รายงานวิจัยฉบับสมบูรณ์

โครงการ
การเตรียมสารสังเคราะห์ไตรเอโซลไกลโคไซด์
เพื่อศึกษาสมบัติการต้านมะเร็งท่อน้ำดี

Preparation of synthetic triazoleglycosides
for cholangiocarcinoma tumor growth inhibitor

รุ่งนภา แซ่เอ็งและคณะ

โครงการวิจัยประเภทงบประมาณเงินรายได้
จากเงินอุดหนุนรัฐบาล (งบประมาณแผ่นดิน)
ประจำปีงบประมาณ 2558
มหาวิทยาลัยบูรพา

รหัสโครงการ 177554
สัญญาเลขที่ 60/2558

รายงานวิจัยฉบับสมบูรณ์

โครงการ
การเตรียมสารสังเคราะห์ไตรเอโซลไกลโคไซด์
เพื่อศึกษาสมบัติการต้านมะเร็งท่อน้ำดี

Preparation of synthetic triazoleglycosides
for cholangiocarcinoma tumor growth inhibitor

รุ่งนภา แซ่เอ็งและคณะ
ภาควิชาเคมี คณะวิทยาศาสตร์
มหาวิทยาลัยบูรพา

10 กันยายน 2559

กิตติกรรมประกาศ

งานวิจัยนี้ได้รับทุนสนับสนุนการวิจัยจากงบประมาณเงินรายได้จากเงินอุดหนุนรัฐบาล
(งบประมาณแผ่นดิน) ประจำปีงบประมาณ พ.ศ. 2558 มหาวิทยาลัยบูรพา
ผ่านสำนักงานคณะกรรมการการวิจัยแห่งชาติ เลขที่สัญญา 60/2558

Acknowledgment

This work was financially supported by the Research Grant of Burapha University
through National Research Council of Thailand (Grant no. 60/2558).

สารบัญ

คำนำ

โครงการวิจัย “การเตรียมสารสังเคราะห์ไตรเอโซลไกลโคไซด์เพื่อศึกษาสมบัติการต้านมะเร็งท่อน้ำดี” ได้รับการสนับสนุนทุนการวิจัยโครงการต่อเนื่องงบประมาณแผ่นดินประจำปีงบประมาณ 2558 มหาวิทยาลัยบูรพา รายงานการวิจัยฉบับนี้เสนอรายละเอียดของการวิจัยซึ่งประกอบด้วยบทนำที่เสนอผลงานวิจัยที่เกี่ยวข้อง ผลการทดลองวิจัย การอภิปรายสรุปผล และผลงานจากการวิจัย

การวิจัย “การเตรียมสารสังเคราะห์ไตรเอโซลไกลโคไซด์เพื่อศึกษาสมบัติการต้านมะเร็งท่อน้ำดี” สำเร็จลุล่วงไปด้วยดี โดยผู้วิจัยต้องขอขอบคุณทีมวิจัยซึ่งประกอบด้วยที่ปรึกษาโครงการ ศ.ดร. อภิชาต สุขสำราญ มหาวิทยาลัยรามคำแหง ศ.ดร. ภาวิณีปิยะจตุรวัฒน์ มหาวิทยาลัยมหิดล ศ. ดร.โสพิศ วงศ์คำ มหาวิทยาลัยขอนแก่น ผู้ร่วมโครงการการสังเคราะห์สาร ดร. อุทัยวรรณ ศิริอ่อน รวมทั้งนิสิตปริญญาโท ภาควิชาเคมี นายวัชระ มังค์สังค์ และนายสุขสำราญ ไชยดำ ขอขอบคุณ คุณสุทธิพร พิกุลทอง มหาวิทยาลัยมหิดลที่ทำการตรวจสอบ High Resolution Mass ของสารสังเคราะห์ที่ได้ งานวิจัยนี้ได้รับการสนับสนุนจากภาควิชาเคมี คณะวิทยาศาสตร์และศูนย์นวัตกรรมความเป็นเลิศทางเคมี PERCH-CIC

ผศ. ดร. รุ่งนภา แซ่เอ็ง
อาจารย์ประจำภาควิชาเคมี คณะวิทยาศาสตร์
หัวหน้าโครงการวิจัย

บทคัดย่อ

มะเร็งท่อน้ำดี (Cholangiocarcinomaหรือ CCA) เป็นมะเร็งของเซลล์เยื่อบุท่อน้ำดีที่ค่อนข้างพบน้อยในโลกตะวันตกแต่อุบัติการณ์ของมะเร็งท่อน้ำดีในไทย ในภาคตะวันออกเฉียงเหนือกลับมีสูงมากที่สุดในโลก โดยเฉพาะในจังหวัดขอนแก่น ในงานวิจัยนี้ได้ศึกษาการเตรียมอนุพันธ์ triazoleglycoside เพื่อศึกษาการต้านมะเร็งท่อน้ำดี โดยได้ทำการสังเคราะห์สารด้วยวิธีใหม่โดยแบ่งงานเป็นสามส่วนได้สารเป็นสามกลุ่มใหญ่ โดยกลุ่มแรกได้สังเคราะห์สารอนุพันธ์ triazolylethyl-2,3-unsaturated-*O*-glycosides จำนวน 17 อนุพันธ์ ด้วยวิธีการทำปฏิกิริยาสามชนิด คือ O-glycosylation azidation และ click reaction ในหม้อทำปฏิกิริยาเดียว สารในกลุ่มที่สอง คือ 2,3-unsaturated-glycosyl triazoles จำนวน 30 อนุพันธ์ ด้วยวิธีการทำปฏิกิริยาสองชนิด glycosylation และ click reaction ในหม้อทำปฏิกิริยาเดียวได้สารที่มีฤทธิ์ต้านมะเร็งท่อน้ำดีคือ สาร **9a** และ**9b** และกลุ่มที่สาม คือสารอนุพันธ์ 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-**α**-D-galactopyranosyls จำนวน 31 อนุพันธ์ซึ่งมีหมู่ triazole สองหมู่บนวงน้ำตาลในตำแหน่งที่ C-1 และ C-6 โดยทำปฏิกิริยาทั้งหมดสี่ขั้นตอน ได้สารที่มีฤทธิ์ต้านมะเร็งท่อน้ำดีคือ สาร **5ee**

Abstract

Cholangiocarcinoma (CCA) is a primary cancer of the bile duct epithelial cells. The incidence of CCA is low in worldwide, however, it is very high in the northeastern part of Thailand especially in KhonKaen province. In this research works, we studied the preparation of triazoleglycoside analogues and their anticancer activities on CCA cell lines. Three type of triazoleglycoside were synthesized using new method. In the first part, we have successfully synthesized of seventeen derivatives of triazolylethyl 2,3-unsaturated *O*-glycoside in three steps-one-pot manner using sequential *O*-glycosylation-azidation and click reaction. In the second part, we have synthesized thirty analogues of 2,3-unsaturated-glycosyl triazoles in two steps-one-pot manner using sequential *O*-glycosylation and click reaction. Of all synthetic analogs, compounds **9a** and **9b** showed good anticancer activity on CCA cell lines. In the third part, Thirty-one analogues of of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-**α**-D-galactopyranosyl bearing two triazole group at C-1 and C-6 were synthesized via four steps. Compounds **5ee** exhibited pronounced cytotoxicity against K-100 cholangiocarcinoma cells.

Chapter 1 Introduction and Literature reviews

Introduction

Cholangiocarcinoma (CC) is a primary cancer of the bile duct epithelial cells. With an incidence of about 3 per 100,000 per year, bile duct cancers represent a rare disease accounting for about 2–3% of all malignant tumours.[1] Risk factors are primary sclerosing cholangitis (PSC), extra- and intrahepatic bile duct cysts, hepatolithiasis, liver fluke infestation.[2]

Prognosis for cholangiocarcinoma is poor. At the time of diagnosis only 30–50% of the patients with extrahepatic CC show local lymph node metastases and 10–20% show distantmetastases (especially in liver and peritoneum). Nevertheless, 70–80% of perihilar tumours are not resectable due to tumour extension to other adjacent anatomical structures.[3] Without treatment, half of the patients die within three to four months due to the indirect consequences of local tumour progression, *i.e.* increasing bile duct obstruction, bacterial cholangitis, gallbladder empyema, liver abscesses, cholestasis and liver failure. Patients with extrahepatic CC usually present with painless icterus, pruritus, anorexia and rapid weight loss, or signs of cholangitis. So far, surgical removal of the tumour is the only curative approach. However, even after curative (R0) resection the 5-year survival rate is limited to 30–40%.[4] In most cases (70–80%) resection is precluded by local tumour extension - especially owing to the distinct anatomical features of the liver hilus comprising three neighbouring vessel systems (arterial, portal venous and biliary ductal). Liver transplantation may be considered in exceptional cases, although non-resectable CCs do not represent an assured indication.[5]

Tumours of the bile duct often show poor response to combination chemotherapy with median overall survival time up to 15 months at best with gemcitabine/oxaliplatin (or cisplatin) or gemcitabine/capecitabine. External beam radiation therapy does not improve the prognosis**;** nevertheless, CCs appear to respond moderately to combination radiochemotherapy. However, many of the patients with CC are never fit for aggressive chemo- or radiochemotherapy because of tumour complications like obstructive cholestasis or cholangitis and, furthermore, the survival benefit of this combined approach could not be demonstrated throughout all studies.

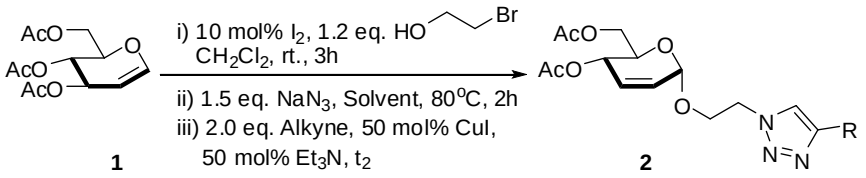
The incidence of CCA is low worldwide, however, it is very high in the northeastern part of Thailand especially in Khon Kaen province.[6] From population-based cancer registry in Khon Kaen, the incidence of CHCA is evidently high in area located near water reservoir

with the liver fluke, *Opisthorchis viverrini*, contamination in the fish. The trend in incidence of CHCA in Khon Kaen has been slowly declining in both sexes with annual percent age changes of 0.7% and 0.4% in male and female, respectively. The survival rate of patient with CHCA is very low according to ineffective treatment modalities. At present, there is no effective chemotherapy regimen for treating patients with advanced cholangiocarcinoma. Therefore, novel and effective therapeutic agents and more effective medical treatment options are urgently needed.

1,2,3-Triazoles are potential targets for drug discovery as they exhibit a broad spectrum of biological properties and many efforts have been made to optimize methods for their preparation. One example is the 1,3-dipolar cycloaddition reaction between an azide and a terminal alkyne in the presence of a copper-based catalyst to give the triazole. This method, developed is potentially useful in the design and synthesis of new compounds with excellent regiocontrol.

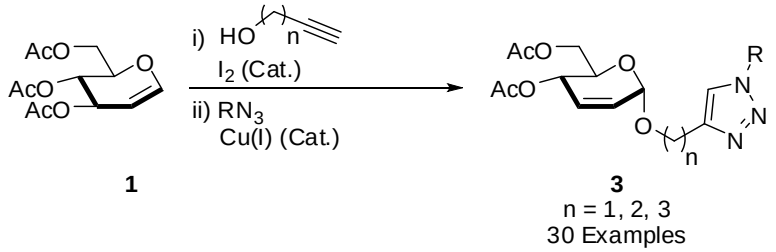
The triazole-linked glycosides have been extensively studied in research for the design of various functionalized glycoconjugates, facilitating a multitude of practical physical, chemical, biological studies and validated pharmaceutical properties. However, they are a few researches study on the synthesis of bis-triazoleglucosides *via* dual click chemistry and elucidation for their biological properties (Song et al., 2011; He et al, 2011).

In this work, part 1, we designed to synthesize a new class of triazolylethyl-2,3-unsaturated-*O*-glycosides using sequential one-pot glycosylation-azidation-CuAAc reactions procedure.



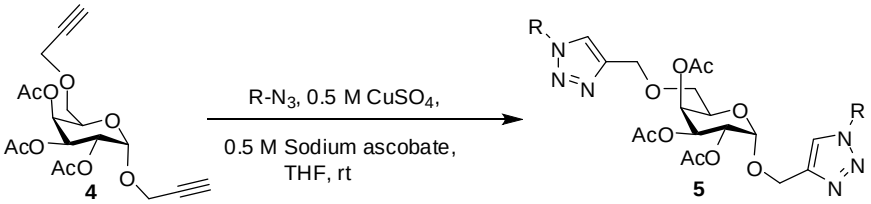
Scheme 1 Synthesis of triazolylethyl-2,3-unsaturated-*O*-glycosides **2**

In part 2, a new class of 2,3-unsaturated-glycosyl triazoles *via* one-pot two steps glycosylation click reaction and investigatin the anti-proliferative effect of triazoleglycoside on cholangiocarcinoma KKU-M213.



Scheme 2 Synthesis of 2,3-unsaturated-glycosyl triazoles **2**

In part 3, 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl analogues were synthesized *via* click chemistry (Scheme 1). All the synthetic anologues of the bistriazole glycosides will be evaluated for anti-proliferative activity on human cholangiocarcinoma cells (KKU-M213, HUCCA-1, K-100), cancer cells.



Scheme 3 Synthesis of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl derivatives

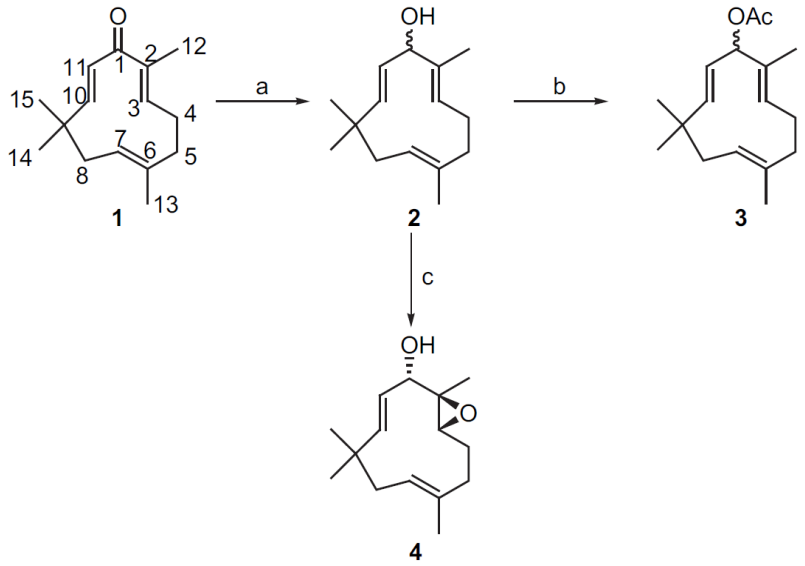
Literature reviews

The highest incidence of cholangiocarcinoma has been reported in the Northeastern area of Thailand. Cholangiocarcinoma has resulted in a high mortality rates and poor prognosis. At present, surgery is potentially curative approach however unfortunately have no improvement with long term survival. In addition, the chemotherapy is ineffective. Therefore, searching for the effective drugs with less adverse effect and high sensitivity to cholangiocarcinoma are needed. During the past years, several compounds have been synthesized and study for their cytotoxicity against cholangiocarcinoma cell lines. Here are some recently reports.

Selected examples of synthetic compounds and their cytotoxicity against cholangiocarcinoma cell lines

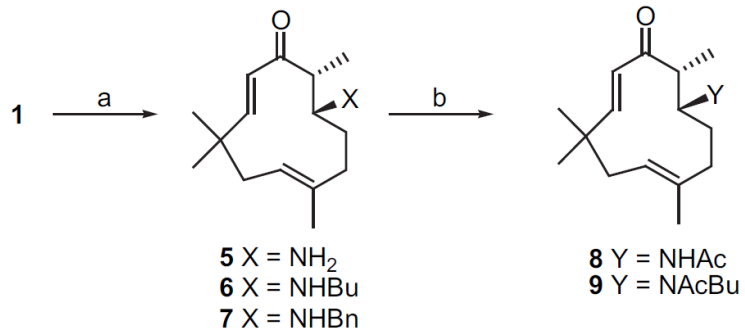
Zerumbone 1, a crystalline sesquiterpene, is the major component in the rhizomes of *Zingiber zerumbet Smith* and is readily available from a widespread natural source. A series of zerumbone derivatives were synthesized and their *in vitro* cytotoxicity against cholangiocarcinoma cell lines was evaluated.

Seventeen zerumbone derivatives were prepared by Yenjai and co-worker using organic reactions.[7] Reduction of zerumbone **1** using $LiAlH_4$ gave crystalline zerumbol **2** and acetylation of this compound using Ac_2O/pyridine afforded **3** while epoxidation of **2** with mCPBA yielded racemic **4** (Scheme 1).



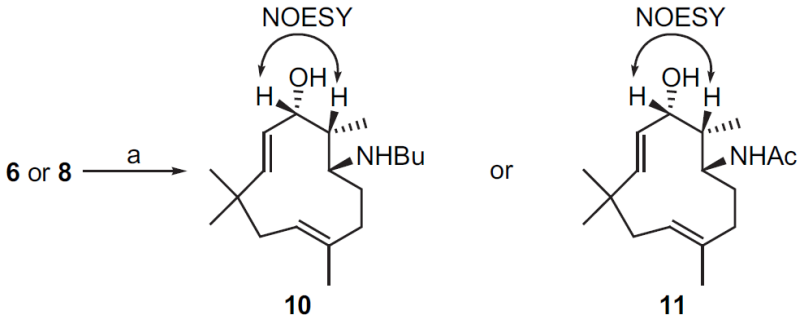
Scheme 1. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 1 h, 88%; (b) Ac_2O, pyridine, reflux, 30 min, 74%; (c) *m*CPBA, EtOAc, rt, 24 h, 15%. **Note**: The stereochemistry shown in all schemes are relative configuration.

Zerumbone **1** was stirred with excess ammonia, butylamine and benzylamine to provide monoamines **5**, **6** and **7**, respectively. Michael addition of amines occurred selectively at the less hindered conjugated double bond (C2-C3) of zerumbone. Acetylation of amine groups at C3 position of **5** and **6** using Ac_2O/pyridine provided the corresponding amides **8** and **9**, respectively.



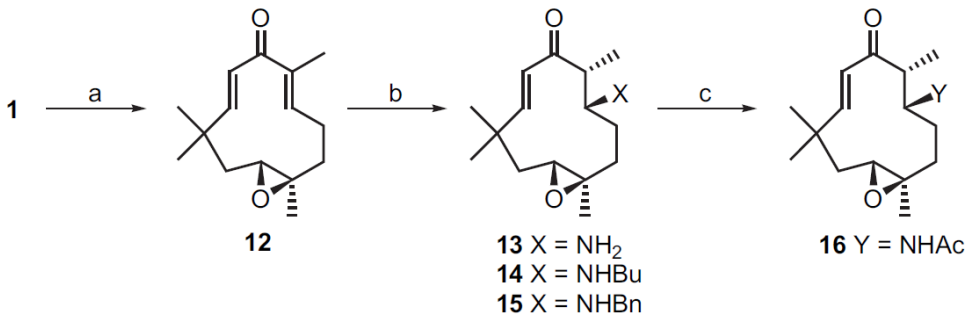
Scheme 2. Reagents and conditions: (a) NH_3 or $BuNH_2$ or $BnNH_2$, MeCN, rt, 5 days, 56% (**5**), 93% (**6**), 68% (**7**); (b) Ac_2O, pyridine, 0 °C, 8 h, 92% (**8**), 85% (**9**).

The reaction of butylamine **6** with $NaBH_4$ afforded hydroxyamine **10** in 81% yield. The reduction of amide **8** with $NaBH_4$ afforded a single diastereoisomer hydroxyamide **11** in the yield of 54% (Scheme 3).



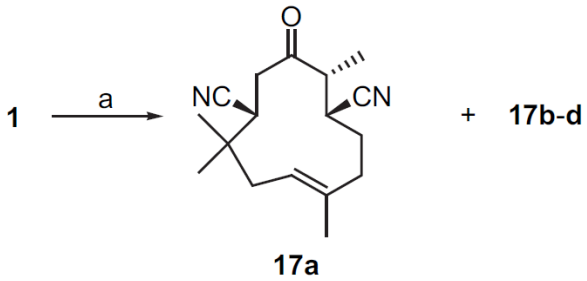
Scheme 3. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 3 h, 81% (**10**), 54% (**11**).

Epoxidation of the isolated double bond in zerumbone at C6 and C7 using m-CPBA provided epoxide **12** in 97% yields and treated with an excess amount of various amines providing corresponding amines **13**-**15**. Further acetylation of **13** using Ac_2O in pyridine gave corresponding amide **16** in 66% yield (Scheme 4).



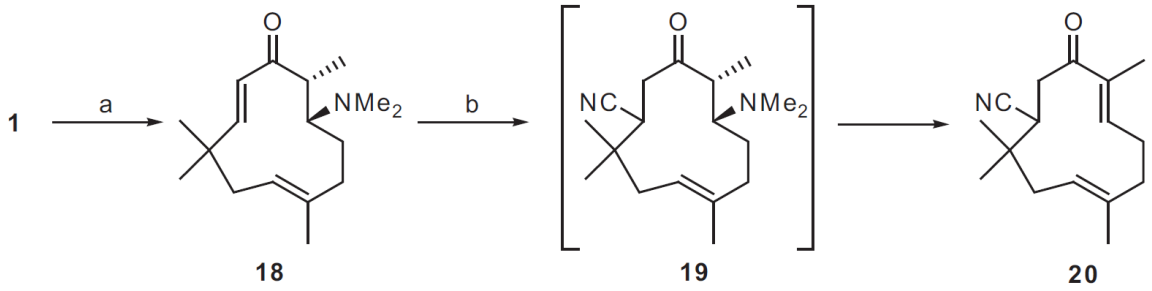
Scheme 4. Reagents and conditions: (a) *m*CPBA, EtOAc, rt, 24 h, 97%; (b) NH_3 or $BuNH_2$ or $BnNH_2$, MeCN, rt, 5 days, 51% (**13**), 15% (**14**), 18% (**15**); (c) Ac_2O, pyridine, 0 °C, 10 h, 66%.

The reaction of 1 with excess KCN at 40 ^oC for 3 days provided a mixture of four diastereoisomeric dicyano derivatives **17**. It was reported that in the major diastereoisomer (**17a**), two cyano groups were located on the same face of the ring while the two methyl groups at C2 and C6 lie on the opposite face (Scheme 5).



Scheme 5. Reagents and conditions: (a) excess KCN, MeCN-H_2O, 40 °C, 3 days, 42% (**17a**).

Treatment of **1** with dimethylamine in the presence of acetonitrile, followed by stirring with excess KCN, the nitrile derivative **20** was detected. This can be explained as that conjugate addition of dimethylamine at C3 gave intermediate **18**, while conjugate addition of the cyanide ion at C10 yielded intermediate **19**. After the easy elimination of the dimethylamino group, cyano **20** was observed as a sole product (Scheme 6).



Scheme 6. Reagents and conditions: (a) Me_2NH, MeCN, rt, 5 days; (b) KCN, MeCN-H_2O, 15 °C, 2 days, 30% in two steps.

Zerumbone (**1**) and its derivatives were tested for their cytotoxicity against CCA cell lines and their activities are shown in Table 1.

Compounds **5**, **10**, **14** and **20** exhibited cytotoxic activity against all CCA cell lines to different extents, indicating their broad spectrum of anti-CCA effects. The chemical structure diversity of the four compounds reflects the biological activities.

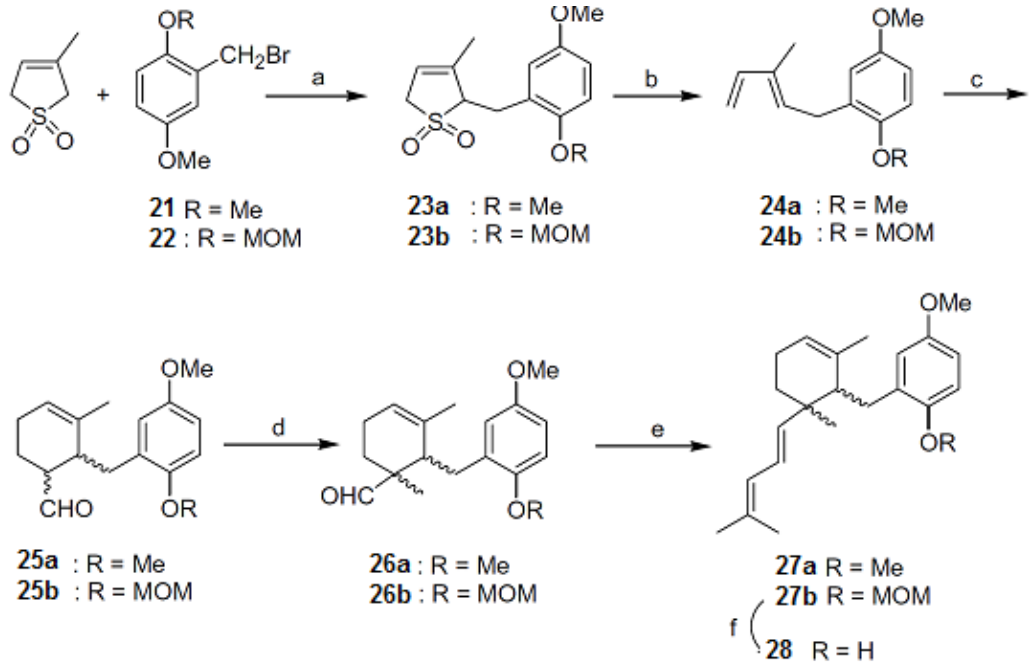
The presence of amine (**5**), hydroxylamine (**10**), epoxyamine (**14**), and nitrile (**20**) groups is believed to play an important role in potent anticancer activities. Among the tested compounds, **5**, which contained an amine group, exhibited higher potency. The docking result also indicates that **5** may inhibit the proliferation of cancer through EGFR inhibition.

Table 1
Cytotoxicity of all compounds against cholangiocarcinoma cell lines.[a]

Compound	IC_{50}(μM)				
	KKU-100	KKU-M139	KKU-M156	KKU-M213	KKU-M214
Zerumbone	NR	NR	NR	NR	NR
5	16.44 ± 0.59	63.26 ± 5.48	69.04 ± 5.40	51.88 ± 2.25	59.65 ± 7.39
6	NR	NR	NR	36.61 ± 0.65	41.55 ± 0.58
10	35.33 ± 5.89	19.63 ± 1.26	26.34 ± 4.0	27.19 ± 1.29	16.05 ± 6.06
12	NR	NR	NR	NR	52.61 ± 3.88
13	NR	NR	NR	NR	18.30 ± 0.39
14	16.52 ± 0.84	NR	48.20 ± 1.85	37.63 ± 2.4	51.00 ± 0.78
17a–d	NR	NR	NR	NR	66.52 ± 3.63
20	25.72 ± 2.60	55.88 ± 4.4	37.30 ± 3.58	45.12 ± 0.89	54.50 ± 1.5
Other	NR	NR	NR	NR	NR
Ellipticine	25.21 ± 0.2	4.5 ± 0.28	9.34 ± 1.66	1.62 ± 0.08	1.01 ± 0.02

NR = no response at > 75 μM.
[a] Data shown are from triplicate experiments.

Khan and co-worker reported a novel approach to synthesize riccardiphenol B analogs and have tested the cytotoxic activity against a variety of cancer cell lines including HuCCT-1 which was derived from an intrahepatic cholangiocarcinoma.[8]



Scheme 7

Reagents: (a) LiHMDS, HMPA, THF; (b) pyridine, reflux; (c) sealed tube, toluene; (d) NaH, MeI, THF; (e) prenyl phosphonate; (f) HCl,

In their synthesis, 3-methyl-3-sufolene was first alkylated with the substituted benzylic bromides in the presence of HMPA and LiHMDS as the base gave a colorless, viscous liquid, which was characterized as 2-(2-methoxymethoxy-5-methoxybenzyl)-3-methyl-3-sulfolene **23b**. The adduct **23b** was subjected to thermolysis by refluxing in pyridine gave compound **24b**. The Diels–Alder reaction was carried out between the diene **24b** and acrolein as the dienophile, in the presence of hydroquinone in a sealed tube at 90 ^{o}C for 2 h yielded the adduct **25b**. The compound **25b** was methylated using methyl iodide and NaH in dry THF yielded **26b** as a colorless, viscous liquid. The reaction of Prenyl phosphonate with the LDA in THF gave the corresponding ylide, which was treated with aldehyde **26b** to give the required product **27b** in 17% yield. Further, the deprotection of MOM with HCl in THF gave compound **28** (Scheme 7). The synthesized compounds were characterized and assessed for its in vitro activity in a panel of human cancer cell lines of differing origin. The leading riccardiphenol analog, **28**, significantly inhibits the growth of different human cancer cells including HuCCT-1 which was derived from an intrahepatic cholangiocarcinoma (Figure 1).

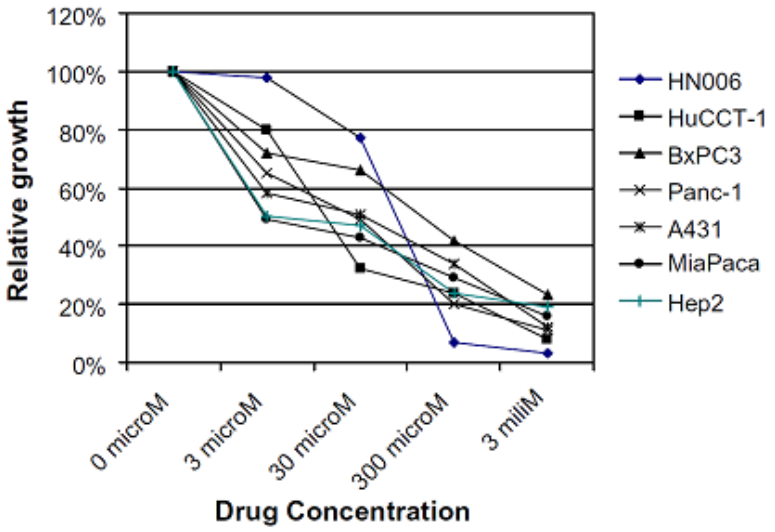
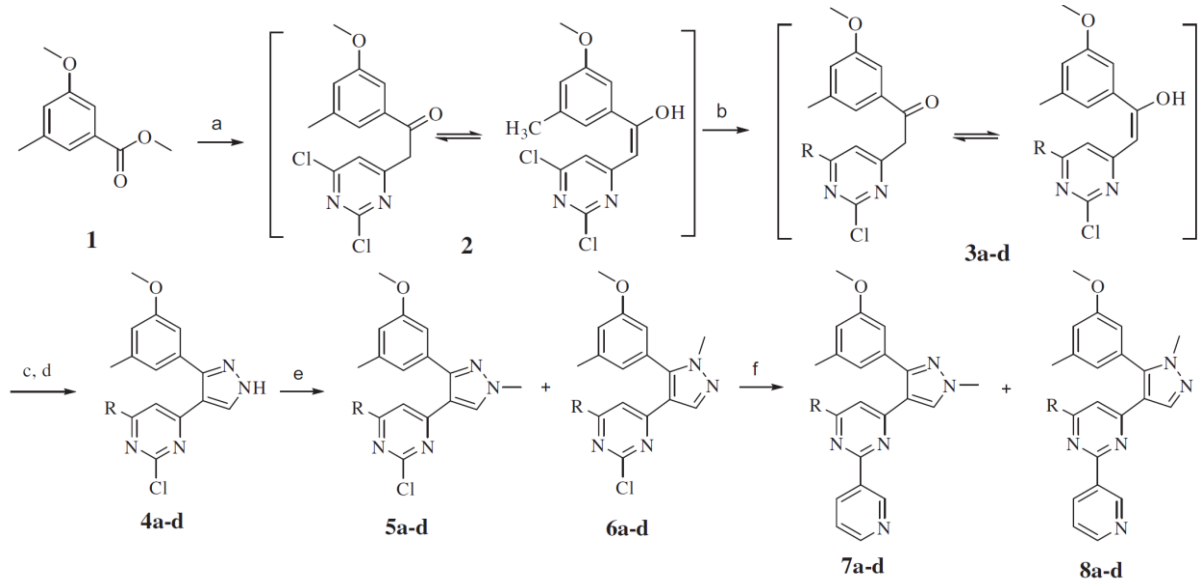
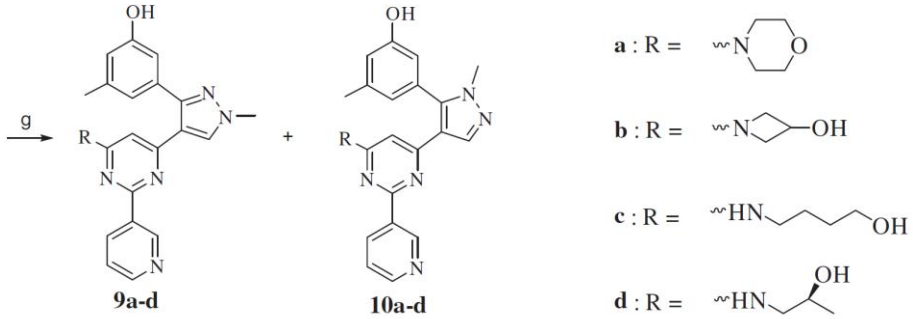


Figure 1. MTT assay in a panel of seven human-derived cancer cell lines from different origins. Relative growth after exposure to increasing concentrations of compound **28**

Recently, inhibition of ROS1 kinase has proven to be a promising strategy for several indications such as glioblastoma, non-small cell lung cancer (NSCLC), and cholangiocarcinoma. So Ha Lee and co-worker reported trisubstituted pyrazole-based ROS1 inhibitors by which two inhibitors showed good IC_{50} values in enzyme-based screening.[9]

Trisubstituted pyrazole-based scaffold has been built for study the SAR for as ROS1 inhibitors. Consequently, 16 compounds have been designed, synthesized and evaluated for ROS1 inhibition.





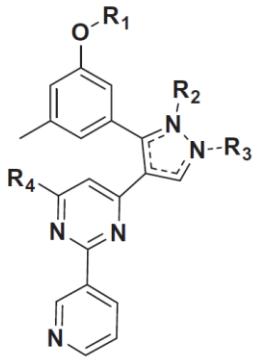
Scheme 8. Reagents and conditions: (a) LHMDS, 2,4-dichloro-6-methylpyrimidine, THF, N_2, rt, 24 h, 81%; (b) various amine, Hünig's base, EtOH, 50 °C, 5 h; (c) DMF-DMA, 90 °C, 12 h; (d) hydrazine hydrate, abs. EtOH, rt, 2 h; (e) K_2CO_3, iodomethane, DMF, rt, 2 h; (f) 3-pyridineboronic acid, $Pd(PPh_3)_2Cl_2$, K_2CO_3, N_2, CH_3CN/H_2O (4:1), 78 °C, 2 h; (g) $BF_3{\cdot}S(CH_3)_2$, dichloromethane, N_2, rt, 24 h.

The synthesis of trisubstituted pyrazole compounds **7**–**10** is outlined in Scheme 8. Lithium hexamethyldisilazide (LHMDS) was selected for attacking a benzoate ester **1** by 2,4-dichloro-6-methylpyrimidine in dry THF to give the adduct with a mixture of keto and enol tautomers **2**. A SNAr reaction was used to substitute 4-chloro group on pyrimidine of the resulted tautomeric unsaturated ketone **2** with four amines, morpholine, 3-hydroxyazetidine, 4-hydroxybutylamine, and (S)-2-hydroxypropylamine to give **3**. The conversion of the resulted 6-substituted products **3a**–**d** to the required pyrazole derivative **4a**–**d** was achieved through two successive steps. In the first step, compound **3a**–**d** was heated with excess N,N-dimethylformamide dimethylacetal for 12 h, and was cyclized with hydrazine monohydrate in absolute ethanol into the pyrazole derivative **4a**–**d**. The reaction of the resulted pyrazole **4a**–**d** with iodomethane in the presence of excess potassium carbonate produced two different regioisomers, compounds **5a**–**d** and **6a**–**d**. Then Suzuki coupling of compound **5a**–**d** and **6a**–**d** with 3-pyridineboronic acid produced compounds **7a**–**d** and **8a**–**d** in the presence of dichlorobis(triphenylphosphine)Pd(II) and potassium carbonate in a mixed solvent of acetonitrile and water (4/1, v/v). The final hydroxyl products **9a**–**d** and **10a**–**d** were obtained by demethylation of the methoxy group of compounds **7a**–**d** and **8a**–**d** using 10 equiv of borontrifluoride–dimethylsulfide complex in dichloromethane (Scheme 8).

The synthesized compounds shown potent IC_{50} values in the enzymatic assay, which are from 13.6 to 283 nM (Table 2). Among these compounds, compound **9a** (IC50 = 13.6 nM) has exerted 5 fold potency than crizotinib and exhibited high degree of selectivity (selectivity score value = 0.028) representing the number of non-mutant kinases with biological activity over 90% at 10 lM. The detailed SAR data demonstrates that pyrazoles having hydrophobic-disubstituted phenyl ring, small alkyl group, and disubstituted nucleus with solvent exposure and hinge region is very effective structure for ROS1 inhibition. All of the final potent compounds possess the essential distal pyridine group which interacts with Met2029 representing the key interaction with ROS1 and being responsible for their inhibitory activity.

Table 2

The IC_{50} values of compounds **7**–**10** against ROS1 kinase

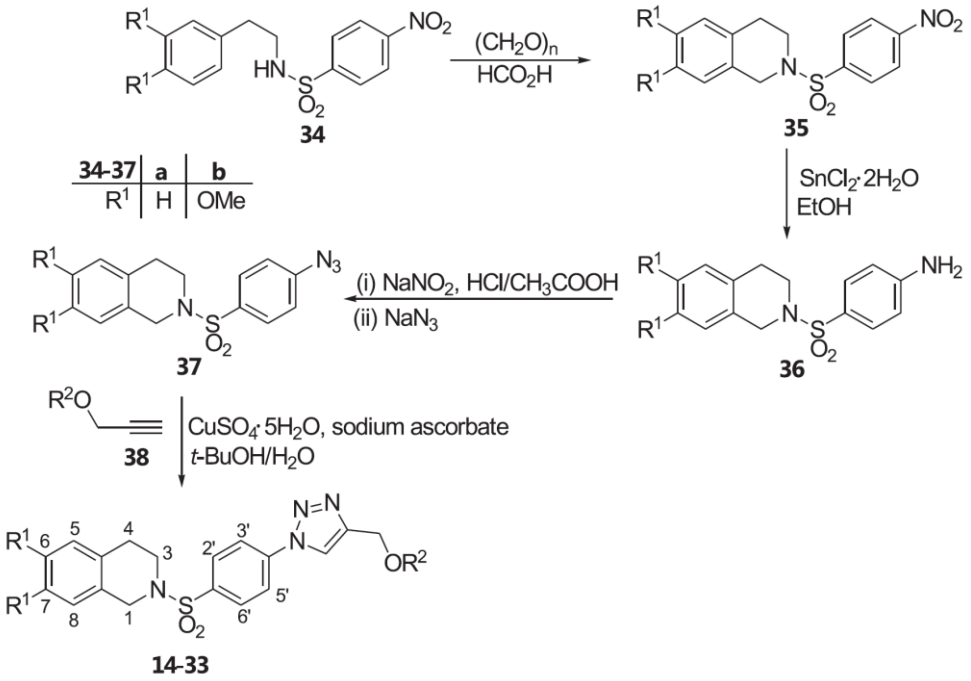


7-10

Compd	R_1	R_2	R_3	R_4	ROS1, (IC_{50}, nM)[a]
7a	CH_3	—	CH_3	Morpholino	59.1
7b	CH_3	—	CH_3	3-Hydroxyazetidin-1-yl	108
7c	CH_3	—	CH_3	4-Hydroxbutylamino	63.8
7d	CH_3	—	CH_3	(*S*)-2-Hydroxypropylamino	241
8a	CH_3	CH_3	—	Morpholino	104
8b	CH_3	CH_3	—	3-Hydroxyazetidin-1-yl	74.2
8c	CH_3	CH_3	—	4-Hydroxbutylamino	138
8d	CH_3	CH_3	—	(*S*)-2-Hydroxypropylamino	283
9a	H	—	CH_3	Morpholino	13.6
9b	H	—	CH_3	3-Hydroxyazetidin-1-yl	86.5
9c	H	—	CH_3	4-Hydroxbutylamino	133
9d	H	—	CH_3	(*S*)-2-Hydroxypropylamino	105
10a	H	CH_3	—	Morpholino	91.5
10b	H	CH_3	—	3-Hydroxyazetidin-1-yl	56.6
10c	H	CH_3	—	4-Hydroxbutylamino	25.4
10d	H	CH_3	—	(*S*)-2-Hydroxypropylamino	139
con[b]	—	—	—	—	60.0

[a] 10-dose IC_{50} mode with 3 fold serial dilutions starting at 20 μM concentration.
[b] Crizotinib.

Several new N-benzenesulfonyl-1,2,3,4-tetrahydroisoquinolines (**14**-**33**) were synthesized using the modified Pictete Spengler reaction by treatments of nitrobenzenesulfonamides **34** with paraformaldehyde in refluxing formic acid to furnish 1,2,3,4-tetrahydroisoquinolines **35** in good yields. Reduction of the nitro derivatives **35** was performed using stannous chloride in refluxing ethanol to give aminobenzenesulfonamides **36**. Conversion of the amino compounds **36** to the corresponding azidobenzensulfonamides **37** was readily achieved through diazotization reaction using sodium nitrite in a mixture of glacial acetic acid and concentrated hydrochloric acid in the presence of sodium azide. Finally, cycloaddition reaction (the Click chemistry) of the azides **37** with various alkynes **38** obtaining from alkylation of the appropriate phenol derivatives with propargyl bromide afforded a variety of the desired triazoles **14**-**33** (Scheme 9) in moderate to good yields (45-94%).[10]



Scheme 9

Synthesis of *N*-benzenesulfonyl-1,2,3,4-tetrahydroisoquinoline based triazoles

A series of N-benzenesulfonyl-1,2,3,4-tetrahydroisoquinolines were preliminarily evaluated in vitro as antiproliferative agents against HuCCA-1 (cholangiocarcinoma) cell line. Results showed that substituents (R^1) on the isoquinoline ring and substituents (R^2) on the triazole core play important roles in governing their cytotoxicities. The ester analog **20** was shown to be the most potent compound against HuCCA-1 (IC_{50} 0.63 μM) (Figure 2).

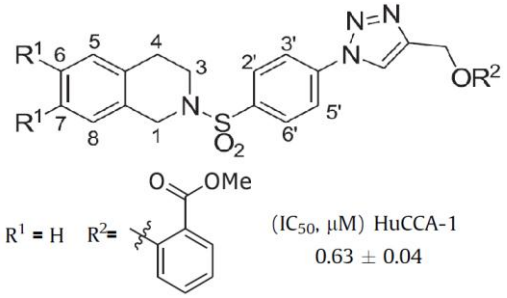
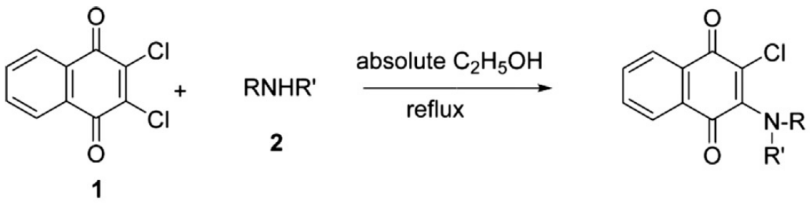


Figure 2 The most potent synthetic N-benzenesulfonyl-1,2,3,4-tetrahydroisoquinolines

A series of 2-substituted amino-3-chloro-1,4-naphthoquinone derivatives (**3**-**12**) were synthesized (Scheme 10) as anticancer agents and tested against HuCCA-1 (cholangiocarcinoma) cell line.



3 : R = H, R' = *n*-C_4H_9
4 : R = H, R' = C_6H_5
5 : R = H, R' = 8-aminoquinolinyl
6 : R = CH_3, R' = C_6H_5
7 : R = H, R' = C_6H_4-CO_2H-*o*
8 : R = H, R' = C_6H_4-$COCH_3$-*m*
9 : R = H, R' = C_6H_4-$COCH_3$-*p*
10 : R = H, R' = CH_2CH_2-C_6H_5
11 : R = H, R' = CH_2CH_2-C_6H_3-3,4-diOMe
12 : R = H, R' = C_6H_4-NH-C_6H_5-*p*

Scheme 10 Synthesis of aminonaphthoquinone derivatives

Cytotoxic activities of the synthesized aminoquinone compounds (**3**-**12**) and parent compound (**1**) were tested against HuCCA-1 (cholangiocarcinoma) cell line using etoposide and doxorubicin as reference drugs (Table 3).

Among all the tested compounds, acetylphenylaminoquinone compounds (**8** and **9**) were shown to be the most active compounds. Compounds **1**, **3**, **7**, **10** and **11** were inactive to weakly active compounds. In addition, compounds **4**, **5**, **6** and **12** displayed cytotoxic activity against HuCCA-1.

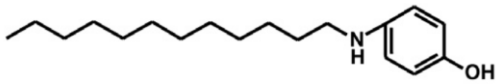
Significantly improved cytotoxic activities were found in compounds bearing acetylphenylamino substitutions (**8** and **9**). The enhanced effect of amino substituents is the following order: acetylphenylamino > quinolinylamino > alkylamino > phenylalkylamino. The most potent cytotoxic activity was found to be macetylphenylamino-1,4-naphthoquinone (**8**) affording IC_{50} values of 2.364 μM.[11]

Table 3
Cytotoxic activity of compounds **1** and **3**–**12**

Compound	IC_{50} (μM)
	HuCCA-1
1	19.204 ± 0.51[a]
3	61.163 ± 4.20[a]
4	8.636 ± 0.35[b]
5	7.916 ± 0.64[b]
6	5.206 ± 0.07[b]
7	50.134 ± 0.66[a]
8	2.364 ± 0.53[b]
9	3.285 ± 1.03[b]
10	inactive[c]
11	inactive[c]
12	10.672 ± 0.42[a]
Etoposide	–[d]
Doxorubicin	0.239 ± 0.02

[a] Weakly active compound.
[b] Moderately active compound.
[c] Inactive compound.
[d] Not tested.

p-Dodecylaminophenol was developed to be an effective anticancer agent without key side-effects of these agents.[12] This compound suppresses cell growth of pancreatic cancer (MIA Paca2) and cholangiocarcinoma (HuCCT1), potentially by inhibiting ras expression and signaling through ERK pathways in MIA Paca2 cells and both ERK and Akt pathways in HuCCT1 cells. p-Dodecylaminophenol may represent a potent and useful anti-cancer drug for use against pancreatic cancer and cholangiocarcinoma that lacks their key side-effects.

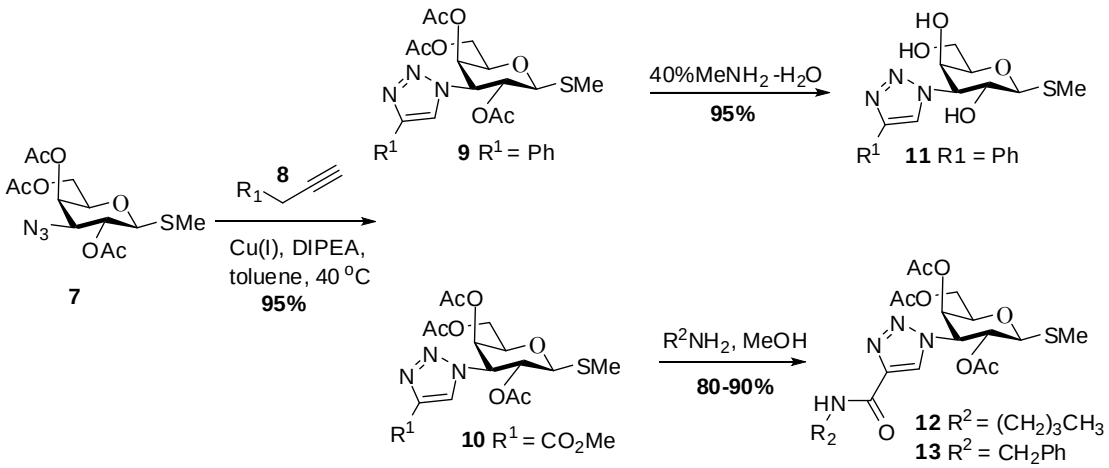


p-Dodecylaminophenol

Carbohydrates are the most abundant group of natural compounds commonly referred to sugars and starches. The glycoconjugates, are involved in important functions, as cell-cell recognition and communication, inflammation, immunological response, bacterial and viral infection, tumorigenesis and metastasis (Kumar,Seenivasan, Kumar V., &Das, 2011). Furthermore, carbohydrates linked to a heterocyclic moiety are important for bioactivity display a significant influence to the pharmacokinetics, drug targeting and mechanism of action (Kamenecka et al., 2009). Similarly, N-heterocyclic compounds, [1,2,3]-triazoles are

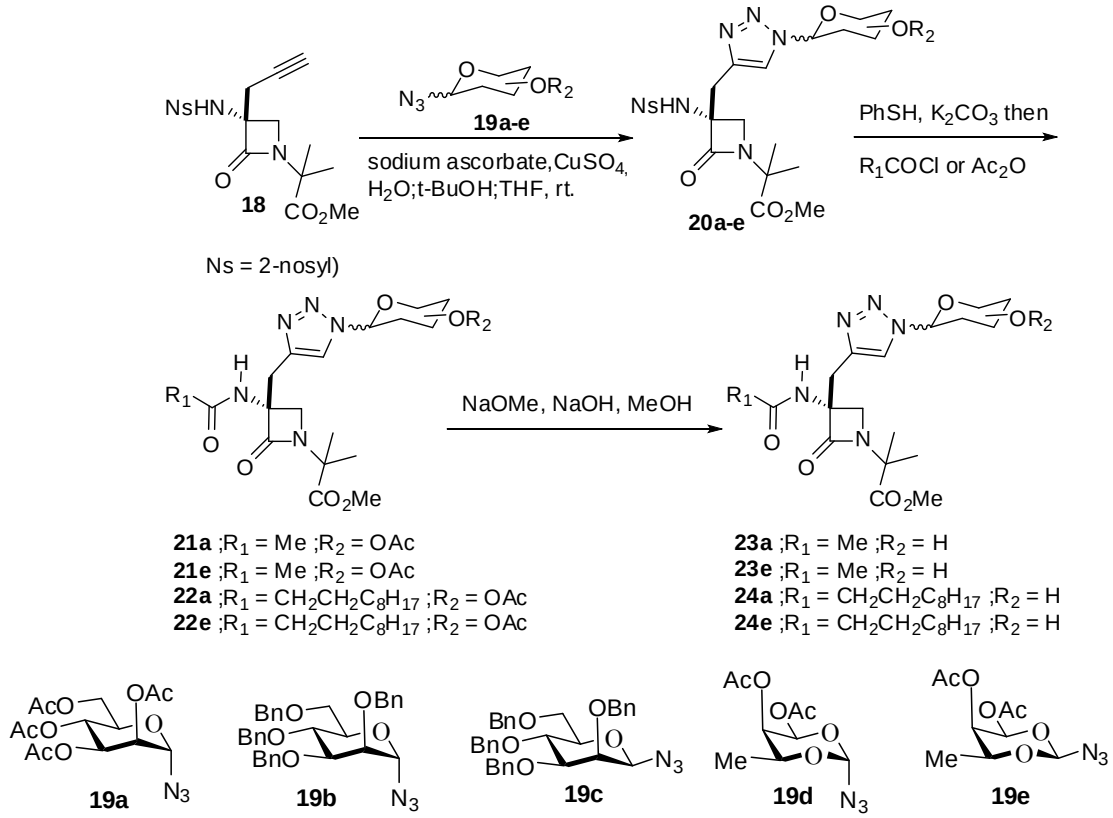
use as a linker with various active functional moiety to improve the ability to drugs discovery and exhibit wide range of bioactivities (Brak et a., 2010).

Galectin is a growing family of beta-galactoside binding protein. More than 10 galectins have been characterized in mammals, of which galectin-1 (Gal-1) and galectin-3 (Gal-3) have been extensively studied. Galectin-3 is an intra and extra-cellular lectin with a correlation of expression and functional implication in inflammation and the aggressiveness and metastatic potential of cancer. Proteomic analysis of the cholangiocarcinoma cell line in Thai people has shown high expression levels of Gal-3 and 93% of the cholangiocarcinoma cells were positive for Gal-3 staining. Contrarily, there were decreased Gal-3 expressions in some tumors, such as prostate and uterine cancers. Natural saccharides have been proposed as inhibitors of galectins. However, they are difficult to synthesize, sensitive to hydrolysis, and they are typically too polar to be used as drugs. One approach to circumvent these disadvantages of glycosides is to prepare inhibitors of galectins in which the saccharide is replaced by simpler and less polar structures. Salameh, Leffler, and Nilsson (2005) reported the three inhibitors **11-13** for the tumor and inflammation related galectin-3 with low K_d values as 107-147 µM. 3-deoxy-3-(1H-1,2,3-triazol-1-yl)-1-thio-galactosides contained with the phenyl-substituted **11**, and the butyl **12** and benzyl amides **13**, were synthesized *via* Cu(I)-catalyzed cycloaddition of methyl-3-azido-3-deoxy-1-thio-*β*-D-galactoside **7** with acetylene derivatives **8** in Cu(I), DIPEA and toluene at 40 ^{o}C. 1,4-Disubstituted triazoles **9** and **10** were obtained in high yield as single regioisomers. Finally, deprotection of **9** with methylamine in water gave **11** in 95% yields, whereas the reaction of methyl ester **10** with different amines gave a panel of 4-carbamoyltriazoles **12** and **13** in 80-90% yields (Scheme 11).



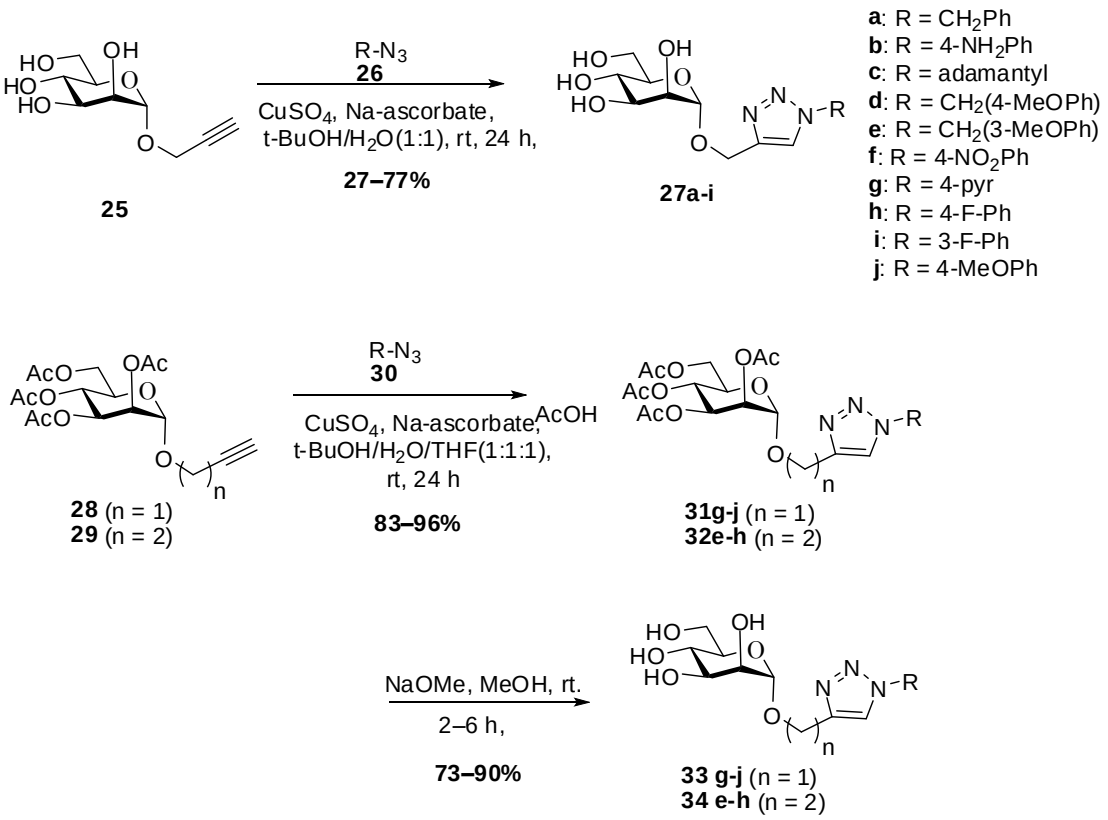
Scheme 11 Synthesis of 3-deoxy-3-(1H-1,2,3-triazol-1-yl)-1-thio-galactosides *via* Cu(I)-catalyzed cycloaddition.

Palomo et al. (2008) reported the "click" cycloaddition method to prepare R-(*N*-Glycosyltriazolyl)-*β*-lactams **20a-e** from *α*-Propargyl-*β*-lactam **18** and *O*-protected 2-azidosugars **19a-e** in the presence of Cu(II) source and ascorbate. Glycoside **20a** and **20e** were employed to *N*-denosylation and in situ *N*-acylation, followed by deprotection of acetyl groups on sugar moieties to get the desired targets **23a**, **23e**, **24a**, and **24e** for lectin binding test (Scheme 12). The results showed a clear interaction between the bind of Hybrid glycopeptide-lactam **23e** to *Ulex Europaeus Lectin-1* (UEL-1) after partially rotatable triazolylmethylene moiety.



Scheme 12 Synthesis of R-(*N*-Glycosyltriazolyl)-*β*-lactams

Schwardt et al. (2011) reported the cycloaddition of mannosyl alkynes **25** and azides **26** under Cu(I)-catalyzed click conditions to yield directly the anti-substituted triazoles **27a-i** in 27-77% yield. The protected mannosyl alkyne **28** and **29** were coupling with azides by click conditions to yield the protected triazoles **31g-j** and **32e-h**. Finally, deacetylation under Zemplen conditions gave unprotected mannosyl triazoles **33g-j** and **34e-h** (Scheme 13). All derivatives showed nanomolar affinities in a cell-based aggregation assay of the lectin FimH antagonists.



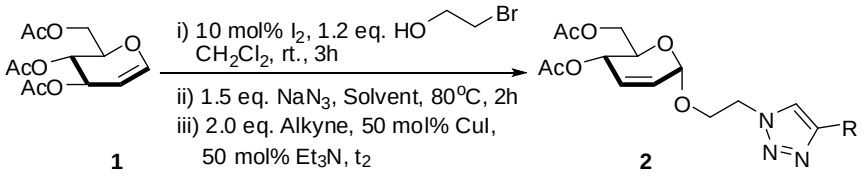
Scheme 13 Synthesis of unprotected mannosyl triazoles

From above literatures review, we displayed applicability for monosubstituted-glycosyl-1,2,3-triazole derivatives and their biological activity which utilize click chemistry for the synthesis. Glycoside substrates such as pyranoses, mannose, fucose, galactose, glucose, furanose, arabinose, ribose, maltose and disaccharide derivative were employed as substances to give several substituted 1,2,3-triazoles and their biological activities such as urinary glucose excretion, chemosensors, anti-mycobacterial, human carbonic anhydrase and enzyme inhibition were studied to obtain bioactivity data for future pharmaceutical uses.

Based on the literature reports of the importance of the triazole linked glycoside toward the tumor and inflammation related galectin-3, in this project, we designed to synthesize a new class of triazolylethyl-2,3-unsaturated-*O*-glycosides**,** 2,3-unsaturated-glycosyl triazoles and 1,4-disubstituted-1,2,3-bistriazole linked C-1, C-6 positions of α-D-glucopyranoside. The synthetic compounds will be studied as the therapeutic agent for treatment of cholangiocarcinoma.

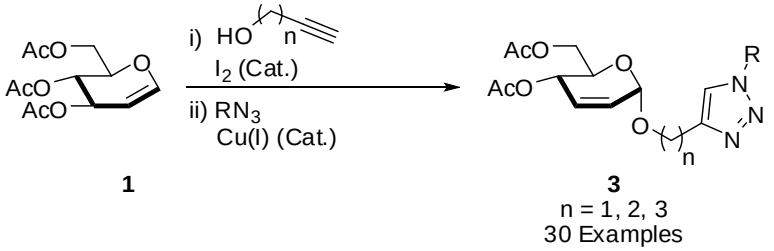
Chapter 2: Results and Discussions

In this work, part 1, we designed to synthesize a new class of triazolylethyl-2,3-unsaturated-*O*-glycosides using sequential one-pot glycosylation-azidation-CuAAc reactions procedure.



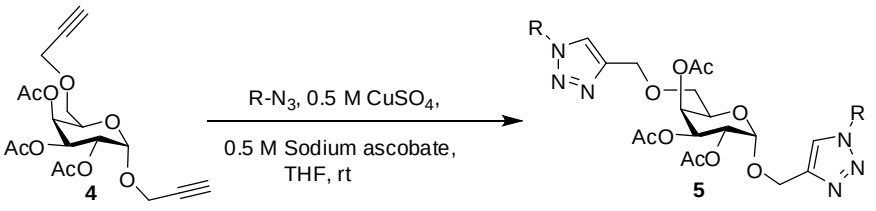
Scheme 1 Synthesis of triazolylethyl-2,3-unsaturated-*O*-glycosides **2**

In part 2, a new class of 2,3-unsaturated-glycosyl triazoles *via* one-pot two steps glycosylation click reaction and investigatation the anti-proliferative effect of triazoleglycoside on cholangiocarcinoma KKU-M213.



Scheme 2 Synthesis of 2,3-unsaturated-glycosyl triazoles **2**

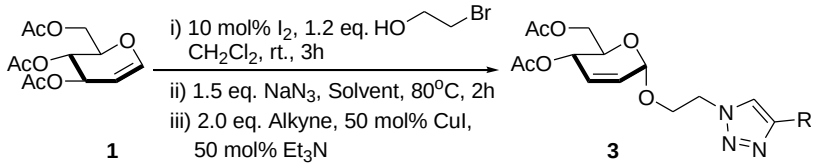
In part 3, 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl analogues were synthesized *via* click chemistry (Scheme 1). All the synthetic anologues of the bistriazole glycosides will be evaluated for anti-proliferative activity on human cholangiocarcinoma cells (KKU-M213, HUCCA-1, K-100), cancer cells.



Scheme 3 Synthesis of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl derivatives

Part 1 Synthesis of 2,3-unsaturated-*O*-glycosyl triazoles *via* one-pot three steps glycosylation azidation click reaction

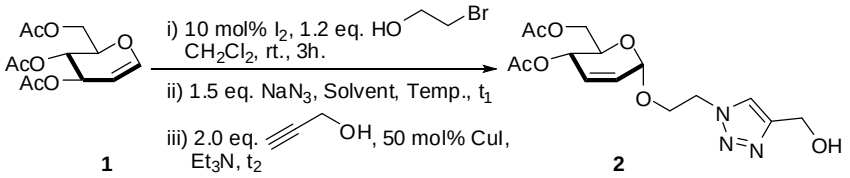
In this work, we developed a facile protocol for the synthesis triazolylethyl-2,3-unsaturated-*O*-glycoside *via* one-pot glycosylation azidation click reaction of D-glucal **1**, 2-bromoethanol, sodium azide and alkynes by using I_2 and CuI as catalysts (Scheme 1).



Scheme 1 Synthesis of 2,3-unsaturated-*O*-glycosyl triazoles **3**

To optimize this new reaction, we conducted a series of experiments to evaluate the effect of various solvents and reaction temperature. The results of the preliminary screening are listed in Table 1.

Table 1 One-pot glycosylation azidation click reaction of D-glucal **1** under various conditions

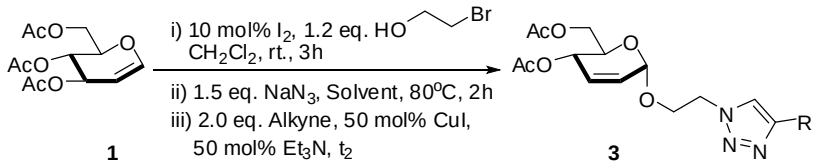


Entry	Solvent	Temp (^oC)	Et_3N (equiv)	t_1(h)	t_2 (h)	Yield[b] (%)
1	CH_3CN	RT[d]	-	20	-	-[c]
2	DMF	RT	-	5	5	94
3	DMF	80	-	2	5	>99
4	DMF	80	0.5	2	1	91

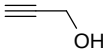
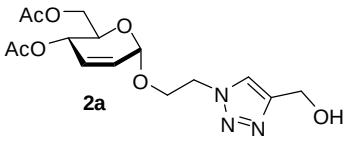
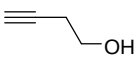
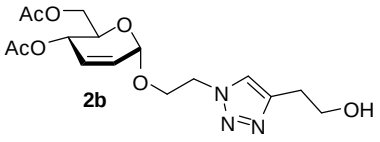
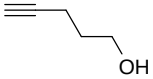
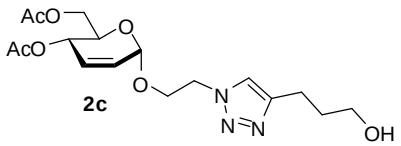
[a] All reactions were carried out with 0.073 mmol of D-glucal (1).
[b] Isolated yield was obtained as a mixture of isomers, α:β = 9:1.
[c] Trace product of 2-azidoethyl-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythrohex-2-enopyranoside.
[d] Room temperature.

One-pot glycosylation click reaction was investigated in DMF and CH_3CN by using iodine (10 mol%), D-glucal **1**, 2-bromoethanol (1.2 equiv), sodium azide (1.5 equiv) and benzyl azide (2.0 equiv). In DMF at room temperature, the product **2** was obtained in 94% yield (Table 1, entry 2). Conversely, 0% yield of product **2** resulted from the reaction carried out in CH_3CN (Table 1, entry 1). Additionally, the influence of the reaction temperature on the yield and reaction time of the reaction was also studied. Stirring the reaction in DMF at room temperature for 5 h (T_1) gave the product **2** in 94% yield (Table 1, entry 2). Increasing the reaction temperature to 80 °C, the glycosylation can be completed in 2 h (T_1) (Table 1, entry 3) and the chemical yield of the final product **2** was afforded in excellent yield. Addition of Et_3N and shorten the reaction time in click step (T_2) to 1 h, 91% yield **2** was obtained. To complete the reaction in short time, the optimized reaction conditions for the one-pot synthesis was found to be 50 mol% of Et_3N with DMF as solvent at 80 ^oC (Table 1, entry 4).

Table 2 Synthesis of 2,3-unsaturated-*O*-glycosyl triazoles **2** *via* one-pot glycosylation azidation click reaction

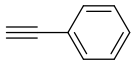
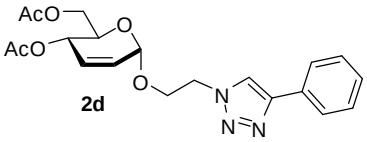
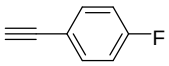
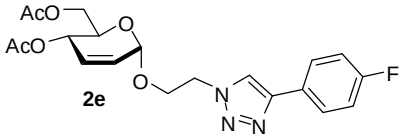
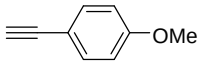
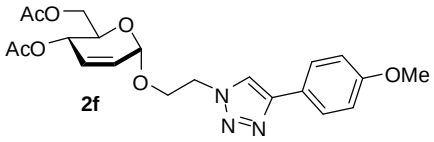
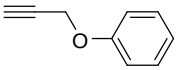
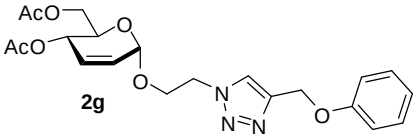
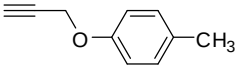
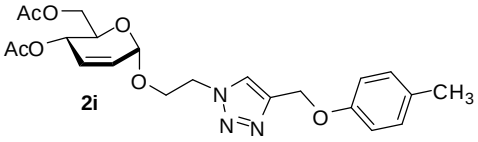
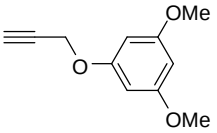
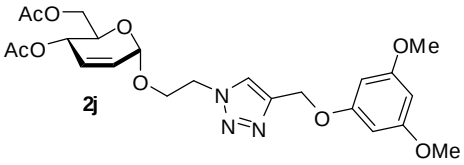
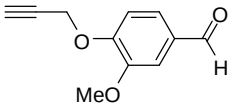
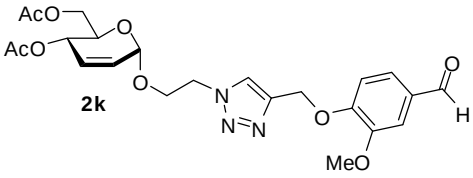


1 **3**

Entry	Akyne	t_2 (h)	Product	Yield[b] (%)
1		1	 **2a**	91
2		1.5	 **2b**	>99
3		2	 **2c**	82

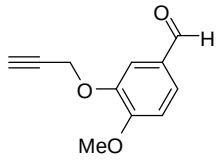
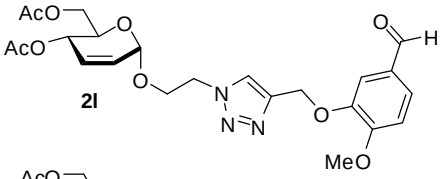
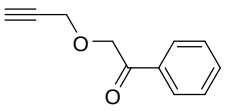
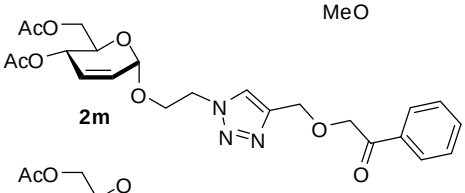
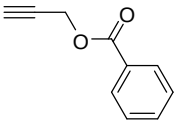
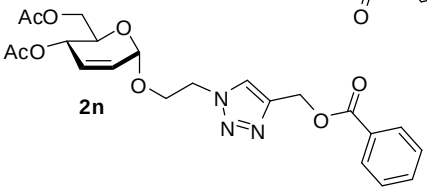
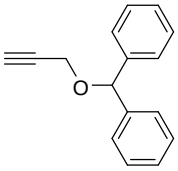
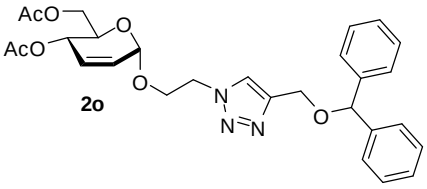
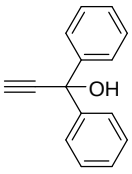
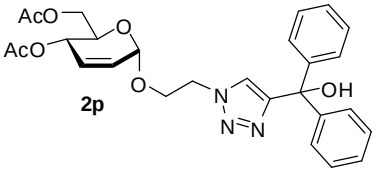
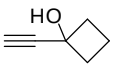
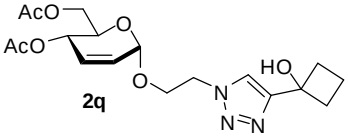
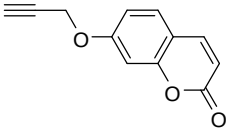
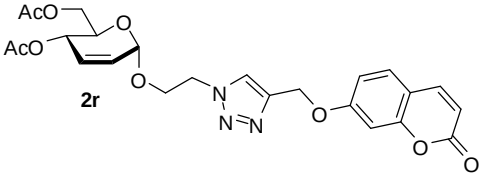
[a] All reactions were carried out with 0.073 mmol of D-glucal **(1)** .
[b] Isolated yield was obtained as a mixture of isomers, α:β = 9:1.
[c] The reactions were carried out at 40 ^oC.

Table 2 (continued)

Entry	Akyne	t_2 (h)	Product	Yield[b] (%)
4		2	 **2d**	79[c]
5		7	 **2e**	78[c]
6		24	 **2f**	88[c]
7		2	 **2g**	96
8		4	 **2i**	>99
9		1	 **2j**	>99
10		4	 **2k**	>99

[a] All reactions were carried out with 0.073 mmol of D-glucal **(1)** .
[b] Isolated yield was obtained as a mixture of isomers, α:β = 9:1.
[c] The reactions were carried out at 40 °C.

Table 2 (continued)

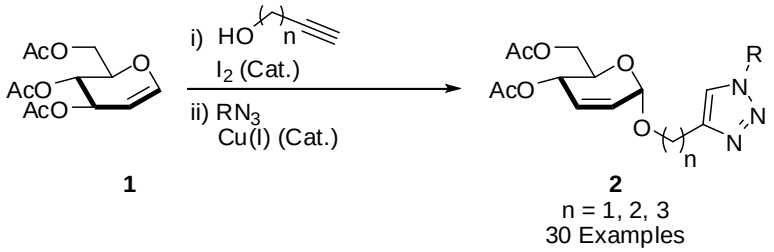
Entry	Akyne	t_2 (h)	Product	Yield[b] (%)
11		5	 **2l**	89
12		1.5	 **2m**	>99
13		4	 **2n**	>99
14		1	 **2o**	>99
15		2	 **2p**	77
16		1	 **2q**	72
17		3	 **2r**	83

[a] All reactions were carried out with 0.073 mmol of D-glucal **(1)** .
[b] Isolated yield was obtained as a mixture of isomers, α:β = 9:1.
c The reactions were carried out at 40 ºC.

To demonstrate the generality of this method, we investigated the scope of this reaction under the optimum conditions and the results are summarized in Table 2. A variety of alkynes reacted smoothly with D-glucal **1**, 2-bromoethanol and sodium azide to produce a range of 2,3-unsaturated-*O*-glycosyl triazoles **2a-2r** in good to excellent isolated yields (up to >99% in many examples). The propargyl alcohol reacted smoothly to afford **2a** in 91% yield, and the longer chain butynyl and pentynyl alcohols afforded products **2b** and **2c** in >99% and 82% yield, respectively (Table 2, entries 1-3). The use of more hindered alkynes still afforded the desired product in good yield, providing the triazole glycosides **2d** and **2e** in 77% and 72% yield (entries 4-5). Alkyne-bearing cyclobutanol was found to readily undergo cycloaddition and is well tolerated. We next examined both electron-rich and electron-deficient phenyl alkynes which were carried out at 40^{o}C and reacted smoothly to give the products **2f**-**2h** in good yields (entries 6-8). The yields were found to excellent with the propargyl ether derivatives (entries 9-12) and (entries 15-17) providing the product in quantitative yield. The benzaldehyde group-bearing propargyl ether in and were well tolerated in this one-pot reaction (entries 12-13). Alkyne containing a coumarin substituent was employed to synthesize triazole glycosides in high yield with this one pot method (entry 14).

Part 2 Synthesis of 2,3-unsaturated-*O*-glycosyl triazoles *via* one-pot glycosylation click reaction

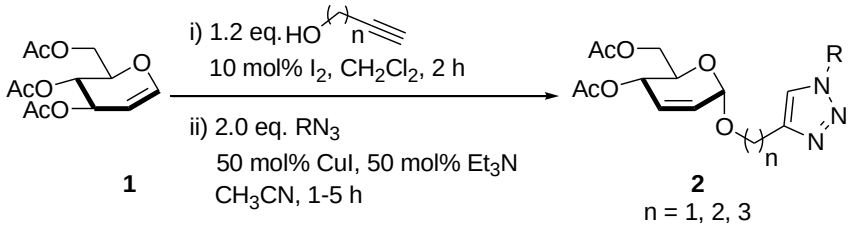
We designed to synthesize a new class of 2,3-unsaturated-glycosyl triazoles **2** *via* one-pot two steps glycosylation click reaction of readily available D-glucal **1** with alkynyl alcohols and azides using I_2 and CuI as a catalysts (Scheme 1). Thirty examples were prepared in good yields (70-99%). Some synthetic anologues will be evaluated for cytotoxic activity against HuCCA-1 (cholangiocarcinoma) cell line.



Scheme 1 Synthesis of 2,3-unsaturated-glycosyl triazoles **2**

Synthesis of 2,3-unsaturated-*O*-glycosyl triazoles *via* one-pot glycosylation click reaction by using I_2/CuI as catalyst

We herein describe the synthesis of 2,3-unsaturated-*O*-glycosyl triazoles **2** *via* one pot glycosylation click reaction from readily available D-glucal **1**, alkynyl alcohols and azides (Scheme 2).



Scheme 2 Synthesis of 2,3-unsaturated-*O*-glycosyl triazoles **2**

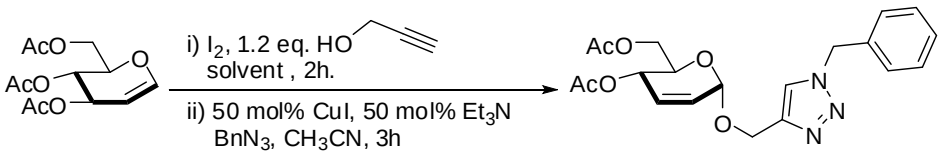
In order to optimize the reaction conditions, including catalyst loading and solvents, the reaction of D-glucal **1**, propargyl alcohol (1.2 equiv) and benzyl azide (2.0 equiv) in the presence of molecular iodine and CuI as catalyst, was selected as a model reaction in different solvents. The results are listed in Table 1.

In the presence of varying amounts of molecular iodine, the best results were obtained with the use of 10 mol% of catalyst (Table 1, entry 2). While 50 mol% of molecular iodine

was found to afford product in low yield due to the formation of side products (Table 1, entry 1).

In order to establish the best reaction conditions, we examined several organic solvents. We found that, the combination of CH_2Cl_2:CH_3CN (1:1) (Table 1, entry 3) was the good solvent system to obtain the high yield of product, while CH_3CN (entry 2) afford poor yield of product. When CH_2Cl_2 (Table 1, entry 5) was used as solvent for the synthesis of 2,3-unsaturated-*O*-glycosyl triazole **2a**, the maximum yield of the product was observed. Moreover, the yield of product decreased when the amount of BnN_3 was decreased to 1.5 equivalent (Table 1, entry 4). As mentioned above, the optimum reaction conditions were determined as following: CH_2Cl_2 was used as solvent and the catalyst loading of molecular iodine was 10 mol% for glycosylation step and the BnN_3 was 2.0 equiv for click reaction step (Table 1, entry 5).

Table 1 One-pot glycosylation click reaction of D-glucal **1** under various conditions



1 **2a**

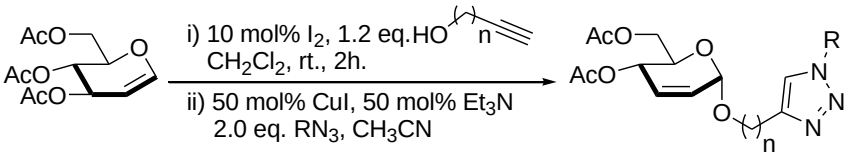
Entry	I_2 (equiv)	Solvent	BnN_3 (equiv)	Yield[a] (%)
1	50	CH_3CN	2.0	27
2	10	CH_3CN	2.0	45
3	10	CH_2Cl_2:CH_3CN (1:1)	2.0	82
4	10	CH_2Cl_2:CH_3CN (1:1)	1.5	76
5	10	CH_2Cl_2	2.0	86

[a] All reactions were carried out with 0.146 mmol of D-glucal **(1)**

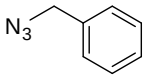
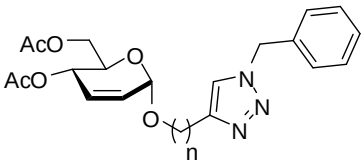
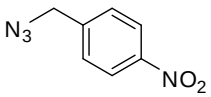
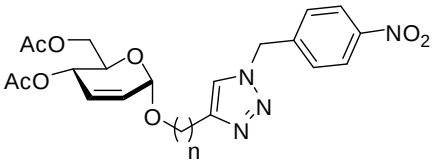
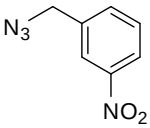
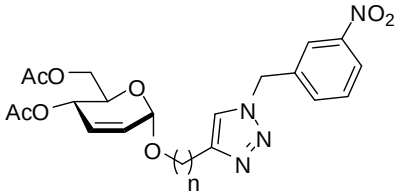
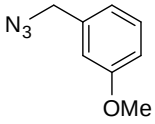
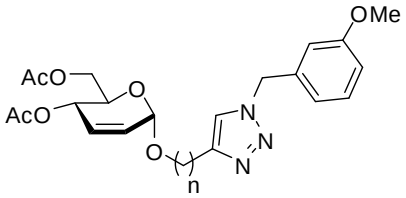
In order to determine the scope of this one pot reaction, the reaction sequence involved glycosylation of D-glucal with propargyl, butynyl, or pentynyl alcohols followed by CuACC reaction using various benzyl and long-chain aliphatic azides which were studied under the optimized reaction conditions (Table 1, entry 5). As shown in Table 2, the tandem glycosylation–click reactions of benzylazide with butynyl and pentynyl-glycosides were performed smoothly as propargyl-glycoside to give products 2b and 2c in good yields (entries

2 and 3). Changing to electron deficient nitro-benzyl azides and electron rich methoxy-and di-methoxy benzyl azides did not show significant differences in terms of the reactivity and reaction yields. The reaction went smoothly with m-nitrobenzylazide to complete conversion in the second step in 1 h, producing 4a–4c in 83–96% yields (entries 7–9). For the synthesis of triazole-glycosides with different substituents on the N-1 atom of triazole moiety, the click reaction was extended using aliphatic azides. The reaction of phenyl ethyl azide works well under this one pot condition to obtain high yield of product in shorter time (entries 19–21). Long chain aliphalic azides such as lauryl, omega-undecylenyl, and oleyl azides can be proceeded smoothly to obtain the product with comparable yield as shown in entries 22–30 (Table 2). However, the reactions of long carbon chain oleyl azide (entries 28–30) were carried out in longer time to complete the reaction.

Table 2 Synthesis of 2,3-unsaturated-*O*-glycosyl triazoles **2** *via* one-pot glycosylation click reaction



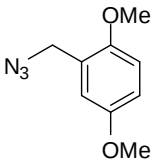
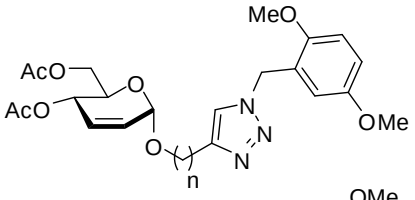
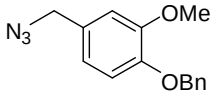
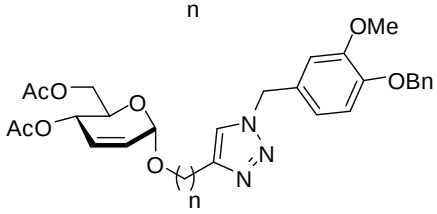
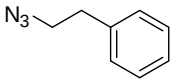
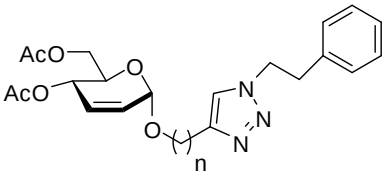
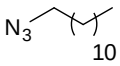
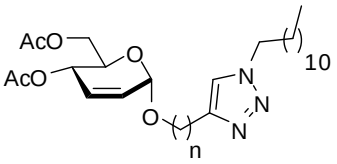
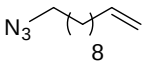
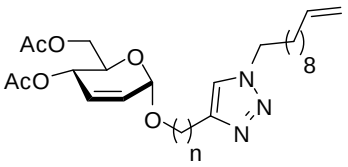
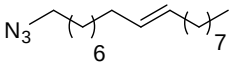
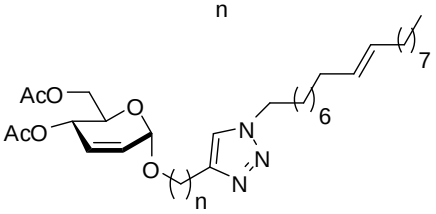
1 **2**
n = 1, 2, 3

Entry	Azide	Time (t_2)/h	Product	Yield (%)[b]
1 2 3		3 5 5		**2a**, n = 1, 86 **2b,** n = 2, 73 **2c,** n = 3, 79
4 5 6		5 2 2		**3a,** n = 1, 71 **3b,** n = 2, 84 **3c**, n = 3, 71
7 8 9		1 1 1		**4a**, n = 1, 96 **4b**, n = 2, 84 **4c**, n = 3, 83
10 11 12		3 3 2		**5a**, n = 1, 78 **5b**, n = 2, 91 **5c**, n = 3, 74

[a] All reactions were carried out with 0.146 mmol of D-glucal **(1)**

[b] Isolated yield was obtained as a mixture of isomers, when n=1, α:β = 9:1 when n=2, α:β= 10:1 when n= 3, α:β= 12:1

Table 2 (continued)

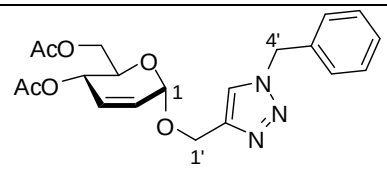
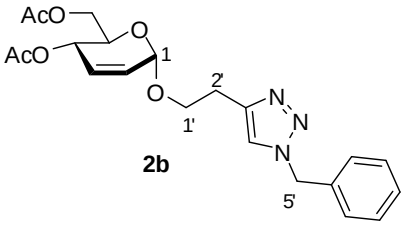
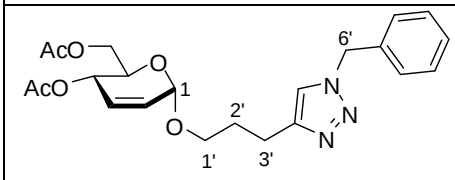
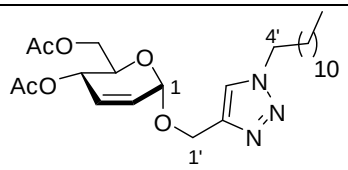
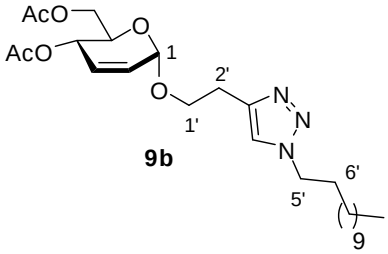
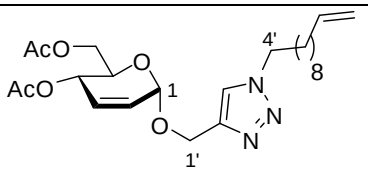
Entry	Azide	Time (t_2)/h	Product	Yield (%)[b]
13 14 15		3 2 5		**6a**, n = 1, 70 **6b**, n = 2, 89 **6c**, n = 3, 91
16 17 18		2 2 2		**7a**, n = 1, 79 **7b**, n = 2, 73 **7c**, n = 3, 73
19 20 21		1 1 1		**8a**, n = 1, 98 **8b**, n = 2, 79 **8c**, n = 3, 75
22 23 24		2 2 2		**9a**, n = 1, 85 **9b**, n = 2, >99 **9c**, n = 3, 90
25 26 27		2 2 2		**10a**, n = 1, 86 **10b**, n = 2, 82 **10c**, n = 3, 73
28 29 30		4 4 4		**11a**, n = 1, 76 **11b**, n = 2, 75 **11c**, n = 3, 71

[a] All reactions were carried out with 0.146 mmol of D-glucal **(1)**

[b] Isolated yield was obtained as a mixture of isomers, when n=1, α:β = 9:1 when n=2, α:β= 10:1 when n= 3, α:β= 12:1

We have developed a convenient and selective one-pot method for the synthesis of 30 corresponding 2,3-unsaturated-*O*-glycosyl triazoles. The method offers significant advantages, such as low toxicity, simple operation, mild reaction conditions, high yields, and low cost, which makes it an attractive process for the synthesis of 2,3-unsaturated-*O*-glycosyl triazoles.

Anti-proliferative of triazoleglycoside on cholangiocarcinoma KKU-M213

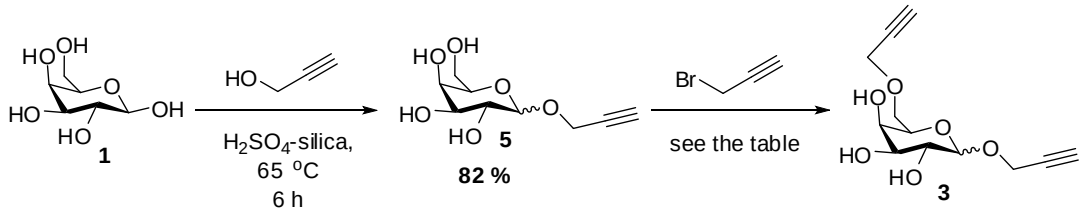
Compounds	Cell viability (% of control)		
	50 µM	100 µM	200 µM
 **2a**	88±5	90±1	82±5
 **2b**	90±2	82±2	62±5
 **2c**	88±6	85±4	69±5
 **9a**	85±2	47±4	1±5
 **9b**	75±2	33±3	1±4
 **10a**	84±7	76±6	29±2

The anti-proliferative activity of the synthesized *O*-glycosyl triazoles compounds (**2**, **9** and **10**) were evaluated on human cholangiocarcinoma cells (KKU-M213), cancer cells derived from Thai patient as shown inTable 1. The compounds **9a** and **9b** showed the greatest effect on cell viability, at the concentrations ranging from 50 to 200 µM.

Part 3 Synthesis of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl analogues

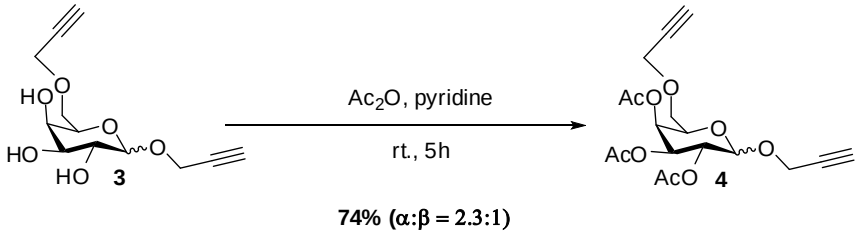
In this work, we designed to synthesize a new class of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl analogues via click chemistry (Scheme 1). All the synthetic anologues of the bistriazole glycosides will be evaluated for anti-proliferative activity on human cholangiocarcinoma cells (KKU-M213, HUCCA-1, K-100), cancer cells.

In the first part, bis-propargyl glycoside was prepared for using as precursor for synthesis of our target 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl analogues. Bis-*O*-propargyl-D-glucopyranosides was prepared *via* three-steps process using commercial available *O*-methyl-D-glucopyranose as a starting material. The reaction was shown in scheme **1**.



Scheme 1 Synthesis of diacetylene glycoside **3** from galactopyranoside

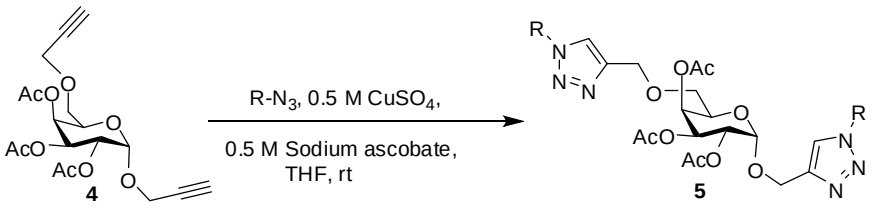
The synthesis of **4** was commenced with selective *O*-glycosylation of D-(+)-galactopyranoside **1** using propargyl alcohol as nucleophile and solvent. H_2SO_4-slilca was used as catalyst, the reaction was heat at 65 ^oC for 6 h to afford the mixture isomer of galactopyranoside **5** in high yields (82%). Regioselective *O*-propargylation reaction of primary alcohol at C-6 position of **5** is a difficult and complicated. Therefore, the optimum conditions for the synthesis of compound **3** to give the best results were studied. With compound **3** in hand, acetylation of the remaining hydroxyl grups were performed by using Ac_2O in pyridine to afford 1,6-di-*O*-propargyl-2,3,4-di-*O*-acetylgalactoside **4** in high yield.



Scheme 2 Acetylation of 1,6-di-*O*-propargyl-2,3,4-tri-hydoxylgalactoside **3**

The new derivative of 1,6-di-*O*-propargyl-2,3,4-tri-*O*-acetylgalactoside **4** was prepared *via* three-steps process using commercial available D-(+)-galactopyranoside **(9)** as a starting material. Diacetylene glycoside **4** will be used as a precursor to prepare various bis-triazole

glycosides as shown in Table 1 for study the cytotoxic activity on human cholangiocarcinoma cells (KKU-M213, HUCCA-1, K-100).



Scheme 3 Synthesis of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl derivatives

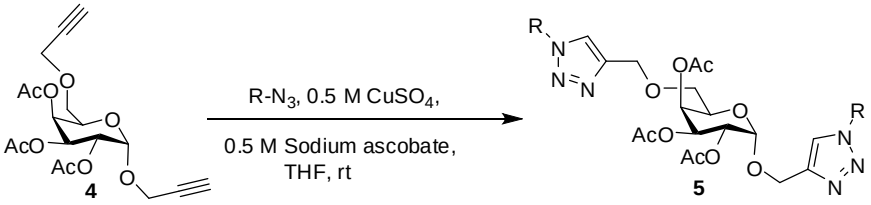
Synthesis of 1,6-di-triazolyl-glycopyranoside analogues

A series of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl derivatives as were synthesized as shown in Scheme 2 and Table 1. The corresponding azides include with derivatives of benzyl, 2-ethoxybenzene, aliphatic, coumarin azides, derivatives of 2-azidoacetates with diacetylene glycosides were performed by dissolve in THF followed by the addition of catalytic sodium ascorbate and $CuSO_45H_2O$. The products were obtained in short reaction time and the results of quantitative conversions and purities were found from 37% to 99% yields.

Reaction of the benzylazide derivatives with diacetylene glucoside **11** (Table 1, entries 1-8) showed moderate to high conversions depending on the substituted on aromatic ring (56-93%yeilds). Click reactions of the phenylether azide derivatives were performed in 5-10 min. to give the product in 67-91%yields (Table 1, entries 10-14). Moreover, long chain aliphatic azides gave good yields of the desired products (Table 1, entries 15-18). Azide with substituted aromatic gave moderate to high yields of the desired bis-triazole glycoside depending on the electronic factor of substituents.

Furthermore, three derivertives of coumarin-glycoside were prepared with the high yields which were showed in the entries 30 and 31, but unstable 3-(2-(triazolyl)acetyl)-coumarin **ee** (entry 2**9)** can be decomposed in purification with silica gel column to give low yield of product.

Table 1 Synthesis of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl derivatives



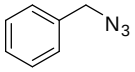
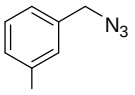
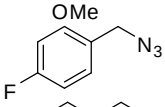
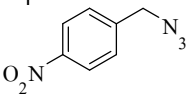
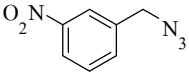
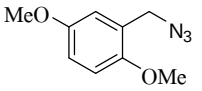
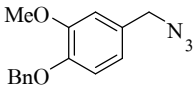
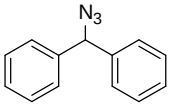
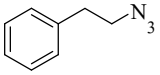
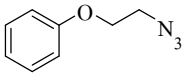
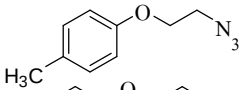
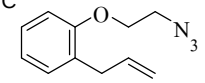
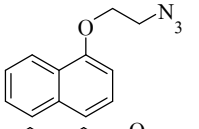
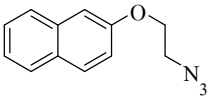
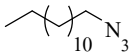
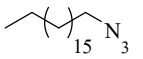
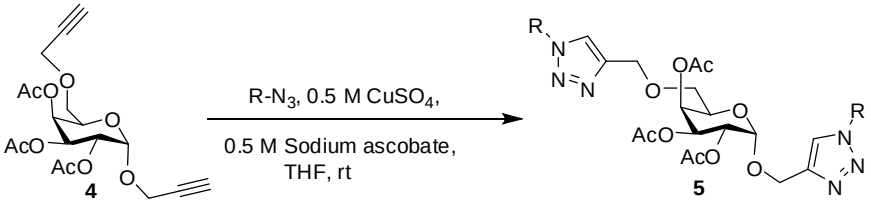
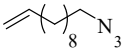
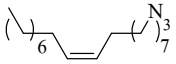
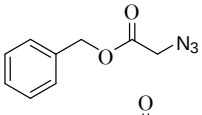
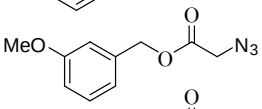
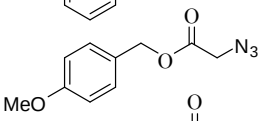
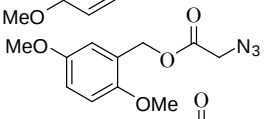
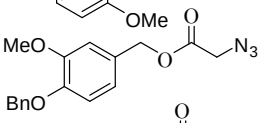
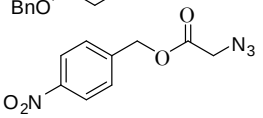
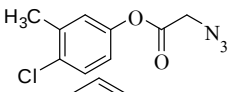
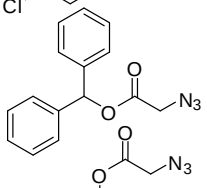
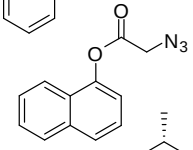
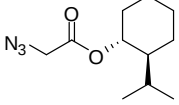
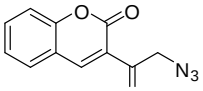
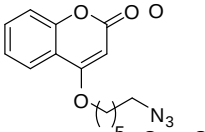
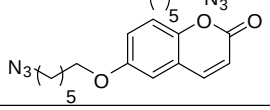
entry		R-N_3	12 t (min)	12 %yield
1	**a**		10	82
2	**b**		30	86
3	**c**		5	72
4	**d**		5	70
5	**e**		5	56
6	**f**		5	93
7	**g**		5	60
8	**h**		5	85
9	**i**		10	91
10	**j**		5	73
11	**k**		5	78
12	**l**		5	83
13	**m**		10	73
14	**n**		5	67
15	**o**		1h	61
16	**p**		5h	63

Table 1 Synthesis of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl derivatives



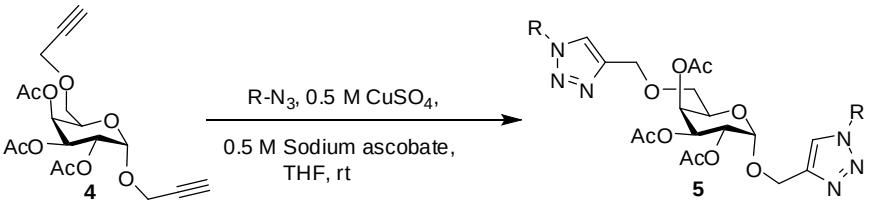
entry		R-N_3	11	
			t (min)	%yield
17	**q**		1.5h	70
18	**r**		12h	67
19	**s**		5	99
20	**t**		5	95
21	**u**		5	99
22	**v**		5	49
23	**w**		5	62
24	**x**		5	99
25	**y**		5	43
26	**z**		10	75
27	**aa**		10	76
28	**bb**		10	99
29	**cc**		5	37
30	**dd**		30	98
31	**ee**		30	99

Cytotoxic activity of 1,6-bis-triazole-tri-*O*-acetyl-α-D-galactopyranosyl derivatives

All the synthetic compounds were assayed for their cytotoxic activity against human cholangiocarcinoma cells (KKU-M213, HUCCA-1, K-100) cancer cells by MTT assay. The results were summarized in Table 2.

The structure activity relationship of the compounds showed that compound 5q with unsaturated aliphatic long chain on triazole rings exhibited moderate activity against all cancer cell lines compared to other tested compounds. Compounds 5k, 5l and 5aa were found to be active against KKU-M213 whereas compounds 4 and 5m were active against K-100 cell lines. Among the tested compounds, compound 5 ee exhibited pronounced cytotoxicity against K-100 cell lines with IC50 4.87 mM. Remaining compounds displayed no activity against the cell lines tested.

Table 2 Cytotoxic activity of 1,6-bis-triazole-tri-*O*-acetyl-α-D-galactopyranosyl derivatives



Entry	Compounds	ED_{50} (μM)[a] (SRB assay)		
		KKU-M213	HUCCA-1	K-100
1	**4**	>50	>50	28.36±1.93
2	**5a**	>50	>50	>50
3	**5b**	>50	>50	>50
4	**5c**	>50	>50	>50
5	**5d**	>50	>50	>50
6	**5e**	>50	>50	>50
7	**5f**	>50	>50	>50
8	**5g**	>50	>50	>50
9	**5h**	>50	>50	>50
10	**5i**	>50	>50	>50
11	**5j**	>50	>50	>50
12	**5k**	48.08±0.28	>50	>50
13	**5l**	37.62±0.96	>50	>50
14	**5m**	>50	>50	42.35±0.82
15	**5n**	>50	>50	>50
16	**5o**	>50	>50	>50
17	**5p**	>50	>50	>50
18	**5q**	22.58±4.53	28.71±1.17	14.87±1.52
19	**5r**	>50	>50	>50
20	**5s**	>50	>50	>50
21	**5t**	>50	>50	>50
22	**5u**	>50	>50	>50
23	**5v**	>50	>50	>50
24	**5w**	>50	>50	>50

25	**5x**	>50	>50	>50

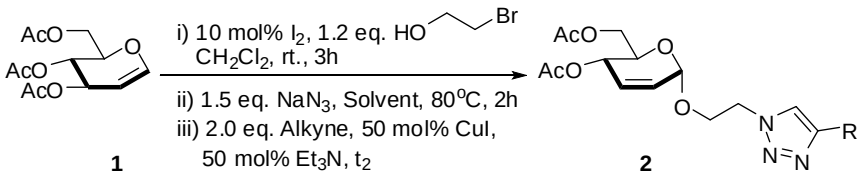
Table 2

Entry	Compounds	ED_{50} (μM)[a] (SRB assay)		
		KKU-M213	HUCCA-1	K-100
27	**5z**	>50	>50	>50
28	**5aa**	48.52±2.58	>50	>50
29	**5bb**	>50	>50	>50
30	**5cc**	>50	>50	>50
31	**5dd**	>50	>50	>50
32	**5ee**	>50	>50	4.87±0.37
ellipticine		3.42±0.74	3.15±1.63	4.51±0.23

[a]Each value represents mean±SD from three different experiments performed in triplicate. Cell lines used are human cholangiocarcinoma cells (KKU-M213, HUCCA-1, K-100), cancer cells derived from Thai patient. Ellipticine (Ellipt) was used as a positive control. The results were expressed as ED_{50} values (drug concentration causing 50% growth inhibition) in μM.

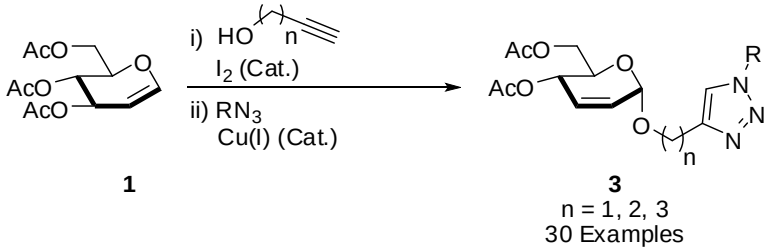
Chapter 3: Conclusions

Part I, We have successfully demonstrated the efficient synthesis of new class of triazolylethyl 2,3-unsaturated *O*-glycoside derivatives with good α-anomeric selectivity in a one-pot manner using sequential *O*-glycosylation-azidation-cycloaddition procedure avoiding the isolation and handling of potentially explosive organic azides. This method can be applied to various alkyne substrates and should be of general utility for the synthesis of this unique scaffold in efficient way.



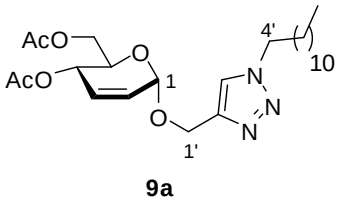
Scheme 1 Synthesis of triazolylethyl-2,3-unsaturated-*O*-glycosides **2**

Part II, we have developed an efficient and convenient method for the synthesis of 2,3-unsaturated-glycosyl triazoles. This method used inexpensive iodine reagent to promote the glycosylation and allows for subsequent copper catalyzed click reaction to proceed in one pot which limiting the experimental, work-up and purification step. Thirty examples of new triazoleglycosideswere obtained in high yields, with a-anomeric selectivity.

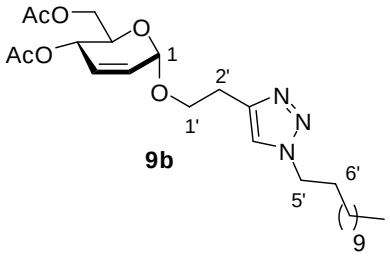


Scheme 2 Synthesis of 2,3-unsaturated-glycosyl triazoles **2**

In this study, eight novel mono-triazole glycosides were tested for their anticancer activities in CCA cell lines. Among glycosides tested, compounds **9a** and **9b** exhibited the most potent anticancer activity. These synthetic triazole glycosides might be a promising anticancer agent for CCA.

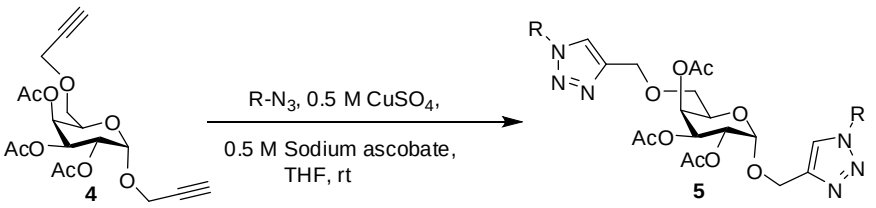


9a



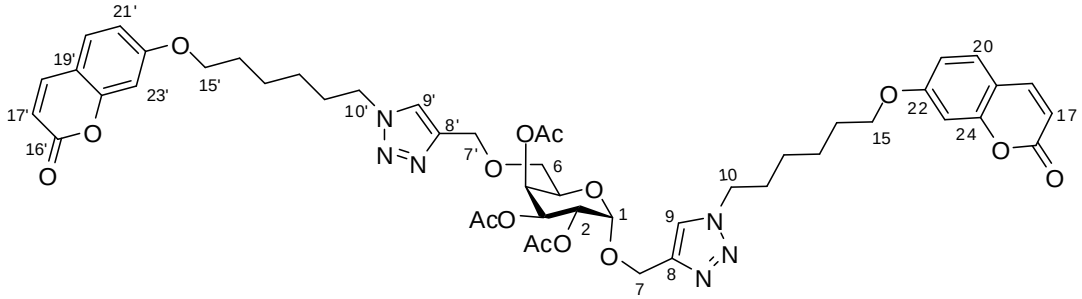
9b

Part 3, A new series of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl derivatives were synthesized and evaluated for their in vitro cytotoxic activities against Thai human cholangiocarcinoma cells.



Scheme 3 Synthesis of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl derivatives

The preliminary screening results indicated that some of the compounds demonstrated low to moderate cytotoxic activities, comparable to the anticancer drug ellipticin. Compounds **5 ee** exhibited pronounced cytotoxicity against K-100 cell lines.



Compounds **5 ee**

References

1. Y. Shaib and H. B. El-Serag, *Semin. Liver Dis.*, 2004, **24**, 115–125**.**

2. S. A. Khan, H. C. Thomas, B. R. Davidson and S.D. Taylor-Robinson , *Lancet*, 2005, **366**, 1303–1314.

3. (a) D. E. Henson, J. Albores-Saavedra and D. Corle, *Cancer*, 1992, **70**, 1498–1501. (b) F. Berr, *Semin. Liver Dis.*, 2004, **24**, 177–187.

4. W. R. Jarnagin and M. Shoup, *Semin. Liver Dis.*, 2004, **24**, 189–199.

5. R. Robles, J. Figueras, V. S. Turrion, C. Margarit, A. Moya, E. Varo, J. Calleja, A. Valdivieso, J. C. Valdecasas, P. Lopez, M. Gomez, E. de Vicente, C. Loinaz, J. Santoyo, M. Fleitas, A. Bernardos, L. Llado, P. Ramirez, F. S. Bueno, E. Jaurrieta and P. Parrilla, *Ann. Surg.*, 2004, **239**, 265–271.

6. V. Bhudhisawasdi, N. Khuntikeo, S. Chur-in, A. Pugkhem**,** C. Talabnin and S. Wongkham, *Srinagarind. Med. J.* 2012, **27** supple (Cholangiocarcinoma), 331-339.

7. U. Songsiang, S. Pitchuanchom, C. Boonyarat, C. Hahnvajanawong and C. Yenjai, *Eur. J. Med. Chem.* 2010, **45**, 3794-3802.

8. S. K. Kumar, M. Amador, M. Hidalgo, S. V. Bhat and S. R. Khana, *Bioorg. Med. Chem.* 2005, **13**, 2873–2880.

9. B. S. Park, M. M. Al-Sanea, A. Z. Abdelazem, H. M. Park, E. J. Roh, H-M. Park, K. H. Yoo, T. Sim, J. S. Tae and S. H. Lee, *Bioorg. Med. Chem.* 2014, *in press*.

10. R. Pingaewa, P. Mandi, C. Nantasenamat, S. Prachayasittikul, S. Ruchirawat, V. Prachayasittikul, *Eur. J. Med. Chem.* 2014, **81**, 192-203.

11. V. Prachayasittikul, R. Pingaew, A. Worachartcheewan,C. Nantasenamat, S. Prachayasittikul, S. Ruchirawat, V. Prachayasittikul, *Eur. J. Med. Chem.* 2014, **84**, 247-263

12. M. Imai, N. Takahashi, *Bioorg. Med. Chem.* 2012, **20**, 2520–2526.

13. (a) Srme, P.; Qian, Y.; Nyholm, P.-G.; Leffler, H.; Nilsson, U. J. ChemBioChem 2002, 3, 183. (b) Cumpstey, I.; Salomonsson, E.; Sundin, A.; Leffler, H.; Nilsson, U. J. Chem. Eur. J. 2008, 14, 4233. (c) Salameh, B. A.; Leffler, H.; Nilsson, U. J. Bioorg. Med. Chem. Lett. 2005, 15, 3344. (d) Tejler, J.; Salameh, B.; Leffler, H.; Nilsson, U. Org. Biomol. Chem. 2009, 7, 3982. (e) Salameh, B. A.; Sundin, A.; Leffler, H.; Nilsson, U. J. Bioorg. Med. Chem. 2006, 14, 1215.

14. (a) Cumpstey, I.; Sundin, A.; Leffler, H.; Nilsson, U. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5110; (b) Srme, P.; Arnoux, P.; Kahl-Knutsson, B.; Leffler, H.; Rini, J. M.; Nilsson, U. J. *J. Am. Chem. Soc.* **2005**, *127*, 1737; (c) Tejler, J.; Skogman, F.; Leffler, H.; Nilsson, U. J. *Carbohydr. Res.* **2007**, *342*, 1869.

15. Salameh; B. A., Cumpstey; I., Anders Sundin; A., Leffler; H., Nilsson, U. J. *Bioorg. Med. Chem. Lett*. **2010**, *18*, 5367.

16. Tejler, J,; Lefflerb, H.; Nilsson, U. J. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 2343.

17. Murakami, T.; Yoshioka, K.; Sato, Y,; Tanaka, M.; Niwa, O,; Yabuki, S. *Bioorg. Med. Chem. Lett*. 2011, 21, 1265–1269.

Output

International Publications

1. Wadchara Mangsang, Uthaiwan Sirion, **Rungnapha Saeeng**[*] One-pot synthesis of O-glycosyl triazoles by O-glycosylation–click reaction, *Carbohydrate Research*, **2013**, *375*, 79–89.

2. Wadchara Mangsang, Uthaiwan Sirion, **Rungnapha Saeeng**[*] Convenient one-pot synthesis of triazolylethyl-2,3-unsaturated-O-glycoside derivatives, *Tetrahedron*, **2015**, 71, 8593-8600.

International Proceeding

1. Suksamran Chaidam, Uthaiwan Sirion, **Rungnapha Saeeng**[*] Synthesis of diacetylene glycoside, Burapha University International Conference **2013**/4-5 July 2013/p.1085-1091.

การผลิตบัณฑิต

1. นิสิตปริญญาโท ภาคเคมี คณะวิทยาศาสตร์ ม.บูรพา จำนวน 2 คน
   นายวัชระ มังค์สังค์
   นายสุขสำราญ ไชยดำ
2. นิสิตปริญญาตรี ภาคเคมี คณะวิทยาศาสตร์ ม.บูรพา จำนวน 2 คน ทำโครงงานนิพนธ์
   นางสาวนริยา มุกสิทธิ์มณี
   นายพีรพงษ์ วงษ์ปุ่น

Carbohydrate Research 375 (2013) 79–89

Contents lists available at SciVerse ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

One-pot synthesis of *O*-glycosyl triazoles by O-glycosylation–click reaction

Wadchara Mangsang, Uthaiwan Sirion, Rungnapha Saeeng *

Department of Chemistry and Center for Innovation in Chemistry, Faculty of Science, Burapha University, Sangsook, Chonburi 20131, Thailand

ARTICLE INFO

Article history:
Received 12 March 2013
Received in revised form 20 April 2013
Accepted 24 April 2013
Available online 1 May 2013

Keywords:
2,3-Unsaturated-*O*-glycosyl triazole
Iodine
Click reaction
D-Glucal
One pot

ABSTRACT

2,3-Unsaturated-glycosyl triazoles were synthesized in a simple one-pot process under mild condition via tandem O-glycosylation using iodine promoter and a mild CuAAC reaction. Thirty examples of a variety of *O*-glycosyl triazoles were obtained in good to excellent yields and α-anomeric selectivity.

1. Introduction

1,2,3-Triazole moiety has proven to be an important structural scaffold in biomaterials[1] for drug discovery that show a broad range of biological activities such as anti-bacterial, anti-viral, anti-fungal, anti-parasitic, anti-HIV, anti-tumor, and anti-tuberculosis. In addition, triazoles are advantageously employed in the fields of materials science and polymer chemistry.[2] Consequently, interest in the development of efficient methods for the synthesis of triazoles, bearing multiple and diverse substitution patterns, has continued. The most prominent method to synthesize 1,2,3-triazole is the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azide and alkyne (CuAAC), the most widely used click reaction.[3]

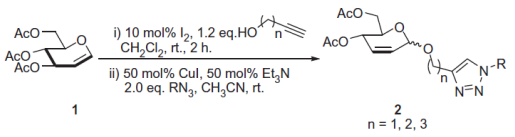
In the field of carbohydrate research, several attempts have been made to utilize click chemistry for the synthesis of bioactive triazole-glycosides and consequently screening for their biological data.[4] 1,2,3-Triazole-glycosides have been reported to posses galactin-3 inhibitory effect[4b] in which galectin-3 has been demonstrated to be involved in cancer and inflammation. Triazole-glycosides can be generally prepared from the reaction of propargyl glycosides and azides or azido glycosides and alkynes.[5] For example, Miller et al.[6a] synthesized analogues of neoglycopeptide using microwave-assisted CuAAC reaction of a propargylated glycoside with an azido-functionalized amino acid. Alternatively, Salunke et al.[6b] reported the synthesis of 1,2,3-benzotriazole-linked glycoconjugates via CuAAC reactions of azido glycosides with various terminal alkynes.

Recently, one-pot synthetic strategies have become a very attractive alternative to traditional sequential approaches for preparing triazole compounds. Muller reported the one-pot three component Sonogashira coupling–TMS–deprotection–CuAAC sequence for the rapid synthesis of triazolyl NH-heterocycle.[7] Yadav et al.,[8] reported the tandem synthesis of 2,3-unsaturated-*N*-glycosyl triazoles which was started with glycosylation of glucal with azide followed by click reaction of the resulting azidoglycoside to obtain the product. However, Yadav's method provided only one type of target with a certain triazole ring bearing directly to the glycoside. To search the new methods for the synthesis of diverse triazole glycosides, alternative ways that could lead to more targets with convenient procedures are desired. In this work, we report herein a concise synthetic approach to new analogues of 2,3-unsaturated-*O*-glycosyl triazoles (**2**) using one pot reaction involving an iodine catalyzed glycosylation followed by click reaction (Scheme 1). 2,3-Unsaturated-*O*-glycosyl triazoles have been reported to posses α-glucosidase, glycogen phosphorylase, and glucose-6-phosphatase inhibitory activities which is important in development of new anti-diabetic agents.[9]

In our previous reports, we demonstrated a practical approach to 2,3-unsaturated *O*-glycosides via Ferrier reaction[10] from glycal by iodine catalyst. Several *O*-glycosides could be obtained in high yield and high stereoselective, for example *O*-propargyl, butynyl, and pentynyl glycosides could be obtained in 94–99% yields in the presence of iodine as a promoter.[11] We envisioned that molecular iodine catalyst in the glycosidation step could be combined with Meldal's copper catalyzed [3+2] cycloaddition of azides and alkynes to produce glycosyl triazoles in one pot.

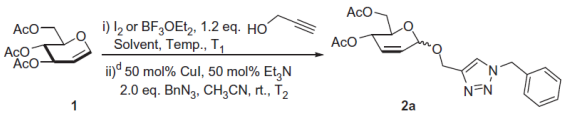
* Corresponding author. Tel.: +66 81 656 7524; fax: +66 3 839 3494.
E-mail addresses: rungnaph@yahoo.com, rungnaph@buu.ac.th (R. Saeeng).

0008-6215/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.carres.2013.04.029



Scheme 1. Synthesis of 2,3-unsaturated-*O*-glycosyl triazoles.

Table 1
Optimization of tandem O-glycosidation–Click reactions[a]



Entry	Lewis acid (equiv)	Solvent[b]	Temp. (°C)	T_1/T_2 (h)	Yield[c] (%)
1	I_2 (0.5)	CH_3CN	rt	2/3	27
2	I_2 (0.1)	CH_3CN	rt	2/3	45
3	I_2 (0.1)	CH_3CN/CH_2Cl_2 (1:1)	rt	2/3	82
4	I_2 (0.1)	CH_2Cl_2	rt	2/3	86
5	BF_3OEt_2 (0.2)	CH_3CN	0	0.5/24	94

[a] All reactions were carried out with 0.146 mmol of D-glucal (**1**), concentration 0.146 M.
[b] Solvent used for step 1.
[c] Isolated yield.
[d] The reaction was completed in longer time when using CuI less than 50 mol %.

2. Results and discussion

We desired the synthesis involving glycosylation of D-glucal (**1**) with different alkynyl alcohols subsequently followed by click reaction with various azides to obtain the target *O*-glycosyl triazoles. The click reaction in the second step was carried out using copper iodide as the Cu(I) source and triethylamine and acetonitrile as the solvent.

First, tandem glycosylation of D-glucal (**1**) with propargyl alcohol followed by CuACC reaction with benzyl triazole in acetonitrile was studied as a model reaction as shown in Table 1. Iodine was used as catalyst in glycosylation step and to study the ability to allow tandem glycosylation–click reaction. When using 0.5 equiv of iodine in acetonitrile, product **2a** was obtained in low yield (entry 1). Using iodine 0.1 equiv, triazole glycoside **2a** was obtained in moderate yield (entry 2). Among the reactions using iodine, the use of dichloromethane as solvent was found to provide triazole glycoside in the highest yields (entries 3 and 4). $BF_3{\cdot}OEt_2$ was used as catalyst to compare the activity with iodine both in the first step and the ability to allow tandem click reaction in the second step. It was observed that *O*-glycoside formation was completed in 30 min on TLC, however finishing the second step of click reaction was observed after 24 h (entry 5).

In order to determine the scope of this one pot reaction, the reaction sequence involved glycosylation of D-glucal with propargyl, butynyl, or pentynyl alcohols followed by CuACC reaction using various benzyl and long-chain aliphatic azides which were studied under the optimized reaction conditions (Table 1, entry 4). As shown in Table 2, the tandem glycosylation–click reactions of benzylazide with butynyl and pentynyl-glycosides were performed smoothly as propargyl-glycoside to give products **2b** and **2c** in good yields (entries 2 and 3). Changing to electron deficient nitro-benzyl azides and electron rich methoxy-and di-methoxy benzyl azides did not show significant differences in terms of the reactivity and reaction yields. The reaction went smoothly with *m*-nitrobenzylazide to complete conversion in the second step in 1 h, producing **4a**–**4c** in 83–96% yields (entries 7–9). For the synthesis of triazole-glycosides with different substituents on the N-1 atom of triazole moiety, the click reaction was extended using aliphatic azides. The reaction of phenyl ethyl azide works well under this one pot condition to obtain high yield of product in shorter time (entries 19–21). Long chain aliphatic azides such as lauryl, omega-undecylenyl, and oleyl azides can be proceeded smoothly to obtain the product with comparable yield as shown in entries 22–30 (Table 2). However, the reactions of long carbon chain oleyl azide (entries 28–30) were carried out in longer time to complete the reaction.

3. Conclusion

In conclusion, we have developed an efficient and convenient method for the synthesis of 2,3-unsaturated-glycosyl triazoles. This method used inexpensive iodine reagent to promote the glycosylation and allows for subsequent copper catalyzed click reaction to proceed in one pot which limiting the experimental, work-up and purification step. Thirty examples of new triazole-glycosides were obtained in high yields, with α-anomeric selectivity.

4. Experimental

4.1. General methods

All chemicals were purchased from commercial sources and used without further purification. Proton NMR spectra were recorded on a Bruker Avance (400 MHz). All spectra were measured in $CDCl_3$ solvent and chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (δ 0.00) or $CDCl_3$ (δ 7.26) as internal standard. Data are reported as follows; chemical shift (multiplicity, integrate intensity or assignment, coupling constants in Hz, and assignment). Carbon NMR spectra were recorded on a BRUKER AVANC (100 MHz). All spectra were measured in $CDCl_3$ solvent and chemical shifts are reported as δ values in parts per million (ppm) relative to $CDCl_3$ (δ 77.0) as internal standard. High-resolution mass spectral (HRMS) data were obtained with a Finnigan MAT 95. Infrared spectra were determined on a PERKIN ELMER FT/IR-2000S spectrophotometer and are reported in wave number (cm^{-1}). Analytical thin-layer chromatography (TLC) was conducted on precoated TLC plates; silica gel 60F-254 [E. Merck, Darmstadt, Germany]. Silica gel columns for open-column chromatography utilized silica gel 60 (0.040–0.063 mm) [E. Merck, Darmstadt, Germany]. Melting points were measured using a Melting point apparatus (Griffin) and are uncorrected.

4.2. General procedure for the synthesis of 2,3-unsaturated *O*-glycosyl triazole derivatives

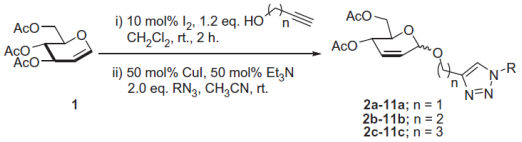
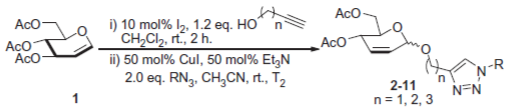
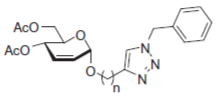
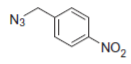
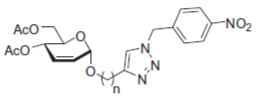
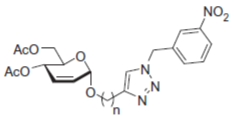
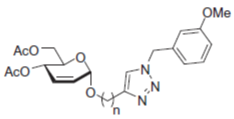
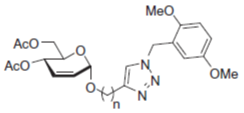
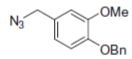
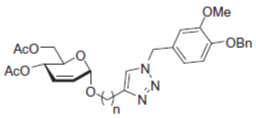
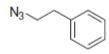
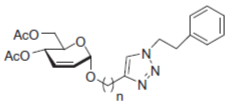
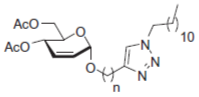
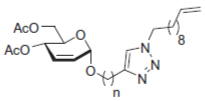
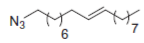
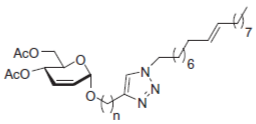


Table 2
O-Glycosidation–Click reactions

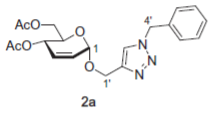


Entry	Azide[a]	Major product	Yield[b,c] (%)	Time[d] (T_2)/h
1 2 3			**2a**, *n* = 1,86 **2b**, *n* = 2, 73 **2c**, *n* = 3, 79	3 5 5
4 5 6			**3a**, *n* = 1,71 **3b**, *n* = 2, 84 **3c**, *n* = 3, 71	5 2 2
7 8 9			**4a**, *n* = 1,96 **4b**, *n* = 2, 84 **4c**, *n* = 3, 83	1 1 1
10 11 12			**5a**, *n* = 1,78 **5b**, *n* = 2, 91 **5c**, *n* = 3, 74	3 3 2
13 14 15			**6a**, *n* = 1,70 **6b**, *n* = 2, 89 **6c**, *n* = 3, 91	3 2 5
16 17 18			**7a**, *n* = 1,79 **7b**, *n* = 2, 73 **7c**, *n* = 3, 73	2 2 2
19 20 21			**8a**, *n* = 1,98 **8b**, *n* = 2, 79 **8c**, *n* = 3, 75	1 1 1
22 23 24			**9a**, *n* = 1,85 **9b**, *n* = 2, >99 **9c**, *n* = 3, 90	2 2 2
25 26 27			**10a**, *n* = 1,86 **10b**, *n* = 2, 82 **10c**, *n* = 3, 73	2 2 2
28 29 30			**11a**, *n* = 1,76 **11b**, *n* = 2, 75 **11c**, *n* = 3, 71	4 4 4

[a] Azides were freshly prepared.
[b] Yields are given for isolated compound.
[c] Mixture of isomers, α:β = 9:1 for *n* = 1, α:β = 10:1 for *n* = 2, α:β = 12:1 for *n* = 3 (determined by ^{1}H NMR of the crude reaction mixture).
[d] T_2 = Reaction time of the second step.

To a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal **1** (40.0 mg, 0.146 mmol) in dried CH_2Cl_2 (1.0 mL) were added alkynyl alcohol (0.176 mmol) and iodine powder (3.7 mg, 0.015 mmol) under gas-nitrogen at room temperature. Stirring was continued at room temperature for 2 h. After TLC showed the completed conversion, the volatiles were removed to obtain the residue which was dissolved with CH_3CN (1.0 mL), followed by the addition of CuI (13.9 mg, 0.073 mmol), Et_3N (10.2 μL, 0.073 mmol), and alkyl azide (0.292 mmol) respectively. The reaction mixture was stirred at room temperature for 1–5 h. After TLC showed the completed conversion, the reaction mixture was diluted with EtOAc (20 mL), washed with satd aq NH_4Cl (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residues were purified by silica gel column chromatography (EtOAc/*n*-hexane) to give the 2,3-unsaturated *O*-glycosyl triazole products **2–11** in good to excellent yields.

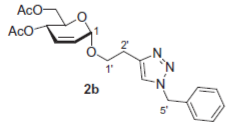
4.3. Spectral data of 2,3-unsaturated *O*-glycosyl triazole derivatives



2a

4.3.1. 1-Benzyl-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (2a)

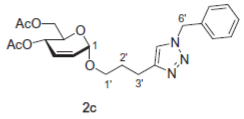
Pale yellow solid; α-anomer R_f = 0.43 (50% EtOAc/*n*-hexane); mp 52–54 °C; $[\alpha]_D^{24}$ +54.3 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2923, 2848, 1741, 1657, 1632, 1494, 1450, 1428, 1370, 1228, 1038, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 1H, triazolyl-H), 7.41–7.36 (m, 3H, Ph), 7.32–7.27 (m, 2H, Ph), 5.90 (br d, 1H, *J* = 10.0 Hz, H-2), 5.82 (ddd, 1H, *J* = 10.0, 2.5, 1.5 Hz, H-3), 5.54 (s, 2H, C*H*$_2$Ph), 5.34 (ddd, 1H, *J* = 10.0, 2.5, 1.0 Hz, H-4), 5.17 (br s, 1H, H-1), 4.90 (d, 1H, *J* = 12.0 Hz, H-1′a), 4.71 (d, 1H, *J* = 12.0 Hz, H-1′b), 4.25 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.16 (dd, 1H, *J* = 12.0, 2.5 Hz, H-6b), 4.13 (ddd, 1H, *J* = 10.0, 5.0, 2.5 Hz, H-5), 2.01 (s, 3H, OAc), 2.00 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.78 (C=O), 170.23 (C=O), 144.92 (C-2′), 134.51 (Ph), 129.52 (C-2), 129.15 (2 × Ph), 128.82 (Ph), 128.19 (2 × Ph), 127.44 (C-3), 122.51 (C-3′), 93.87 (C-1), 67.07 (C-5), 65.25 (C-4), 62.82 (C-6), 61.64 (C-1′), 54.20 (C-4′), 20.93 (CH_3), 20.79 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{23}N_3O_6Na$ $[M+Na]^+$ 424.1485, found 424.1484.



2b

4.3.2. 1-Benzyl-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (2b)

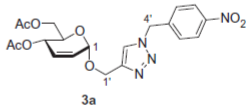
Pale orange oil; α-anomer R_f = 0.39 (50% EtOAc/*n*-hexane); $[\alpha]_D^{23}$ +57.1 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2923, 2848, 1740, 1657, 1633, 1465, 1454, 1421, 1370, 1275, 1260, 1225, 1038, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.24 (m, 5H, Ph), 7.32 (br s, 1H, triazolyl-H), 5.88 (br d, 1H, *J* = 10.0 Hz, H-2), 5.76 (dm, 1H, *J* = 10.0 Hz, H-3), 5.52 (s, 2H, C*H*$_2$Ph), 5.29 (d, 1H, *J* = 10.0 Hz, H-4), 5.03 (br s, 1H, H-1), 4.21 (dd, 1H, *J* = 12.0, 5.5 Hz, H-6a), 4.12 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.08–3.97 (m, 2H, H-5, H-1′a), 3.84–3.75 (m, 1H, H-1′b), 3.05 (t, 2H, *J* = 6.0 Hz, H-2′), 2.01 (s, 3H, OAc), 1.97 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.80 (C=O), 170.22 (C=O), 145.33 (C-3′), 134.83 (Ph), 129.24 (C-2), 129.08 (2 × Ph), 128.69 (Ph), 128.00 (2 × Ph), 127.60 (C-3), 121.60 (C-4′), 94.52 (C-1), 67.63 (C-1′), 67.00 (C-5), 65.31 (C-4), 62.91 (C-6), 54.11 (C-5′), 26.58 (C-2′), 20.97 (CH_3), 20.76 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{25}N_3O_6Na$ $[M+Na]^+$ 438.1641, found: 438.1599.



2c

4.3.3. 1-Benzyl-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (2c)

Pale yellow oil; α-anomer R_f = 0.42 (50% EtOAc/*n*-hexane); $[\alpha]_D^{24}$ +66.4 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$): 2928, 2870, 1740, 1550, 1497, 1456, 1435, 1370, 1230, 1039, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (br s, 1H, triazolyl-H), 7.39–7.35 (m, 2H, Ph), 7.30–7.22 (m, 3H, Ph), 5.89 (br d, 1H, *J* = 10.0 Hz, H-2), 5.82 (ddd, 1H, *J* = 10.0, 3.0, 2.0 Hz, H-3), 5.51 (s, 2H, C*H*$_2$Ph), 5.32 (ddd, 1H, *J* = 10.0, 3.0, 2.0 Hz, H-4), 5.02 (br s, 1H, H-1), 4.24 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.0, 2.5 Hz, H-6b), 4.10 (ddd, 1H, *J* = 10.0, 5.0, 2.5 Hz, H-5), 3.82 (dt, 1H, *J* = 10.0, 6.0 Hz, H-1′a), 3.56 (dt, 1H, *J* = 10.0, 6.0 Hz, H-1′b), 2.85–2.76 (m, 2H, H-3′), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.04–1.95 (m, 2H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.79 (C=O), 170.28 (C=O), 147.94 (C-4′), 134.89 (Ph), 129.08 (2 × Ph), 129.06 (C-2), 128.68 (Ph), 128.01 (2 × Ph), 127.82 (C-3), 120.63 (C-5′), 94.43 (C-1), 67.94 (C-1′), 66.94 (C-5), 65.32 (C-4), 63.00 (C-6), 54.04 (C-6′), 29.38 (C-2′), 22.49 (C-3′), 20.97 (CH_3), 20.77 (CH_3); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{27}N_3O_6Na$ $[M+Na]^+$ 452.1798, found: 452.1793.

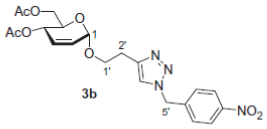


3a

4.3.4. 1-(4-Nitrobenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (3a)

Orange solid; α-anomer R_f = 0.24 (50% EtOAc/*n*-hexane); mp 78–80 °C; $[\alpha]_D^{23}$ +31.2 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$): 2922, 2852, 1741, 1657, 1632, 1524, 1465, 1421, 1260, 1229, 1038, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 2H, *J* = 8.0 Hz, Ph), 7.61 (br s, 1H, triazolyl-H), 7.44 (d, 2H, *J* = 8.0 Hz, Ph), 5.91 (d, 1H, *J* = 10.0 Hz, H-2), 5.83 (d, 1H, *J* = 10.0 Hz, H-3), 5.66 (s, 2H, C*H*$_2$Ph), 5.34 (d, 1H, *J* = 10.0 Hz, H-4), 5.19 (br s, 1H, H-1), 4.92 (d, 1H, *J* = 12.0 Hz, H-1′a), 4.74 (d, 1H, *J* = 12.0 Hz, H-1′b), 4.23 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.15–4.08 (m, 1H, H-5), 2.03 (s, 3H, OAc), 2.01 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.80 (C=O), 170.23 (C=O), 148.13 (Ph), 145.50 (C-2′), 141.51 (Ph), 129.68 (C-2), 128.72 (2 × Ph), 127.28 (C-3), 124.32 (2 × Ph), 122.97 (C-3′), 94.03 (C-1), 67.07 (C-5),

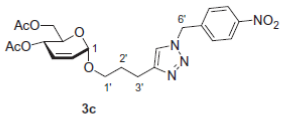
65.26 (C-4), 62.77 (C-6), 61.61 (C-1′), 53.16 (C-4′), 20.93 (CH_3), 20.81(CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_4O_8Na$ $[M+Na]^+$ 469.1335, found: 469.1282.



3b

4.3.5. 1-(4-Nitrobenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3b)

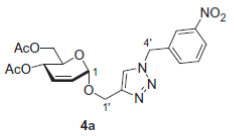
Pale yellow oil; α-anomer R_f = 0.24 (50% EtOAc/*n*-hexane); $[\alpha]_D^{26}$ +70.9 (*c* 0.26, $CHCl_3$); IR ($CHCl_3$): 2922, 2852, 1739, 1659, 1633, 1521, 1468, 1421, 1421, 1346, 1273, 1260, 1225, 1036, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, 2H, *J* = 9.0 Hz, Ph), 7.44 (br s, 1H, triazolyl-H), 7.41 (d, 2H, *J* = 9.0 Hz, Ph), 5.89 (br d, 1H, *J* = 10.0 Hz, H-2), 5.79 (dt, 1H, *J* = 10.0, 2.0 Hz, H-3), 5.66 (s, 2H, CH_2Ph), 5.31 (dm, 1H, *J* = 10.0 Hz, H-4), 5.06 (br s, 1H, H-1), 4.22 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.0, 2.5 Hz, H-6b), 4.12–4.04 (m, 1H, H-1′a), 4.10 (ddd, 1H, *J* = 10.0, 5.0, 2.5 Hz, H-5), 3.87–3.78 (m, 1H, H-1′b), 3.09 (t, 2H, *J* = 6.0 Hz, H-2′), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84 (C=O), 170.24 (C=O), 148.03 (Ph), 145.95 (C-3′), 141.94 (Ph), 129.40 (C-2), 128.49 (2 × Ph), 127.49 (C-3), 124.27 (2 × Ph), 121.89 (C-4′), 94.54 (C-1), 67.49 (C-1′), 65.00 (C-5), 65.34 (C-4), 62.90 (C-6), 53.00 (C-5′), 26.57 (C-2′), 20.97 (CH_3), 20.79 (CH_3); HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_4O_8Na$ $[M+Na]^+$ 483.1492, found: 483.1435.



3c

4.3.6. 1-(4-Nitrobenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (3c)

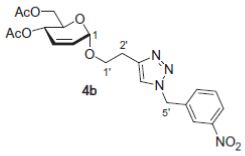
Pale yellow oil; α-anomer R_f = 0.28 (50% EtOAc/*n*-hexane); $[\alpha]_D^{26}$ +32.7 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$): 2922, 2848, 1738, 1657, 1627, 1522, 1465, 1421, 1346, 1275, 1260, 1229, 1039, 975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 2H, *J* = 8.5 Hz, Ph), 7.41 (d, 2H, *J* = 8.5 Hz, Ph), 7.34 (br s, 1H, triazolyl-H), 5.90 (br d, 1H, *J* = 10.0 Hz, H-2), 5.83 (dt, 1H, *J* = 10.0, 3.0 Hz, H-3), 5.63 (s, 2H, CH_2Ph), 5.33 (ddd, 1H, *J* = 10.0, 3.0, 2.0 Hz, H-4), 5.03 (br s, 1H, H-1), 4.24 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.0, 2.5 Hz, H-6b), 4.10 (ddd, 1H, *J* = 10.0, 5.0, 2.5 Hz, H-5), 3.84 (dt, 1H, *J* = 10.0, 6.0 Hz, H-1′a), 3.58 (dt, 1H, *J* = 10.0, 6.0 Hz, H-1′b), 2.89–2.80 (m, 2H, H-3′), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.06–1.97 (m, 2H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84 (C=O), 170.30 (C=O), 148.49 (C-4′), 148.03 (Ph), 141.96 (Ph), 129.18 (C-2), 128.51 (2 × Ph), 127.72 (C-3), 124.30 (2 × Ph), 120.96 (C-5′), 94.45 (C-1), 67.85 (C-1′), 66.91 (C-5), 65.27 (C-4), 62.93 (C-6), 52.99 (C-6′), 29.33 (C-2′), 22.46 (C-3′), 21.00 (CH_3), 20.82 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{26}N_4O_8Na$ $[M+Na]^+$ 497.1648, found: 497.1613.



4a

4.3.7. 1-(3-Nitrobenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (4a)

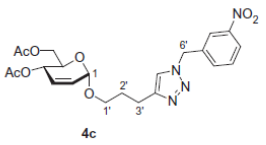
Pale yellow solid; α-anomer R_f = 0.32 (50% EtOAc/*n*-hexane); mp: 96–98 °C; $[\alpha]_D^{25}$ +36.8 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 2922, 2851, 1740, 1659, 1633, 1533, 1468, 1421, 1351, 1230, 1039, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 1H, *J* = 8.0 Hz, Ph), 8.19 (br s, 1H, Ph), 7.69 (br s, 1H, triazolyl-H), 7.64 (d, 1H, *J* = 8.0 Hz, Ph), 7.59 (t, 1H, *J* = 8.0 Hz, Ph), 5.91 (d, 1H, *J* = 10.0 Hz, H-2), 5.83 (d, 1H, *J* = 10.0 Hz, H-3), 5.67 (s, 2H, CH_2Ph), 5.34 (d, 1H, *J* = 10.0 Hz, H-4), 5.19 (br s, 1H, H-1), 4.92 (d, 1H, *J* = 10.0 Hz, H-1′a), 4.74 (d, 1H, *J* = 10.0 Hz, H-1′b), 4.24 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.12 (ddd, 1H, *J* = 10.0, 5.0, 2.0 Hz, H-5), 2.02 (s, 3H, OAc), 2.00 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.82 (C=O), 170.24 (C=O), 148.57 (Ph), 146.00 (C-2′), 136.63 (Ph), 134.03 (Ph), 130.33 (Ph), 129.65 (C-2), 127.31 (C-3), 123.76 (Ph), 122.95 (Ph, C-3′), 94.02 (C-1), 67.06 (C-5), 65.27 (C-4), 62.78 (C-6), 61.34 (C-1′), 53.17 (C-4′), 20.93 (CH_3), 20.81 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_4O_8Na$ $[M+Na]^+$ 469.1335, found: 469.1273.



4b

4.3.8. 1-(3-Nitrobenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (4b)

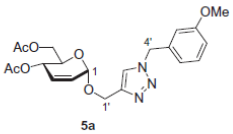
Pale yellow oil; α-anomer R_f = 0.35 (50% EtOAc/*n*-hexane); $[\alpha]_D^{25}$ +39.2 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 2923, 2852, 1740, 1659, 1632, 1531, 1468, 1421, 1350, 1229, 1038, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.26–8.21 (m, 1H, Ph), 8.16 (br s, 1H, Ph), 7.63–7.55 (m, 2H, Ph), 7.43 (br s, 1H, triazolyl-H), 5.89 (br d, 1H, *J* = 10.0 Hz, H-2), 5.79 (ddd, 1H, *J* = 10.0, 3.0, 2.0 Hz, H-3), 5.65 (s, 2H, CH_2Ph), 5.30 (ddd, 1H, *J* = 10.0, 3.0, 2.0 Hz, H-4), 5.06 (br s, 1H, H-1), 4.22 (dd, 1H, *J* = 12.5, 5.0 Hz, H-6a), 4.16 (dd, 1H, *J* = 12.5, 2.0 Hz, H-6b), 4.12–4.06 (m, 1H, H-1′a), 4.03 (ddd, 1H, *J* = 10.0, 5.0, 2.0 Hz, H-5), 3.82 (ddd, 1H, *J* = 10.0, 6.0, 3.0 Hz, H-1′b), 3.08 (t, 2H, *J* = 6.0 Hz, H-2′), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc); ^{v} (100 MHz, $CDCl_3$): δ 170.82 (C=O), 170.24 (C=O), 148.58 (Ph), 145.97 (C-3′), 136.98 (Ph), 133.98 (Ph), 130.26 (Ph), 129.38 (C-2), 127.51 (C-3), 123.69 (Ph), 122.75 (Ph), 121.76 (C-4′), 94.57 (C-1), 67.52 (C-1′), 67.01 (C-5), 65.36 (C-4), 62.94 (C-6), 53.02 (C-5′), 26.59 (C-2′), 20.97 (CH_3), 20.77 (CH_3); HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_4O_8Na$ $[M+Na]^+$ 483.1492, found: 483.1448.



4c

4.3.9. 1-(3-Nitrobenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (4c)

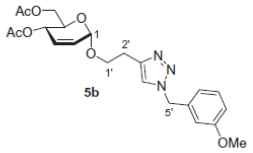
Pale orange oil; α-anomer R_f = 0.25 (50% EtOAc/*n*-hexane); $[\alpha]_D^{24}$ +43.1 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 2922, 2848, 1734, 1528, 1454, 1365, 1349, 1273, 1260, 1222, 1035, 975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.25–8.20 (m, 1H, Ph), 8.15 (br s, 1H, Ph), 7.61–7.55 (m, 3H, triazolyl-H, Ph), 5.89 (br d, 1H, *J* = 10.0 Hz, H-2), 5.83 (dm, 1H, *J* = 10.0 Hz, H-3), 5.65 (s, 2H, CH_2Ph), 5.32 (d, 1H, *J* = 10.0 Hz, H-4), 5.03 (br s, 1H, H-1), 4.24 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.18 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.15–4.07 (m, 1H, H-5), 3.91–3.79 (m, 1H, H-1′a), 3.66–3.54 (m, 1H, H-1′b), 2.93–2.75 (m, 2H, H-3′), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.11–2.07 (m, 2H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.82 (C=O), 170.28 (C=O), 148.50 (Ph), 148.48 (C-4′), 137.04 (Ph), 133.81 (Ph), 130.26 (Ph), 129.14 (C-2), 127.75 (C-3), 123.67 (Ph), 122.75 (Ph), 120.88 (C-5′), 94.46 (C-1), 67.85 (C-1′), 67.23 (C-5), 65.33 (C-4), 62.97 (C-6), 52.98 (C-6′), 29.32 (C-2′), 22.45 (C-3′), 20.97 (CH_3), 20.78 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{26}N_4O_8H$ $[M+H]^+$ 475.1857, found: 475.1784.



5a

4.3.10. 1-(3-Methoxybenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (5a)

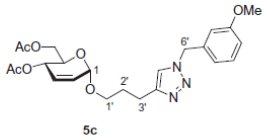
Pale yellow solid; α-anomer R_f = 0.27 (50% EtOAc/*n*-hexane); mp: 74–76 °C; $[\alpha]_D^{24}$ +50.0 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$): 2922, 2848, 1735, 1649, 1598, 1487, 1457, 1432, 1365, 1260, 1233, 1038, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 1H, triazolyl-H), 7.29 (t, 1H, *J* = 8.0 Hz, Ph), 6.91–6.83 (m, 2H, Ph), 6.81 (br s, 1H, Ph), 5.89 (br d, 1H, *J* = 10.0 Hz, H-2), 5.82 (dt, 1H, *J* = 10.0, 2.5 Hz, H-3), 5.44 (s, 2H, CH_2Ph), 5.32 (ddd, 1H, *J* = 10.0, 2.5, 1.0 Hz, H-4), 5.16 (br s, 1H, H-1), 4.89 (d, 1H, *J* = 12.0 Hz, H-1′a), 4.70 (d, 1H, *J* = 12.0 Hz, H-1′b), 4.24 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.15 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.15–4.08 (m, 1H, H-5), 3.80 (s, 3H, OMe), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.80 (C=O), 170.25 (C=O), 160.13 (Ph), 144.89 (C-2′), 135.91 (Ph), 130.22 (Ph), 129.50 (C-2), 127.44 (C-3), 122.57 (C-3′), 120.37 (Ph), 114.20 (Ph), 113.88 (Ph), 93.86 (C-1), 67.06 (C-5), 65.25 (C-4), 62.82 (C-6), 61.61 (C-1′), 55.31 (C-4′), 54.13 (OMe), 20.93 (CH_3), 20.79 (CH_3); HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_3O_7Na$ $[M+Na]^+$ 454.1590, found: 454.1547.



5b

4.3.11. 1-(3-Methoxybenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (5b)

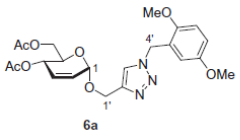
Pale yellow oil; α-anomer R_f = 0.46 (50% EtOAc/*n*-hexane); $[\alpha]_D^{26}$ +80.7 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$): 2923, 2848, 1723, 1659, 1627, 1601, 1587, 1410, 1369, 1321, 1273, 1260, 1225, 1041, 975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (br s, 1H, triazolyl-H), 7.29 (t, 1H, *J* = 8.0 Hz, Ph), 6.89 (dd, 1H, *J* = 8.0, 2.5 Hz, Ph), 6.85 (d, 1H, *J* = 8.0 Hz, Ph), 6.79 (br s, 1H, Ph), 5.88 (br d, 1H, *J* = 10.0 Hz, H-2), 5.77 (dt, 1H, *J* = 10.0, 2.5 Hz, H-3), 5.48 (s, 2H, CH_2Ph), 5.29 (ddd, 1H, *J* = 10.0, 2.5, 1.0 Hz, H-4), 5.03 (br s, 1H, H-1), 4.21 (dd, 1H, *J* = 12.0, 5.5 Hz, H-6a), 4.12 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.08–3.98 (m, 1H, H-1′a), 4.01 (ddd, 1H, *J* = 10.0, 5.5, 2.0 Hz, H-5), 3.83–3.73 (m, 1H, H-1′b), 3.80 (s, 3H, OMe), 3.04 (t, 2H, *J* = 6.0 Hz, H-2′), 2.10 (s, 3H, OAc), 2.06 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.82 (C=O), 170.26 (C=O), 160.10 (Ph), 145.36 (C-3′), 136.38 (Ph), 130.15 (Ph), 129.23 (C-2), 127.61 (C-3), 121.54 (C-4′), 120.17 (Ph), 114.00 (Ph), 113.73 (Ph), 94.53 (C-1), 67.66 (C-1′), 67.00 (C-5), 65.29 (C-4), 62.91 (C-6), 55.30 (OMe), 54.00 (C-5′), 26.53 (C-2′), 20.97 (CH_3), 20.76 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}N_3O_7Na$ $[M+Na]^+$ 468.1747, found: 468.1706.



5c

4.3.12. 1-(3-Methoxybenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (5c)

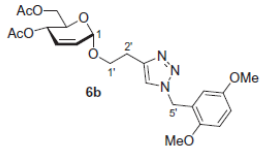
Pale yellow oil; α-anomer R_f = 0.29 (50% EtOAc/*n*-hexane); $[\alpha]_D^{24}$ +70.2 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$): 2922, 2848, 1736, 1657, 1631, 1598, 1587, 1465, 1432, 1368, 1273, 1260, 1225, 1038, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.23 (m, 2H, triazolyl-H, Ph), 6.92–6.79 (m, 3H, Ph), 5.89 (br d, 1H, *J* = 10.0 Hz, H-2), 5.82 (dt, 1H, *J* = 10.0, 3.0 Hz, H-3), 5.47 (s, 2H, CH_2Ph), 5.32 (ddd, 1H, *J* = 10.0, 3.0, 2.0 Hz, H-4), 5.03 (br s, 1H, H-1), 4.25 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.16 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.11 (ddd, 1H, *J* = 10.0, 5.0, 2.0 Hz, H-5), 3.84 (dt, 1H, *J* = 10.0, 6.0 Hz, H-1′a), 3.81 (s, 3H, OMe), 3.57 (dt, 1H, *J* = 10.0, 6.0 Hz, H-1′b), 2.85–2.76 (m, 2H, H-3′), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.04–1.96 (m, 2H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.75 (C=O), 170.25 (C=O), 160.08 (Ph), 147.88 (C-4′), 136.35 (Ph), 130.11 (Ph), 129.01 (C-2), 127.82 (C-3), 120.70 (C-5′), 120.16 (Ph), 114.02 (Ph), 113.67 (Ph), 94.39 (C-1), 67.90 (C-1′), 66.92 (C-5), 65.31 (C-4), 62.99 (C-6), 55.26 (OMe), 53.92 (C-6′), 29.35 (C-2′), 22.46 (C-3′), 20.93 (CH_3), 20.73 (CH_3); HRMS (ESI) *m/z* calcd for $C_{23}H_{29}N_3O_7Na$ $[M+Na]^+$ 482.1903, found: 482.1890.



6a

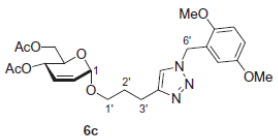
4.3.13. 1-(2,5-Dimethoxybenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (6a)

Pale orange solid; α-anomer R_f = 0.35 (50% EtOAc/*n*-hexane); mp: 90–92 °C; $[\alpha]_D^{24}$ +57.5 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$): 2923, 2852, 1742, 1657, 1632, 1505, 1466, 1428, 1227, 1042, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (br s, 1H, triazolyl-H), 6.89–6.86 (m, 2H, Ph), 6.81 (br s, 1H, Ph), 5.90 (br d, 1H, *J* = 10.0 Hz, H-2), 5.84 (br d, 1H, *J* = 10.0 Hz, H-3), 5.52 (s, 2H, CH_2Ph), 5.35 (d, 1H, *J* = 10.0 Hz, H-4), 5.19 (br s, 1H, H-1), 4.90 (d, 1H, *J* = 12.0 Hz, H-1′a), 4.70 (d, 1H, *J* = 12.0 Hz, H-1′b), 4.27 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.17–4.11 (m, 1H, H-5), 3.85 (s, 3H, OMe), 3.76 (s, 3H, OMe), 2.02 (s, 3H, OAc), 2.00 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.86 (C═O), 170.28 (C═O), 153.65 (Ph), 151.28 (Ph), 144.32 (C-2′), 129.91 (C-2), 127.49 (C-3), 123.61 (Ph), 122.91 (C-3′), 116.28 (Ph), 114.92 (Ph), 111.88 (Ph), 93.75 (C-1), 67.05 (C-5), 65.25 (C-4), 62.83 (C-6), 61.52 (C-1′), 55.99 (OMe), 55.75 (OMe), 49.07 (C-4′), 20.93 (CH_3), 20.77 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}N_3O_8Na$ $[M+Na]^+$ 484.1696, found: 484.1640.



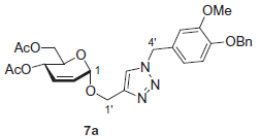
4.3.14. 1-(2,5-Dimethoxybenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (6b)

Pale orange oil; α-anomer R_f = 0.39 (50% EtOAc/*n*-hexane); $[\alpha]_D^{24}$ -0.53 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2924, 2852, 1742, 1660, 1633, 1505, 1466, 1430, 1371, 1227, 1044, 975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (br s, 1H, triazolyl-H), 6.88–6.85 (m, 2H, Ph), 6.75 (br s, 1H, Ph), 5.88 (br d, 1H, *J* = 10.0 Hz, H-2), 5.78 (dt, 1H, *J* = 10.0, 2.0 Hz, H-3), 5.50 (s, 2H, CH_2Ph), 5.31 (dm, 1H, *J* = 10.0 Hz, H-4), 5.04 (br s, 1H, H-1), 4.23 (dd, 1H, *J* = 12.0, 5.5 Hz, H-6a), 4.13 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.08–3.99 (m, 2H, H-5, H-1′a), 3.87–3.73 (m, 1H, H-1′b), 3.85 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.04 (t, 2H, *J* = 6.0 Hz, H-2′), 2.10 (s, 3H, OAc), 2.07 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84 (C═O), 170.27 (C═O), 153.71 (Ph), 151.18 (Ph), 144.80 (C-3′), 129.22 (C-2), 127.66 (C-3), 124.06 (Ph), 121.79 (C-4′), 116.03 (Ph), 114.63 (Ph), 111.78 (Ph), 94.59 (C-1), 67.82 (C-1′), 66.99 (C-5), 65.26 (C-4), 62.90 (C-6), 56.01 (OMe), 55.76 (OMe), 48.95 (C-5′), 26.63 (C-2′), 20.84 (CH_3), 20.79 (CH_3); HRMS (ESI) *m/z* calcd for $C_{23}H_{29}N_3O_8Na$ $[M+Na]^+$ 498.1852, found: 498.1801.



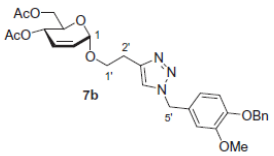
4.3.15. 1-(2,5-Dimethoxybenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (6c)

Pale yellow oil; α-anomer R_f = 0.30 (50% EtOAc/*n*-hexane); $[\alpha]_D^{24}$ +71.6 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2923, 2848, 1740, 1657, 1632, 1504, 1467, 1428, 1369, 1273, 1260, 1225, 1043, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (br s, 1H, triazolyl-H), 6.88–6.81 (m, 2H, Ph), 6.76 (br s, 1H, Ph), 5.89 (br d, 1H, *J* = 10.0 Hz, H-2), 5.83 (dm, 1H, *J* = 10.0 Hz, H-3), 5.49 (s, 2H, CH_2Ph), 5.31 (dm, 1H, *J* = 10.0 Hz, H-4), 5.02 (br s, 1H, H-1), 4.25 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.16 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.08–4.07 (m, 1H, H-5), 3.85 (s, 3H, OMe), 3.76–3.68 (m, 1H, H-1′a), 3.75 (s, 3H, OMe), 3.60–3.58 (dt, 1H, *J* = 10.0, 6.0 Hz, H-1′b), 2.85–2.75 (m, 2H, H-3′), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.02–1.94 (m, 2H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84 (C═O), 170.32 (C═O), 153.68 (2 × Ph), 147.40 (C-4′), 129.05 (C-2), 127.83 (C-3), 123.93 (Ph), 121.05 (C-5′), 116.04 (Ph), 114.52 (Ph), 111.45 (Ph), 94.42 (C-1), 68.01 (C-1′), 66.92 (C-5), 65.29 (C-4), 63.01 (C-6), 55.95 (OMe), 55.71 (OMe), 49.09 (C-6′), 31.24 (C-2′), 22.82 (C-3′), 21.00 (CH_3), 20.79 (CH_3); HRMS (ESI) *m/z* calcd for $C_{24}H_{31}N_3O_8Na$ $[M+Na]^+$ 512.2009, found: 512.1985.



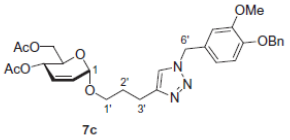
4.3.16. 1-(4-Benzyloxy-3-methoxybenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (7a)

White solid; α-anomer R_f = 0.27 (50% EtOAc/*n*-hexane); mp: 64–66 °C; $[\alpha]_D^{26}$ +13.9 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$): 2923, 2848, 1741, 1657, 1633, 1515, 1465, 1417, 1369, 1261, 1229, 1037, 964 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (br s, 1H, triazolyl-H), 7.48–7.29 (m, 5H, Ph), 6.87 (d, 1H, *J* = 8.5 Hz, Ph), 6.84 (br s, 1H, Ph), 6.81 (dd, 1H, *J* = 8.5, 2.0 Hz, Ph), 5.90 (br d, 1H, *J* = 10.0 Hz, H-2), 5.82 (dt, 1H, *J* = 10.0, 2.0 Hz, H-3), 5.44 (s, 2H, CH_2Ph), 5.34 (dm, 1H, *J* = 10.0 Hz, H-4), 5.16 (br s, 3H, H-1, CH_2Ph), 4.89 (d, 1H, *J* = 12.0 Hz, H-1′a), 4.70 (d, 1H, *J* = 12.0 Hz, H-1′b), 4.25 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.0, 2.5 Hz, H-6b), 4.12 (ddd, 1H, *J* = 10.0, 5.0, 2.5 Hz, H-5), 3.88 (s, 3H, OMe), 2.00 (s, 3H, OAc), 1.99 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.78 (C═O), 170.24 (C═O), 150.13 (Ph), 148.64 (Ph), 144.82 (C-2′), 136.75 (Ph), 129.53 (C-2), 127.34 (Ph), 128.60 (2 × Ph), 127.97 (Ph), 127.42 (C-3), 127.22 (2xPh), 122.41 (C-3′), 120.86 (Ph), 113.98 (Ph), 111.88 (Ph), 93.86 (C-1), 71.00 (CH_2Ph), 67.05 (C-5), 65.24 (C-4), 62.80 (C-6), 61.31 (C-1′), 56.09 (OMe), 54.09 (C-4′), 20.94 (CH_3), 20.80 (CH_3); HRMS (ESI) *m/z* calcd for $C_{28}H_{31}N_3O_8Na$ $[M+Na]^+$ 560.2009, found: 560.2008.



4.3.17. 1-(4-Benzyloxy-3-methoxybenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (7b)

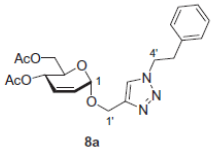
Pale yellow oil; α-anomer R_f = 0.36 (50% EtOAc/*n*-hexane); $[\alpha]_D^{26}$ +67.9 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$): 2923, 2848, 1734, 1605, 1590, 1508, 1455, 1417, 1366, 1260, 1273, 1222, 1031, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.30 (m, 6H, triazolyl-H, Ph), 6.88–6.75 (m, 3H, Ph), 5.87 (br d, 1H, *J* = 10.0 Hz, H-2), 5.76 (dt, 1H, *J* = 10.0, 2.5 Hz, H-3), 5.42 (s, 2H, CH_2Ph), 5.30 (ddd, 1H, *J* = 10.0, 2.5, 1.0 Hz, H-4), 5.16 (s, 2H, CH_2Ph), 5.03 (br s, 1H, H-1), 4.22 (dd, 1H, *J* = 12.0, 5.5 Hz, H-6a), 4.14 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.04 (dt, 1H, *J* = 9.5, 7.0 Hz, H-1′a), 4.02 (ddd, 1H, *J* = 10.0, 5.5, 2.0 Hz, H-5), 3.85 (s, 3H, OMe), 3.79 (dt, 1H, *J* = 9.5, 7.0 Hz, H-1′b), 3.06–2.98 (m, 2H, H-2′), 2.08 (s, 3H, OAc), 2.05 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.80 (C=O), 170.26 (C=O), 150.07 (Ph), 148.52 (Ph), 145.00 (C-3′), 136.77 (Ph), 129.28 (C-2), 128.60 (2 × Ph), 127.97 (Ph), 127.69 (Ph), 127.59 (C-3), 127.22 (2 × Ph), 121.32 (C-4′), 120.60 (Ph), 113.88 (Ph), 111.69 (Ph), 94.53 (C-1), 70.98 (CH_2Ph), 67.66 (C-1′), 66.99 (C-5), 65.25 (C-4), 62.88 (C-6), 56.07 (OMe), 53.94 (C-5′), 26.61 (C-2′), 20.96 (CH_3), 20.77 (CH_3); HRMS (ESI) *m/z* calcd for $C_{29}H_{33}N_3O_8Na$ $[M+Na]^+$ 574.2165, found: 574.2091.



7c

4.3.18. 1-(4-Benzyloxy-3-methoxybenzyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (7c)

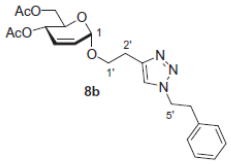
Pale yellow oil; α-anomer R_f = 0.35 (50% EtOAc/*n*-hexane); $[\alpha]_D^{26}$ +42.1 (*c* 0.51, $CHCl_3$); IR ($CHCl_3$): 2923, 2848, 1738, 1657, 1632, 1517, 1465, 1421, 1365, 1275, 1260, 1034, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.30 (m, 6H, triazolyl-H, Ph), 6.89–6.77 (m, 3H, Ph), 5.89 (br d, 1H, *J* = 10.0 Hz, H-2), 5.82 (dt, 1H, *J* = 10.0, 3.0 Hz, H-3), 5.42 (s, 2H, CH_2Ph), 5.32 (ddd, 1H, *J* = 10.0, 3.0, 2.0 Hz, H-4), 5.17 (s, 2H, CH_2Ph), 5.03 (br s, 1H, H-1), 4.25 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.0, 2.0 Hz, H-6b), 4.14–4.07 (m, 1H, H-5), 3.90–3.79 (m, 1H, H-1′a), 3.86 (s, 3H, OMe), 3.56 (dt, 1H, *J* = 10.0, 6.0 Hz, H-1′b), 2.84–2.75 (m, 2H, H-3′), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.02–1.94 (m, 2H, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84 (C=O), 170.33 (C=O), 150.08 (Ph), 148.52 (Ph), 148.00 (C-4′), 136.78 (Ph), 129.09 (C-2), 128.62 (2xPh), 127.98 (Ph), 127.80 (C-3), 127.71 (Ph), 127.24 (2 × Ph), 120.65 (Ph), 120.50 (C-5′), 113.88 (Ph), 111.68 (Ph), 94.42 (C-1), 71.00 (CH_2Ph), 67.93 (C-1′), 66.92 (C-5), 65.29 (C-4), 62.99 (C-6), 56.08 (OMe), 53.96 (C-6′), 29.39 (C-2′), 22.50 (C-3′), 21.00 (CH_3), 20.80 (CH_3); HRMS (ESI) *m/z* calcd for $C_{30}H_{35}N_3O_8Na$ $[M+Na]^+$ 588.2322, found: 588.2291.



8a

4.3.19. 1-(2-Phenylethyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (8a)

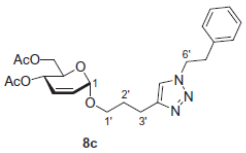
Pale yellow oil; α-anomer R_f = 0.33 (50% EtOAc/*n*-hexane); $[\alpha]_D^{24}$ +58.9 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$): 2923, 2851, 1740, 1454, 1435, 1368, 1228, 1038, 1020, 965 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.03 (br s, 1H, triazolyl-H), 7.32 (t, 2H, *J* = 7.0 Hz, Ph), 7.24 (t, 2H, *J* = 7.0 Hz, Ph), 7.23 (d, 1H, *J* = 7.0 Hz, Ph), 5.89 (m, 2H, H-2, H-3), 5.24 (d, 1H, *J* = 10.0 Hz, H-4), 5.16 (s, 1H, H-1), 4.74 (d, 1H, *J* = 12.0 Hz, H-1′a), 4.64 (t, 2H, *J* = 7.0 Hz, H-4′), 4.62 (d, 1H, *J* = 12.0 Hz, H-1′b), 4.18 (dd, 1H, *J* = 12.0, 5.0 Hz, H-6a), 4.14 (dd, 1H, *J* = 12.0, 3.0 Hz, H-6b), 4.00 (ddd, 1H, *J* = 10.0, 5.0, 2.0 Hz, H-5), 3.19 (t, 2H, *J* = 7.0 Hz, H-5′), 2.09 (s, 3H, OAc), 2.07 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.85 (C=O), 170.30 (C=O), 144.90 (C-2′), 136.96 (Ph), 129.48 (C-2), 128.83 (2 × Ph), 128.63 (2 × Ph), 127.48 (Ph), 127.13 (C-3), 123.05 (C-3′), 93.53 (C-1), 67.19 (C-5), 65.28 (C-4), 62.86 (C-6), 61.33 (C-1′), 54.64 (C-4′), 37.03 (C-5′), 20.98 (CH_3), 20.85 (CH_3); HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_3O_6H$ $[M+H]^+$ 416.1822, found: 416.1822.



8b

4.3.20. 1-(2-Phenylethyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (8b)

Pale yellow oil; α-anomer R_f = 0.26 (50% EtOAc/*n*-hexane); $[\alpha]_D^{26}$ +94.2 (*c* 0.52, $CHCl_3$); IR ($CHCl_3$): 2924, 2851, 1741, 1454, 1435, 1370, 1256, 1228, 1068, 971 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.84 (br s, 1H, triazolyl-H), 7.31 (t, 2H, *J* = 7.0 Hz, Ph), 7.25 (d, 1H, *J* = 7.0 Hz, Ph), 7.23 (t, 2H, *J* = 7.0 Hz, Ph), 5.88 (m, 2H, H-2, H-3), 5.20 (d, 1H, *J* = 10.0 Hz, H-4), 5.11 (s, 1H, H-1), 4.60 (t, 2H, *J* = 7.0 Hz, H-5′), 4.14 (d, 2H, *J* = 4.0 Hz, H-6), 3.95–3.87 (m, 2H, H-5, H-1′a), 3.77–3.70 (m, 1H, H-1′b), 3.17 (t, 2H, *J* = 7.0 Hz, H-6′), 2.92 (t, 2H, *J* = 7.0 Hz, H-2′), 2.07 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.78 (C=O), 170.67 (C=O), 144.59 (C-3′), 137.15 (Ph), 129.19 (C-2), 128.77 (2 × Ph), 128.66 (2 × Ph), 127.68 (Ph), 127.05 (C-3), 121.88 (C-4′), 94.50 (C-1), 67.78 (C-1′), 66.99 (C-5), 65.33 (C-4), 62.93 (C-6), 51.47 (C-5′), 36.76 (C-6′), 26.54 (C-2′), 20.94 (CH_3), 20.77 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{27}N_3O_6H$ $[M+H]^+$ 430.1978, found: 430.1975.

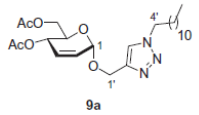


8c

4.3.21. 1-(2-Phenylethyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (8c)

Yellow oil; α-anomer R_f = 0.23 (50% EtOAc/*n*-hexane); $[\alpha]_D^{26}$ +45.5 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$): 2924, 2874, 1741, 1454, 1435,

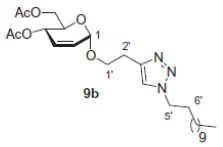
1370, 1253, 1230, 1040, 979 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.83 (br s, 1H, triazolyl-H), 7.31 (t, 2H, J = 7.0 Hz, Ph), 7.25 (d, 1H, J = 7.0 Hz, Ph), 7.22 (t, 2H, J = 7.0 Hz, Ph), 5.93 (dt,1H, J = 10.0, 1.0 Hz, H-2), 5.88 (d, 1H, J = 10.0 Hz, H-3), 5.20 (d, 1H, J = 10.0 Hz, H-4), 5.06 (s, 1H, H-1), 4.58 (t, 2H, J = 7 Hz, H-6′), 4.17 (dd, 1H, J = 12.0, 5.0 Hz, H-6a), 4.12 (dd, 1H, J = 12.0, 3.0 Hz, H-6b), 4.00 (ddd, 1H, J = 10.0, 5.0, 2.0 Hz, H-5), 3.70 (dt, 1H, J = 10.0, 7.0 Hz, H-1′a), 3.60 (dt, 1H, J = 10.0, 7.0 Hz, H-1′b), 3.17 (t, 2H, J = 7 Hz, H-7′), 2.67 (t, 2H, J = 7.0 Hz, H-3′), 2.09 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.87 (p, 2H, J = 7.0 Hz, H-2′); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.79 (C=O), 170.28 (C=O), 147.08 (C-4′), 137.18 (Ph), 129.36 (C-2), 128.84 (2 × Ph), 128.67 (2 × Ph), 127.83 (Ph), 127.03 (C-3), 121.13 (C-5′), 94.43 (C-1), 67.90 (C-1′), 66.94 (C-5), 65.33 (C-4), 63.00 (C-6), 51.48 (C-6′), 36.78 (C-7′), 29.46 (C-2′), 22.34 (C-3′), 20.95 (CH_3), 20.77 (CH_3); HRMS (ESI) m/z calcd for $C_{23}H_{29}N_3O_6H$ $[M+H]^+$ 444.2135, found: 444.2129.



9a

4.3.22. 1-(Dodecyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (9a)

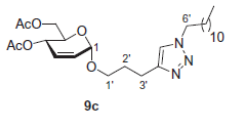
Pale yellow oil; α-anomer R_f = 0.55 (50% EtOAc/*n*-hexane); $[\alpha]_D^{27}$ +53.1 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$): 2925, 2851, 1745, 1460, 1437, 1370, 1228, 1039, 1018, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H, triazolyl-H), 5.84 (d, 1H, J = 10.0 Hz, H-2), 5.77 (d, 1H, J = 10.0 Hz, H-3), 5.27 (d, 1H, J = 10.0 Hz, H-4), 5.12 (s, 1H, H-1), 4.85 (dd, 1H, J = 12.0, 1.2 Hz, H-1′a), 4.65 (dd, 1H, J = 12.0, 1.2 Hz, H-1′b), 4.27 (t, 2H, J = 7.6 Hz, H-4′), 4.20 (dd, 1H, J = 12.0, 5.0 Hz, H-6a), 4.13 (dd, 1H, J = 12.0, 2.0 Hz, H-6b), 4.13–4.05 (m, 1H, H-5), 2.05 (s, 3H, OAc), 2.01 (s, 3H, OAc), 1.90–1.77 (m, 2H, H-5′), 1.33–1.10 (m, 18H, CH_2), 0.81 (dd, 3H, J = 7.0, 5.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.81 (C=O), 170.25 (C=O), 144.35 (C-2′), 129.51 (C-2), 127.49 (C-3), 122.40 (C-3′), 93.77 (C-1), 67.32 (C-5), 65.30 (C-4), 62.88 (C-6), 61.59 (C-1′), 50.41 (C-4′), 31.88 (CH_2), 30.29 (CH_2), 29.57 (2 × CH_2), 29.43 (CH_2), 29.36 (CH_2), 29.30 (CH_2), 28.99 (CH_2), 26.51 (CH_2), 22.66 (CH_2), 20.94 (CH_3), 20.80 (CH_3), 14.09 (CH_3); HRMS (ESI) m/z calcd for $C_{25}H_{41}N_3O_6H$ $[M+H]^+$ 480.3074, found: 480.3068.



9b

4.3.23. 1-(Dodecyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (9b)

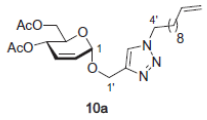
Pale yellow oil; α-anomer R_f = 0.44 (50% EtOAc/*n*-hexane); $[\alpha]_D^{25}$ +81.7 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2925, 2851, 1744, 1460, 1435, 1368, 1256, 1227, 1040, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H, triazolyl-H), 5.89 (d, 1H, J = 10.0 Hz, H-2), 5.81 (d, 1H, J = 10.0 Hz, H-3), 5.31 (d, 1H, J = 10.0 Hz, H-4), 5.07 (s, 1H, H-1), 4.33 (t, 2H, J = 7.6 Hz, H-5′), 4.23 (dd, 1H, J = 12.0, 5.6 Hz, H-6a), 4.15 (dd, 1H, J = 12.0, 2.4 Hz, H-6b), 4.10–4.00 (m, 2H, H-5, H-1′a), 3.80 (dt, 1H, J = 10.0, 3.2 Hz, H-1′b), 3.05 (dt, 2H, J = 6.8, 5.2 Hz, H-2′), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 1.96–1.83 (m, 2H, H-6′), 1.43–1.18 (m, 18H, CH_2), 0.88 (t, 3H, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.81 (C=O), 170.23 (C=O), 144.75 (C-3′), 129.26 (C-2), 127.67 (C-3), 121.33 (C-4′), 94.53 (C-1), 67.77 (C-1′), 67.03 (C-5), 65.33 (C-4), 62.93 (C-6), 50.24 (C-5′), 31.89 (CH_2), 30.33 (CH_2), 29.59 (2 × CH_2), 29.51 (CH_2), 29.39 (CH_2), 29.31 (CH_2), 29.01 (CH_2), 26.60 (C-2′), 26.52 (CH_2), 22.66 (CH_2), 20.96 (CH_3), 20.77 (CH_3), 14.09 (CH_3); HRMS (ESI) m/z calcd for $C_{26}H_{43}N_3O_6H$ $[M+H]^+$ 494.3230, found: 494.3225.



9c

4.3.24. 1-(Dodecyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (9c)

Pale yellow oil; α-anomer R_f = 0.45 (50% EtOAc/*n*-hexane); $[\alpha]_D^{23}$ +62.7 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2925, 2851, 1744, 1460, 1435, 1371, 1229, 1041, 1018, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H, triazolyl-H), 5.89 (d, 1H, J = 10.0 Hz, H-2), 5.84 (ddd, 1H, J = 10.0, 2.4, 1.6 Hz, H-3), 5.31 (ddd, 1H, J = 10.0, 2.4, 1.2 Hz, H-4), 5.05 (s, 1H, H-1), 4.30 (t, 2H, J = 7.6 Hz, H-6′), 4.25 (dd, 1H, J = 12.0, 5.2 Hz, H-6a), 4.17 (dd, 1H, J = 12.0, 2.4 Hz, H-6b), 4.08–4.15 (m, 1H, H-5), 3.84 (dt, 1H, J = 10.0, 6.0 Hz, H-1′a), 3.58 (dt, 1H, J = 10.0, 6.0 Hz, H-1′b), 2.81 (m, 2H, H-3′), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.07–1.95 (m, 2H, H-2′), 1.93–1.82 (m, 2H, H-7′), 1.38–1.18 (m, 18H, CH_2), 0.88 (t, 3H, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.81 (C=O), 170.30 (C=O), 147.37 (C-4′), 129.08 (C-2), 127.84 (C-3), 120.49 (C-5′), 94.46 (C-1), 68.01 (C-1′), 66.95 (C-5), 65.33 (C-4), 63.02 (C-6), 50.24 (C-6′), 31.89 (CH_2), 30.34 (CH_2), 29.59 (2 × CH_2), 29.50 (C-2′, CH_2), 29.38 (CH_2), 29.31 (CH_2), 29.00 (CH_2), 26.52 (CH_2), 22.67 (CH_2), 22.47 (C-3′), 20.96 (CH_3), 20.77 (CH_3), 14.10 (CH_3); HRMS (ESI) m/z calcd for $C_{27}H_{45}N_3O_6H$ $[M+H]^+$ 508.3387, found: 508.3389.

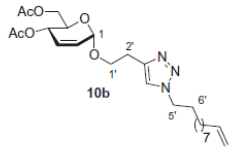


10a

4.3.25. 1-(Undecylenyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (10a)

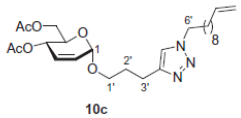
Pale yellow oil; α-anomer R_f = 0.26 (40% EtOAc/*n*-hexane); $[\alpha]_D^{26}$ +66.5 (*c* 0.25, $CHCl_3$); IR ($CHCl_3$): 2927, 2851, 1744, 1457, 1438, 1368, 1256, 1228, 1039, 1015, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 1H, triazolyl-H), 5.91 (d, 1H, J = 10.0 Hz, H-2), 5.89–5.73 (m, 2H, H-3, C*H*=CH_2), 5.35 (d, 1H, J = 10.0 Hz, H-4), 5.19 (s, 1H, H-1), 5.05–4.87 (m, 2H, CH=CH_2), 4.92 (d, 1H, J = 12.0 Hz, H-1′a), 4.72 (d, 1H, J = 12.0 Hz, H-1′b), 4.34 (t, 2H, J = 6.8 Hz, H-4′), 4.27 (dd, 1H, J = 12.0, 5.2 Hz, H-6a), 4.24–4.11 (m, 2H, H-6b, H-5), 2.19–1.99 (m, 2H, CH_2CH=CH_2), 2.09 (s, 3H,

OAc), 2.08 (s, 3H, OAc), 1.97–1.84 (m, 2H, H-5′), 1.45–1.20 (m, 12H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.87 (C=O), 170.80 (C=O), 144.34 (C-2′), 139.14 (HC=CH_2), 129.53 (C-2), 127.48 (C-3), 122.46 (C-3′), 114.19 (HC=CH_2), 93.78 (C-1), 67.06 (C-5), 65.27 (C-4), 62.87 (C-6), 61.59 (C-1′), 50.40 (C-4′), 33.77 (CH_2), 30.31 (CH_2), 29.32 (2 × CH_2), 29.03 (CH_2), 28.97 (CH_2), 28.87 (CH_2), 26.50 (CH_2), 20.98 (CH_3), 20.85 (CH_3); HRMS (ESI) *m/z* calcd for $C_{24}H_{37}N_3O_6H$ $[M+H]^+$ 464.2761, found: 464.2755.



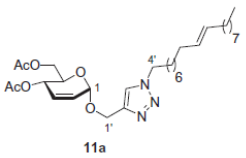
4.3.26. 1-(Undecylenyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (10b)

Yellow oil; α-anomer R_f = 0.37 (50% EtOAc/*n*-hexane); $[\alpha]_D^{25}$ +58.3 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2926, 2851, 1744, 1460, 1438, 1368, 1227, 1039, 973 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H, triazolyl-H), 5.90 (d, 1H, *J* = 10.0 Hz, H-2), 5.87–5.74 (m, 2H, H-3, C*H*=CH_2), 5.31 (dd, 1H, *J* = 9.6, 1.6 Hz, H-4), 5.07 (s, 1H, H-1), 5.04–4.90 (m, 2H, CH=CH_2), 4.32 (t, 2H, *J* = 7.2 Hz, H-5′), 4.24 (dd, 1H, *J* = 12.0, 5.2 Hz, H-6a), 4.16 (dd, 1H, *J* = 12.0, 2.4 Hz, H-6b), 4.10–4.00 (m, 2H, H-5, H-1′a), 3.90–3.70 (m, 1H, H-1′b), 3.06 (t, 2H, *J* = 6.4 Hz, H-2′), 2.17–1.98 (m, 2H, CH_2CH=CH_2), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 1.96–1.77 (m, 2H, H-6′), 1.45–1.20 (m, 12H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.81 (C=O), 170.23 (C=O), 144.76 (C-3′), 139.11 (HC=CH_2), 129.25 (C-2), 127.66 (C-3), 121.33 (C-4′), 114.17 (HC=CH_2), 94.52 (C-1), 67.76 (C-1′), 67.02 (C-5), 65.32 (C-4), 62.92 (C-6), 50.23 (C-5′), 33.75 (CH_2), 30.32 (CH_2), 29.32 (2 × CH_2), 29.02 (CH_2), 28.97 (CH_2), 28.86 (CH_2), 26.60 (C-2′), 26.50 (CH_2), 20.96 (CH_3), 20.77 (CH_3); HRMS (ESI) *m/z* calcd for $C_{25}H_{39}N_3O_6H$ $[M+H]^+$ 478.2917, found: 478.2919.



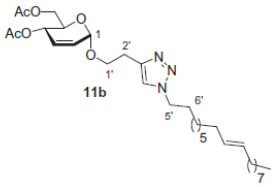
4.3.27. 1-(Undecylenyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (10c)

Pale yellow oil; α-anomer R_f = 0.40 (50% EtOAc/*n*-hexane); $[\alpha]_D^{26}$ +49.8 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$): 2927, 2851, 1743, 1454, 1435, 1368, 1275, 1260, 1228, 1040, 1018, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H, triazolyl-H), 5.89 (d, 1H, *J* = 10.0 Hz, H-2), 5.87–5.75 (m, 2H, H-3, C*H*=CH_2), 5.31 (d, 1H, *J* = 9.6, 1.2 Hz, H-4), 5.04 (s, 1H, H-1), 4.99–4.89 (m, 2H, CH=CH_2), 4.30 (t, 2H, *J* = 7.6 Hz, H-6′), 4.25 (dd, 1H, *J* = 12.0, 5.2 Hz, H-6a), 4.17 (dd, 1H, *J* = 12.0, 2.4 Hz, H-6b), 4.14–4.08 (m, 1H, H-5), 3.84 (dt, 1H, *J* = 9.6, 6.0 Hz, H-1′a), 3.58 (dt, 1H, *J* = 9.6, 6.0 Hz, H-1′b), 2.91–2.73 (m, 2H, H-3′), 2.10–1.95 (m, 4H, H-2′, CH_2CH=CH_2), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 1.95–1.80 (m, 2H, H-7′), 1.45–1.20 (m, 12H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.78 (C=O), 170.28 (C=O), 147.36 (C-4′), 139.12 (HC=CH_2), 129.07 (C-2), 127.84 (C-3), 120.47 (C-5′), 114.16 (HC=CH_2), 94.45 (C-1), 68.00 (C-1′), 66.95 (C-5), 65.33 (C-4), 63.01 (C-6), 50.19 (C-6′), 33.74 (CH_2), 30.32 (2 × CH_2), 29.30 (C-2′, CH_2), 29.02 (CH_2), 28.96 (CH_2), 28.86 (CH_2), 26.49 (CH_2), 22.47 (C-3′), 20.95 (CH_3), 20.77 (CH_3); HRMS (ESI) *m/z* calcd for $C_{26}H_{41}N_3O_6H$ $[M+H]^+$ 492.3074, found: 492.3078.



4.3.28. 1-(Oleyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxymethyl)-1,2,3-1*H*-triazole (11a)

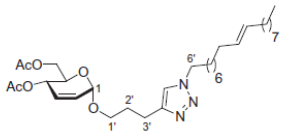
Pale yellow oil; α-anomer R_f = 0.28 (30% EtOAc/*n*-hexane); $[\alpha]_D^{24}$ +52.9 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2928, 2851, 1744, 1457, 1438, 1371, 1230, 1040, 1018, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H, triazolyl-H), 5.92 (d, 1H, *J* = 10.0 Hz, H-2), 5.85 (ddd, 1H, *J* = 10.0, 2.8, 2.0 Hz, H-3), 5.42–5.29 (m, 3H, H-4, C*H*=C*H*), 5.19 (s, 1H, H-1), 4.93 (d, 1H, *J* = 12.0 Hz, H-1′a), 4.73 (d, 1H, *J* = 12.0 Hz, H-1′b), 4.35 (t, 2H, *J* = 7.2 Hz, H-4′), 4.28 (dd, 1H, *J* = 12.0, 5.2 Hz, H-6a), 4.21 (dd, 1H, *J* = 12.0, 2.4 Hz, H-6b), 4.20–4.13 (m, 1H, H-5), 2.13 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.07–1.97 (m, 4H, CH_2CH=CHCH_2), 1.96–1.86 (m, 2H, H-5′), 1.42–1.21 (m, 22H, CH_2), 0.89 (t, 3H, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84 (C=O), 170.27 (C=O), 144.36 (C-2′), 130.05 (HC=CH), 129.68 (HC=CH), 129.52 (C-2), 127.49 (C-3), 122.40 (C-3′), 93.78 (C-1), 67.08 (C-5), 65.30 (C-4), 62.88 (C-6), 61.60 (C-1′), 50.40 (C-4′), 31.90 (CH_2), 30.30 (CH_2), 29.75 (CH_2), 29.68 (2 × CH_2), 29.51 (CH_2), 29.31 (2 × CH_2), 29.15 (CH_2), 28.98 (CH_2), 27.21 (CH_2), 27.15 (CH_2), 26.52 (CH_2), 22.67 (CH_2), 20.95 (CH_3), 20.82 (CH_3), 14.10 (CH_3); HRMS (ESI) *m/z* calcd for $C_{31}H_{51}N_3O_6H$ $[M+H]^+$ 562.3856, found: 562.3856.



4.3.29. 1-(Oleyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (11b)

Pale yellow oil; α-anomer R_f = 0.20 (30% EtOAc/*n*-hexane); $[\alpha]_D^{24}$ +66.8 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2927, 2851, 1745, 1460, 1438, 1371, 1228, 1040, 1015, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H, triazolyl-H), 5.90 (d, 1H, *J* = 10.0 Hz, H-2), 5.82 (d, 1H, *J* = 10.0 Hz, H-3), 5.42–5.27 (m, 3H, H-4, C*H*=C*H*), 5.07 (s, 1H, H-1), 4.32 (t, 2H, *J* = 7.2 Hz, H-5′), 4.24 (dd, 1H, *J* = 12.0, 5.6 Hz, H-6a), 4.16 (dd, 1H, *J* = 12.0, 2.4 Hz, H-6b), 4.10–4.00 (m, 2H, H-5, H-1′a), 3.81 (dt, 1H, *J* = 9.6, 6.8 Hz, H-1′b), 3.06 (t, 2H, *J* = 6.4 Hz, H-2′), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.07–1.94 (m, 4H,

$CH_2CH{=}CHCH_2$), 1.94–1.80 (m, 2H, H-6′), 1.50–1.19 (m, 22H, CH_2), 0.88 (t, 3H, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.82 (C=O), 170.24 (C=O), 144.76 (C-3′), 130.04 (HC=CH), 129.68 (HC=CH), 129.26 (C-2), 127.66 (C-3), 121.32 (C-4′), 94.52 (C-1), 67.77 (C-1′), 67.02 (C-5), 65.32 (C-4), 62.92 (C-6), 50.22 (C-5′), 31.89 (CH_2), 30.34 (CH_2), 29.75 (CH_2), 29.69 ($2 \times CH_2$), 29.51 (CH_2), 29.31 ($2 \times CH_2$), 29.16 (CH_2), 28.99 (CH_2), 27.21 (CH_2), 27.15 (CH_2), 26.60 (C-2′), 26.52 (CH_2), 22.67 (CH_2), 20.96 (CH_3), 20.77 (CH_3), 14.10 (CH_3); HRMS (ESI) m/z calcd for $C_{32}H_{53}N_3O_6Na$ $[M+Na]^+$ 598.3832, found: 598.3829.



11c

4.3.30. 1-(Oleyl)-4-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxypropyl)-1,2,3-1*H*-triazole (11c)

Pale yellow oil; α-anomer R_f = 0.26 (40% EtOAc/*n*-hexane); $[\alpha]_D^{24}$ +62.3 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 2927, 2851, 1743, 1457, 1435, 1370, 1275, 1260, 1228, 1041, 1015, 976 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1H, triazolyl-H), 5.82 (d, 1H, J = 10.0 Hz, H-2), 5.77 (d, 1H, J = 10.0 Hz, H-3), 5.35–5.20 (m, 3H, H-4, $CH{=}CH$), 4.97 (s, 1H, H-1), 4.23 (t, 2H, J = 7.6, H-6′), 4.18 (dd, 1H, J = 12.0, 5.6 Hz, H-6a), 4.14–4.01 (m, 1H, H-5), 4.10 (dd, 1H, J = 12.0, 2.4 Hz, H-6b), 3.77 (dt, 1H, J = 9.6, 3.6 Hz, H-1′a), 3.50 (dt, 1H, J = 9.6, 6.0 Hz, H-1′b), 2.85–2.67 (m, 2H, H-3′), 2.11–1.75 (m, 6H, H-2′, $CH_2CH{=}CHCH_2$), 2.02 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.00–1.75 (m, 2H, H-7′), 1.37–1.05 (m, 22H, CH_2), 0.80 (t, 3H, J = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.81 (C=O), 170.29 (C=O), 147.38 (C-4′), 130.04 (HC=CH), 129.70 (HC=CH), 129.09 (C-2), 127.84 (C-3), 120.47 (C-5′), 94.46 (C-1), 68.02 (C-1′), 66.96 (C-5), 65.34 (C-4), 63.02 (C-6), 50.22 (C-6′), 32.21 (CH_2), 30.35 (CH_2), 29.76 (CH_2), 29.69 ($3 \times CH_2$), 29.51 (CH_2), 29.31 ($2 \times CH_2$), 29.16 (CH_2), 29.00 (CH_2), 27.22 (CH_2), 27.16 (CH_2), 26.40 (CH_2), 22.68 (CH_2), 22.49 (C-3′), 20.97 (CH_3), 20.79 (CH_3), 14.11 (CH_3); HRMS (ESI) m/z calcd for $C_{33}H_{55}N_3O_6Na$ $[M+Na]^+$ 612.3989, found: 612.3986.

Acknowledgments

This work was supported by the Burapha University annual grant (to R.S) and the Center of Excellence for Innovation in Chemistry (PERCH-CIC). Special thanks to Miss Suthiporn Pikulthong (Mahidol University) for high resolution mass analysis and to Dr. Poolsak Sahakitpichan (Chulabhorn Research Institute) for specific rotation measurement.

References

1. (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137; (b) Link, A. J.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 11164–11165; (c) Link, A. J.; Vink, M. K. S.; Tirrell, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 10598–10602; (d) Speers, A. E.; Cravatt, B. F. *ChemBioChem* **2004**, *5*, 41–47; (e) Speers, A. E.; Cravatt, B. F. *Chem. Biol.* **2004**, *11*, 535–546; (f) Ballell, L.; Scherpenzeel, M.; Buchalova, K.; Liskamp, R. M. J.; Pieters, R. J. *Org. Biomol. Chem.* **2006**, *4*, 4387–4394.
2. (a) Altintas, O.; Hizal, G.; Tunca, U. *J. Polym. Sci.* **2006**, *44*, 5699–5707; (b) Dichtel, W. R.; Miljanic, O. S.; Spruell, J. M.; Heath, J. R.; Stoddart, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10388–10390; (c) Malkoch, M.; Vestberg, R.; Gupta, N.; Mespouille, L.; Dubois, P.; Mason, A. F.; Hedrick, J. L.; Liao, Q.; Frank, C. W.; Kingsbury, K.; Hawker, C. J. *Chem. Commun.* **2006**, *26*, 2774–2776; (d) Yilmaz, M. D.; Bozdemir, O. A.; Akkaya, E. U. *Org. Lett.* **2006**, *8*, 2871–2873; (e) Bew, S. P.; Brimage, R. A.; L'Hermite, N.; Sharma, S. V. *Org. Lett.* **2007**, *9*, 3713–3716; (f) Agalave, S. G.; Maujan, S. R; Pore, V. S. *Chem. Asian J.* **2011**, *6*, 2696–2718.
3. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021; (b) Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (c) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
4. (a) Rossi, L. L.; Basu, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3596–3599; (b) Salameh, B. A.; Leffler, H.; Nilsson, U. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3344–3346; (c) Li, J.; Zheng, M.; Tang, W.; He, P. L.; Zhu, W.; Li, T.; Zuo, J. P.; Liu, H.; Jiang, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5009–5013; (d) Tejler, J.; Skogman, F.; Leffler, H.; Nilsson, U. J. *Carbohydr. Res.* **2007**, *342*, 1869–1875; (e) Wilkinson, B. L.; Bornaghi, L. F.; Houston, T. A.; Innocenti, A.; Vullo, D.; Supuranc, C. T.; Poulsen, S. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 987–992; (f) Wilkinson, B. L.; Bornaghi, L. F.; Houston, T. A.; Innocenti, A.; Vullo, D.; Supuran, C. T.; Poulsen, S. A. *J. Med. Chem.* **2007**, *50*, 1651–1657; (g) Wilkinson, B. L.; Innocenti, A.; Vullo, D.; Supuran, C. T.; Poulsen, S. A. *J. Med. Chem.* **2008**, *51*, 1945–1953; (h) Cheng, K.; Liu, J.; Liu, X.; Li, H.; Sun, H.; Xie, J. *Carbohydr. Res.* **2009**, *344*, 841–850; (i) Yeoh, K. K.; Butters, T. D.; Wilkinson, B. L.; Fairbanks, A. J. *Carbohydr. Res.* **2009**, *344*, 586–591; (j) Dedola, S.; Hughes, D. L.; Nepogodiev, S. A.; Rejzek, M.; Field, R. A. *Carbohydr. Res.* **2010**, *345*, 1123–1134; (k) Li, T.; Guo, L.; Zhang, Y.; Wang, J.; Li, Z.; Lin, L.; Zhang, Z.; Li, L.; Lin, J.; Zhao, W.; Li, J.; Wanga, P. G. *Carbohydr. Res.* **2011**, *346*, 1083–1092; (l) Song, Z.; He, X. P.; Jin, X. P.; Gao, L. X.; Sheng, L.; Zhou, Y. B.; Li, J.; Chen, G. R. *Tetrahedron Lett.* **2011**, *52*, 894–898; (m) Singh, B. K.; Yadav, A. K.; Kumar, B.; Gaikwad, A.; Sinha, S. K.; Chaturvedi, V.; Tripathi, R. P. *Carbohydr. Res.* **2008**, *343*, 1153–1162.
5. (a) Stefani, H. A.; Silva, N. C. S.; Manarin, F.; Ludtke, D. S.; Schpector, J. Z.; Madureira, L. S.; Tiekink, E. R. T. *Tetrahedron Lett.* **2012**, *53*, 1742–1747; (b) Nascimento, W. S.; Camara, C. A.; Oliveira, R. N. *Synthesis* **2011**, 3220–3224; (c) Leoneti, V. A.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I. *Tetrahedron* **2010**, *66*, 9475–9492.
6. (a) Miller, N.; Williams, G. M.; Brimble, M. A. *Org. Lett.* **2009**, *11*, 2409–2412; (b) Salunke, S. B.; Babu, N. S.; Chen, C. *Chem. Commun.* **2011**, *47*, 10440–10442.
7. Merkul, E.; Klukas, F.; Dorsch, D.; Gradler, U.; Greiner, H. E.; Muller, T. J. J. *Org. Biomol. Chem.* **2011**, *9*, 5129–5136.
8. Yadav, J. S.; Subba Reddy, B. V.; Narasimha Chary, D.; Suresh Reddy, Ch. *Tetrahedron Lett.* **2008**, *49*, 2649–2652.
9. Anand, N.; Jaiswal, N.; Pandey, S. K.; Srivastava, A. K.; Tripathi, R. P. *Carbohydr. Res.* **2011**, *346*, 16–25.
10. (a) Ferrier, R. J.; Prasad, N. J. *J. Chem. Soc. C* **1969**, 570–574; (b) Ferrier, R. J. *Top. Curr. Chem.* **2001**, *215*, 153–175.
11. (a) Saeeng, R.; Sirion, U.; Sirichan, Y.; Trakulsujaritchok, T.; Sahakitpichan, P. *Heterocycles* **2010**, *81*, 2569–2580; (b) Sirion, U.; Purintawarrakun, S.; Sahakitpichan, P.; Saeeng, R. *Carbohydr. Res.* **2010**, *345*, 2401–2407.

Tetrahedron 71 (2015) 8593–8600

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Convenient one-pot synthesis of triazolylethyl-2,3-unsaturated-*O*-glycoside derivatives

Wadchara Mangsang, Uthaiwan Sirion, Rungnapha Saeeng *

Department of Chemistry and Center for Innovation in Chemistry, Faculty of Science, Burapha University, Sangsook, Chonburi 20131, Thailand

ARTICLE INFO

Article history:
Received 15 April 2015
Received in revised form 20 August 2015
Accepted 10 September 2015
Available online 14 September 2015

Keywords:
Triazolylethyl-2,3-unsaturated-*O*-glycosides
Huisgen 1,3-dipolar cycloaddition
Glycosylation
Azidoethylglycoside
One pot

ABSTRACT

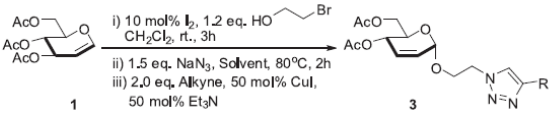
An efficient and convenient synthesis of new derivatives of triazolylethyl-2,3-unsaturated-*O*-glycoside has been developed using sequential one-pot glycosylation-azidation-CuAAc reactions procedure. Various substituted alkynes have been employed for the click reaction to obtain a variety of *O*-glycosylethyl triazole adducts in good to excellent yields with good α-anomeric selectivity.

1. Introduction

The Huisgen 1,3-dipolar cycloaddition of azides and alkynes catalyzed by Cu(I) (CuAAC) to afford triazoles is one of the most powerful reactions in click chemistry to connect two distinct molecules, used in various fields of organic and medicinal chemistry.[1] In the field of carbohydrate chemistry, the application of CuAAc reaction has gained increasing interested for the synthesis of triazole-glycoside substrates for drug discovery.[2] Glycosides with a 1,2,3-triazole ring possess a variety of biological activities such as α-glucosidase inhibitory,[3] anti-oxidant,[4] anti-tuberculosis,[5] anti-proliferative,[6] anti-microbial,[7] SGLT2 inhibitors,[8] anti-inflammatory,[9] cytotoxicity,[10] anti-cancer,[11] anti-parasite[12] and galactin-3 inhibitory effects.[13] Since 1,2,3-triazole glycosides have become increasingly useful and important, the development of a simple and efficient method for their synthesis in a one-pot operation, thus avoiding isolation, handling and chromatography, would be desirable to provide the desired products in good yield and in the most efficient way.[14]

Triazole-glycosides can be prepared from the coupling of propargyl glycosides and azides, or azido glycosides and alkynes. The azide and alkyne functionalities can be introduced at the desired position but generally at the C-1 position of the glycoside. Although a large number of triazole-glycosides derivatives have been synthesized so far, the development of the unique structure of triazolyl-2,3-unsaturated-*O*-glycosides has been limited.[15]

In our previous reports, we demonstrated a convenient one-pot approach to 2,3-unsaturated-glycosyl triazoles via tandem O-glycosylation using an iodine promoter and a mild CuAAC reaction.[16] In this work, we report herein the convenient and efficient procedure for synthesizing new analogs of triazolylethyl-2,3-unsaturated-*O*-glycosides from D-glucal by using a sequential one-pot glycosylation-azidation-CuAAc procedure, without any purification of the intermediates generated at each stage (Scheme 1).



Scheme 1. Synthesis of triazolylethyl-2,3-unsaturated-*O*-glycosides.

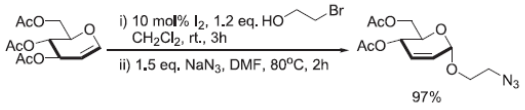
2. Results and discussion

In our initial investigations, the synthesis of azidoethyl glycoside was studied and was found to be easily prepared by iodine catalyzed glycosylation of D-glucal with bromoethanol, for in situ generation of *O*-glycosyl ethyl bromide, followed by subsequent

* Corresponding author. Tel.: +66 81 656 7524; fax: +66 3 839 3494; e-mail address: rungnaph@buu.ac.th (R. Saeeng).

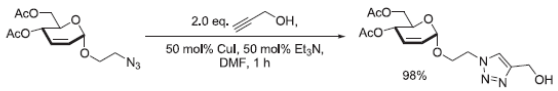
http://dx.doi.org/10.1016/j.tet.2015.09.026
0040-4020/

nucleophilic substitution in the presence of sodium azide to obtain azidoethylglycoside in excellent yield in one pot (Scheme 2).



Scheme 2. Synthesis of azidoethyl glycosides.

The presence of the 2-azidoethyl aglycon would enable click reaction approaches with a variety of alkynes. The click reaction of the resulting isolated azidoethylglycoside with propargyl alcohol was performed smoothly using CuI as catalyst to afford triazolylethyl-2,3-unsaturated-*O*-glycosides in excellent yield (Scheme 3). Based on the good results of two reactions process, we chose to combine and examine the sequential addition of reagents and other reactants in one-pot. We first performed the glycosylation for in situ generation of *O*-glycosyl ethyl bromide, followed by addition of sodium azide to obtain azidoethyl glycoside, which underwent the Huisgen CuACC reaction with a variety of alkynes to furnish a series of *O*-glycosyl ethyl triazole derivatives.



Scheme 3. Synthesis of triazolylethyl-2,3-unsaturated-*O*-glycosides.

As shown in Table 1, our initial investigations focused on glycosylation via Ferrier rearrangement of D-glucal with bromoethanol using 10 mol% iodine to promote the reaction at room temperature. It was observed on TLC that *O*-glycoside formation was completed to obtain *O*-glycosylethylbromide in 3 h. Next, to the reaction was added 1.5 equiv of sodium azide to generate in situ glycosyl azide, followed by the click reaction with 2.0 equiv of propargyl alcohol in the presence of 50 mol% CuI. The use of DMF as solvent in the second step was found to be necessary to promote the azidation reaction to furnish the product in 5 h at RT (Table 1, entry 2). When using acetonitrile, we were unable to obtain the desired product (entry 1).

To shorten the reaction time in the azidation step, the reaction temperature was raised to 80 °C. Under these conditions, azidation could be complete to afford product in 2 h, however the click reaction step took as long as 5 h to afford a quantitative yield of product (entry 3). The use of Et_3N as a base was found to promote the click reaction to completion in 1 h affording the desired product in 91% yield with α-anomeric selectivity (Table 1, entry 4). The one pot reaction progress can be conveniently monitored at each step by TLC, and the reactions clearly proceed without noticeable amount of by product.

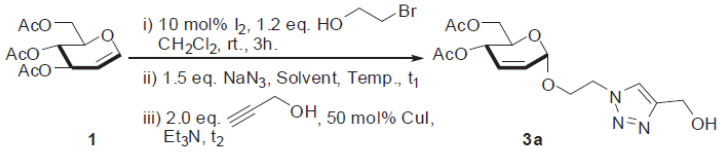
Using the optimal conditions shown in Table 1, entry 4, the scope and limitations of this one pot methodology have been examined. Various substituted alkynes have been employed to furnish a series of *O*-glycosylethyl triazole adducts and the results are summarized in Table 2.

The propargyl alcohol **2a** reacted smoothly to afford **3a** in 91% yield, and the longer chain butynyl and pentynyl alcohols afforded products **3b** and **3c** in >99% and 82% yield, respectively (Table 2, entries 1–3). The use of more hindered alkynes **2d** and **2e** still afforded the desired product in good yield, providing the triazole glycosides **3d** and **3e** in 77% and 72% yield (entries 4–5). Alkyne-bearing cyclobutanol was found to readily undergo cycloaddition and is well tolerated. We next examined both electron-rich and electron-deficient phenyl alkynes **2f**–**2h**, which were carried out at 40 °C and reacted smoothly to give the products **3f**–**3h** in good yields (entries 6–8). The yields were found to excellent with the propargyl ether derivatives **2i**-**2l** (entries 9–12) and **2o**-**2q** (entries 15–17) providing the product in quantitative yield. The benzaldehyde group-bearing propargyl ether in **2l** and **2m** were well tolerated in this one-pot reaction (entries 12–13). Alkyne **2n** containing a coumarin substituent was employed to synthesize triazole glycosides in high yield with this one pot method (entry 14).

3. Conclusion

We have successfully demonstrated the efficient synthesis of new class of triazolylethyl 2,3-unsaturated *O*-glycoside derivatives with good α-anomeric selectivity in a one-pot manner using sequential O-glycosylation-azidation-cycloaddition procedure, thus avoiding the isolation and handling of potentially explosive organic azides. This method can be applied to various alkyne substrates and should be of general utility for the synthesis of this unique scaffold in an efficient way.

Table 1
One-pot glycosylation azidation click reaction of D-glucal **1** under various conditions



Entry	Solvent[b]	Temp (°C)	Et_3N (equiv)	t_1(h)	t_2(h)	Yield[a,c] (%)
1	CH_3CN	RT	—	20	—	—[d]
2	DMF	RT	—	5	5	94
3	DMF	80	—	2	5	>99
4	DMF	80	0.5	2	1	91

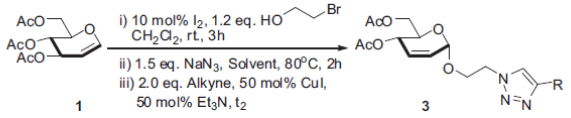
[a] All reactions were carried out with 0.073 mmol of D-glucal (**1**).
[b] Solvent used for step 2.
[c] Yields are given for isolated compound. The ratio α:β=9:1 was determined on the basis of ^1H NMR integration of the crude reaction mixture.
[d] Trace product of 2-azidoethyl-4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythrohex-2-enopyranoside.

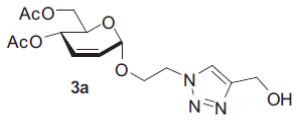
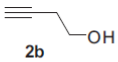
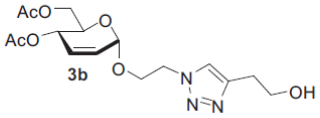
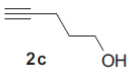
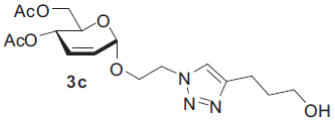
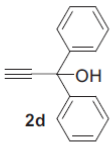
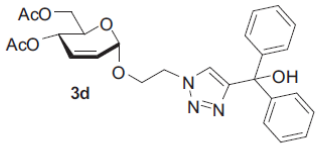
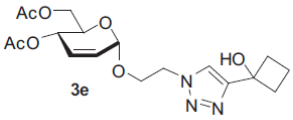
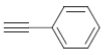
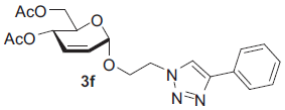
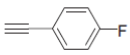
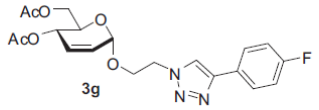
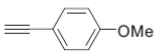
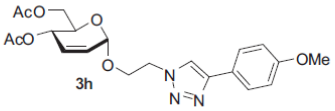
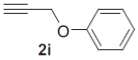
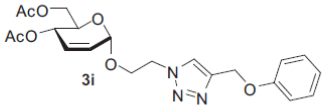
4. Experimental

4.1. General methods

All chemicals were purchased from commercial sources and used without further purification. Proton NMR spectra were

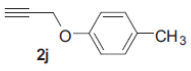
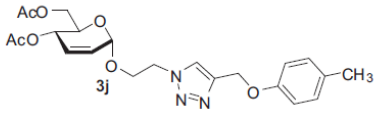
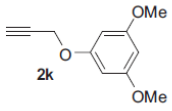
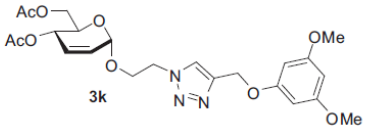
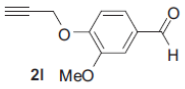
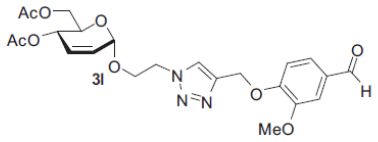
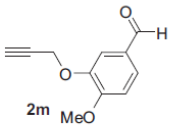
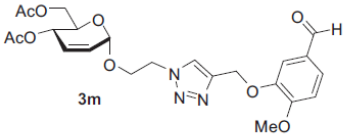
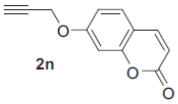
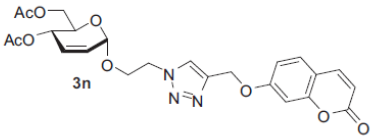
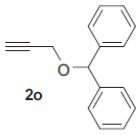
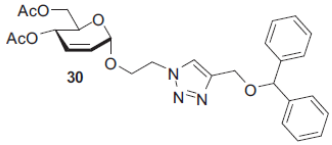
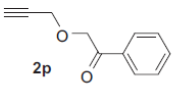
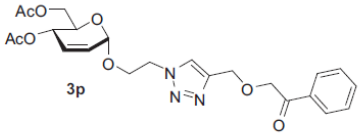
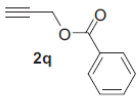
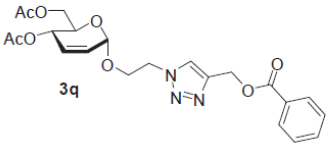
Table 2
Synthesis of 2,3-unsaturated-*O*-glycosyl triazoles **3** via one-pot glycosylation azidation click reaction



Entry	Alkyne	t_2 (h)	Product	Yield[a,b] (%)
1	 **2a**	1	 **3a**	91
2	 **2b**	1.5	 **3b**	>99
3	 **2c**	2	 **3c**	82
4	 **2d**	2	 **3d**	77
5	 **2e**	1	 **3e**	72
6	 **2f**	2	 **3f**	79[c]
7	 **2g**	7	 **3g**	78[c]
8	 **2h**	24	 **3h**	88[c]
9	 **2i**	2	 **3i**	96

(*continued on next page*)

Table 2 (*continued*)

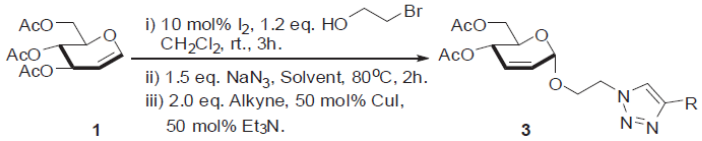
Entry	Alkyne	t_2 (h)	Product	Yield[a,b] (%)
10	 2j	4	 3j	>99
11	 2k	1	 3k	>99
12	 2l	4	 3l	>99
13	 2m	5	 3m	89
14	 2n	3	 3n	83
15	 2o	1	 30	>99
16	 2p	1.5	 3p	>99
17	 2q	4	 3q	>99

[a] All reactions were carried out with 0.073 mmol of D-glucal (**1**).
[b] Yields are given for isolated compound. The ratio α:β=9:1 was determined on the basis of ^{1}H NMR integration of the crude reaction mixture.
[c] The reactions were carried out at 40 °C.

recorded on a Bruker Avance (400 MHz). All spectra were measured in $CDCl_3$ solvent and chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (δ 0.00) or $CDCl_3$ (δ 7.26) as internal standard. Data are reported as follows; chemical shift (multiplicity, integrate intensity or assignment, coupling constants in Hertz, assignment). Carbon NMR spectra were recorded on a BRUKER AVANC (100 MHz). All spectra were measured in $CDCl_3$ solvent and chemical shifts are reported as δ values in parts per million (ppm) relative to $CDCl_3$ (δ 77.0) as internal standard. High-resolution mass spectra (HRMS) data were obtained with a Finnigan MAT 95. Infrared spectra were determined on a PERKIN ELMER FT/IR-2000S spectrophotometer and are reported in wave number (cm^{-1}). Analytical thin-layer chromatography (TLC) was conducted on precoated TLC plates; silica gel 60F-254 [E. Merck,

Darmstadt, Germany]. Silica gel columns for open-column chromatography utilized silica gel 60 (0.040–0.063 mm) [E. Merck, Darmstadt, Germany]. Melting points were measured using a Melting point apparatus (Griffin) and are uncorrected. Yields are given for isolated compound after purification. The ratio of isomer α:β was determined on the basis of 1H NMR integration of the crude reaction mixture. The spectroscopic data for major isomer (α) outlined as followed.

4.2. General procedure for synthesis of 2,3-unsaturated *O*-glycosyl triazole derivatives



For the first step, a stirred solution of 3,4,6-tri-*O*-acetyl-D-glucal **1** (20.0 mg, 0.073 mmol) in dried CH_2Cl_2 (1.0 mL) was added 2-bromoethanol (0.088 mmol) and I_2 catalyst (10 mol%) under nitrogen at room temperature. The stirring was continued at room temperature for 3.0 h. After TLC showed complete conversion, the volatiles were removed using a rotary evaporator. The obtained residue was redissolved in DMF (1.0 mL), followed by addition of sodium azide (7.1 mg, 0.109 mmol). The reaction mixture was stirred at 80 °C for 2.0 h. After TLC showed complete conversion, the following reagents were added in the order: CuI (6.6 mg, 0.037 mmol), Et_3N (3.7 mg, 0.037 mmol) and alkyne (0.146 mmol), respectively. The reaction mixture was stirred at room temperature for 1–24 h. After TLC showed complete conversion, the reaction mixture was diluted with EtOAc (20 mL), washed with satd aq NH_4Cl (20 mL), and extracted with EtOAc (3×20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residues were purified by silica gel column chromatography to give the 2,3-unsaturated-*O*-glycosyl triazole products **3**.

5. Spectroscopic data of 2,3-unsaturated *O*-glycosyl triazole derivatives

5.1. 4-(1-Hydroxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3a)

91% yield (23.6 mg) as a mixture (α:β=9:1); isolated α-form was obtained as a pale yellow oil; R_f (80% EtOAc/*n*-hexane) 0.23; $[\alpha]_D^{20}$ +35.98 (*c* 1.02, $CHCl_3$); ν_{max} ($CHCl_3$): 3468, 2952, 2924, 2851, 1740, 1454, 1435, 1371, 1047, 1015, 982 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.67 (1H, s), 5.89 (1H, d, *J*=10.0 Hz), 5.77 (1H, dt, *J*=10.0, 2.0 Hz), 5.25 (1H, ddd, *J*=10.0, 4.0, 2.0 Hz), 4.99 (1H, s), 4.78 (2H, s), 4.62–4.56 (2H, m), 4.18–4.05 (3H, m), 3.94–3.84 (1H, m), 3.84 (1H, ddd, *J*=10.0, 5.0, 2.0 Hz), 2.09 (3H, s), 2.04 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.9, 170.3, 147.9, 129.8, 126.9, 122.1, 94.5, 67.2, 66.8, 65.2, 62.9, 50.4, 20.9, 20.8; HRMS (ESI): found: 378.1272; $C_{15}H_{21}N_3O_7Na$ $(M+Na)^+$ requires 378.1277.

5.2. 4-(2-Hydroxyethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3b)

>99% yield (27.1 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a pale yellow oil; R_f (80% EtOAc/*n*-hexane) 0.23; $[\alpha]_D^{20}$ +74.30 (*c* 1.01, $CHCl_3$); ν_{max} ($CHCl_3$): 3468, 2952, 2924, 2851, 1741, 1454, 1432, 1371, 1275, 1259, 1236, 1048, 1021, 982 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.55 (1H, br s), 5.87 (1H, d, *J*=10.0 Hz), 5.76 (1H, dt, *J*=10.0, 2.0 Hz), 5.25 (1H, d, *J*=10.0 Hz), 4.98 (1H, s), 4.56 (2H, t, *J*=5.0 Hz), 4.18–4.07 (5H, m), 4.05–3.85 (1H, m), 3.86–3.78 (1H, m), 2.99–2.87 (2H, m), 2.08 (3H, s), 2.05 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.8, 170.2, 145.6, 129.7, 126.9, 122.7, 94.5, 67.2, 66.8, 65.1, 62.8, 61.8, 50.2, 28.7, 20.9, 20.7; HRMS (ESI): found 392.1434; $C_{16}H_{23}N_3O_7Na$ $(M+Na)^+$ requires 392.1434.

5.3. 4-(3-Hydroxypropyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3c)

82% yield (23.0 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a pale yellow oil; R_f (100% EtOAc) 0.31; $[\alpha]_D^{20}$ +55.36 (*c* 0.50, $CHCl_3$); ν_{max} ($CHCl_3$): 3468, 2947, 2924, 2851, 1743, 1454, 1438, 1368, 1273, 1256, 1231, 1046, 1018, 973 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42 (1H, s), 5.89 (1H, d, *J*=10.0 Hz), 5.77 (1H, dt, *J*=10.0, 2.0 Hz), 5.26 (1H, d, *J*=10.0 Hz), 4.99 (1H, s), 4.55 (2H, t, *J*=5.0 Hz), 4.20–4.10 (2H, m), 4.10 (1H, dd, *J*=12.0, 2.0 Hz), 3.89 (1H, dt, *J*=11.0, 5.0 Hz), 3.84 (1H, ddd, *J*=10.0, 5.0, 2.0 Hz), 3.69 (2H, t, *J*=7.0 Hz), 2.83 (2H, t, *J*=7.0 Hz), 2.08 (3H, s), 2.06 (3H, s), 1.97–1.88 (2H, m); δ_C (100 MHz, $CDCl_3$) 170.8, 170.2, 147.5, 129.8, 126.9, 121.9, 94.5, 67.3, 66.9, 65.1, 62.8, 61.8, 50.2, 31.9, 22.0, 20.9, 20.7; HRMS (ESI): found 406.1590; $C_{17}H_{25}N_3O_7Na$ $(M+Na)^+$ requires 406.1590.

5.4. 4-(1,1-Diphenyl-1-hydroxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3d)

77% yield (28.5 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a pale yellow oil; R_f (50% EtOAc/*n*-hexane) 0.45; $[\alpha]_D^{20}$ +40.83 (*c* 1.01, $CHCl_3$); ν_{max} ($CHCl_3$): 3468, 2941, 2924, 2846, 1742, 1491, 1449, 1371, 1234, 1046, 1015, 973 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40–7.24 (10H, m), 7.23 (1H, s), 5.88 (1H, d, *J*=10.0 Hz), 5.66 (1H, d, *J*=10.0 Hz), 5.25 (1H, d, *J*=10.0 Hz), 4.96 (1H, s), 4.63–4.49 (2H, m), 4.22–4.10 (2H, m), 4.08 (1H, dd, *J*=12.0, 2.0 Hz), 3.90–3.76 (2H, m), 2.05 (6H, s); δ_C (100 MHz, $CDCl_3$) 170.8, 170.2, 154.0, 145.9, 145.7, 129.8, 128.0, 127.5, 127.2, 127.2, 126.8, 123.9, 94.4, 77.2, 67.2, 66.6, 65.2, 62.9, 50.2, 20.9, 20.7; HRMS (ESI): found 530.1903; $C_{27}H_{29}N_3O_7Na$ $(M+Na)^+$ requires 530.1903.

5.5. 4-(1-Hydroxycyclobutyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3e)

72% yield (20.8 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a pale yellow oil; R_f (60% EtOAc/*n*-hexane) 0.19; $[\alpha]_D^{20}$ +50.58 (*c* 0.50, $CHCl_3$); ν_{max} ($CHCl_3$): 3445, 2926, 2851, 1743, 1463, 1449, 1432, 1371, 1230, 1046, 1015, 971 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.56 (1H, s), 5.89 (1H, d, *J*=10.0 Hz), 5.78 (1H, d, *J*=10.0 Hz), 5.24 (1H, ddd, *J*=10.0, 4.0, 2.0 Hz), 4.99 (1H, s),

4.65–4.50 (2H, m), 4.18–4.08 (3H, m), 3.93–3.84 (1H, m), 3.83–3.75 (1H, m), 2.08 (3H, s), 2.05 (3H, s), 2.02–1.92 (2H, m) 1.92–1.82 (2H, m), 1.82–1.69 (2H, m); δ_C (100 MHz, $CDCl_3$): δ 170.9, 170.2, 155.6, 129.7, 126.9, 120.7, 94.3, 69.4, 67.2, 66.7, 65.2, 62.8, 50.2, 38.2, 22.0, 20.9, 20.8; HRMS (ESI): found 418.1825; $C_{18}H_{25}N_3NaO_7$ $(M+Na)^+$ requires 418.1590.

5.6. 4-(Phenyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3f)

79% yield (23.1 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a orange s oil; R_f (50% EtOAc/*n*-hexane) 0.44; $[\alpha]_D^{20}$ +0.27 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$): 2952, 2925, 1741, 1483, 1466, 1441, 1412, 1370, 1229, 1071, 1042, 968 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.88 (1H, s), 7.83 (2H, d, *J*=7.0 Hz), 7.43 (2H, t, *J*=7.0 Hz), 7.34 (1H, t, *J*=7.0 Hz), 5.90 (1H, d, *J*=10.0 Hz), 5.79 (1H, dt, *J*=10.0, 2.0 Hz), 5.26 (1H, d, *J*=10.0 Hz), 5.02 (1H, s), 4.65 (2H, t, *J*=5.0 Hz), 4.20 (1H, dt, *J*=11.0, 5.0 Hz), 4.14 (1H, dd, *J*=12.0, 5.0 Hz), 4.07 (1H, dd, *J*=12.0, 2.0 Hz), 3.95 (1H, dt, *J*=11.0, 5.0 Hz), 3.86 (1H, ddd, *J*=10.0, 5.0, 2.0 Hz), 2.06 (3H, s), 2.03 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.2, 147.7, 130.6, 129.7, 128.8, 128.3, 126.9, 125.7, 120.7, 94.5, 67.2, 66.8, 65.0, 62.8, 50.3, 20.8, 20.7; HRMS (ESI): found 424.1481; $C_{20}H_{23}N_3O_6Na$ $(M+Na)^+$ requires 424.1485.

5.7. 4-(4-Fluorophenyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3g)

78% yield (23.9 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as an orange oil; R_f (80% EtOAc/*n*-hexane) 0.84; $[\alpha]_D^{20}$ +97.49 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$): 2952, 2924, 2851, 1741, 1608, 1558, 1497, 1454, 1435, 1407, 1370, 1227, 1155, 1041, 973 cm^{-1}; δ_H (400 MHz, $CDCl_3$): δ 7.83 (1H, s), 7.83–7.76 (2H, m), 7.20–7.08 (2H, m), 5.91 (1H, d, *J*=10.0 Hz), 5.80 (1H, dt, *J*=10.0, 2.0 Hz), 5.27 (1H, d, *J*=10.0 Hz), 5.02 (1H, s), 4.65 (2H, t, *J*=5.0 Hz), 4.27–4.16 (1H, m), 4.14 (1H, dd, *J*=12.0, 5.0 Hz), 4.08 (1H, dd, *J*=12.0, 2.0 Hz), 4.00–3.90 (1H, m), 3.90–3.82 (1H, m), 2.06 (3H, s), 2.04 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.1, 163.9, 146.9, 135.2, 129.8, 127.5, 127.4, 126.9, 120.4, 115.9, 115.7, 94.5, 67.3, 66.8, 65.1, 62.8, 50.4, 20.9, 20.7; HRMS (ESI): found 442.1390; $C_{20}H_{22}FN_3NaO_6$ $(M+Na)^+$ requires 442.1390.

5.8. 4-(4-Methoxyphenyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3h)

88% yield (27.7 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as an orange oil; R_f (80% EtOAc/*n*-hexane) 0.81; $[\alpha]_D^{20}$ +0.68 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$): 2947, 2923, 2853, 1741, 1617, 1558, 1499, 1456, 1440, 1371, 1247, 1225, 1074, 1040, 973 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.79 (1H, s), 7.75 (2H, d, *J*=9.0 Hz), 6.95 (2H, d, *J*=9.0 Hz), 5.89 (1H, d, *J*=10.0 Hz), 5.78 (1H, dt, *J*=10.0, 2.0 Hz), 5.26 (1H, d, *J*=10.0 Hz), 5.02 (1H, s), 4.63 (2H, t, *J*=5.0 Hz), 4.20 (1H, dt, *J*=11.0, 5.0 Hz), 4.14 (1H, dd, *J*=12.0, 5.0 Hz), 4.08 (1H, dd, *J*=12.0, 2.0 Hz), 3.95 (1H, dt, *J*=11.0, 5.0 Hz), 3.91–3.82 (1H, m), 3.84 (3H, s), 2.06 (3H, s), 2.04 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.2, 159.6, 147.7, 135.2, 129.8, 127.0, 126.9, 119.8, 114.3, 94.5, 67.3, 66.9, 65.1, 62.8, 55.3, 50.3, 20.9, 20.7; HRMS (ESI): found 454.1597; $C_{21}H_{25}N_3O_7Na$ $(M+Na)^+$ requires 454.1590.

5.9. 4-(Phenoxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3i)

96% yield (30.2 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a orange oil; R_f (50% EtOAc/*n*-hexane) 0.39; $[\alpha]_D^{20}$ +25.70 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$): 2952, 2923, 2851, 1741, 1597, 1586, 1491, 1454, 1429, 1371, 1239, 1045, 1029, 1010, 987 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.73 (1H, s), 7.29 (1H, t, *J*=8.0 Hz), 7.28 (1H, t, *J*=8.0 Hz), 6.99 (2H, d, *J*=8.0 Hz), 6.97 (1H, t, *J*=8.0 Hz), 5.90 (1H, d, *J*=10.0 Hz), 5.72 (1H, dt, *J*=10.0, 2.0 Hz), 5.27 (1H, d, *J*=10.0 Hz), 5.23 (2H, s), 4.98 (1H, s), 4.66–4.57 (2H, m), 4.23–4.13 (2H, m), 4.09 (1H, dd, *J*=12.0, 2.0 Hz), 3.96–3.84 (2H, m), 2.06 (6H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.2, 158.2, 144.3, 129.8, 129.5, 126.9, 123.6, 121.3, 114.8, 94.6, 67.3, 66.9, 65.1, 62.8, 61.9, 50.3, 20.9, 20.7; HRMS (ESI): found 454.1593; $C_{21}H_{25}N_3O_7Na$ $(M+Na)^+$ requires 454.1590.

5.10. 4-(4-Methylphenoxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3j)

>99% yield (32.8 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as an orange oil; R_f (50% EtOAc/*n*-hexane) 0.29; $[\alpha]_D^{20}$ +22.57 (*c* 1.02, $CHCl_3$); ν_{max} ($CHCl_3$): 2952, 2922, 2851, 1741, 1611, 1583, 1510, 1460, 1435, 1370, 1230, 1045, 1013, 976 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.71 (1H, s), 7.08 (2H, d, *J*=8.0 Hz), 6.87 (2H, d, *J*=8.0 Hz), 5.88 (1H, d, *J*=10.0 Hz), 5.71 (1H, dt, *J*=10.0, 2.0 Hz), 5.27 (1H, d, *J*=10.0 Hz), 5.19 (2H, s), 4.97 (1H, s), 4.60 (2H, dt, *J*=6.0, 4.0 Hz), 4.24–4.12 (2H, m), 4.09 (1H, dd, *J*=12.0, 2.0 Hz), 3.96–3.84 (2H, m), 2.28 (3H, s), 2.07 (3H, s), 2.06 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.2, 156.1, 144.5, 130.5, 129.9, 129.8, 126.9, 123.6, 114.6, 94.7, 67.3, 66.9, 65.1, 62.8, 62.1, 50.3, 20.9, 20.7, 20.5; HRMS (ESI): found 468.1731; $C_{22}H_{27}N_3O_7Na$ $(M+Na)^+$ requires 468.1747.

5.11. 4-(3,5-Dimethoxyphenoxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3k)

>99% yield (35.9 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a pale yellow oil; R_f (50% EtOAc/*n*-hexane) 0.20; $[\alpha]_D^{20}$ +34.82 (*c* 1.02, $CHCl_3$); ν_{max} ($CHCl_3$): 2952, 2925, 2851, 1740, 1597, 1471, 1459, 1429, 1368, 1229, 1203, 1192, 1152, 1046, 976 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.73 (1H, s), 6.17 (2H, s), 6.16 (1H, s), 5.88 (1H, d, *J*=10.0 Hz), 5.73 (1H, dt, *J*=10.0, 2.0 Hz), 5.26 (1H, d, *J*=10.0 Hz), 5.16 (2H, s), 4.97 (1H, s), 4.66–4.54 (2H, m), 4.22–4.13 (2H, m), 4.10 (1H, dd, *J*=12.0, 2.0 Hz), 3.96–3.84 (2H, m), 3.75 (6H, s), 2.06 (6H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.2, 161.5, 160.1, 144.0, 129.8, 126.9, 123.6, 94.7, 93.7, 93.4, 67.8, 66.9, 65.1, 62.8, 62.0, 55.4, 50.3, 20.9, 20.8; HRMS (ESI): found 514.1806; $C_{23}H_{29}N_3O_9Na$ $(M+Na)^+$ requires 514.1801.

5.12. 4-Vanillinyloxymethyl-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3l)

>99% yield (35.9 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as an orange oil; R_f (70% EtOAc/*n*-hexane) 0.32; $[\alpha]_D^{20}$ +16.65 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$): 2952, 2924, 2851, 1740, 1678, 1594, 1583, 1510, 1488, 1452, 1427, 1371, 1260, 1233, 1074, 1045, 982 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.85 (1H, s), 7.81 (1H, s), 7.44 (1H, d, *J*=8.0 Hz), 7.42 (1H, s), 7.25 (1H, d, *J*=8.0 Hz), 5.89 (1H, d, *J*=10.0 Hz), 5.73 (1H, dt, *J*=10.0, 2.0 Hz), 5.40 (2H, s), 5.28 (1H, d, *J*=10.0 Hz), 4.98 (1H, s), 4.68–4.53 (2H, m), 4.24–4.12 (2H, m), 4.12 (1H, dd, *J*=12.0, 2.0 Hz), 3.97–3.84 (2H, m), 3.93 (3H, s), 2.09 (3H, s), 2.07 (3H, s); δ_C (100 MHz, $CDCl_3$) 190.9, 170.7, 170.2, 153.0, 149.9, 143.5, 130.6, 129.8, 126.9, 126.9, 123.8, 114.5, 114.0, 94.7, 67.3, 66.8, 65.1, 62.8, 56.9, 50.3, 20.9, 20.7; HRMS (ESI): found 512.1644: $C_{23}H_{27}N_3O_9Na$ $(M+Na)^+$ requires 512.1645.

5.13. 4-(Isovanillinyloxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3m)

89% yield (31.8 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a yellow oil; R_f (70% EtOAc/*n*-hexane) 0.42; $[\alpha]_D^{20}$ +24.65 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$): 2963, 2925, 2846, 1740, 1684, 1594, 1585, 1510, 1460, 1435, 1370, 1266, 1236, 1134, 1134, 1046, 1010, 973 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.85 (1H, s), 7.78 (1H, s), 7.57 (1H, s), 7.51 (1H, d, *J*=8.0 Hz), 7.00 (1H, d, *J*=8.0 Hz), 5.89 (1H, d, *J*=10.0 Hz), 5.74 (1H, dt, *J*=10.0, 2.0 Hz), 5.32 (2H, s), 5.27 (1H, d, *J*=10.0 Hz), 4.99 (1H, br s), 4.68–4.53 (2H, m), 4.24–4.12 (1H, m), 4.20 (1H, dd, *J*=12.0, 5.0 Hz), 4.12 (1H, dd, *J*=12.0, 2.0 Hz), 3.97–3.86 (2H, m), 3.94 (3H, s), 2.07 (3H, s), 2.06 (3H, s); δ_C (100 MHz, $CDCl_3$) 190.7, 170.8, 170.2, 154.9, 148.2, 143.4, 130.0, 129.8, 126.9, 126.8, 124.0, 112.1, 111.0, 94.7, 67.3, 66.9, 65.1, 62.9, 62.8, 56.2, 50.4, 20.9, 20.7; HRMS (ESI): found 512.1646; $C_{23}H_{27}N_3O_9Na$ $(M+Na)^+$ requires 512.1645.

5.14. 4-(Coumarinyloxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3n)

83% yield (30.3 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a orange oil; R_f (50% EtOAc/*n*-hexane) 0.12; $[\alpha]_D^{20}$ +26.43 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$): 2947, 2924, 2851, 1734, 1612, 1552, 1505, 1460, 1426, 1401, 1373, 1275, 1230, 1124, 1046, 1004, 985 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.78 (1H, s), 7.63 (1H, d, *J*=9.0 Hz), 7.39 (1H, d, *J*=9.0 Hz), 6.97–6.91 (2H, m), 6.27 (1H, d, *J*=9.0 Hz), 5.89 (1H, d, *J*=10.0 Hz), 5.73 (1H, dt, *J*=10.0, 2.0 Hz), 5.28 (1H, d, *J*=10.0 Hz), 5.26 (2H, s), 4.99 (1H, s), 4.70–4.55 (2H, m), 4.25–4.14 (1H, m), 4.18 (1H, dd, *J*=12.0, 5.0 Hz), 4.10 (1H, dd, *J*=12.0, 2.0 Hz), 3.97–3.84 (2H, m), 2.07 (3H, s), 2.06 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.1, 160.3, 160.9, 155.7, 143.3, 142.9, 129.9, 128.9, 127.8, 123.9, 113.5, 112.8, 102.1, 94.6, 67.3, 66.8, 65.1, 62.8, 62.3, 50.4, 20.9, 20.7; HRMS (ESI): found 522.1487; $C_{24}H_{25}N_3O_9Na$ $(M+Na)^+$ requires 522.1488.

5.15. 4-(Benzhydryloxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3o)

>99% yield (38.2 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as an orange oil; R_f (50% EtOAc/*n*-hexane) 0.43; $[\alpha]_D^{20}$ +21.17 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$): 2952, 2924, 2851, 1742, 1488, 1454, 1367, 1275, 1256, 1228, 1088, 1049, 1029, 973 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.59 (1H, s), 7.34–7.15 (10H, m), 5.82 (1H, d, *J*=10.0 Hz), 5.67 (1H, dt, *J*=10.0, 2.0 Hz), 5.45 (1H, s), 5.20 (1H, d, *J*=10.0 Hz), 4.92 (1H, s), 4.60 (2H, s), 4.57–4.47 (2H, m), 4.18–4.06 (2H, m), 4.04 (1H, dd, *J*=12.0, 2.0 Hz), 3.90–3.79 (2H, m), 1.99 (3H, s), 1.96 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.2, 145.5, 141.7, 129.8, 128.4, 127.6, 123.1, 126.9, 123.5, 94.7, 82.9, 67.3, 66.9, 65.1, 62.8, 62.4, 50.2, 20.9, 20.7; HRMS (ESI): found 544.2061; $C_{28}H_{31}N_3O_7Na$ $(M+Na)^+$ requires 544.2060.

5.16. 4-(Phenacyloxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3p)

>99% yield (34.8 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a pale yellow oil; R_f (50% EtOAc/*n*-hexane) 0.48; $[\alpha]_D^{20}$ +16.18 (*c* 0.50, $CHCl_3$); ν_{max} ($CHCl_3$): 2952, 2925, 2851, 1741, 1629, 1600, 1510, 1463, 1438, 1382, 1370, 1256, 1228, 1046, 1029, 1007, 962 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80–7.70 (4H, m), 7.43 (1H, t, *J*=7.0 Hz), 7.34 (1H, t, *J*=7.0 Hz), 7.29–7.14 (2H, m), 5.85 (1H, d, *J*=10.0 Hz), 5.66 (1H, dt, *J*=10.0, 2.0 Hz), 5.33 (2H, s), 5.25 (1H, d, *J*=10.0 Hz), 4.95 (1H, s), 4.65–4.54 (2H, m), 4.22–4.11 (2H, m), 4.09 (1H, dd, *J*=12.0, 2.0 Hz), 3.96–3.84 (2H, m), 2.05 (3H, s), 2.04 (3H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.2, 156.1, 144.1, 134.4, 129.8, 129.6, 127.6, 126.9, 126.9, 126.5, 123.9, 123.7, 118.8, 94.6, 67.3, 66.8, 65.1, 62.7, 62.0, 50.4, 20.9, 20.7; HRMS (ESI): found 496.1675; $C_{23}H_{27}N_3NaO_8$ $(M+Na)^+$ requires 496.1696.

5.17. 4-(Benzoyloxymethyl)-1-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranos-1-yloxyethyl)-1,2,3-1*H*-triazole (3q)

>99% yield (33.5 mg) as a configuration mixture (α:β=9:1); isolated α-form was obtained as a pale orange oil; R_f (50% EtOAc/*n*-hexane) 0.27; $[\alpha]_D^{20}$ +45.61 (*c* 0.52, $CHCl_3$); ν_{max} ($CHCl_3$): 2952, 2924, 2851, 1741, 1717, 1600, 1583, 1452, 1371, 1272, 1237, 1108, 1068, 1046, 1024, 971 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.03 (2H, d, *J*=8.0 Hz), 7.81 (1H, s), 7.55 (1H, t, *J*=8.0 Hz), 7.42 (2H, t, *J*=8.0 Hz), 5.88 (1H, d, *J*=10.0 Hz), 5.73 (1H, dt, *J*=10.0, 2.0 Hz), 5.47 (2H, s), 5.26 (1H, d, *J*=10.0 Hz), 4.97 (1H, s), 4.67–4.54 (2H, m), 4.22–4.13 (2H, m), 4.09 (1H, dd, *J*=12.0, 2.0 Hz), 3.95–3.84 (2H, m), 2.06 (6H, s); δ_C (100 MHz, $CDCl_3$) 170.7, 170.2, 166.5, 142.9, 133.3, 129.8, 129.7, 128.4, 126.8, 124.4, 94.7, 67.3, 66.8, 65.1, 62.8, 58.1, 50.3, 20.9, 20.8; HRMS (ESI): found 482.1539; $C_{22}H_{25}N_3O_8Na$ $(M+Na)^+$ requires 482.1539.

Acknowledgements

This work was supported by a Research Grant of Burapha University through the National Research Council of Thailand (60/2558) and the Center of Excellence for Innovation in Chemistry (PERCH-CIC). Partial support from the Strategic Basic Research Grant of The Thailand Research Fund (DBG5680004) is gratefully acknowledged. Special thanks to Professor Apichart Suksamrarn (Ramkhamhaeng University) for providing specific rotation measurement.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.09.026.

References and notes

1. (a) Sokolova, N. V.; Nenajdenko, V. G. *RSC Adv.* **2013**, *3*, 16212–16242; (b) Prakasam Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905–4979.
2. Leoneti, V. A.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, C. I. *Tetrahedron* **2010**, *66*, 9475–9492.
3. Dedola, S.; Hughes, D. L.; Nepogodieva, S. A.; Rejzek, M.; Field, R. A. *Carbohydr. Res.* **2010**, *345*, 1123–1134.
4. (a) Rajaganesh, R.; Jayakumar, J.; Sivaraj, C.; Raaman, N.; Das, T. M. *Carbohydr. Res.* **2010**, *345*, 1649–1657; (b) Singh, A. K.; Gopu, K. *Tetrahedron Lett.* **2010**, *51*, 1180–1184.
5. (a) Kumar, K. K.; Seenivasan, S. P.; Kumar, V.; Das, M. *Carbohydr. Res.* **2011**, *346*, 2084–2090; (b) Singh, B. K.; Yadav, A. K.; Kumar, B.; Gaikwad, A.; Sinha, S. K.; Chaturvedic; Tripathia, R. P. *Carbohydr. Res.* **2008**, *343*, 1153–1162.
6. Freitas, L. B.; Borgati, T. F.; Freitas, R. P.; Ruiz, A. L.; Marchetti, G. M.; Carvalho, J. E.; Cunha, E. F.; Ramalho, T. C.; Alves, R. B. *Eur. J. Med. Chem.* **2014**, *84*, 595–604.
7. Sharmaa, S.; Saquiba, M.; Vermaa, S.; Mishrab, N. N.; Shukla, P. K.; Srivastavac, R.; Prabhakar, Y. S.; Shaw, A. K. *Eur. J. Med. Chem.* **2014**, *83*, 474–489.
8. Li, L. T.; Zhou, L. F.; Li, Y. J.; Huang, J.; Liu, R. H.; Wang, B.; Wang, P. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 642–644.
9. Silva, J. B.; Guimaraes, B. M.; Assis, S. P. O.; Limab, V. L. M.; Oliveira, R. N. *J. Braz. Chem. Soc.* **2013**, *24*, 914–921.
10. (a) Song, S. X.; Zhang, H. L.; Kim, C. G.; Sheng, L.; He, X. P.; Long, Y. T.; Li, J.; Chen, J. R. *Tetrahedron* **2010**, *66*, 9974–9980; (b) Hradilova, L.; Polakova, M.; Dvorakova, B.; Hajduch, M.; PetruS, L. *Carbohydr. Res.* **2012**, *361*, 1–6.

11. Zi, C. T.; Xu, F. Q.; Li, G. T.; Li, Y.; Ding, Z. T.; Zhou, J.; Jiang, Z. H.; Hu, J. M. *Molecules* **2013**, *18*, 13992–14012.
12. Carvalho, I.; Andrade, P.; Campo, V. L.; Guedes, P. M. M.; Costa, R. S.; Silva, J. S.; Sergio Schenkman, c; Dedola, S.; Hill, L.; Rejzek, M.; Nepogodiev, S. A.; Field, R. A. *Bioorg. Med. Chem.* **2010**, *18*, 2412–2427.
13. Salame, B. A.; Cumpstey, I.; Sundin, A.; Leffler, H.; Nilsson, U. J. *Bioorg. Med. Chem.* **2010**, *18*, 5367–5378.
14. Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331–2336.
15. (a) Reddy, B. V. S.; Praneeth, K.; Yadav, J. S. *Carbohydr. Res.* **2011**, *346*, 995–998; (b) Stefani, H. A.; Silva, N. C. S.; Manarin, F.; Ludtke, D. S.; Schpector, J. Z.; Madureira, L. S.; Tiekink, E. R. T. *Tetrahedron Lett.* **2012**, *53*, 1742–1747; (c) Yadav, J. S.; Subba Reddy, B. V.; Narasimha Chary, D.; Suresh Reddy, Ch *Tetrahedron Lett.* **2008**, *49*, 2649–2652; (d) Gildas, B. R.; Jean-Pierre, J.; Lionel, V. L.; Chapleur, Y. *Lett. Org. Chem.* **2009**, *6*, 106–109.
16. Mangsang, W.; Sirion, U.; Saeeng, R. *Carbohydr. Res.* **2013**, *375*, 79–89.

รายงานสรุปการเงิน

เลขที่โครงการระบบบริหารงานวิจัย 177554 สัญญาเลขที่ 60/2558

โครงการวิจัยประเภทงบประมาณเงินรายได้จากเงินอุดหนุนรัฐบาล (งบประมาณแผ่นดิน)

ประจำปีงบประมาณ พ.ศ. 2558

มหาวิทยาลัยบูรพา

ชื่อโครงการ : การเตรียมสารสังเคราะห์ไตรเอโซลไกลโคไซด์เพื่อศึกษาสมบัติการต้านมะเร็งท่อน้ำดี

ชื่อหัวหน้าโครงการวิจัยผู้รับทุน ผศ.ดร. รุ่งนภา แซ่เอ็ง

รายงานในช่วงตั้งแต่วันที่ 30 ตุลาคม 2556 ถึง วันที่ 1 กันยายน 2559

ระยะเวลาดำเนินการ 1 ปี ตั้งแต่วันที่ 1 ตุลาคม 2557 ถึง วันที่ 30 กันยายน 2558

จำนวนเงินที่ได้รับ

งวดที่ 1 (50% มหาวิทยาลัยหัก 10% ออกแล้ว) 382,500 บาท เมื่อ 13/01/58

งวดที่ 2 (50% มหาวิทยาลัยหัก 10% ออกแล้ว) 306,000 บาท เมื่อ 11/08/58

งวดที่ 3 -

รวม 688,500 บาท

<u>รายจ่าย</u>

หมวด	งบประมาณที่ตั้งไว้	งบประมาณที่ใช้จริง	จำนวนเงินคงเหลือ/เกิน
1. ค่าตอบแทน	48,000	48,000	-
2. ค่าจ้าง	144,000	144,000	-
3. ค่าวัสดุ	358,000	358,000	-
4. ค่าใช้สอย	215,000	215,000	-
5. ค่าครุภัณฑ์	-	-	-
6. ค่าใช้จ่ายอื่นๆ -ค่าธรรมเนียม 10%	85,000	85,000	-
รวม	850,000	850,000	-

(ผศ.ดร. รุ่งนภา แซ่เอ็ง)

หัวหน้าโครงการวิจัยผู้รับทุน

บทสรุปสำหรับผู้บริหาร
(Executive Summary)

ข้าพเจ้า ผศ. ดร. รุ่งนภา แซ่เอ็ง ได้รับทุนสนับสนุนโครงการวิจัย จากมหาวิทยาลัยบูรพา ประเภทงบประมาณเงินรายได้ จากเงินอุดหนุนรัฐบาล (งบประมาณแผ่นดิน) มหาวิทยาลัยบูรพา
โครงการวิจัยเรื่อง การเตรียมสารสังเคราะห์ไตรเอโซลไกลโคไซด์เพื่อศึกษาสมบัติการต้านมะเร็งท่อน้ำดี
Preparation of synthetic triazoleglycosides for cholangiocarcinoma tumor growth inhibitor
รหัสโครงการ 177554 / สัญญาเลขที่ 60/2558 ได้รับงบประมาณรวมทั้งสิ้น 850,000 บาท (แปดแสนห้าหมื่นบาทถ้วน)

ระยะเวลาดำเนินการ 1 ปี ตั้งแต่วันที่ 1 ตุลาคม 2557 ถึง วันที่ 30 กันยายน 2558

บทคัดย่อ

มะเร็งท่อน้ำดี (Cholangiocarcinomaหรือ CCA) เป็นมะเร็งของเซลล์เยื่อบุท่อน้ำดีที่ค่อนข้างพบน้อยในโลกตะวันตกแต่อุบัติการณ์ของมะเร็งท่อน้ำดีในไทย ในภาคตะวันออกเฉียงเหนือกลับมีสูงมากที่สุดในโลก โดยเฉพาะในจังหวัดขอนแก่น ในงานวิจัยนี้ได้ศึกษาการเตรียมอนุพันธ์ triazoleglycoside เพื่อศึกษาการต้านมะเร็งท่อน้ำดี โดยได้ทำการสังเคราะห์สารด้วยวิธีใหม่โดยแบ่งงานเป็นสามส่วนได้สารเป็นสามกลุ่มใหญ่ โดยกลุ่มแรกได้สังเคราะห์สารอนุพันธ์ triazolylethyl-2,3-unsaturated-*O*-glycosides จำนวน 17 อนุพันธ์ ด้วยวิธีการทำปฏิกิริยาสามชนิด คือ O-glycosylation azidation และ click reaction ในหม้อทำปฏิกิริยาเดียว สารในกลุ่มที่สอง คือ 2,3-unsaturated-glycosyl triazoles จำนวน 30 อนุพันธ์ ด้วยวิธีการทำปฏิกิริยาสองชนิด glycosylation และ click reaction ในหม้อทำปฏิกิริยาเดียวได้สารที่มีฤทธิ์ต้านมะเร็งท่อน้ำดีคือ สาร **9a** และ**9b** และกลุ่มที่สาม คือสารอนุพันธ์ 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-**α**-D-galactopyranosyls จำนวน 31 อนุพันธ์ซึ่งมีหมู่ triazole สองหมู่บนวงน้ำตาลในตำแหน่งที่ C-1 และ C-6 โดยทำปฏิกิริยาทั้งหมดสี่ขั้นตอน ได้สารที่มีฤทธิ์ต้านมะเร็งท่อน้ำดีคือ สาร **5ee**

Abstract

Cholangiocarcinoma (CCA) is a primary cancer of the bile duct epithelial cells. The incidence of CCA is low in worldwide, however, it is very high in the northeastern part of Thailand especially in KhonKaen province. In this research works, we studied the preparation of triazoleglycoside analogues and their anticancer activities on CCA cell lines. Three type of triazoleglycoside were synthesized using new method. In the first part, we have successfully synthesized of seventeen derivatives of triazolylethyl 2,3-unsaturated *O*-glycoside in three steps-one-pot manner using sequential *O*-glycosylation-azidation and click reaction. In the second part, we have synthesized thirty analogues of 2,3-unsaturated-

glycosyl triazoles in two steps-one-pot manner using sequential *O*-glycosylation and click reaction. Of all synthetic analogs, compounds **9a** and **9b** showed good anticancer activity on CCA cell lines. In the third part, Thirty-one analogues of of 1,6-bis-triazole 2,3,4-tri-*O*-acetyl-**α**-D-galactopyranosyl bearing two triazole group at C-1 and C-6 were synthesized via four steps. Compounds **5ee** exhibited pronounced cytotoxicity against K-100 cholangiocarcinoma cells.

Output / Outcome

International Publications

1. Wadchara Mangsang, Uthaiwan Sirion, **Rungnapha Saeeng**[*] One-pot synthesis of O-glycosyl triazoles by O-glycosylation–click reaction, *Carbohydrate Research*, **2013**, *375*, 79–89.

2. Wadchara Mangsang, Uthaiwan Sirion, **Rungnapha Saeeng**[*] Convenient one-pot synthesis of triazolylethyl-2,3-unsaturated-*O*-glycoside derivatives, *Tetrahedron*, **2015**, 71, 8593-8600.

International Proceeding

1. Suksamran Chaidam, Uthaiwan Sirion, **Rungnapha Saeeng**[*] Synthesis of diacetylene glycoside, Burapha University International Conference **2013**/4-5 July 2013/p.1085-1091.

การผลิตบัณฑิต

1. นิสิตปริญญาโท ภาคเคมี คณะวิทยาศาสตร์ ม.บูรพา จำนวน 2 คน
   นายวัชระ มังค์สังค์
   นายสุขสำราญ ไชยดำ
2. นิสิตปริญญาตรี ภาคเคมี คณะวิทยาศาสตร์ ม.บูรพา จำนวน 2 คน ทำโครงงานนิพนธ์
   นางสาวนริยา มุกสิทธิ์มณี
   นายพีรพงษ์ วงษ์ปุ่น