UNIVERSITI SAINS MALAYSIA

Pejabat Pengurusan Dan Kreativiti Penyelidikan
Research Creativity and Management Office

Canselori,
Universiti Sains Malaysia
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: www.research.usm.my

No. Fail : F0409
Tarikh : 12 Disember 2011

Dr. Aisyah Saad Abdul Rahim
Pusat Pengajian Sains Farmasi
Universiti Sains Malaysia

Puan,

LAPORAN AKHIR SKIM GERAN PENYELIDIKAN FUNDAMENTAL (FRGS)
Tajuk Projek : Investigating into the Expedient Construction of Naturally Occuring Glycopeptodes Containing a -O-Fucoside Motif
No. Akaun : 203/PFARMASI/671159

Dengan hormatnya perkara di atas dirujuk.

2. Terlebih dahulu saya ucapkan ribuan terima kasih di atas satu salinan laporan akhir untuk projek penyelidikan seperti tajuk di atas.

3. Adalah dimaklumkan walaupun projek ini telah selesai, kerjasama Jabatan Bendahari dipohon untuk menguruskan penutupan akaun projek pada selewat-lewatnya **31 Disember 2011**. Tempoh ini bertujuan untuk menyelesaikan semua urusan tuntutan dan bayaran yang telah dibelanjakan di dalam tempoh projek. Walau bagaimanapun, puan dinasihatkan supaya tidak mengeluarkan borang-borang pesanan baru di dalam tempoh ini.

4. Selanjutnya sila ambil perhatian terhadap perkara-perkara berikut sekiranya berkaitan:

(i) Semua penerbitan harus merakamkan penghargaan kepada **Skim Geran Penyelidikan Fundamental (FRGS)** dan puan dipohon mengemukakan satu salinan ke Pejabat ini.

(ii) Bahagian Penyelidikan & Inovasi boleh/akan mengagihkan semula peralatan yang telah dibeli menggunakan peruntukan geran ini seandainya terdapat penyelidik lain yang memerlukan peralatan tersebut.

5. Akhir sekali, tahniah di atas usaha dan kejayaan pihak puan dapat menyelesaikan projek ini dengan jayanya.

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"
'Memastikan Kelestarian Hari Esok'

Yang menjalankan tugas,

HAH, HAR, ISM

(AMRA OTHMAN)
Penolong Pendaftar
Unit Pengurusan Geran & Kontrak

LAPORAN AKHIR SKIM GERAN PENYELIDIKAN FUNDAMENTAL (FRGS)
Tajuk Projek : Investigating into the Expedient Construction of Naturally Occuring Glycopeptodes Containing a -O-Fucoside Motif
No. Akaun : 203/PFARMASI/671159

s.k. Dekan Penyelidikan
Pelantar Sains Fundamental
Pejabat Pelantar Penyelidikan
Universiti Sains Malaysia

Dekan
Pusat Pengajian Sains Farmasi
Universiti Sains Malaysia

Timbalan Dekan
(Ijazah Tinggi & Penyelidikan)
Pusat Pengajian Sains Farmasi
Universiti Sains Malaysia

Ketua Pustakawan
Perpustakaan Hamzah Sendut
Universiti Sains Malaysia

} Disampaikan satu salinan laporan akhir projek untuk simpanan Perpustakaan

Penolong Bendahari Kanan
Unit Kumpulan Wang Penyelidikan
Jabatan Bendahari
Universiti Sains Malaysia

Pegawai Sains
Pelantar Sains Fundamental
Pejabat Pelantar Penyelidikan
Universiti Sains Malaysia

} Mohon kerjasama pihak puan untuk menguruskan penutupan akaun projek selewat-lewatnya pada **31 Disember 2011** dan mohon kemukakan satu salinan penyata kewangan terakhir ke Pejabat ini untuk tujuan rekod

FINAL REPORT
FUNDAMENTAL RESEARCH GRANT SCHEME (FRGS)

Laporan Akhir Skim Geran Penyelidikan Asas (FRGS) IPT
Pindaan 1/2009

A

RESEARCH TITLE : Investigation into the expedient construction of naturally-occurring glycopeptides containing α-*O*-fucoside motif

Tajuk Penyelidikan

PROJECT LEADER : **Aisyah Saad Abdul Rahim**
Ketua Projek

PROJECT MEMBERS (including GRA) : 1. Nornisah Mohamed
2. Hasnah Osman
3. Shafida Abd Hamid
4. Bharath Reddy Deevireddy* (April – June 2009)
5. Narendra Babu SN (September-October 2009)

Ahli Projek

PROJECT ACHIEVEMENT *(Prestasi Projek)*

B

ACHIEVEMENT PERCENTAGE			
Project progress according to milestones achieved up to this period	0 - 50%	51 - 75%	76 - 100%
Percentage	30%		

RESEARCH FINDINGS		
Number of articles/ manuscripts/ books	Indexed Journal	*Non-Indexed Journal*
	NIL	NIL
Paper presentations	International	*National*
	NIL	NIL
Others (Please specify)	Poster presentation "A facile route towards Dmc-protected Fucosyl-Thr-OtBu building block *via* the Vilsmeier's bromide" at Gordon Research Conference in Oxford University, United Kingdom. Aug, 2008.	

HUMAN CAPITAL DEVELOPMENT

Human Capital	Number	
	On-going	Graduated
PhD Student*	-	-
Masters Student	-	-
Undergraduate Students	-	-
Temporary Research Officer	-	
Temporary Research Assistant	-	
Total	-	

Others (Please specify):

Note:
* Bharath Reddy Deevireddy (PhD Candidate)

EXPENDITURE *(Perbelanjaan)*

C

Budget Approved *(Peruntukan diluluskan)*	:	**RM** 103,200.00
Amount Spent *(Jumlah Perbelanjaan)*	:	**RM** 102,376.90
Balance *(Baki)*	:	RM 823.10
Percentage of Amount Spent *(Peratusan Belanja)*	:	99.2%

ADDITIONAL RESEARCH ACTIVITIES THAT CONTRIBUTE TOWARDS DEVELOPING SOFT AND HARD SKILLS
(Aktiviti Penyelidikan Sampingan yang menyumbang kepada pembangunan kemahiran insaniah)

D

International		
Activity	Date (Month, Year)	Organizer
Poster presenter at Gordon Research Conference for High Throughput Chemistry	Aug, 2008	Magdalen College, Oxford University, United Kingdom
National		
Activity	Date (Month, Year)	Organizer
Participant at the Symposium on "RECENT DEVELOPMENTS IN MEDICINAL CHEMISTRY" at University of Malaya, Kuala Lumpur Malaysia.	10 Oct 2008	Jointly by the Royal Society of Chemistry (RSC). Malaysian, Institute of Chemistry (IKM), British High Commission (BHC) and University of Malaya (UM).

PROBLEMS / CONSTRAINTS IF ANY *(Masalah/ Kekangan sekiranya ada)*

E

1. Lacking skills in synthetic organic chemistry. Malaysian chemistry graduates that applied in lack the skills in organic chemistry due to little or no exposure to synthetic organic chemistry during their undergraduate or Master's degree years. Secondly, there is a trend of doing courses that are considered 'popular' and 'easy' - and in synthetic organic chemistry research, students have to work long and hard to synthesise, purify and characterise compounds. Thus, it is hard to get students who's willing, interested and skillful to work on organic synthesis problems.

2. Poor access to analytical services in USM and other universities. World class Mass spectrometers are on campus – but its access is virtually for their own collaborators. Other universities – the charge is a little inhibitory for sending samples in continuous basis.

That said, I believe USM is moving towards common-users labs and equipment, so hopefully the access would be better in the future.

RECOMMENDATION (*Cadangan Penambahbaikan*)

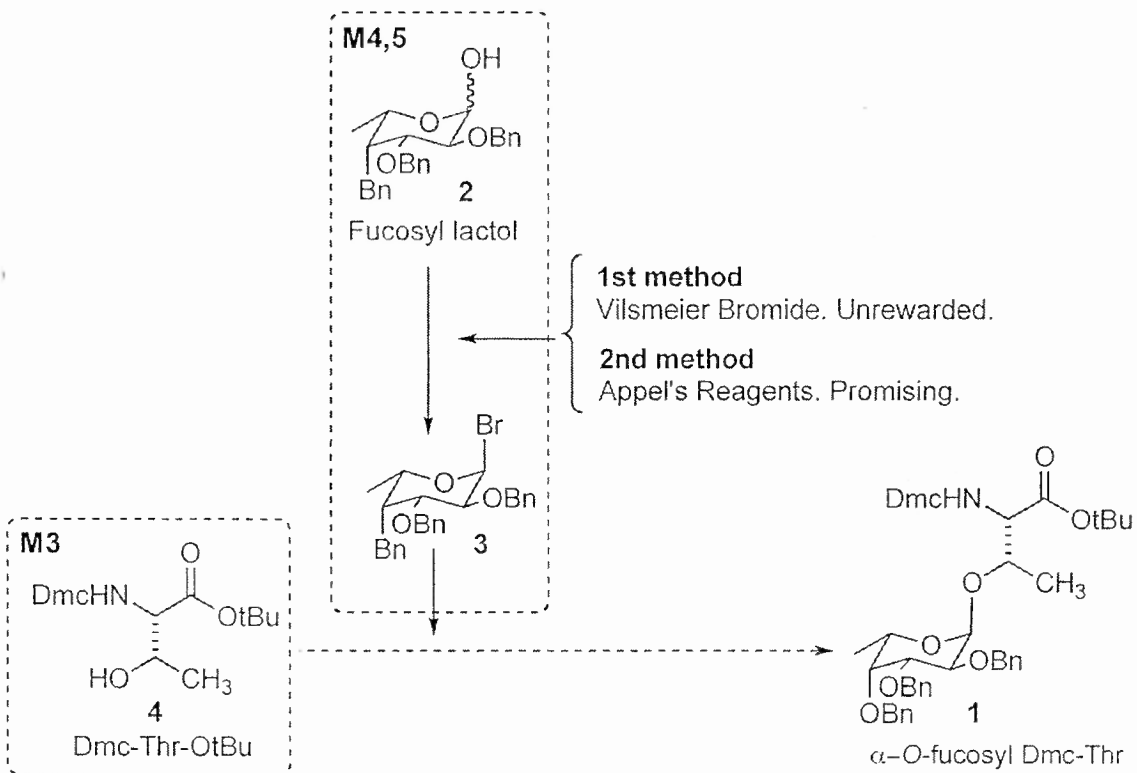
F

Please invest more in synthetic organic chemistry as this is one field that generates creative compounds toward Drug Discovery efforts in Malaysia.

RESEARCH ABSTRACT – Not More Than 200 Words *(Abstrak Penyelidikan – Tidak Melebihi 200 patah perkataan)*

G

The ultimate aim of this FRGS study is to establish a way to rapidly construct α-*O*-fucosyl glycopeptides from suitable fucosyl amino acid e.g. **1**. The first challenge was to find quicker way to obtain bromo glycosides before one could access the α-*O*-fucosyl Threonine **1**. We began with fucosyl lactol **2** as this is accessible synthetically or commerciablly. In our initial attempt, the lactol was treated with Vilsmeier's bromide, which gave us the bromo sugar **3**. But on glycosylation with alcohol **4**, we obtained a mixture of a dissacharide and unknown compounds. Attempts to further isolate them went unrewarded. We attempted then the second method using the one-pot Appel's reaction to generate the desired bromide **3**. Glycosylations were conducted with simple alcohols first, at room temperature. The TLCs showed consumption of the alcohols, and formation of new spots, presumably the desired glycosides. We repeated the glycosylation reactions under various microwave conditions. TLC and NMR of the glycosylation products indicated the desired glycosylated alcohols. In short, glycosylations of simple alcohols (as model reactions) with lactol **2**, under microwave conditions, seemed to be a promising method that warrants further development for a quicker access into building blocks for glycopeptides construction.



Graphical abstract of this FRGS investigation in establishing a facile method for *O*-fucosyl amino acid synthesis. Milestones **M3, M4** and **M5** correspond to the summary of progress (please see the attached summary).

Date : *Tarikh* 11/1/10

Project Leader's Signature: *Tandatangan Ketua Projek*

	COMMENTS, IF ANY/ ENDORSEMENT BY RESEARCH MANAGEMENT CENTER (RMC) *(Komen, sekiranya ada/ Pengesahan oleh Pusat Pengurusan Penyelidikan)*
H	.... **Name:** *Nama:* **Signature:** *Tandatangan:* **Date:** *Tarikh:*

Summary of FRGS project: 203/PFARMASI/671159 Aisyah Saad Abdul Rahim

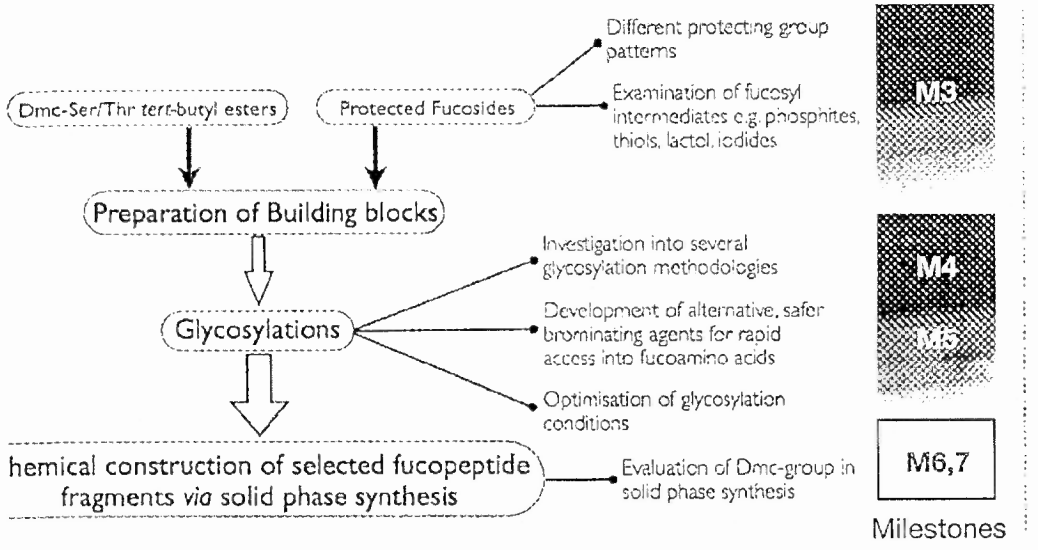
Amount requested: **RM 298,087** for **3 years**
Amount approved & received: **RM 103,200** for **2 years**

Amount spent: **RM 102,376.90 (99.2% spent)**
Amount left: **RM 823.10**

Work accomplished: **~30%** of the work proposed in the grant.

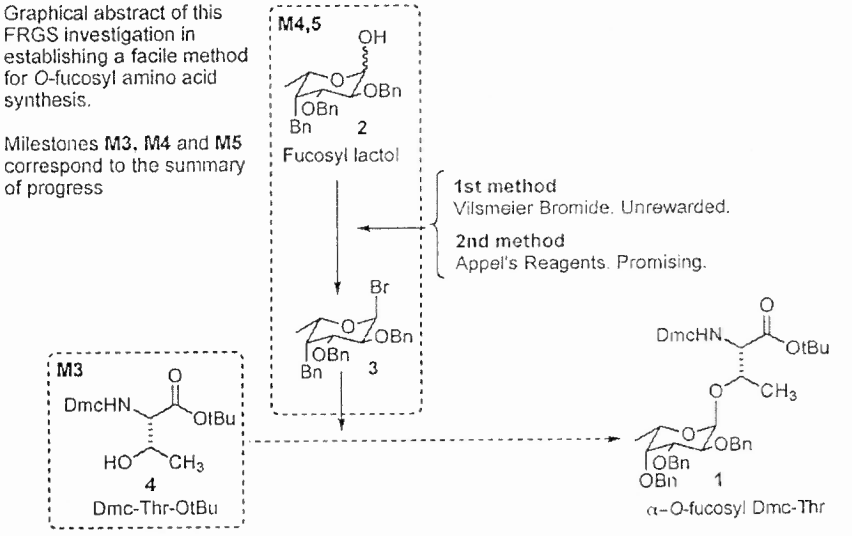
Proposed milestones/objectives against % completion

Milestones	Duration	Objectives	% completion
M1	Oct 07-Dec 2008	Lit. review	100
M2	Oct 07-Jan 2008	Procurement of Chemicals and Apparatus	100
M3	Feb-Dec 2008	Synthesis of Building Blocks (Dmc-fucosyl amino acids (Dmc-aa)	50
M4	Jan-July 2009	Glycosylation, 1. Examination of several glycosylation methods on Dmc-aa	25
M5	May-Oct 2009	Glycosylation, 2. Alternative brominations; 3. Optimisation	25
M6	Nov-June 2010	Construction of selected fucopeptides *via* solid phase synthesis	0
M7	July-Sept 2010	Writing publication/thesis	0



Graphical abstract of this FRGS investigation in establishing a facile method for *O*-fucosyl amino acid synthesis.

Milestones **M3**, **M4** and **M5** correspond to the summary of progress



Summary of FRGS project: 203/PFARMASI/671159 Aisyah Saad Abdul Rahim

People who worked on this project:
1. Dr Narendra Babu SN, Postdoctoral fellow
2. Siti Marina Mohd Maidin, RA
3. Bharathreddy Deevireddy, PhD candidate

Conferences/Seminar etc:

International

Poster presenter for the work titled "A facile route towards Dmc-protected Fucosyl-Thr-OtBu building block *via* the Vilsmeier's bromide" at Gordon Research Conference at Magdalen College, Oxford University, United Kingdom. 31 Aug - 5 September, 2008 (please see the attached copy of the poster).

Local

Participant at the Symposium on "RECENT DEVELOPMENTS IN MEDICINAL CHEMISTRY" at University of Malaya, Kuala Lumpur Malaysia. Organised jointly by the Royal Society of Chemsitry (RSC). Malaysian, Institute of Chemistry (IKM), British High Commission (BHC) and University of Malaya (UM). 10 Oct 2008

Equipment purchased using this grant (Vot 35000):

1. **IKA Magnetic Stirrers (4 units)**
2. **Dewar for Liquid Nitrogen 25L**
3. **iMac 20"**

Via Vilsmeier bromide

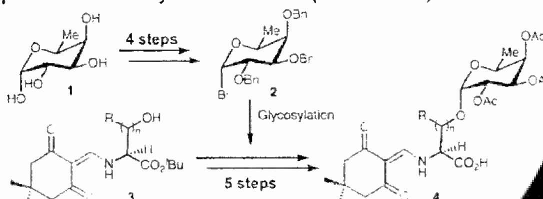
A facile route towards Dmc-protected Fucosyl-Thr-O^{t}Bu building block

UNIVERSITI SAINS MALAYSIA

Aisyah Saad
Abdul Rahim
School of Pharmaceutical Sciences
Universiti Sains Malaysia
Penang, Malaysia

INTRODUCTION

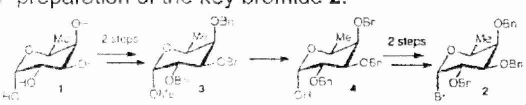
Glycopeptides and proteins, containing α-O-fucosyl moiety, are known to participate in many important biological processes e.g. embryo development and host-microbe attachment.[1] Obtaining pure α-O-fucopeptides to study these biological processes remains a challenge due to arduous multistep fucopeptide synthesis, characterised by protecting group exhanges. Recently we reported the synthesis of hydrogenolysis-stable Dmc-protected fucosyl amino acids (**Scheme 1**).[2]



Scheme 1 General synthetic routes towards Dmc-protected fucoamino acid building blocks. (Ser, R=H, n=1; Thr, R=CH_3, n=1; *homo*-Ser, R=H, n=2; Dmc=N$^{\alpha}$-(4,4-dimethyl-2,6-dioxocyclohexylidenemethylene)

DIFFICULTIES

While this procedure gave the Dmc-protected amino acids in good yields, the ten-step construction of the 1-bromofucoside **2** involved tedious purifications and the use of HBr gas which is malodorous and costly. **Scheme 2** shows the preparation of the key bromide **2**:

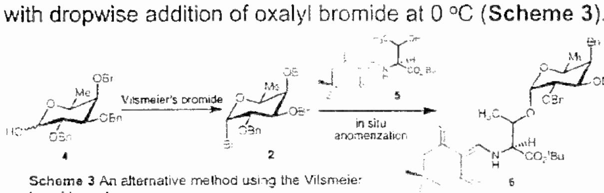


Scheme 2 Acid hydrolysis of the fucoside 3 afforded the lactol intermediate 4, which is amenable to further modifications at the anomeric position.

In view of the difficulties experienced during the preparation of the fucosyl bromide **2**, we decided to examine other bromination procedures[3,4] that could employ the lactol **4** as a convenient access to the bromide.

ALTERNATIVE METHOD

We wondered whether the bromination of the lactol **4** by the Vilsmeier bromide would afford the desired 1-bromofucoside **2** in fewer steps and purifications, therefore is readily used in the next glycosylation step. The lactol **4** in dimethylformamide (DMF) was treated with with dropwise addition of oxalyl bromide at 0 °C (**Scheme 3**).



Scheme 3 An alternative method using the Vilsmeier bromide route.

This marked by the effervescence observed upon the addition of DMF followed by colour change from colourless to an orange-coloured reaction mixture. Upon the removal of DMF, the resulting syrup was used directly for in the next coupling step between the bromide **2** and Dmc-Thr-O^{t}Bu **5**.

RESULTS

A quick ^{1}H NMR analysis of the crude orange syrup showed a tell-tale signal at δ 5.25 indicating the α proton of the bromide **2**. *In situ* anomerization of Dmc-Thr-O^{t}Bu with the bromofucoside **2** furnished the perbenzylated Dmc-α-*O*-L-fucosyl Thr-O^{t}Bu **6** plus a small quantities of a disaccharide.

CONCLUSIONS

In this work, the preparation of the perbenzylated 1-bromofucoside from the lactol intermediate employing an alternative brominating reagent, the Vilsmeier's bromide, was accomplished in four-step instead of the usual five-step with lesser purification.

References

1. Varki, A. Glycobiology **1993**, 3, 97-130
2. Kellam B, Ward PA, Abdul Rahim AS, Chhabra SR [illegible] Lett **2005**, 46, 1703-1706
3. Cromer R, Spohr U, Khare D P [illegible] Lemieux R U Can J Chem **1992**, 70, 1511-[illegible]
4. [illegible] J Carb Chem [illegible]

Acknowledgments

I am grateful to the Government of Malaysia, in particular Ministry of Science, Technology and Innovations (MOSTI) for the funding under the Fundamental Research Grant Scheme (FRGS: 203/PFARMAS/671159) Universiti Sains Malaysia for facilitating the research and the Embassy of France for the travel funding

PENYATA PERBELANJAAN PADA 30 NOVEMBER 2009

EXPEDIENT CONSTRUCTION OF NATURALLY-OCCURING GLYCOPEPTIDES CONTAINING A-O-FUCOSIDE MOTIF

AH SAAD ABDUL RAHIM

EK	DONOR	PERUNTUKAN PROJEK	PERBELANJAAN TERKUMPUL SEHINGGA THN LALU	PERUNTUKAN SEMASA	TANGUNGAN SEMASA	BAYARAN SEMASA	BELANJA SEMASA	BAKI PROJEK
59		24,000.00	4,257.94	19,742.06	0.00	0.00	0.00	19,742.06
59		8,000.00	6,714.67	1,285.33	0.00	0.00	0.00	1,285.33
59		1,000.00	0.00	1,000.00	0.00	0.00	0.00	1,000.00
59		32,700.00	18,392.09	14,307.91	7,649.68	36,566.92	44,216.60	-29,908.69
59		5,000.00	0.00	5,000.00	0.00	0.00	0.00	5,000.00
59		12,500.00	5,865.60	6,634.40	0.00	3,000.00	3,000.00	3,634.40
59		20,000.00	19,930.00	70.00	0.00	0.00	0.00	70.00
		103,200.00	55,160.30	48,039.70	7,649.68	39,566.92	47,216.60	823.10

AH KECIL :

	24,000.00	4,257.94	19,742.06	0.00	0.00	0.00	19,742.06
AN BEKALAU	59,200.00	30,972.36	28,227.64	7,649.68	39,566.92	47,216.60	-18,988.96
	20,000.00	19,930.00	70.00	0.00	0.00	0.00	70.00