Laporan
30885

UNIVERSITI SAINS MALAYSIA

LAPORAN AKHIR PROJEK PENYELIDIKAN JANGKA PENDEK

"Synthetic study of *C-Arylglycoside*"

No. Akaun Geran: 304/PKimia/636104

Tempoh kelulusan :15 November 2005-15 November 2007

Jumlah Geran: RM 19,700.00

Oleh

Dr. Hasnah Osman
Pusat Pengajian Sains Kimia
Universiti Sains Malaysia

UNIVERSITI SAINS MALAYSIA

LAPORAN AKHIR PROJEK PENYELIDIKAN JANGKA PENDEK

"Synthetic study of *C-Arylglycoside*"

No. Akaun Geran: 304/PKimia/636104

Tempoh kelulusan :15 November 2005-15 November 2007

Jumlah Geran: RM 19,700.00

Oleh

Dr. Hasnah Osman
Pusat Pengajian Sains Kimia
Universiti Sains Malaysia

PENDAHULUAN

Geran penyelidikan ini telah digunakan untuk membiayai projek seorang pelajar sarjana penyelidikan dan empat pelajar projek tahun akhir Pusat Pengajian Sains Kimia. Laporan ini mengandungi laporan kewangan projek, hasil keputusan daripada penyelidikan yang di laporkan dalam Kertas Kerja seminar dan abstrak projek pelajar tahun akhir.

PENGHARGAAN

Saya ingin merakamkan setinggi terima kasih kepada kepimpinan Universiti Sains Malaysia yang menggalakkan penyelidikan dengan sumbangan bantuan kewangan dalam penyelidikan ini dan kepada para pentadbir universiti yang memudahkan urusan penyelidikan ini. Tanpa sokongan dan bantuan tersebut penyelidikan ini tidak dapat dijalankan.

Yang Benar

(DR. HASNAH OSMAN)

KANDUNGAN

Kajian Sintetik *C*-arilglykosida

ABSTRAK

Sintesis *C*-arilglikosida telah menarik perhatian disebabkan oleh kestabilannya terhadap tindakbalas enzim dan hidrolisis asid. Dalam sintesis ini, skandium triflat telah digunakan sebagai Asid Lewis untuk mempercepatkan tindak balas *C*-arilglikosida. Tindak balas antara D-olivosida dan 2- naftol telah dimangkinkan dengan efisien oleh skandium triflat (0.25 equivalent) kepada D-olivosida menghasilkan sebatian 2-hidroksil-1-[3',4'-di-*O*-asetil-5'-metil-2-deoksi-*β*-D-arabino-heksopiranosil]-naftalene sebanyak 75%. *C*-glycosida yang disintesis telah dicirikan oleh IR, ^{1}H-NMR, dan^{13}C-NMR spektroskopi

Kata kunci: sintesis, *C*-arilglikosida, skandium triflat, pencirian

The Synthetic Study of *C*-arylglycoside

ABSTRACT

The synthesis of *C*-arylglycoside have attracted much attention due to the stability towards the enzymatic and acid hydrolysis. In this synthesis, scandium triflate was used as the Lewis acid to promote *C*-glycosylation reactions. The reaction between D-olivoside and 2- naphthol was efficiently catalysed by 0.25 equivalents of scandium triflate with respect to the D-olivoside and afforded a novel 2-hydroxy-1-[3',4'-di-*O*-acetyl-5'-methyl-2-deoxy-*β*-D-arabino-hexopyranosyl]-naphthalene in 75% yield. The synthesised *C*-glycoside are characterised by IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy

Keyword: synthesis, c-glycoside, scandium triflate, characterization

PROJEK OUTPUT

1. Menghasilkan satu kertas kerja, yang merupakan sebahagian daripada hasil penyelidikan ini oleh pelajar sarjana dan pelajar tahun akhir yang telah dibentangkan secara poster: "Catalytic Scandium Triflate Mediated the Synthesis of a Novel *C*-glycoside, 2-Hydroxy-1-[3',4'-di-*O*-acetyl-5'-methyl-2-deoxy-β-D-arabino-hexopyranosyl]-naphthalene" at 22nd Annual Seminar of the Malaysian Natural Products Society Beyond Medicinal Plants. Cititel, Midvalley City, Kuala Lumpur. Malaysia, 8-10 November 2006. Kertas kerja tersebut di lampirkan di Lampiran A

2. Menghasilkan empat tesis penyelidikan KUE 309 untuk empat pelajar tahun akhir. Abstrak tesis dilampirkan

ABSTRAK PROJEK PENYELIDIKAN TAHUN AKHIR

Seperti di senaraikan di bawah

TAJUK TESIS: KAJIAN SINTETIK KE ARAH PENGHASILAN *C*-GLIKOSIDA

Oleh

SITI MARINA MOHD MAIDIN

ABSTRAK

Suatu kaedah untuk mensintesis *C*-glikosida telah dilakukan .Kunci kepada tindak balas ini adalah pembentukan *O*-gliksida dengan menggunakan asid Lewis sebagai promoter dan penukarannya kepada C-glikosida secara *in situ* yang dikenali sebagai penyusunan semula *O*→*C*-glikosida . Dua jenis asid Lewis digunakan dalam sintesis ini iaitu boron trifluoro diethil etherat (BF_3OEt_2) and scandium triflat ($Sc(OTf)_3$). Tiga jenis analog yang telah disintesis adalah 6-[2',3',4',6'-tetra-*O*-asetil-β-D-*arabino*-heksapiranosil]-5-hidroksi naftalena-1,4-dion, 2-hidroksi-1-[2',3',4',6',-tetra-*O*-asetil-β-D-*arabino*-heksopiranosil]-naftalena, dan 2-hidroksi-1-[D-*arabino*-glukopiranosida]-naftalena. Juglon sebagai penerima glikosil dan D(+)-galaktosa sebagai penderma glikosil disintesis dahulu kerana diperlukan untuk menghasilkan 6-[2',3',4',6'-tetra-*O*-asetil-β-D-*arabino*-heksapiranosil]-5-hidroksi naftalena-1,4-dion. Tiga jenis penderma glikosil dan dua jenis penerima glikosil digunakan untuk menghasilkan *C*-glikosida yang berbeza. Sintesis 6-[2',3',4',6'-tetra-*O*-asetil-β-D-*arabino*-heksapiranosil]-5-hidroksi naftalena-1,4-dion tidak memberi sebarang hasil tetapi berkemungkinan memberikan campuran Ferrier. 2-Naftol sebagai penerima glikosil dan α-D(+)-glukosa pentaasetat sebagai penderma glikosil digunakan untuk mensintesis 2-hidroksi-1- [2', 3', 4', 6'–tetra-*O*- asetil- β-D-arabino- heksopiranosil]-naftalena tetapi tidak memberi sebarang hasil dan mungkin hasil adalah campuran Ferrier. 2-Hidroksi-1-[D-*arabino*-glukopiranosida]-naftalena yang di sintesis hanya memberi semula 2-naftol. Sebab-sebab utama mengapa kajian ini gagal adalah kerana tindak balas bergantung kepada jenis asid Lewis dan jenis penerima glikosil yang digunakan.

ESTERIFICATION STUDIES ON FERULIC ACID: PROTECTION OF HYDROXYL GROUP

BY:

ANTONIA LIM FANG-LIN

Abstract

Hydroxyl group in ferulic acid was protected by indirect benzylation method. First methylation was done to form an ester with the carboxylic group by refluxing ferulic acid (3.00 g) in methanol (50.0 mL) with concentrated sulphuric acid in catalytic amount (1.0 mL) for 8 hours. The yielded product was immediately benzylated with benzyl bromide (3.00 g) with potassium carbonate (K_2CO_3) (13.0 g) as base medium, tetrabutyl ammonium iodide (TBAI) (0.065 g) as catalyst in acetone (50.0 mL) as solvent. Purified product was found to give 0.43% with the melting point of 66-68 °C.

KAJIAN ANTIOKSIDAN KE ATAS TUMBUHAN *PAEDERIA FOETIDA* DAN *SYZYGIUM AQUEUM*

Oleh

NORHAFIZAH MD ISA

ABSTRAK

Bahagian pertama Projek ini merangkumi kajian antioksidan ke atas tumbuhan *Paederia foetida* dan *Syzygium aqueum*. Kandungan antioksidan untuk ekstrak metanol bagi tumbuhan-tumbuhan ini diukur dengan menggunakan 2 sistem ujian; pelunturan β-karotena dan 2,2'-azinobis(3-etilbenzotiazolina-6-asid sulfonik) radikal kation (ABTS) dengan quercetin dan α-tokoferol sebagai kawalan. Peratus

antioksidan bagi kesemua sampel-sampel ekstrak dengan menggunakan kaedah pelunturan β-karotena dan ABTS adalah dalam julat 58%-80%. Peratus antioksidan bagi α-tokoferol dan quercetin ialah 79.69% dan 42.37%. Sampel segar bagi kedua-dua tumbuhan menunjukkan aktiviti antioksidan yang baik. Manakala, sampel kering bagi kedua-dua tumbuhan menunjukkan aktiviti antioksidan yang kurang memberangsangkan. Keputusan bagi kaedah pengoksidaan β-karotena menunjukkan korelasi yang baik dengan kaedah ABTS.

Bahagian kedua projek ini adalah pengkajian struktur bagi quercetin dengan menggunakan kaedah spektrometri 1D dan 2D NMR.

Manakala bahagian ketiga adalah penentuan sebatian dengan menggunakan beberapa kaedah untuk menguji kehadiran sebatian bioaktif seperti tannin, flavonoid, alkoloid, terpenoid dan steroid. Daripada eksperimen didapati ekstrak tumbuhan berikut mengandungi sebatian bioaktif yang di kaji.

KAJIAN ANTIOKSIDAN KE ATAS TUMBUHAN *GARCINIA ATROVIRIDIS* DAN KAJIAN MINYAK PATI KE ATAS TUMBUHAN *OCIMUM BASILICUM*

Oleh

NOR HAFIZAH BINTI MOHD SHUKRI

ABSTRAK

Bahagian pertama dalam penyelidikan ini adalah kajian antioksidan ke atas *Garcinia atroviridis*. Dalam kajian ini perbezaan kandungan antioksidan pada buah *Garcinia atroviridis* yang segar dengan buah *Garcinia atroviridis* yang kering telah dijalankan. Peratusan antioksidan diperolehi daripada bacaan keserapan daripada Spektrofotometer Ultra-Lembayung (UV) pada jarak gelombang 450 nm. Daripada kajian didapati sampel kering mempunyai kandungan peratus antioksidan yang lebih tinggi daripada sampel yang segar.

Bahagian kedua dalam kajian ini adalah mengkaji struktur Vitamin E dengan menggunakan Peralatan Resonans Magnet Nukleus (NMR). Eksperimen ^{1}H NMR, ^{13}C NMR dan 2D NMR dijalankan. Semua jalur pada spektrum yang jelas dapat dikenalpasti.

Bahagian ketiga dalam kajian ini adalah penentuan sebatian mudah meruap daripada tumbuhan *Ocimum basilicum*. kompaun-kompaun yang mudah meruap di kenalpasti melalui Kromatografi Gas (GC) dan Kromatografi Gas – Spektroskopi Jisim (GC – MS).

30892

LAMPIRAN A

Catalytic Scandium Triflate Mediated the Synthesis of a Novel *C*-glycoside, 2-Hydroxy-1-[3',4'-di-*O*-acetyl-5'-methyl-2-deoxy-*β*-D-arabino-hexopyranosyl]-naphthalene

Hasnah Osman[1], Siti Marina Mohd Maidin[1] and D. S. Larsen[2]

[1]*School of Chemical Sciences, Universiti Sains Malaysia, Penang, Malaysia*

[2] *Department of Chemistry, University of Otago, Dunedin, New Zealand*

ohasnah@usm.my, 604-6533558, fax: 604-6574854

Abstract

Synthesis of novel *C*-glycoside, 2-Hydroxy-1-[3',4'-di-*O*-acetyl-5'-methyl-2-deoxy-*β*-D-arabino-hexopyranosyl]-naphthalene is achieved by the reaction of 2-naphthol with D-olivoside. The reaction is efficiently catalyst by 0.25 equivalents of scandium triflate with respect to the D-olivoside. The characterisation of the synthesised *C*-glycoside has been described by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy, HRMS and elemental analysis.

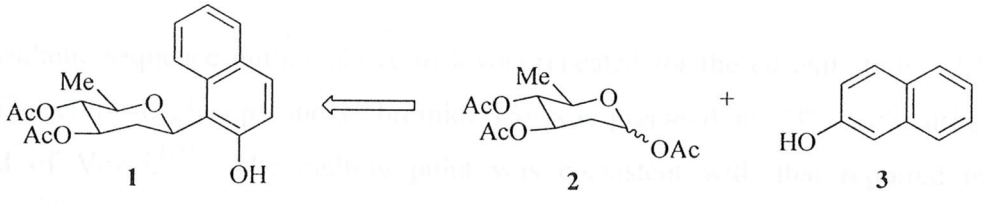
Keywords: *C*-glycoside, D-Olivoside, Catalysis, Scandium triflate.

1. Introduction

Glycosides are commonly found in the plant, animal kingdom and bacteria. *C*-glycoside, in which the glycosidic oxygen is replaced by a carbon atom where the glycosidic linkage is formed from a glycosyl donor and a glycosyl acceptor. The synthesis of *C*-arylglycoside have attracted much attention due to their biological activities and stability towards the enzymatic and acid hydrolysis. [1, 2] Many methods are available for the syntheses of *C*- arylglycosides and these have been reviewed by Postema[1] and Hua.[2]

Andrews and Larsen reported the first syntheses of *C*-glycosyljuglone derivatives.[3] Boron trifluoride diethyl etherate was used as the Lewis acid to promote the *C*-glycosylation reactions. In this synthesis, naphthoquinone was obtained and subsequently used for the synthesis of angucycline antibiotic.

The Suzuki group have been very active in the development of methodology for the formation of *C*- arylglycosides.[4-11] They successfully used a range of Lewis acids and different glycosyl donors in their studies. A promoter formed from a 1:1 mixture of hafnocene dichloride and silver perchlorate (Cp_2HfCl_2-$AgClO_4$) proved to be very effective in the *C*-glycosylation reactions. Recently, Suzuki *et al.* have described the use of scandium triflate [$Sc(OTf)_3$] to promote *C*-glycosylation reactions of various phenols with glycosyl acetates.[12] High yields (81-89%) of the β-*C*-glycoside were obtained upon decreasing the amount of $Sc(OTf)_3$ to half an equivalent. Here, we report the ability of $Sc(OTf)_3$ to promote the synthesis of a novel 2-Hydroxy-1-[3',4'-di-*O*-acetyl-5'-methyl-2-deoxy-*β*-D-arabino-hexopyranosyl]-naphthalene (**1**) between D-olivoside (**2**) and 2- naphthol (**3**).



1 2 3

2. Experimental

D-Olivoside (**2**) (80 mg, 0.30 mmol), $Sc(OTf)_3$ (18 mg, 0.10 mmol), 2-naphthol (**3**) (25 mg, 0.40 mmol) and Drierite (300 mg) was stirred in dichloroethane (2 mL) at 0 °C. The cooling bath was removed and the mixture was stirred for 1 hour at room temperature. The mixture was poured into saturated aqueous sodium hydrogen carbonate solution (50 mL), extracted with ethyl acetate (2 x 50 mL) and washed with brine (50 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent

was removed in vacuo and purification by silica gel column chromatography [hexane/ethyl acetate (2:1) as eluant] gave **1**.

.

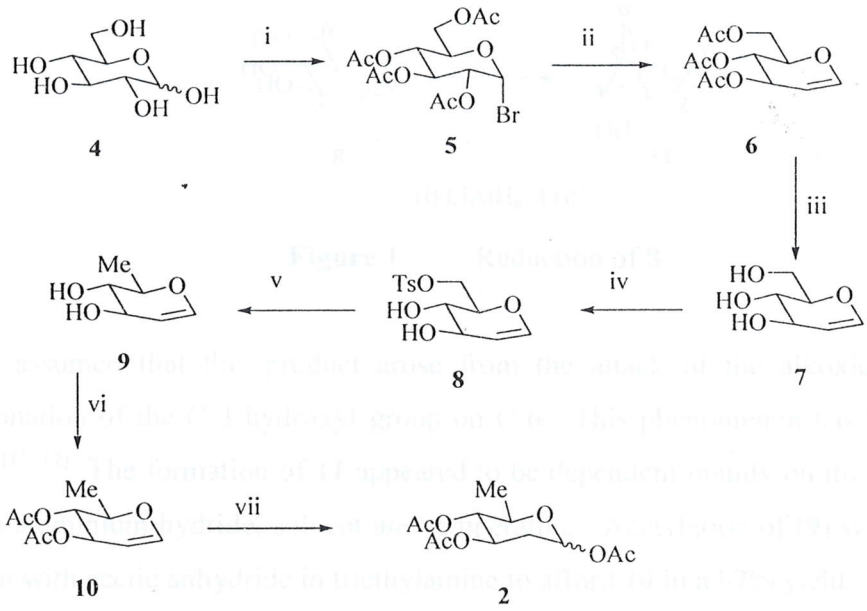
3. Results And Discussion

3.1 Synthesis of Glycosyl Donor

The current research requires adequate quantities of glycosyl donor, D-olivoside as starting materials for a synthesis of *C*-glycosyl-naphthalenes. The carbohydrate moiety of *C*-glycosyl-naphthalenes is a D-olivosyl (2,6-dideoxy-D-glucopyranosyl) residue. Hasnah[13], Andrews and Larsen[3-5] used 2-deoxysugars possessing anomeric acetate groups as glycosyl donors in their synthesis of aryl *C*-glycosides. The current study would use the same approach in the synthesis of 1,3,4-tri-*O*-acetyl-2,6-dideoxy-D-*arabino*-hexopyranose (**2**) (Scheme 1).[5]

The synthetic sequence outline above to **2** was repeated for the current study. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**5**) was prepared in 78% yield using the method of Vogel.[14] The melting point was consistent with that reported in the literature[14] and the ^{1}H NMR spectrum also confirmed the structure of the product.

Reductive elimination of the bromide and C-2 acetate group of **5** was achieved by treatment with zinc dust in aqueous acetic acid to give tri-*O*-acetyl-D-glucal (**6**) in 86% yield. Deacetylation of a methanol solution of **6** was effected by treatment with sodium carbonate to give D-glucal in a 92% yield.



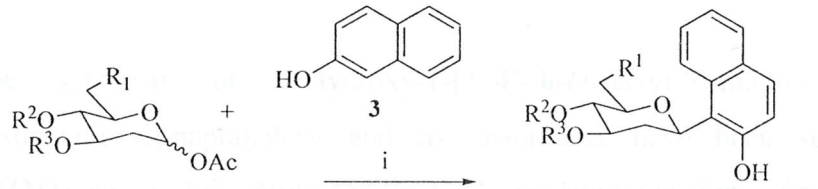
(i) a) Ac_2O, $HClO_4$, b) P, Br_2, H_2O; (ii) Zn dust, 50% AcOH; (iii) Na_2CO_3, MeOH; (iv) *p*-TsCl, py; (v) $LiAlH_4$, THF; (vi) Et_3N, DMAP, Ac_2O; (vii) AcOH, TPPHBr.

Scheme 1 Synthesis of D-olivoside (**2**).

The next three steps of the synthesis involved a sequence of tosylation, reduction and then acetylation of **7**. The methods of Fraser-Reid[15] and Pathak[16] were employed. Tosylation of D-glucal (**7**) using tosyl chloride in pyridine gave tosylate (**8**) in 56% yield as a slightly impure syrup. This product was used for the next step without further purification.

Reduction of **8** was effected with lithium aluminium hydride ($LiAlH_4$) in dry tetrahydrofuran (THF) to give 6-deoxy-D-glucal (**9**) in yields which ranged between 0 and 86%. The reproducibility of this reaction was worrying. Low yields and poor recovery of material persisted. In some experiments anhydro-sugar **11** was formed (Figure 1).

The reaction of L-olivoside *ent*-(**2**) and 2-naphthol (**3**) was also investigated (entry 1, Table 1). This reaction, promoted by 1 equivalent of $Sc(OTf)_3$, proceeded smoothly in 20 minutes to afford *C*-glycoside *ent*-(**1**) in 88% yield. The IR spectrum of *ent*-(**1**) showed an absorption at 3373 cm^{-1} which was assigned to the hydroxyl group. The anomeric proton resonated at δ 5.50 ppm in the ^1H NMR spectrum as a double doublet, with coupling constants, $J_{1',2'eq}$ = 2.3 Hz and $J_{1',2'ax}$ = 12.1 Hz. A one proton singlet at δ 8.61 ppm was assigned to the phenolic proton.



2 R^1 = H, R^2 = R^3 = Ac
ent-**2** R^1 = H, R^2 = R^3 = Ac

1 R^1 = H, R^2 = R^3 = Ac
ent-**1** R^1 = H, R^2 = R^3 = Ac

(i) $Sc(OTf)_3$, $ClCH_2CH_2Cl$.

Scheme 2 *C*-Glycosylation reactions of glycosyl donors and **3**.

Table 1 *C*-Glycosylation of 2-naphthol (**3**)

Entry	Donor	Equivalents of $Sc(OTf)_3$	Time (min)	Product (yields) (%)
1	*ent*-**2**	**1**	20	*ent*-**1** (88%)
2	*ent*-**2**	**0.25**	90	*ent*-**1** (72%)
3	**2**	**0.25**	90	**1** (75%)

All reactions were carried out using 1.2 equiv. of **3** with respect to the donor.

The reaction was repeated where the amount of $Sc(OTf)_3$ was reduced to 0.25 equivalents, with respect to donor *ent*-**2** (entry 2, Table 1). No starting material was evident after 1 hour and 30 minutes and the reaction afforded *C*-glycoside *ent*-(**1**) in 72% yield.

The above reaction conditions were also used for the reaction of D-olivoside (**2**) and **3**. Reaction of glycosyl donor **2** promoted by 0.25 equivalents of $Sc(OTf)_3$ gave the desired *C*-glycoside **1** in 75% yield (entry 3, Table 1). The spectral data were consistent with those of *ent*-(**1**). The optical rotation of **1**, $[\alpha]_D$ = +43.0 (*c* 1.9, CH_2Cl_2), as expected, was opposite in sign but numerically equivalent (within experimental error) to that obtained for its enantiomer, *ent*-**1** {$[\alpha]_D$ = -39.0 (*c* 0.4, CH_2Cl_2)}.

Conclusions

The synthesis of 2-Hydroxy-1-[3',4'-di-*O*-acetyl-5'-methyl-2-deoxy-*β*-D-arabino-hexopyranosyl]-naphthalene and its enantiomer have been successfully achieved. $Sc(OTf)_3$ successfully promoted the *C*-glycosylation reactions of naphthol **3** with donors **2**, and *ent*-**2**. The yields were moderate to good and are comparable to $BF_3.Et_2O$ promoted *C*-glycosylation reactions carried out by Andrews.[5]

Acknowledgements

The author wish to thank Universiti Sains Malaysia, Penang for the financial support (Grant No: pkimia/304/636104).

References

[1] M. H. D. Postema, *Tetrahedron* **1992**, *48*, 8545-8599.

[2] D. H. Hua and S. Saha, *Recueil des Travaux Chimiques des Pays-Bas* **1995**, *114*, 341-355.

[3] F. L. Andrews and D. S. Larsen, *Tetrahedron Letters* **1994**, *35*, 8693-8696.

[4] T. Matsumoto, M. Katsuki and K. Suzuki, *Tetrahedron Letters* **1988**, *29*, 6935-6938.

[5] T. Matsumoto, H. Maeta, K. Suzuki and G. Tsuchihashi, *Tetrahedron Letters* **1988**, *29*, 3567-3570.

[6] T. Matsumoto, M. Katsuki and K. Suzuki, *Tetrahedron Letters* **1989**, *30*, 833-836.

[7] T. Matsumoto, M. Katsuki, H. Jona and K. Suzuki, *Tetrahedron Letters* **1989**, *30*, 6185-6188.

[8] K. Suzuki, H. Maeta and T. Matsumoto, *Tetrahedron Letters* **1989**, *30*, 4853-4856.

[9] T. Matsumoto, T. Hosoya and K. Suzuki, *Tetrahedron Letters* **1990**, *31*, 4629-4632.

[10] T. Matsumoto, M. Katsuki, H. Jona and K. Suzuki, *Journal of the American Chemical Society* **1991**, *113*, 6982-6992.

[11] T. Matsumoto, T. Hosoya and K. Suzuki, *Synlett* **1991**, 709-711.

[12] A. Ben, T. Yamauchi, T. Matsumoto and K. Suzuki, *Synlett* **2004**, *2*, 225-230.

[13] Hasnah Osman, *Ph.D. Thesis, Synthetic approaches to the angucycline antibiotics.*, University of Otago, Dunedin, New Zealand, **2005**

[14] A. I. Vogel, B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, John Wiley, New York, **1978**.

[15] B. Fraser-Reid, D. R. Kelly, D. B. Tulshian and P. S. Ravi, *Journal of Carbohydrate Chemistry* **1983**, *2*, 105-114.

[16] V. P. Pathak, *Synthetic Communications* **1993**, *23*, 83-85.

[17] I. D. Blackburne, P. M. Fredericks and R. D. Guthrie, *Australian Journal of Chemistry* **1976**, *29*, 381-391.

[18] V. Bolitt, C. Mioskowski, S. G. Lee and J. R. Falck, *Journal of Organic Chemistry* **1990**, *55*, 5812-5813.