UNIVERSITI SAINS MALAYSIA

LAPORAN AKHIR PROJEK PENYELIDIKAN JANGKA *PENDEK*

FINAL REPORT OF SHORT TERM RESEARCH PROJECT

Sila kemukakan laporan akhir ini melalui Jawatankuasa Penyelidikan di Pusat Pengajian dan Dekan/Pengarah/Ketua Jabatan kepada Pejabat Pelantar Penyelidikan

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1. **Nama Ketua Penyelidik: Aisyah Saad Abdul Rahim**
Name of Research Leader

☐ Profesor Madya/ *Assoc. Prof.*   ☑ Dr./ *Dr.*   ☐ Encik/Puan/Cik *Mr/Mrs/Ms*

2. **Pusat Tanggungjawab (PTJ):** PP Sains Farmasi
School/Department

3. **Nama Penyelidik Bersama:**
Name of Co-Researcher

NIL

4. **Tajuk Projek:** **Synthesis of Enzymatically stable C-glycosyl modified benzimidazoles as novel selectin inhibitors**
Title of Project

5. **Ringkasan Penilaian**/*Summary of Assessment*:

	Tidak Mencukupi *Inadequate*		Boleh Diterima *Acceptable*	Sangat Baik *Very Good*	
	1	2	3	4	5
i) **Pencapaian objektif projek:** *Achievement of project objectives*	☑	☐	☐	☐	☐
ii) **Kualiti output:** *Quality of outputs*	☑	☐	☐	☐	☐
iii) **Kualiti impak:** *Quality of impacts*	☑	☐	☐	☐	☐
iv) **Pemindahan teknologi/potensi pengkomersialan:** *Technology transfer/commercialization potential*	☑	☐	☐	☐	☐
v) **Kualiti dan usahasama :** *Quality and intensity of collaboration*	☑	☐	☐	☐	☐
vi) **Penilaian kepentingan secara keseluruhan:** *Overall assessment of benefits*	☐	☑	☐	☐	☐

6. Abstrak Penyelidikan

(Perlu disediakan di antara 100 - 200 perkataan di dalam **Bahasa Malaysia dan juga Bahasa Inggeris**. Abstrak ini akan dimuatkan dalam Laporan Tahunan Bahagian Penyelidikan & Inovasi sebagai satu cara untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti & masyarakat luar).

Abstract of Research
(An abstract of between 100 and 200 words must be prepared in Bahasa Malaysia and in English). This abstract will be included in the Annual Report of the Research and Innovation Section at a later date as a means of presenting the project findings of the researcher/s to the University and the community at large)

C-glikosida merupakan bioisoter yang penting untuk O-glikosida dan stabil terhadap rencatan enzim yang terdapat di usus. Sintesis blok asas untuk C-glikosida telah dijalankan dalam projek ini. Terdapat beberapa cara untuk mengakses C-glikosida seperti *sugar halides, glycans*. Satu cara yang dapat memperolehi C-glikosida adalah melalui pengasetilan galaktosa dengan refluks atau di suhu bilik. Galaktosa yang mempunyai kumpulan asetil telah disintesiskan mengunakan 3 pemangkin iaitu piridina, zink chlorida dan natrium asetat. Penghasilan yang terbaik (>70%) didapati menggunakan piridina dan natrium asetat yang memberi campuran anomer-anomer α and β. Campuran ini amat susah diasingkan, dan ianya telah dicirikan dengan TLC, proton NMR dan IR.

C-glycosides can be an important bioisostere to O-glycosides and are stable to enyzmatic degradation in intestines. Synthesis of building blocks for C-glycosides have been attempted in this project. There are various ways to access C-glycosides e.g. sugar halides, glycans. One accessible way is via acetylation of galactoside under reflux or at room temperature. Acetyl-protected galactose was synthesised using 3 catalysts i.e. pyridine, zinc chloride and sodium acetate. Best yields (>70%) were obtained using pyridine and sodium acetate giving a mixture of α- and β-anomers. This mixture was difficult to separate, and they have been characterised using TLC, proton NMR and IR.

7. Sila sediakan laporan teknikal lengkap yang menerangkan keseluruhan projek ini.

[Sila gunakan kertas berasingan]
Applicant are required to prepare a Comprehensive Technical Report explaning the project.
(This report must be appended separately)
As attached.

Senaraikan kata kunci yang mencerminkan penyelidikan anda:
List the key words that reflects your research:

Bahasa Malaysia: C-glikosida, Pengasetilan, Sintesis

Bahasa Inggeris: C-glycoside, Acetylation, Synthesis

8. Output dan Faedah Projek

Output and Benefits of Project

(a) * **Penerbitan Jurnal**
Publication of Journals
(Sila nyatakan jenis, tajuk, pengarang/editor, tahun terbitan dan di mana telah diterbit/diserahkan)
(State type, title, author/editor, publication year and where it has been published/submitted)

Nil.

(b) **Faedah-faedah lain seperti perkembangan produk, pengkomersialan produk/pendaftaran paten atau impak kepada dasar dan masyarakat.**
State other benefits such as product development, product commercialisation/patent registration or impact on source and society.

Nil

* Sila berikan salinan/*Kindly provide copies*

(c) **Latihan Sumber Manusia**
Training in Human Resources

i) Pelajar Sarjana:
(Perincikan nama, ijazah dan status)

Muthanna F. Abdul Karim, Masters, P-FM005/06
(5 months, then changed to Pharm. Tech supervisor)

ii) Lain-lain:
Siti Marina Mohd Maidin
(Research Assistant, worked 5 months on Part II)

9. Peralatan yang Telah Dibeli:
Equipment that has been purchased

Nil.

Tandatangan Penyelidik
Signature of Researcher

2/3/12

Tarikh
Date

Komen Jawatankuasa Penyelidikan Pusat Pengajian/Pusat
Comments by the Research Committees of Schools/Centres

Kurang memuaskan kerana masaalah tidak ada student yang mahu menceburi bidang sintisis.

Mohd

Professor Mohd. Zaini Bin Asmawi
Lecturer
Pharmacology Discipline
School of Pharmaceutical Sciences
Universiti Sains Malaysia
11800 USM, Penang
Malaysia

2/3/2012

TANDATANGAN PENGERUSI
JAWATANKUASA PENYELIDIKAN
PUSAT PENGAJIAN/PUSAT
Signature of Chairman
[Research Committee of School/Centre]

Tarikh
Date

Short-term grant
304/PFARMASI/637046

Final report

Dr Aisyah Saad Abdul Rahim

Dr. Aisyah Saad Abdul Rahim
Lecturer in Pharm. Chemistry
School of Pharmaceutical Sciences
Universiti Sains Malaysia
11800 Minden, Penang

PART I
Project progress until May 2007

Submitted as 1-year report to Pelantar Sains Hayat

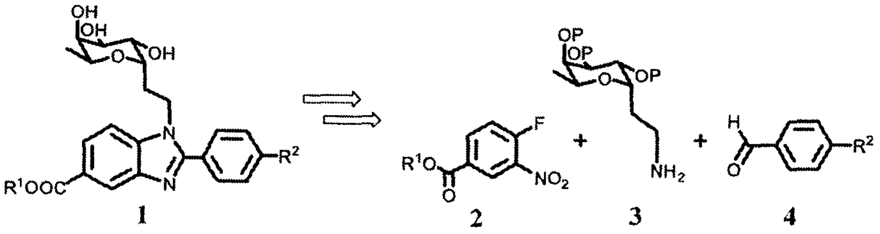
This is a short report of what happened for the past one year.

The account for the above short term grant was opened in August 2006, even though, on paper, the start date of the grant is 14 May 2006. There was a time lapse of almost three months before procurement of chemicals could take place.

Procurement of chemicals (in August 2006)

Procurement of chemicals and consumables for the synthesis of glycosyl-substituted benzimidazoles started sometime in August 2006. During this time, I learned that the delivery of chemicals were not that reliable – commonly used chemicals took about three weeks to come in; some took longer six weeks and one or two would not get delivered at all. This is the main problem in Malaysia since we don't have big chemical industries that produce fine chemicals. We rely heavily on fine chemicals imported from Europe, Japan or Australia.

During the investigation of the synthetic routes of glycosyl-substituted benzimidazoles, I figured out a quicker way to access the target compounds. This modified route requires the use a chemical called allylamine at the second step of the synthesis. This is the critical ingredient before I could cyclise the o-phenylenediamine to form the benzimidazole ring. After several inquiries to Sigma-Aldrich during the chemical procurement period, I was informed that allylamine is air-forbidden due to its explosive nature. The only way to bring allylamine in is by shipping it – which would take six months. I requested that Sigma-Aldrich to ship the chemical, but until now they could not identify a shipping company that would be willing to take the risk.



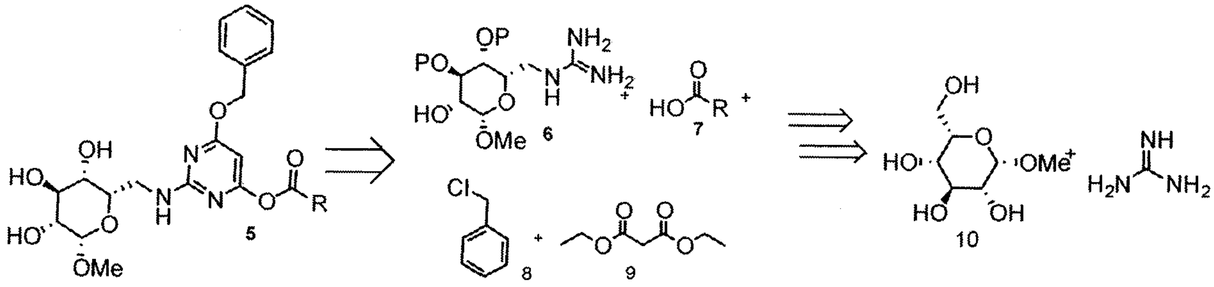
P : protecting group

Back to the drawing board (November 2006)

At this time, it was already almost at the end of the 'theoretical' 6 months (around November 2006). Realising that the situtation above wouldn't change for the better, I performed more literature search – looking for a synthetic route which is do-able in Malaysia.

Honestly, the literature search confirmed my biggest fear i.e. any other routes would take longer and more tedious. This is mainly due to the incorporation of the protected glycosyl moiety which requires extra care during its handling as it is labile to acids and bases.

Re-thinking of different glycosyl-modified heterocycles led me to a new do-able route (Figure 2). Thus, instead of glycosyl-substituted benzimidazole, the new target would be a C-glycosyl modified pyrimidine. It quite similar to the previous benzimidazole target as it retains the three hydroxyl groups on the glycoside that are essential for binding. Additionally, glucose is inexpensive than L-fucose. The pyrimidine group has two additional handles to which different groups could be attached to study its structure-activity relationship. The presence of hydroxyl handles also are attractive since they amenable for small library construction based on solid phase synthesis.



The new project assigned to a Master student (Jan 2007)

Around this time (end of Dec 2006), I agreed to supervise a Masters student, Muthanna F. Abdul Karim, P-FM005/06(R), whose sponsor directed him to change his research field from Pharm. Technology to Pharm. Chemistry. I assigned him the new project, during which he spent the first three months on background reading. I thought he needed to brush up his knowledge in organic chemistry since the last time he did it was in his undergraduate days. During the three months, orders for chemicals were put in to Aldrich – and indeed, they all arrived in good time for Muthanna to start his labwork.

Muthanna started his labwork this first week of April 2007 – he synthesised the methyl-*O*-glucoside, *via* the Fischer glycosidation method. The glucoside unfortunately appeared as α- and β-anomers. The proton NMR of the anomeric mixture was quite uninterpretable, thus we decided to isolate one of the anomers *via* recrystallisation method. It is quite usual that one anomer would crystalise out in preference to the other. Muthanna attempted different crystallisation method, but still couldn't isolate one of the anomers. He then tried the isolation by TLC by varying different mobile phases; this also failed to separate the anomeric mixture.

End of the Master student supervision

I think at this time, into his second month in the lab, he was quite demoralised because he couldn't get good results as quickly as he had expected. Also, it is a quite steep learning curve to climb in synthetic medicinal chemistry. According to Muthanna, he could not bring himself to love the chemistry field. He thought he might be better off if he was to return to Pharm. Technology. I had to let me go. This took place last week on 25th May 2007.

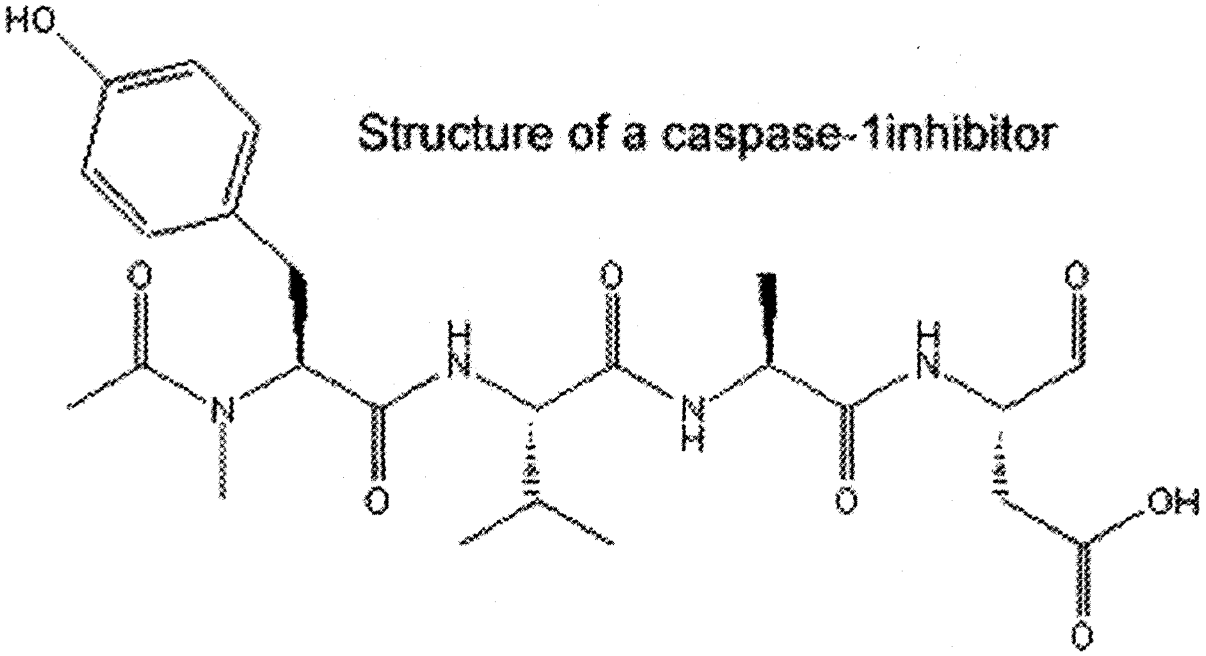
In short, the project has taken a small step forward, after taking several steps back. This is what happened so far – one year into this project funded by USM short term grant.

PART II

C-glycoamino acids: Synthesis of the building blocks

PSEUDO- PEPTIDE

Pseudo peptide or artificial peptide is very important because peptides are used extensively in nature for a variety of signaling functions in both unicellular and multicelullar organisms including man. Pseudo-peptides that are polyamides composed of amino acids other than α-amino acids which include for instance peptoids, β-amino acid oligomers and also compounds such as peptide nucleic acids and DNA binding polyamides. For example, many peptide hormones and analogues short peptides exert their action by binding to membrane receptors. Peptides also show some biological activities in the form of nerve toxins, antibacterial agents or general cell toxins.



Structure of a caspase-1inhibitor

However, most natural peptides are composed of L-form α-amino acids and because of the ubiquitous prevalence of peptidase they have limited biostability and consequently low bioavailability. Thus, a novel field of peptidomimetics has emerged in drug discovery, in attempts to design non-peptide compounds mimicking the pharmacophore and thus the activity of the original peptide. [1]

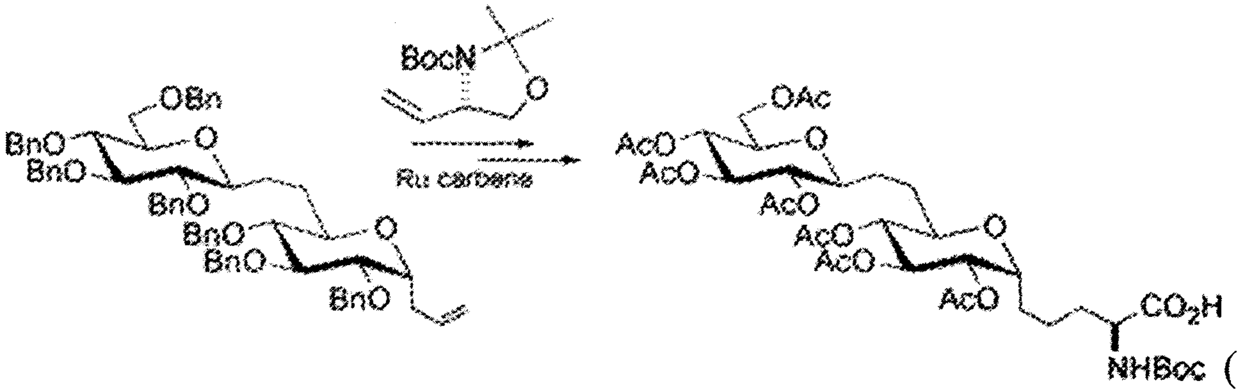
Peptide aldehyde, an example of pseudo peptide is a common feature of enzyme inhibitors, for example HIV protease inhibitors, or caspase inhibitors (see diagram). Peptide aldehydes are also used in chemoselective ligation, for example in the production of peptide dendrimers. They are also used in the formation of reduced peptide bonds (pseudo peptide bond peptidomimetics).

PREVIOUS RESEARCH

Cross metathesis has emerged as an extraordinarily powerful method for fusing highly functionalized reaction partners. The functional group tolerance of this method is particularly attractive for the present application of carbohydrate fusion to amino acids.

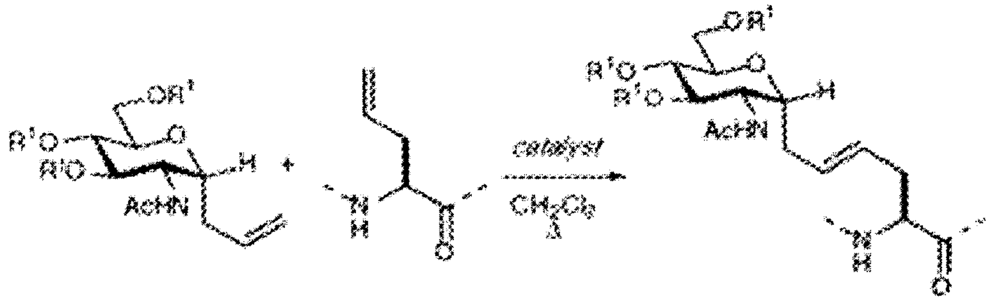
Previous synthetic work has explored a wide variety of C-C bond forming reactions for the preparation of C-glycosyl amino acids, and has been reviewed by Dondoni.[2] Since that review there have been several reports furthering the development the development of concise and broadly applicable routes to C-glycosyl amino acids utilizing the Ramberg-Bäcklund rearrangement [3], acetylide couplings [4], homochiral enolate additions [5], and an asymmetric Strecker reaction [6].

The availability of the second generation Grubbs catalyst [7] has prompted the application of its use for elaboration of the O-glycosyl amino acids [8] and for the construction of C-glycosides. [9] Recently the ruthenium-catalyzed olefin cross- metathesis has been employed for the preparation of C-glycosyl amino acids. Dondoni made use of benzyl-protected C-alkenyl glycosides and affected cross-metathesis with a vinyl oxazolidine, derived from Garner's aldehyde, yielding products with 2-4 carbons linking the anomeric position to the glycinyl moiety. (Scheme 1) [10]



(1)

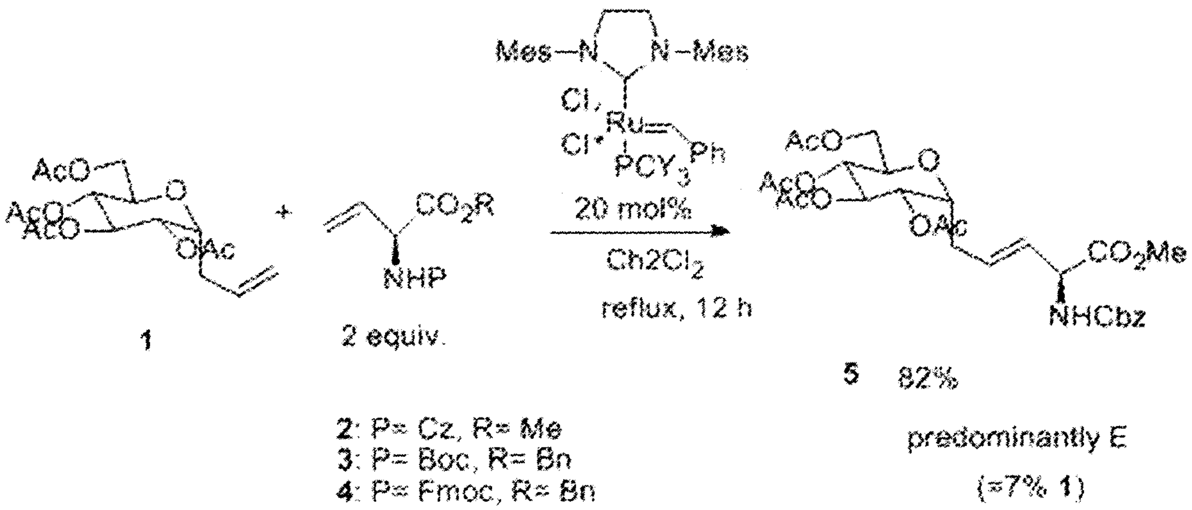
Mc Garvey has described the success of the cross-metathesis approach between C- alkenyl glycosides and L-allyl gycine to yield a 3 or 4 carbon linkage. (Scheme 2)[11] Recently, Mc Garvey has done an investigation on the structural features directing olefin cross-metathesis to afford C-glycoamino acids. (Scheme 3)[12]



(2)

Ernest G. Nolen has employed Grubbs second generation ruthenium catalyst for the cross metathesis between stable α- and β-C-allyl glycosides and suitably protected L-vinyl glycines to furnish olefinic products in 57-94% yields. (Scheme 4) [13]

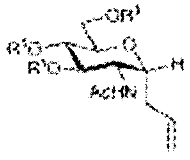
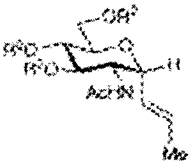
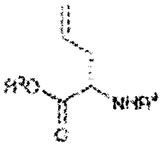
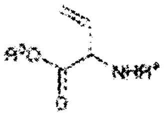
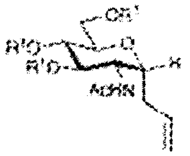
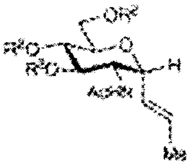
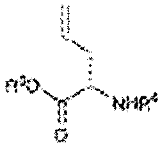
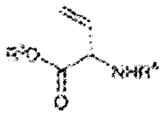
Roy and co-workers have used a selective cross-metathesis reaction as a key C-C bond forming step in the preparation of co-called "molecular asterisk". An initial cross metathesis reaction between peracetylated α-D-allylgalactopyranoside with protected amine catalyzed by second generation Grubbs catalyst afforded cross-product in moderate yield with a complete E selectivity. (Scheme 5) [14]



(4)

This research

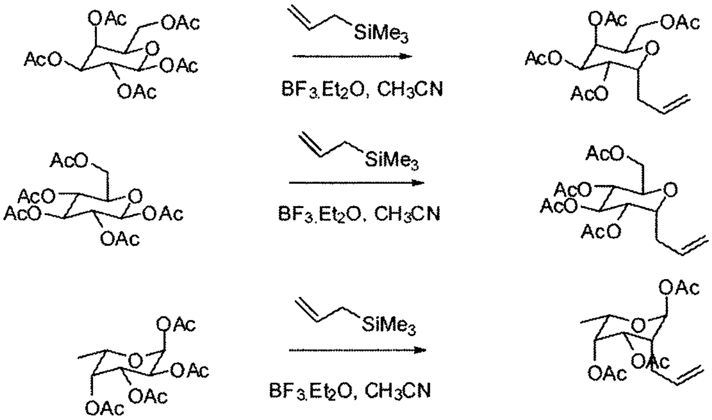
In this investigation studies, we are going to look at the interaction between stable α-C- allyl glycosides and suitably protected L-vinyl glycines by using second generation Grubbs catalyst. The goal of these studies is to gain insight to what structural features favoured the desired course of the reaction in an effort to minimize the unwanted self- metathesis. Besides that, the most crucial part is cross metathesis between Dmc protected L-vinyl glycine and α-C-allyl glycosides. Originally, the use of Nα-(4,4-dimethyl-2,6- dioxocyclohexylidenemethylene) (Dmc) as an orthogonal amino protecting group for solid-phase peptide synthesis became redundant as it was superseded by its methyl derivative Dde due to the latter's improved stability towards the Fmoc deprotection conditions. However the former's stability to hydrogenolysis and labilty towards piperidine would be an asset.[15]

	 A	 B	 C	 D	 E
 A	1a (78%) 1b (81%)	2a (84%) 2b (82%) 2c (80%)	NA	6a (74%) 6b (78%) 6c (70%) 6d (60%) 6e (70%)	8 (90%)
 B	2a (84%) 2b (82%) 2c (80%)	3 (trace) + 2b (47%)	NA	7a (82%) 7b (77%) 7c (69%) 7d (77%) 7e (62%)	9 (none)
 C	NA	NA	3 (none)	7e (77%)	9 (none)
 D	6a (74%) 6b (78%) 6c (70%) 6d (60%) 6e (70%)	7a (82%) 7b (77%) 7c (69%) 7d (77%) 7e (62%)	7e (77%)	4a (76%) 4b (86%)	NA
 E	8 (80%)	9 (none)	9 (none)	NA	5 (<5%)

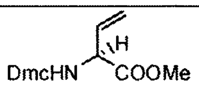
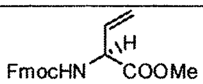
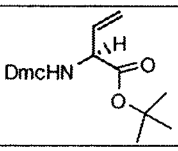
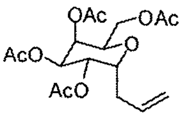
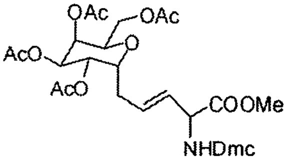
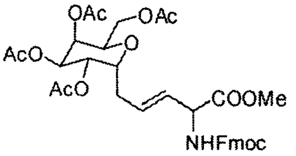
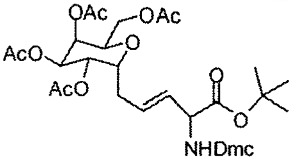
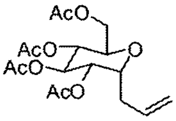
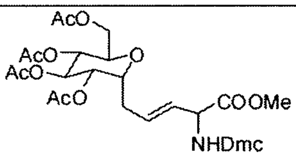
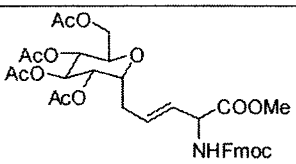
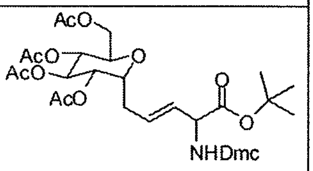
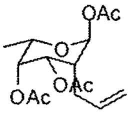
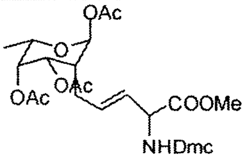
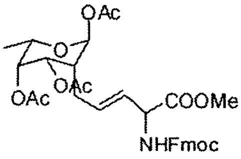
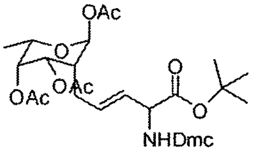
(3)

Overall synthesis steps can be divided into 4 parts as follows: Part A: Acetylation of D (+)-galactose and L(+)- fucose.

Part C: Allylation of peracetylated galactose, glucose, and fucose



Part D: Cross metathesis investigations

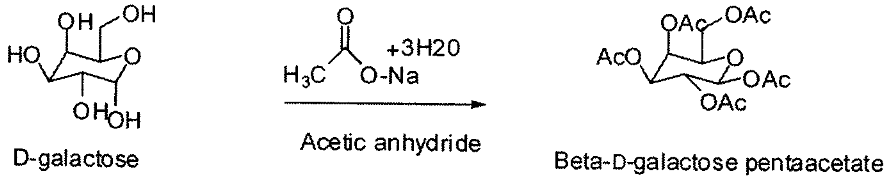
			
			
			
			

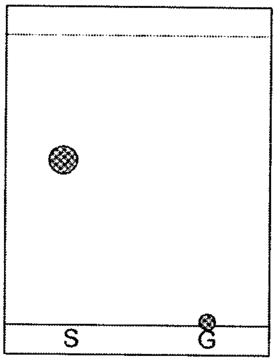
Reagents and conditions: (i) paraformaldeyhde, TsOH, toluene, reflux using dean stark apparatus; (ii) Na, MeOH dried; (iii) Pb(OAc)4, Cu(OAc)2, H2O, toluene, N2 gas; (iv) 6N HCl; (v) DMMD, EtOH ; (vi) Fmoc-Cl, Na2CO3, H2O/ dioxane; (vii) tert-butyl trichloroacetimidate, DMMD, EtOH

Part A: Preparation of peracetylated D(+)- galactose

In this part, we will discuss four ways of synthesizing D(+)-galactose pentaacetate.

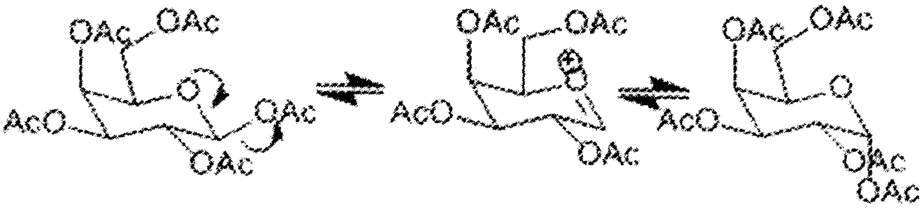
Preparation of D(+)-Galactose Pentaacetate Using Sodium Acetate.

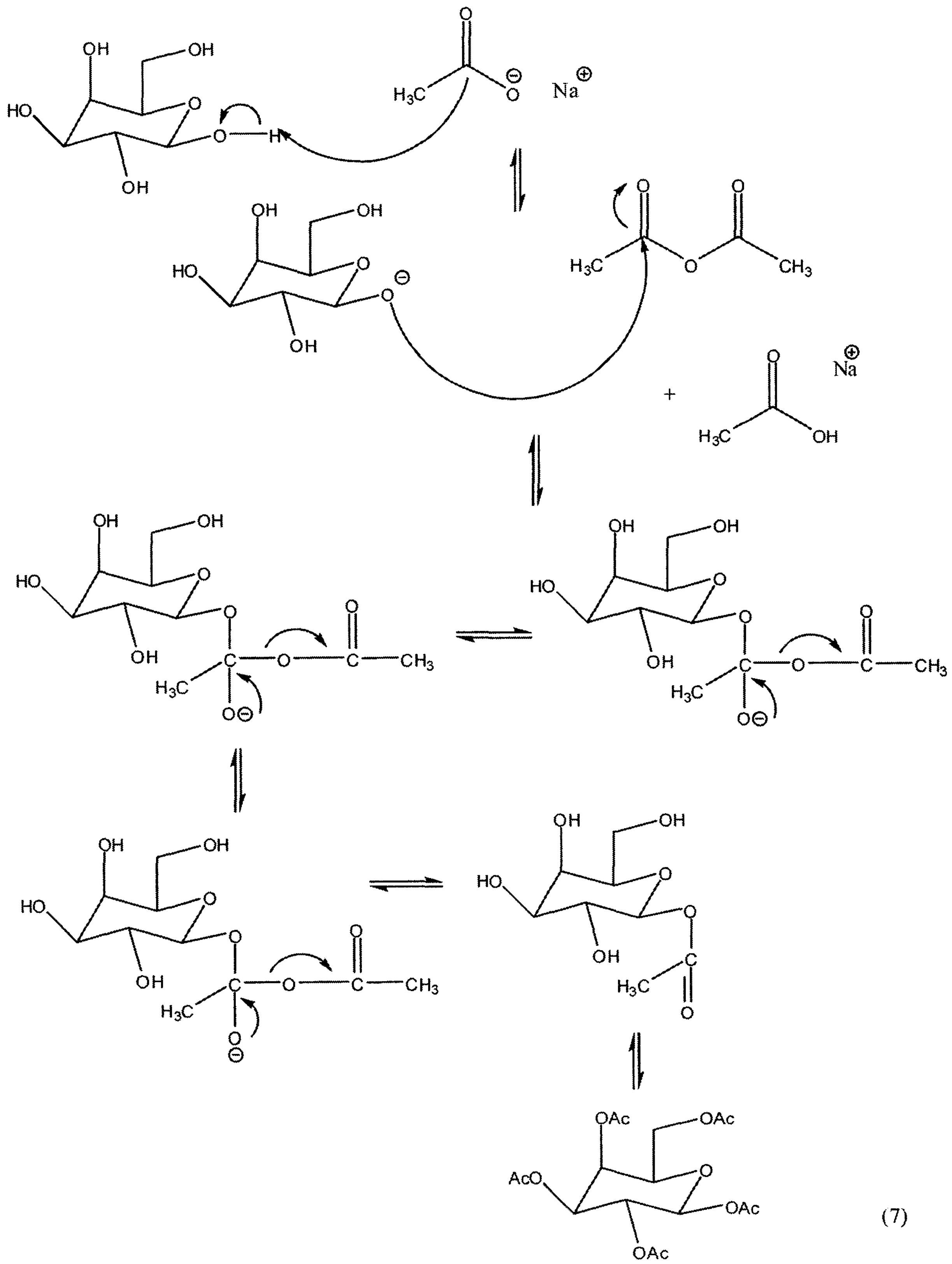




S: product ; G: galactose

Acetylation of D(+)-galactose with acetic anhydride and sodium acetate will only gives one anomer which is β-D(+)-galactose pentaacetate. Sodium acetate is a base catalyst. The anomeric acetate is more reactive than the other acetate groups. β-anomer is a kinetically controlled product, being initially formed from the more rapid acetylation of the equatorial hydroxyl group at C-1 of β-D-galactose pentaacetate. In this reaction, the resonance-stabilized carbocation formation do not happen (Scheme 6).

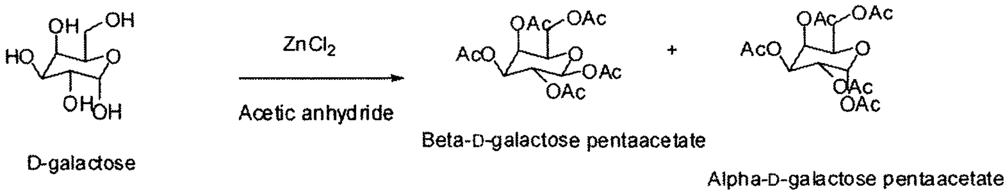

(6)

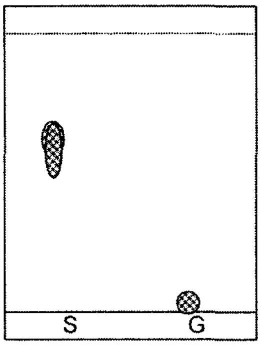


(7)

Scheme 7: Proposed mechanism of acetylation galactose pentaacetate using sodium acetate.

Preparation of D(+)-Galactose Pentaacetate Using Zinc Chloride

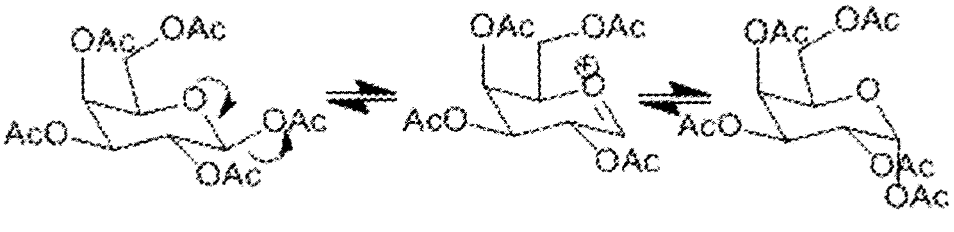




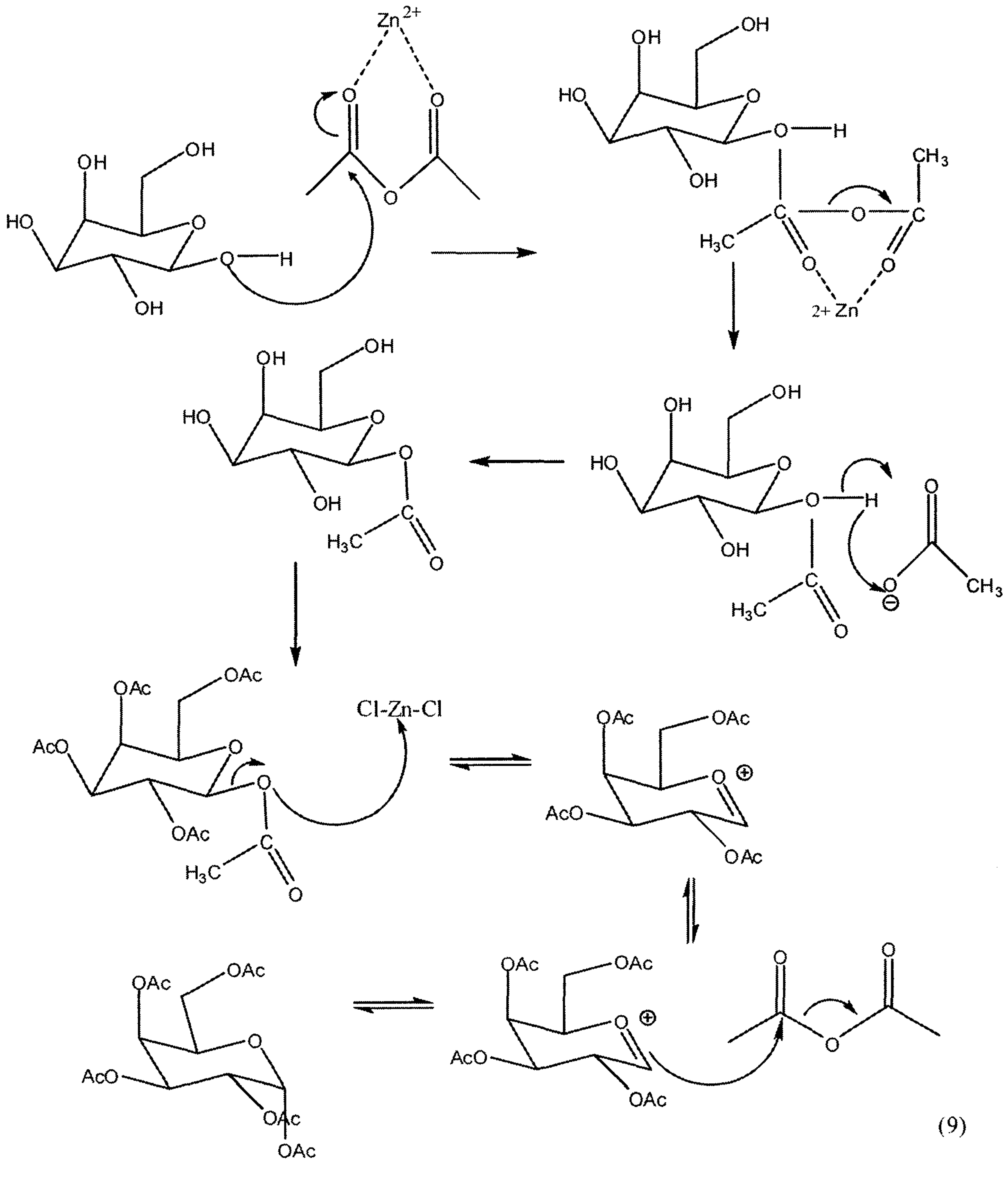
S: product ; G: galactose

Crystallization of syrup with hot chloroform gave small colourless crystal, however the crystals melt into syrup the next day. By using zinc chloride as a catalyst to produce α- anomer of galactose pentaacetate failed when the product contains both α-anomer and β- anomer with ratio 1:2. This might be because the catalyst has reacted with moisture in the room before it could react with galactose and this might left only a minimum of zinc chloride which is still reactive to catalyze the reaction for 1 hour.

Zinc chloride which is an acidic catalyst catalyzed loss of acateate ion from the anomeric carbon, leaving a resonance-stabilized carbocation. Attack by acetate from the bottom will produced the α-anomer which in this case happens to be thermodynamically stable. (Scheme 8)

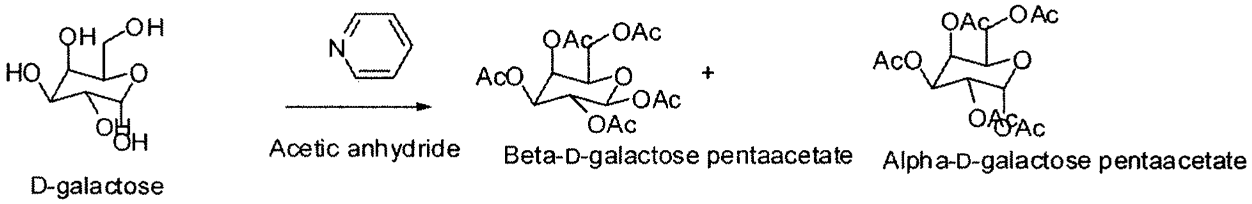


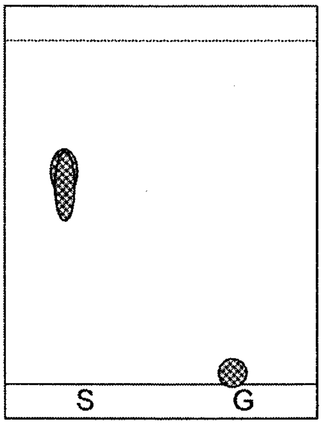
(8)



Scheme 9: Proposed mechanism of acetylation galactose pentaacetate using zinc chloride.

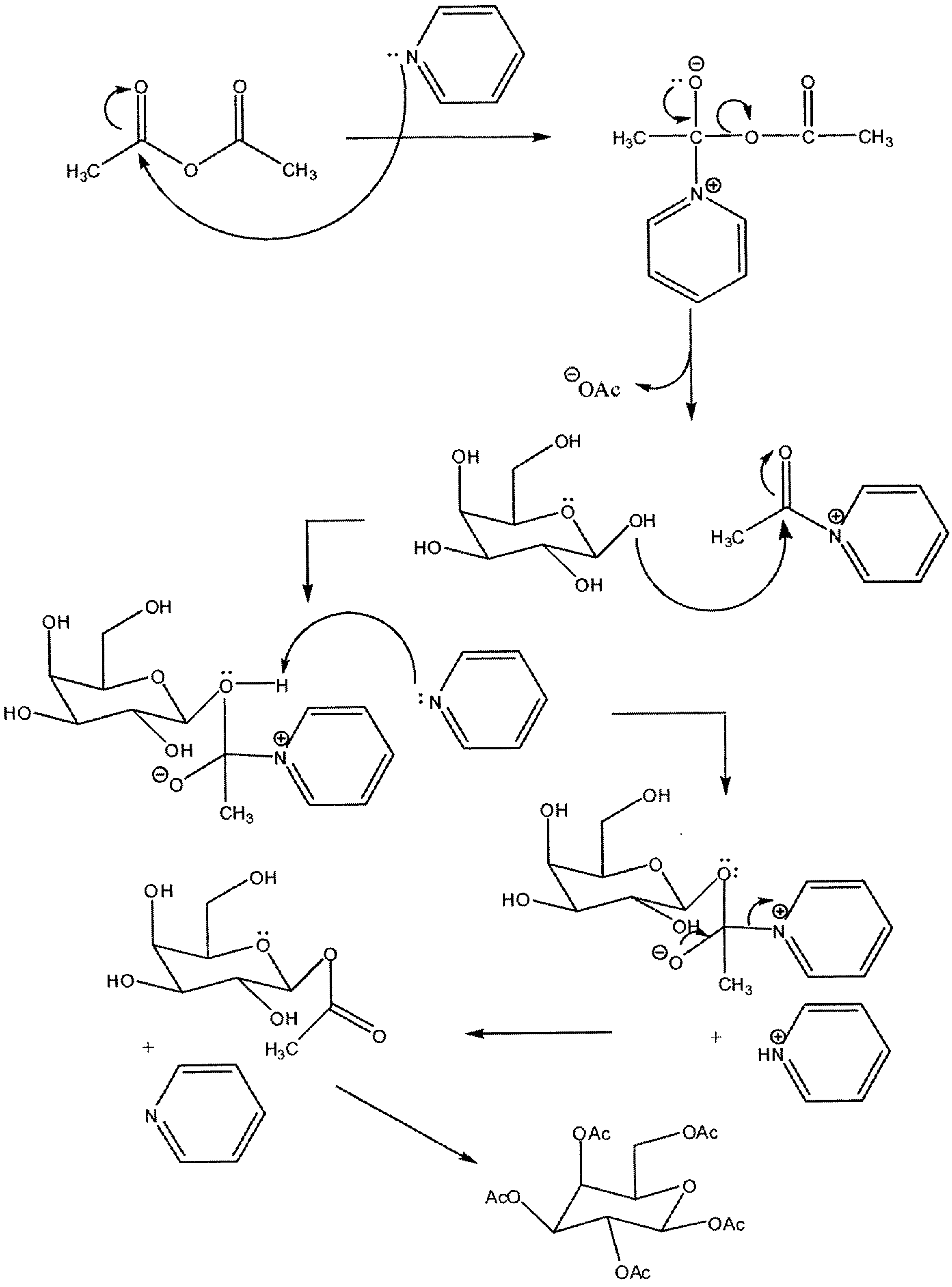
Preparation of D(+)-Galactose Pentaacetate Using Pyridine





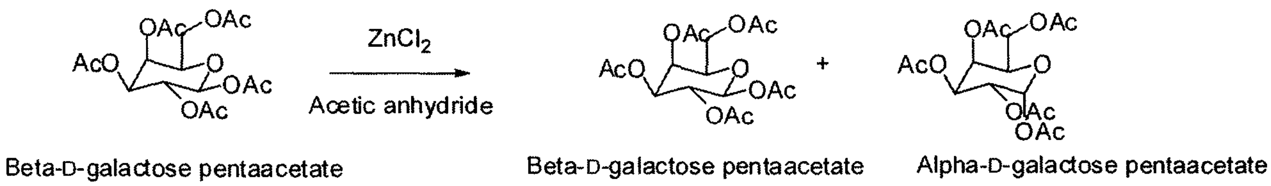
S: product ; G: galactose

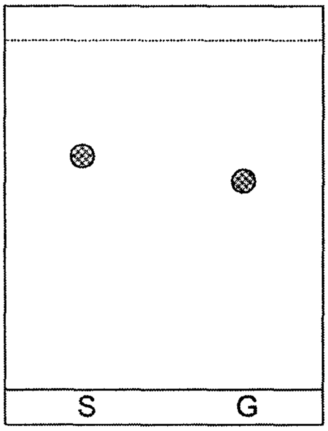
Colourless syrup which turn into white, damp powder at the bottom of the flask after left it for 24 hours. The ratio between α-anomer and β-anomer is 1:2. Pyridine acts as nucleophilic catalyst (Scheme 10)



Scheme 10: Proposed mechanism of acetylation galactose pentaacetate using pyridine.

Conversion of β-D- to α-D-anomers in Fully acetylated Sugars; α-D- Galactopyranose Pentaacetate



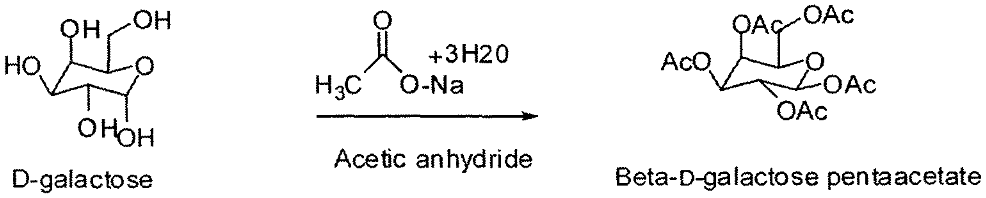


S: product ; G: galactose

Crystallization of syrup with hot chloroform gave small colourless crystal, however the crystals melt into syrup the next day same case with SMA2. Conversion of β-anomer to α-anomer in this case produced a mixture of both with ration 2:9.

PREPARATION OF PERACETYLATED D(+)-GALACTOSE

Preparation of D(+)-Galactose Pentaacetate Using Sodium Acetate.



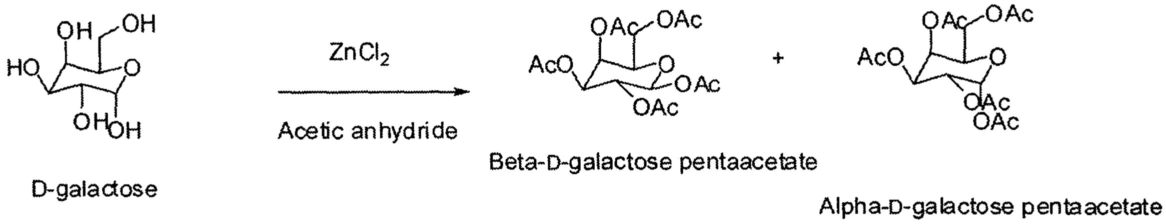
To a 50 mL round bottom flask, add D-galactose (1g, 5.6 mmol) and sodium acetate (0.8 g, 5.88 mmol). Attach a reflux condenser and add 5 mL acetic anhydride to the reaction mixture. Heat the reaction mixture in a hot water bath at 900C for 2 hours. Cool the reaction to room temperature and pour the contents of the 50 mL round bottom flask very slowly into a beaker containing 100 mL of ice water. Collect the crude crystals of beta-D-galactose pentaacetate by suction filtration. Recrystallize the product with hot methanol to afford white powder (1.7635 g, 80.73%). [16]

Rf (Hexane: Ethyl Acetate, 4:3) 0.60

vmaz 1739 cm-1 (C=O), 1225 cm-1 (C-O-C)

δH (300 MHz) 2.01 (3H,s,OAc), 2.07 (6H, s, OAc), 2.14 (3H, s, OAc), 2.19 (3H, s, OAc), 4.0- 4.22 (3H,m, C-5, C-6), 5.07 (1H, dd, C-4, J= 2.486 Hz , 7.91 Hz), 5.32 (1H, t, C-3, J= 9.7 Hz), 5.44 (1H,d, C-2, J= 3.27 Hz), 5.70 (1H, d, C-1, J= 8.29 Hz)

Preparation of D(+)-Galactose Pentaacetate Using Zinc Chloride

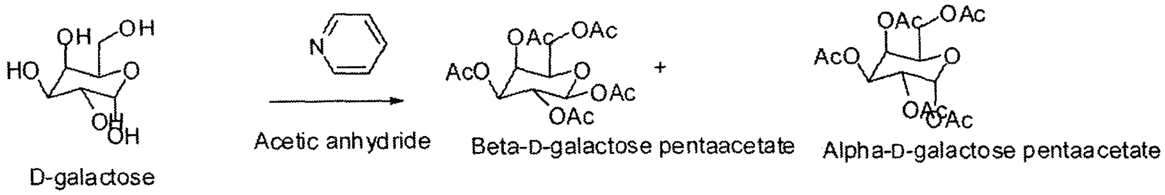


D-galactose (1 g, 5.6 mmol) is dissolved in 5 mL acetic anhydride containing zinc chloride (0.2 g, 1.47 mmol) and heated for 1 hour on a boiling steam bath. The mixture is then poured into 100 mL of ice and water and extracted with chloroform. The chloroform solution is washed with 50 mL water twice, 50 mL sodium hydrogen carbonate solution twice, and with 50 mL water once. After that, the organic part is dried with anhydrous magnesium sulfate and evaporated under reduced pressure to a syrup. Discolourization of the yellow colour by using flash chromatography will give a colourless syrup (1.5306 g, 70 %). [16]

α: β (1:2)
Rf (Hexane: Ethyl Acetate, 4:3) 0.60
vmaz 1751 cm-1 (C=O), 1225 cm-1 (C-O-C)

δH (300 MHz) 2.01 (3H,s,OAc), 2.03 (3H, s, OAc), 2.05 (3H, s, OAc), 2.17 (6H, s, OAc), 4.1- 4.39 (3H,m, C-5,C-6), 5.07- 5.10(1H, m, C-4), 5.32- 5.34 (1H,m, C-3), 5.43 (1H, d, C-2, J= 3.38 Hz), 5.69 (1H, d, C-1, J= 8.3 Hz, β-anomer), 6.32 (1H,d, C-1, J= 4.6 Hz, α- anomer)

Preparation of D(+)-Galactose Pentaacetate Using Pyridine

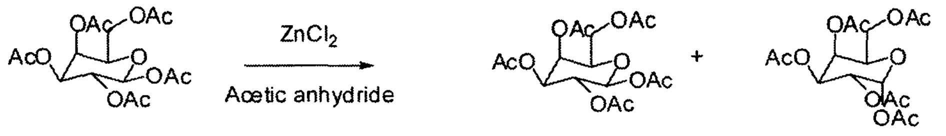


D- Galactose (1g, 5.6 mmol) was added slowly to an iced cold mixture of 5 mL acetic anhydride and 5 mL pyridine. The mixture was allowed to slowly warm to room temperature and stirred over night. The solvent was removed in vucou and dissolved in dichloromethane. The mixture was poured into 1M hydrochloric acid (50 mL) and extracted with dichloromethane (50 mL). The extract was washed with saturated aqueous sodium hydrogen carbonate (2 x 50 mL) and water (2 x 50 mL). The organic extract was separate and dried over anhydrous magnesium sulfate. Then, the solvent was removed under pressure. Purification of the yellow colour by using flash chromatography gave a colourless syrup (1.80 g, 83%). [17]

α: β (1:2)
Rf (Hexane: Ethyl Acetate, 4:3) 0.60
vmaz 1751 cm-1 (C=O), 1225 cm-1 (C-O-C)

δH (300 MHz) 2.01 (3H,s,OAc), 2.03 (3H, s, OAc), 2.05 (3H, s, OAc), 2.17 (6H, s, OAc), 4.01- 4.40 (3H,m, C-5,C-6), 5.06-5.11 (1H, m, C-4), 5.33-5.39 (1H,m, C-3), 5.43 (1H, d, C-2, J= 3.38 Hz), 5.65 (1H, d, C-1, J= 8.29 Hz, β-anomer), 6.32 (1H,d, C-1, J= 4.68 Hz, α-anomer)

Conversion of β-D- to α-D-anomers in Fully acetylated Sugars; α-D-Galactose Pentaacetate



Beta-D-galactose pentaacetate Beta-D-galactose pentaacetate Alpha-D-galactose pentaacetate

β-D-Galactose pentaacetate (500 mg, 1.28 mmol) is dissolved in 3 mL acetic anhydride containing zinc chloride (0.2 g, 1.47 mmol) and heated for 15 minutes on a boiling steam bath. The mixture is then poured into 100 mL of ice and water and extracted with chloroform. The chloroform solution is washed with 50 mL water twice , 50 mL sodium hydrogen carbonate solution twice, and with 50 mL water once. After that, the organic part is dried with anhydrous sodium sulfate and evaporated under reduced pressure to a syrup. Discolourization of the yellow colour by using flash chromatography will give a colourless syrup (0.1683 g, 33.67 %) [18]

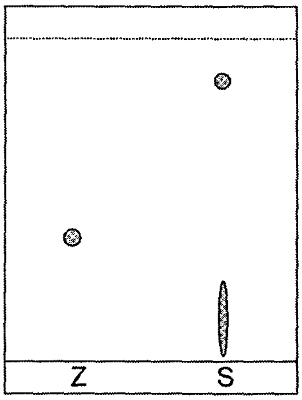
α: β (9:2)
Rf (Hexane: Ethyl Acetate, 4:3) 0.60

vmaz 1751 cm-1 (C=O), 1227 cm-1 (C-O-C)

δH (300 MHz) 1.96 (3H,s,OAc), 1.98 (3H, s, OAc), 2.00 (3H, s, OAc), 2.12 (3H, s, OAc), 2.18 (3H,s,OAc), 4.01- 4.40 (2H,m, C-5,C-6), 5.02 (1H, dd, C-4, J=3.42, 10 Hz) , 5.24- 5.32 (1H, m,C-3), 5.37 (1H, d, C-2, J= 3.38 Hz), 5.65 (1H, d, C-1, J= 8.29 Hz, β- anomer), 6.32 (1H,d, C-1, J= 2.44 Hz, α-anomer)

Synthesis of protected L-vinyl glycine

Synthesis of N-Cbz-5-oxo-4-oxazolidinine propionic acid.



Z= N-cbz-glutamic acid ; S= product

A mixture of commercially available N-Cbz-glumatic acid (0.2, 0.711 mmol), paraformaldehyde (0.035 g, 1.165 mmol), p-toulene sulfonic acid monohydrate (0.007g, 0.0368 mmol) , and toluene(25 mL) was refluxed using a Dean-Stark apparatus for the azeotropic removal of water. Reflux for 7 hours. Toluene solution was then decanted from brown residue and wash with water (2x 50 mL) and 5% NaHCO3. The combined ice-cooled aqueous layers were acidified with 6M HCl and then extracted with EtOAc (3x 20 mL). Dried over MgSO4 and concentrated in vacuo to yield a sticky pale yellow syrup. [19]

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Final statement for S/term grant 637046

Aisyah Saad [aisyahsaad@gmail.com]
Sent: Wednesday, March 21, 2012 4:44 PM
To: Nur Ruzanna Jaapar

Salam Zanna,

This is the last financial statement for grant 304/PFARMASI/637046 that I have in my keeps.
Thanks.

Aisyah

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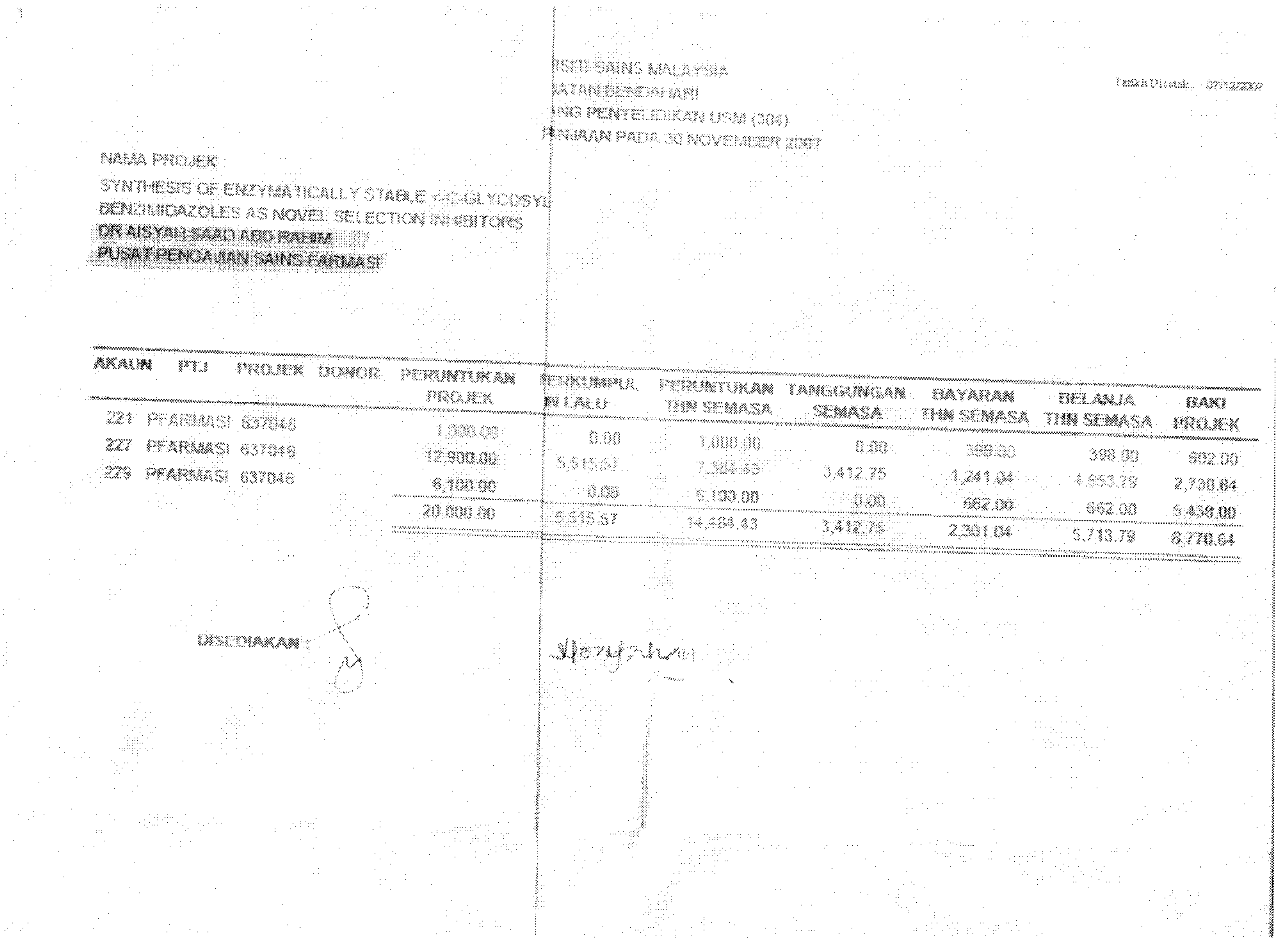

RSITI SAINS MALAYSIA
BATAN BENDAHARI
NG PENYELIDIKAN USM (304)
ANJAAN PADA 30 NOVEMBER 2007

Tarikh Dicetak : 07/12/2007

NAMA PROJEK :
SYNTHESIS OF ENZYMATICALLY STABLE [illegible]-C-GLYCOSYL
BENZIMIDAZOLES AS NOVEL SELECTION INHIBITORS
DR AISYAH SAAD ABD RAHIM
PUSAT PENGAJIAN SAINS FARMASI

AKAUN	PTJ	PROJEK	DONOR	PERUNTUKAN PROJEK	TERKUMPUL N LALU	PERUNTUKAN THN SEMASA	TANGGUNGAN SEMASA	BAYARAN THN SEMASA	BELANJA THN SEMASA	BAKI PROJEK
221	PFARMASI	637046		1,000.00	0.00	1,000.00	0.00	398.00	398.00	602.00
227	PFARMASI	637046		12,900.00	5,515.57	7,384.43	3,412.75	1,241.04	4,653.79	2,730.64
229	PFARMASI	637046		6,100.00	0.00	6,100.00	0.00	662.00	662.00	5,438.00
				20,000.00	5,515.57	14,484.43	3,412.75	2,301.04	5,713.79	8,770.64

DISEDIAKAN :