REPUBLIQUE ALGERIENNE DEMOCRATIQUE ET POPULAIRE
MINISTERE DE L'ENSEIGNEMENT SUPERIEUR ET DE LA RECHERCHE SCIENTIFIQUE

UNIVERSITE ABOU-BEKR BELKAID - TLEMCEN

MEMOIRE

Présenté à :

FACULTE DES SCIENCES – DEPARTEMENT DE CHIMIE

Pour l'obtention du diplôme de :

MASTER EN CHIMIE

Spécialité : Chimie Organique

Par :

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Sur le thème

Synthesis of highly functionalised chiral 2-Fluoropiperidine

Soutenu publiquement le 09 juin 2024 à Tlemcen devant le jury composé de :

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Année Universitaire : 2023 ~ 2024

Acknowledgements

I would like to thank The Almighty God; He has given me the strength and encouragement throughout all the challenging moments of completing this master's thesis. I am truly grateful for his unconditional and endless love, mercy, and grace.

I would also like to express my heartfelt gratitude to the Algerian government for the Algerian government scholarship for which I was granted this opportunity to pursue my master's degree in organic chemistry at the University of Tlemcen.

I would also like to express my heartfelt gratitude to the Ugandan government for the financial assistance granted to me during my studies in Algeria.

I would also like to express the deepest appreciation for my supervisor Mr. Ziani-Cherif Chewki for his continual supervision, his guidance, his trust, his time and valuable feedback. He has provided me with insightful comments on my research that have been a substantial aid in this accomplishment.

I extend my gratitude to, Mr. Choukchou-Braham Noureddine for agreeing to chair the jury, Mr. Ziani-Cherif Houcine and Mrs. Keniche Assia, for kindly agreeing to examine my present work and to participate in this jury.

All my appreciation to the teachers and professors of organic chemistry who helped us directly and indirectly and particularly those of the chemistry department for their dedication to teaching and their unconditional support throughout my university career. Their expertise and know-how greatly helped me deepen my knowledge in the field of chemistry.

I would also like to extend my gratitude to the staff and doctoral students of the LCSCO laboratory for welcoming us and ensuring that we had all we needed during our research.

Dedications

I dedicate this thesis to my beloved family; I wish to express my sincere gratitude to my parents for their exceptional love and support.

Their constant prayers for me and my progress during this entire journey have allowed me to successfully complete this project. Without such a supportive team behind me, I know I could never be where I am today.

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List of abbreviations.

MeOH: *Methanol.*

Rh/C: *Rhodium on charcoal.*

DMF : *N, N-Dimethylformamide.*

LDA : *lithium diisopropylamide.*

THF: *Tetrahydrofuran.*

BnBr : *Benzyl bromide.*

MsOH: *Methylsulfonic acid.*

BsOH: *Benzene sulfonamide.*

DCM: *Dichloromethane.*

UV: *Ultra-violet light.*

$(Boc)_2O$: *tert-butyloxy carbonyl.*

DIB: *diacetate Iodobenzene.*

OAc : *Acetate.*

KOH : *Potassium hydroxyde.*

rt : room *emperature Ambiante.*

PCC: *Pyridinium chlorochromate.*

NFSI: *N-fluorobenzene sulfonimide.*

PIDA: *(Diacetoxyiodo)benzenze*

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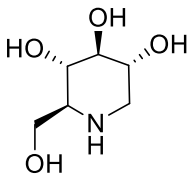
Introduction.

The fluorine atom is increasingly found in bioactive compounds that span all therapeutic categories. Drugs containing fluorine are amongst the best-performing and top-selling pharmaceutical products[1]. The history of inclusion of fluorine atom into biologically active compounds roots directly from the earliest synthetic fluorinated drug 5-fluorouracil, an molecule first synthesized in 1957 that showed high anti-cancer activity by inhibiting thymidylate synthase, preventing cellular synthesis of thymidine[2].

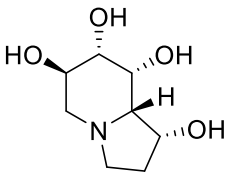
The inclusion of a fluorine atom into biologically active molecules has shown to improve metabolic stability, bioavailability and protein ligand interactions, by comparison to their non-fluorinated counterparts[3]. This has driven forward the development of new fluorinating reagents and processes giving birth to a set of new fluorinated building blocks such as chiral fluoropiperidines[4].

Problematic.

Glycosidases, enzymes that catalyse the cleavage of glycosidic bonds in oligosaccharides and glycoconjugates, are fundamental to a broad range of biological processes including the degradation of dietary polysaccharides, biosynthesis of the oligosaccharide units in glycoproteins and glycolipids, which are involved in a broad range of cellular communication[5]. Nevertheless, a few glycosidase enzymes possess undesired secondary effects associated with a variety of diseases. Inhibitors of these enzymes possess strong therapeutic potential for the treatment of illnesses such as diabetes[6], lysosomal storage disorders[7], viral infection and cancer[8].



1-Deoxynojirimycin



Castanospermine

Highly functionalised piperidines such as 1-deoxynojirimycin or Castanospermine have been sought as potential inhibitors of these enzymes, but their failure in clinical trials can be attributed to their lack of sufficient anomeric selectivity towards alpha- or beta-glucosidase enzymes. Its expected selectivity within alpha-or beta glucosidases could be achieved by

including anomeric stereochemistry in the natural substrate. This has made highly functionalised chiral 2-fluoropiperidines to become potential building blocks in medicinal chemistry[9-11]. Despite their biological relevance, their synthesis is challenging[12] and only one asymmetric synthesis methodology has been developed over the years hence the need for a new methodology.

Objective.

In this project, we tried to develop a new methodology of synthesis of a highly functionalised chiral 2-fluoro-piperidine. The approach is based on the utilisation of the Suarez C-C oxidative cleavage reaction on a protected (+)-D-glucosamine derivative.

Literature Review

Literature review.

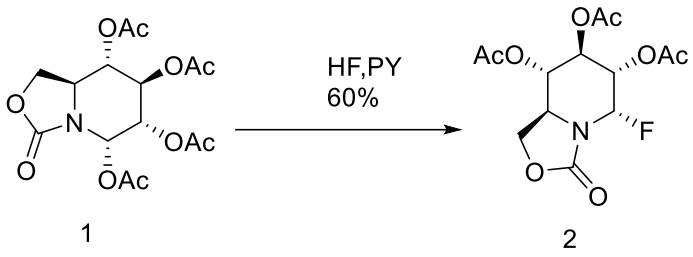
1.0 Introduction to highly functionalised chiral 2-fluoro piperidines.

Fluoropiperidines represent a class of molecules that are scarce in the organic and medicinal chemistry world. Their significance can be attributed to their therapeutical potential and have been used as potential inhibitors of glycosidase enzymes, but their failure in clinical trials is mainly attributed to their lack of sufficient selectivity toward the iso-enzyme series. This has prompted researchers to examine a couple of methodologies of achieving anomeric selectivity finding success via fluorinating a naturally occurring iminosugar based on Castanospermine derivative[5].

1.1 Synthesis of a highly functionalised 2-fluoropiperidine.

Sanchez-Fernandez et al[5] had envisioned the use of tri-O-acetyl-protected derivative of the 2-oxa-3-oxo-Castano spermine bearing a 5-O-trichloroacetimidate as a suitable sp2 - iminosugar pseudoglycosyl donor for the construction of the isomaltoside and maltoside. However, reactions with the corresponding glycosyl acceptors resulted in formation of various products of hydrolysis. This prompted them to adopt a pseudoglycosyl fluoride[5].

The pseudoglycosyl fluoride was synthesized by reacting a tetra-O-acetyl-protected derivative of Castanospermine with Olah's reagent, giving a highly functionalised chiral 2-fluoropiperidine with a good yield[5].(scheme 1)



Scheme 1. Synthesis of a chiral 2-fluoropiperidine derivative using Olah's reagent

1.2 Synthesis of other functionalised chiral fluorinated piperidines.

From the earlier successes of synthesis of highly functionalised chiral 2-fluoropiperidines using the Olah's reagent to introduce fluorine atom in the anomeric position of a naturally existing highly functionalised piperidine ring, we decided to investigate further other

methods organic chemists have adopted to build piperidine rings and simultaneously introduce a chiral fluorine atom on the different positions of the piperidine ring.

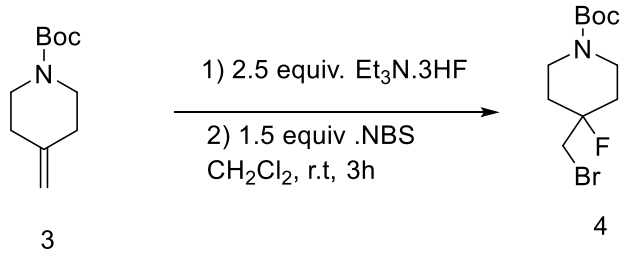
1.3 Synthesis of 4-fluoropiperidine building blocks.

Functionalised chiral 4-Fluorinated piperidines are usually referred to as antagonists of T-type calcium channels and are used in the treatment of neurological and psychiatric diseases[13]. There various reports of 4-aminomethyl-4-fluoropiperidines being used as selective 5-HT1A agonist.

Among the methods that have been used to synthesize chiral 4-fluoropiperidines include bromo-methylation and the Aza-Prins reaction.

1.3.1 Using bromo-fluorination.

The bromo-fluorination is an electrophilic addition reaction on a double bond which involves a simultaneous bromination and fluorination using a bromination and an electrophilic fluorinating reagent. The 4-methylenepiperidine(3) underwent a bromo-fluorination using N-bromo succinimide and triethylamine trihydrofluoride as an electrophilic fluorinating reagent[11]. (scheme 2)

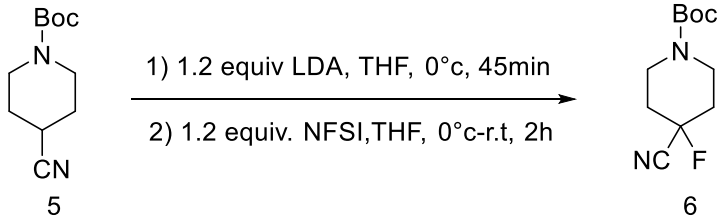


3 4

Scheme 2. bromo-fluorination reaction.

1.3.2 Using a nucleophilic substitution reaction.

It involves the deprotonation of acidic alpha proton of an active methylene based on 1-Boc-4-cyanopiperidine **5** using LDA dissolved in THF as a solvent at 0 ◦C and quenching with NFSI (figure 1), giving 1-Boc-4-cyano-4-fluoropiperidine **6** [11]. (scheme 3)



5 6

Scheme 3. nucleophilic substitution reaction

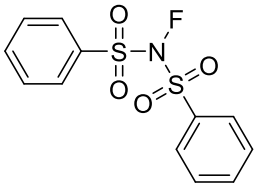
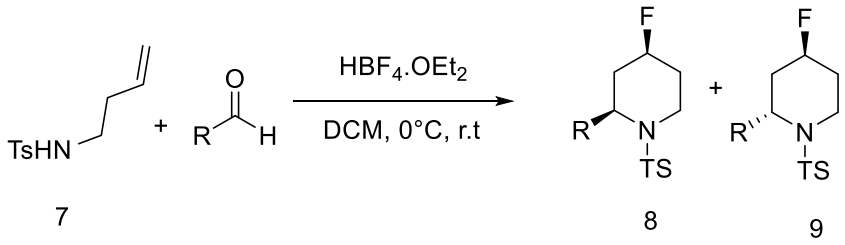


Figure 1. NFSI

1.3.3 Using the Aza-Prins reaction.

The aza-prins reaction is a nucleophile catalysed intramolecular cyclisation reaction and has been used to incorporate a fluorine at the 4-position of a piperidine ring[14,15]. The cyclization reaction was performed using the N-tosyl homoallylic amine **7**, an aldehyde and catalysed by tetrafluoroboric acid-diethyl ether complex at ambient temperature. The reaction demonstrated a high cis-selectivity[16]. (scheme 4)



7 8 9

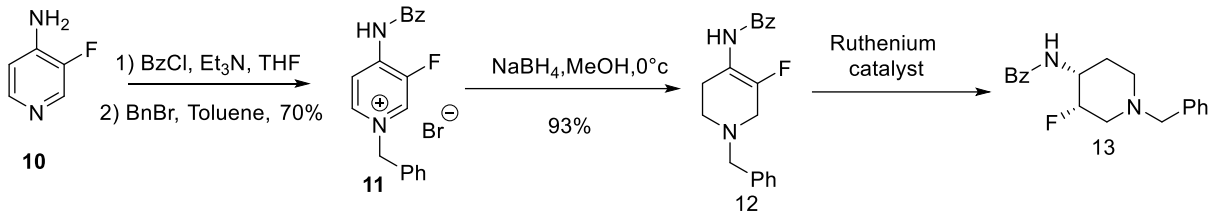
Scheme 4.The Aza-Prins reaction.

1.4 Synthesis of 3-fluoropiperidines building blocks.

Functionalised chiral 3-fluoropiperidines have been used in the synthesis of potential CGRP receptor antagonists whose mode of action is to eliminate the undesired secondary effects of usage of the triptan class of 5-HT1B/1D receptor agonists in treating migraine[17]. Among the methods that have been adopted in their synthesis they included the asymmetric hydrogenation of fluorinated piperidines, and an enzyme-catalysed dynamic asymmetric transamination.

1.4.1 Asymmetric hydrogenation of a Fluorinated precursor.

Molinaro *et al* adopted asymmetric hydrogenation because it enabled the usage a fluorine-containing precursor, which eliminated the problematic stereoselective fluorination[18]. The authors began by activating the pyridine through an alkylation reaction. The formed pyridinium underwent a regioselective $NaBH_4$ - mediated reduction to yield an enamide **12**[19]. An asymmetric hydrogenation of the enamide gave the desired chiral fluoropiperidine **13**[20]. (scheme 5)

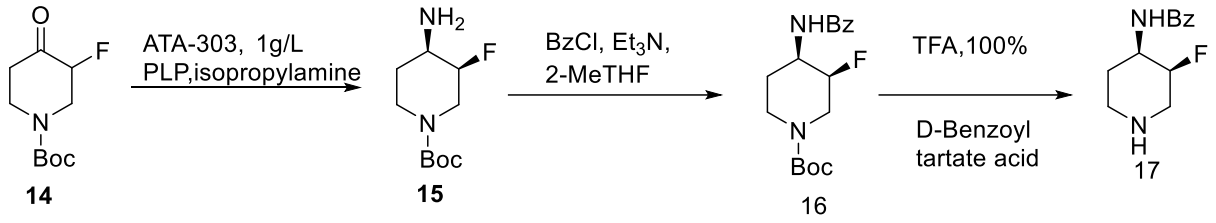


Scheme 5. Asymmetric hydrogenation of a Fluorinated precursor

1.4.2 Enzyme-catalysed dynamic asymmetric transamination (DATA) of ketones

The authors used a biocatalytic technology involving transamination of ketones[21]. α-fluoropiperidinone 14 was subjected to an enzyme catalysed asymmetric transamination reaction and this allowed to simultaneously add two desired stereocenters in one step[22]. This route offered higher enantioselectivity and minimization of by-product.

The DA-TA was performed using a commercially available transaminase enzyme (Codexis ATA-303), pyridoxal 5'-phosphate (PLP) as the cofactor, and isopropyl amine as the nitrogen source[23] at a pH 10.5. The reaction led to synthesis of piperidine **17** in 3 steps and delivered high selectivity of the syn-isomer with the (R)-configuration at the amine centre. Benzoylation and TFA-mediated Boc deprotection provided the chiral fluoropiperidine[22]. (scheme 6)

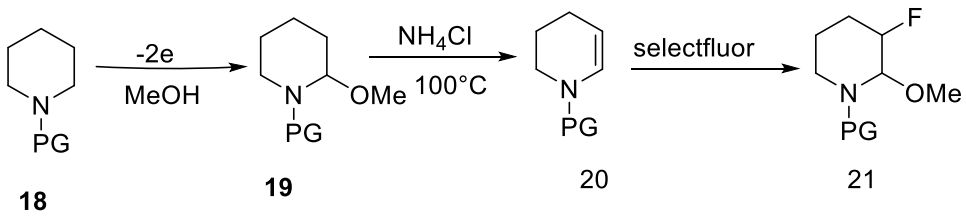


Scheme 6. Enzyme-catalysed dynamic asymmetric transamination (DA-TA) of ketones

1.4.3 Usage of nucleophilic addition to N-acyliminium ions

Shono *et al* used Selectfluor, an electrophilic fluorinating reagent, taking advantage of N-acyliminium ion precursors to produce a 3-fluorinated piperidine building block, where the fluorine atom on the ring influences the Diastereoselectivity of the product[24].

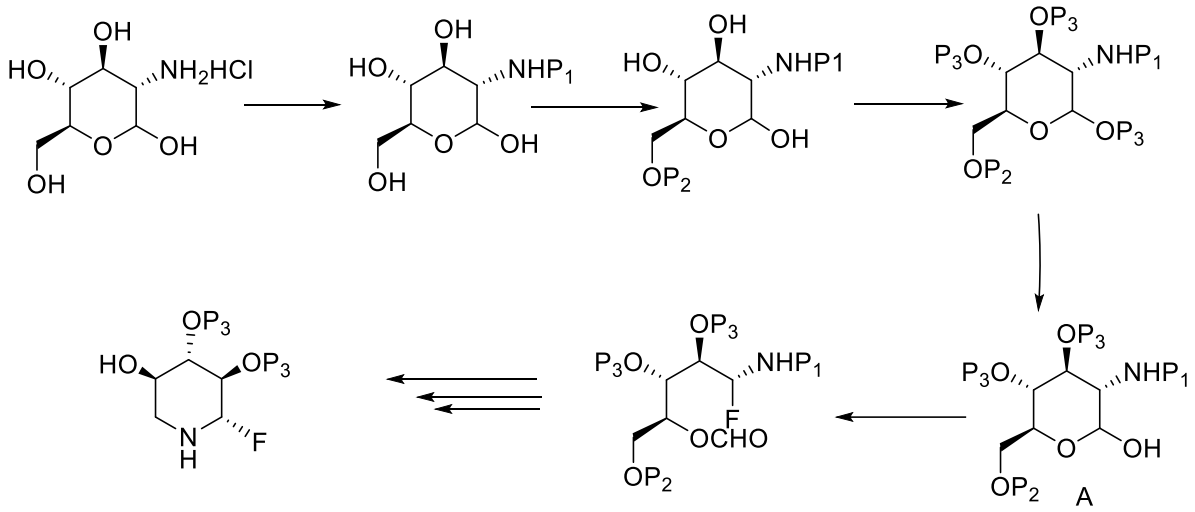
The reaction starts with an N-protected cyclic enamines **20** which is prepared from a protected piperidine **18** using an electrochemical oxidation method[24] to produce **19** which then undergoes a demethoxylation reaction[25]. Electrophilic fluorination of **20** using Selectfluor, followed by a Lewis acid mediated nucleophilic substitution leads to a trans-substituted 3-fluoropiperidine building block. (scheme 7)



Scheme 7. Nucleophilic addition to N-acyliminium ions.

1.5 Our methodology.

Our contribution is based on a synthetic methodology using an environmentally sustainable precursor that is glucosamine, which offered us the desirable stereocenters. This enabled us to focus on manipulating protecting groups to set in place the fundamental intermediate **A** for the Suarez reaction and a consecutive fluorination. The Suarez radical reaction would allow us to avoid the usage of heating or cooling conditions.



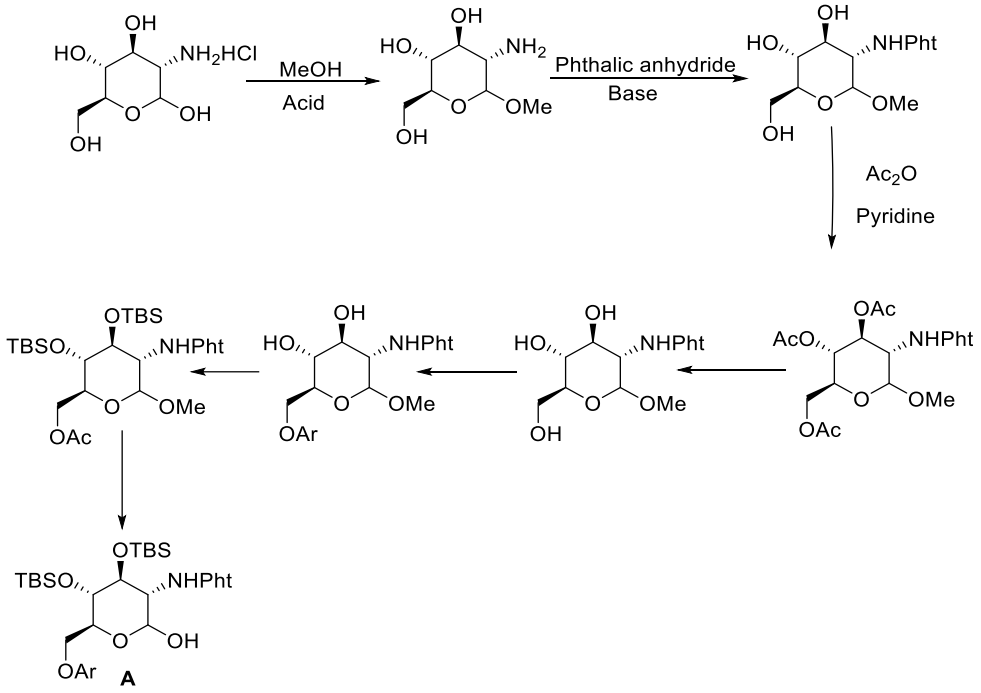
Scheme 8. Our methodology

Results and Discussion

Results and Discussion.

2.0 Introduction.

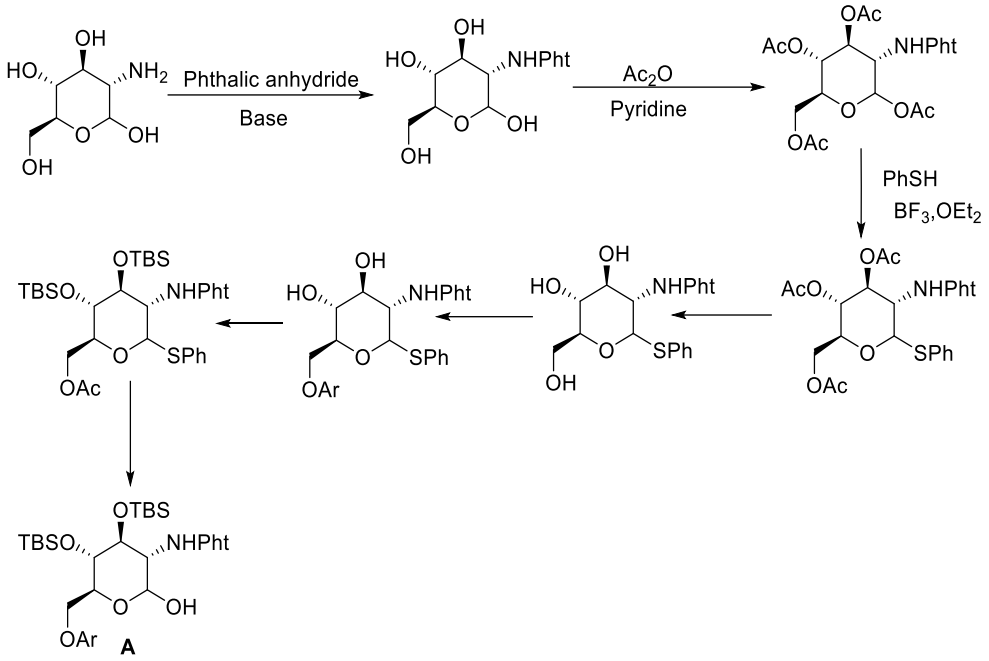
This present work represents a continuation to the efforts brought previously by Benhamidat and Cherrak[29]. With an aim of putting in place intermediate **A** required for the Suarez reaction, two methodologies were utilised to achieve selective protection of particular alcohol groups. The first approach involved selective protections, that is the anomeric alcohol as a methoxide, the amine group as a phthalimide, and then a total acetylation of the remaining alcohols. Unfortunately, Benhamidat and Cherrak methoxide protection failed in the first step, mostly due to the difficulties in isolating the product. (scheme 9)



Scheme 9. First approach by Benhamidat and Cherrak.

The authors were then forced to develop a second approach independent of the methoxide protection. They maintained the phthalimide protection of the amine, followed by total acetylation of alcohol groups (scheme 10). They then converted the anomeric acetyl into a thiophenol.

In brief, in order to put in place the fundamental intermediate **A**, they carried out further manipulation of the protecting groups. This greatly increased the number of steps in their synthesis proposal.

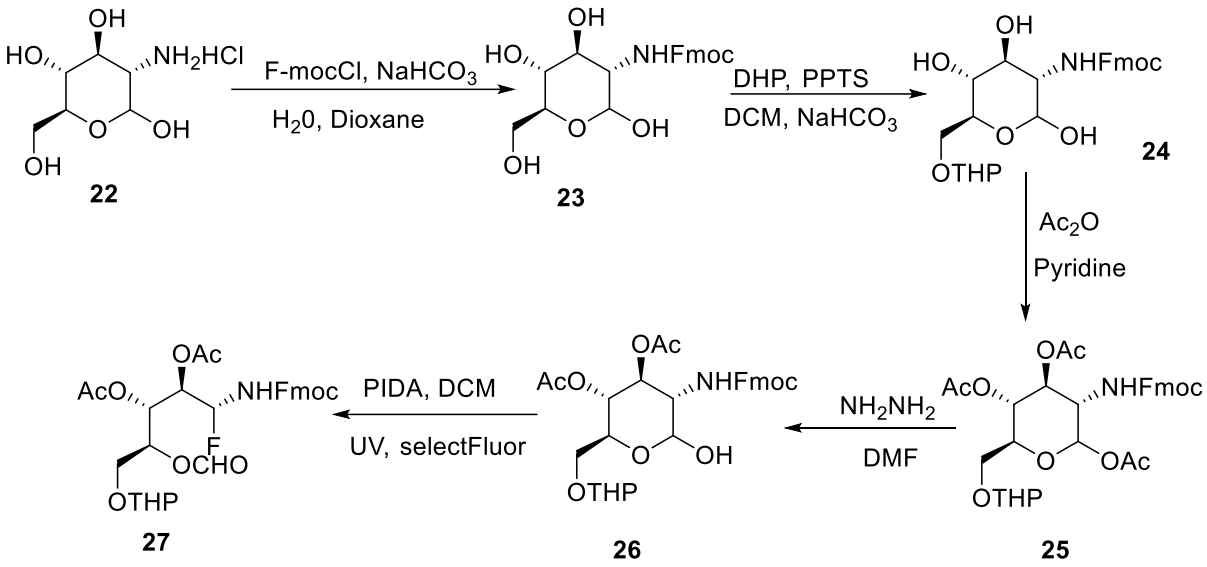


Scheme 10. Second approach by Benhamidat and Cherrak.

2.1 Introduction to our methodology.

As a continuation to the work of Benhamidat and Cherrak, our focus was not only to develop a new methodology of synthesis of highly functionalised chiral fluoropiperidines, but also to shorten the number of steps involved in obtaining the intermediate **A**. This led us to the work of Hao He *et al*[26], involving the synthesis of N-acetyl glucosaminosides of shikonin/alkannin, where the authors demonstrated a short synthetic methodology involving only three steps: the amine group protection using Fmoc-Cl, the complete acetylation of the alcohols then the regiospecific hydrolysis of the anomeric acetate into alcohol using hydrazine. This led the authors to synthesise their glucosaminosides in the least number of steps possible.

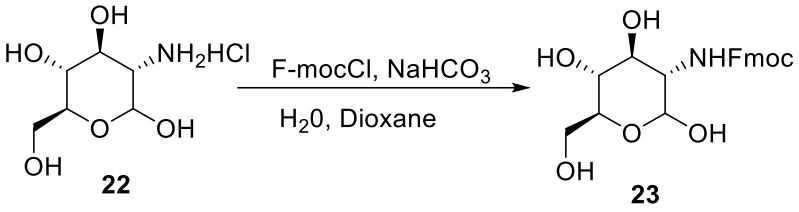
On such basis, our first methodology was based on the protection of the amino group using Fmoc-Cl, followed by the protection of the primary alcohol using DHP, and then acetylation of the secondary alcohols. This would permit us to access the intermediate (A) for the Suarez scissor reaction and also to easily access the primary alcohol for further amine cyclisation. This methodology would allow us to reduce the synthesis workload by at least 5 steps. (scheme 11)



Scheme 11. Revised methodology based on Fmoc-Cl.

2.2 Protection of glucosamine using Fmoc-Cl.

In our first reaction, we neutralised 1eq of commercially available glucosamine hydrochloride using 5eq of sodium hydrogen carbonate. The resulting solution was then reacted with 0.96eq of Fmoc-Cl dissolved in dioxane, giving the crude product as a white precipitate in 68% yield (Scheme 12). To this stage, no confirmation by NMR was performed, as we decided to do it after the next step.

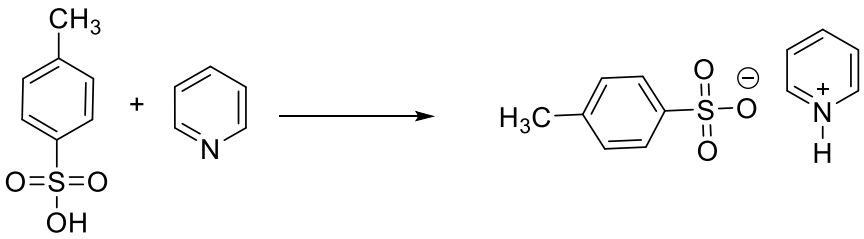


Scheme 12. Fmoc-Cl protection of glucosamine.

Performing the next step required the utilisation of PPTS catalyst. Unfortunately, PPTS wasn't available in the inventory and we were obligated to synthesize it before our second reaction.

2.3 Synthesis of Pyridinium Para-toluene sulfonate.

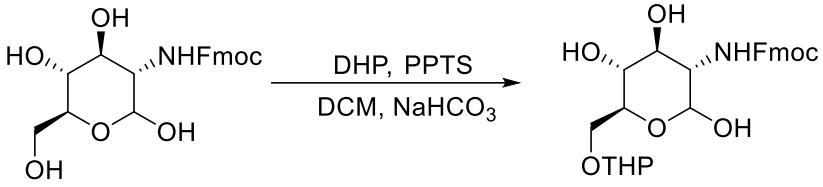
The pyridinium para-toluene sulfonate was synthesized by reacting 0.029moles of para-toluene sulfonic acid monohydrate with 0.145moles of pyridine at ambient temperature, the reaction mixture was left standing under stirring overnight, forming white crystals which were washed using diethyl ether to remove excess pyridine. (Scheme 12)



Scheme 13. Synthesis of pyridinium para-toluene sulfonate.

2.4. Protection of the primary alcohol using DHP.

With PPTS in hand, we proceeded to the protection of the primary alcohol using DHP and this was achieved by reacting 1eq of N-Fmoc glucosamine with 1eq of DHP using 6eq of PPTS catalyst. The reaction mixture was left to stand overnight at ambient temperature. After a classical workup, a brown oily-liquid was formed in a 76% yield.



23 **24**

Scheme 14. DHP protection of N-Fmoc glucosamine.

On analysis of the brown oily-liquid using the H-NMR, it was confirmed that the first reaction involving Fmoc-Cl protection of glucosamine worked fine on the basis of the presence of peaks in the aromatic part, as well as the proton of the amine at 8.6 ppm. However, some of the signals related to the formed THP group seemed absent. Instead, we detected the presence of unexplained 36 protons in the zone of [0.9-1.7] ppm. (figure 1)

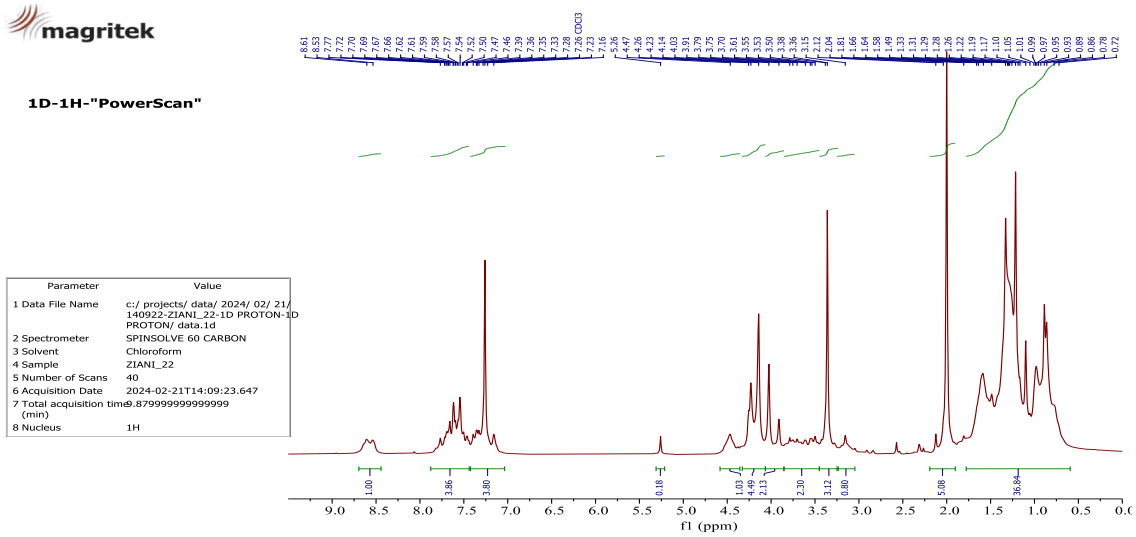
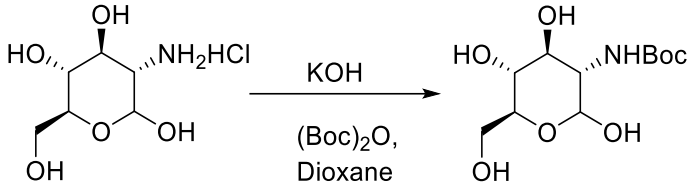


Figure 2. H-NMR of crude DHP protected N-Fmoc glucosamine.

Due to the surprising failure of the DHP protection reaction, we repeated the reaction 4 times but we did not achieve any success and we decided to investigate another amine protecting group.

2.5. Protection of glucosamine using Di-tert butyl dicarbonate.

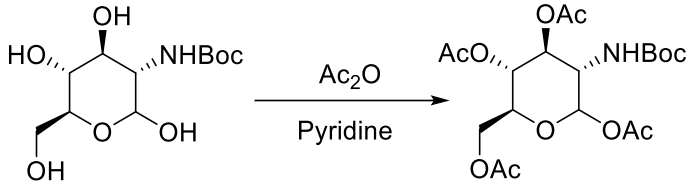
We protected the amine group of glucosamine using the di-tert butyl dicarbonate, , following the protocol described by Bouleghlem[27]. Hence, 1eq of glucosamine hydrochloride was neutralised using 1N solution of potassium hydroxide and then submitted to reaction with 3.3eq of di tert butyl dicarbonate in dioxane. The reaction was left overnight and a white precipitate was formed in a 58% yield.



Scheme 15. $(Boc)_2O$ protection of glucosamine.

2.6. Acetylation of the N-Boc glucosamine.

The white precipitate of N-Boc glucosamine was then subjected to an acetylation reaction and this was performed by reacting 1eq of N-Boc glucosamine with 8eq of acetic anhydride in presence of 8eq of pyridine added dropwise and the reaction left to stand overnight. After workup a white precipitate was formed in 85% yield.



Scheme 16. Acetylation of N-Boc glucosamine

On analysis of our acetylated product using the H-NMR, it was observed that the desired product was not obtained due to the absence of peaks corresponding to the glucosamine part. (figure 3) Upon checking the starting material by proton NMR, we realized the same issue, as the glucosamine peaks were missing.

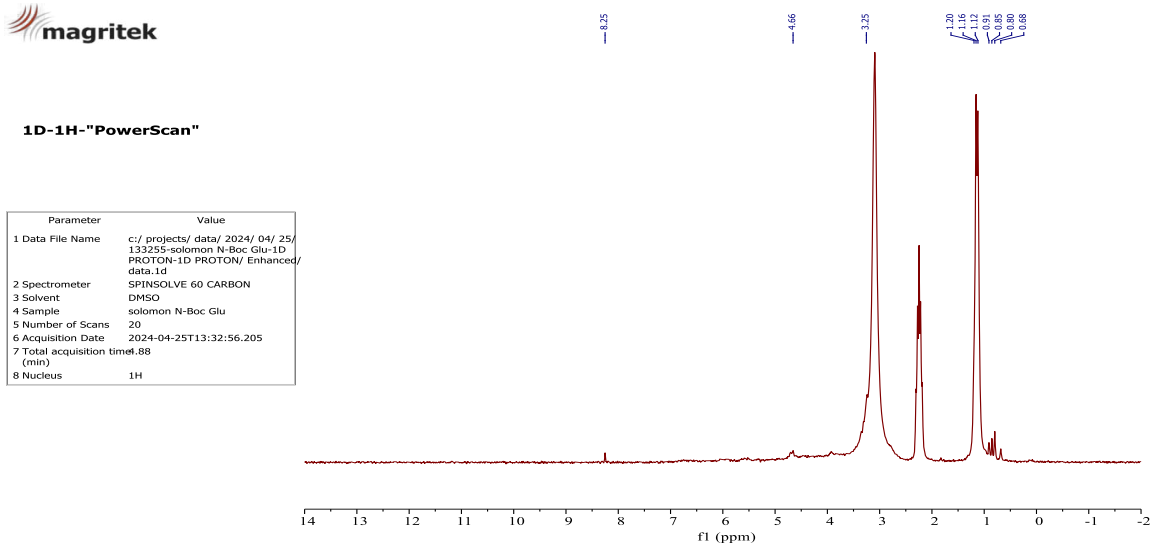


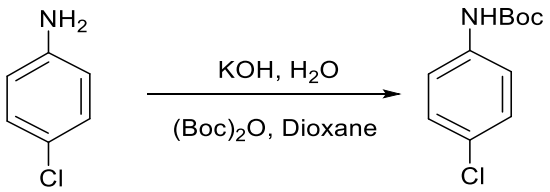
Figure 3. H-NMR of N-Boc glucosamine

This meant that we have very likely performed an acetylation on a wrong product starting material. We decided therefore to investigate further the N-Boc protection by repeating the reaction 3 times but once again, there was no success. Since glucosamine isn't chromophore at all, we could not follow the reaction using a TLC. On another side, what disturbed us was the fact that during the BOC placement, we followed a protocol that is well described in the literature, which emphasises clearly that the right product is the one that is filtered off. Such product for us was the wrong product. Moreover, on a logical point of view, that white solid, that is insoluble in water/dioxane mixture, could not be an inorganic salt. Such results left us puzzled.

To verify further the validity of the protocol, we decided to test the procedure of $(Boc)_2O$ protection of amine on 4-chloroanilin, which should react quite efficiently.

2.7. Protection of para-chloroanilin using di-tert butyl dicarbonate.

1eq of 4-chloroaniline was solubilized in a mixture of dioxane and potassium hydroxide 1N (1/1) (dioxane/ potassium hydroxide). To the solution was add 2eq of di tert-butyl dicarbonate. The reaction was followed using TLC until completion and after an extractive workout using ethyl acetate a brown liquid was obtained.



Scheme 17. $(Boc)_2O$ protection of para-chloroanilin.

On analysis of the obtained brown liquid using the H-NMR, the spectrum shocked us with the absence of the Aniline peaks (figure 4). If there has been any protection, the final compound should have gone in the aqueous phase.

Due to the time-factor of the internship, we decided to continue our work using the familiar phthalic anhydride.

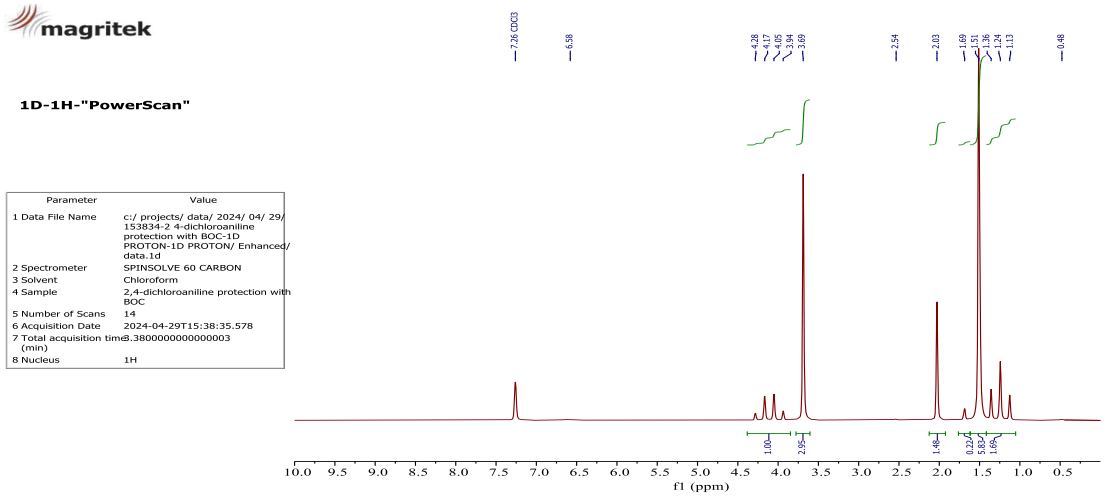
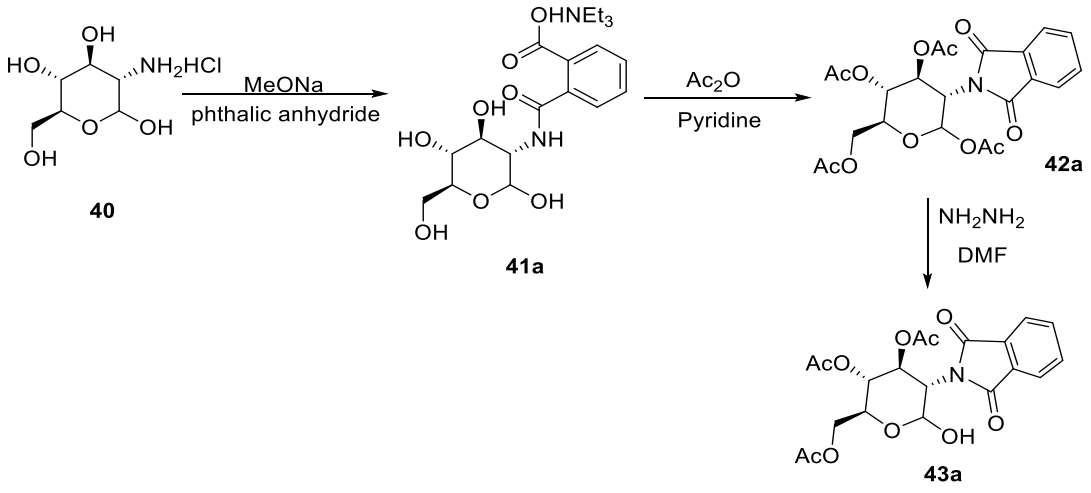


Figure 4. H-NMR of N-Boc para chloroaniline.

In front of the series of failures that we encountered, we decided to test a final approach based on phthalimide as protecting group.



Scheme 18. Revised methodology based on phthalic anhydride.

2.8. protection of glucosamine using phthalic anhydride.

The protection of glucosamine with phthalic anhydride was performed twice. In the first trial, we began by neutralising the commercially available glucosamine hydrochloride using 1eq of

sodium methoxide and the resulting filtrate was reacted with 2eq of phthalic anhydride using triethylamine as base. The reaction mixture was heated at 50°C for an hour and cooled giving **41a** as a white precipitate in a poor 30% yield. (Scheme 17)

The poor yield of the obtained phthalimide made us question the purity of reactants, since earlier experiments gave yields of up to 95%. This demanded for an analysis of phthalic anhydride on the H-NMR which indeed confirmed that the phthalic anhydride had degraded in quality.

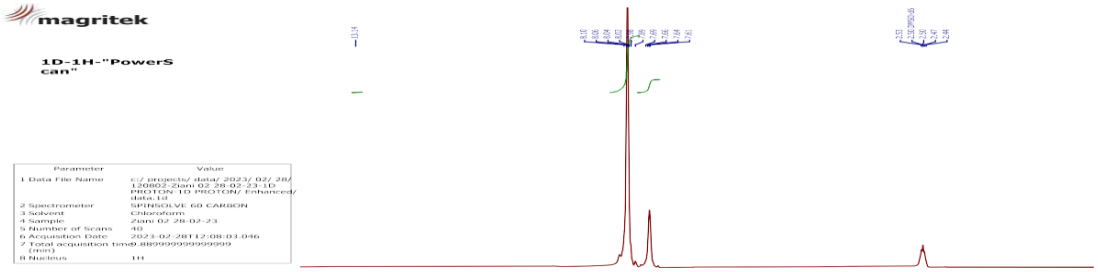


Figure 5. H-NMR of degraded phthalic anhydride.

Clearly, this called for a recrystallisation of the phthalic anhydride.

The second trial following the same procedure but using the freshly recrystallized phthalic anhydride allowed for an obvious improvement of the yield, from 30% to 85%. The proton NMR shows clearly a clean enough crude product. Also, all necessary pics for the confirmation of the right product were present. (Figure 6)

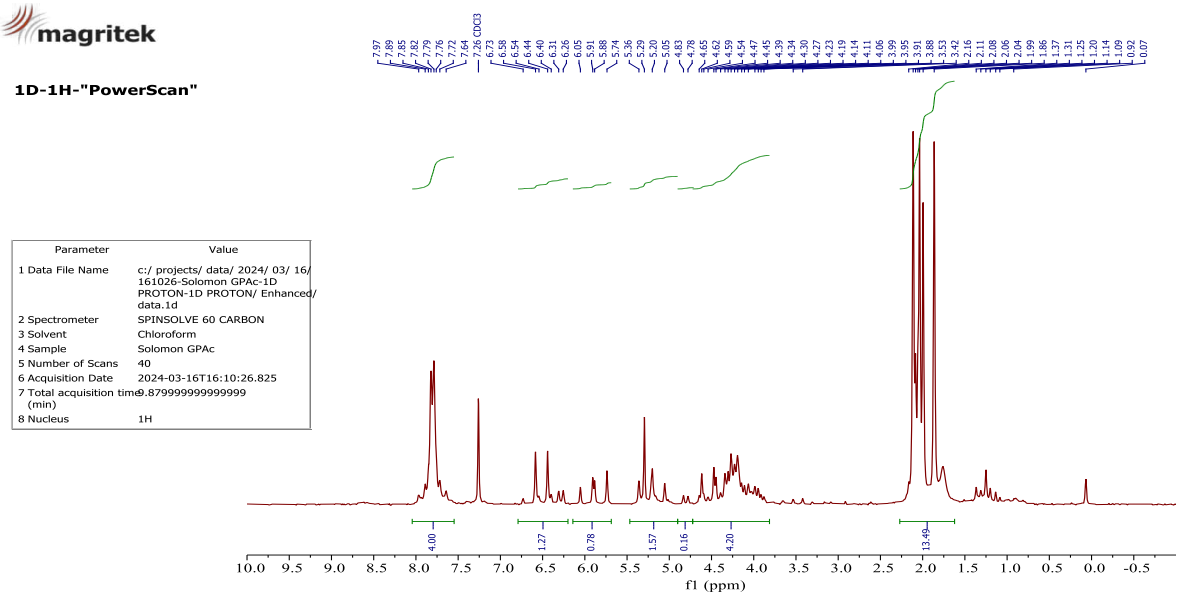
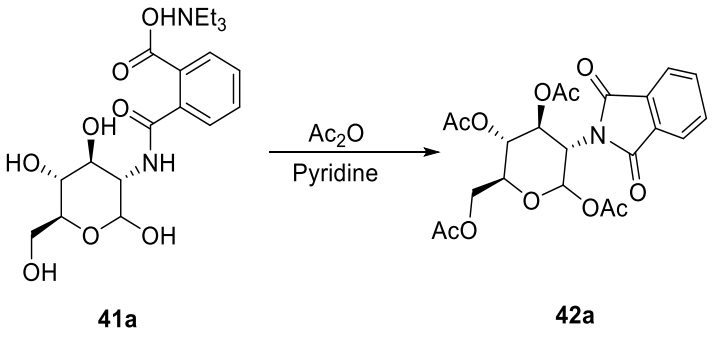


*Figure 6. H-NMR of product **41a***

2.9. Cyclisation and acetylation of product 41a

With **41a** at hands, we proceeded to the cyclisation reaction of the phthalimide and this was achieved by dissolving 1eq of **41a** in 26eq of acetic anhydride and adding 26eq of pyridine dropwise, under cooling conditions. The mixture was left to stand overnight at ambient temperature and, after workup, our product **42a** was obtained as a white precipitate in 91% yield. (Scheme 18)



Scheme 19. Cyclisation of phthalimide and acetylation.

On analysis of the white precipitate using the H-NMR, the 4 peaks of aromatic protons between [7.5-8.0] ppm, the glucosamine peaks between [3.6-6.75] ppm and the 4 X CH_3 peaks between [1.75-2.25] ppm on the spectrum correlate well with the structure of the **42a** confirming that the product was successfully obtained. (Figures 7 and 8)

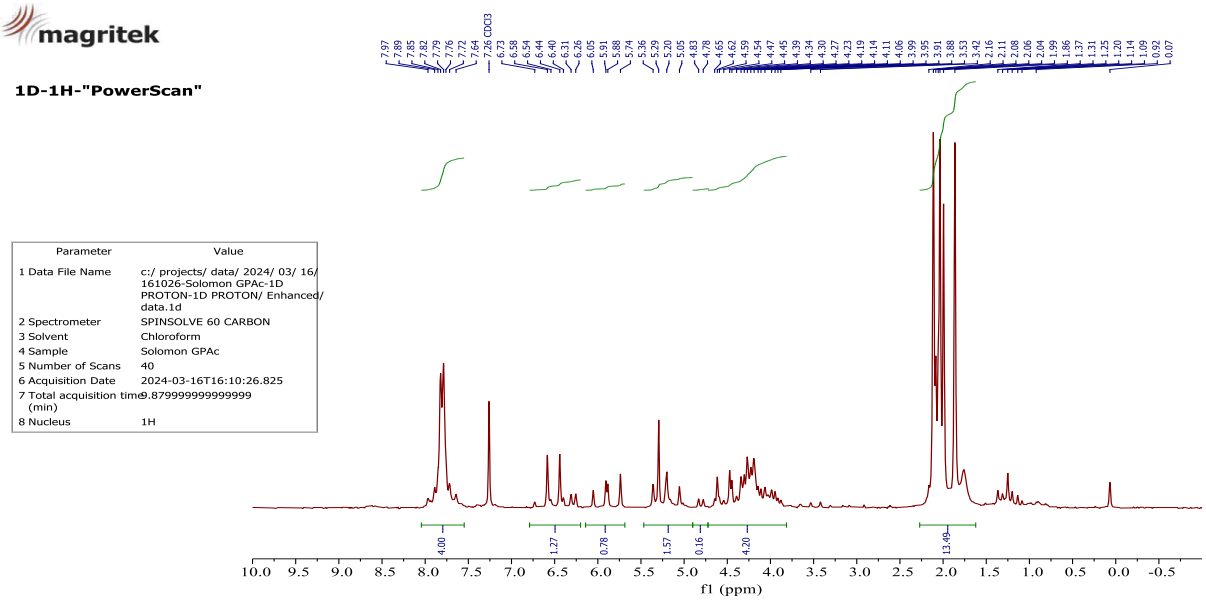


*Figure 7. H-NMR of product **42a***

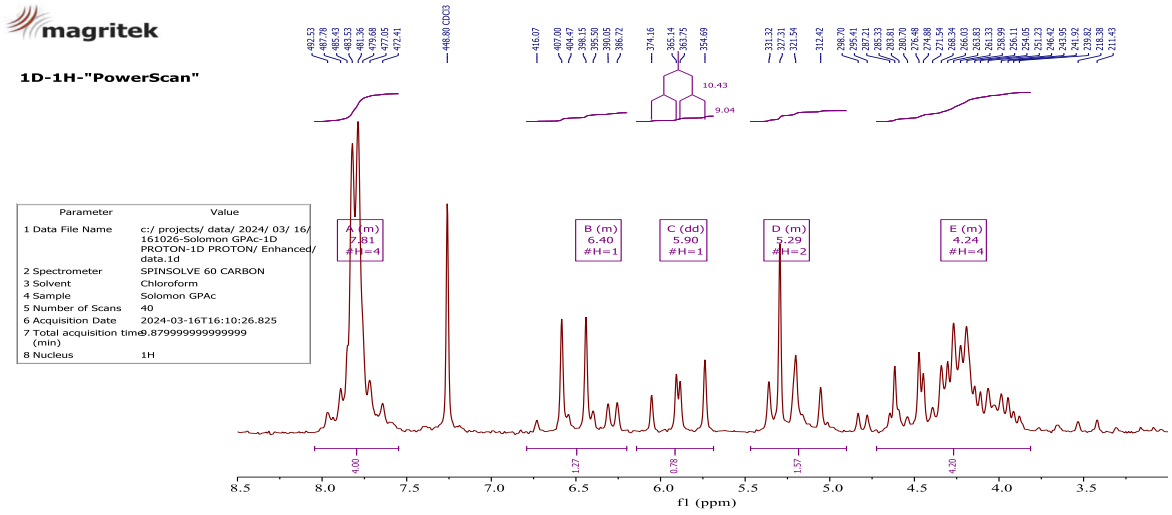
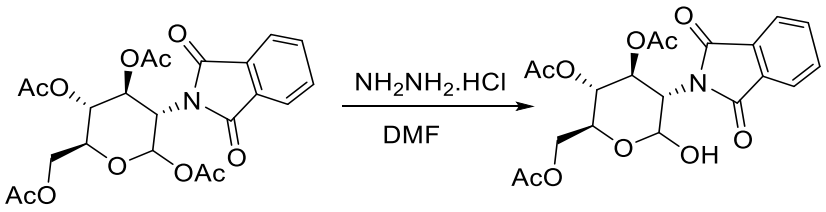


*Figure 8. H-NMR of product **42a (Zoomed area)***

2.10. Deacetylation of the anomeric alcohol.

In order to access the intermediate **A** which possesses the required anomeric alcohol, we once again called upon the conditions reported by Hao He *et al*[26] to remove acetyl group at the anomeric position. This required the use of hydrazine. The challenge we encountered is that hydrazine is also known to deprotect phthalimide and liberate the amine. Yet, based on reaction kinetics, the deacetylation of the anomeric alcohol is a magnitude of times faster

than the phthalimide deprotection reaction. Hence, we tried the reaction with only 1.03eq of 80% hydrazine.HCl in water solution, and in DMF as solvent.



Scheme 20. Hydrazine deprotection of the anomeric alcohol.

The mixture was stirred for 50 minutes and after a classic workup, a brown oily-residue was obtained in 56% yield.

Unfortunately, H-NMR analysis showed the complete absence of the glucosamine part, demonstrating that the desired product was not obtained. (Figure 9)

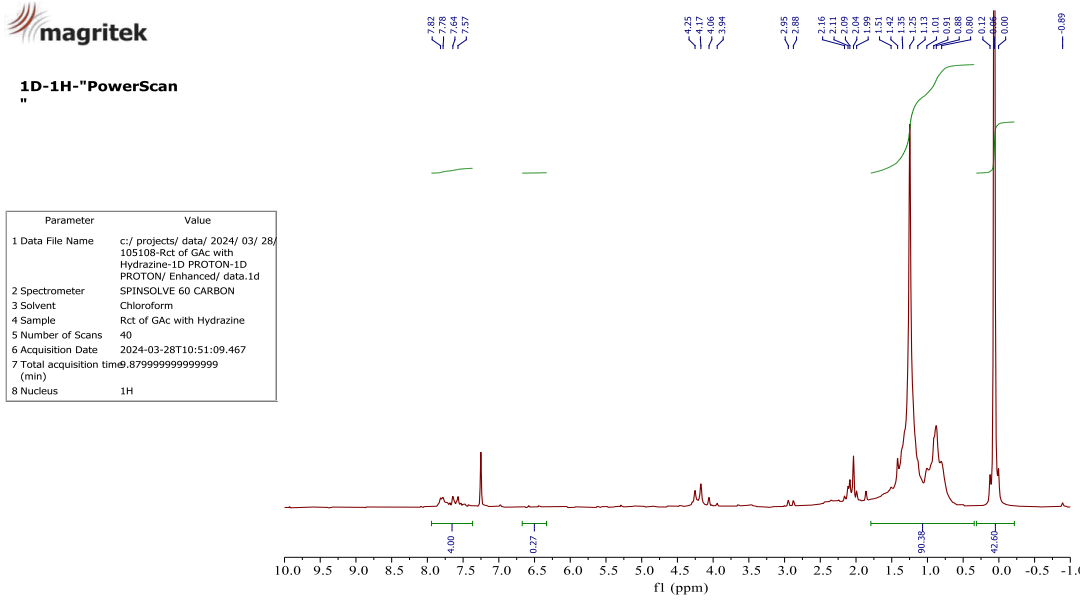


Figure 9. N-NMR of crude product obtained from the above-described reaction

This can be explained by the fact that hydrazine did not only deprotect the anomeric acetyl but also deprotected the phthalimide, exposing the amine which might have made our product more polar and soluble in the aqueous phase.

Conclusion

In this part of the thesis, we have been able to experiment with a number of protecting groups for the different functional groups of (+)- D-glucosamine, a number of synthesis

challenges have been faced, overcame and we have been able to experiment with three synthesis methodologies.

In the first two methodologies, we were able to investigate the amine protection using Fmoc-cl, $(Boc)_2O$ and in the third one we investigated the Phthalimide protection, going as far as the deacetylation of the anomeric alcohol.

The most notable contribution our work involves the different methodologies and protocols recorded for the amine protection which yielded positive results.

Experimental part

Materials and methods.

1. **Melting Temperature:**

The melting temperature (Tf) were measured on a Kofler HEIZBANK type WME device with a temperature range ranging from (50 -260) °C.

2. **Thin layer chromatography:**

Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F254 (Merck) plates (40-63) nm. The developers used are UV (254nm), iodine, phosphomolybdic acid (5% solution in ethanol).

3. **Nuclear magnetic resonance:**

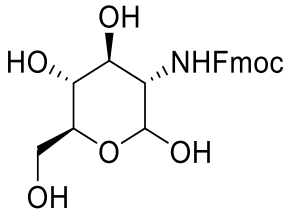
The structural studies were carried out using compact SpinSolve 60 NMR which is equipped with an internal reference of 10% H_20 in D_2O at 4.74ppm.

4. Chemicals:

The used reagents were purchased from Sigma-Aldrich, and used as purchased, unless described otherwise.

Experimental part

N-Fmoc glucosamine.



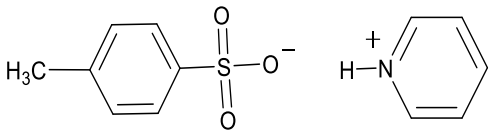
Chemical Formula: $C_{21}H_{23}NO_7$
Molecular Weight: 401.42

To a 100ml round bottomed flask, 1.0g (4.63mmol) of (+) D-glucosamine hydrochloride, 1.95g (23mmol) of sodium hydrogen carbonate is dissolved in 10ml of water and cooled at 0°C.

A solution of 0.96g (3.71mmol) of Fmoc-Cl in 6ml dioxane was added and the mixture stirred for 1hr at room temperature to form a white precipitate which is filtered off. The white precipitate was washed with water (4x25) ml and then dried in an oven at 60°C (68%, 1.26g).

H^1-NMR (60 MHz, $CDCl_3$): δ 7.85-7.79(m,2H), 7.66-7.61(m,2H), 7.45-7.31(m,2H), 5.36(s,1H), 5.03(s,1H), 4.59-4.35(m,2H), 4.08-3.96(m,2H), 3.87-3.32(m,5H).

Pyridinium para toluene sulphonate.



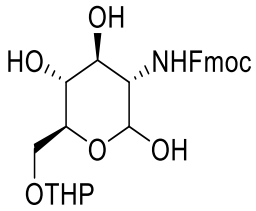
Chemical Formula: $C_5H_6N^+$
Molecular Weight: 80.11
Chemical Formula: $C_7H_7O_3S^-$
Molecular Weight: 171.19

To a 100ml round bottomed flask, add 5g (29mmol) of para-toluene sulphonic acid monohydrate, 11.7ml (145mmol) of pyridine while stirring at ambient temperature. The reaction mixture is left to stand overnight while the crystals form.

The formed crystals were filtered off and washed using diethyl ether to remove the excess pyridine and then left to dry (81.2%, 6.0g).

H^1-NMR (60 MHz, $CDCl_3$): δ 9.00(d, 1H), 8.41(dd, 1H), 7.85(dd, 1H), 7.8(d, 1H), 7.0(d, 1H), 2.2(s, 3H).

Selective protection of the primary alcohol of the N-Fmoc glucosamine.

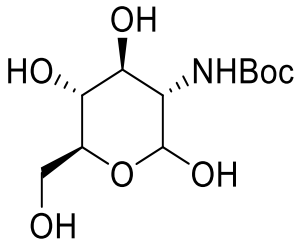


Chemical Formula: $C_{26}H_{31}NO_8$
Molecular Weight: 485.53

To a 100ml flask, 0.25g (0.623mmol) of N-Fmoc glucosamine was dissolved in 40ml of dichloromethane. To that, 0.66mol of 3,4 dihydropyran and 1.25mmol of pyridinium para toluene sulfonate while agitating at ambient temperature and the reaction left to stand overnight in an inert environment and then hydrolysed with 20ml of a half-saturated solution of sodium hydrogen carbonate.

The aqueous phase was extracted with dichloromethane (3x30ml); the combined organic phases were washed with a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The excess solvent was removed under vacuum, giving a brown oily-liquid (76%, 0.22g).

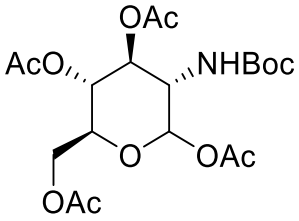
Synthesis of N-Boc glucosamine.



Chemical Formula: $C_{11}H_{21}NO_7$
Molecular Weight: 279.29

To a 50ml round bottomed flask, 0.2g (1eq) of glucosamine hydrochloride is solubilized in a mixture of dioxane and potassium hydroxide 1N (1/1) dioxane/ potassium hydroxide. To the solution, 3.3eq of di-tert-butyl dicarbonate are added. The reaction is left under agitation overnight at ambient temperature. The formed-white precipitate is filtered and washed using a mixture of water/dioxane. The white precipitate is left to dry (58%, 0.15g).

Acetylation of N-Boc glucosamine.



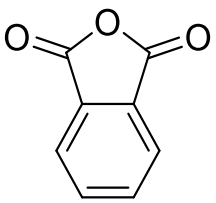
Chemical Formula: $C_{19}H_{29}NO_{11}$
Molecular Weight: 447.44

To a 50ml round bottomed flask, add 0.21g (1eq) of N-Boc glucosamine, 0.6ml (8eq) of acetic anhydride while stirring and the reaction mixture is heated for 10 minutes at 40°c and then cooled to 0°C.

0.06ml (1eq) of pyridine is added dropwise while stirring and the reaction is left to stand for 3hours at ambient temperature before it is concentrated. Multiple Co-evaporations with

diethyl ether is necessary to remove the excess acetic anhydride, forming a white precipitate which is then washed with diethyl ether to remove the excess pyridine (85%, 0.29g).

Purification of phthalic anhydride.



Chemical Formula: $C_8H_4O_3$
Molecular Weight: 148.12

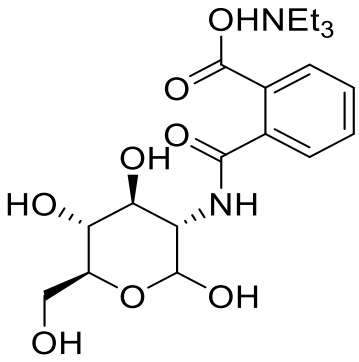
To a round bottomed flask, add 20g of phthalic anhydride, 30ml of acetic anhydride and heat the mixture under reflux, until phthalic anhydride has dissolved totally to give a solution.

The hot solution is filtered and the filtrate is left to cool down gradually forming beautiful white crystals of pure phthalic anhydride.

The phthalic anhydride crystals are then filtered off and left to dry (81%, 16.2g).

H^1-NMR (60 MHz, $CDCl_3$): δ 7.90 (m, 1H), 1.60 (s, 1H).

Protection of glucosamine using phthalic anhydride.



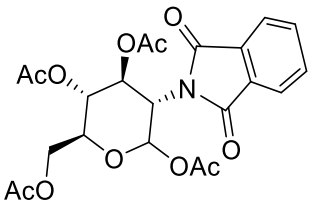
Chemical Formula: $C_{20}H_{32}N_2O_8$
Molecular Weight: 428.48

To 5ml of a 1.0M sodium methoxide solution, 1.0g (4.64mmol) of (+) D glucosamine hydrochloride is added with agitation for 10 minutes. The formed sodium chloride is removed by filtration and washed with 25ml of methanol.

The combined filtrates are treated with 0.4g (2.7mmol) of phthalic anhydride under agitation at room temperature for 10 minutes, 0.6ml of trimethylamine is added and the clear solution is treated with another 0.4g (2.7mmol) of phthalic anhydride. After shaking for 10 minutes, a white precipitate is formed.

The mixture is heated to 50°c and stirred for 20 minutes, then the mixture is kept at 0°C for 1hr. The white precipitate is collected by filtration and washed using 30ml of methanol, yielding 1.3g.

Acetylation and cyclisation of phthalimide.



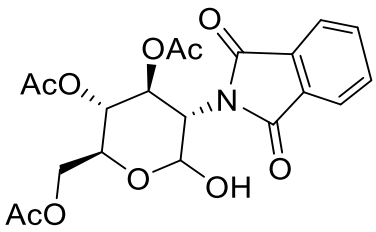
Chemical Formula: $C_{22}H_{23}NO_{11}$
Molecular Weight: 477.42

To 1.0g (2.33mmol) of 2-(2-carboxybenzamide)-2-deoxy-D-glucopyranose in a 50ml round bottomed flask, a mixture of 4.1ml (14.0eq) of acetic anhydride and 6.7ml (27eq) of pyridine are added under cooling conditions.

The mixture is kept at room temperature overnight; the reaction mixture is washed with cold water, 10% HCl to remove the bulk of pyridine, then with 5% HCl to remove the traces of left pyridine, and then with saturated sodium hydrogen carbonate solution and H_2O successively, then dried over anhydrous magnesium sulfate. On removal of the solvent residues, a brown precipitate is formed (91%, 1.33g).

H^1-NMR (60 MHz, $CDCl_3$): δ 7.8-7.6(m,4H), 6.7-6.45(d,1H), 6.0-5.75(t,1H), 5.25(m,2H), 4.5-4.0(m,4H), 2.25-2.0(m,12H).

Deacetylation of the anomeric alcohol.



Chemical Formula: $C_{20}H_{21}NO_{10}$
Molecular Weight: 435.39

0.2g (0.419mmol) of **A** in a 2ml of dry DMF is treated with 0.01ml of 80% hydrazinium solution and stirred for 50 minutes at 25°C. It is then diluted with 12ml of ethyl acetate, washed with brine (4 X 40ml) and dried over anhydrous magnesium sulfate.

Solvent is removed in vacuo leading to a brown oil residue (56%, 0.1g).

Conclusion:

In conclusion, this project was a continuation of the earlier efforts brought about by Benhamidat and Cherak in synthesis of highly functionalised chiral 2-fluoropiperidine from glucosamine using the Suarez reaction.

Among my objectives was to develop a new methodology of synthesis of highly functionalised chiral 2-fluoropiperidine with the usage of the least number of steps to obtain intermediate A which would then be subject to the Suarez scissor reaction.

In this project we were able to investigate three synthesis methodologies, in the first two methodologies, we were able to investigate the amine protection using Fmoc-cl and $(Boc)_2O$ protections. In the third methodology we investigated the Phthalimide protection, going as far as the deacetylation of the anomeric alcohol.

The most notable contribution our work involves the different methodologies and protocols recorded for the amine protection which yielded insightful results.

Despite the challenges encountered, I believe the positive results obtained would serve as a basis for the continuation of this project in the future.

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Summary

In summary, the objective of this work was to develop a new methodology of synthesis of highly functionalised chiral 2-fluoropiperidines from glucosamine which is a sustainable carbohydrate precursor with the usage of the Suarez scissor reaction.

Fluoropiperidines are rare potential building blocks in medicinal chemistry. Despite their biological relevance, their synthesis is challenging and only one asymmetric synthesis methodology has been developed over the years hence the need for a new methodology.

In this project we were able to develop and investigate three methodologies of synthesis of highly functionalised chiral 2-fluoropiperidines, in the third methodology, we were able to investigate the amine protection, acetylation as far as deacetylation of the anomeric alcohol.

Despite the numerous challenges encountered, we were able to experiment, obtain and record insightful protocols which will be fundamental in the further developments concerning synthesis of highly functionalised chiral 2-fluoropiperidines.