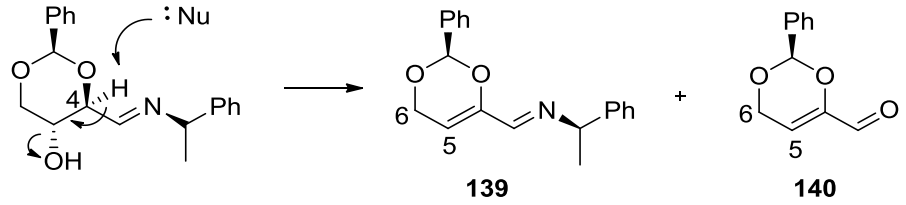
Unfortunately, the imine crude products were reacted with carbon nucleophiles, without success (**scheme 24**). The instability of the imine may in part explain the failure of the attempts to obtain polyhydroxylated pyrrolidines **138**. **Table 4** summarize reagents and conditions of the attempts made.



Scheme 24

Grignard reagents led to intractable mixtures, except in entry 9 where it was possible to identify two of the products formed; they were formed by water elimination as shown in **scheme 25**. Compounds **139** and **140** were isolated in 4.8 % and 3.1 % respectively. The compounds were identified by ^{1}H, ^{13}C NMR spectroscopy combined with bidimentional HMBC and HSQC spectra. From the mechanistic point of view, the formation of these compounds is possible due to the acidic nature of *H*-4 under the influence of the imine bond. The nucleophile used, acts as a base, removing this proton, promoting water molecule elimination. Hydrolysis of the imine function in compound **139**, explains the formation of aldehyde **140**.

^{1}H NMR spectra of compounds **139** and **140** showed two doublet of doublets corresponding to the *H*-5 at δ_H 5.58/6.12 ppm, with *J*= 3.6 and 2.4 Hz to the two *H*-6. On the other hand, each *H*-6 is also a doublet of doublets with a large geminal coupling *J*= 17.2/18.8 Hz and the vicinal coupling described to *H*-5. The imine peak appears at δ_H 7.69 ppm in compound **139**, and the aldehyde proton at δ_H 9.27 ppm in compound **140**, both as a singlet.



Scheme 25

Boronates also gave intractable mixtures, except for methyl boronates, which gave back the starting material probably for being less reactive.

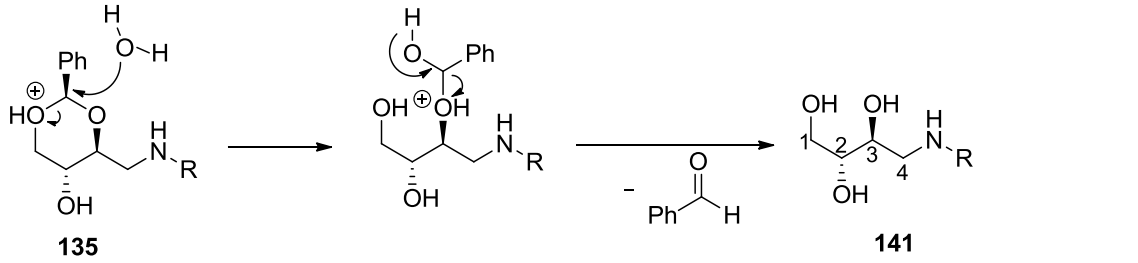
Table 4 Reaction conditions and results of C-nucleophiles attack to imines **134**.

Entry	Imine 122 (R)	Conditions	Results[a)]
1	Bn	1.1 eq. MeMgBr Dry THF, MS 4 Å 0 °C → rt, 20 h	Recovery of starting material
2	Bn	6 eq. MeMgBr Dry DCM, MS 4 Å, rt, 24 h	Complex mixture
3	Pr	5 eq. vinylMgBr Dry DCM, MS 4 Å, rt, 23 h	Complex mixture
4	Pr	3 eq. vinylMgBr Dry DCM, MS 4 Å -78 °C → rt, 5.30 h	Complex mixture
5	Pr	vinyl$B(OCH_3)_2$ dry THF, rt, 7 days	Complex mixture
6	Pr	methyl $B(OCH_3)_2$ (*S*)-Binol Dry toluene, MS 4 Å, rt, 2 days	No reaction
7	Pr	methyl $B(OCH_3)_2$ Dry toluene, MS 4 Å, rt, 2 days	No reaction
8	*R*-methylbenzyl-amine	3 eq. vinylMgBr -78 °C → rt, 24 h	Imine + unknown product
9	*S*-methylbenzyl-amine	4 eq. vinylMgBr 0 °C → rt, 18 h	Compounds **139** and **140**
10	Phthalimide	4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane Dry THF rt → 55 °C, 3 days	Recovery of the starting material
11	Pr	vinylMgBr $BF_3{\cdot}OEt_2$ Dry THF, -20 °C → rt, 24 h	Complex mixture
12	Bn	Tri-*o*-tolyl borate Dry DCM MS 4 Å, -78 °C → rt, 24 h	Complex mixture
13	Phthalimde	Tri-*o*-tolyl borate 20 % mol $BF_3{\cdot}OEt_2$ Dry DCM MS 4 Å, -78 °C → rt, 18 h	Complex mixture

a) By ^{1}H NMR spectroscopy.

2.4. Acetal cleavage of amines 135a-c,e

The removal of the acetal was obtained by dissolving the amine **135a-c,e** in 1,4-dioxane, followed by addition of HCl 1 M at rt (**scheme 26**). The solvent and the benzaldehyde formed were evaporated in the rotary evaporator. Crude products were dissolved in 1,4-dioxane and passed through basic resin. Removal of the solvent in the rotary evaporator, provided compounds **141a-c,e** as pure products in moderate to good yields (57.7-85.8 %).

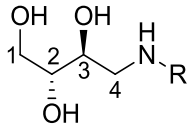


Scheme 26

^{1}H NMR spectra showed the absence of the proton of the acetal moiety and the phenyl group, as expected. Protons *H*-1, *H*-2 and *H*-3 appeared usually as multiplets, except for *H*-4 which showed up as doublet of doublets between δ_H 2.55-3.28 ppm with the geminal coupling constants *J*= 12.0-13.2 Hz.

The ^{13}C NMR spectra showed expected values compared to the precursors amines **135**.

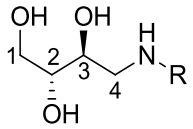
Table 5 ^{1}H NMR spectroscopic data of amino-alcohols **141a-c,e** (400 MHz, D_2O, ppm).



Comp.	*H*-1	*H*-2	*H*-3	*H*-4
141a	3.63-3.65 (m); 3.76-3.79 (m)	3.92 (ddd, *J*= 9.6, 6.8, 3.2 Hz)	3.67-3.70 (m)	3.07 (dd, *J*= 13.2, 9.6 Hz); 3.28 (dd, *J*= 12.8, 2.8 Hz)
141b	3.59-3.64 (m); 3.77 (dd, *J*= 10.8, 2.4 Hz)	3.64-3.70 (m)*	3.64-3.70 (m)*	2.64 (dd, *J*= 12.0, 8.0 Hz); 2.79 (dd, *J*= 12.0, 3.2 Hz)
141c	3.58-3.66 (m); 3.73-3.76 (m)	3.80-3.85 (m)	3.58-3.66 (m)	2.80 (dd, *J*= 12.8, 9.2 Hz); 2.99 (dd, *J*= 12.8, 2.8 Hz)
141e	3.52-3.59 (m)*; 3.65-3.70 (m)*	3.52-3.59 (m)*; 3.65-3.70 (m)*	3.52-3.59 (m)*; 3.65-3.70 (m)*	2.55 (dd, *J*= 12.4, 8.4 Hz); 2.64 (dd, *J*= 12.4, 3.6 Hz)

*indistinguishable

Table 6 ^{13}C NMR spectroscopic data of amino-alcohols **141a-c,e** (100 MHz, D_2O, ppm).



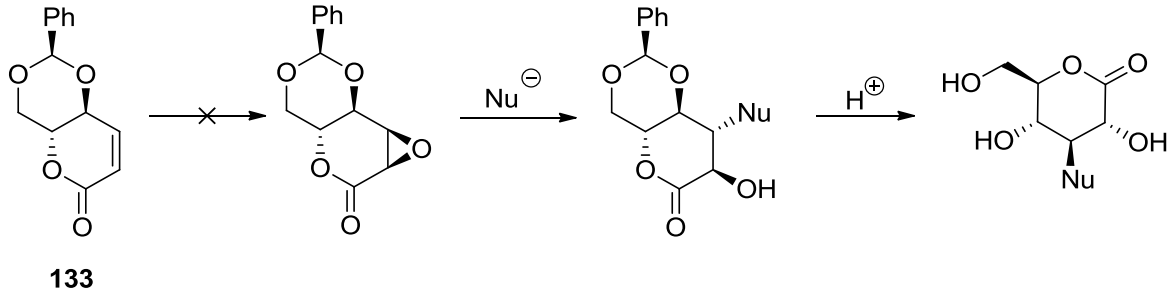
Comp.	C_1	C_2	C_3	C_4
141a	62.1	67.3	73.1	49.6
141b	61.8	70.8 or 73.5	70.8 or 73.5	43.4
141c	62.3	69.3	73.5	49.7
141e	61.8	70.1 or 73.3	70.1 or 73.3	48.5

Part B. Reactions with lactone 133

2.5. Attempts to epoxidation of 133

Epoxides are a 3-member ring *O*-heterocycles, very useful in synthesis due to the possibility of ring-opening with a large range of nucleophiles, including many times the control of stereo- and regio-selectivities[51].

Epoxidation of the C=C bond in lactone **133**, followed by ring-opening, would led to the introduction of two vicinal functions, according to **scheme 27**, that we found interesting to explore.



Scheme 27

Standard epoxidation procedures[52,53] were followed, namely *m*-CPBA protocol, oxone method and hydrogen peroxide 30 %. The reactions did not work, and the amount of starting reagent was totally recovered pure or contaminated with the product formed after benzylidene acetal cleavage (**table 7**).

Table 7 Attempts to epoxidation of compound **133**.

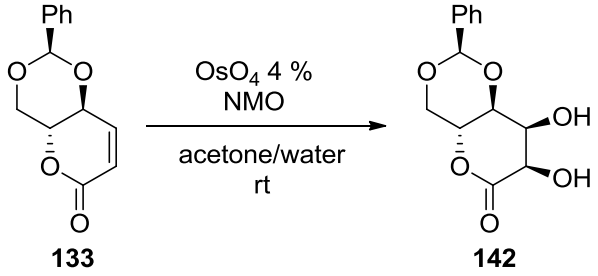
Entry	Conditions	Results[a)]
1	**133** (1 eq.), 1,1,1-trifluoracetone (10 eq.), $NaHCO_3$ (18 eq.), oxone (25 eq.), CH_3CN/H_2O, 0 ºC → rt, 24 h.	**133**[b)]
2	**133** (1 eq.), *m*-CPBA (1 eq.+2), DCM, rt → reflux, 21 h.	**133**[b)]
3	**133** (1 eq.), H_2O_2 30 % (1.5 eq.) 1,4-dioxane, rt → 40 ºC, 7 days.	**133**
4	**133** (1 eq.), 1,1,1-trifluoracetone (10 eq.), $NaHCO_3$ (15 eq. + 25), oxone (5 eq. + 10), CH_3CN/H_2O, rt, 15 days.	**133**

a) By ^1H NMR spectroscopy.
b) Contaminated with benzylidene acetal cleaved compound.

2.6. Osmilation of 133

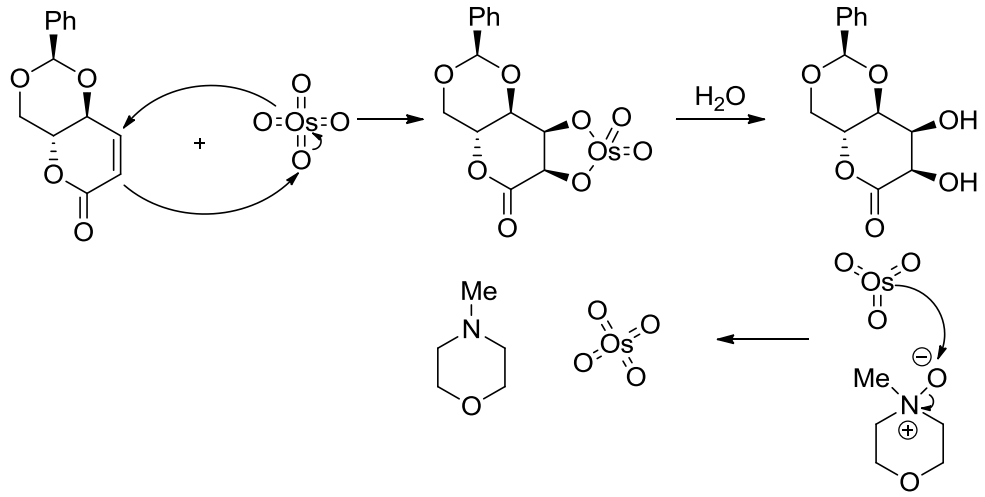
Upjohn dihydroxylation[54] methodology is used for *cis* hydroxylation of C=C bonds, using a catalytic solution of osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide as the oxidant agent, in acetone (10)/water (1) as solvents.

Applying the same conditions to lactone **133** was isolated pure compound **142**, after extraction, in moderate yield (40 %) as a white oil (**scheme 28**).



Scheme 28

One of the proposed mechanism for the Upjohn dihydroxylation is a 1,3-dipolar cycloaddition, that is represented in **scheme 29** for the conversion of lactone **133** into product **142**.



Scheme 29

Before in our laboratory, lactone **133** was reacted with various 1,3-dipoles, having been shown that the cycloaddition occurred by the *re* face, leading to the stereochemistry shown in **142**. In **figure 12** is shown compound **142** and compound **143** drawn in perspective. The structure of compound **143** had been fixed by single crystal X-ray[48].

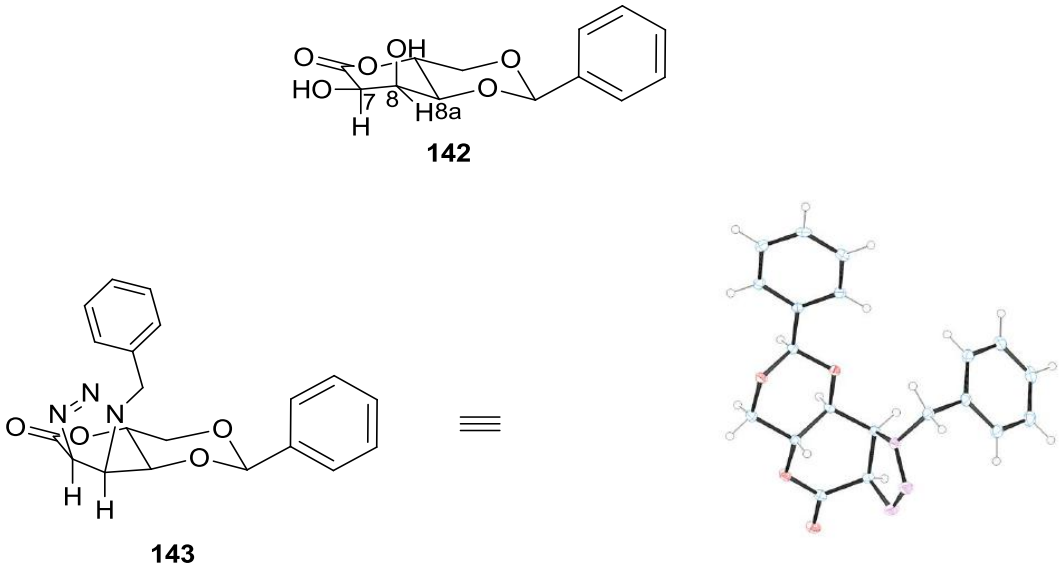
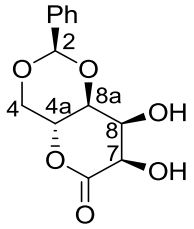


Figure 12

In the ^{1}H NMR spectrum, the acetal proton of the D-erythrose moiety appeared following the usual pattern. *H*-7 is a doublet, with *J*= 4.0 Hz, due to the vicinal *H*-8. *H*-8 is a doublet of doublets, coupling with *H*-7 (*J*= 4.0 Hz) and with *H*-8a (*J*= 6.4 Hz).

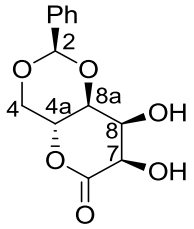
^{13}C NMR data was expected for the dihydroxylated compound, with the aliphatic peaks appearing in the low field aliphatic region.

Table 8 ^{1}H NMR spectroscopic data of compound **142** (400 MHz, D_2O, ppm).



Comp.	*H*-2	*H*-4	*H*-4a	*H*-8a	*H*-7	*H*-8
142	5.68 (s)	3.76 (dd, *J*= 11.2, 10.0 Hz); 4.32 (dd, *J*= 10.8, 5.2 Hz)	4.00-4.07 (m)	3.98 (dd, *J*= 9.6, 6.4 Hz)	4.49 (d, *J*= 4.0 Hz)	4.35 (dd, *J*= 6.0, 3.6 Hz)

Table 9 ^{13}C NMR spectroscopic data of **142** (100 MHz, D_2O, ppm).

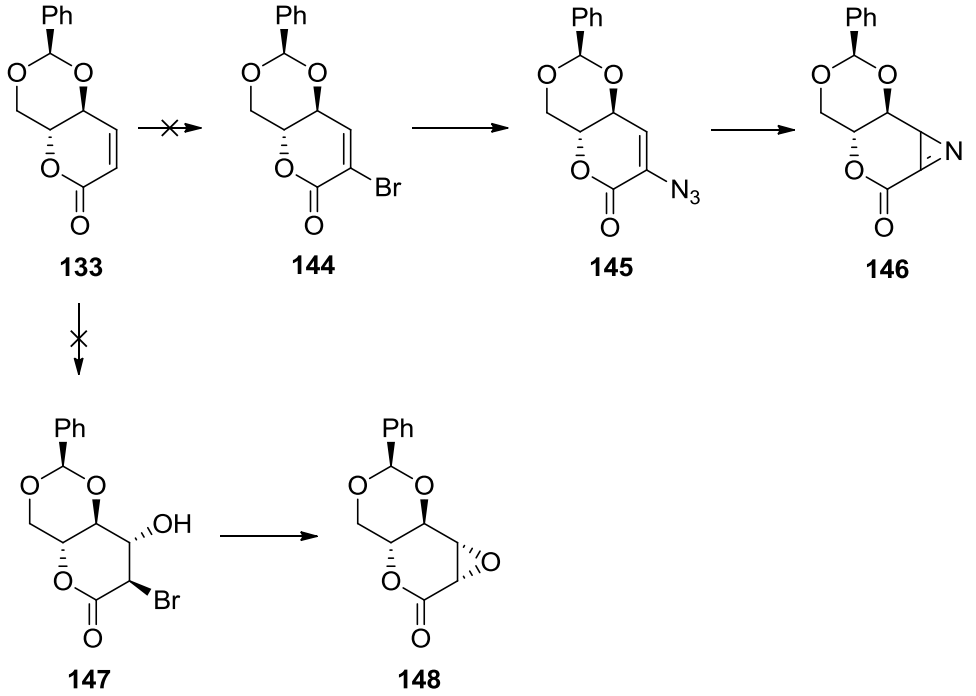


Comp.	C_2	C_4	C_{4a}	C_{8a}	C_7	C_8	C=O
142	100.9	69.9	63.3	78.7	71.8	74.0	175.4

2.7. Attempts to bromination of 133

The addition of bromine to double bonds has been widely described in the lit[55-57]. The introduction of bromide at the α-position of the carbonyl group in compound **133** can led to intermediate **144** that would be transformed either into the α-azido-carbonyl compound **145** or led to the α-bromohydrin compound **147** (**scheme 30**). The last, would be an alternative approach to achieve an epoxide **148**, this time with opposite configuration at the functional carbon atom, in relation to the first epoxide tried. The α-azido compound **145** would be pyrolysed to give 2*H*-azirine **146** and this

tested to several nucleophiles. None of the attempts made were effective, leading to the recovery of the starting material or complex mixtures (**table 10**).



Scheme 30

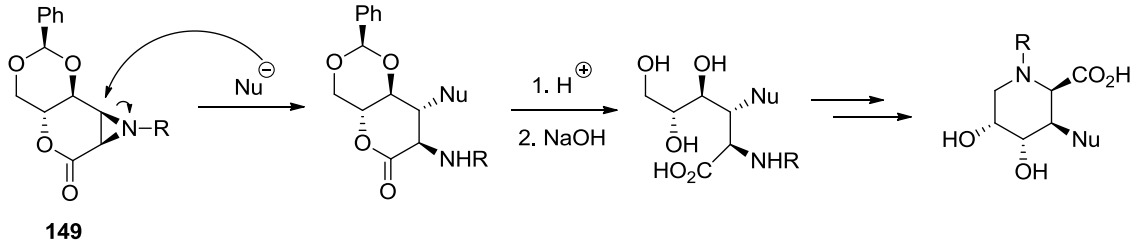
Table 10 Attempts to bromination of compound **133**.

Entry	Conditions	Results[a)]
1	**133** (1 eq.), NBS (1 eq. +1+1), rt, 7 days.	**133**
2	**133** (1 eq.), *N*-methylmorpholine *N*-oxide (1.5 eq.), NBS (1 eq.), rt, 6 days.	**133**
3	**133** (1 eq.), bromine (1 eq.) 0 ºC → rt, 30 min.	Complex mixture
4	**133** (1 eq.), bromine (1 eq.), NEt_3 (3 eq.), 0 ºC → rt, 24 h.	Complex mixture
5	**133** (1 eq.), bromine (1 eq.), NEt_3 (2 eq.), -15 ºC → rt, 3 days.	Complex mixture
6	**133** (1 eq.), pyridine *N*-oxide (1.5 eq. +1), NBS (1 eq. +1) rt, 9 days.	**133**

a) By ^{1}H NMR spectroscopy.

2.8. Attempts to aziridination of 133

In **scheme 31** is shown a reaction sequence in order to achieve piperidine products, an interesting type of compound from the biological point of view. Aziridine **149** has been obtained before[48] by photolysis of the adduct formed by addition of alkyl azides to lactone **133**. Now it was sought to turn the aziridine formation more expeditious.



Scheme 31

Several methods[58-63], using different combinations of *N*-aminophthalimide with lead(IV) acetate (entry 1-3), (diacetoxyiodo)benzene (entry 5) or 2-iodoxybenzoic acid (entry 6) appeared to be successful in the lit., as well as the use of *O*-(diphenylphosphinyl)hydroxylamine combined with *N*-methylmorpholine (entry 4) have been used. However, none of these procedures had showed to work in the present case. The starting material (**133**) was recovered in all cases, except in entry 5 (**table 11**), where the lactone opened to give the respective carboxylic acid.

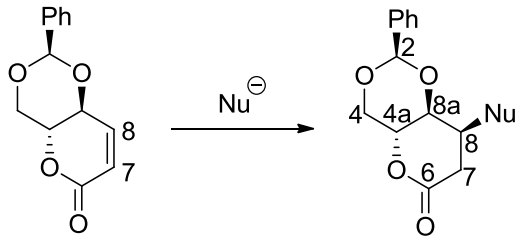
Table 11 Attempts to aziridination of compound **133**.

Entry	Conditions	Results[a)]
1	**133** (1 eq.), NH_2Pht (1.5 eq.), $Pb(OAc)_4$ (1.6 eq.), dry THF, 0 ºC → rt, 24 h.	**133**
2	**133** (1 eq.), NH_2Pht (1.5 eq.), $Pb(OAc)_4$ (1.6 eq. +1), dry THF, rt → reflux, 7 days.	**133**
3	**133** (1 eq.), NH_2Pht (1.5 eq.), $Pb(OAc)_4$ (1.5 eq. +1), K_2CO_3 (2.8 eq.), dry DCM, 0 ºC → rt, 17 days.	**133**
4	**133** (1 eq.), $DppONH_2$ (1.05 eq.), *N*-methylmorpholine (1.05 eq.), NaOH (2 eq.), dry DCM, rt, 8 h.	**133** as carboxylic acid derivative
5	**133** (1 eq.), $PhI(OAc)_2$ (1.5 eq.), K_2CO_3 (2.8 eq.+1), NH_2Pht (1.4 eq.+1), DCM, rt → reflux, 7 days.	**133**
6	**133** (1 eq.), NH_2Pht (1.5 eq.), 2-iodoxybenzoic acid (1.4 eq.), Na_2CO_3 (2.8 eq.), dry AcOEt, reflux, 40 h.	**133**

a) by ^1H NMR spectroscopy.

2.9. Nucleophilic additions to lactone 133

1,4-Nucleophilic additions to α,β-unsaturated esters are widely described in the lit[64-69]. In this work it was consistently found that nucleophiles as carbon, amines and thiols were added to lactone **133** in a stereoselective way. Single products **150a-d** were formed in all cases in moderate to good yields η= 51.4-85.9 % (**scheme 32**).



133 **150**

150a R= CH_2NO_2, **85.9 %**
150b R= $S(CH_2)_2OH$, **62.6 %**
150c R= SCH_2Ph, **51.4 %**
150d R= NHOH, **82.1 %**

Scheme 32

The nucleophilic attack at C_8 would be controlled by *H*-8a. This proton is on the way of the nucleophile when this attacks by the bottom face; the attack at the upper face is of course open as shown in **figure 13**.

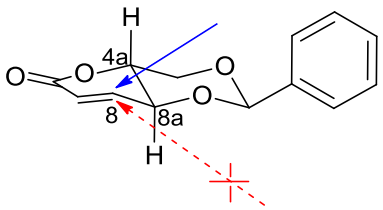


Figure 13

Studies in our group have showed that the *R*-configuration at the C_{4a} is crucial for the stereo-selectivity in the Michael addition. With the galacto-configuration, the lactone in **figure 14** (*S*-configuration at *H*-4a), is showed the complete loss of stereo-selectivity when reacted with osmium tetroxide, giving a mixture of two diastereomers in 1:1 ratio.

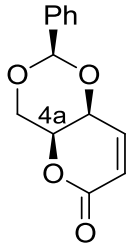


Figure 14

^{1}H NMR of products **150a-d** showed two doublet of doublets between δ_H 2.72-3.21 ppm due to *H*-7, instead of the olefin protons of the starting material. The geminal coupling constant between the two *H*-7 is very large *J*= 16.8-18.8 Hz. *H*-8 appeared as doublet of doublet of doublets in compounds **150b,c** and a multiplet in other cases. The coupling constant between *H*-8a and *H*-8 is lower (*J*= 4.0 Hz), except for compound **150a** (*J*= 8.4 Hz). A possible explanation is that compound **150a** adopts a different conformation, leading to different dihedral angle between the protons. All other protons appeared with the chemical shift and coupling constants of the starting material.

The stereochemistry was confirmed by NOE spectra of compound **150a** (**figure 15**). Irradiation of *H*-8 showed *H*-4 signal to increase in intensity (7 %), which shows that the protons are in the same side of the molecule.

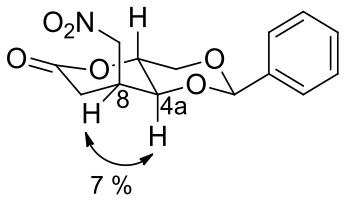
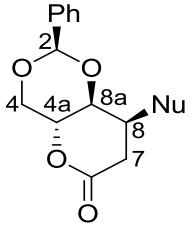


Figure 15

^{13}C NMR spectra show comparable values in all lactones **150**. C_8 and the carbonyl group are the only exceptions for compound **150d**, appearing a little higher than in the others, for obvious reasons.

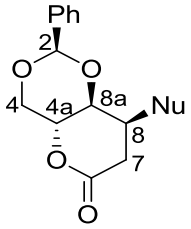
Table 12 ^{1}H NMR spectroscopic data of lactones **150a-d** (400 MHz, $CDCl_3$, ppm).



Comp.	H-2	H-4	H-4a	H-8a	H-7	H-8
150a	5.60 (s)	3.85 (dd, *J*= 10.8, 10.0 Hz); 4.52 (dd, *J*= 10.8, 5.2 Hz)	4.32 (td, *J*= 9.6, 4.8 Hz)	4.14 (dd, *J*= 9.6, 8.4 Hz)	2.72 (dd, *J*= 16.8, 7.2 Hz); 2.92 (dd, *J*= 16.8, 8.0 Hz)	3.42-3.52 (m)
150b	5.61 (s)	3.85 (t, *J*= 10.4 Hz); 4.48 (dd, *J*= 10.8, 5.2 Hz)	4.87 (td, *J*= 10.0, 5.2 Hz)	4.13 (dd, *J*= 9.6, 4.0 Hz)	2.90 (dd, *J*= 18.8, 2.4 Hz); 3.21 (dd, *J*= 18.4, 7.6 Hz)	3.66 (ddd, *J*= 7.6, 4.0, 2.4 Hz)
150c	5.63 (s)	3.87 (t, *J*= 10.8 Hz); 4.51 (dd, *J*= 10.8, 5.2 Hz)	4.98 (td, *J*= 10.0, 5.2 Hz)	4.13 (dd, *J*= 9.6, 4.0 Hz)	2.75 (dd, *J*= 18.4, 2.4 Hz); 3.09 (dd, *J*= 18.4, 7.6 Hz)	3.45 (ddd, *J*= 7.6, 4.0, 2.4 Hz)
150d	5.53 (s)	3.66 (t, *J*= 10.8 Hz); 4.35 (dd, *J*= 10.8, 4.8 Hz)	3.80-3.86 (m)* or 4.10-4.20 (m)*	3.72-3.76 (m)	2.86 (dd, *J*= 17.6, 7.2 Hz); 2.98 (dd, *J*= 17.6, 4.4 Hz)	3.80-3.86 (m)* or 4.10-4.20 (m)*

*indistinguishable

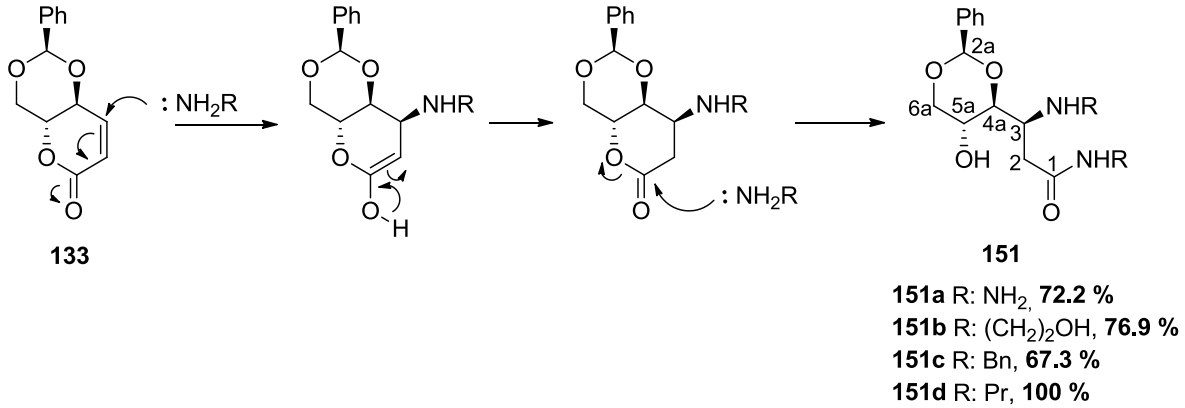
Table 13 ^{13}C NMR spectroscopic data of lactones **150a-d** (100 MHz, $CDCl_3$, ppm).



Comp.	C_2	C_4	C_{4a}	C_{8a}	C_7	C_8	C=O
150a	101.9	68.3	67.1	74.6	31.8	31.2	167.7
150b	102.2	68.3	66.8	77.7	36.8	40.0	167.0
150c	102.2	68.3	66.9	78.4	36.1	38.1	167.1
150d	101.2	70.6	61.6 or 65.3*	78.4	31.9	61.6 or 65.3*	176.8

2.10. Nucleophilic additions to lactone 133 leading to amides

Amines attacked the position 4 and 2 of the α,β-unsaturated carbonyl system of lactone **133** (**scheme 31**), even at low temperature (-78 ºC), and with 1 eq. of the amine. Supposedly, the amine attacks first at C=C bond, followed by lactone ring-opening in a second step.



Scheme 33

Hydroxylamine, probably for being a weaker nucleophile, attacks only C_4 position giving lactone **150d**. Many cases in the lit[70,71] showed that hydroxylamine adds exclusively at C-4 of a α,β-unsaturated ester.

In compounds **151** the geminal coupling constant between the two *H*-2 is *J*= 14.4-15.2 Hz, lower than the geminal coupling of related protons in compounds **150** which is *J*= 16.8-18.8 Hz. This indicates that a higher angle occurs between the two protons[72] in compounds **151**, which is consistent with its incorporation in an open chain.

The ^{1}H NMR spectroscopy of compounds **151a-d** also showed the signal of the amide proton between δ_H 5.71-8.01 ppm. In compounds **151c,d**, runned in $CDCl_3$, this signals showed up as broad singlets, where in **151b** is a triplet in DMSO-d_6. ^{1}H NMR of compound **151a** runned in D_2O completely exchanged the mobile proton with deuterium.

H-4a couples differently to *H*-3, depending on the solvent used to run the spectrum. In $CDCl_3$, *H*-4a couples to *H*-3 with large coupling constant (*J*= 8.8 Hz). The signal of *H*-4a is in this case a triplet, because the coupling to *H*-3 and *H*-5a is the same. When the solvent is changed to CD_3OD or DMSO-d_6, *H*-4a showed up as doublet of doublets. The large coupling with *H*-5a remains but the *J* with *H*-3 is smaller (*J*= 4.0/4.4 Hz).

Minimization of energy in a 3D structure of compound **151c** (**figure 16**), showed a π-π stacking between the phenyl groups, giving *H*-4a and *H*-3 in an antiparalel disposition of the two *H*, which explains the large *J* between those protons.

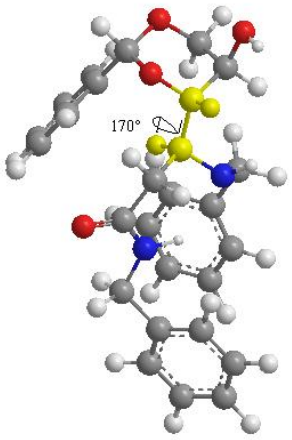


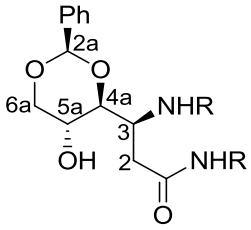
Figure 16 3D Structure of compound **151c** as is minimum energy state with the dihedral angle between *H*-3 and *H*-4a.

A possible explanation for a different pattern in compounds **151** dissolved in polar solvents is the ability of the solvent to be involved in hydrogen bonding, leading to a different conformation.

To confirm this assumption, compound **151d** was dissolved in CD_3OD and in $CDCl_3$. *H*-4 showed up as a triplet in $CDCl_3$, and as a doublet of doublets in CD_3OD proving that different conformations occur in these two solvents.

^{13}C NMR spectra of compounds **151a-d** showed up at the expected regions, with values that agree with those of compounds **151a-d**. The chemical shift of C_3 is of course only similar to **150d**, due to the nature of the attached atom (N).

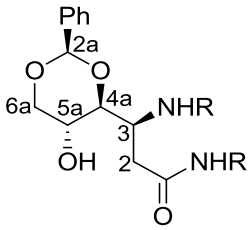
Table 14 ^{1}H NMR spectroscopic data of amides **151a-d** (400 MHz, deuterated solvent, ppm).



Comp.	H-2	H-3	H-2a	H-4a	H-5a	H-6a	N*H*CO
151a[a)]	2.42 (dd, *J*= 15.2, 8.0 Hz); 2.60 (dd, *J*= 15.2, 4.4 Hz)	3.48 (dt, *J*= 8.0, 4.0 Hz)	5.57 (s)	3.88 (dd, *J*= 8.8, 4.0 Hz)	3.74 (td, *J*= 10.0, 4.8 Hz)	3.66 (t, *J*= 10.0 Hz); 4.25 (dd, *J*= 10.4, 4.8 Hz)	---
151b[b)]	2.23 (dd, *J*= 14.8, 8.4 Hz); 2.36 (dd, *J*= 14.8, 4.0 Hz)	3.20-3.23 (m)	5.48 (s)	3.59 (dd, *J*= 8.8, 4.4 Hz)	3.53 (td, *J*= 9.6, 4.4 Hz)	3.47 (t, *J*= 9.6 Hz); 4.07 (dd, *J*= 9.6, 4.0 Hz)	8.01 (t, *J*= 5.6 Hz)
151c[c)]	2.46 (dd, *J*= 14.4, 4.0 Hz); 2.65 (dd, *J*= 14.4, 3.6 Hz)	3.22 (dt, *J*= 9.6, 4.0 Hz)	5.13 (s)	3.45 (t, *J*= 8.8 Hz)	3.73 (td, *J*= 10.0, 5.2 Hz)	3.50 (t, *J*= 10.8 Hz); 4.24 (dd, *J*= 10.8, 5.2 Hz)	5.96 (br s)
151d[c)]	2.42 (dd, *J*= 14.4, 4.8 Hz); 2.58 (dd, *J*= 14.8, 3.6 Hz)	3.08-3.17 (m)	5.46 (s)	3.50 (t, *J*= 8.8 Hz)	3.84 (td, *J*= 10.0, 5.2 Hz)	3.61 (t, *J*= 10.4 Hz) 4.29 (dd, *J*= 10.8, 5.2 Hz)	5.71 (br s)

a) in CD_3OD + 1 drop of D_2O; b) DMSO-d_6; c) $CDCl_3$.

Table 15 ^{13}C NMR spectroscopic data of amides **151a-d** (100 MHz, deuterated solvent, ppm).



Comp.	C_2	C_3	C_{2a}	C_{4a}	C_{5a}	C_{6a}	C=O
151a	33.3	61.3	102.4	81.8	64.4	72.0	174.0
151b	35.7	55.9	100.1	81.3	63.6	70.6	171.5
151c	33.1	59.1	101.4	79.6	67.2	70.9	171.0
151d	33.5	60.1	101.5	79.8	67.5	71.0	171.3

2.11. Other nucleophilic additions to lactone 133

In this sections were compiled a group of reactions, shown in **table 16**, that for one or other reason were not successful. Trimethylsilyl cyanide (entry 1) have been combined with lactone **133** in large excess for a long period of time, but the ^{1}H NMR spectrum of the reaction crude showed exclusively the lactone after 12 days. *Tert*-butylamine (entry 2) in excess and even in the presence of triethylamine did not react, probably due to steric impediment. Grignard reagents showed to be much aggressive leading to complexes mixtures from which no product could be separated by column chromatography (entry 3). Reaction with trimethylsilyl azide (entry 4) showed by ^{1}H NMR the presence of a lactone of type **150**, together with the amide **151** and impurities. The reaction did not evolved to one of the compounds after 15 days at 40 ºC. *p*-Toluenesulfonyl hydrazine and *N*-aminophthalimide (entry 5,6) showed to be unreactive. Finally, (entry 7) bubbling ammonia thought a solution of lactone **133** in acetonitrile formed a mixture of lactone type **150** and amide type **151**. Even longer periods of time led the reaction no further. Products showed to be instable and purification was infeasible.

Table 16 Reaction conditions and results of attack of several C and N nucleophiles to lactone **133**.

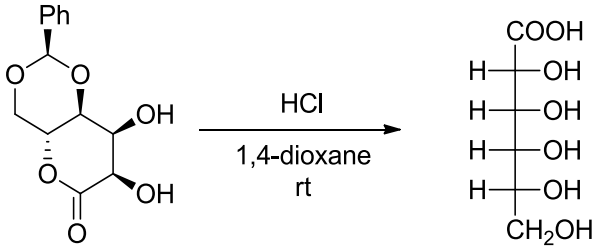
Entry	Nucleophile	Conditions	Results[a)]
1	TMSCN	**133** (1 eq.), TMSCN (2.5 eq. +2.5), 2-propanol (2.5 eq. + 2.5), toluene, rt, 12 days.	**133**
2	$^{t}BuNH_2$	**133** (1 eq.), *tert*-Butylamine (2 eq.), NEt_3 (1 eq.), dry CH_3CN, 0 ºC → rt, 24 h.	**133**
3	MeMgBr	1. $CoBrSMe_2$ (0.5 eq.), MeMgBr (2 eq.), rt 1 h. 2. **133** (1 eq.), dry THF, -15 ºC → rt, 2 h.	Complex mixture
4	$TMSN_3$	1. $TMSN_3$ (5 eq.), AcOH (5 eq.) rt, 20 min. 2. **133** (1 eq.), dry CH_3CN, 40 ºC, 15 days.	Complex mixture
5	*p*-toluenesulfon-hydrazide	**133** (1 eq.), *p*-toluenesulfonhydrazide (1 eq.), dry CH_3CN, -15 ºC → 35 ºC, 5 days.	**133**
6	*N*-aminophthalimide	**133** (1 eq.), *N*-aminophthalimide (1 eq.), NEt_3 (2 eq. +10), dry CH_3CN, rt → 40 ºC, 7 days.	**133**
7	NH_3	**133** (1 eq.), NH_3 (g), dry CH_3CN, -10 ºC → rt, 1 h.	----[b)]

a) By ^{1}H NMR spectroscopy. b) Probably a compound with the structure **151** was formed but is instable which prevent its isolation and characterization.

2.12. Acetal cleavage

2.12.1. of the lactone 142

Acetal cleavage with hydrochloric acid at rt provides the D-allonic acid **152** in low yield (28.3 %) as a colourless oil (**scheme 34**). The acid medium promotes the opening of the lactone, giving the carboxylic acid. The low yield can be explained by the used of basic resin that would retain the allonic acid.

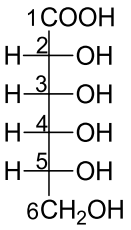


142 **152**

Scheme 34

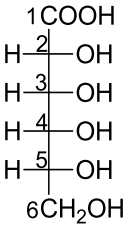
^{1}H and ^{13}C NMR spectra of compound **152** were consistent to what its described in the lit[43].

Table 17 ^{1}H NMR spectroscopic data of compound **152** (400 MHz, D_2O, ppm).



Comp.	*H*-2	*H*-3	*H*-4	*H*-5	*H*-6
152	4.26 (d, *J*= 3.2 Hz)	4.06 (dd, *J*= 6.8, 3.2 Hz)	3.85 (dd, *J*= 6.8, 5.6 Hz)	3.88-3.92 (m)	3.68 (dd, *J*= 12.0, 6.8 Hz); 3.83 (dd, *J*= 12.0, 3.2 Hz)

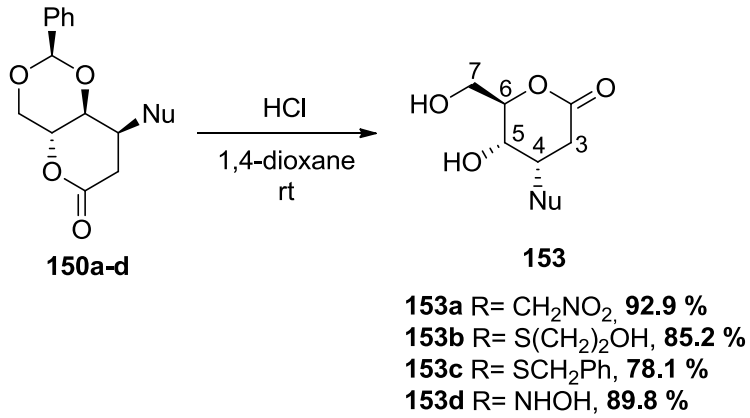
Table 18 ^{13}C NMR spectroscopic data of compound **152 (**100 MHz, D_2O, ppm).



Comp.	C_2	C_3	C_4	C_5	C_6	C=O
152	73.5	72.5	71.7	73.5	62.3	178.1

2.12.2. of the lactones 150a-d

Lactones **150a-d** were treated under acidic medium in order to cleave the acetal group. The ^{1}H NMR spectra presented the absence of the typical singlet *H*-2 and the phenyl group showing the end of the reaction. All the products were isolated in good to excellent yields η= 78.1-92.9 % (**scheme 35**).

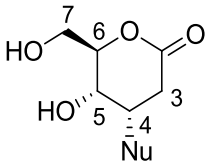


Scheme 35

In the ^{1}H NMR spectra of the compounds **153**, *H*-3 appeared at δ_H 2.41-3.27 ppm as doublet of doublets with a high geminal coupling constant $J \approx 19$ Hz, larger than in lactone **150**. The geminal coupling of *H*-7 protons are typically between *J*= 10.8-12.4 Hz, except for **153c** in which the geminal coupling disappeared; this signal is a doublet with *J*= 6.0 Hz due to coupling to the vicinal *H*-6. *H*-6 appeared with different type of signals, probably depending on the conformation adopted by the structure. *H*-5 showed up as a triplet in compounds **153a-c** with coupling constants between *J*= 3.6-5.2 Hz, and in compound **153d** as doublet of doublets, with *J*= 4.4, 2.0 Hz.

^{13}C NMR spectra showed signals at expected chemical shifts for the structures. There is a consistency of the signals in all the spectra, except for **153d**, due to the different nature of the attached atom.

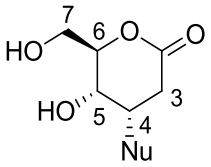
Table 19 ^{1}H NMR spectroscopic data of lactones **153a-d** (400 MHz, deuterated solvent, ppm).



Comp.	*H*-3	*H*-4	*H*-5	*H*-6	*H*-7
153a[a)]	2.66 (dd, *J*= 18.8, 5.6 Hz); 3.08 (dd, *J*= 18.8, 10.0 Hz)	3.35-3.44 (m)	4.58 (t, *J*= 5.2 Hz)	3.95-3.99 (m)	3.69 (dd, *J*= 12.4, 6.0 Hz); 3.77 (dd, *J*= 11.6, 4.4 Hz)
153b[a)]	2.73 (dd, *J*= 18.8, 5.2 Hz); 3.27 (dd, *J*= 18.8, 9.2 Hz)	3.83-3.87 (m)	4.60 (t, *J*= 4.4 Hz)	3.99 (dt, *J*= 6.8, 4.4 Hz)	3.71 (dd, *J*= 10.8, 6.8 Hz); 3.76-3.79 (m)
153c[b)]	2.41 (dd, *J*= 18.4, 3.6 Hz); 3.03 (dd, *J*= 18.4, 8.8 Hz)	3.65 (dt, *J*= 8.8, 3.6 Hz)	4.52 (t, *J*= 3.6 Hz)	3.81 (td, *J*= 6.0, 4.0 Hz)	3.54 (d, *J*= 6.0 Hz)
153d[a)]	2.94 (dd, *J*= 19.2, 2.4 Hz); 3.27 (dd, *J*= 19.2, 9.2 Hz)	4.55 (dt, *J*= 9.2, 2.0 Hz)	5.00 (dd, *J*= 4.4, 2.0 Hz)	4.02 (q, *J*= 4.8 Hz)	3.72 (dd, *J*= 12.0, 5.6 Hz); 3.77 (dd, *J*= 12.0, 4.4 Hz)

a) D_2O; b) CD_3OD.

Table 20 ^{13}C NMR spectroscopic data of lactones **153a-d** (100 MHz, deuterated solvent, ppm).



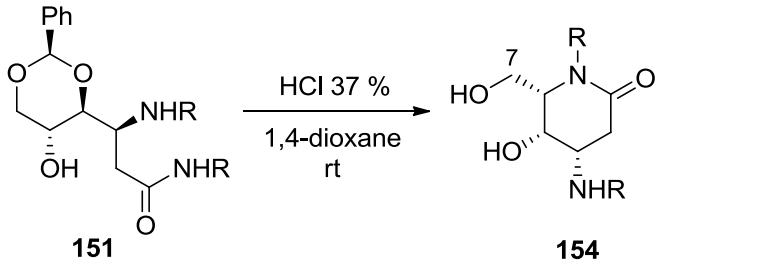
Comp.	C_3	C_4	C_5	C_6	C_7	C=O
153a[a)]	32.4	34.1	82.4	72.2	61.7	179.2
153b[a)]	36.5	38.3	86.1	71.3	61.6	178.9
153c[b)]	37.6	39.3	87.4	73.2	63.4	178.0
153d[a)]	29.9	57.1	80.6	70.6	61.4	176.7

a) D_2O; b) CD_3OD.

2.12.3. of the amides 151b-d

The acetal cleavage procedure used in previous reactions did not led to the expected product in the case of amides **151b-d** (**scheme 36**).

Compound **151a** gave an untreatable complex mixture; compounds **151b-d** gave lactams **154b-d**.

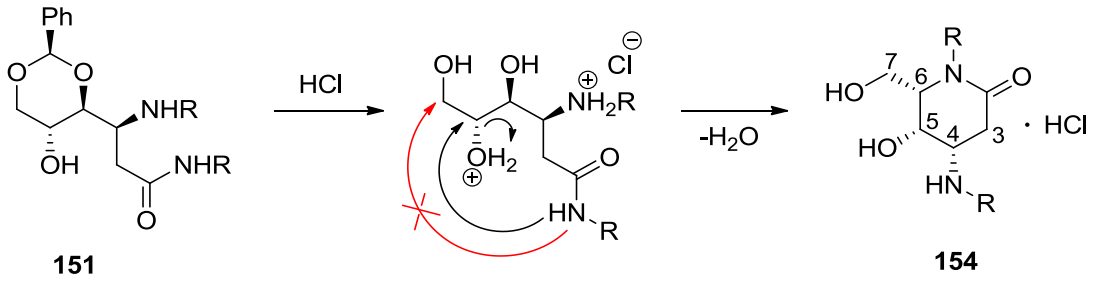


151 **154**

154b R= $(CH_2)_2OH$, **100 %**
154c R= CH_2Ph, **100 %**
154d R= $(CH_2)_2CH_3$, **100 %**

Scheme 36

By ^{1}H NMR analysis, the acetal group cleaved first, and then the product cyclized to lactam **154**, isolated in quantitative yield, as a single product. The mechanism of cyclization should be a S_N2 process according to **scheme 37**. The nitrogen atom of the amide group attacks carbon 5, inverting the configuration of this chiral centre.



151 **154**

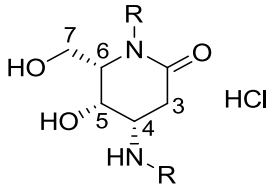
Scheme 37

The main clue for the identification of the cyclic structure **154** is the ^{1}H NMR spectra, showing the two *H*-3 with a geminal coupling constant near *J*= 19 Hz, similar to *H*-3 in lactones **153**. Geminal coupling constants in six-membered ring compounds **154** (*H*-3) are larger than in the open chain counterpart **151**. There is another geminal coupling constant (*J*= 12.0-12.4 Hz) in the spectra. It was attributed to *H*-7. The chemical shift value for *H*-7 is similar to *H*-7 of lactones **153**. *H*-6 protons appeared as quartets in these structures. *H*-5 are doublet of doublets in all cases, with low coupling constants between *J*= 2.4-5.2 Hz. All other signals are very similar to the open-chain precursor.

^{13}C NMR spectra of lactams **154b-d** showed comparable values to lactones **153**.

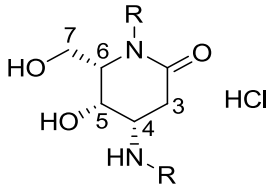
Of course the seven-membered ring closure was also possible to occur, according to **scheme 37**, but the ^{1}H NMR spectra is consistent with the six-membered ring compounds (compare with lactones **153**).

Table 21 ^{1}H NMR spectroscopic data of lactams **154b-d** (400 MHz, D_2O, ppm).



Comp.	*H*-3	*H*-4	*H*-5	*H*-6	*H*-7
154b	2.96 (dd, *J*= 19.2, 3.2 Hz); 3.31 (dd, *J*= 20.0, 9.2 Hz)	4.35 (dt, *J*= 9.2, 2.8 Hz)	4.89 (dd, *J*= 4.8, 2.4 Hz)	3.99 (q, *J*= 4.4 Hz)	3.75 (t, *J*= 4.8 Hz)
154c	3.02 (dd, *J*= 19.2, 3.2 Hz); 3.35 (dd, *J*= 19.2, 9.2 Hz)	4.38-4.43 (m)	4.97 (dd, *J*= 5.2, 2.4 Hz)	4.01 (q, *J*= 4.8 Hz)	3.73 (dd, *J*= 12.3, 5.2 Hz); 3.80 (dd, *J*= 12.4, 4.4 Hz)
154d	2.97 (dd, *J*= 19.2, 2.8 Hz); 3.36 (dd, *J*= 19.2, 9.2 Hz)	4.35 (dt, *J*= 9.2, 2.4 Hz)	4.93 (dd, *J*= 4.8, 2.4 Hz)	4.03 (q, *J*= 5.2 Hz)	3.78 (dd, *J*= 12.4, 5.2 Hz); 3.83 (dd, *J*= 12.0, 4.4 Hz)

Table 22 ^{13}C NMR spectroscopic data of lactams **154b-d** (100 MHz, D_2O, ppm).

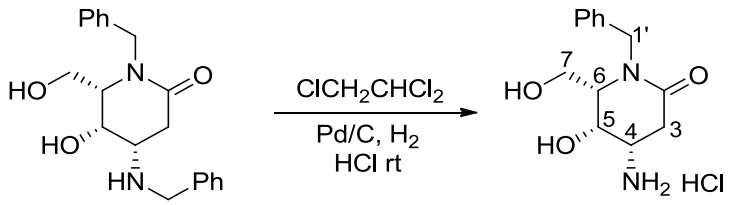


Comp.	C_3	C_4	C_5	C_6	C_7	C=O
154b	31.9	54.5	81.7	70.3	61.5	175.9
154c	31.8	54.2	81.8	70.3	61.2	175.9
154d	32.0	54.7	81.9	70.5	61.6	176.2

2.13. Cleavage of benzylamine

Cheng *et al*[73], reported an efficient hydrogenolysis method to cleave the benzyl group in benzylamines, using 1,1,2-trichloroethane, a catalytic amount of palladium on carbon and hydrogen gas.

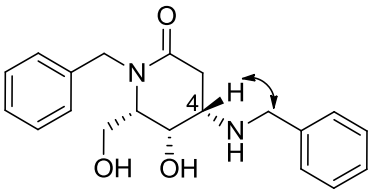
Lactam **154c** was subjected to this procedure (**scheme 38**). After stirring at rt overnight, a single product (**155**) was isolated with good yield (η= 69.6 %).



154c **155**

Scheme 38

Only one benzyl group remained, according to the ^{1}H NMR spectrum. The spectrum of this compound showed the absence of the amide proton in DMSO-d_6 that usually appeared above δ_H 5-8 ppm, and the disappearance of the two doublets corresponding to the CH_2 of the benzylamine moiety. The singlet due to CH_2 of the benzylamide moiety remained in the spectrum. HSQC showed the disappearance of the correlation between *H*-4 and the CH_2 of the benzylamine moiety (**figure 17**), present in the starting material.



154c

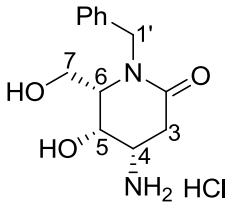
Figure 17 C-H correlation in bidimentional HSQC of compound **154c**.

The cleavage of the benzyl group attached to the amide function was tried by increasing the amount of carbon palladium, 1,1,2-trichloroethane, together with longer periods of time, without success. This means that the methodology is chemo-selective for benzylamine group and led untouched the benzyl group at the amide nitrogen.

H-4 proton appeared in the ^{1}H NMR spectrum as a doublet of doublets with coupling constants of *J*= 8.8, 3.2 Hz. *H*-6 was a quartet in the previous structure (**154c**), being a doublet of triplets in this one with *J*= 5.6, 4.0 Hz.

^{13}C NMR showed similar values that the previous lactam, with a little decrease of the C_4 value as expected, from δ_C 54.2 to 47.6 ppm.

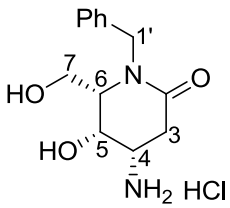
Table 23 ^{1}H NMR spectroscopic data of lactam **155** (400 MHz, D_2O, ppm).



Comp.	*H*-3	*H*-4	*H*-5	*H*-6	*H*-7	*H*-1'
155	2.88 (dd, *J*= 19.2, 3.6 Hz); 3.31 (dd, *J*= 19.2, 9.2 Hz)	4.38 (dd, *J*= 8.8, 3.2 Hz)	--[a]	4.02 (dt, *J*= 5.6, 4.0 Hz)	3.76 (dd, *J*= 12.0, 5.2 Hz); 3.81 (dd, *J*= 12.4, 4.0 Hz)	4.23 (s)

a) this signal is under residual peak of HOD.

Table 24 ^{13}C NMR spectroscopic data of lactam **155** (100 MHz, D_2O, ppm).

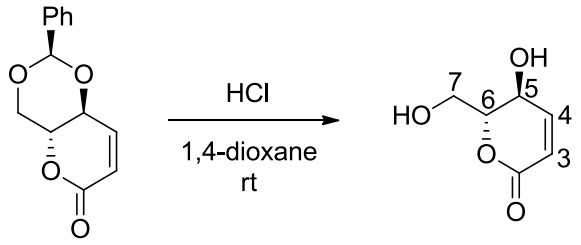


Comp.	C_3	C_4	C_5	C_6	C_7	C=O	$C_{1'}$
155	33.1	47.6	82.9	70.6	61.6	176.3	43.0

2.14. Synthesis of lactone 156

To test if the acetal group in lactone **133** is important for the addition reaction's selectivity of nucleophiles, the acetal group was removed in order to use the new template in addition reactions. The acetal was removed under aq. HCl giving the expected product **156** (**scheme 39**).

The product showed two doublet of doublets, corresponding to the *H*-7 with a geminal coupling constant of *J*= 12.0 Hz. *H*-6 appeared as a doublet of triplets with *J*= 6.0, 4.4 Hz. *H*-4 have a vicinal constant with *H*-5 of *J*= 1.6 Hz, and with *H*-3 of *J*= 6.0 Hz. ^{13}C NMR spectrum showed two carbons in the allyl region, corresponding to *H*-3 and *H*-4, and all the others signals in the regions expected. ^{1}H and ^{13}C NMR spectra were compared with the NMR spectra of **133** described in the lit[48].

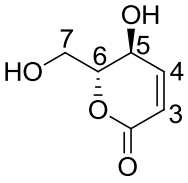


133 **156**

Scheme 39

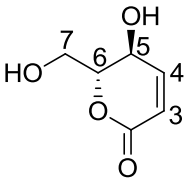
The neutralization of the product of the acetal cleavage was obtained by adding basic resin, but the compound showed to be unstable when the contact time was prolonged. Reaction with propylamine gave a mixture of products, and the selectivity could not be proved.

Table 25 ^{1}H NMR spectroscopic data of diene **156** (400 MHz, D_2O, ppm).



Comp.	*H*-7	*H*-6	*H*-5	*H*-4	*H*-3
156	3.72 (dd, *J*= 12.0, 6.0 Hz); 3.79 (dd, *J*= 12.0, 4.4 Hz)	4.08 (dt, *J*= 6.0, 4.4 Hz)	5.36 (dt, *J*= 3.6, 1.6 Hz)	7.85 (dd, *J*= 6.0, 1.6 Hz)	6.31 (dd, *J*= 6.0, 2.0 Hz)

Table 26 ^{1}H NMR spectroscopic data of lactones **156** (400 MHz, D_2O, ppm).



Comp.	C_7	C_6	C_5	C_4	C_3	C=O
156	61.8	70.9	84.9	156.1	121.5	176.2

2.15. Enzymatic assays

Compound **152**, lactones **153a-d** and lactams **154b-d** and **155** were submitted to enzymatic assays, against different glycosidases: α-glucosidase, β-glucosidase and β-galactosidase to evaluate its inhibitory potency in a primary assay at 0.5 mM.

Is possible to visualize in **table 27**, that compound **154c**, a lactam bearing two phenyl rings, is the most and the only active compound against α-glucosidase. This compound showed no inhibition in β-glucosidase, which represents the discovery of a selective and potent inhibitor, with an IC_{50} of 129 μM, three times more potent that the positive control acarbose (IC_{50} = 337 μM).

Comparing this result with compound **155**, where it was removed a benzyl group, is possible to rationalize that this group is important to the linkage to the active site of the enzyme, since the inhibition was reduced in almost 50 %, from 98.6 % to 49.4 %.

Any of the compounds **152** and **153a-d** did not showed significant activity against any of the enzymes tested.

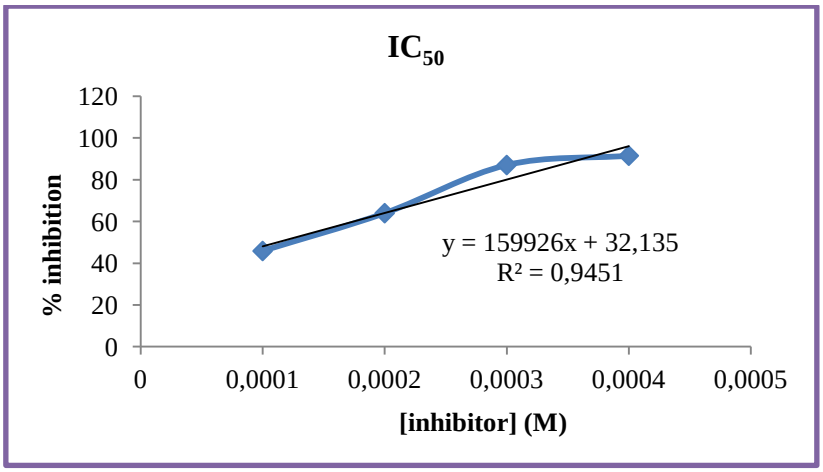
Compound **153c** showed 71.4 % inhibition in β-galactosidase, near the 80 % needed for IC_{50} calculation. This lactone bears a thiobenzyl group at position 4. For future work, extension of the carbon chain next to the phenyl group might be interesting. Selectivity needs to be confirmed by testing this compound against α-galactosidase.

Hereafter, these compounds, especially **154c** would be tested in cancer cell lines to search for its activity.

Table 27 Enzymatic inhibition and IC_{50} data of lactones and lactams tested at 0.5 mM against to different glycosidases.

Entry	Compound	α-glucosidase		β-glucosidase	β-galactosidase
		% inhibition ± SEM	**IC_{50} (μM) ± SEM**	% inhibition ± SEM	% inhibition ± SEM
1	**152**	3.8 ± 0.9	--	37.5 ± 3.3	N.I.
2	**153a**	8.9 ± 6.4	--	14.0 ± 2.2	15.8 ± 3.6
3	**153b**	N.I.	--	4.9 ± 1.0	17.6 ± 5.7
4	**153c**	13.8 ± 3.1	--	N.I.	71.4 ± 5.2
5	**153d**	38.8 ± 2.9	--	N.I.	18.7 ± 7.3
6	**154b**	12.9 ± 8.5	--	20.2 ± 4.3	10.9 ± 3.2
7	**154c**	**98.6 ± 0.3**	**129 ± 3.4**	N.I.	69.0 ± 0.4
8	**154d**	21.6 ± 3.2	--	N.I.	25.2 ± 4.2
9	**155**	49.4 ± 0.4	--	N.I.	42.4 ± 4.5
10	**Acarbose**	65.3 ± 0.3	337 ± 9.1	N.I.	43.9 ± 10.6

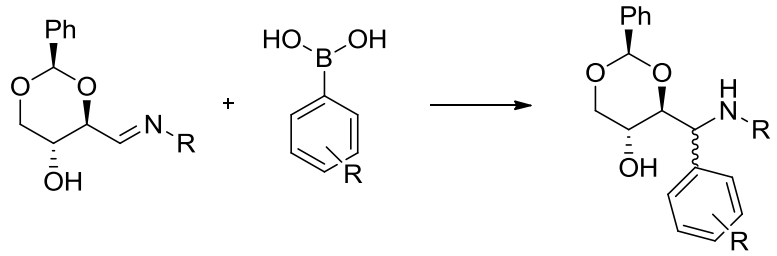
N.I.: No inhibition at 0.5 mM;
SEM: Standard mean error of the experiments.



Graphic 1 Linear correlation in the determination of IC_{50} of compound **154c**.

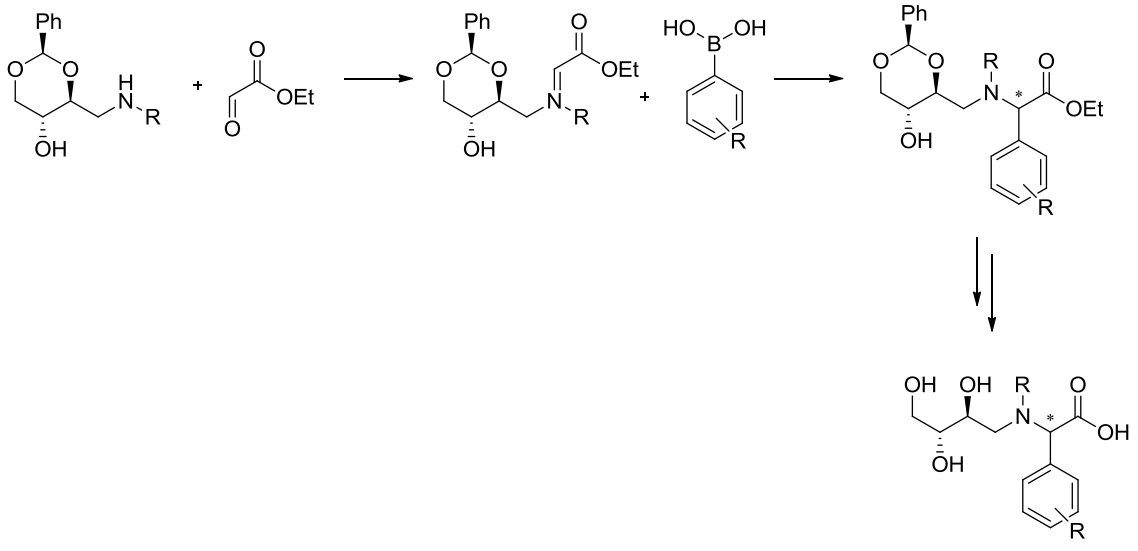
Future perspectives

From the results obtained it would be interesting to develop new synthetic strategies for the synthesis of compounds with potential biological interest. Imines would be tested against aromatic boronic acids. Methyl boronic acids have been tested and found to fail due to it's low reactivity. Aromatic as are more reactive could produce the kind of adducts represented in **scheme 40**, that could further evolve to pyrrolidine type compounds.



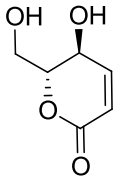
Scheme 40

Amino-acids can also be achieved from the secondary amine **136** previously synthesized, by the reaction of the amine with ethyl glyoxalate followed by one pot addition of a boronic acid (**scheme 41**). This would consist in an interesting pathway for the synthesis of polyhydroxylated α-amino-acids.



Scheme 41

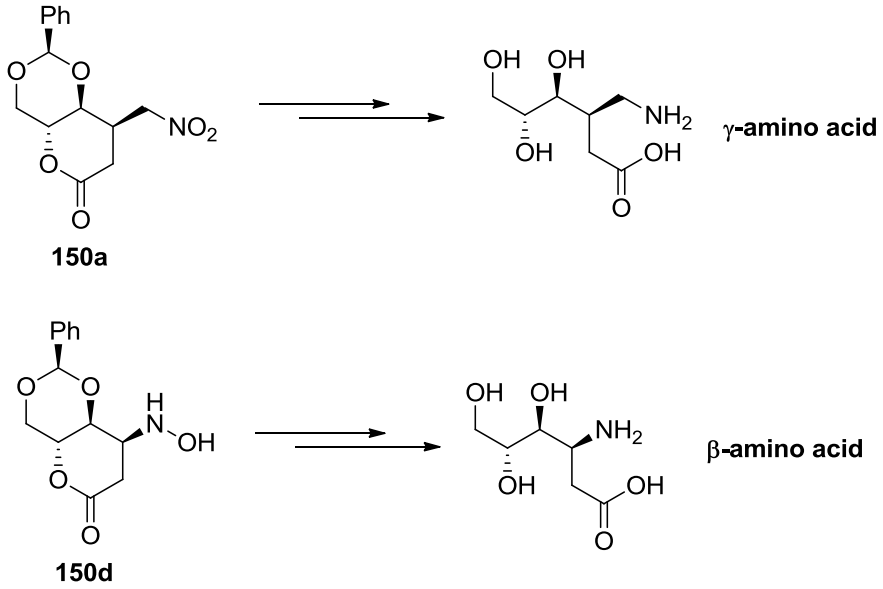
Lactone **156** (**figure 18**) showed to be very similar to Goniotriol **22**. It can be further tested against tumor cells.



156

Figure 18

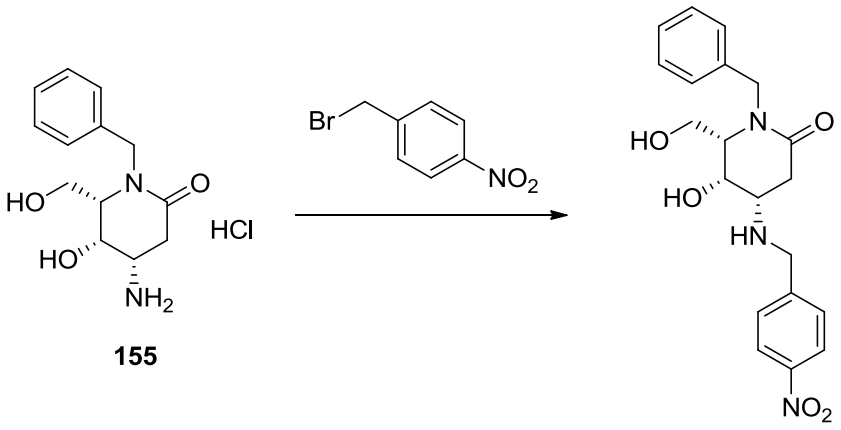
Using compound **150a** and **150d** is possible to achieve new β and γ amino-acids (**scheme 42**). These amino-acids would be easy to achieve and would be interesting also from a synthetic point of view.



Scheme 42

The incorporation of bulkier thiols than benzyl mercaptan in the lactone **133** will be carried out to test its activity against α-galactosidase. Also different groups can be easily introduced in lactone **133** to achieve other derivatives. These compounds would

be tested with the aim of finding more potent and selective α-glucosidase inhibitors than **154c**. A structure/activity relationship in the enzyme can be deduced (ex. **scheme 43**).



155

Scheme 43

CHAPTER 3

EXPERIMENTAL SECTION

3.1. General

^{1}H and ^{13}C NMR spectra were runned in a Bruker Avance III 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C), using as intern reference the solvent peak. The chemical shifts are reported as δ (ppm) and the coupling constants (*J*) in hertz (Hz). $CDCl_3$, DMSO-d_6, D_2O and CD_3OD were used as solvents. The multiplicities of the signals are: singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet of doublets (td), triplet (t), doublet of triplets (dt), quartet (q), quintet (quint), sextet (sext) and multiplet (m).

All reagents were purchased from Sigma-Aldrich, Acros, TCI or Alfa Aesar and used without further purification, except for *p*-toluenesulfonic acid monohydrate which was dried under a vacuum pistol at 120 °C.

Aldehyde **3**[42] and lactone **133**[48] were synthesised following the procedures described in the literature.

Dried DCM, CH_3CN and EtOAc were obtained by reflux under calcium hydride, and THF under reflux with metallic sodium and benzophenone. Toluene was dried by simple distillation eliminating the head fraction; DMF and NEt_3 were obtained dried by fractionated distillation.

Basic resin Dowex 1x2 50-100 Cl was swollen in water, and exchanged with NaOH 2 M; Acidic resin Amberlite IR-120 H^+ was swollen in water. Resins were filtrated-off using glass microfiber filter (whatman®) and water pump.

Dry-flash chromatography was performed in silica gel 0.035-0.070 mm Kieselgel 60, using water pump vacuum; Column chromatography was performed in silica gel 0.060-0.200 mm Kieselgel 60 silica gel.

TLC plates (silica gel 60 F_{254}, Macherey-Nagel) were visualized either with an UV lamp or with I_2.

The melting points were determined on a Gallenkamp melting point apparatus, and are uncorrected.

IR spectra were recorded on a FT-IR Bomem MB 104 using nujol mulls or oils as thin films in sodium chloride cells.

The optical rotation [α] of chiral compounds were measured in a micro-polarimeter AA-1000 optical activity, being expresses in $°dm^{-1}c^{-1}$ (c= g/100mL).

Elementary analysis was performed in an LECO-CHNS-932 apparatus.

HRMS were recorded by ESI-MS methodology in a Bruker Microtof. Low mass spectroscopy was recorded by ESI-MS methodology in a HPLC Finnigan LXQ.

3.2. Glicosidases assays procedure

α-Glucosidase from *Saccharomyces Cerevisiae* (substrate: *p*-nitrophenyl-α-D-glucopyranoside), β-glucosidase from almonds (substrate: *p*-nitrophenyl-β-D-glucopyranoside), β-galactosidase from bovine liver (substrate: *p*-nitrophenyl-β-D-galactopyranoside) and their substrates were purchased from Sigma-Aldrich. Acarbose was used as positive control and purchased from TCI.

Enzymatic assays were conducted in a total of 100 μL reaction mixture, containing 70 μL of phosphate buffer (50 mM, pH= 6.8), 10 μL of the respective test compound (0.5 mM) followed by the addition of 10 μL of the enzyme (0.2 units/mL). The contents were mixed, pre-incubated for 10 min at 37 ºC and pre-read at 400 nm. The reaction was initiated by the addition of 10 μL of the respective substrate (0.5 mM). After 30 min of incubation at 37 ºC absorbance of the yellow colour produced due the formation of *p*-nitrophenol was measured at 400 nm using a Thermo Scientific Varioskan Flash 96-well microplate reader. All experiments were carried out in triplicate. The percent of inhibition was calculated by the following equation[74]:

$$\text{Inhibition (\%)} = \frac{\textbf{abs of control} - \textbf{abs of test}}{\textbf{abs of control}} \textbf{ x 100}$$

IC_{50} values (concentration at which there is 50 % inhibition in enzyme) were calculated varying the concentration of the test compound.

Part A: Synthesis of aminopolyols bases on D-erythrose structure

3.3. Synthesis of amines 135a-e

3.3.1. General procedure

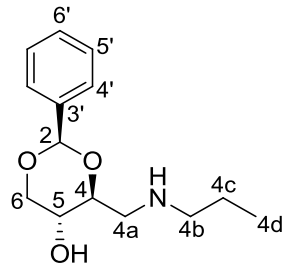
i) Synthesis of imines **134a-e**

To a solution of the aldehyde **3** (0.10−0.24 mg, 0.49−1.15 mmol) in dry solvent (2−5 mL), activated molecular sieves 4 Å (1 g), was added the amine (59−126 μL, 41−124 mg, 0.49−1.15 mmol) under N_2 atmosphere at rt. The reaction was completed after 0.5−3 h. The reaction mixture was passed through a pad of Celite®, and washed with DCM (10 mL). The solvent was removed in the rotary evaporator to give the product as an oil or a solid. The resulting imines were used in the next step without purification.

ii) Reduction of imines **134a-e**

To the crude residue was added a mixture of THF (5 mL) and MeOH (5 mL), followed by $NaBH_4$ (38−87 mg, 0.98−2.30 mmol) with continued stirring at rt for 1.15−12 h. The solvent was evaporated and the crude dissolved in DCM (30 mL), washed with water (3x30 mL). The organic layer was dried over $MgSO_4$ and filtered. After removing the solvent in the rotary evaporator compounds **135a-e** were obtained (58−300 mg, 0.19−1.01 mmol, 37.1−87.2 %).

3.3.1.1. Synthesis of (2*R*,4*S*,5*R*)-2-phenyl-4-((propylamino)methyl)-1,3-dioxan-5-ol **135a**

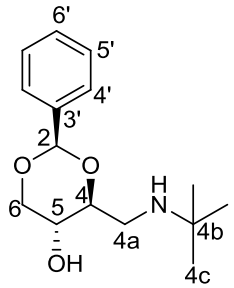


135a

Synthesis of imine **134a**: Aldehyde **3** (0.14 g, 0.71 mmol); Solvent: DCM (2 mL); Propylamine (64 μL, 46 mg, 0.78 mmol); 30 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, *J*= 7.6 Hz, 3H, *H*-4d), 1.64 (sext, *J*= 7.2 Hz, 2H, *H*-4c), 3.38-3.44 (m, 2H, *H*-4b), 3.72 (t, *J*= 10.4 Hz, 1H, *H*-6), 3.98 (td, *J*= 8.8, 4.8 Hz, 1H, *H*-4 or *H*-5), 4.15 (dd, *J*= 9.2, 1.2 Hz, 1H, *H*-4 or *H*-5), 4.37 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-6), 5.57 (s, 1H, *H*-2), 7.37-7.41 (m, 3H, *H*-5' and *H*-6'), 7.51-7.53 (m, 2H, *H*-4'), 7.86 (s, 1H, N=C*H*) ppm.

Reduction of imine **134a**: THF (5 mL)/ MeOH (5 mL); $NaBH_4$ (0.05 g, 1.43 mmol); 2 h. Yellow oil **135a** (0.13 g, 0.52 mmol). Yield: 72.8 %. $[\alpha]_D^{28}$ + 12.6 (*c* 0.7, DCM). IR (nujol) ν_{max} 3311, 3067 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, *J*= 7.2 Hz, 3H, *H*-4d), 1.54 (sext, *J*= 7.2 Hz, 2H, *H*-4c), 2.60-2.64 (m, 1H, *H*-4b), 2.66-2.74 (m, 1H, *H*-4b), 2.97 (dd, *J*= 12.0, 8.8 Hz, 1H, *H*-4a), 3.14 (dd, *J*= 12.2, 4.8 Hz, 1H, *H*-4a), 3.62 (t, *J*= 10.8 Hz, 1H, *H*-6), 3.69 (td, *J*= 8.4, 4.0 Hz, 1H, *H*-4), 3.82 (td, *J*= 10.0, 5.2 Hz, 1H, *H*-5), 4.31 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-6), 5.52 (s, 1H, *H*-2), 7.34-7.40 (m, 3H, *H*-5' and *H*-6'), 7.48 (dd, *J*= 7.6, 2.0, 2H, *H*-4') ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.5 (C_{4d}), 22.9 (C_{4c}), 51.9 (C_{4b}), 53.2 (C_{4a}), 67.7 (C_5), 70.9 (C_6), 78.2 (C_4), 101.3 (C_2), 126.1 ($C_{4'}$), 128.2, 128.9 ($C_{5'}$ and $C_{6'}$), 137.6 (C_q) ppm.

3.3.1.2. Synthesis of (2*R*,4*S*,5*R*)-4-((*tert*-butylamino)methyl)-2-phenyl-1,3-dioxan-5-ol **135b**

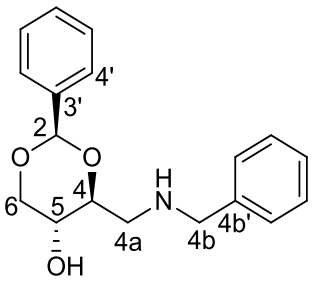


135b

Synthesis of imine **134b**: Aldehyde **3** (0.11 g, 0.51 mmol); Solvent: THF (3 mL); *Tert*-butylamine (59 μL, 41 mg, 0.56 mmol); 1 h. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (s, 9H, *H*-4c), 3.72 (t, *J*= 10.4 Hz, 1H, *H*-6), 3.97 (td, *J*= 10.4, 5.2 Hz, 1H, *H*-4 or *H*-5), 4.14 (dd, *J*= 8.8, 1.2 Hz, 1H, *H*-4 or *H*-5), 4.37 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-6), 5.59 (s, 1H, *H*-2), 7.38-7.40 (m, 3H, *H*-5' and *H*-6'), 7.52-7.55 (m, 2H, *H*-4'), 7.82 (s, 1H, N=C*H*) ppm.

Reduction of imine **134b**: THF (5 mL)/ MeOH (5 mL); $NaBH_4$ (0.04 g, 1.02 mmol); 2 h. Colourless oil **135b** (0.10 g, 0.38 mmol). Yield: 74.0 %. $[\alpha]_D^{22}$ + 36.0 (*c* 0.68, DCM). IR (nujol) ν_{max} 3283, 3120 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H, *H*-4c), 2.87 (dd, *J*= 11.6, 10.0 Hz, 1H, *H*-4a), 3.17 (dd, *J*= 11.6, 4.4 Hz, 1H, *H*-4a), 3.59 (td, *J*= 9.6, 4.0 Hz, 1H, *H*-4), 3.62 (t, *J*= 10.4 Hz, 1H, *H*-6), 3.82 (td, *J*= 10.0, 5.2 Hz, 1H, *H*-5), 4.31 (dd, *J*= 10.4, 5.2 Hz, 1H, *H*-6), 5.52 (s, 1H, *H*-2), 7.36-7.38 (m, 3H, *H*-5' and *H*-6'), 7.49 (dd, *J*= 7.6, 1.6 Hz, 2H, *H*-4') ppm.^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6 (C_{4c}), 46.9 (C_{4a}), 50.9 (C_{4b}), 64.7 (C_5), 70.9 (C_6), 79.0 (C_4), 101.3 (C_2), 126.1 ($C_{4'}$), 128.3, 128.9 ($C_{5'}$ and $C_{6'}$), 137.7 (C_q) ppm.

3.3.1.3. Synthesis of (2*R*,4*S*,5*R*)-4-((benzylamino)methyl)-2-phenyl-1,3-dioxan-5-ol **135c**

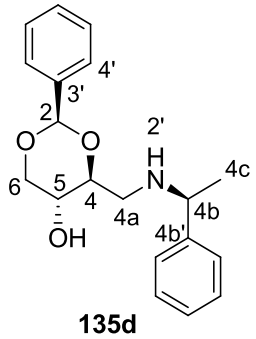


135c

Synthesis of imine **134c**: Aldehyde **3** (0.24 g, 1.15 mmol); Solvent: THF (5 mL); Benzylamine (126 μL, 124 mg, 1.15 mmol); 2 h. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84 (t, *J*= 10.4 Hz, 1H, *H*-6), 4.16 (td, *J*= 10.4, 5.2 Hz, 1H, *H*-4 or *H*-5), 4.34 (dd, *J*= 8.8, 1.2 Hz, 1H, *H*-4 or *H*-5), 4.49 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-6), 4.77 (s, 2H, *H*-4b), 5.69 (s, 1H, *H*-2), 7.36-7.65 (m, 10H, Ph-C*H*), 7.98 (s, 1H, N=C*H*) ppm.

Reduction of imine **134c**: THF (5 mL)/ MeOH (5 mL); $NaBH_4$ (87 mg, 2.30 mmol); 12 h. White solid **135c** (0.30 g, 1.01 mmol). Yield: 87.2 %. M.p.: 72−75 °C. $[\alpha]_D^{23}$ + 25.5 (*c* 0.67, DCM). IR (nujol) ν_{max} 3350, 3200 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.98 (dd, *J*= 12.0, 8.8 Hz, 1H, *H*-4a), 3.17 (dd, *J*= 12.0, 4.4 Hz, 1H, *H*-4a), 3.63 (t, *J*= 10.4 Hz, 1H, *H*-6), 3.70 (td, *J*= 8.8, 4.4 Hz, 1H, *H*-4), 3.84 (td, *J*= 9.6, 5.2 Hz, 1H, *H*-5), 3.83 (d, *J*= 12.8 Hz, 1H, *H*-4b), 3.90 (d, *J*= 12.8 Hz, 1H, *H*-4b), 4.31 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-6), 5.51 (s, 1H, *H*-2), 7.29-7.38 (m, 8H, *H*-Ph), 7.46-7.49 (m, 2H, *H*-4') ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.6 (C_{4a}), 54.1 (C_{4b}), 67.5 (C_5), 70.9 (C_6), 78.4 (C_4), 101.3 (C_2), 126.1 ($C_{4'}$), 127.1, 127.5, 128.3, 128.7, 129.0 (CH, Ph), 137.6 ($C_{3'}$), 138.8 ($C_{4b'}$) ppm.

3.3.1.4. Synthesis of (2*R*,4*S*,5*R*)-2-phenyl-4-((((*S*)-1-phenylethyl)amino)methyl)-1,3-dioxan-5-ol **135d**

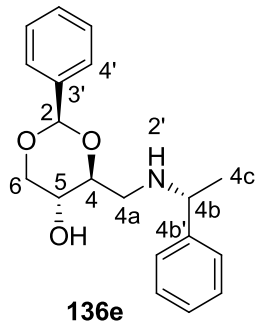


135d

Synthesis of imine **134d**: Aldehyde **3** (0.10 g, 0.49 mmol); Solvent: THF (3 mL); (*S*)-(−)-α-methylbenzylamine (64 μL, 61 mg, 0.49 mmol); 45 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (d, *J*= 6.8 Hz, 3H, *H*-4c), 3.75 (t, *J*= 10.8 Hz, 1H, *H*-6), 4.06 (td, *J*= 8.0, 4.0 Hz, 1H, *H*-4 or *H*-5), 4.14 (q, *J*= 6.4 Hz, 1H, *H*-4b), 4.03-4.11 (m, 1H, *H*-4 or *H*-5), 4.39 (dd, *J*= 10.4, 5.2 Hz, 1H, *H*-6), 5.57 (s, 1H, *H*-2), 7.27-7.54 (m, 10H, Ph-C*H*), 7.95 (s, 1H, N=C*H*) ppm.

Reduction of imine **134d**: THF (5 mL)/ MeOH (5 mL); $NaBH_4$ (38 mg, 0.98 mmol); 1:15 h. White oil **135d** (58 mg, 0.19 mmol). Yield: 37.1 %. $[\alpha]_D^{28}$ − 18.9 (*c* 1.13, DCM). IR (neat) ν_{max} 3300, 2964 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (d, *J*= 6.4 Hz, 3H, *H*-4c), 2.86 (dd, *J*= 12.0, 8.4 Hz, 1H, *H*-4a), 2.97 (dd, *J*= 12.0, 4.8 Hz, 1H, *H*-4a), 3.24 (br s, 1H, N*H*), 3.58 (td, *J*= 8.4, 4.4 Hz, 1H, *H*-4), 3.61 (t, *J*= 10.4 Hz, 1H, *H*-6), 3.81 (q, *J*= 6.8 Hz, 1H, *H*-4b), 3.86 (td, *J*= 10.0, 5.2 Hz, 1H, *H*-5), 4.31 (dd, *J*= 10.4, 5.2 Hz, 1H, *H*-6), 5.47 (s, 1H, *H*-2), 7.27-7.39 (m, 8H, *H*-Ph), 7.47 (dd, *J*= 7.6, 2.4 Hz, 2H, *H*-4') ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.3 (C_{4c}), 51.1 (C_{4a}), 58.7 (C_{4b}), 67.3 (C_5), 70.8 (C_6), 79.1 (C_4), 101.2 (C_2), 126.1 ($C_{4'}$), 126.3, 127.4, 128.2, 128.7, 128.9 (CH, Ph), 137.6 ($C_{3'}$), 144.1 ($C_{4b'}$) ppm.

3.3.1.5. Synthesis of (2*R*,4*S*,5*R*)-2-phenyl-4-((((*R*)-1-phenylethyl)amino)methyl)-1,3-dioxan-5-ol **135e**



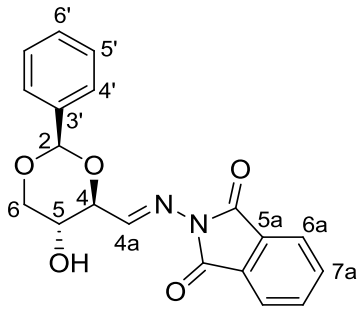
136e

Synthesis of imine **134e**: Aldehyde **3** (0.12 g, 0.58 mmol); Solvent: THF (3 mL); (*R*)-(+)-α-methylbenzylamine (74 μL, 55 mg, 0.58 mmol); 45 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53 (d, *J*= 6.4 Hz, 3H, *H*-4c), 3.72 (t, *J*= 10.4 Hz, 1H, *H*-6), 3.98 (td, *J*= 9.6, 4.8 Hz, 1H, *H*-4 or *H*-5), 4.13 (q, *J*= 6.8 Hz, 1H, *H*-4b), 4.22 (dd, *J*= 8.8, 0.8 Hz, 1H, *H*-4 or *H*-5), 4.36 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-6), 5.58 (s, 1H, *H*-2), 7.27-7.49 (m, 10H, Ph-C*H*), 7.95 (s, 1H, N=C*H*) ppm.

Reduction of imine **134e**: THF (5 mL)/ MeOH (5 mL); $NaBH_4$ (44 mg, 1.20 mmol); 1 h. Orange oil **135e** (125 mg, 0.40 mmol). Yield: 69.2 %. $[\alpha]_D^{28}$ + 50.7 (*c* 0.7, DCM). IR (neat) ν_{max} 3300, 2965 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, *J*= 6.8 Hz, 3H, *H*-4c), 2.75 (dd, *J*= 12.0, 8.4 Hz, 1H, *H*-4a), 2.98 (dd, *J*= 12.0, 4.4 Hz, 1H, *H*-4a), 3.41 (br s, 1H, N*H*), 3.58 (t, *J*= 10.4 Hz, 1H, *H*-6), 3.59-3.70 (m, 2H, *H*-4 and *H*-5), 3.78 (q, *J*= 6.8 Hz, 1H, *H*-4b), 4.25 (dd, *J*= 10.4, 4.4 Hz, 1H, *H*-6), 5.46 (s, 1H, *H*-2), 7.23-7.35 (m, 8H, *H*-Ph), 7.43 (dd, *J*= 7.6, 2.4 Hz, 1H, *H*-4') ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0 (C_{4c}), 50.6 (C_{4a}), 58.4 (C_{4b}), 67.0 (C_5), 70.7 (C_6), 78.7 (C_4), 101.1 (C_2), 126.0 ($C_{4'}$), 126.5, 127.4, 128.1, 128.6, 128.9 (CH, Ph), 137.6 ($C_{3'}$), 143.8 ($C_{4b'}$) ppm.

3.4. Synthesis of imine derivative 134f

3.4.1. Synthesis of 2-((*E*)-(((2*R*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)methylene)imino)isoindoline-1,3-dione **134f**

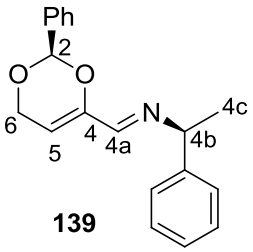


134f

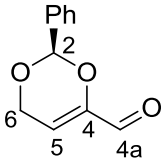
To a flask containing activated molecular sieves 4 Å (1 g) was added a solution of aldehyde **3** (0.19 g, 0.89 mmol) in dry CH_3CN (4 mL) followed by *N*-aminophthalimide (0.15 g, 0.89 mmol) under N_2 atmosphere. Stirring was continued at rt for 12 h. The solution was then passed through a pad of Celite®, washed with DCM (10 mL) and EtOH (10 mL), and solvents removed in the rotary evaporator to give the pure product. Beige solid **134f** (0.26 g, 0.75 mmol). Yield: 83.9 %. M.p.: 198−200 °C. $[\alpha]_D^{27}$ + 21.1 (*c* 0.6, CH_3CN). IR (nujol) ν_{max} 3466, 1716 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 3.65 (t, *J*= 10.4 Hz, 1H, *H*-6), 3.74-3.79 (m, 1H, *H*-5), 4.26 (dd, *J*= 10.4, 4.8 Hz, 1H, *H*-6), 4.34 (dd, *J*= 9.2, 6.4 Hz, 1H, *H*-4), 5.51 (d, *J*= 6.0 Hz, 1H, O*H*), 5.69 (s, 1H, *H*-2), 7.34-7.38 (m, 3H, *H*-5' and *H*-6'), 7.45 (dd, *J*= 7.6, 2.4 Hz, 2H, *H*-4'), 7.82-7.92 (m, 4H, *H*-6a and *H*-7a), 8.73 (d, *J*= 6.0 Hz, 1H, *H*-4a) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz) δ 62.6 (C_5), 70.7 (C_6), 81.5 (C_4), 99.9 (C_2), 123.6 (C_{6a} or C_{7a}), 126.3 ($C_{4'}$), 127.9 ($C_{5'}$ or $C_{6'}$), 128.1 (C_{5a}), 129.8 ($C_{5'}$ or $C_{6'}$), 135.1 (C_{6a} or C_{7a}), 137.6 ($C_{3'}$), 158.0 (C_{4a}), 164.5 (C=O) ppm.

3.5. Attempts to functionalize imine

3.5.1. Synthesis of the mixture of (*S*,*E*)-1-phenyl-*N*-(((*R*)-2-phenyl-4*H*-1,3-dioxin-6-yl)methylene)ethanamine **139** and (*R*)-2-phenyl-4*H*-1,3-dioxine-6-carbaldehyde **140**



139



140

To a solution of aldehyde **3** (0.34 g, 1.60 mmol) in dry THF (3 mL) contained in round bottom flask, together with activated molecular sieves 4 Å was added (*S*)-(−)-*α*-methylbenzylamine (218 μL, 0.193 g, 1.6 mmol) under N_2 atmosphere. After stirring at rt for 1:30 h, the reaction was placed in an ice bath and vinylmagnesium bromide (0.7 M, 9.40 mL, 0.84 g, 6.40 mmol) added. The mixture was stirred at rt overnight. Then sat. sol. NH_4Cl was added, followed by water (40 mL) and the mixture extracted with AcOEt (5x40mL). The organic layers were combined, washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent removed in the rotary evaporator, to give an orange oil that was purified by dry-flash chromatography (n-hexane/AcOEt), giving a brown oil (30 mg of mixture), that consisted in a mixture of **139** (η= 3.1 %) and **140** (η= 4.8 %).

Compound **139**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, *J*= 6.4 Hz, 3H, *H*-4c), 4.47 (dd, *J*= 17.2, 4.0 Hz, 1H, *H*-6), 4.49 (q, *J*= 6.8 Hz, 1H, *H*-4b), 4.62 (dd, *J*= 17.2, 2.4 Hz, 1H, *H*-6), 5.58 (dd, *J*= 3.6, 2.4 Hz, 1H, *H*-5), 5.93 (s, 1H, *H*-2), 7.69 (s, 1H, *H*-4a) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3 (C_{4c}), 64.1 (C_6), 69.4 (C_{4b}), 98.9 (C_2), 108.9 (C_5), 144.3 (C_q), 150.1 (C_4), 154.5 (C_{4a}) ppm.*

Compound **140**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (dd, *J*= 18.8, 4.0 Hz, 1H, *H*-6), 4.74 (dd, *J*= 18.8, 2.0 Hz, 1H, *H*-6), 5.85 (s, 1H, *H*-2), 6.12 (dd, *J*= 3.6, 2.4 Hz, 1H, *H*-

5), 9.27 (s, 1H, *H*-4a) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 64.4 (C_6), 98.6 (C_2), 119.6 (C_5), 151.7 (C_4), 185.0 (C_{4a}) ppm.*

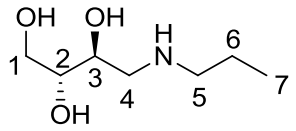
*The peaks were not discriminated to one or the other compound: in the region δ_H 7.34-7.56 ppm (m, 15H, *H*-Ph) and in the region δ_C 126.5-136.8 ppm.

3.6. Acetal cleavage in amines 135a-c,e

3.6.1. General procedure for the cleavage of the acetal – formation of compounds **141a-c,e**

Compound **135a-c,e** (62−150 mg, 0.29−0.49 mmol) was dissolved in 1,4-dioxane (4−5 mL) and HCl 1 M (0.5 mL) was added dropwise at rt and stirred for further 12 h. Basic resin was added to the mixture and filtered. The solvent was evaporated in the rotary evaporator to give the respective product **141a-c,e** (34−89 mg, 0.20−0.42 mmol, 57.7−85.8 %).

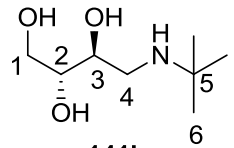
3.6.1.1. Synthesis of (2*R*,3*S*)-4-(propylamino)butane-1,2,3-triol **141a**



141a

Compound **135a** (62 mg, 0.25 mmol); 1,4-dioxane (4 mL); HCl 1M (0.5 mL); 12 h. Yellow oil **141a** (34 mg, 0.20 mmol). Yield: 84.4 %. $[\alpha]_D^{22}$ − 3.60 (*c* 0.78, MeOH). IR (neat) ν_{max} 3356, 2960 cm^{-1}. ^{1}H NMR (D_2O, 400 MHz) δ 0.99 (t, *J*= 7.6 Hz, 3H, *H*-7), 1.71 (m, 2H, *H*-6), 3.01 (t, *J*= 7.6 Hz, 2H, *H*-5), 3.07 (dd, *J*= 13.2, 9.6 Hz, 1H, *H*-4), 3.28 (dd, *J*= 12.8, 2.8 Hz, 1H, *H*-4), 3.63-3.65 (m, 1H, *H*-1), 3.67-3.70 (m, 1H, *H*-3), 3.76-3.79 (m, 1H, *H*-1), 3.92 (ddd, *J*= 9.6, 6.8, 3.2 Hz, 1H, *H*-2) ppm. ^{13}C NMR (D_2O, 100 MHz) δ 10.2 (C_7), 19.3 (C_6), 49.5 (C_5), 49.6 (C_4), 62.1 (C_1), 67.3 (C_2), 73.1 (C_3) ppm.

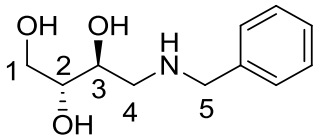
3.6.1.2. Synthesis of (2*R*,3*S*)-4-(*tert*-butylamino)butane-1,2,3-triol **141b**



141b

Compound **135b** (76 mg, 0.29 mmol); 1,4-dioxane (4 mL); HCl 1M (0.5 mL); 12 h. Colourless oil **141b** (30 mg, 0.17 mmol). Yield: 59.1 %. $[\alpha]_D^{22} - 4.20$ (*c* 0.7, MeOH). IR (neat) ν_{max} 3397, 2986 cm^{-1}. ^1H NMR (D_2O, 400 MHz) δ 1.12 (s, 9H, *H*-6), 2.64 (dd, *J*= 12.0, 8.0 Hz, 1H, *H*-4), 2.79 (dd, *J*= 12.0, 3.2 Hz, 1H, *H*-4), 3.59-3.64 (m, 1H, *H*-1), 3.64-3.70 (m, 2H, *H*-2 and *H*-3), 3.77 (dd, *J*= 10.8, 2.4 Hz, 1H, *H*-1) ppm. ^{13}C NMR (D_2O, 100 MHz) δ 26.9 (C_6), 43.4 (C_4), 49.5 (C_5), 61.8 (C_1), 70.8 (C_2 or C_3), 73.5 (C_2 or C_3) ppm.

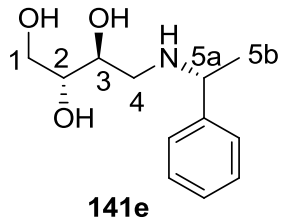
3.6.1.3. Synthesis of (2*R*,3*S*)-4-(benzylamino)butane-1,2,3-triol **141c**



141c

Compound **135c** (0.15 g, 0.49 mmol); 1,4-dioxane (5 mL); HCl 1 M (0.5 mL); 12 h. Yellow oil **141c** (89 mg, 0.42 mmol). Yield: 85.8 %. $[\alpha]_D^{23}$ – 6.0 (*c* 0.47, MeOH). IR (neat) ν_{max} 3362, 2932 cm^{-1}. ^1H NMR (D_2O, 400 MHz) δ 2.80 (dd, *J*= 12.8, 9.2 Hz, 1H, *H*-4), 2.99 (dd, *J*= 12.8, 2.8 Hz, 1H, *H*-4), 3.58-3.66 (m, 2H, *H*-1 and *H*-3), 3.73-3.76 (m, 1H, *H*-1), 3.80-3.85 (m, 1H, *H*-2), 3.93 (d, *J*= 13.2 Hz, 1H, *H*-5), 3.98 (d, *J*= 13.2 Hz, 1H, *H*-5), 7.40-7.49 (m, 5H, *H*-Ph) ppm. ^{13}C NMR (D_2O, 100 MHz) δ 49.7 (C_4), 51.9 (C_5), 62.3 (C_1), 69.3 (C_2), 73.5 (C_3), 128.1, 128.9, 129.0 (CH, Ph), 136.5 (C_q) ppm.

3.6.1.4. Synthesis of (2*R*,3*S*)-4-(((*R*)-1-phenylethyl)amino)butane-1,2,3-triol **141e**



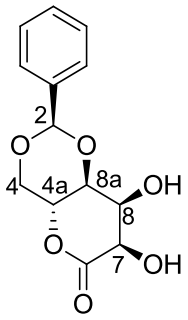
141e

Compound **135e** (41 mg, 0.13 mmol); 1,4-dioxane (4 mL); HCl 1 M (1 mL); 12 h. Colourless oil **141e** (17 mg, 0.08 mmol). Yield: 57.7 %. $[\alpha]_D^{27}$ + 43.8 (*c* 0.75, MeOH). IR (neat) ν_{max} 3373, 3307, 2922 cm^{-1}. ^1H NMR (D_2O, 400 MHz) δ 1.39 (d, *J*= 6.4 Hz, 3H, *H*-5b), 2.55 (dd, *J*= 12.4, 8.4 Hz, 1H, *H*-4), 2.64 (dd, *J*= 12.4, 3.6 Hz, 1H, *H*-4), 3.52-3.59 (m, 2H, *H*-1 and *H*-2 or *H*-3), 3.65-3.70 (m, 2H, *H*-1 and *H*-2 or *H*-3), 3.85 (q, *J*= 6.4 Hz, 1H, *H*-5a), 7.34-7.47 (m, 5H, *H*-Ph) ppm. ^{13}C NMR (D_2O, 100 MHz) δ 21.6 (C_{5b}), 48.5 (C_4), 57.1 (C_{5a}), 61.8 (C_1), 70.1 (C_2 or C_3), 73.3 (C_2 or C_3), 126.4, 126.9, 128.3 (CH, Ph), 143.9 (C_q) ppm.

Part B: Synthesis of functionalized lactones and lactams

3.7. Osmilation of 133

3.7.1. Synthesis of (2*S*,4a*R*,7*R*,8*S*,8a*S*)-7,8-dihydroxy-2-phenyltetrahydripyrano[3,2-*d*][1,3]dioxin-6(7*H*)-one **142**



142

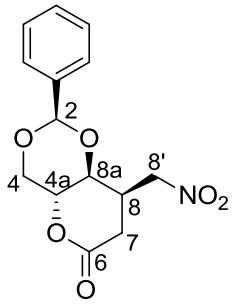
To a solution of lactone **133** (35 mg, 0.15 mmol) in acetone (1.6 mL) and water (0.16 mL) was added *N*-methylmorpholine *N*-oxide (26 mg, 0.23 mmol) and then a solution of osmium tetroxide 4 % in water (16 μL, 2.5 μmol) and the solution stirred at rt overnight. A aqueous solution of $Na_2S_2O_3$ 5 % (6 mL) was added, stirred for 10 min, and extracted with ethyl acetate (3×20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed in the rotary evaporator to give the pure product. Colourless oil **142** (16 mg, 0.06 mmol). Yield: 40 %. $[\alpha]_D^{22} + 21.2$ (*c* 0.48, AcOEt). IR (nujol) ν_{max} 3362, 1732 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 3.76 (dd, *J*= 11.2, 10.0 Hz, 1H, *H*-4), 3.98 (dd, *J*= 9.6, 6.4 Hz, 1H, *H*-8a), 4.00-4.07 (m, 1H, *H*-4a), 4.32 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-4), 4.35 (dd, *J*= 6.0, 3.6 Hz, 1H, *H*-8), 4.49 (d, *J*= 4.0 Hz, 1H, *H*-7), 5.68 (s, 1H, *H*-2), 7.47−7.51 (m, 5H, *H*-Ph) ppm. ^{13}C NMR (100 MHz, D_2O) δ 63.3 (C_{4a}), 69.9 (C_4), 71.8 (C_7), 74.0 (C_8), 78.7 (C_{8a}), 100.9 (C_2), 126.0, 128.6, 129.6 (CH, Ph), 136.4 (C_q), 175.4 (C=O) ppm.

3.8. 1,4-Nucleophilic additions to lactone 133 to give lactones 150a-d

3.8.1. General procedure

To a solution of lactone **133** (23−173 mg, 0.10−0.74 mmol) in CH_3CN (4−15 mL) refrigerated in an ice/salt bath, and under N_2 atmosphere was added the nucleophile (48−53 μL, 51−60 mg, 0.41−0.99 mmol), followed by NEt_3 (57−138 μL, 42−100 mg, 0.41−0.99 mmol). The reaction was carried out for specific time (2−12 h) at specific temperature (rt−50 °C). After treatment, pure products **150** were isolated (25−149 mg, 0.09−0.48 mmol, 51.4−85.9 %).

3.8.1.1. Synthesis of (2*S*,4*aR*,8*R*,8*aS*)-8-(nitromethyl)-2-phenyltetrahydropyrano[3,2-*d*][1,3]dioxin-6(7*H*)-one **150a**

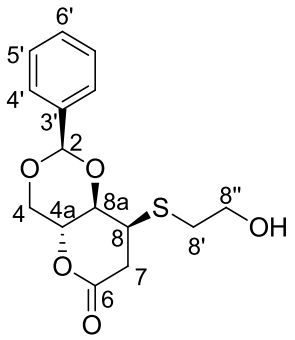


150a

Compound **133** (23 mg, 0.10 mmol); CH_3CN (4 mL); nitromethane (53 μL, 60 mg, 0.99 mmol); NEt_3 (138 μL, 0.10 g, 0.99 mmol); 50 ºC; 12 h. Treatment: evaporation of the solvent in the rotary evaporator, followed by addition of chloroform (2 mL). The solid was filtered. White solid **150a** (25 mg, 0.90 mmol). Yield: 85.9 %. M.p.: 170−173 °C. $[\alpha]_D^{15}$ + 111.5 (*c* 0.48, acetone). IR (nujol) ν_{max} 1745, 1557, 1460 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.72 (dd, *J*= 16.8, 7.2 Hz, 1H, *H*-7), 2.92 (dd, *J*= 16.8, 8.0 Hz, 1H, *H*-7), 3.42−3.52 (m, 1H, *H*-8), 3.85 (dd, *J*= 10.8, 10.0 Hz, 1H, *H*-4), 4.14 (dd, *J*= 9.6, 8.4 Hz, 1H, *H*-8a), 4.32 (td, *J*= 9.6, 4.8 Hz, 1H, *H*-4a), 4.42 (dd, *J*= 14.0, 8.4 Hz, 1H, *H*-8'), 4.52 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-4), 4.82 (dd, *J*= 13.6, 6.0 Hz, 1H, *H*-8'), 5.60 (s, 1H, *H*-2), 7.40 (s, 5H, *H*-Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2

(C_8), 31.8 (C_7), 67.1 (C_{4a}), 68.3 (C_4), 74.3 ($C_{8'}$), 74.6 (C_{8a}), 101.9 (C_2), 125.9, 128.4, 129.5 (CH, Ph), 135.9 (C_q), 167.7 (C=O) ppm. Anal. calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 56.16; H, 5.16; N, 4.76.

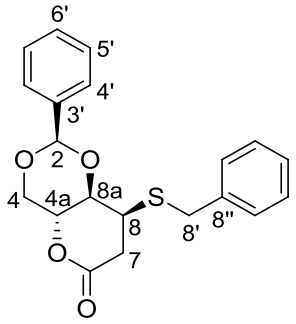
3.8.1.2. Synthesis of (2*R*,4a*R*,8*S*,8a*R*)-8-((2-hydroxyethyl)thio)-2-phenyltetrahydropyrano[3,2-*d*][1,3]dioxin-6(7*H*)-one **150b**



150b

Compound **133** (173 mg, 0.74 mmol); CH_3CN (10 mL); 2-mercaptoethanol (52 μL, 58 mg, 0.74 mmol); NEt_3 (104 μL, 75 mg, 0.74 mmol); rt; 2 h. Treatment: the solvent was evaporated in the rotary evaporator to give the product. White oil **150b** (149 mg, 0.48 mmol). Yield: 62.6 %. $[\alpha]_D^{23}$ + 22.2 (*c* 0.53, DCM). IR (nujol) ν_{max} 3500, 1745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.80 (ddd, *J*= 12.8, 6.4, 5.2 Hz, 1H, *H*-8'), 2.90 (dd, *J*= 18.8, 2.4 Hz, 1H, *H*-7), 2.99 (dt, *J*= 12.8, 6.4 Hz, 1H, *H*-8'), 3.21 (dd, *J*= 18.4, 7.6 Hz, 1H, *H*-7), 3.66 (ddd, *J*= 7.6, 4.0, 2.4 Hz, 1H, *H*-8), 3.69−3.73 (m, 2H, *H*-8''), 3.85 (t, *J*= 10.4 Hz, 1H, *H*-4), 4.13 (dd, *J*= 9.6, 4.0 Hz, 1H, *H*-8a), 4.48 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-4), 4.87 (td, *J*= 10.0, 5.2 Hz, 1H, *H*-4a), 5.61 (s, 1H, *H*-2), 7.39−7.41 (m, 3H, *H*-5' and *H*-6'), 7.46−7.49 (m, 2H, *H*-4') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.9 ($C_{8'}$), 36.8 (C_7), 40.0 (C_8), 61.2 ($C_{8''}$), 66.8 (C_{4a}), 68.3 (C_4), 77.7 (C_{8a}), 102.2 (C_2), 126.0 ($C_{4'}$), 128.4, 129.5 ($C_{5'}$ and $C_{6'}$), 136.4 (C_q), 167.0 (C=O) ppm. HRMS (ESI): calcd for $C_{15}H_{18}O_5S$: 333.0767 ($M+Na^+$); obtained: 333.0766.

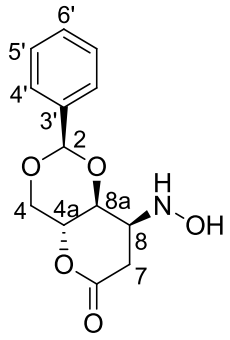
3.8.1.3. Synthesis of (2*R*,4*aR*,8*S*,8*aR*)-8-(benzylthio)-2-phenyltetrahydropyrano[3,2-*d*][1,3]dioxin-6(7*H*)-one **150c**



150c

Compound **133** (95 mg, 0.41 mmol); CH_3CN (15 mL); benzyl mercaptan (48 μL, 51 mg, 0.41 mmol); NEt_3 (57 μL, 41 mg, 0.41 mmol); rt; 2 h. Treatment: the solvent was removed in the rotary evaporator, and the crude product purified by column chromatography using a mixture of petroleum ether and ethyl acetate with increasing polarity (starting with PE (5) : EA (1)). White solid **150c** (75 mg, 0.21 mmol). Yield: 51.4 %. M.p.: 117−118 °C. $[\alpha]_D^{22}$ − 154.1 (*c* 0.94, AcOEt). IR (nujol) ν_{max} 1740, 1397, 1378, 1362 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.75 (dd, *J*= 18.4, 2.4 Hz, 1H, *H*-7), 3.09 (dd, *J*= 18.4, 7.6 Hz, 1H, *H*-7), 3.45 (ddd, *J*= 7.6, 4.0, 2.4 Hz, 1H, *H*-8), 3.84 (d, *J*= 13.2 Hz, 1H, *H*-8'), 3.87 (t, *J*= 10.8 Hz, 1H, *H*-4), 4.04 (d, *J*= 13.2 Hz, 1H, *H*-8'), 4.13 (dd, *J*= 9.6, 4.0 Hz, 1H, *H*-8a), 4.51 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-4), 4.98 (td, *J*= 10.0, 5.2 Hz, 1H, *H*-4a), 5.63 (s, 1H, *H*-2), 7.27−7.29 (m, 5H, *H*-$SCH_2\underline{Ph}$), 7.41−7.43 (m, 3H, *H*-5' and *H*-6'), 7.53−7.55 (m, 2H, *H*-4') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.1 (C_7), 36.7 ($C_{8'}$), 38.1 (C_8), 66.9 (C_{4a}), 68.3 (C_4), 78.4 (C_{8a}), 102.2 (C_2), 126.1 ($C_{4'}$), 127.2, 128.5, 129.1 (-$SCH_2\underline{Ph}$), 128.4, 129.4 ($C_{5'}$ and $C_{6'}$), 136.7 ($C_{3'}$), 137.3 ($C_{8''}$), 167.1 (C=O) ppm. HRMS (ESI): calcd for $C_{20}H_{20}O_4S$: 357.1155 (M+1); obtained: 357.1153.

3.8.1.4. Synthesis of (2*S*,4*aR*,8*S*,8*aS*)-8-(hydroxyamino)-2-phenyltetrahydropyrano[3,2-*d*][1,3]dioxin-6(7*H*)-one **150d**



150d

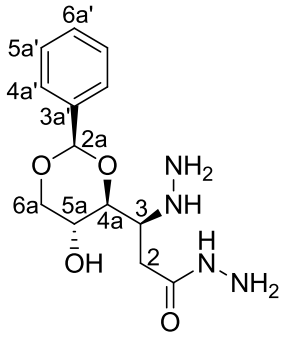
To a solution of **133** (80 mg, 0.34 mmol) in CH_3CN (1 mL), H_2O (1 mL) and EtOH (1 mL) was added hydroxylamine hydrochloride (24 mg, 0.34 mmol) and $NaHCO_3$ (58 mg, 0.68 mmol). The mixture was stirred at rt for 2 h. The solvent was removed in the rotary evaporator, DCM (20 mL) added, followed by water (15 mL) and extracted with DCM (5x20 mL). The organic layers were combined and dried over $MgSO_4$, filtered and the solvent removed in the rotary evaporator to give the pure product. Colourless oil **150d** (75 mg, 0.28 mmol). Yield: 82.1 %. $[\alpha]_D^{20} - 10.0$ (*c* 0.7, $CHCl_3$). IR (neat) ν_{max} 3350, 1776, 1260 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.86 (dd, *J*= 17.6, 7.2 Hz, 1H, *H*-7), 2.98 (dd, *J*= 17.6, 4.4 Hz, 1H, *H*-7), 3.66 (t, *J*= 10.8 Hz, 1H, *H*-4), 3.72−3.76 (m, 1H, *H*-8a), 3.80−3.86 (m, 1H, *H*-4a or *H*-8), 4.10−4.20 (m, 1H, *H*-4a or *H*-8), 4.35 (dd, *J*= 10.8, 4.8 Hz, 1H, *H*-4), 5.53 (s, 1H, *H*-2), 7.38−7.41 (m, 3H, *H*-5' and *H*-6'), 7.44−7.46 (m, 2H, *H*-4') ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9 (C_7), 61.6 (C_{4a} or C_8), 65.3 (C_{4a} or C_8), 70.6 (C_4), 78.4 (C_{8a}), 101.2 (C_2), 126.0 ($C_{4'}$), 128.4, 129.3 ($C_{5'}$ and $C_{6'}$), 136.8 (C_q), 176.8 (C=O) ppm. HRMS (ESI): calcd for $C_{13}H_{15}NO_5$: 266.1023 (M+1); obtained: 266.1022.

3.9. 1,4-Nucleophilic additions to lactone 133 to give amides 151a-d

3.9.1. General procedure

To a solution of lactone **133** (51−75 mg, 0.22−0.32 mmol) in dry CH_3CN (4−12 mL) refrigerated in an ice/salt bath under N_2 atmosphere, was added the amine (39−439 μL, 14−47 mg, 0.44−0.64 mmol). The solution was allowed to warm to rt and stirred for specific time (0.5−1 h). Products were obtained after evaporation or precipitation of the solid **151** (47−96 mg, 0.15−0.27 mmol, 67.3−quantitative yield).

3.9.1.1. Synthesis of (*S*)-3-hydrazinyl-3-((2*S*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)propanehydrazide **151a**

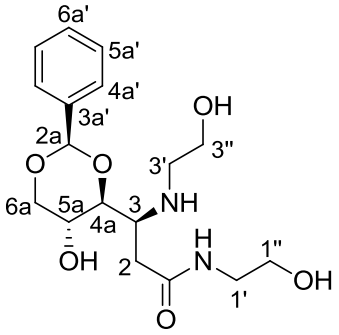


151a

Compound **133** (51 mg, 0.22 mmol); CH_3CN (10 mL); Anhydrous hydrazine (1 M, 439 μL, 14 mg, 0.44 mmol); 30 min. White solid **151a** (47 mg, 0.16 mmol). Yield: 72.2 %. M.p.: 135−136 °C. $[\alpha]_D^{26}$ − 59.8 (*c* 0.60, MeOH). IR (nujol) ν_{max} 3583, 3297, 3245, 3199, 1664 cm^{-1}. ^1H NMR (400 MHz, CD_3OD + 1 drop of D_2O) δ 2.42 (dd, *J*= 15.2, 8.0 Hz, 1H, *H*-2), 2.60 (dd, *J*= 15.2, 4.4 Hz, 1H, *H*-2), 3.48 ($dt_{ap,}$ *J*= 8.0, 4.0 Hz, 1H, *H*-3), 3.66 (t, *J*= 10.0 Hz, 1H, *H*-6a), 3.74 (td, *J*= 10.0, 4.8 Hz, 1H, *H*-5a), 3.88 (dd, *J*= 8.8, 4.0 Hz, 1H, *H*-4a), 4.25 (dd, *J*= 10.4, 4.8 Hz, 1H, *H*-6a), 5.57 (s, 1H, *H*-2a), 7.37−7.39 (m, 3H, *H*-5a' and *H*-6a'), 7.47−7.49 (m, 2H, *H*-4a') ppm. ^{13}C NMR (100 MHz, CD_3OD + 1 drop of D_2O) δ 33.3 (C_2), 61.3 (C_3), 64.4 (C_{5a}), 72.0 (C_{6a}), 81.8 (C_{4a}),

102.4 (C_{2a}), 127.4 ($C_{4a'}$), 129.2, 130.1 ($C_{5a'}$ and $C_{6a'}$), 139.1 (C_q), 174.0 (C=O) ppm. HRMS (ESI): calcd for $C_{13}H_{20}N_4O_4$: 297.1557 (M+1); obtained: 297.1550.

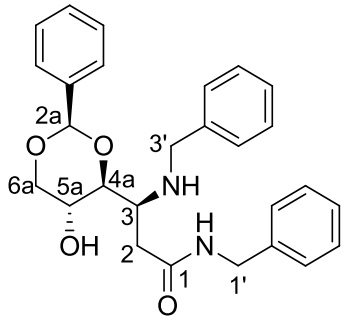
3.9.1.2. Synthesis of (*S*)-3-((2*S*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)-*N*-(2-hydroxyethyl)-3-((2-hydroxyethyl)amino)propamide **151b**



151b

Compound **133** (75 mg, 0.32 mmol); CH_3CN (12 mL); ethanolamine (39 μL, 39 mg, 0.64 mmol); 1 h. White solid **151b** (88 mg, 0.25 mmol). Yield: 76.9 %. M.p.: 158−160 °C. $[\alpha]_D^{26}$ − 50.6 (*c* 0.60, MeOH). IR (nujol) ν_{max} 3410, 3294, 1624 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 2.23 (dd, *J*= 14.8, 8.4 Hz, 1H, *H*-2), 2.36 (dd, *J*= 14.8, 4.0 Hz, 1H, *H*-2), 2.60−2.69 (m, 2H, *H*-3'), 3.04−3.17 (m, 2H, *H*-1'), 3.20−3.23 (m, 1H, *H*-3), 3.37 (q, *J*= 6.0 Hz, 2H, *H*-1''), 3.41 (q, *J*= 5.6 Hz, 2H, *H*-3''), 3.47 (t, *J*= 9.6 Hz, 1H, *H*-6a), 3.53 (td, *J*= 9.6, 4.4 Hz, 1H, *H*-5a), 3.59 (dd, *J*= 8.8, 4.4 Hz, 1H, *H*-4a), 4.07 (dd, *J*= 9.6, 4.0 Hz, 1H, *H*-6a), 4.49 (t, *J*= 5.6 Hz, 1H, H-3: O*H*), 4.61 (t, *J*= 5.6 Hz, 1H, H-1: O*H*), 5.48 (s, 1H, *H*-2a), 5.73 (br s, 1H, H-3: N*H*), 7.33−7.36 (m, 3H, *H*-5a' and *H*-6a'), 7.40−7.42 (m, 2H, *H*-4a'), 8.01 (t, *J*= 5.6 Hz, 1H, H-1: N*H*) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 35.7 (C_2), 41.4 ($C_{1'}$), 48.9 ($C_{3'}$), 55.9 (C_3), 59.9 ($C_{1''}$), 60.7 ($C_{3''}$), 63.6 (C_{5a}), 70.6 (C_{6a}), 81.3 (C_{4a}), 100.1 (C_{2a}), 126.1 ($C_{4a'}$), 127.9, 128.5 ($C_{5a'}$ and $C_{6a'}$), 138.2 (C_q), 171.5 (C=O) ppm. Anal. calcd for $C_{17}H_{26}N_2O_6$: C, 57.61; H, 7.39; N, 7.90. Found: C, 57.07; H, 7.35; N, 8.07.

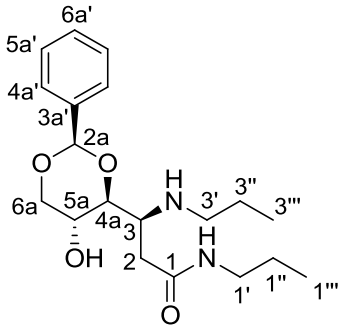
3.9.1.3. Synthesis of (*S*)-*N*-benzyl-3-(benzylamino)-3-((2*S*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)propanamide **151c**



151c

Compound **133** (51 mg, 0.22 mmol); CH_3CN (4 mL); benzylamine (48 μL, 47 mg, 0.44 mmol); 1 h. White solid **151c** (66 mg, 0.15 mmol). Yield: 67.3 %. M.p.: 164−166 °C. $[\alpha]_D^{15}$ + 30.3 (*c* 0.76, DCM). IR (nujol) ν_{max} 3303, 3285, 3169, 1614 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 2.46 (dd, *J*= 14.4, 4.0 Hz, 1H, *H*-2), 2.65 (dd, *J*= 14.4, 3.6 Hz, 1H, *H*-2), 3.22 (dt, *J*= 9.6, 4.0 Hz, 1H, *H*-3), 3.45 (t, *J*= 8.8 Hz, 1H, *H*-4a), 3.50 (t, *J*= 10.4 Hz, 1H, *H*-6a), 3.73 (td, *J*= 10.0, 5.2 Hz, 1H, *H*-5a), 3.80 (d, *J*= 12.8 Hz, 1H, *H*-3'), 4.05 (d, *J*= 12.4 Hz, 1H, *H*-3'), 4.20 (dd, *J*= 14.8, 5.2 Hz, 1H, *H*-1'), 4.24 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-6a), 4.63 (dd, *J*= 14.4, 6.8 Hz, 1H, *H*-1'), 5.13 (s, 1H, *H*-2a), 5.96 (br s, 1H, N*H*CO), 7.22−7.35 (m, 15H, *H*-Ph) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1 (C_2), 43.5 ($C_{1'}$), 51.1 ($C_{3'}$), 59.1 (C_3), 67.2 (C_{5a}), 70.9 (C_{6a}), 79.6 (C_{4a}), 101.4 (C_{2a}), 125.9, 127.5, 127.8, 128.1, 128.3, 128.5, 128.7, 128.9, 129.1 (CH, Ph), 137.6, 138.2, 138.5 (C_q), 171.0 (C=O) ppm. Anal. calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.37; H, 6.63; N, 6.27.

3.9.1.4. Synthesis of (*S*)-3-((2*R*,4*R*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)-*N*-propyl-3-(propylamino)propamide **151d**



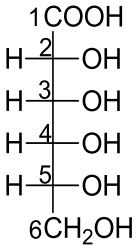
151d

Compound **133** (63 mg, 0.27 mmol); CH_3CN (10 mL); propylamine (45 μL, 32 mg, 0.54 mmol); 1 h. Pale yellow **151d** (96 mg, 0.27 mmol). Yield: quantitative. M.p.: 98−100 °C. $[\alpha]_D^{24} - 15.7$ (*c* 0.52, DCM). IR (nujol) ν_{max} 3297, 3277, 3105, 1723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J*= 7.2 Hz, 3H, *H*-1’’’), 0.95 (t, *J*= 7.2 Hz, 3H, *H*-3’’’), 1.42−1.51 (m, 2H, *H*-1’’), 1.52−1.59 (m, 2H, *H*-3’’), 2.42 (dd, *J*= 14.4, 4.8 Hz, 1H, *H*-2), 2.51−2.55 (m, 1H, *H*-3’), 2.58 (dd, *J*= 14.8, 3.6 Hz, 1H, *H*-2), 2.85 (dt, *J*= 11.2, 6.8 Hz, 1H, *H*-3’), 3.08−3.17 (m, 2H, *H*-3 and *H*-1’), 3.21−3.30 (m, 1H, *H*-1’), 3.50 (t, *J*= 8.8 Hz, 1H, *H*-4a), 3.61 (t, *J*= 10.4 Hz, 1H, *H*-6a), 3.84 (td, *J*= 10.0, 5.2 Hz, 1H, *H*-5a), 4.29 (dd, *J*= 10.8, 5.2 Hz, 1H, *H*-6a), 5.46 (s, 1H, *H*-2a), 5.71 (br s, 1H, CON*H*), 7.37−7.39 (m, 3H, *H*-5a’ and *H*-6a’), 7.43−7.45 (m, 2H, *H*-4a’) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 ($C_{1'''}$), 11.7 ($C_{3'''}$), 22.9 ($C_{1''}$), 23.2 ($C_{3''}$), 33.5 (C_2), 41.0 ($C_{1'}$), 48.9 ($C_{3'}$), 60.1 (C_3), 67.5 (C_{5a}), 71.0 (C_{6a}), 79.8 (C_{4a}), 101.5 (C_{2a}), 126.0 ($C_{4a'}$), 128.4, 129.1 ($C_{5a'}$ and $C_{6a'}$), 137.8 (C_q), 171.3 (C=O) ppm. HRMS (ESI): calcd for $C_{19}H_{30}N_2O_4$: 351.2277 (M+1); obtained: 351.2278.

3.10. Acetal cleavage

3.10.1. of lactone 142

3.10.1.1. Synthesis of (2*S*,3*R*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexanoic acid **152**



152

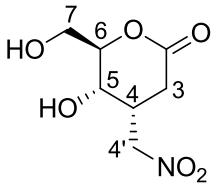
To a solution of **142** (25 mg, 0.09 mmol) in 1,4-dioxane (3 mL) was added HCl 1M (500 μL) and stirred at rt overnight. The solvent was removed in the rotary evaporator, and then basic resin was added, filtered and the solvent evaporated to give the pure product. Colourless oil **152** (5 mg, 0.03 mmol). Yield: 28.3 %. $[\alpha]_D^{22} + 8.22$ (*c*, 0.75, H_2O). IR (neat) ν_{max} 3358, 1620 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 3.68 (dd, *J*= 12.0, 6.8 Hz, 1H, *H*-6), 3.83 (dd, *J*= 12.0, 3.2 Hz, 1H, *H*-6), 3.85 (dd, *J*= 6.8, 5.6 Hz, 1H, *H*-4), 3.90 (ddd, *J*= 8.4, 6.4, 2.8 Hz, 1H, *H*-3), 4.06 (dd, *J*= 6.8, 3.2 Hz, 1H, *H*-5), 4.26 (d, *J*= 3.2 Hz, 1H, *H*-2) ppm. ^{13}C NMR (100 MHz, D_2O) δ 62.3 (C_6), 71.7 (C_4), 72.5 (C_3), 73.5 (C_2 and C_5), 178.1 (C=O) ppm.

3.10.2. of lactones 150a-d

3.10.1.1. General procedure

To a solution of respective compound **150a-d** (21−40 mg, 0.07−0.14 mmol) in solvent (3−4 mL) was added HCl (0.04−1.0 mL) and stirred at rt overnight. The solution was concentrated in the rotary evaporator, basic resin was added, then filtered and the solvent removed in the rotary evaporator to give the pure product **153a-d** (12−26 mg, 0.06−0.13 mmol, 78.1−92.9 %).

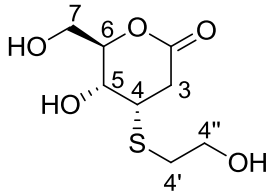
3.10.1.2.1. Synthesis of (4*R*,5*S*,6*R*)-5-hydroxy-6-(hydroxymethyl)-4-(nitromethyl)tetrahydro-2*H*-pyran-2-one **153a**



153a

Compound **150a** (40 mg, 0.14 mmol); 1,4-dioxane (2 mL) and CH_3CN (1 mL); HCl 3 M (1 mL); overnight. Yellow oil **153a** (26 mg, 0.13 mmol). Yield: 92.9 %. $[\alpha]_D^{23}$ +17.5 (*c* 0.6, MeOH). IR (neat) ν_{max} 3373, 1775, 1553, 1423, 1381 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 2.66 (dd, *J*= 18.8, 5.6 Hz, 1H, *H*-3), 3.08 (dd, *J*= 18.8, 10.0 Hz, 1H, *H*-3), 3.35−3.44 (m, 1H, *H*-4), 3.69 (dd, *J*= 12.4, 6.0 Hz, 1H, *H*-7), 3.77 (dd, *J*= 11.6, 4.4 Hz, 1H, *H*-7), 3.95−3.99 (m, 1H, *H*-6), 4.58 (t, *J*= 5.2 Hz, 1H, *H*-5), 4.77 (dd, *J*= 14.4, 7.2 Hz, 1H, *H*-4'), 4.86 (dd, *J*= 14.4, 6.4 Hz, 1H, *H*-4') ppm. ^{13}C NMR (100 MHz, D_2O) δ 32.4 (C_3), 34.1 (C_4), 61.7 (C_7), 72.2 (C_6), 76.5 ($C_{4'}$), 82.4 (C_5), 179.2 (C=O) ppm. MS: m/z 205.

3.10.1.2.2. Synthesis of (4*S*,5*R*,6*R*)-5-hydroxy-4-((2-hydroxyethyl)thio)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-one **153b**

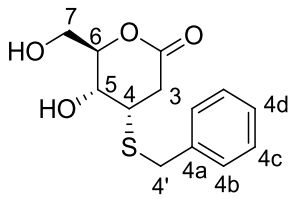


153b

Compound **150b** (21 mg, 0.07 mmol); 1,4-dioxane (4 mL); HCl 1M (135 μL, 0.14 mmol); overnight. Colourless oil **153b** (12 mg, 0.05 mmol). Yield: 79.8 %. $[\alpha]_D^{24}$ −32.2 (*c* 0.6, CH_3OH). IR (neat) ν_{max} 3364, 1769 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 2.73 (dd, *J*= 18.8, 5.2 Hz, 1H, *H*-3), 2.86 (t, *J*= 6.4 Hz, 2H, *H*-4'), 3.27 (dd, *J*= 18.8,

9.2 Hz, 1H, *H*-3), 3.71 (dd, *J*= 10.8, 6.8 Hz, 1H, *H*-7), 3.76−3.79 (m, 1H, *H*-7), 3.81 (t, *J*= 6.4 Hz, 2H, *H*-4''), 3.83−3.87 (m, 1H, *H*-4), 3.99 (dt, *J*= 6.8, 4.4 Hz, 1H, *H*-6), 4.60 (t, *J*= 4.4 Hz, 1H, *H*-5) ppm. ^{13}C NMR (100 MHz, D_2O) δ 32.9 ($C_{4'}$), 36.5 (C_3), 38.3 (C_4), 60.1 ($C_{4''}$), 61.6 (C_7), 71.3 (C_6), 86.1 (C_5), 178.9 (C=O) ppm. HRMS (ESI): calcd for $C_8H_{14}O_5S$: 245.0429 (M+Na); obtained: 245.0454.

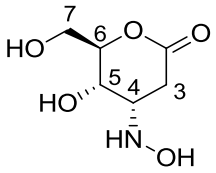
3.10.1.2.3. Synthesis of (4*S*,5*R*,6*R*)-4-(benzylthio)-5-hydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-one **153c**



153c

Compound **150c** (25 mg, 0.08 mmol); 1,4-dioxane (4 mL); HCl 1M (40 μL, 0.40 mmol); overnight. Yellow oil **153c** (17 mg, 0.06 mmol). Yield: 78.1 %. $[\alpha]_D^{24}$ −14.3 (*c* 0.57, MeOH). IR (neat) ν_{max} 3323, 1782 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) δ 2.41 (dd, *J*= 18.4, 3.6 Hz, 1H, *H*-3), 3.03 (dd, *J*= 18.4, 8.8 Hz, 1H, *H*-3), 3.54 (d, *J*= 6.0 Hz, 2H, *H*-7), 3.65 (dt, *J*= 8.8, 3.6 Hz, 1H, *H*-4), 3.81 (td, *J*= 6.0, 4.0 Hz, 1H, *H*-6), 3.88 (d, *J*= 2.4 Hz, 2H, *H*-4'), 4.52 (t, *J*= 3.6 Hz, 1H, *H*-5), 7.23 (t, *J*= 7.6 Hz, 1H, *H*-4d), 7.33 (t, *J*= 8.0 Hz, 2H, *H*-4c), 7.39 (d, *J*= 7.2 Hz, 2H, *H*-4b) ppm. ^{13}C NMR (100 MHz, CD_3OD) δ 36.4 ($C_{4'}$), 37.6 (C_3), 39.3 (C_4), 63.4 (C_7), 73.2 (C_6), 87.4 (C_5), 128.3 (C_{4d}), 129.6 (C_{4c}), 130.0 (C_{4b}), 139.2 (C_q), 178.0 (C=O) ppm. HRMS (ESI): calcd for $C_{13}H_{16}O_4S$: 291.0664 (M+Na); obtained: 291.0662.

3.10.1.2.4. Synthesis of (4*S*,5*S*,6*R*)-5-hydroxy-4-(hydroxyamino)-6-(hydroxylmethyl)tetrahydro-2*H*-pyran-2-one **153d**



153d

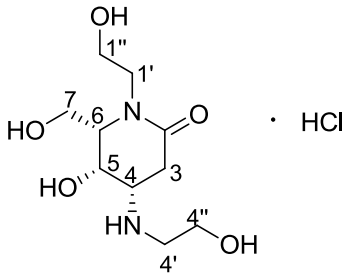
Compound **150d** (25 mg, 0.09 mmol); 1,4-dioxane (4 mL); HCl 1M (100 μL, 0.27 mmol); overnight. Yellow oil **153d** (15 mg, 0.09 mmol). Yield: 89.8 %. $[\alpha]_D^{24}$ −11.0 (*c* 1.0, H_2O). IR (neat) ν_{max} 3582, 3371, 2928, 1779, 1630 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 2.94 (dd, *J*= 19.2, 2.4 Hz, 1H, *H*-3), 3.27 (dd, *J*= 19.2, 9.2 Hz, 1H, *H*-3), 3.72 (dd, *J*= 12.0, 5.6 Hz, 1H, *H*-7), 3.77 (dd, *J*= 12.0, 4.4 Hz, 1H, *H*-7), 4.02 (q, *J*= 4.8 Hz, 1H, *H*-6), 4.55 (dt, *J*= 9.2, 2.0 Hz, 1H, *H*-4), 5.00 (dd, *J*= 4.4, 2.0 Hz, 1H, *H*-5) ppm. ^{13}C NMR (100 MHz, D_2O) δ 29.9 (C_3), 57.1 (C_4), 61.4 (C_7), 70.6 (C_6), 80.6 (C_5), 176.7 (C=O) ppm. HRMS (ESI): calcd for $C_6H_{11}NO_5$: 178.0707 (M+1); obtained: 178.0710.

3.10.3. of amides 151b-d

3.10.3.1. General Procedure

To a solution of the amides **151b-d** (27−49 mg, 0.08−0.11 mmol) in 1,4-dioxane (3−5 mL) was added aq. HCl 37 % (2.0−2.5 mL). The solution was stirred at rt for 4 days. The solvents were removed in the rotary evaporator, MeOH was added to give the pure products **154b-d** (22−41 mg, 0.08−0.11 mmol, quantitative yield) as solids.

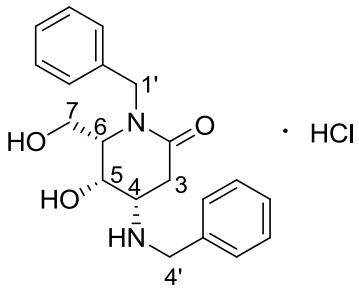
3.10.3.1.1. Synthesis of (4*S*,5*S*,6*S*)-5-hydroxy-1-(2-hydroxyethyl)-4-((2-hydroxyethyl)amino-6-(hydroxymethyl)piperidine-2-one hydrochloride salt **154b**



154b

Compound **151b** (37 mg, 0.10 mmol); 1,4-dioxane (4 mL); HCl 37 % (2 mL). Orange oil **154b** (30 mg, 0.10 mmol). Yield: quantitative. $[\alpha]_D^{23} - 4.7$ (*c* 1.2, MeOH). IR (nujol) ν_{max} 3392, 1781 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 2.96 (dd, *J*= 19.2, 3.2 Hz, 1H, *H*-3), 3.12 (t, *J*= 5.2 Hz, 2H, *H*-4'), 3.27−3.29 (m, 2H, *H*-1'), 3.31 (dd, *J*= 20.0, 9.2 Hz, 1H, *H*-3), 3.75 (t, *J*= 5.8 Hz, 2H, *H*-7), 3.79 (t, *J*= 5.6 Hz, 2H, *H*-4''), 3.85−3.87 (m, 2H, *H*-1''), 3.99 (q, *J*= 4.4 Hz, 1H, *H*-6), 4.35 (dt, *J*= 9.2, 2.8 Hz, 1H, *H*-4), 4.89 (dd, *J*= 4.8, 2.4 Hz, 1H, *H*-5) ppm. ^{13}C NMR (100 MHz, D_2O) δ 31.9 (C_3), 41.2 ($C_{4'}$), 47.8 ($C_{1'}$), 54.5 (C_4), 56.5 ($C_{1''}$), 57.5 ($C_{4''}$), 61.5 (C_7), 70.3 (C_6), 81.7 (C_5), 175.9 (C=O) ppm.

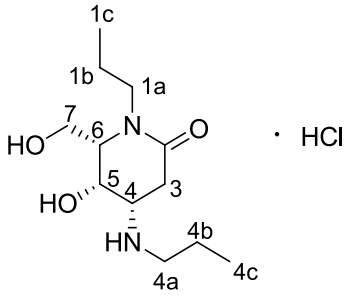
3.10.3.1.2. Synthesis of (4*S*,5*S*,6*S*)-1-benzyl-4-(benzylamino)-5-hydroxy-6-(hydroxymethyl)piperidine-2-one hydrochloride salt **154c**



154c

Compound **151c** (49 mg, 0.11 mmol); 1,4-dioxane (5 mL); HCl 37 % (2.5 mL). Beige solid **154c** (41 mg, 0.11 mmol). Yield: quantitative. M.p.: 165−167 °C. $[\alpha]_D^{24}$ + 3.80 (*c* 0.8, MeOH). IR (nujol) ν_{max} 3583, 3344, 3292, 1791 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 3.02 (dd, *J*= 19.2, 3.2 Hz, 1H, *H*-3), 3.35 (dd, *J*= 19.2, 9.2 Hz, 1H, *H*-3), 3.73 (dd, *J*= 12.4, 5.2 Hz, 1H, *H*-7), 3.80 (dd, *J*= 12.4, 4.4 Hz, 1H, *H*-7), 4.01 (q, *J*= 4.8 Hz, 1H, *H*-6), 4.22 (s, 2H, *H*-1'), 4.34 (d, *J*= 13.2 Hz, 1H, *H*-4'), 4.41 (d, *J*= 12.8 Hz, 1H, *H*-4'), 4.38−4.43 (m, 1H, *H*-4), 4.97 (dd, *J*= 5.2, 2.4 Hz, 1H, *H*-5), 7.48−7.53 (m, 10H, *H*-Ph) ppm. ^{13}C NMR (100 MHz, D_2O) δ 31.8 (C_3), 43.0 ($C_{1'}$), 49.6 ($C_{4'}$), 54.2 (C_4), 61.2 (C_7), 70.3 (C_6), 81.8 (C_5), 128.7, 129.1, 129.3, 129.7, 129.81 (CH, Ph), 129.83, 132.5 (C_q), 175.9 (C=O) ppm. HRMS (ESI): calcd for $C_{20}H_{24}N_2O_3$: 252.1230 (M+1-Bn); obtained: 252.1230.

3.10.3.1.3. Synthesis of (4*S*,5*S*,6*S*)-5-hydroxy-6-(hydroxymethyl)-1-propyl-4-(propylamino)piperidine-2-one hydrochloride salt **154d**

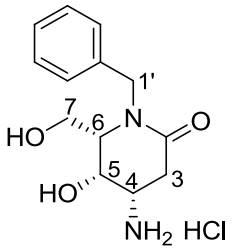


154d

Compound **151d** (27 mg, 0.08 mmol); 1,4-dioxane (3 mL); HCl 37 % (2.5 mL). Beige solid hydroscopic **154d** (22 mg, 0.08 mmol). Yield: quantitative. $[\alpha]_D^{25} + 6.50$ (*c* 1.0, MeOH). IR (nujol) ν_{max} 3395, 1783 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 1.01 (t, *J*= 7.6 Hz, 3H, *H*-1c), 1.03 (t, *J*= 7.6 Hz, 3H, *H*-4c), 1.71 (quint, *J*= 7.6 Hz, 2H, *H*-1b), 1.79 (quint, *J*= 7.6 Hz, 2H, *H*-4b), 2.97 (dd, *J*= 19.2, 2.8 Hz, 1H, *H*-3), 3.01 (t, *J*= 6.4 Hz, 2H, *H*-1a), 3.15 (t, *J*= 7.6 Hz, 2H, *H*-4a), 3.36 (dd, *J*= 19.2, 9.2 Hz, 1H, *H*-3), 3.78 (dd, *J*= 12.4, 5.2 Hz, 1H, *H*-7), 3.83 (dd, *J*= 12.0, 4.4 Hz, 1H, *H*-7), 4.03 (q, *J*= 5.2 Hz, 1H, *H*-6), 4.35 (dt, *J*= 9.2, 2.4 Hz, 1H, *H*-4), 4.93 (dd, *J*= 4.8, 2.4 Hz, 1H, *H*-5) ppm. ^{13}C NMR (100 MHz, D_2O) δ 10.2 (C_{1c} and C_{4c}), 19.3 (C_{4b}), 20.3 (C_{1b}), 32.0 (C_3), 41.2 (C_{1a}), 47.8 (C_{4a}), 54.7 (C_4), 61.6 (C_7), 70.5 (C_6), 81.9 (C_5), 176.2 (C=O) ppm. HRMS (ESI): calcd for $C_{12}H_{25}N_2O_3$: 245.1862 (M+1); obtained: 245.1860.

3.11. Benzylamine cleavage

3.11.1. Synthesis of (4*S*,5*S*,6*S*)-4-amino-1-benzyl-5-hydroxy-6-(hydroxymethyl)piperidine-2-one hydrochloride salt **155**

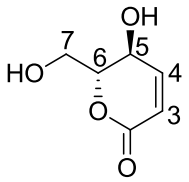


155

To a solution of **154c** (100 mg, 0.27 mmol) in methanol (5 mL) contained in a 50 mL two-necked flask was added $ClCH_2CHCl_2$ (54 μL, 79 mg, 0.59 mmol), HCl 37 % (7 μL) and Pd/C (10 %, 10 mg). The solution was purged 5 times with H_2 (g) and left stirring at rt overnight. Basic resin was added, the suspension passed through a pad of Celite®, and the solvent removed in the rotary evaporator to give the pure product. Orange solid **155** (53 mg, 0.18 mmol). Yield: 69.6 %. M.p.: >300 °C. $[\alpha]_D^{24} + 8.0$ (*c* 0.83, H_2O). IR (nujol) ν_{max} 3379, 3247, 1785 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 2.88 (dd, *J*= 19.2, 3.6 Hz, 1H, *H*-3), 3.31 (dd, *J*= 19.2, 9.2 Hz, 1H, *H*-3), 3.76 (dd, *J*= 12.0, 5.2 Hz, 1H, *H*-7), 3.81 (dd, *J*= 12.4, 4.0 Hz, 1H, *H*-7), 4.02 (dt, *J*= 5.6, 4.0 Hz, 1H, *H*-6), 4.23 (s, 2H, *H*-1'), 4.38 (dd, *J*= 8.8, 3.2 Hz, 1H, *H*-4), 4.80 (under HOD peak, *H*-5), 7.51 (s, 5H, *H*-Ph) ppm. ^{13}C NMR (100 MHz, D_2O) δ 33.1 (C_3), 43.0 ($C_{1'}$), 47.6 (C_4), 61.6 (C_7), 70.6 (C_6), 82.9 (C_5), 128.8, 129.1 (CH, Ph), 132.5 (C_q), 176.3 (C=O) ppm.

3.12. Synthesis of lactone 156

3.12.1. Synthesis of (5*S*,6*R*)-5-hydroxy-6-(hydroxymethyl)-5,6-dihydro-2*H*-pyran-2-one **156**



156

To a solution of lactone **133** (53 mg, 0.23 mmol) in 1,4-dioxane (4 mL) was added HCl 3 M (1 mL) at rt and stirred overnight. Then HCl 37 % (5 drops) were added and the solution allowed to stirring for another day. The solvent was evaporated in the rotary evaporator to give pure product. Yellow oil **156** (33 mg, 0.23 mmol). Yield: quantitative. $[\alpha]_D^{22}$ − 148.9 (*c* 0.95, H_2O). IR (nujol) ν_{max} 3331, 3096, 1741 cm^{-1}. ^1H NMR (400 MHz, D_2O) δ 3.72 (dd, *J*= 12.0, 6.0 Hz, 1H, *H*-2'), 3.79 (dd, *J*= 12.0, 4.4 Hz, 1H, *H*-2'), 4.08 (dt, *J*= 6.0, 4.4 Hz, 1H, *H*-2), 5.36 (dt, *J*= 3.6, 1.6 Hz, 1H, *H*-3), 6.31 (dd, *J*= 6.0, 2.0 Hz, 1H, *H*-5), 7.85 (dd, *J*= 6.0, 1.6 Hz, 1H, *H*-4) ppm. ^{13}C NMR (100 MHz, D_2O) δ 61.8 (C_7), 70.9 (C_6), 84.9 (C_5), 121.5 (C_3), 156.1 (C_4), 176.2 (C=O) ppm. M= m/z: 144.

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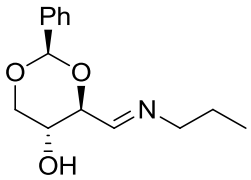
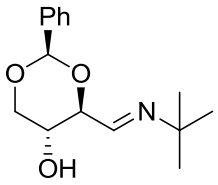
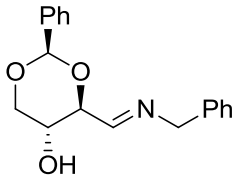
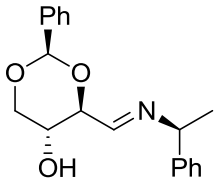
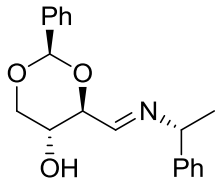
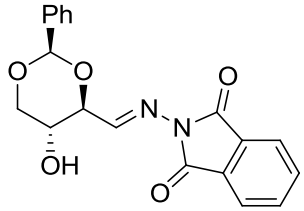
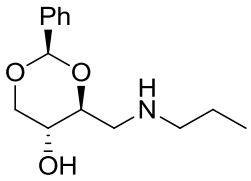
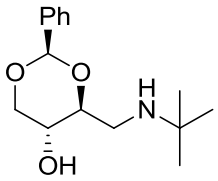
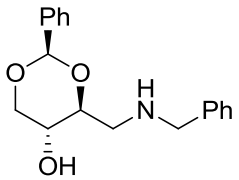
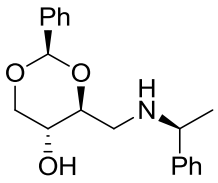
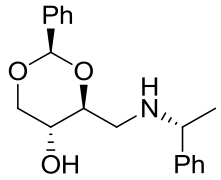
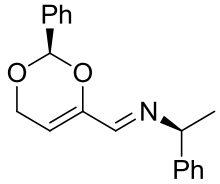
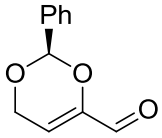
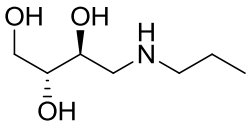
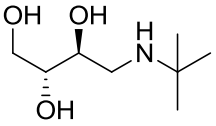
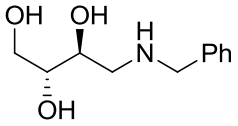
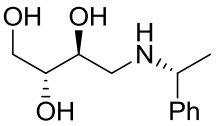
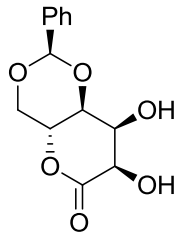
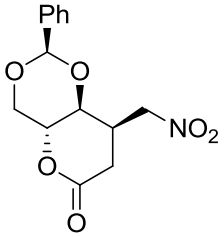
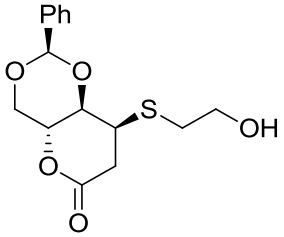
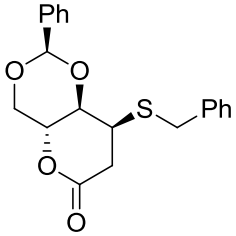
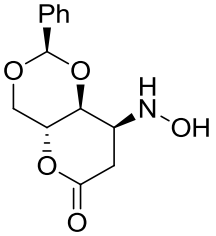
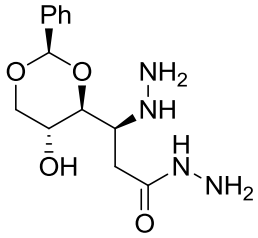
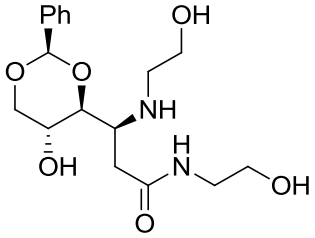
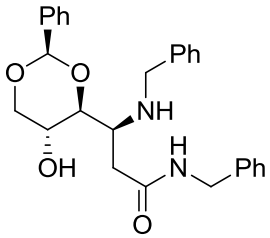
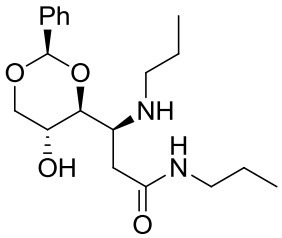
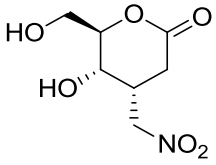
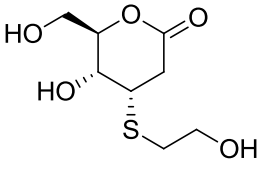
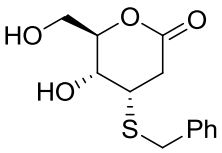
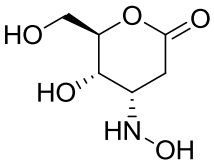
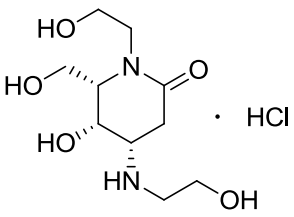
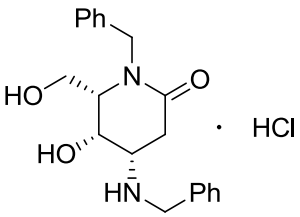
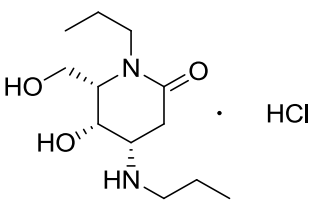
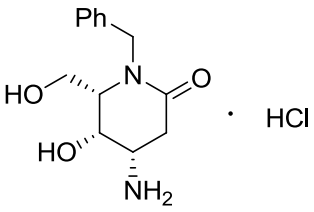
ATTACHMENTS

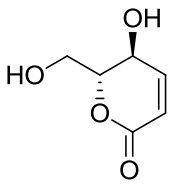
Attachment A

List of new compounds

Number of compound	Structure	Number of compound	Structure
134a		**134b**	
134c		**134d**	
134e		**134f**	
135a		**135b**	
135c		**135d**	

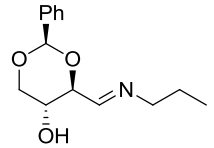
135e		**139**	
140		**141a**	
141b		**141c**	
141e		**142**	
150a		**150b**	
150c		**150d**	

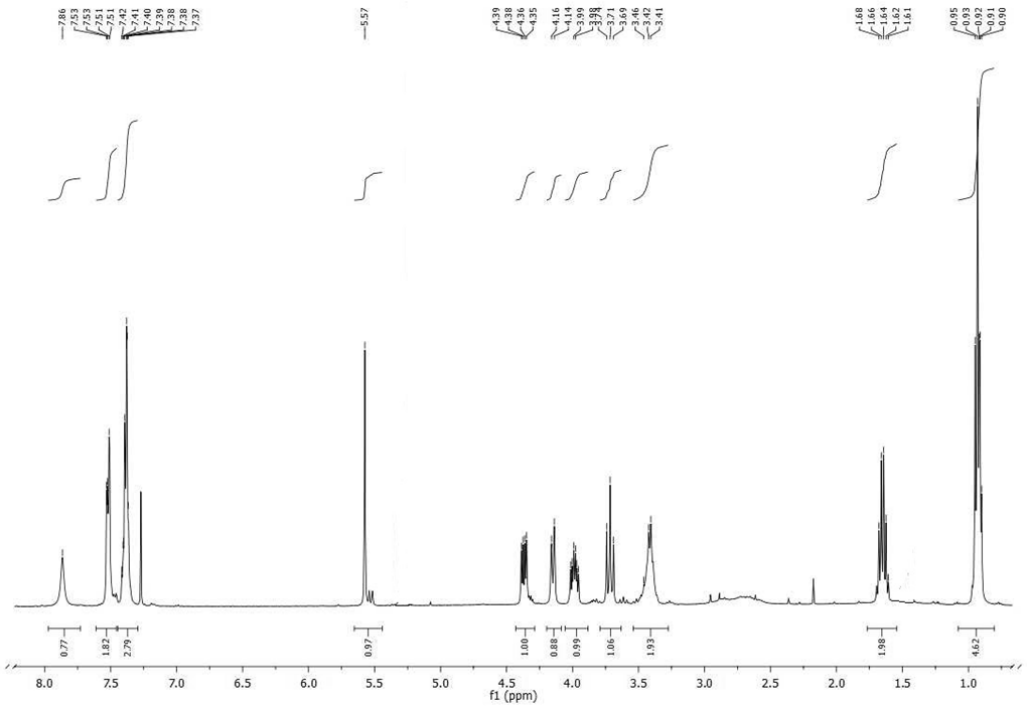
151a		**151b**	
151c		**151d**	
153a		**153b**	
153c		**153d**	
154b		**154c**	
154d		**155**	

156			

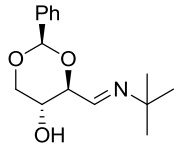
Attachments B

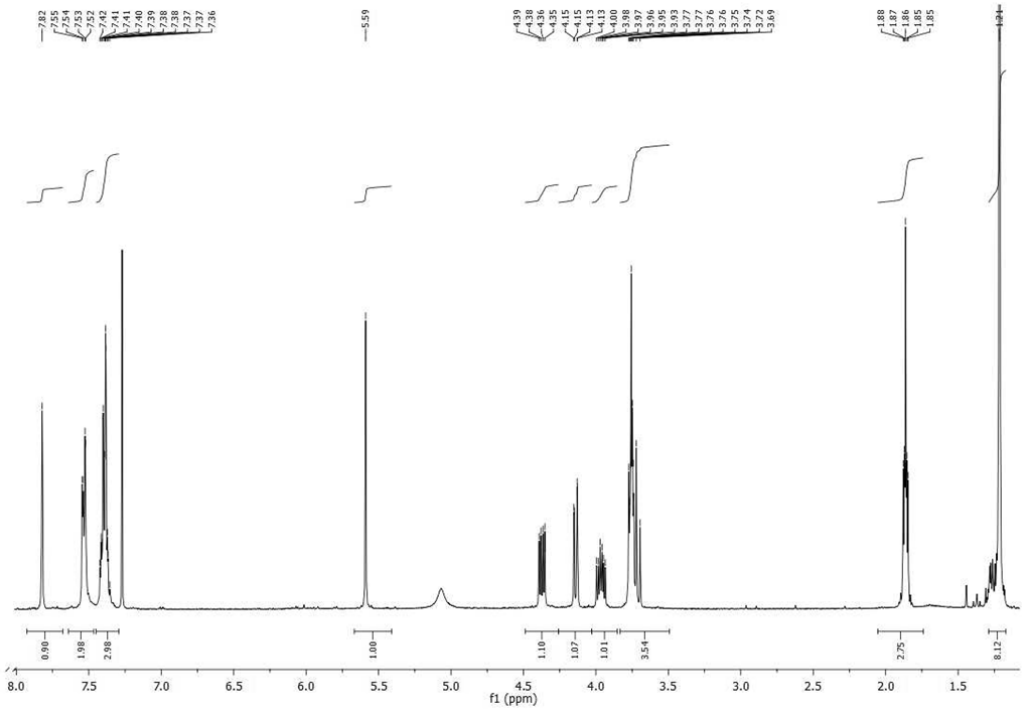
^{1}H NMR of compound **134a**



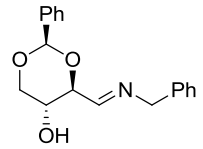


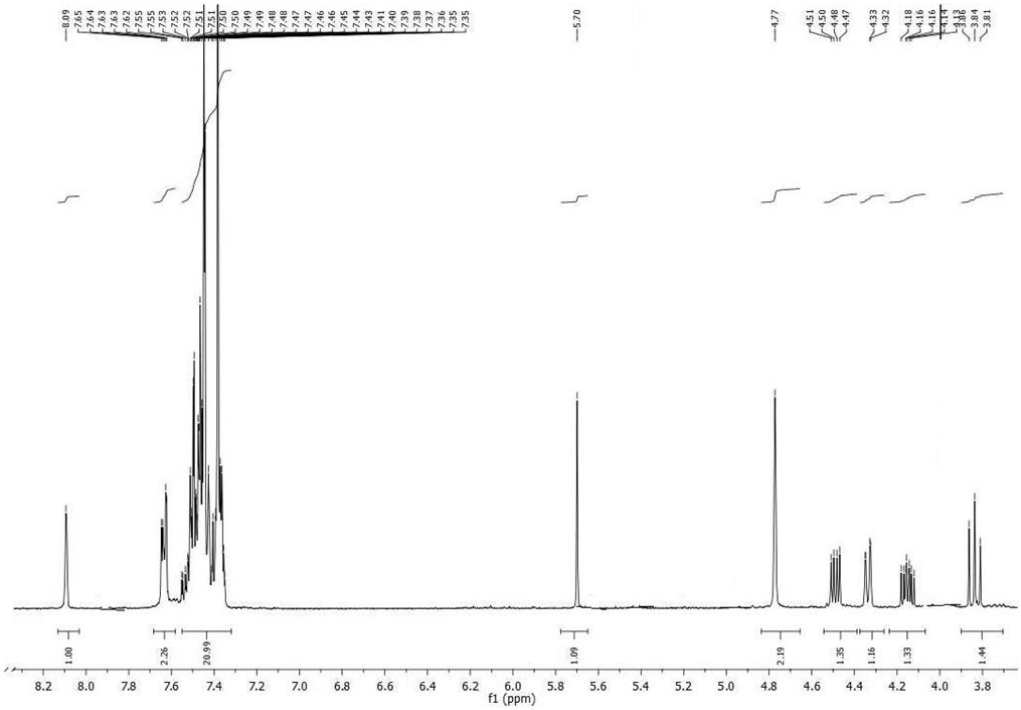
^{1}H NMR of compound **134b**



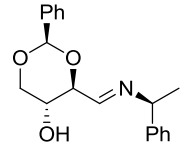


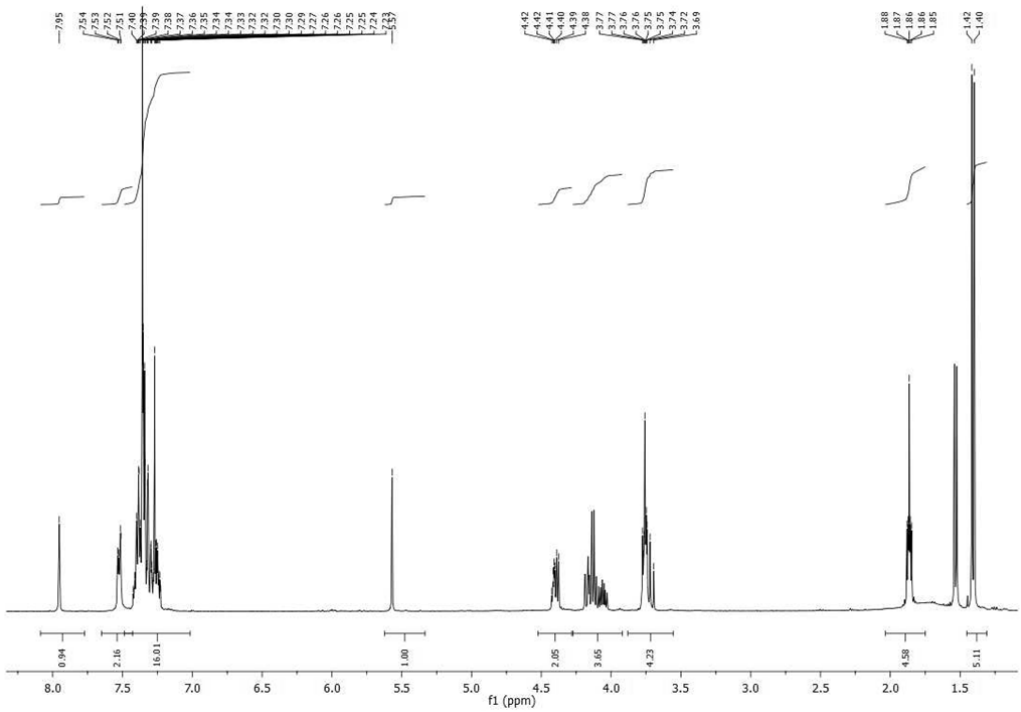
^{1}H NMR of compound **134c**



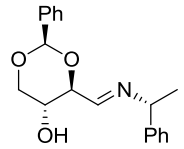


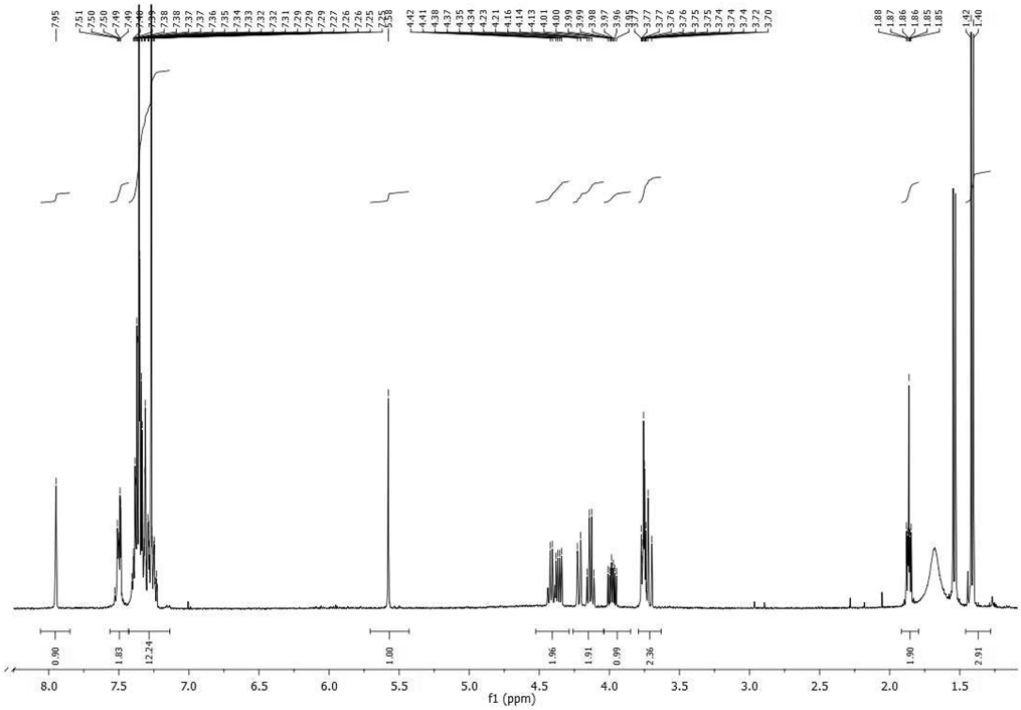
^{1}H NMR of compound **134d**



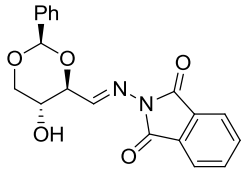


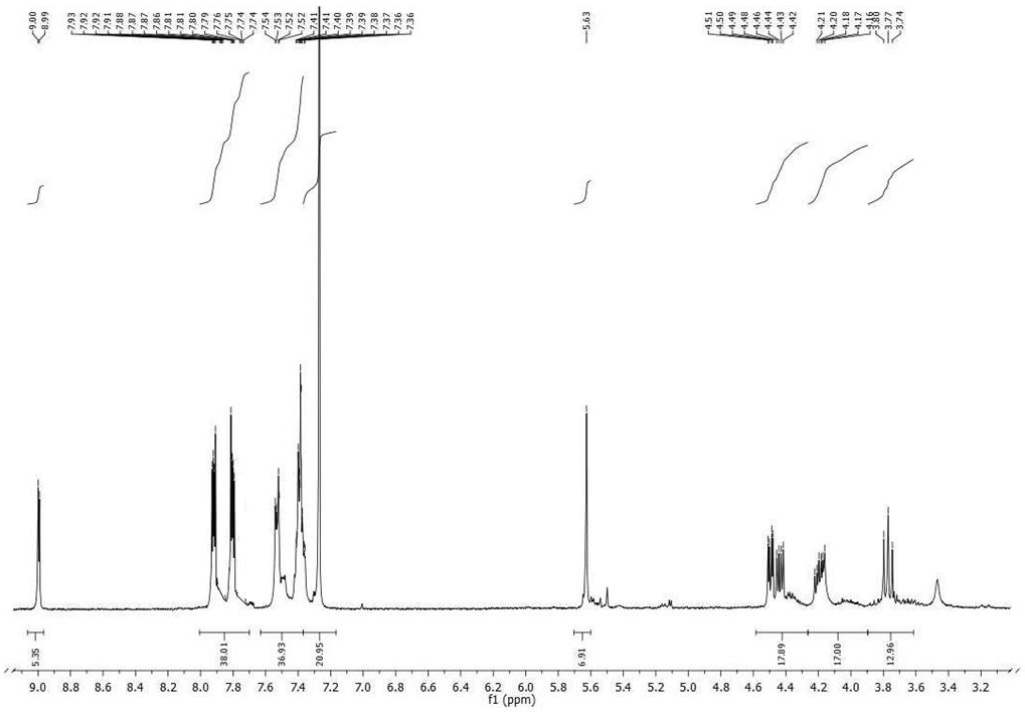
^{1}H NMR of compound **134e**

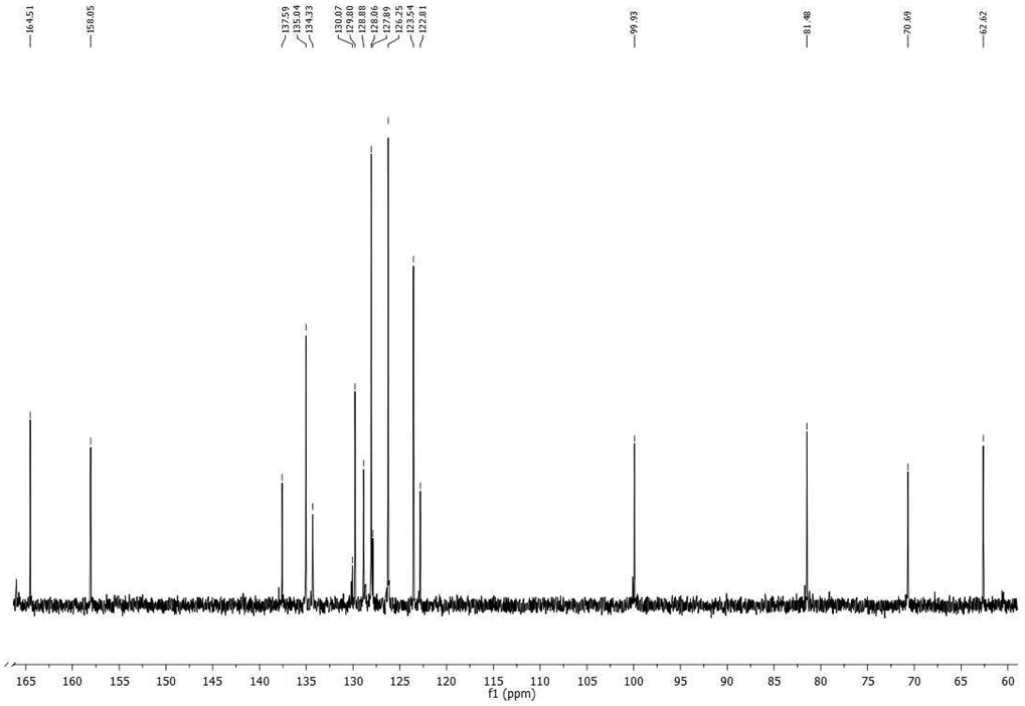




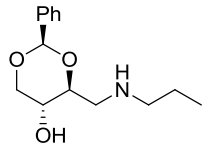
^{1}H and ^{13}C NMR of compound **134f**

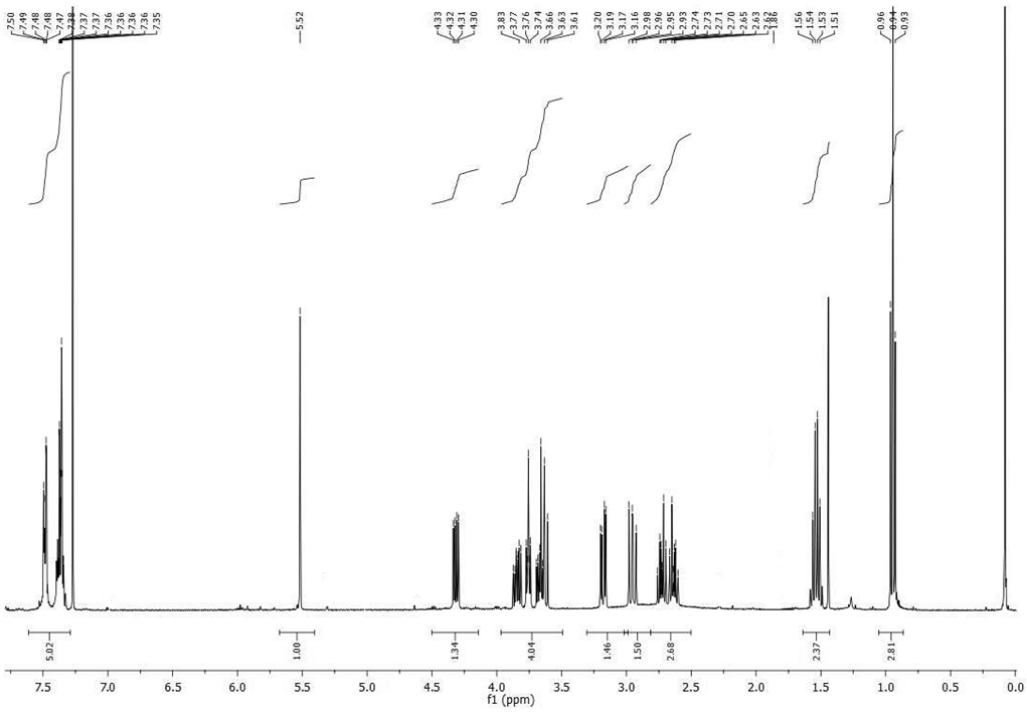


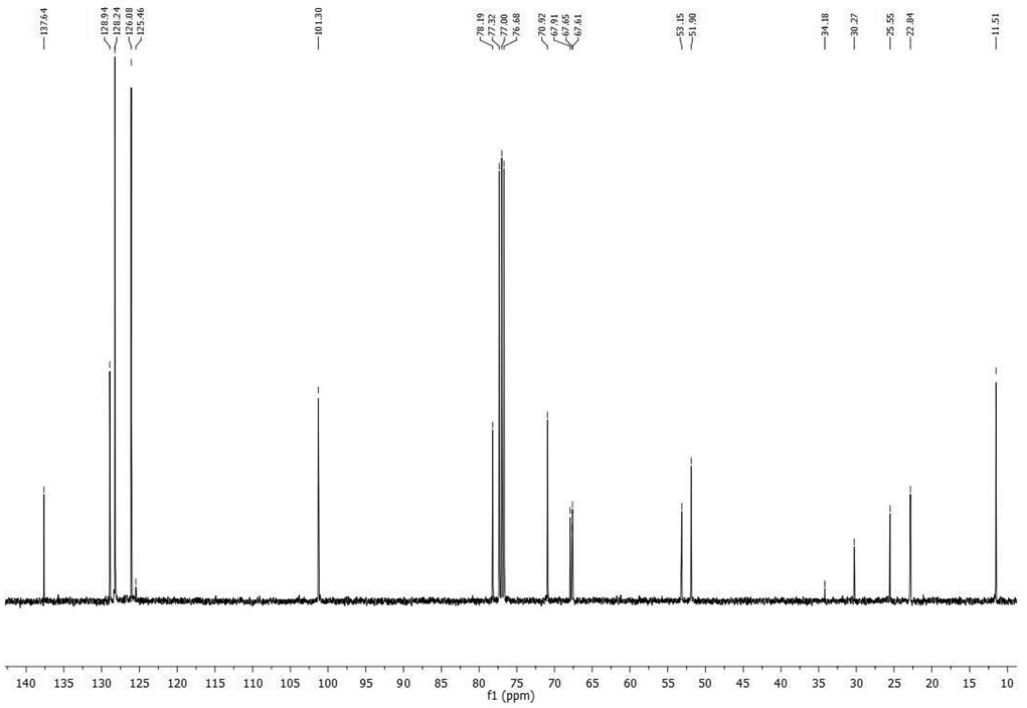




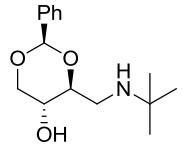
^{1}H and ^{13}C NMR of compound **135a**

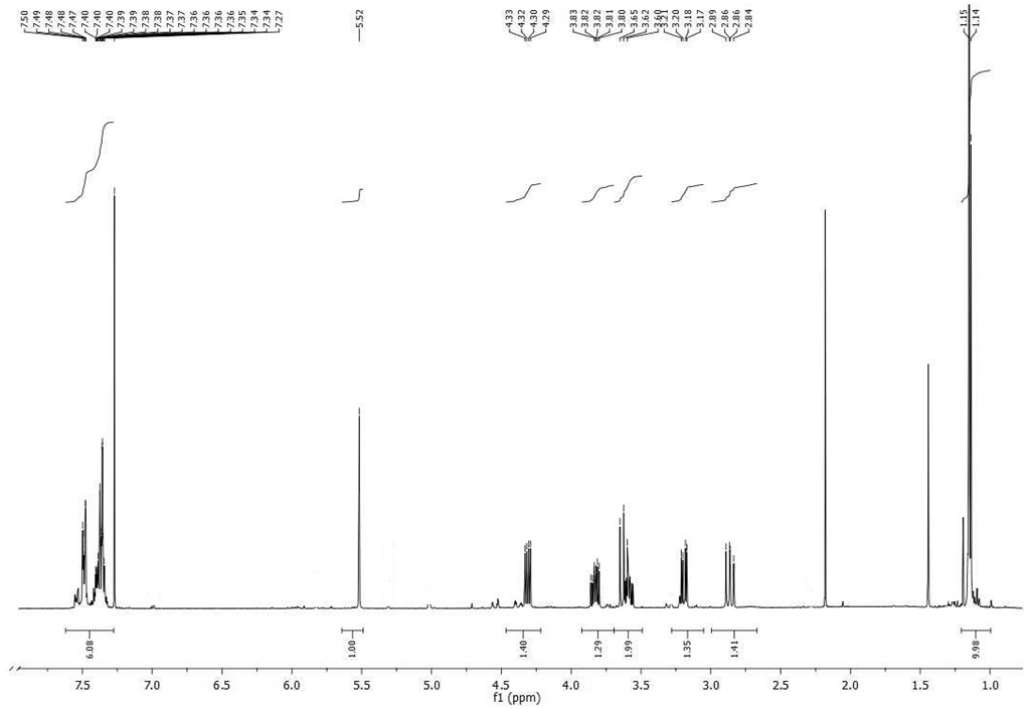


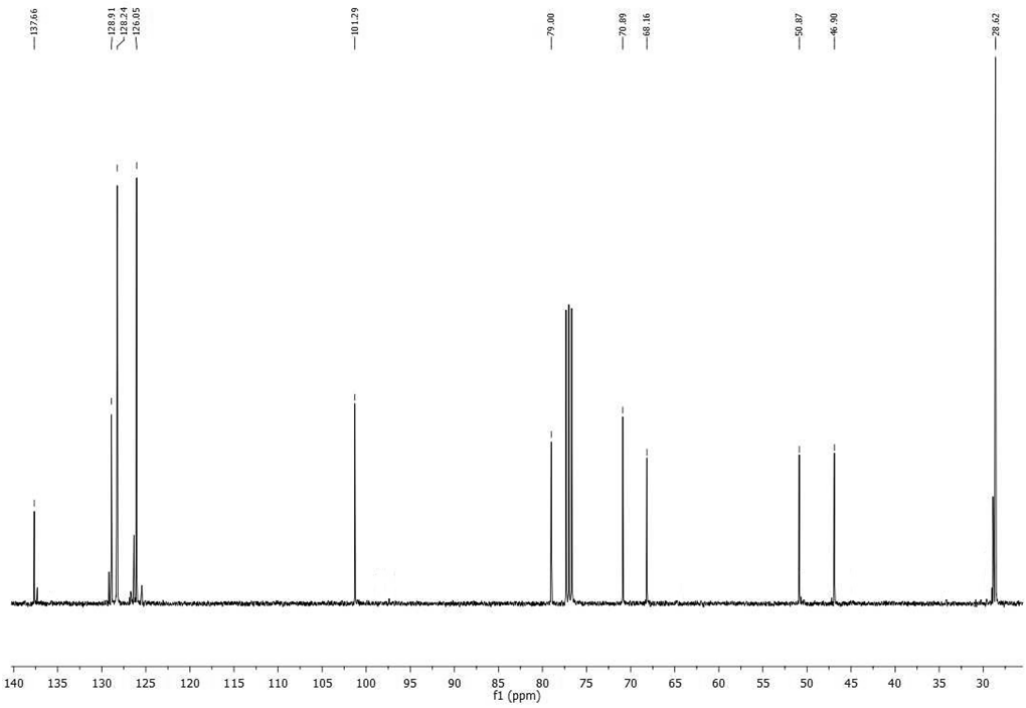




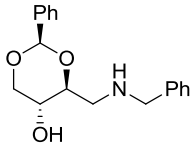
^{1}H and ^{13}C NMR of compound **135b**

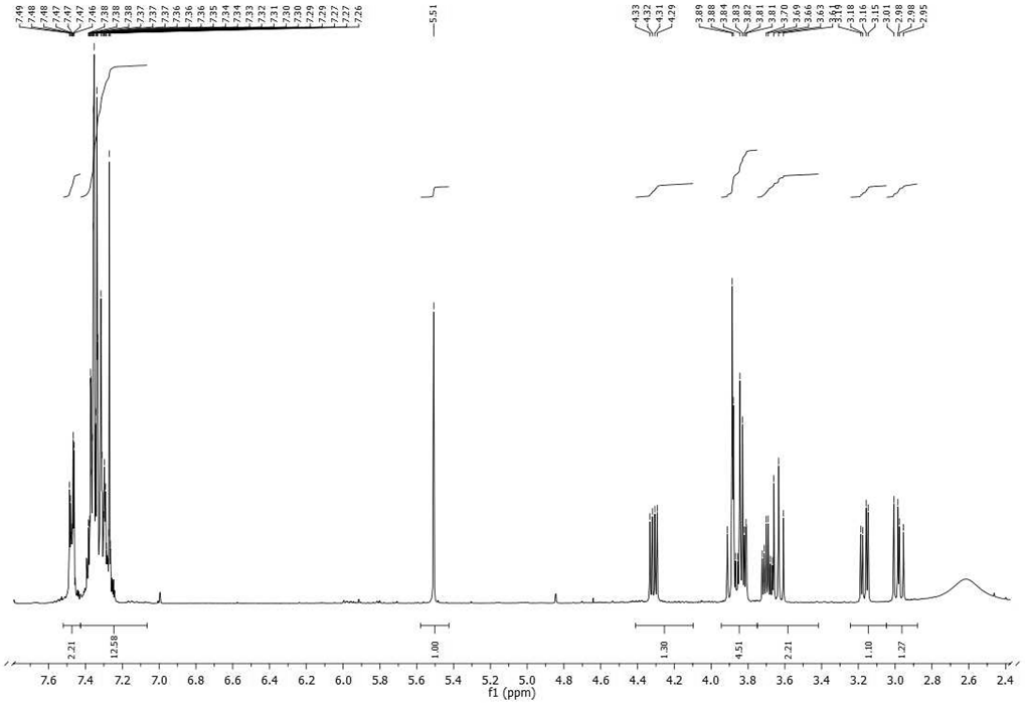


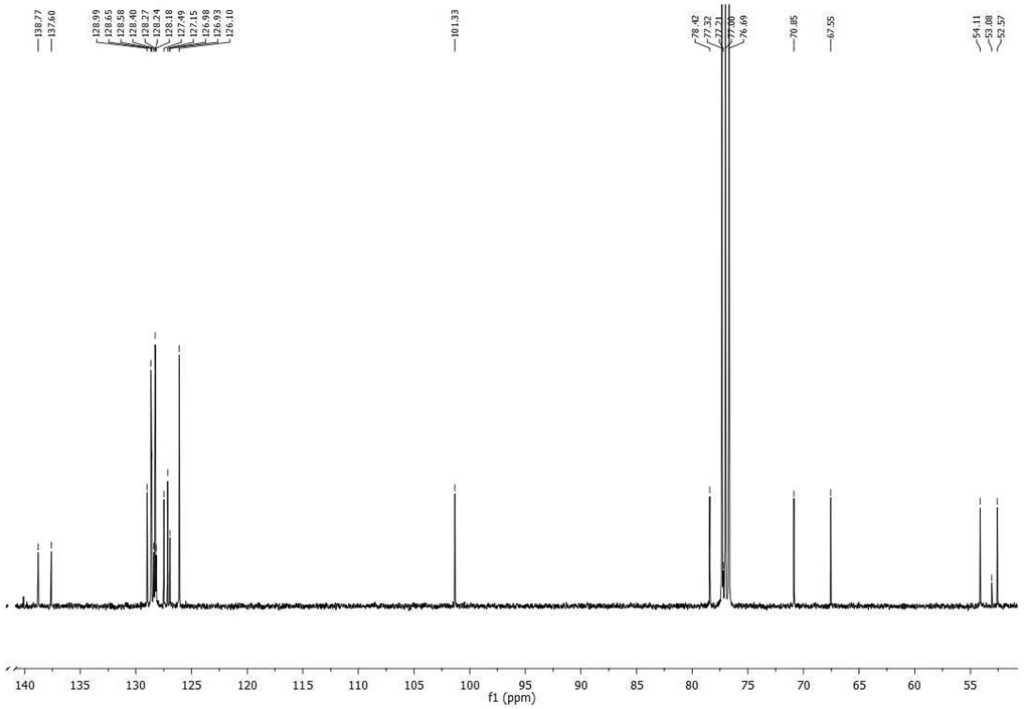




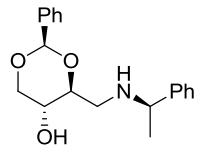
^{1}H and ^{13}C NMR of compound **135c**

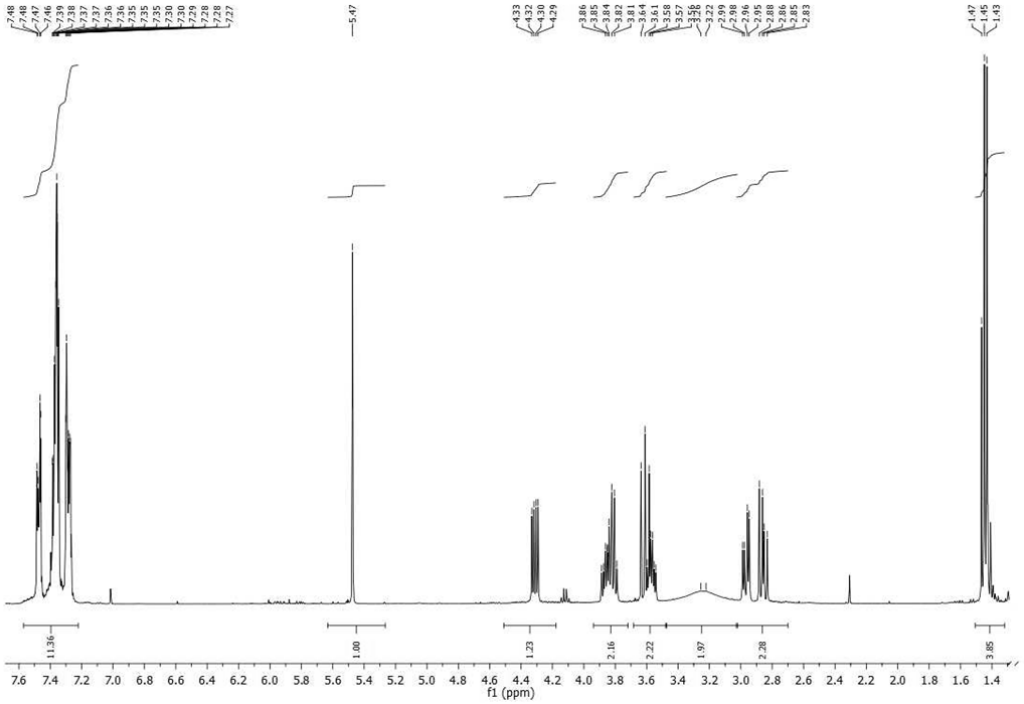


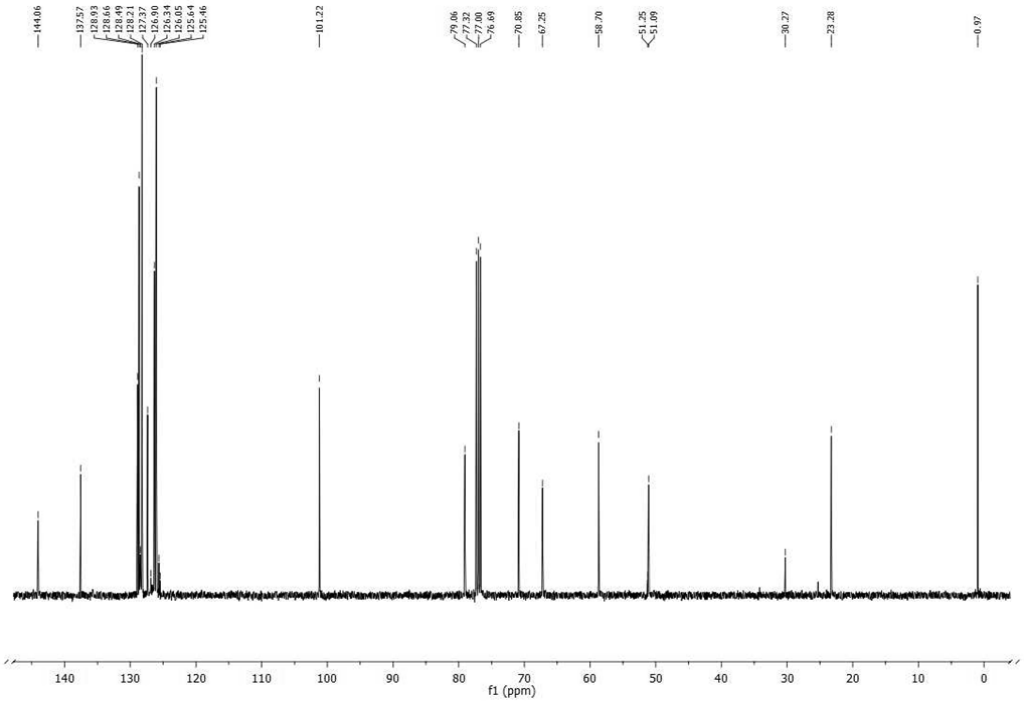




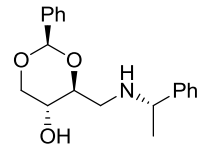
^{1}H and ^{13}C NMR of compound **135d**

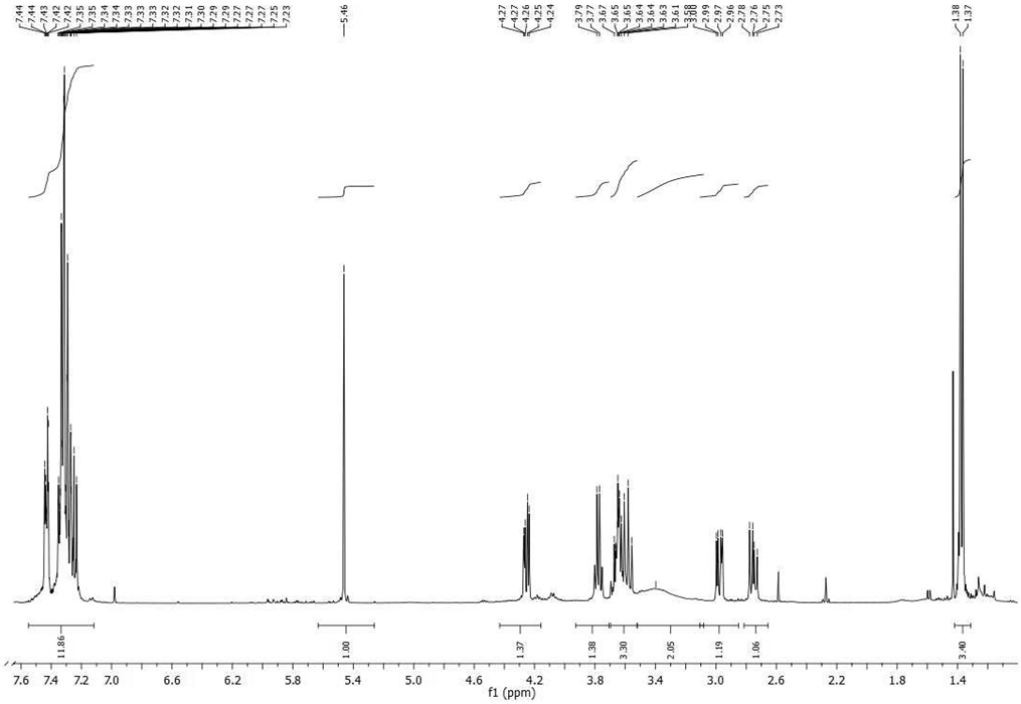


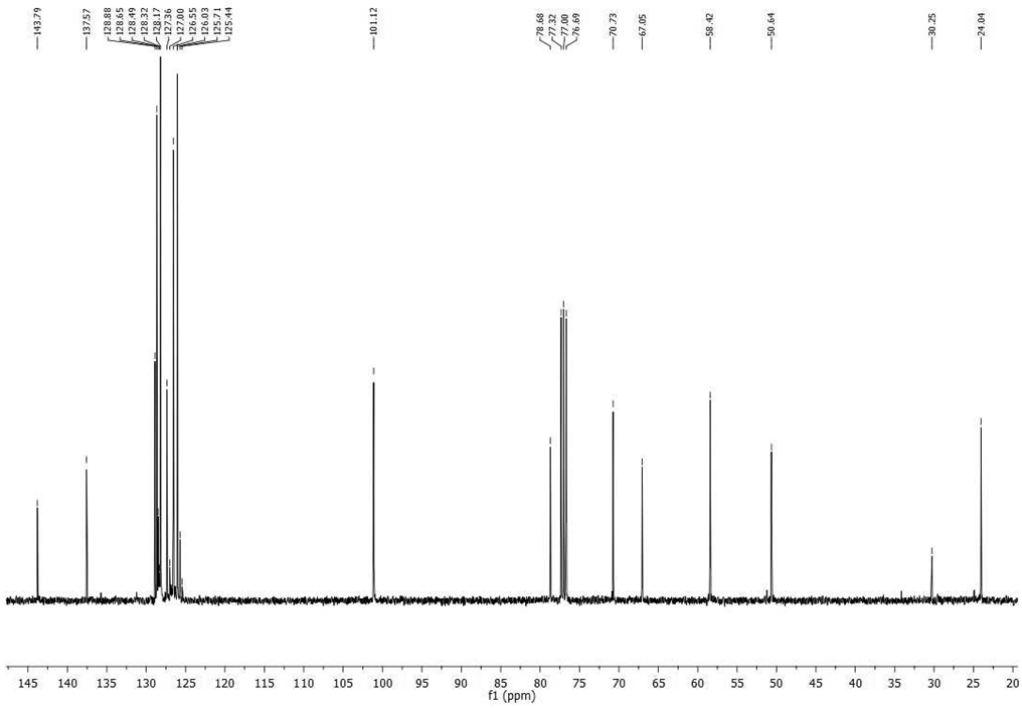




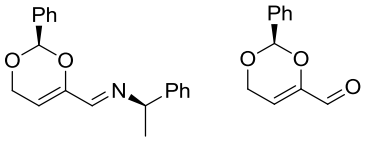
^{1}H and ^{13}C NMR of compound **135e**

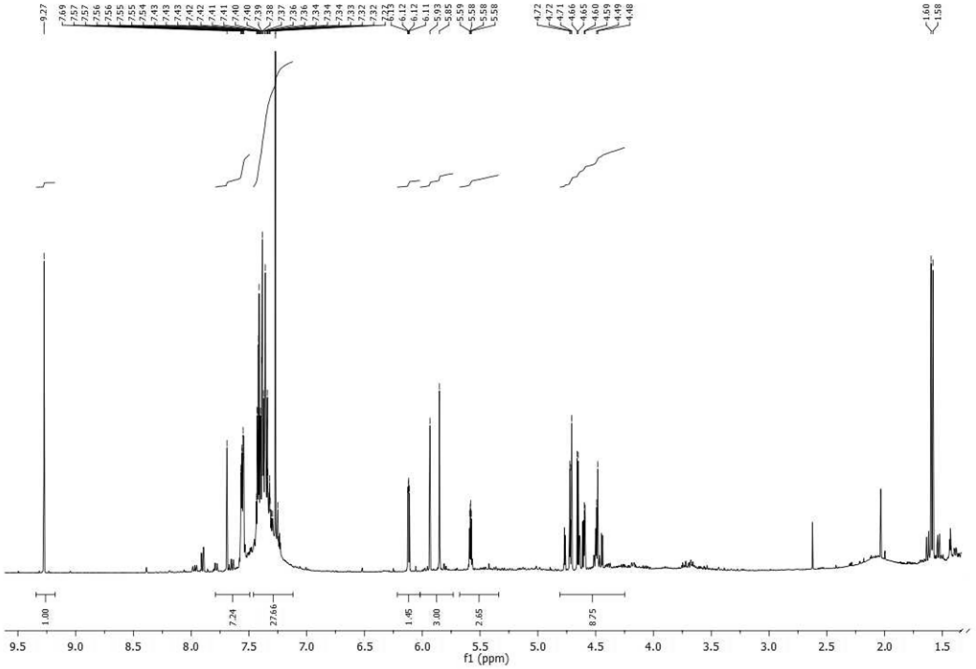


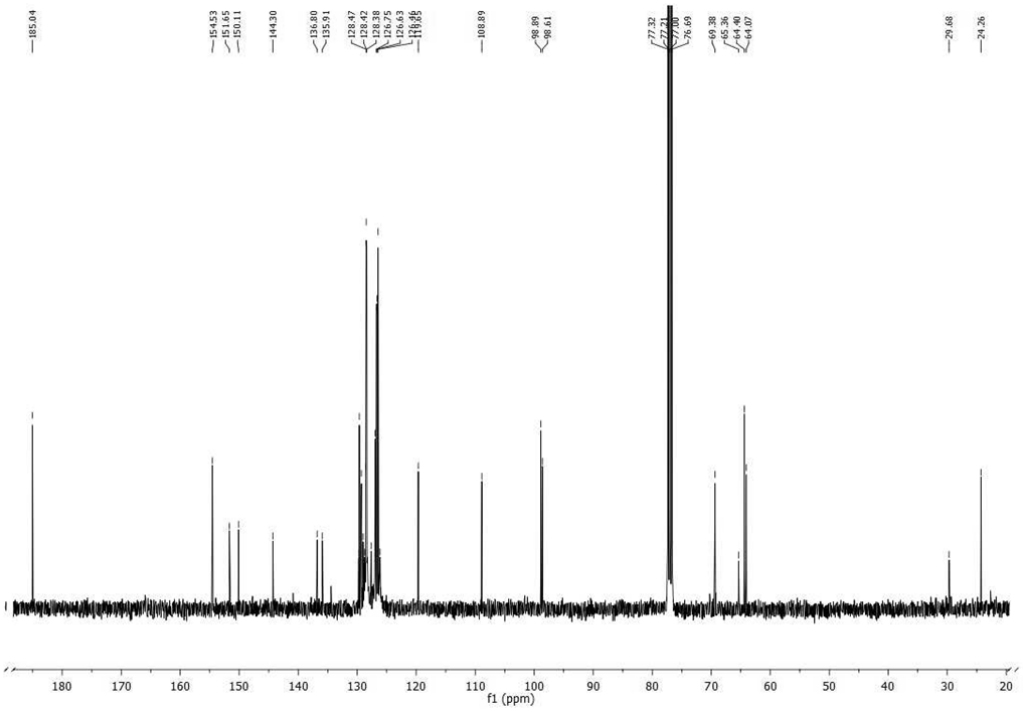




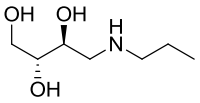
^{1}H and ^{13}C NMR of compounds **139** and **140**

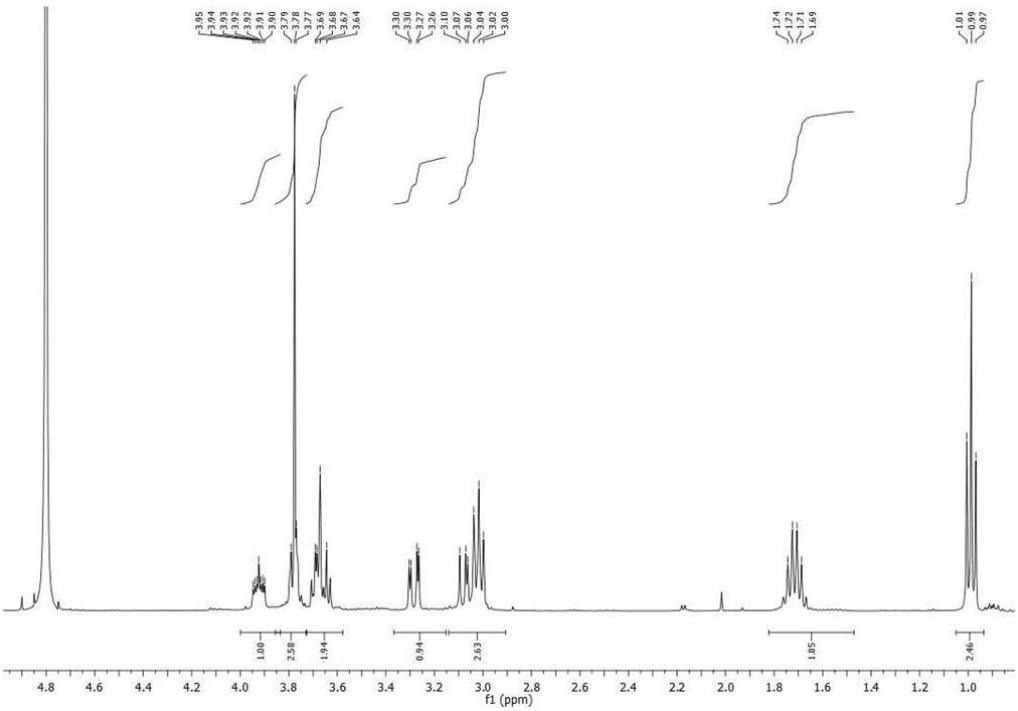


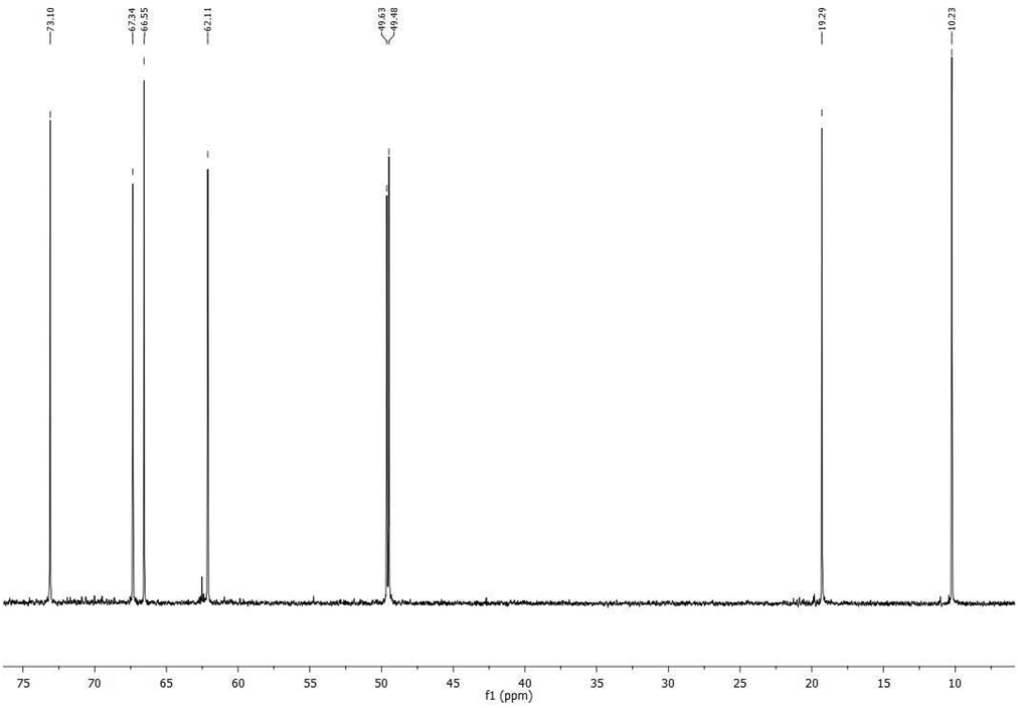




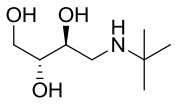
^{1}H and ^{13}C NMR of compound **141a**

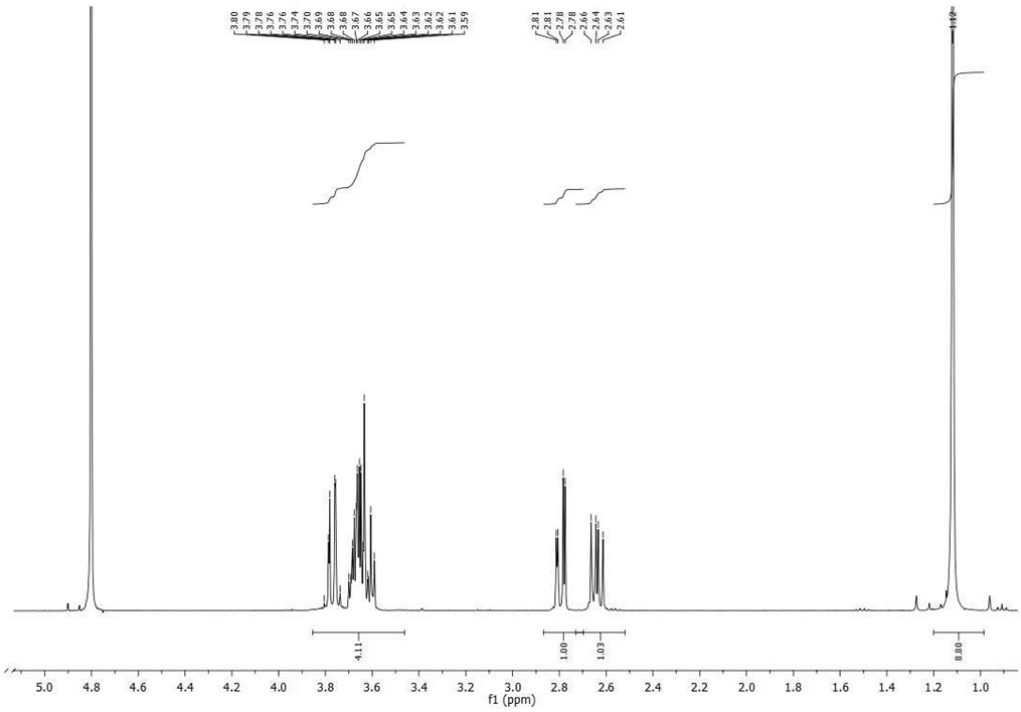


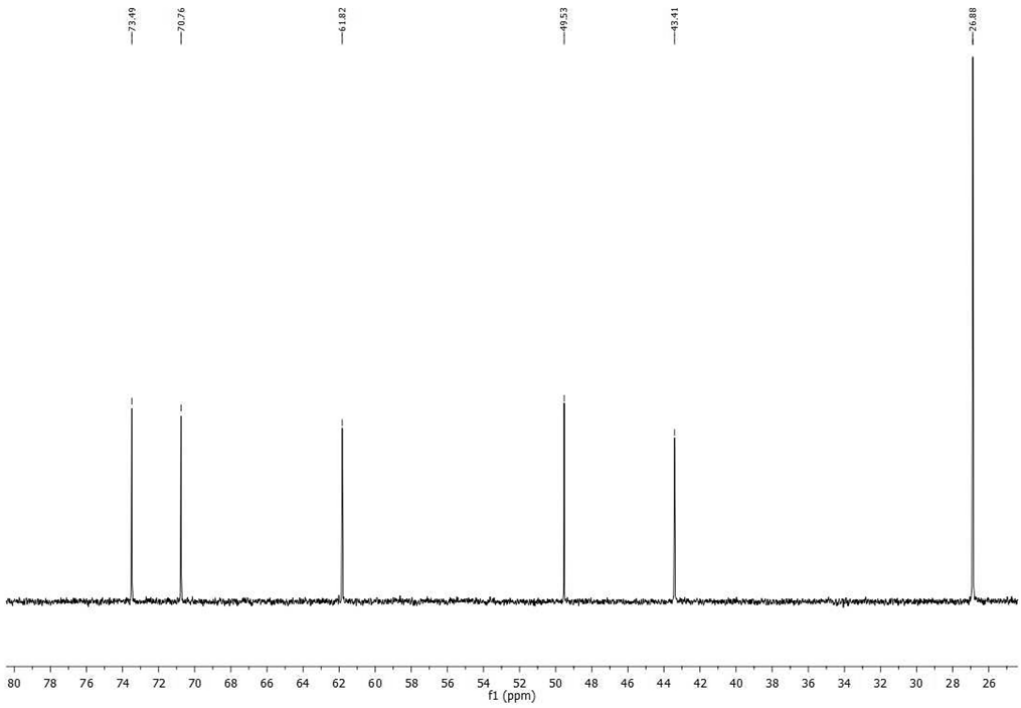




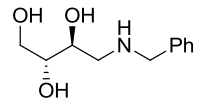
^{1}H and ^{13}C NMR of compound **141b**

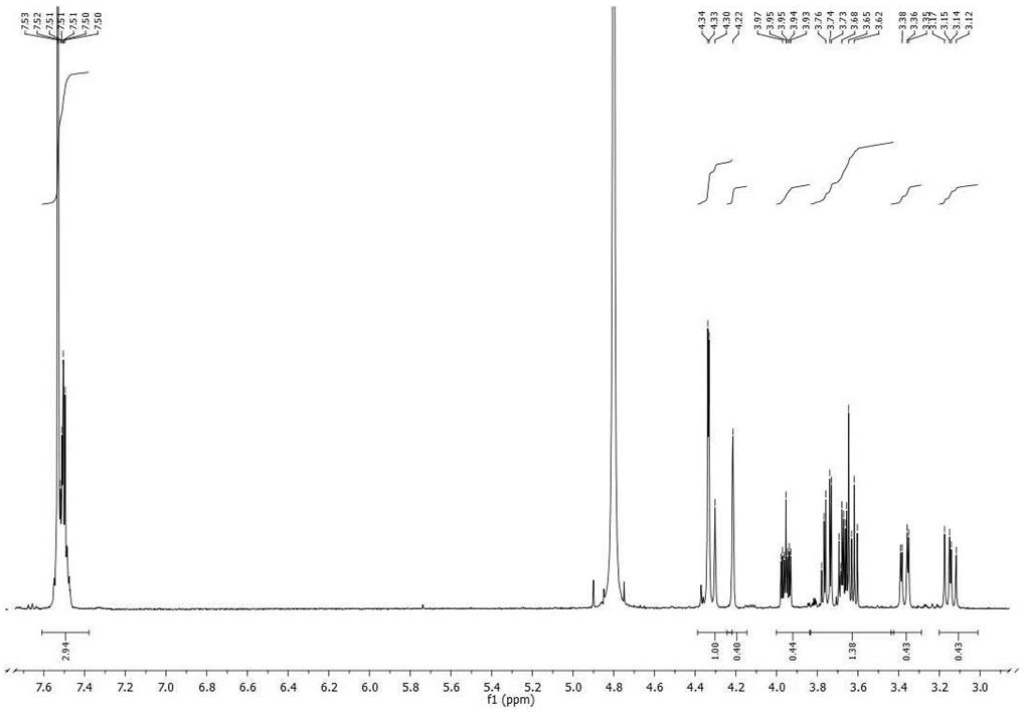


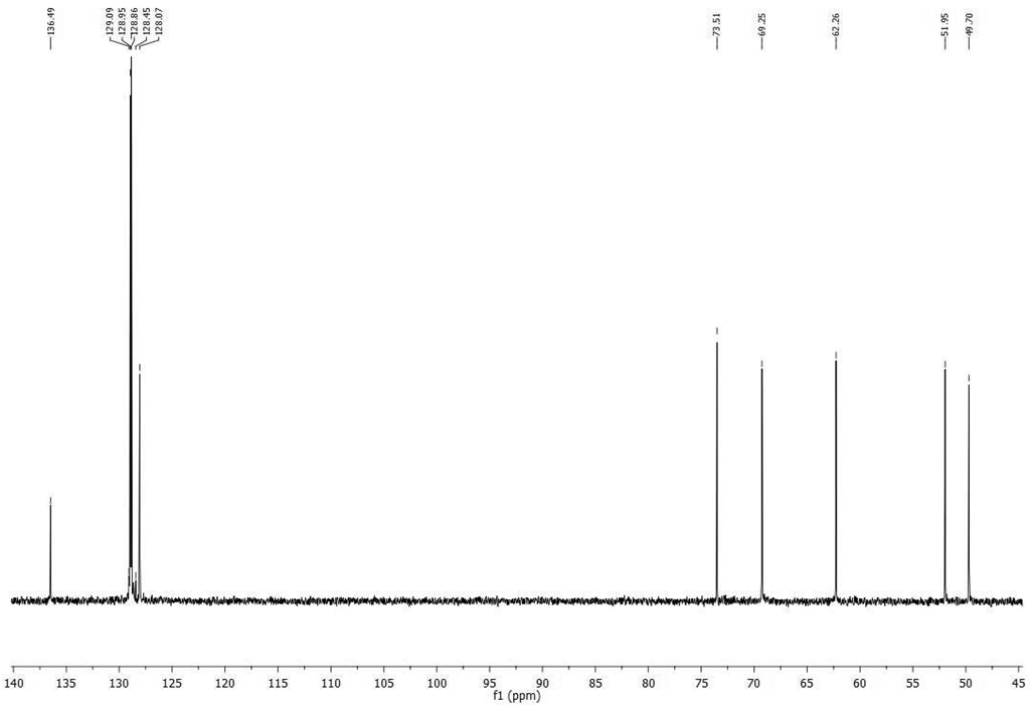




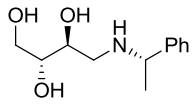
^{1}H and ^{13}C NMR of compound **141c**

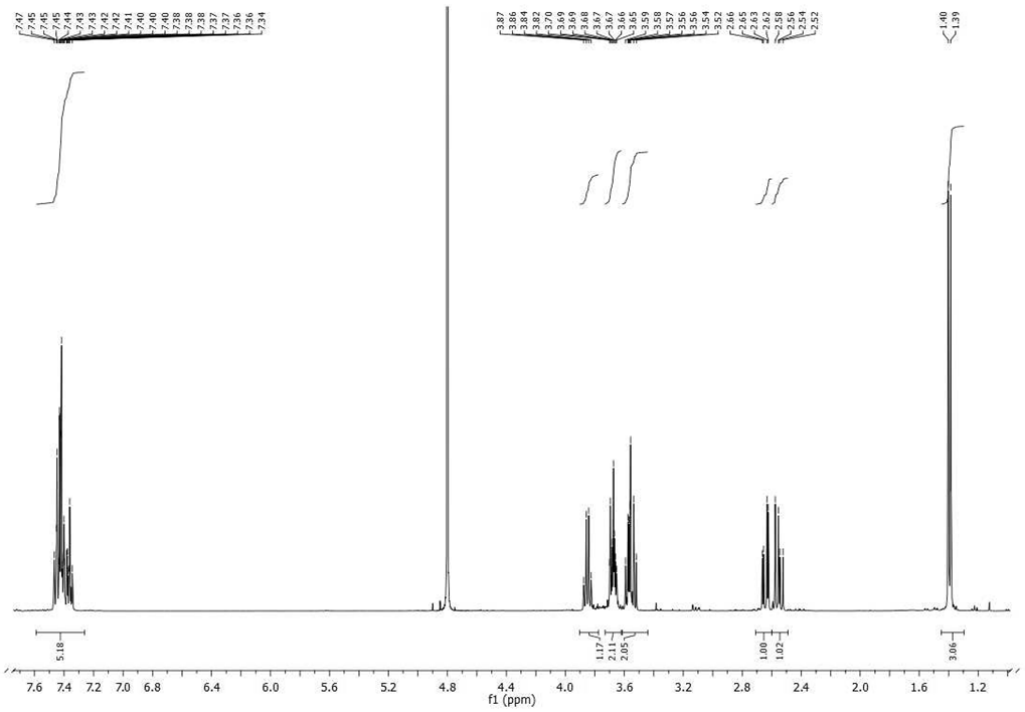


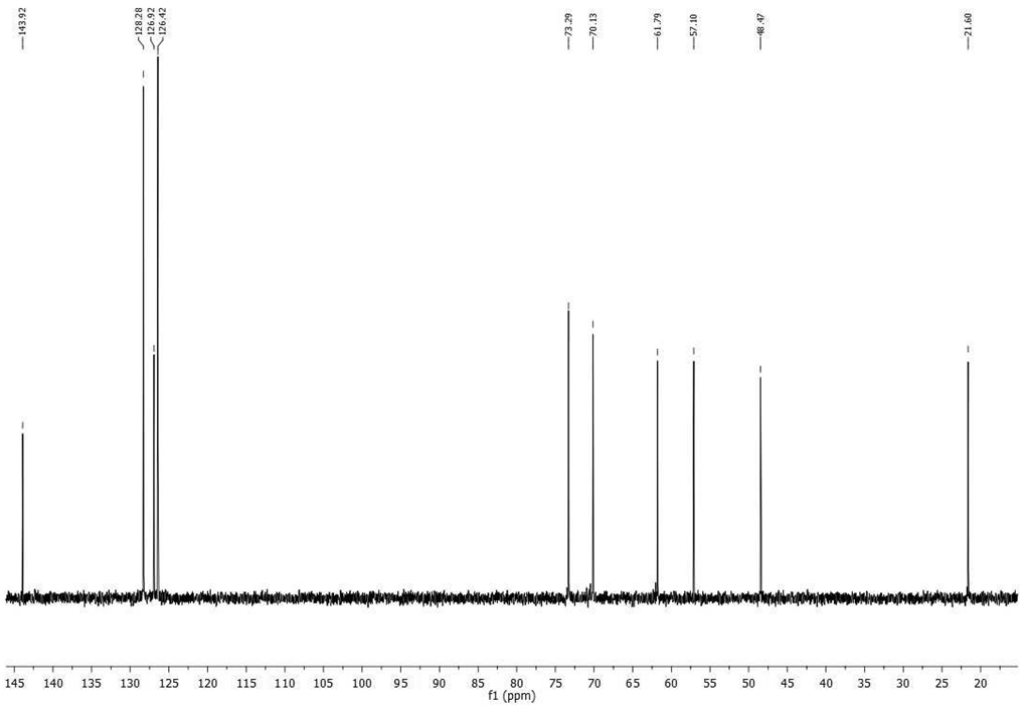




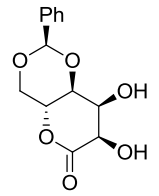
^{1}H and ^{13}C NMR of compounds **141e**

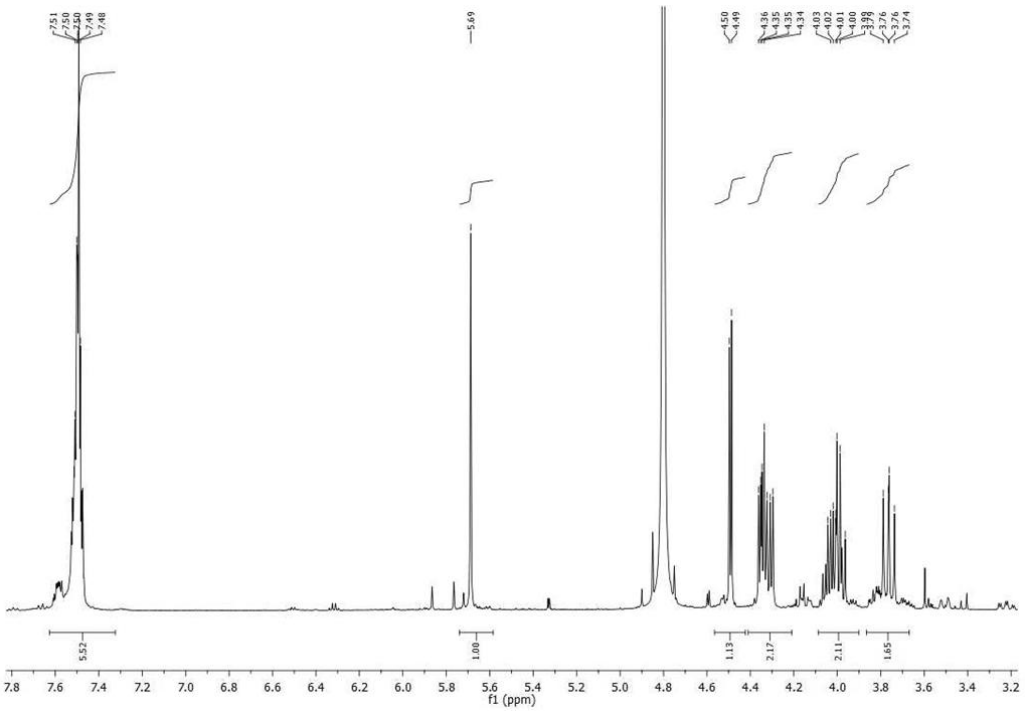


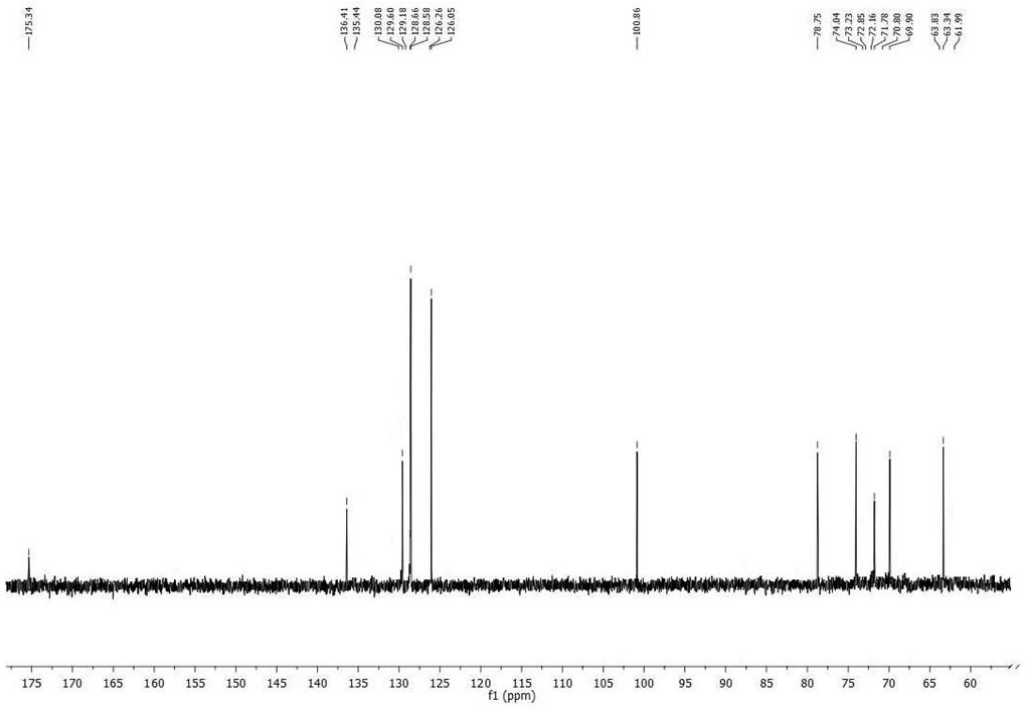




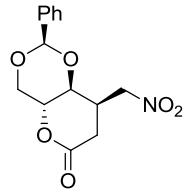
^{1}H and ^{13}C NMR of compound **142**

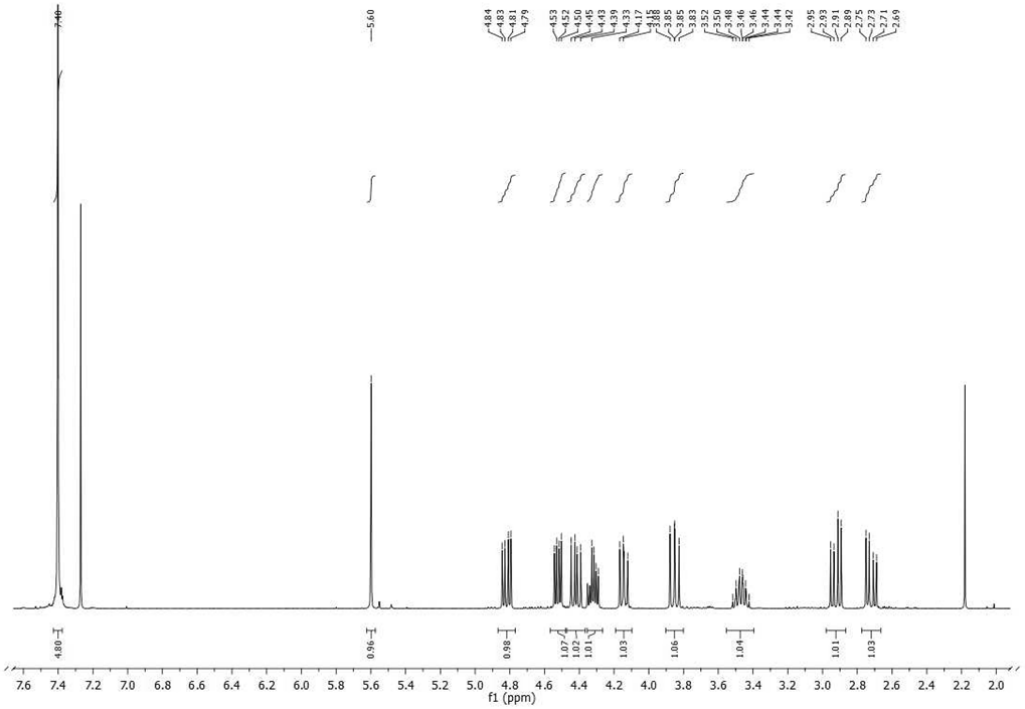


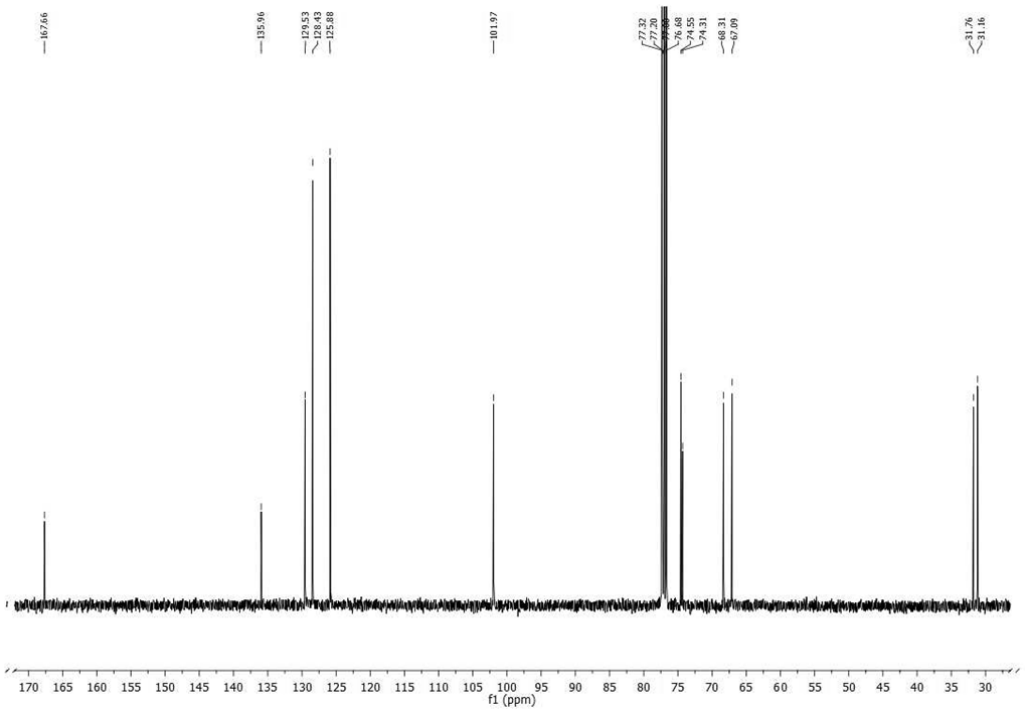




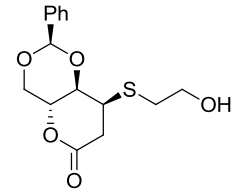
^{1}H and ^{13}C NMR of compound **150a**

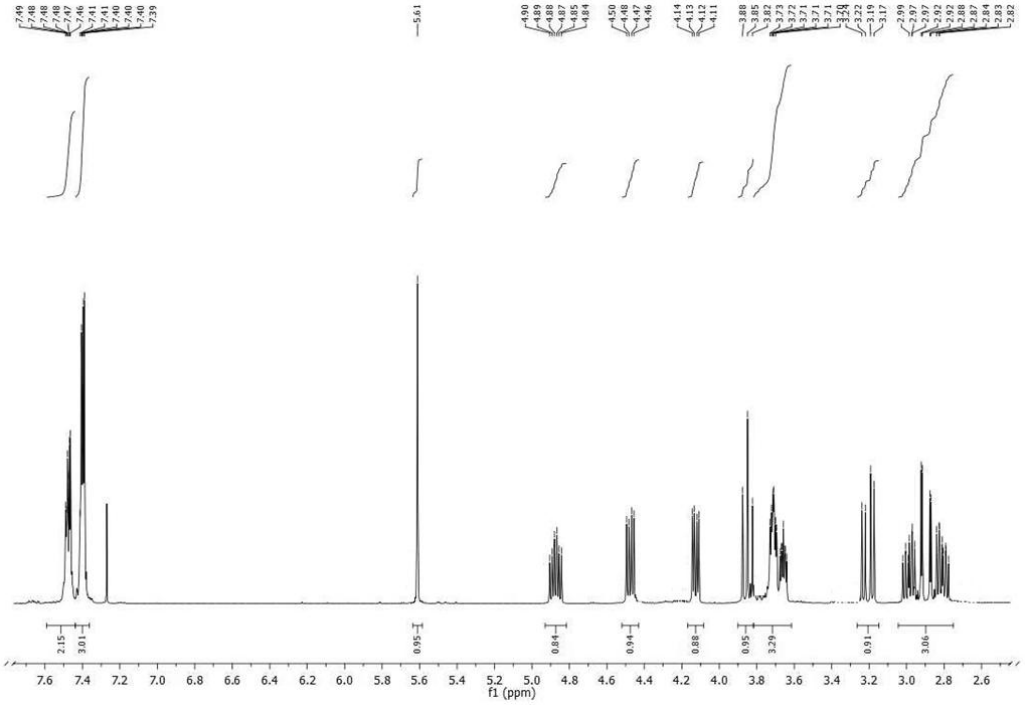


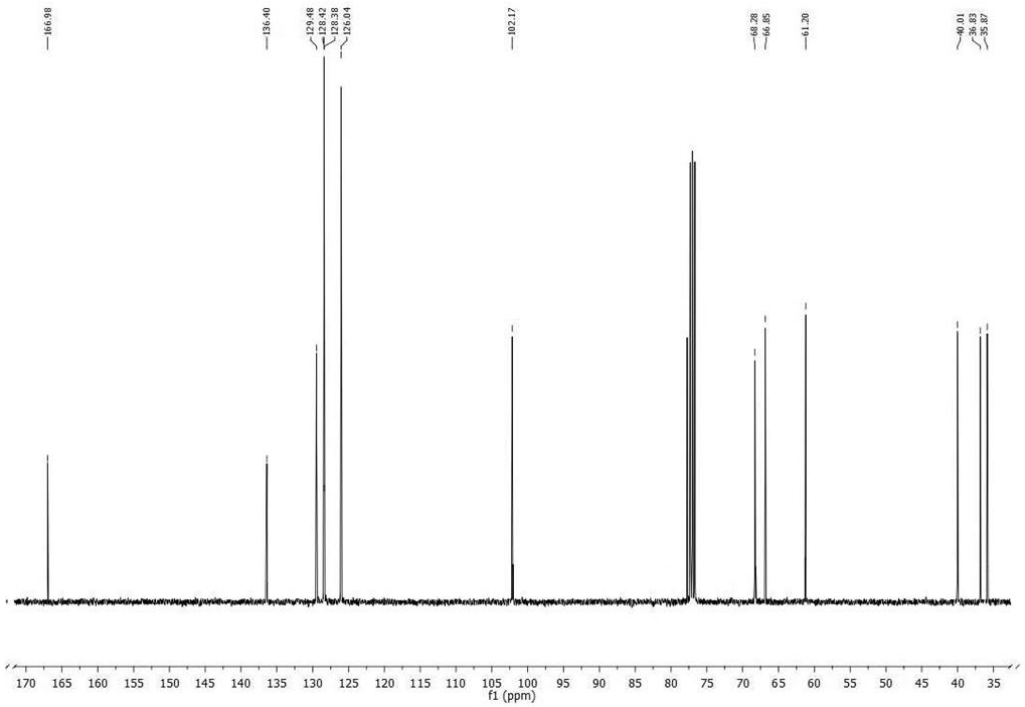




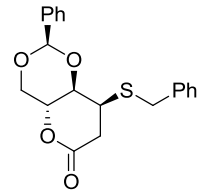
^{1}H and ^{13}C NMR of compound **150b**

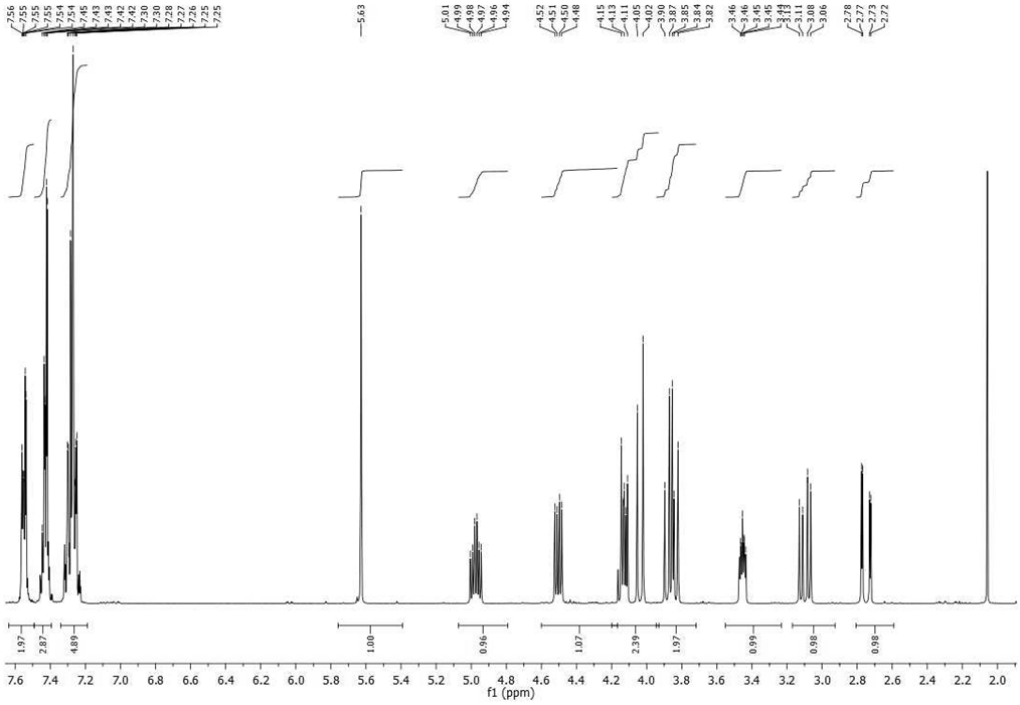


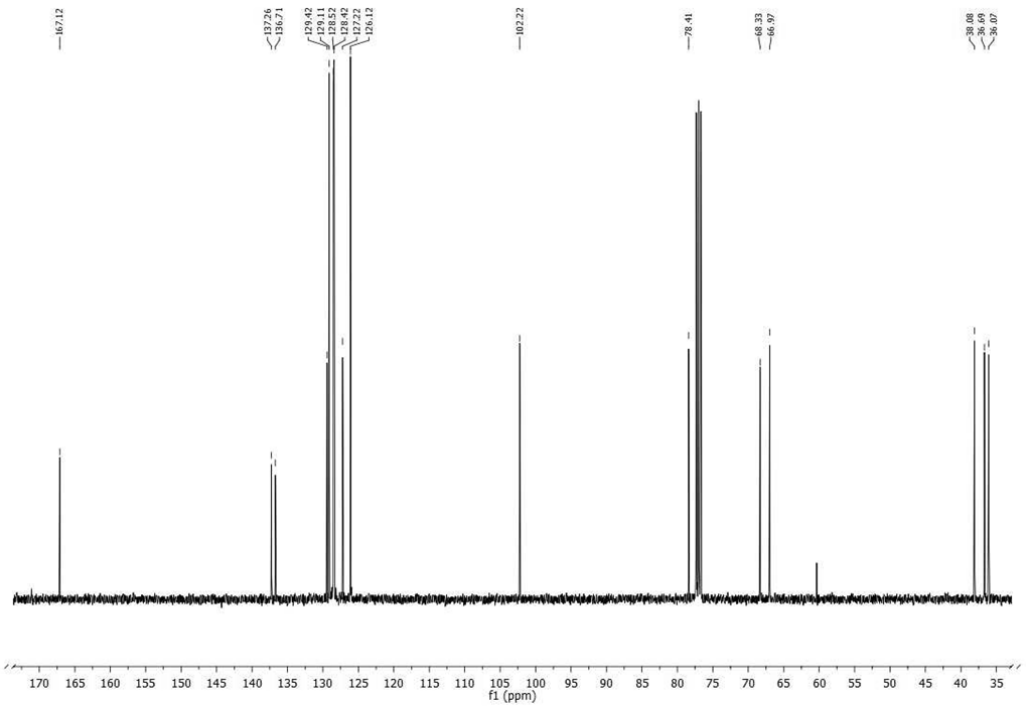




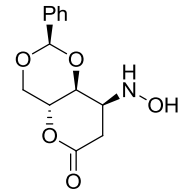
^{1}H and ^{13}C NMR of compound **150c**

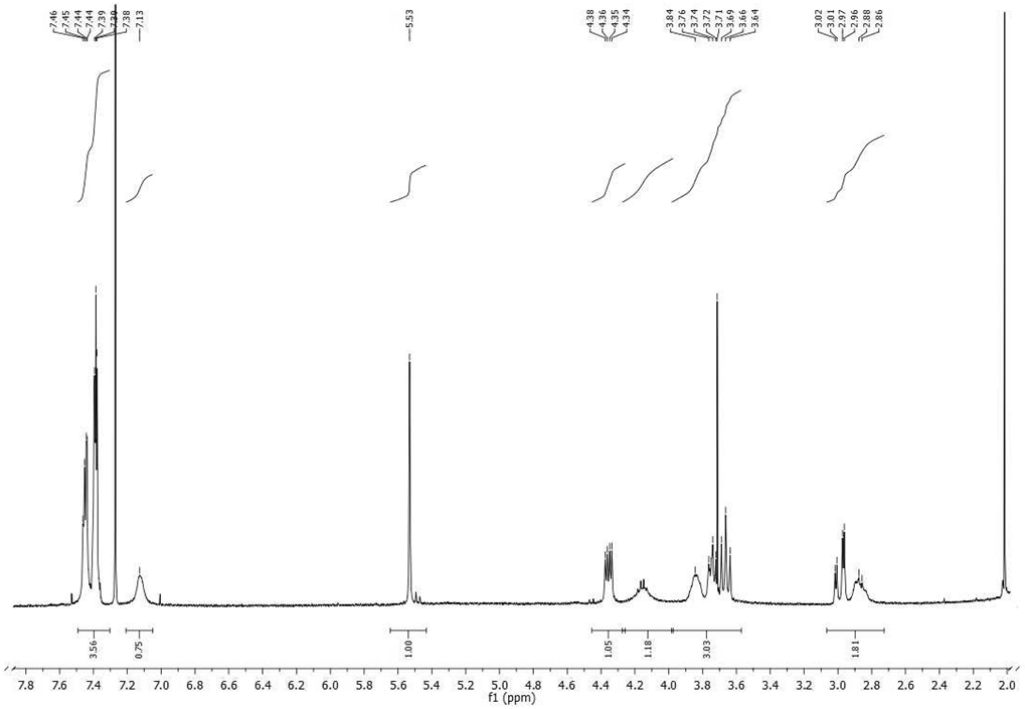


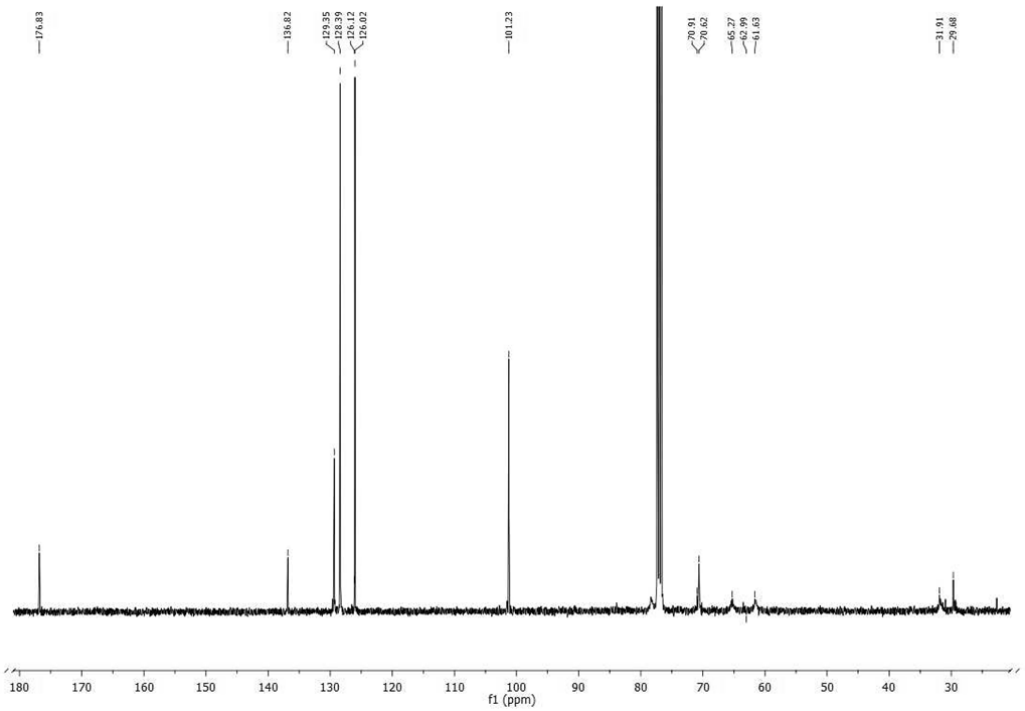




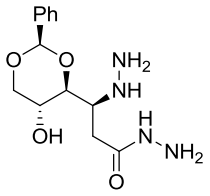
^{1}H and ^{13}C NMR of compound **150c**

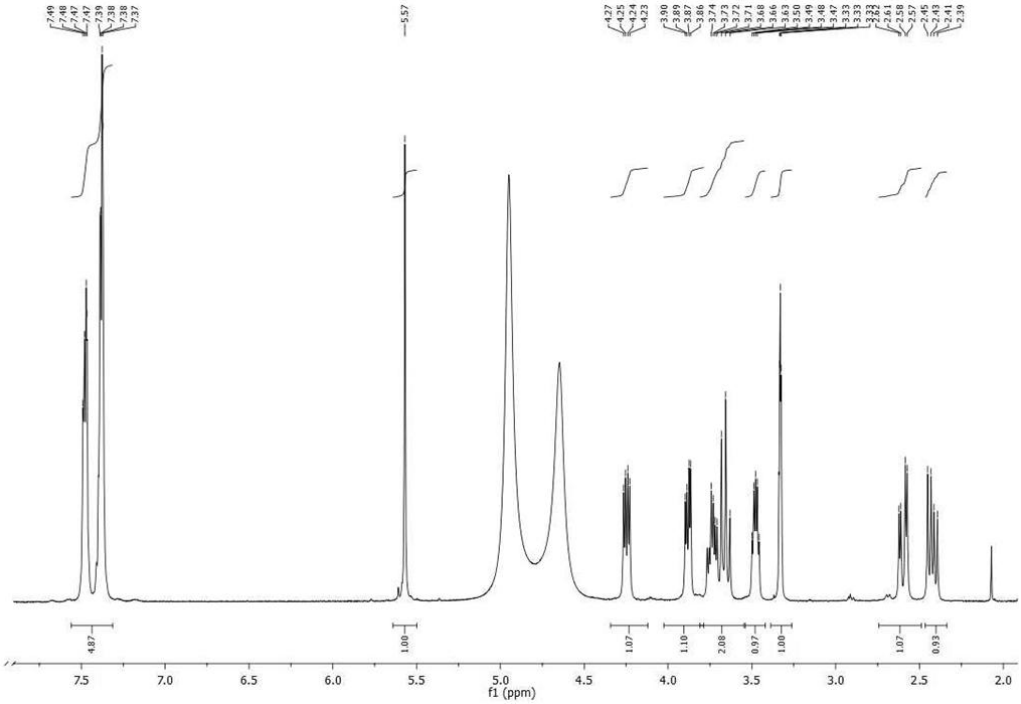


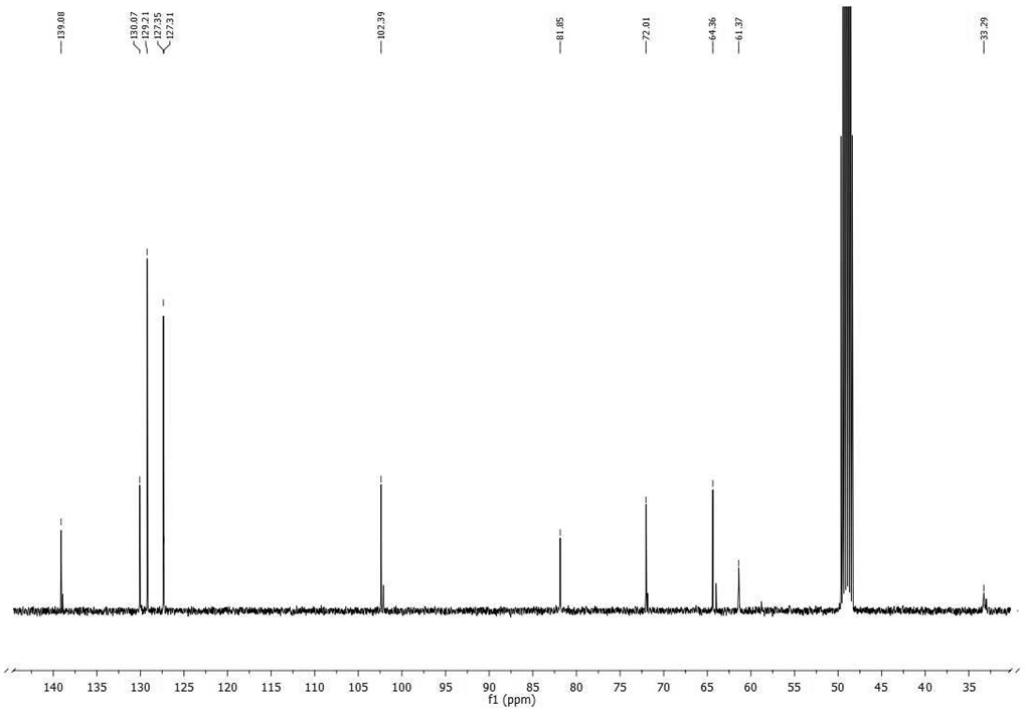




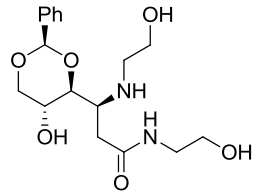
^{1}H and ^{13}C NMR of compound **151a**

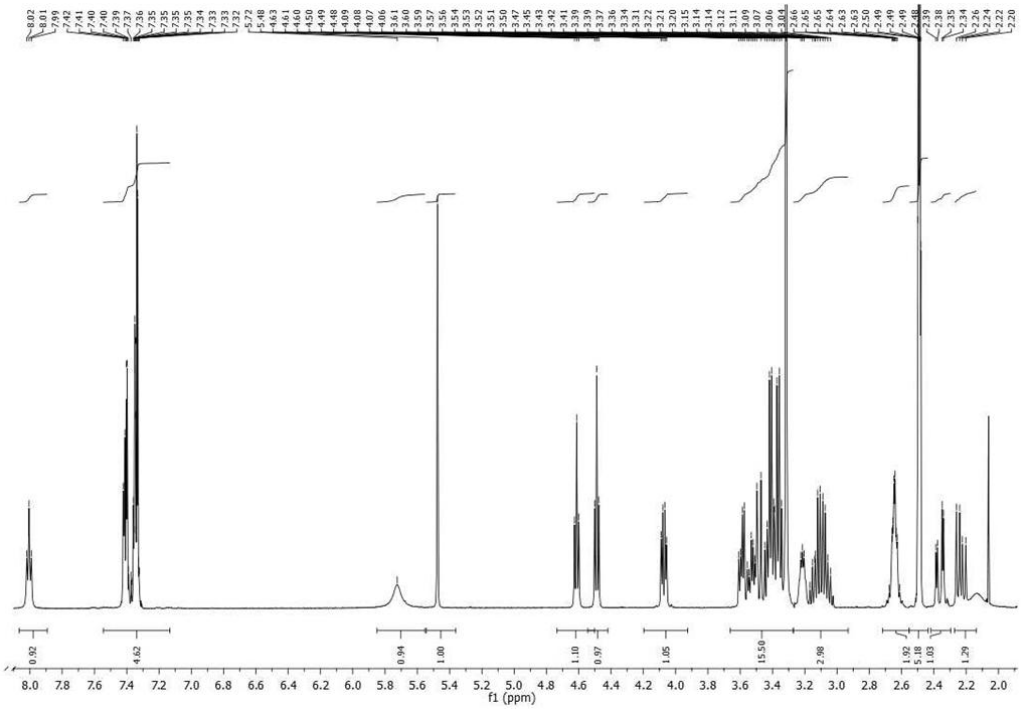


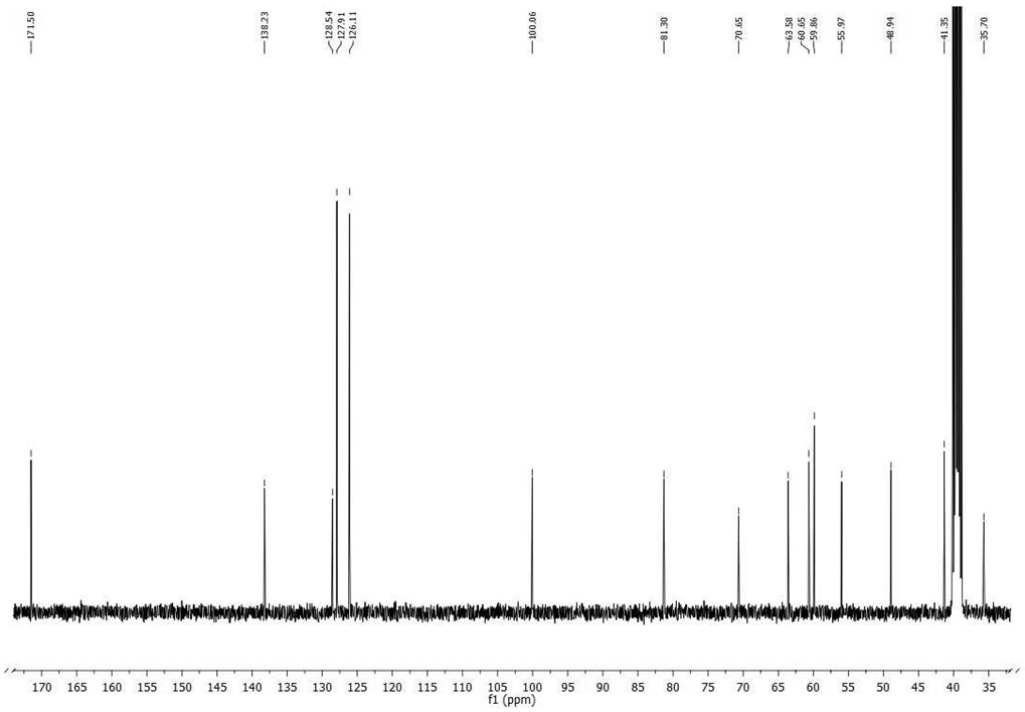




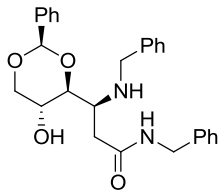
^{1}H and ^{13}C NMR of compound **151b**

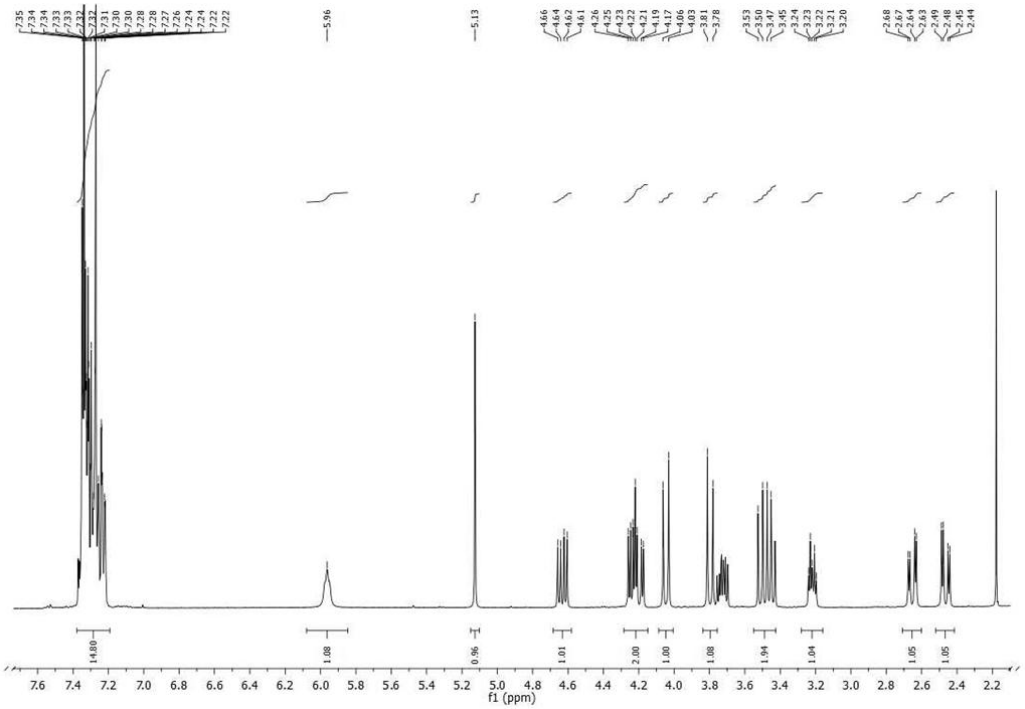


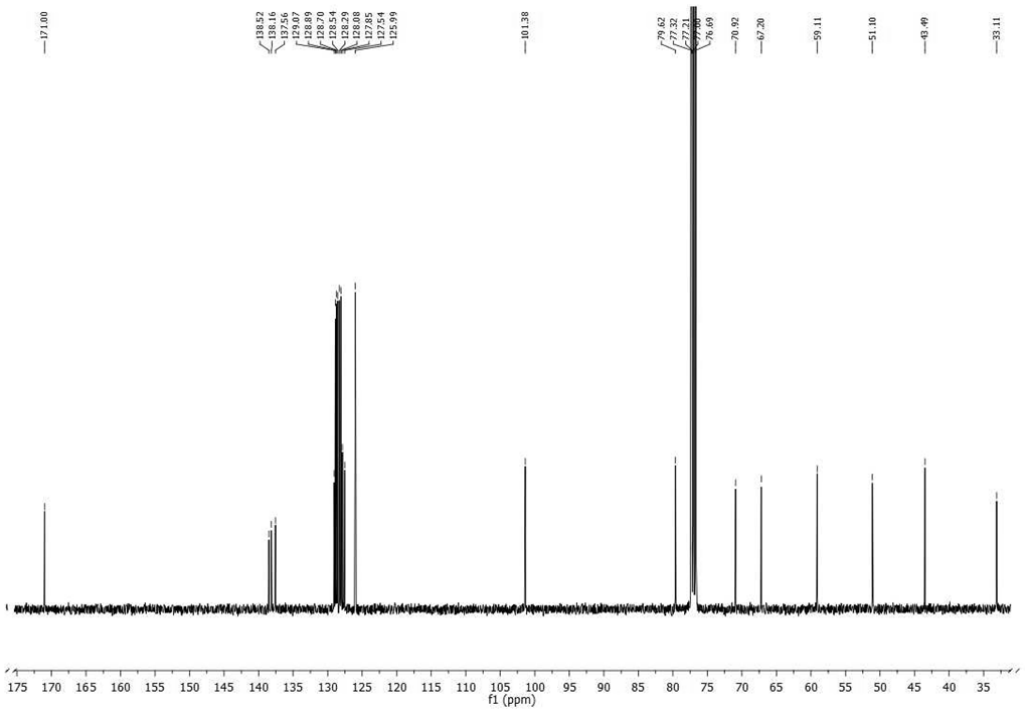




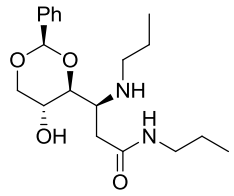
^{1}H and ^{13}C NMR of compound **151c**

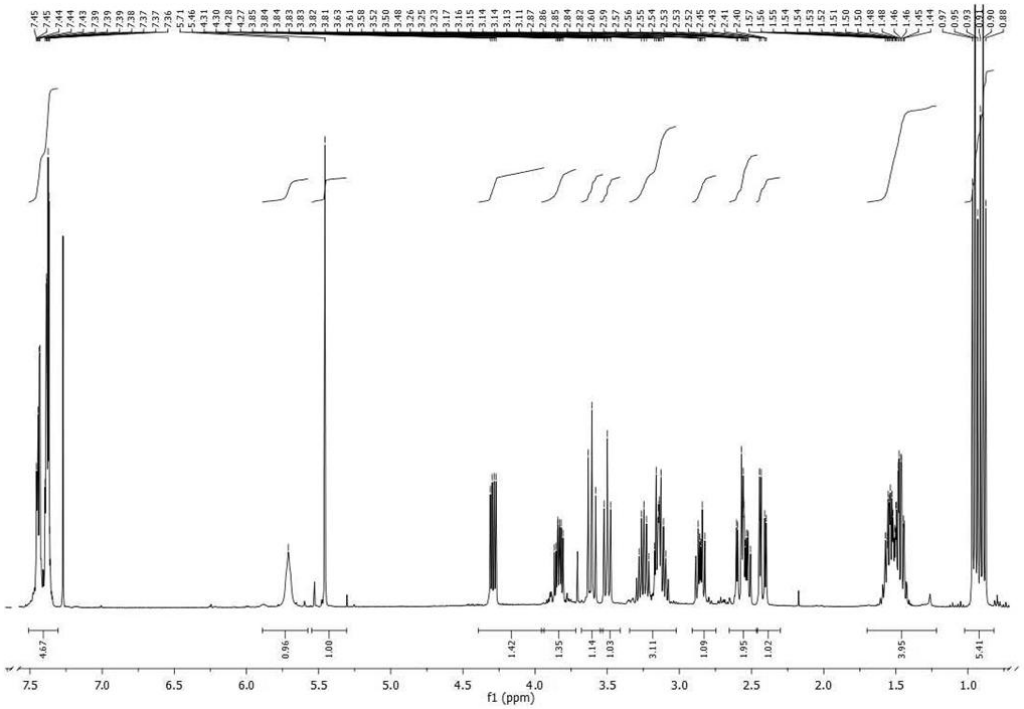


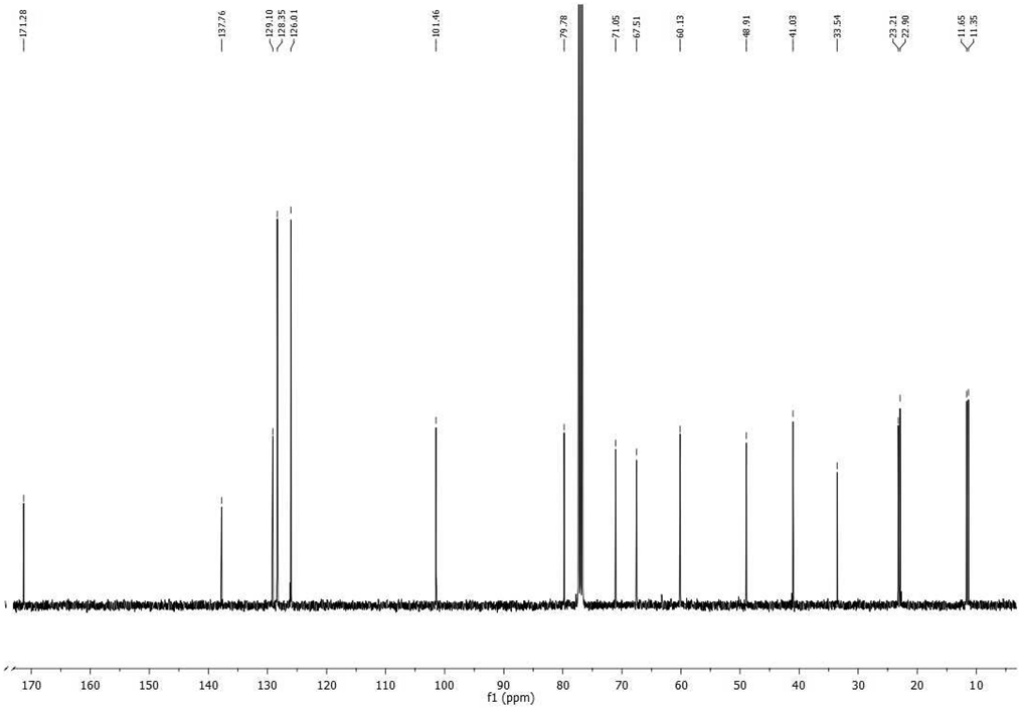




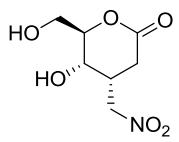
^{1}H and ^{13}C NMR of compound **151d**

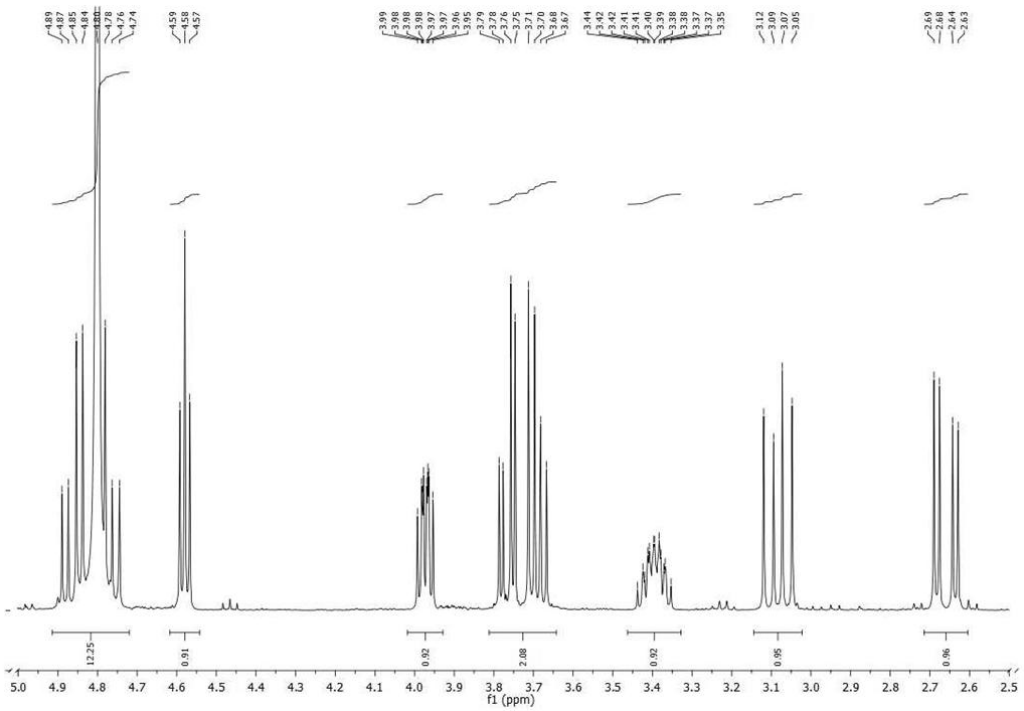


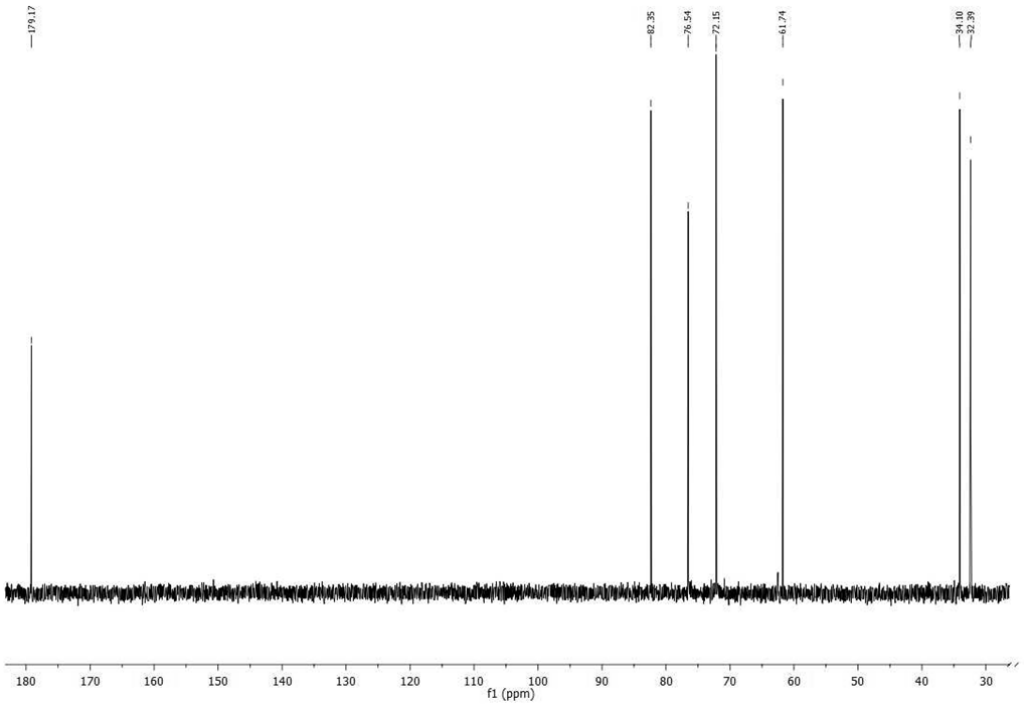




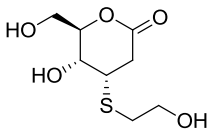
^{1}H and ^{13}C NMR of compound **153a**

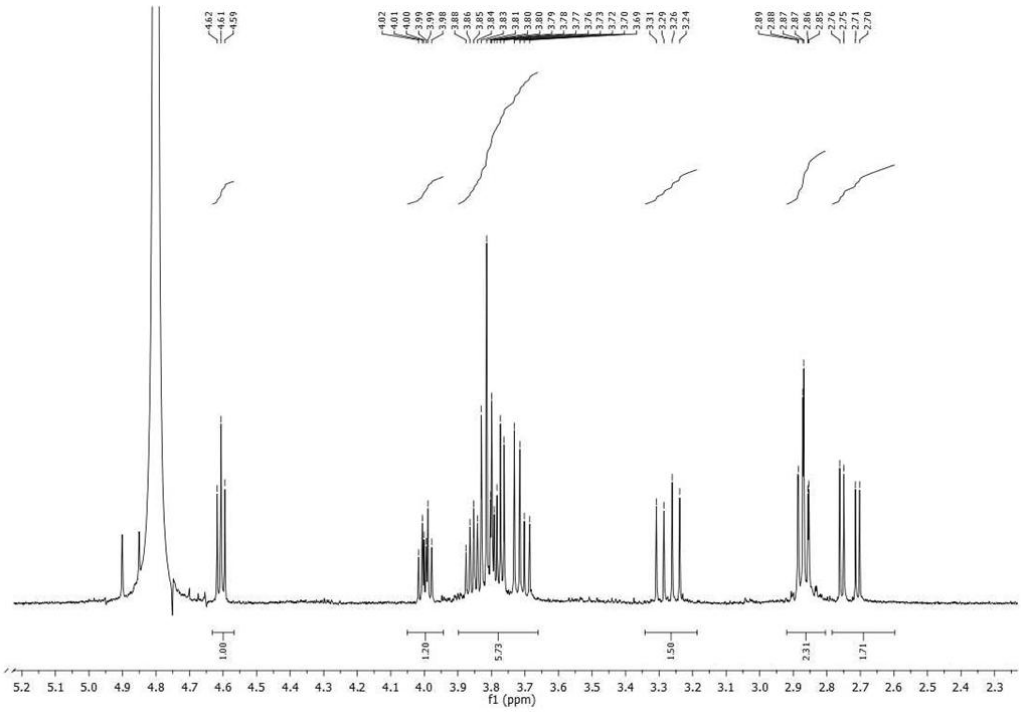


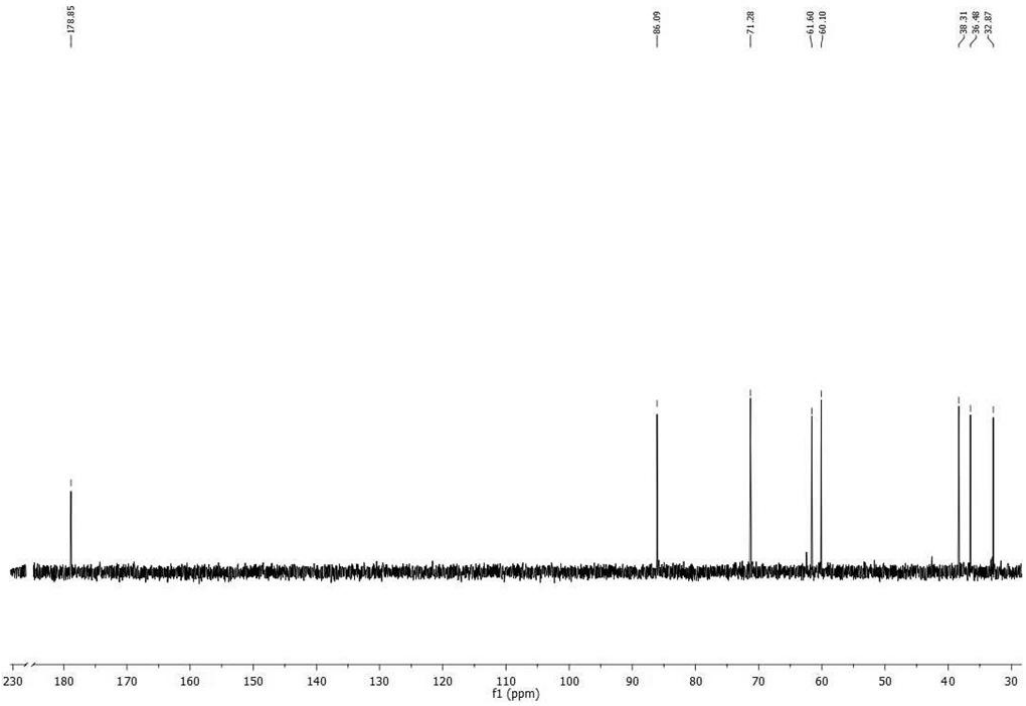




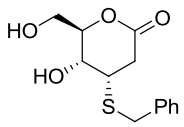
^{1}H and ^{13}C NMR of compound **153b**

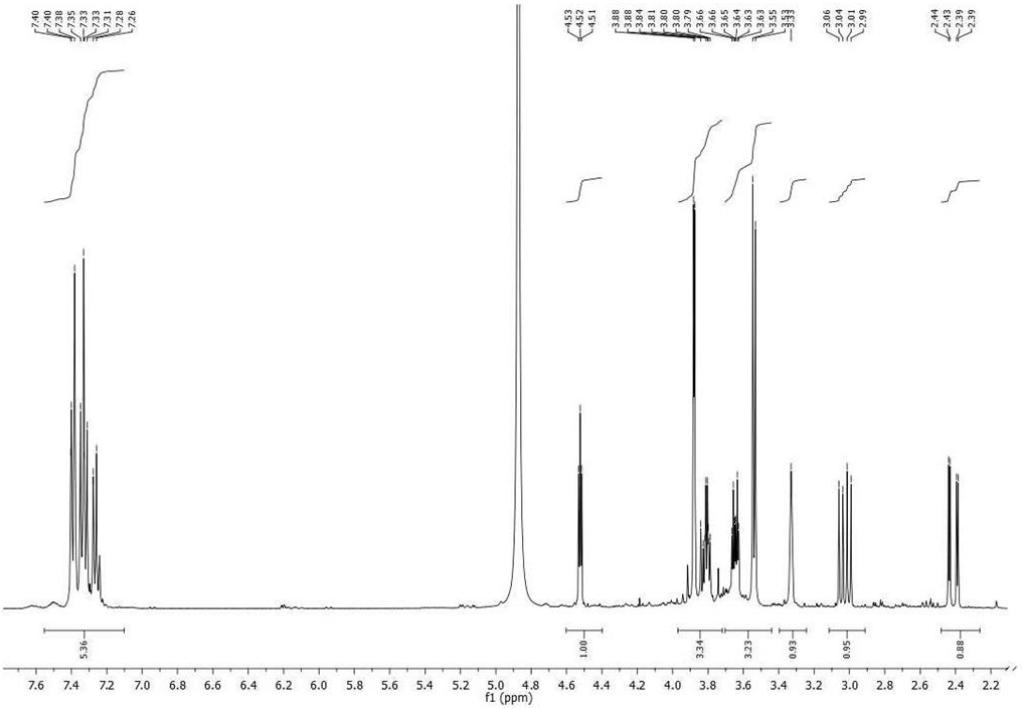


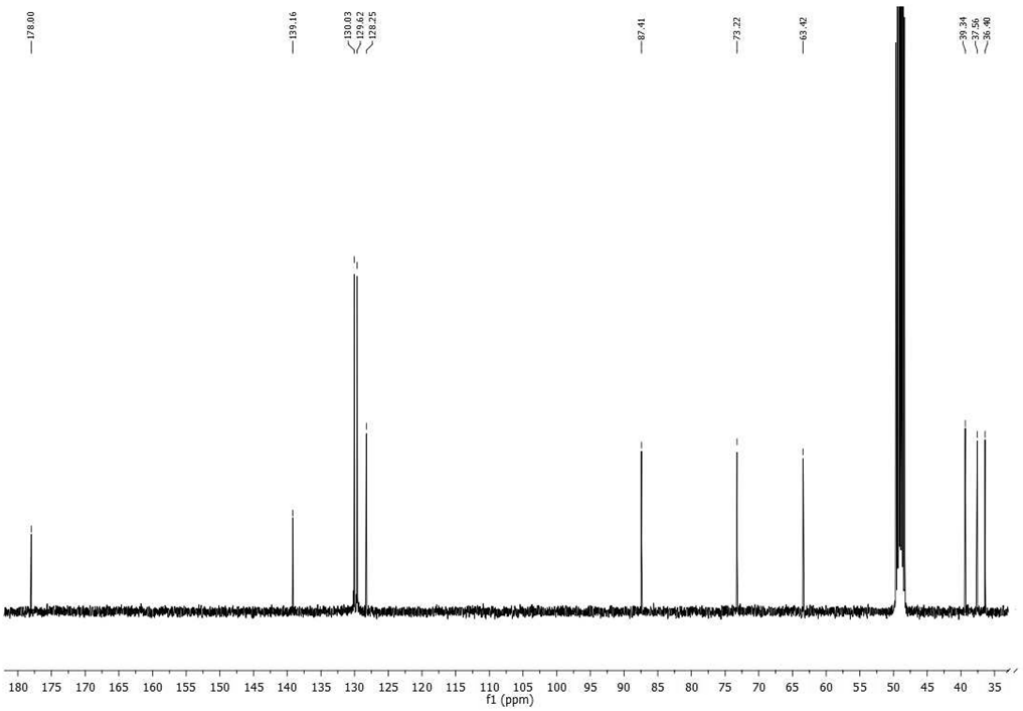




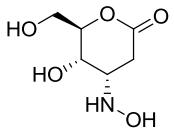
^{1}H and ^{13}C NMR of compound **153c**

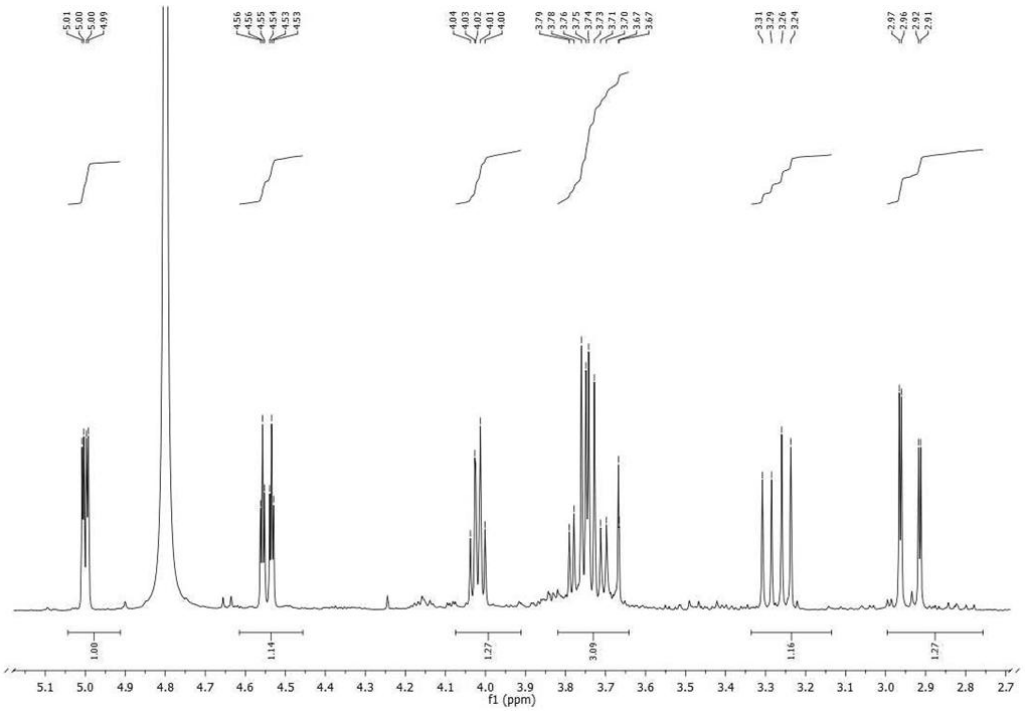


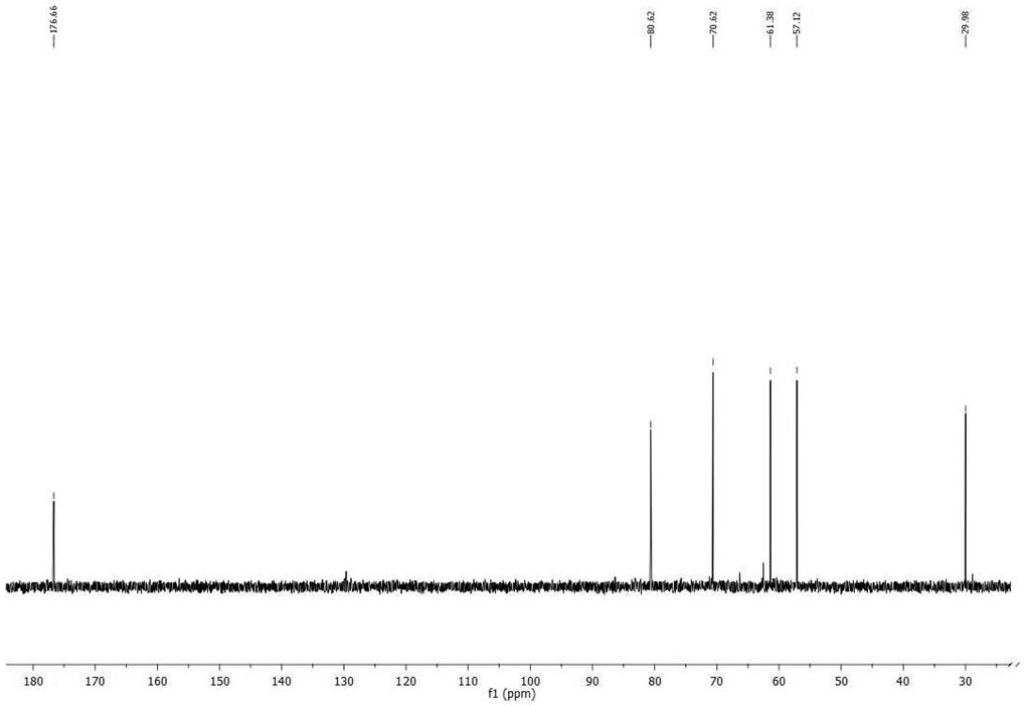




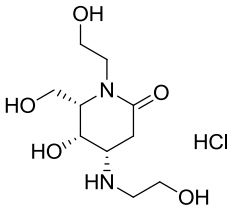
^{1}H and ^{13}C NMR of compound **153d**

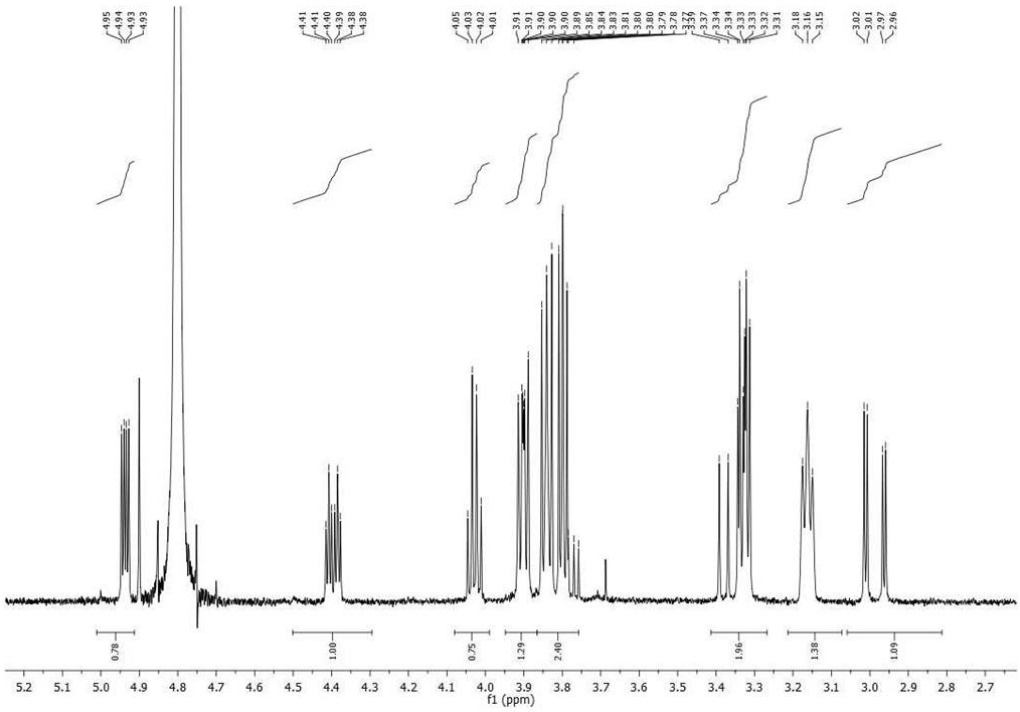


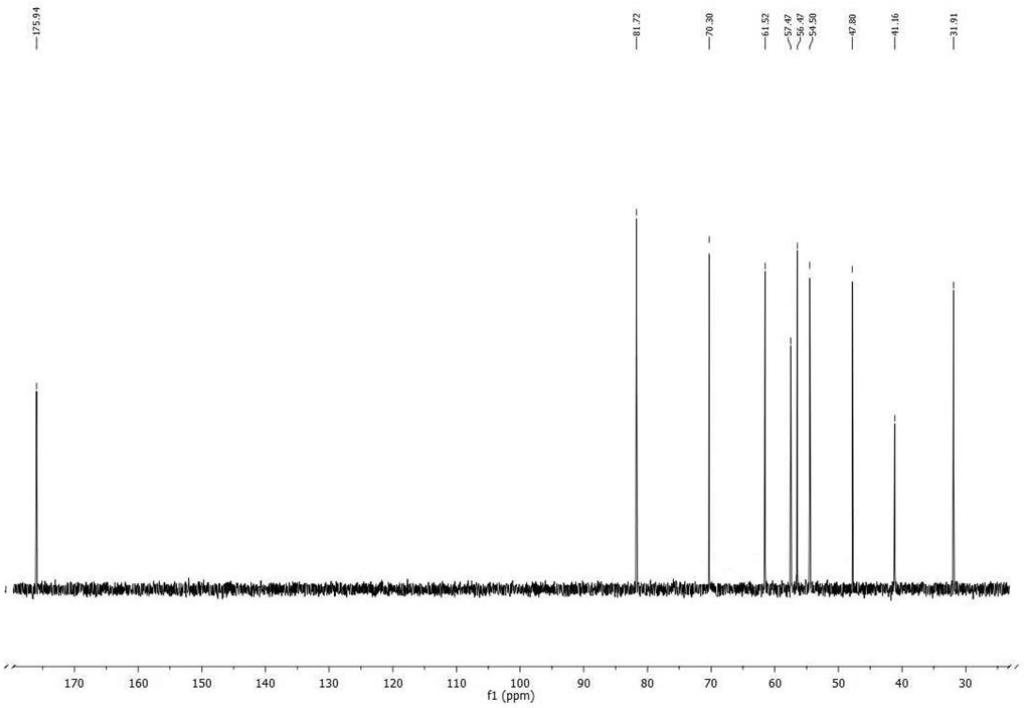




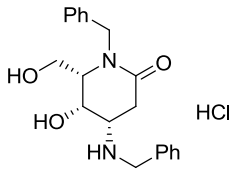
^{1}H and ^{13}C NMR of compound **154b**

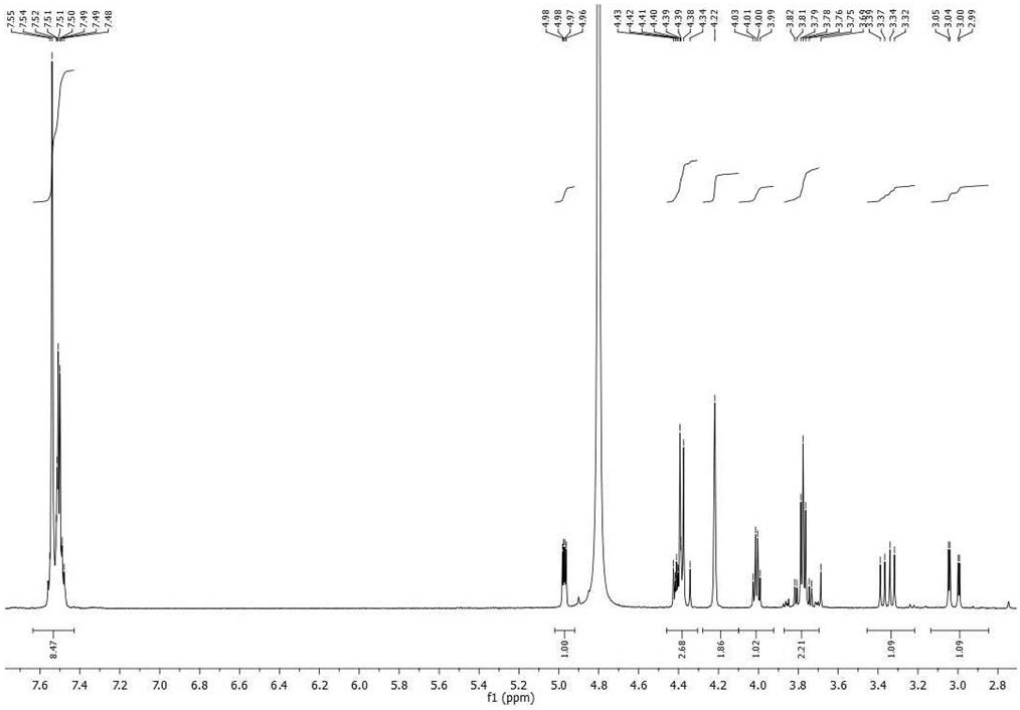


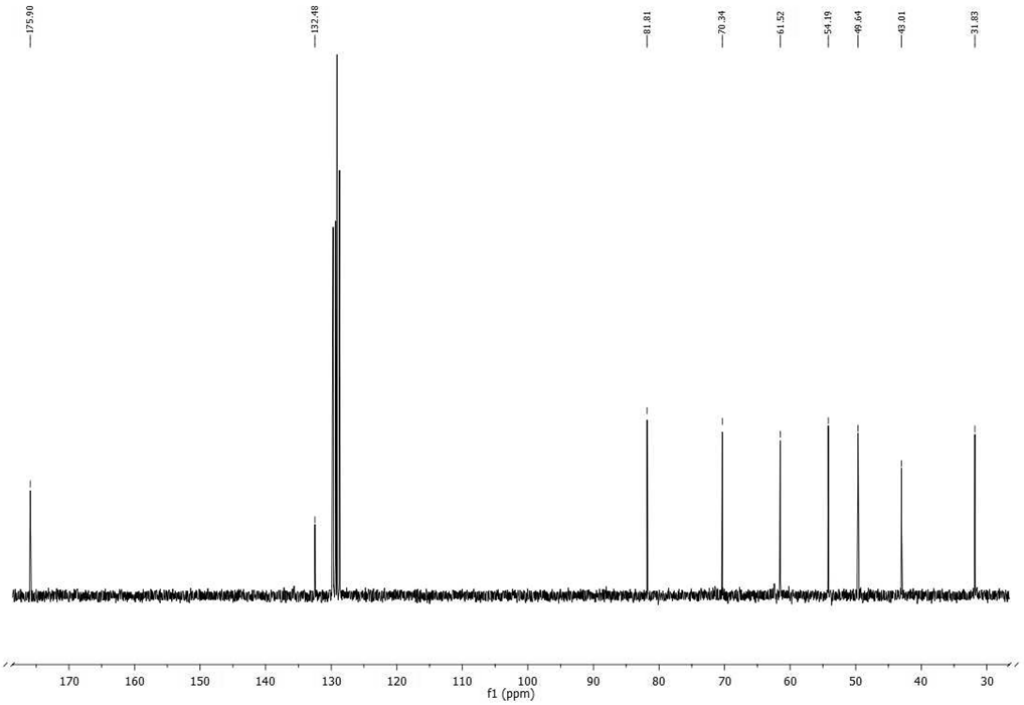




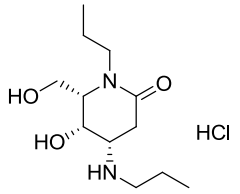
^{1}H and ^{13}C NMR of compound **154c**

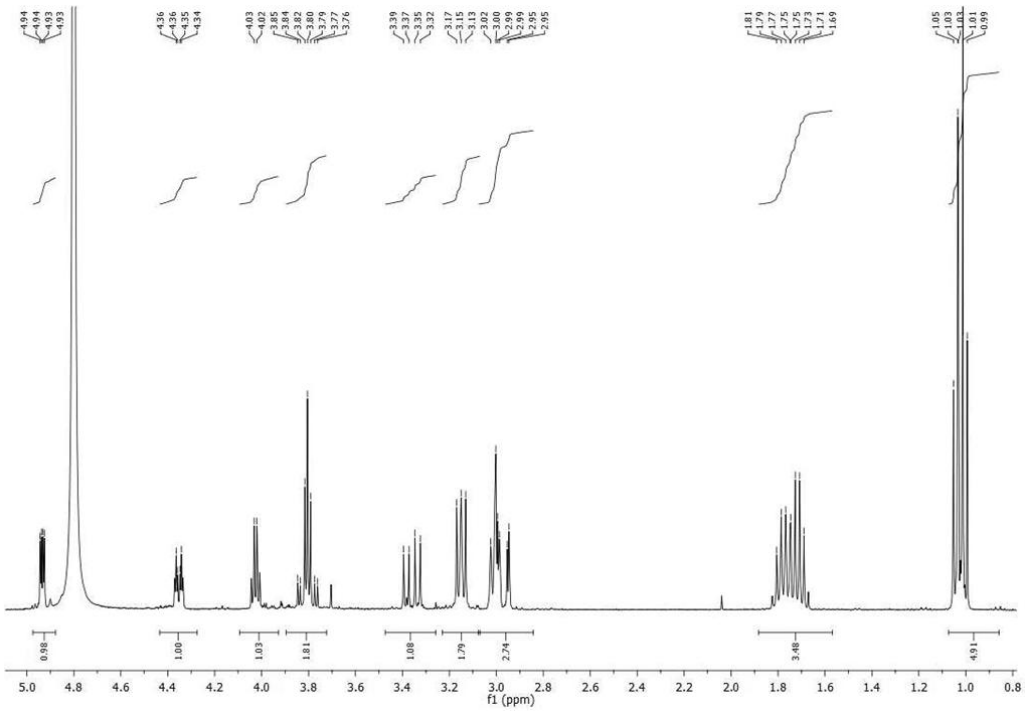


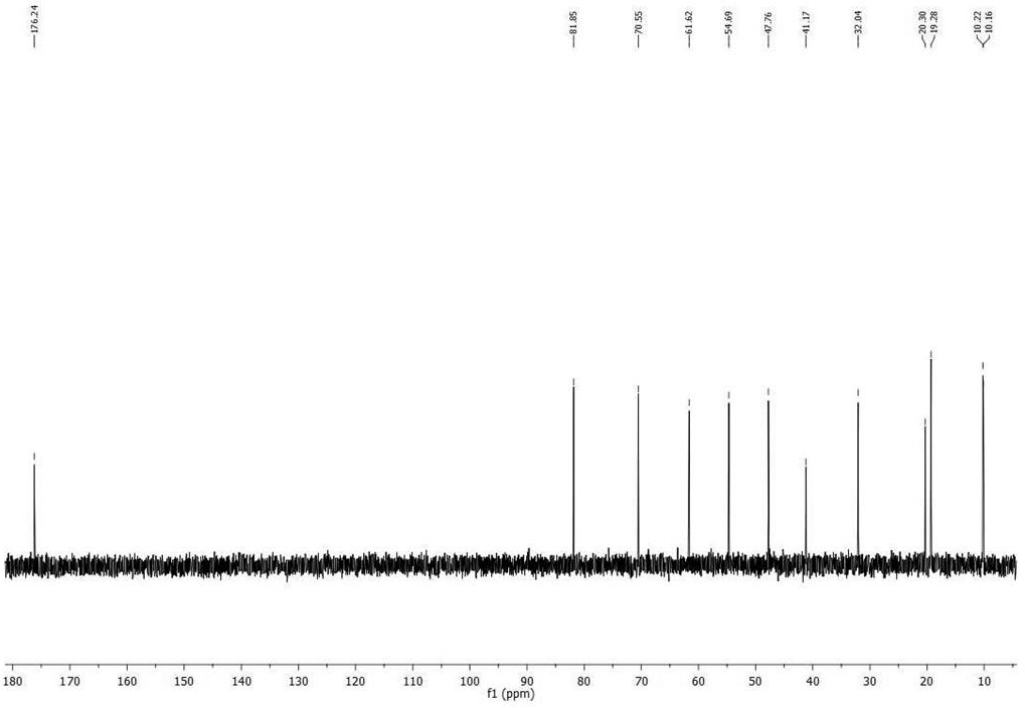




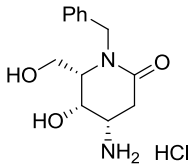
^{1}H and ^{13}C NMR of compound **154d**

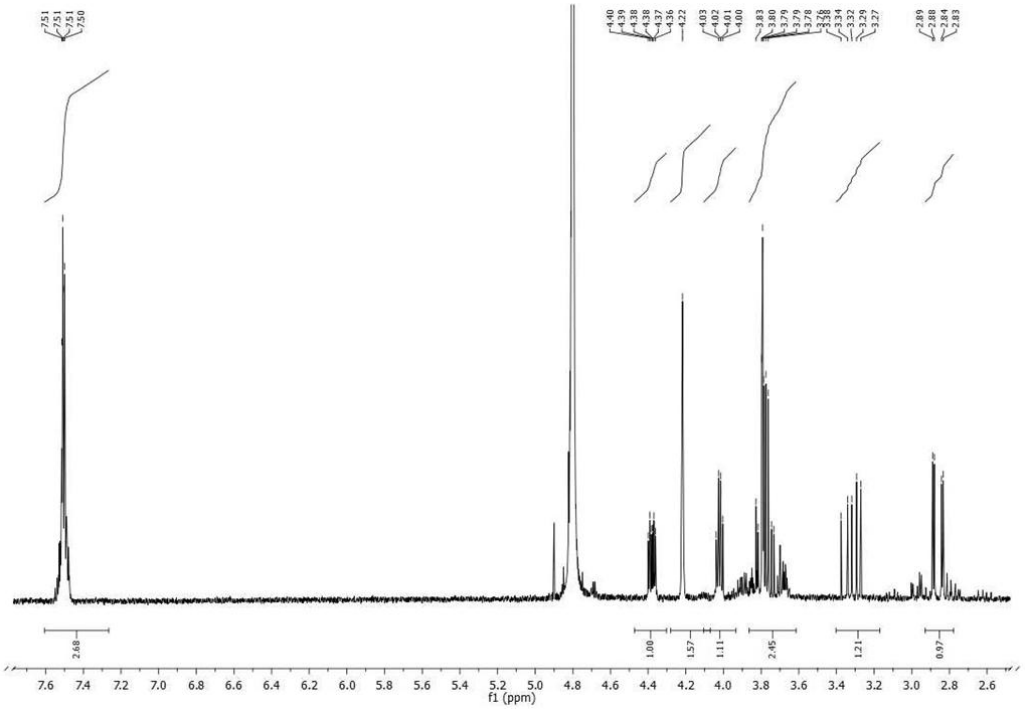


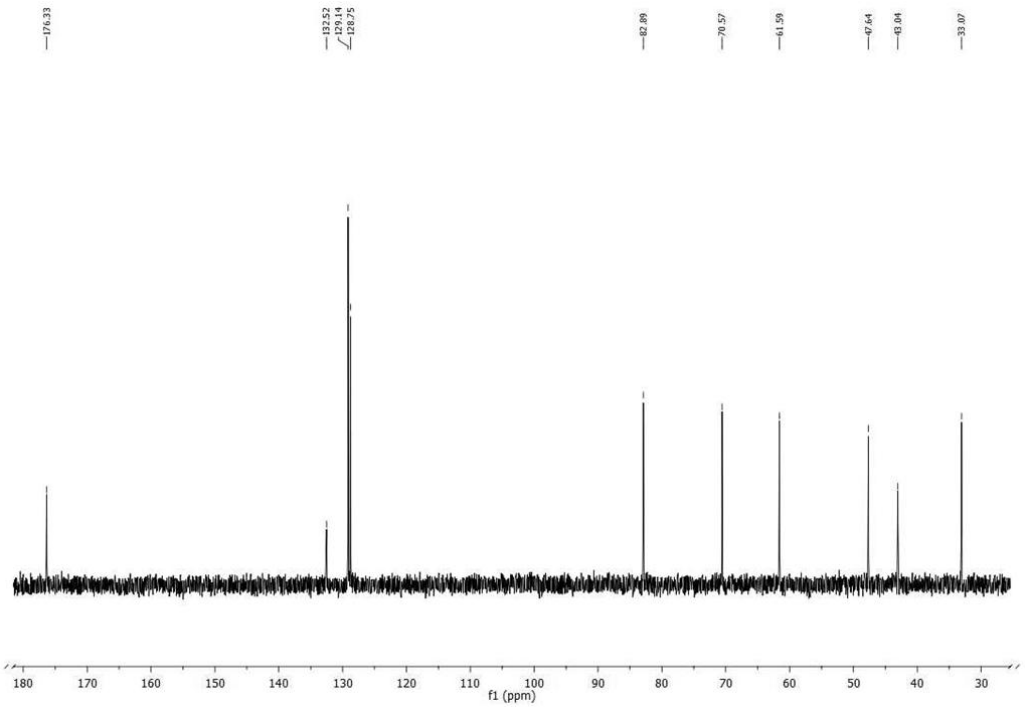




^{1}H and ^{13}C NMR of compound **155**







^{1}H and ^{13}C NMR of compound **156**