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Chenjiang Zhu

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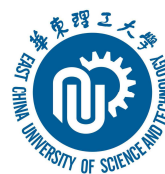
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N° ENSC-2008/

**THESE DE DOCTORAT
DE L'ECOLE NORMALE SUPERIEURE DE CACHAN
ET DE L'EAST CHINA UNIVERSITY OF SCIENCE AND TECHNOLOGY**

Présenté par

Monsieur Chenjiang ZHU

Pour obtenir le grade de

**DOCTEUR DE L'ECOLE NORMALE SUPERIEURE DE CACHAN
ET DE L'EAST CHINA UNIVERSITY OF SCIENCE AND TECHNOLOGY**

Domaine : **CHIMIE**

Sujet de la thèse :

**Conception, synthèse et étude biologique des nouveaux dérivés
de sucre**

Thèse présentée et soutenue à Shanghai le 4 novembre 2008 devant le jury compose de :

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Design, Synthesis and Bioactivity Studies of Novel Sugar Derivatives

Abstract

Sugar widely exists in the nature. It plays a key role in a variety of biological processes including signal transmit and immune response. Because of the importance of sugar to human beings, its structure and bioactive effects have become the mainstream of scientific research. Meanwhile, the synthesis of multifunctional sugar derivatives is the major focus. Aiming at probing sugar derivatives and their synthetic study, four series of compounds were designed and synthesized; their bioactivities were evaluated.

[1] Arbutin as a kind of natural product for cosmetic, its preparative and structure modification are very important. In this work, a series of novel, stable, mono- and oligo-*C*-glycosides analogues of arbutin were designed and synthesized. 16 new compounds have been prepared. The inhibition for tyrosinase of compound **44** is similar to that of α -arbutin at 100 $\mu\text{g/mL}$, compounds **32**, **43**, **44** showed the same range inhibition as α -arbutin at 200 $\mu\text{g/mL}$, while compounds **21**, **32**, **43**, **44** are better than α -arbutin at higher concentration (400 $\mu\text{g/mL}$).

[2] Vitamin E is one of the most important antioxidant in lipid. In this work, a series of novel mono- and oligo-*C*-glycosides analogues of vitamin E were designed and synthesized. They are more stable and more effective. Six compounds have never being reported.

[3] Sugar biochip as a super tool to solve many difficult problems in the field of glycobiology has attracted lots of attention of scientists. This work takes up with synthesis of photolabile sugars as biochip's basic blocks. By regioselective opening of 4, 6-*O*-(*o*-nitro)benzylidene ring with Et_3SiH and $\text{BF}_3 \cdot \text{Et}_2\text{O}$, a series of 6-*O*-(*o*-nitro)benzyl protected glycopyranosides were synthesized. Syntheses of 15 new compounds are reported.

[4] Diabetes Mellitus is a very serious disease in 21st century. Since Protein-tyrosine phosphatase 1B is a potential target to treat diabetes, a series of glycosyl amino acids have been designed and synthesized as potential inhibitors of PTP-1B. Alkyne sugars and azide acids were connected via click chemistry to afford a series of sugar amino acids derivatives. Amongst tested molecules, the glycosyl tyrosine **111** showed 83.4% inhibition of PTP-1B at 5 $\mu\text{g/mL}$.

Keywords: Sugar Biochip Photolabile Protecting Groups PTP-1B Amino acids
Arbutin Vitamin E Synthesis

General Introduction

Study of carbohydrates began in the late nineteenth century with the work of Emil Fischer. Carbohydrate ring structure was elucidated in the 1930s by Haworth and colleagues.¹

Carbohydrates have long been underappreciated by the scientific community, and many scientists approach the complex structures and elaborate nomenclature of carbohydrates with trepidation. In 2001, a special issue about *Carbohydrates and Glycobiology* was published in <science>, they declared that sugar is “a Cinderella field: an area that involves much work but, alas, does not get to show off at the ball with her cousins, the genomes and proteins”.² Like amino acids and nucleic acids, sugars are abundant in nature: many natural products contain oligosaccharides that are vital for their biological activity, and carbohydrates have key roles in a broad range of biological processes, including signal transduction and immune responses.

Although fewer scientists work with carbohydrates than with other biopolymers, researchers in this field have been prolific. Chemists and biochemists have developed new methods to rapidly synthesize oligosaccharides, enabling them to generate complex polysaccharides and analogues of natural products that have increased activity *in vivo*. Biologists have explored the physiological roles of various sugars, discovering that many have essential roles in all of the major organ systems and are involved in several disease states.³

The number of chemists, biochemists and biologists in this field is steadily increasing, and this interest underscores the fact that there are so many discoveries to be made. To quote Ajit Varki⁴, it is “a fertile area for the new generation of young scientists”.

Chapter 1 Synthesis of Novel Arbutin C-glycoside Derivatives for Inhibition of Tyrosinase

1.1 Introduction

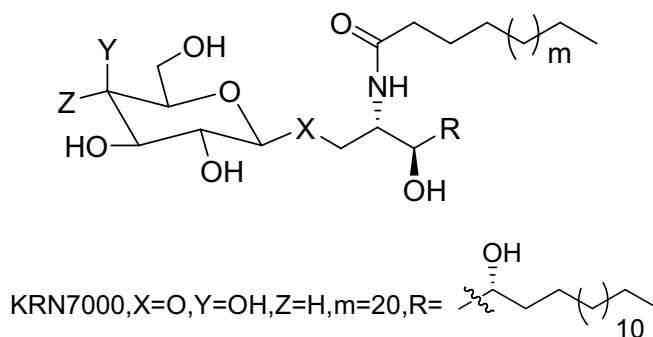
Arbutin, 4-hydroxyphenyl- β -D-glucopyranoside, is a white needle crystal or powder, often got from natural green plants.⁵ Arbutin is very important to human being, such as relieve a cough, prevent and cure asthma, cure burn. Furthermore, arbutin is an inhibitor of tyrosinase of human pigment cells which catalyzes the production of melanin and other pigments from tyrosine by oxidation.⁶ Moreover, arbutin has been a focus for its effect of whitening skin.⁶

The structure of natural arbutin is a β type, but its anomer, α -arbutin, has a similar whitening skin effect. According to recent research result, it has been confirmed that arbutin can inhibit the synthesis of melanin, with no obvious side-effect.⁷

1.2 C-glycoside

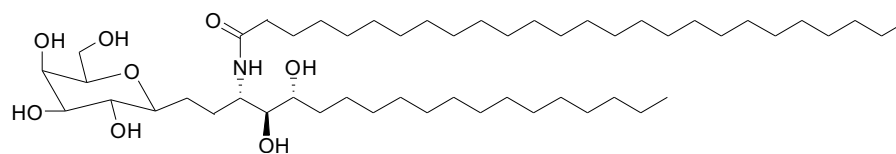
As the unique class of carbohydrates, aryl C-glycosides are stable analogs of the corresponding O-, N- and S-glycosides owing to uncleavability of the glycosidic C-C bond under the presence of acids and enzymes.^{8, 9} Because of their favorable pharmacological profiles such as the treatment of stroke, cancer, cardiovascular and diabetic diseases, aryl C-glycosides have gained increasing popularity as drug candidates.^{10, 11}

Some C-glycosides have better bioactivity than their corresponding O-glycoside. For example, KRN7000, found from a structure–function study on the naturally occurring ceramide derivative agelasphin-9b by Koezuka and co-workers,¹² possessed potent anti-tumor activity in B16-bearing mice.¹³



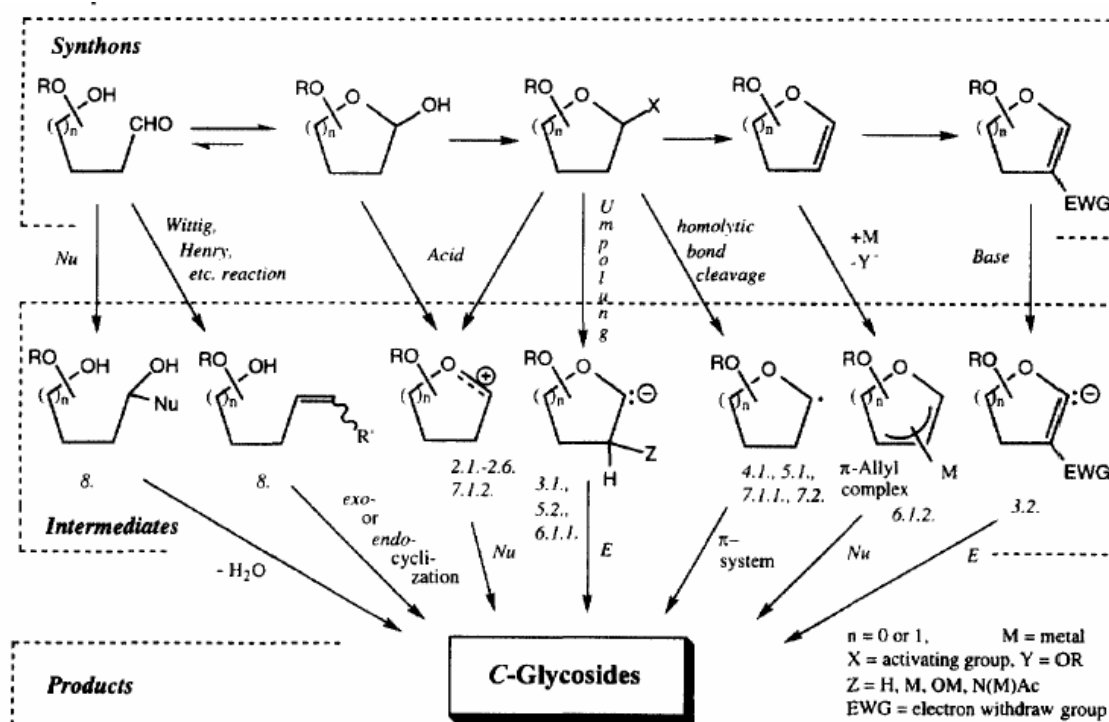
For improving its bioactivity and stability, Mani Ranj Chaulagain¹⁴ synthesized a stable β -C-glycoside analog of the KRN7000 in 2004. The anti-solid tumor activity in vitro was carried out using the Valeriate disk-diffusion assay. Result shows that the bioactivity and stability of these

C-glycoside analogues are obviously improved.

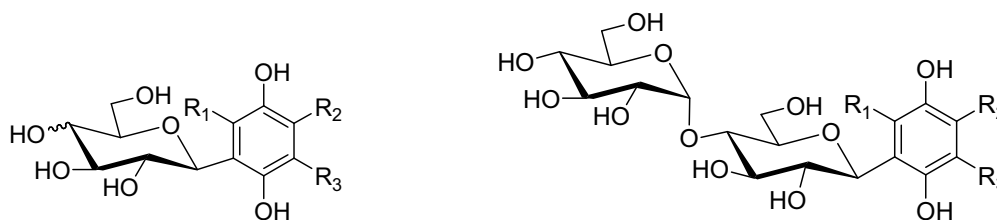


β -C-KRN7000 analogue

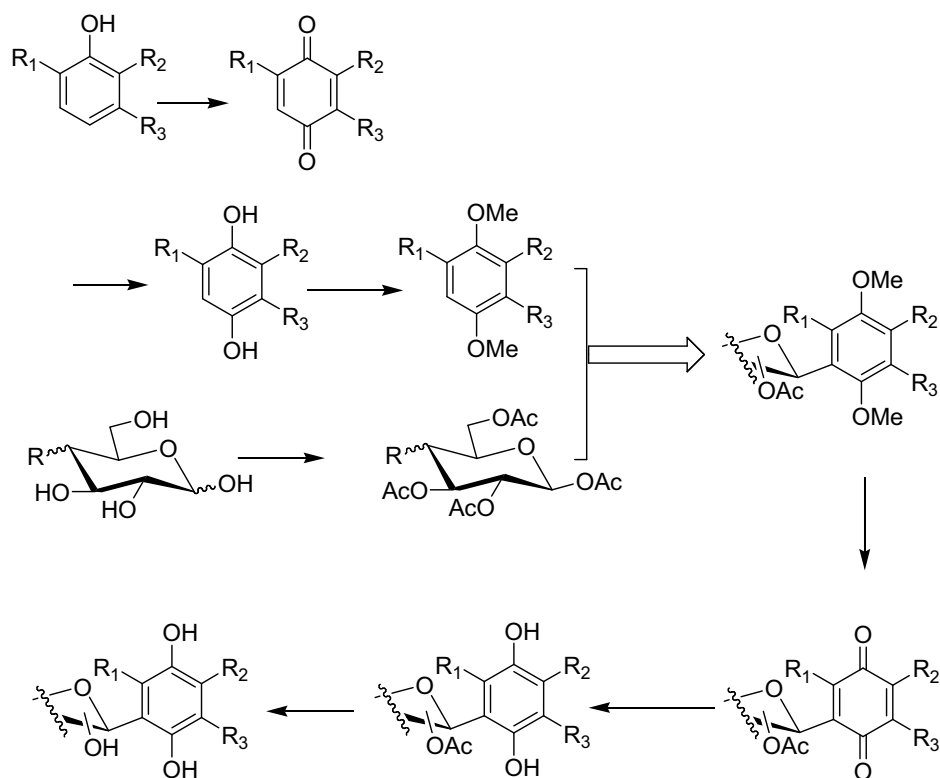
In our work, a series of C-glycoside arbutin analogues were designed and synthesized. There are lots of methods for forming a C-C bond and synthesizing a C-glycoside as shown below:



Based on our previous work, we designed an appropriate route^{15, 16} for synthesizing the C-glycoside analogues of arbutin. The target structures are as follows:



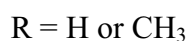
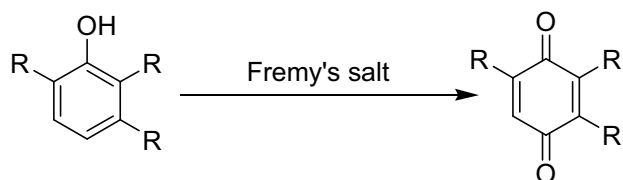
$R_1, R_2, R_3 = \text{H or CH}_3$



The synthetic route of C-glycoside analogues of arbutin

1.3 Results and discussion

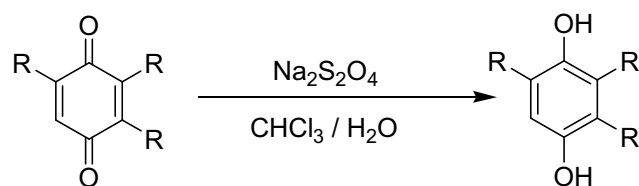
1.3.1 Synthesis of methyl benzoquinone



There are many methods for synthesizing benzoquinone. Method using Fremy's salt (KSO₃)₂NO to oxidate phenol is mild and economical.

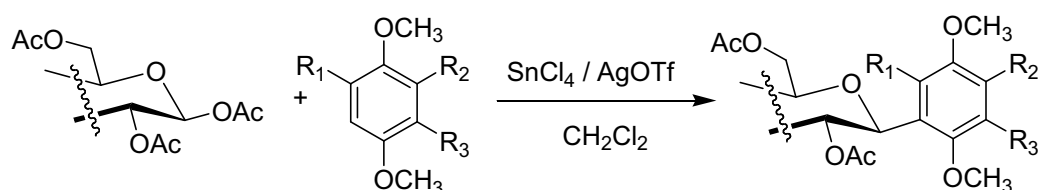
The key of this process is the amount of ammonia for the preparation of Fremy's salt. If too much or too little ammonia was added, the yield will be reduced, even to 10~20%. The pH should be controlled between 8 and 10; the usual yield is over 90%. The crude product can be used for next step without further purification.

1.3.2 Synthesis of methyl hydroquinone

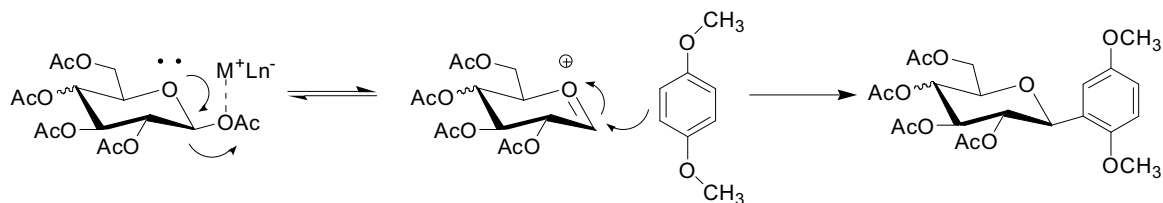


We used $\text{Na}_2\text{S}_2\text{O}_4$ as reducing agent to reduce benzylquinone in $\text{CHCl}_3/\text{H}_2\text{O}$ at room temperature. After 30 min, most starting material has been consumed and the color of reaction suspension changed from yellow to white. The reaction is very mild and quick, and the yield is over than 90%, the crude product can be used in next step without further purification.

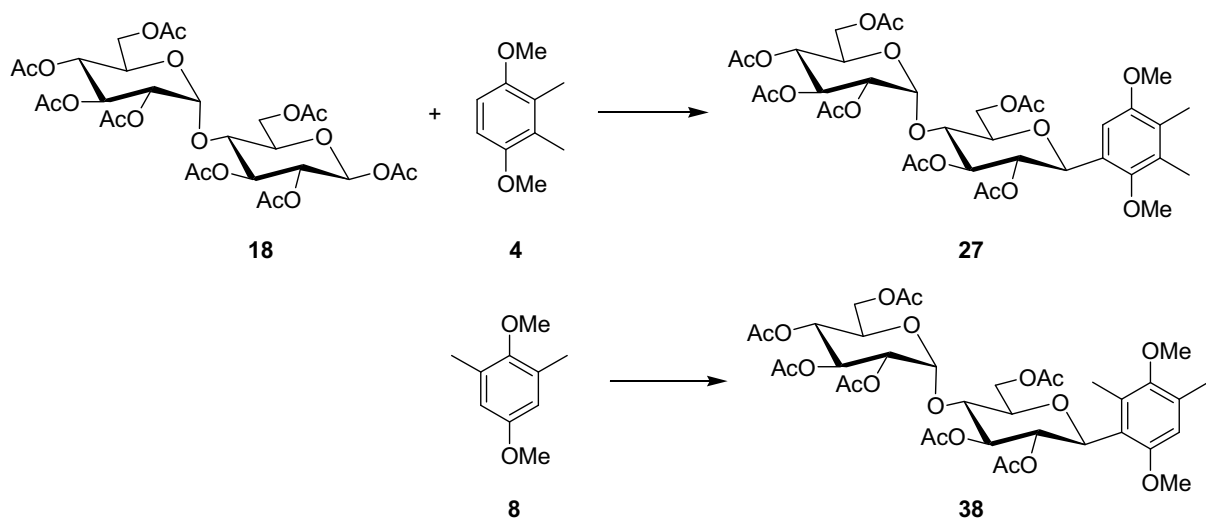
1.3.3 Synthesis of aryl C-glycoside



Takeshi Kuribayashi¹⁷ reported a method of using Lewis acids and AgOTf as catalyst to synthesize C-glycoside. It is a Friedel-Crafts reaction and the mechanism might be as follows:



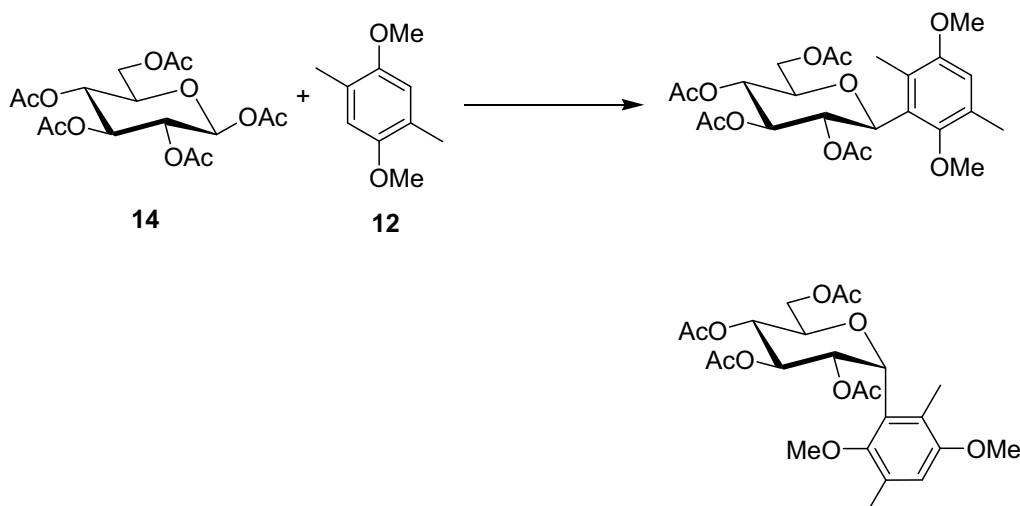
We found that the temperature is very important to this reaction, result for the two following reactions is summarized in the table:



The results of synthesis of C-D-Glycopyranosylmaltoside under various temperatures

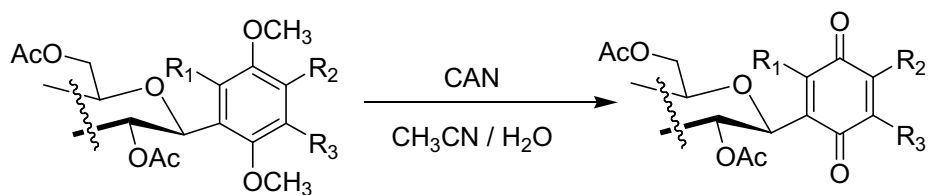
Materials	Product	Temperature (°C)	Yield%
18 and 4	27	20	37
18 and 4	27	25	45
18 and 4	27	30	61
18 and 4	27	35	54
18 and 4	27	reflux	52
18 and 8	38	20	40
18 and 8	38	25	51
18 and 8	38	30	63
18 and 8	38	35	67
18 and 8	38	reflux	61

Best result can be obtained at 35 °C. However, reaction of 1,2,3,4,6-penta-*O*-acetyl- β -D-glucopyranoside **14** (1.0 equiv) with 4-dimethoxy-2,5-dimethylbenzene **12** (2.0 equiv) gave a mixture of α - and β - anomers with 17 % yield.

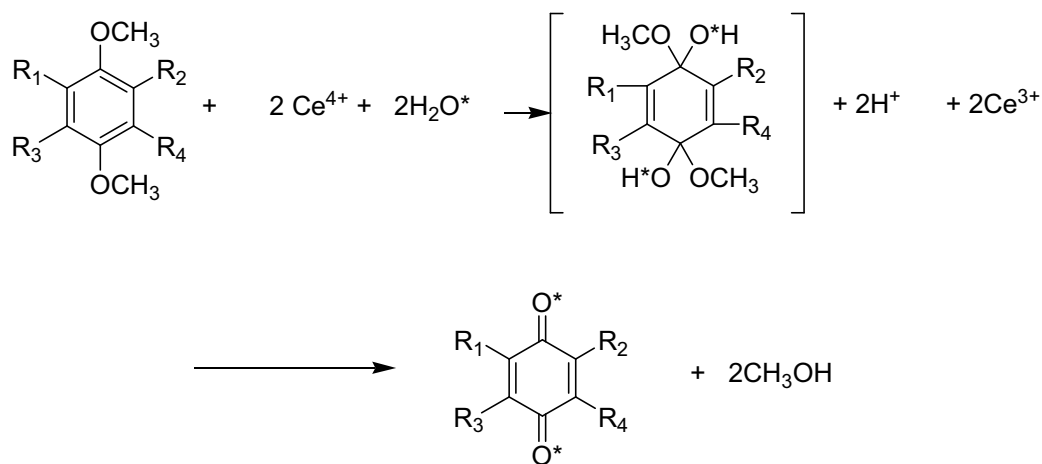


Separation of the mixture is very difficult, and the yield is too low, so we didn't synthesize this type of analogues.

1.3.4 Synthesis of acetylated glycosyl benzoquinone

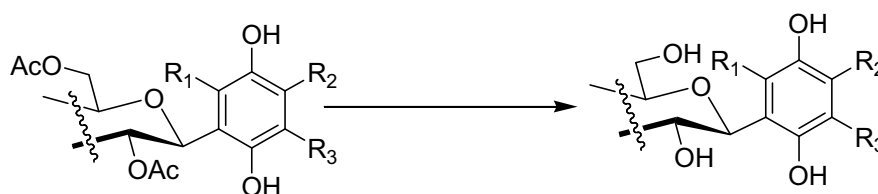


CAN is a good choice for oxidation of methoxy benzene. The reaction is mild and quick. The mechanism¹⁸ is as follows:



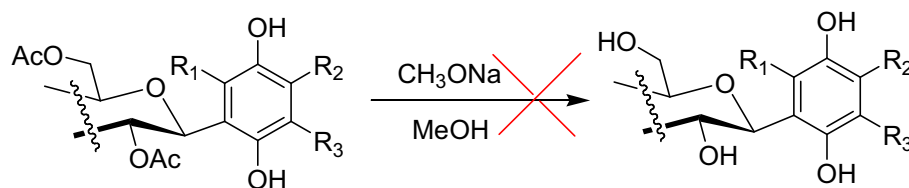
O* is isotope of O

1.3.5 Deprotection of hydroxyl group

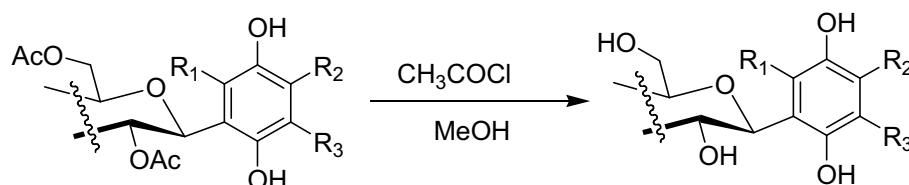


As people known, removing of acetyl can be realized in acidic or basic conditions. Normal, NaOMe/MeOH are used most commonly as basic condition, and $\text{CH}_3\text{COCl}/\text{MeOH}$ as acidic condition.

At first, we tried to remove acetyl in basic condition, but all the reactions were failed.

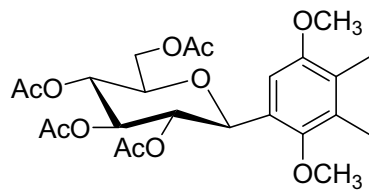


So we tried to remove acetyl in acidic condition, and finally got desired product.

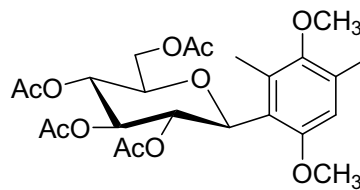


1.3.6 Spectral analysis

For compound **30**, HPLC showed it is pure more than 95%, but its ^1H NMR spectra is illegible. Though the structure of compound **19** is similar, its ^1H NMR spectra is very clear.



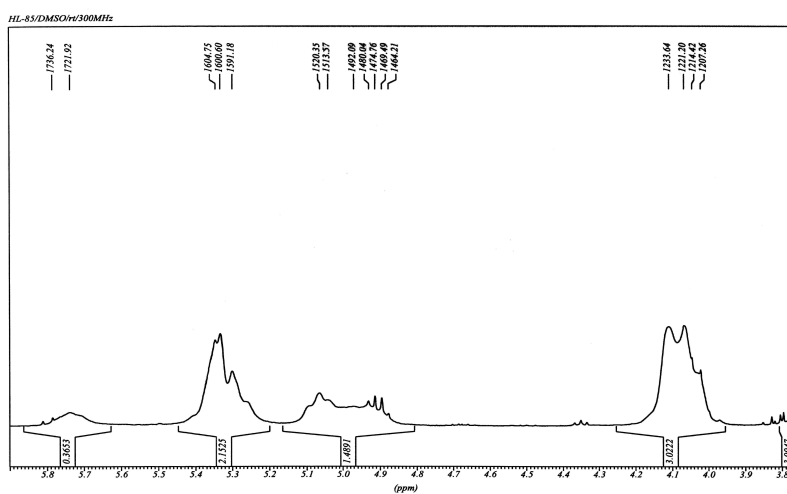
19



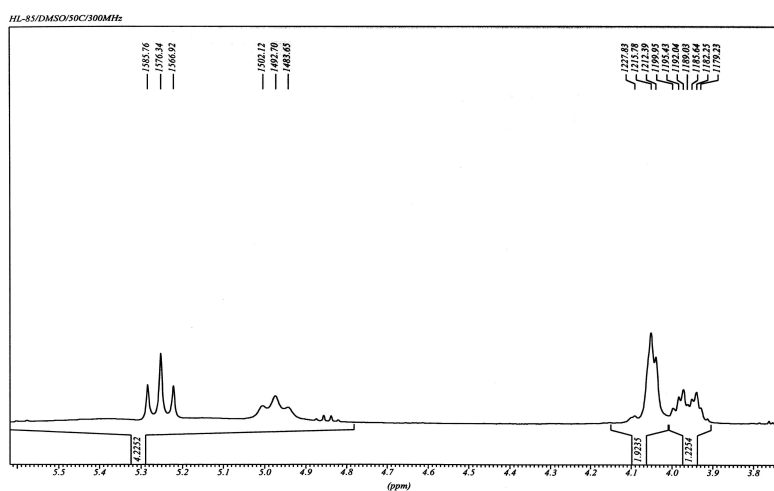
30

We tried to make spectra of compound **30** at different temperature: 25 °C, 50 °C and 90 °C. The results are as follows::

a. r.t.

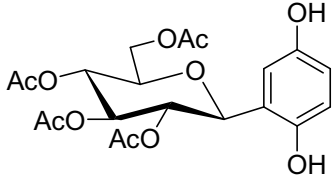
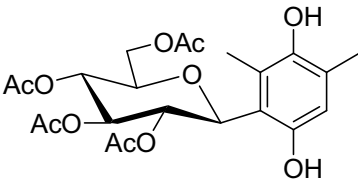
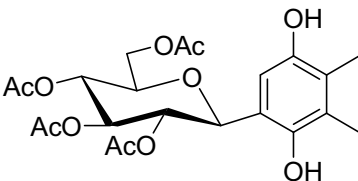
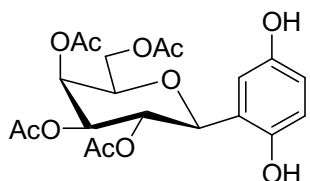
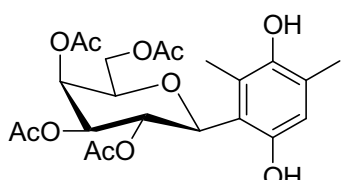


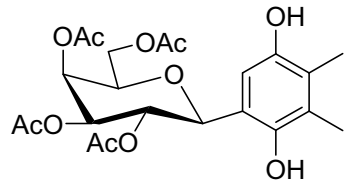
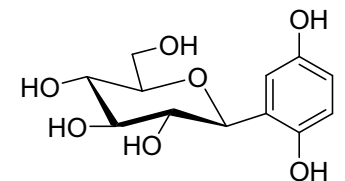
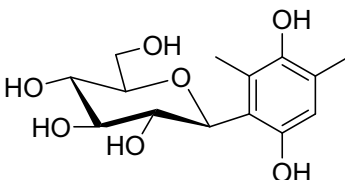
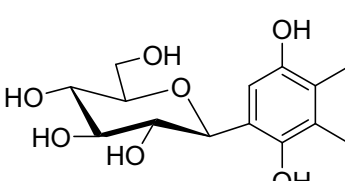
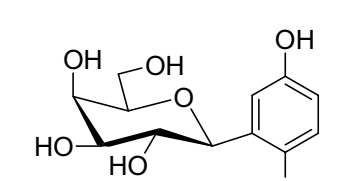
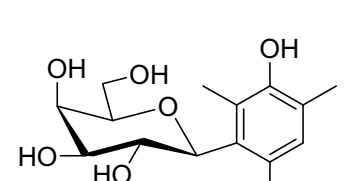
b. 50 °C.



agent for whitening skin. And as we known, the melanin is mainly produced by tyrosinase, so arbutin derivatives as inhibitors of tyrosinase may be the one which we are looking for.

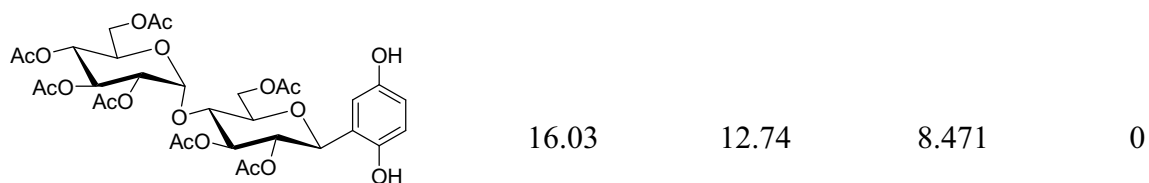
The tyrosinase inhibition result

Compd.	Inhibition rate %			
	400 μ g/mL	200 μ g/mL	100 μ g/mL	0 μ g/mL
Hydroquinone	21.35	20.98	20.88	0
penta-<i>O</i>-acetyl-β-D-glucose	15.88	9.28	5.37	0
penta-<i>O</i>-acetyl-β-D-galactose	18.27	12.83	1.04	0
β-D-glucose	19.93	17.20	17.56	0
β-D-galactose	10.84	10.35	10.90	0
α-arbutin	31.62	29.49	31.30	0
β-arbutin	21.29	23.21	20.43	0
 43	47.02	27.36	15.05	0
 32	33.65	8.30	3.24	0
 21	31.39	11.48	4.78	0
 47	25.90	27.52	21.17	0
 15	15.34	11.89	7.42	0

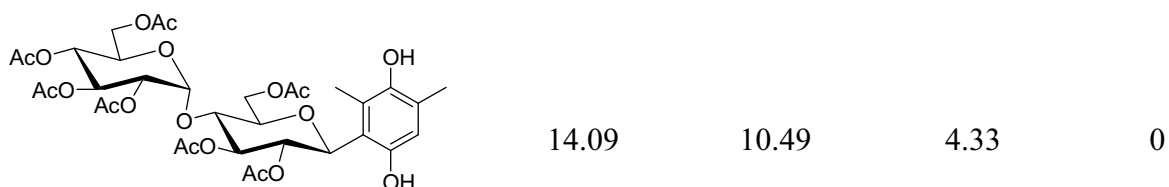
36		14.33	12.93	3.11	0
25		32.52	26.10	30.36	0
44		19.98	22.38	19.34	0
33		17.46	15.23	12.34	0
22		22.68	23.90	25.16	0
48		26.06	25.97	21.45	0
37					



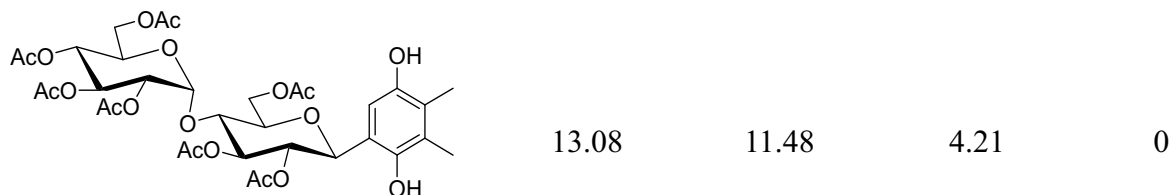
26



51



40



29

1.4 Conclusion

In this part of work, we tried to find compounds with better whitening effect than natural arbutin. So based on bioisostere, we designed and synthesized 45 aryl C-glycoside analogues of arbutin, 16 of them are new compounds.

The inhibition for tyrosinase of compound **44** is similar to that of α -arbutin at 100 $\mu\text{g}/\text{mL}$, compounds **32**, **43**, **44** showed the same range inhibition as α -arbutin at 200 $\mu\text{g}/\text{mL}$, while compounds **21**, **32**, **43**, **44** are better than α -arbutin at higher concentration (400 $\mu\text{g}/\text{mL}$). It proved that C-glycoside analogues of arbutin are potential whitening reagents, worthing further research.

1.5 Experimental section

1.5.1 Synthesis of compound 2



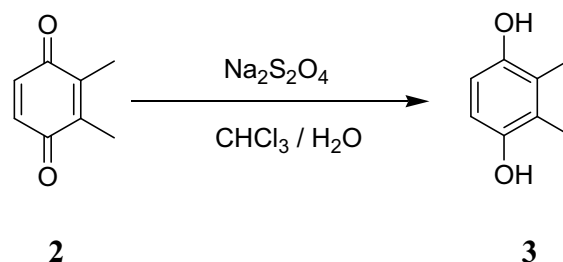
1) The preparation of Fremy's Salt

To a solution of NaNO_2 (10 g, 0.145 mol) in 20 mL H_2O , ice cooled, a soln of $\text{Na}_2\text{S}_2\text{O}_5$ (11.5 g, 0.061 mol) in 30 mL H_2O was added dropwise at ice bath, after 5 min, 6 mL $\text{CH}_3\text{CO}_2\text{H}$ was added, the reaction solution was stirred for 10 min, then 20 mL ammonia (6 M) was added, followed by adding dropwise (over 30 min) KMnO_4 (4.2 g, 0.026 mol) in 100 mL H_2O , the mixture was filtered and the filtrate was added to a sat. aq soln of KCl 100 mL, stirred for 30 min, filtered, the filter cake is Fremy's salt.

2) Synthesis of compound 2

To the solution of the Fremy's salt (obtained above) in 200 mL H_2O , 2,3-dimethyl-phenol (4.5 g, 36.88 mmol) in 200 mL MeOH was added dropwise. After addition, the mixture was stirred at room temperature overnight. TLC showed the starting material was consumed completely, the reaction solution was extracted with CH_2Cl_2 (3×100 mL). The combined organic layer was washed with brine, dried over MgSO_4 , evaporated, purified with column chromatography (DCM:petroleum ether = 1:3) to give compound 2 (4.62 g, 92.1%) as yellow solid. TLC: $R_f=0.49$ (Pet:EtOAc=3:1); $^1\text{H NMR}$ (250 MHz, CDCl_3): δ 1.92(s, 6H, $2 \times \text{CH}_3$), 6.61(s, 2H, PhH).

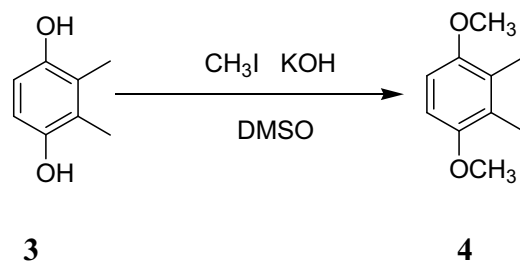
1.5.2 Synthesis of compound 3



To a solution of compound 2 (1.36 g, 10 mmol) in CHCl_3 30 mL, $\text{Na}_2\text{S}_2\text{O}_4$ (10.4 g, 60 mmol) in H_2O (30 mL) was added. The reaction mixture was then stirred at room temperature for 45

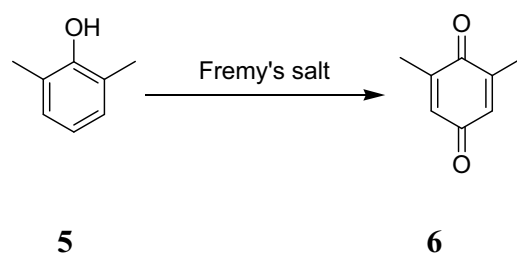
min, and evaporated. The residue was partitioned with Et₂O(3×20 mL) and H₂O (30 mL). The combined organic layer was washed with brine, dried over MgSO₄, evaporated to give compound **3** (1.31 g, 95%) as white solid. TLC: $R_f=0.27$ (Pet:EtOAc=3:1); ¹H NMR (500 MHz, CDCl₃): δ 2.11 (s, 6H, 2×PhCH₃), 4.52 (s, 1H, OH), 4.92 (s, 1H, OH), 6.32 (s, 2H, PhH).

1.5.3 Synthesis of compound 4



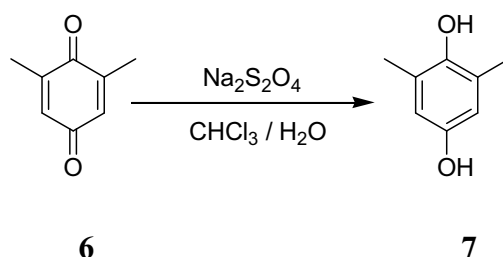
To a solution of compound **3** (1.38 g, 10 mmol) in DMSO (8 mL), KI (3.2 mL, 50 mmol) was added dropwise at room temperature, followed by KOH (4 g, 70 mmol). After addition, the reaction solution was stirred for 5 h. Then the solution was diluted with H₂O (20 mL), extracted with CH₂Cl₂ (3×30 mL). The combined organic layer was washed with sat. aq. Na₂S₂O₃, brine, dried over MgSO₄, evaporated, and purified with column chromatography (petroleum ether: EtOAc=3:1) to afford compound **4** (1.52 g, 92%) as white solid. TLC: $R_f=0.59$ (Pet:EtOAc=3:1); ¹H NMR (500 MHz, CDCl₃): δ 2.18 (s, 6H, 2×PhCH₃), 3.79 (s, 6H, 2×OCH₃), 6.68 (s, 2H, PhH).

1.5.4 Synthesis of compound 6



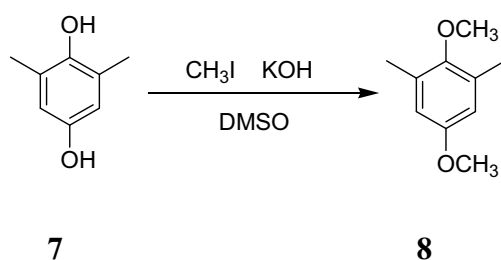
To a soln of 20 g Fremy's salt in 100 mL ice water, compound **5** (4.5 g, 37 mmol) in MeOH (400 mL) was added dropwise, stirred for 4 h at room temperature, extracted with CH₂Cl₂ (3×100 mL), the combined organic layers were washed with brine, dried over MgSO₄, evaporated and purified with column chromatography (Pet:EtOAc =3:1) to afford compound **6** (4.8 g, 95%) as yellow needle crystal. TLC: $R_f=0.52$ (Pet:EtOAc=3:1); ¹H NMR (500 MHz, CDCl₃): δ 2.05 (d, 6H, $J=6.83$ Hz, 2×PhCH₃), 6.56 (s, 2H, PhH).

1.5.5 Synthesis of compound 7



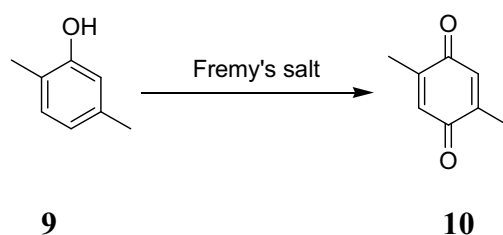
To a soln of compound **6** (1.36 g, 10 mmol) in 30 mL of CHCl_3 , $\text{Na}_2\text{S}_2\text{O}_4$ (10.4 g, 60 mmol) in H_2O (30mL) was added at room temperature. The reaction mixture was stirred for 45 min, evaporated to remove solvents. The residue was partitioned with Et_2O (3×20 mL) and H_2O (20 mL), and the combined organic layer was washed with brine, dried over MgSO_4 to afford compound **7** (1.27 g, 92%). TLC: $R_f=0.19$ (Pet:EtOAc=2:1); ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 2.20 (s, 6H, $2 \times \text{PhCH}_3$), 4.22 (s, 1H, OH), 4.28 (s, 1H, OH), 6.48 (s, 2H, PhH).

1.5.6 Synthesis of compound 8



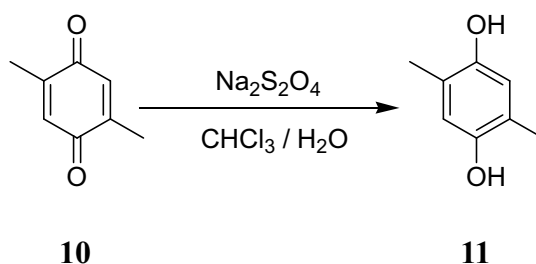
To a soln of compound **7** (1.38 g, 10 mmol) in DMSO (8 mL), KI (3.2 mL, 50 mmol) was added dropwise at room temperature, followed by KOH (4 g, 70 mmol). After addition, the reaction solution was stirred for 5 h. Then the solution was diluted with H_2O (20 mL), extracted with CH_2Cl_2 (3×30 mL), the combined organic layers were washed with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$, brine, dried over MgSO_4 , evaporated to give crude product, purified with column chromatography (petroleum ether: EtOAc=3:1), to afford compound **8** (1.50 g, 90%) as white solid. TLC: $R_f=0.51$ (Pet:EtOAc=2:1); ^1H NMR (500 MHz, CDCl_3): δ 2.25 (s, 6H, $2 \times \text{CH}_3$), 3.65 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 6.53 (s, 2H, PhH).

1.5.7 Synthesis of compound 10



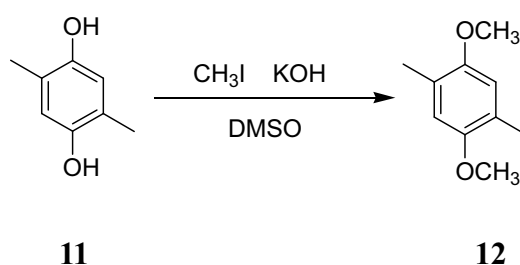
To a soln of 20 g Fremy's salt in 100 mL ice water, compound **9** (4.5 g, 37 mmol) in MeOH 400 mL was added dropwise, stirred for 4 h at room temperature, extracted with CH₂Cl₂ (3×100 mL), the combined organic layers were washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **10** (4.7 g, 94%) as yellow solid. TLC: *R_f* = 0.51(Pet:EtOAc=3:1); ¹H NMR (500 MHz, CDCl₃): δ 1.97 (d, 6H, *J* = 1.7 Hz, 2×CH₃), 6.53 (d, 2H, *J* = 1.7 Hz, PhH).

1.5.8 Synthesis of compound **11**



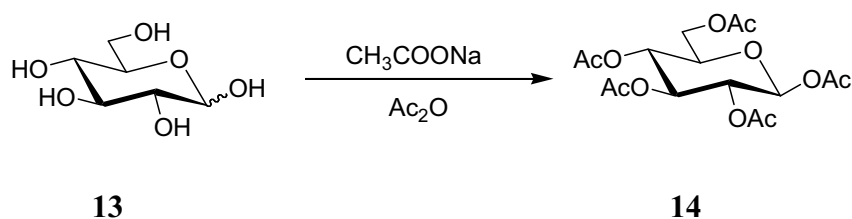
To a soln of compound **10** (1.36 g, 10 mmol) in 30 mL CHCl₃, Na₂S₂O₄ (10.4 g, 60 mmol) in H₂O (30mL) was added at room temperature. The reaction mixture was stirred for 45 min, evaporated to remove solvents. The residue was partitioned with Et₂O (3×20 mL) and H₂O (20 mL), and the combined organic layer was washed with brine, dried over MgSO₄ to afford compound **11** (1.29 g, 93%) as white solid. TLC: *R_f*=0.18 (Pet:EtOAc=2:1); ¹H NMR (500 MHz, DMSO-*d*₆): δ 1.99 (s, 6H, 2×CH₃), 6.45 (s, 2H, PhH), 8.34(s, 2H, 2×OH).

1.5.9 Synthesis of compound **12**



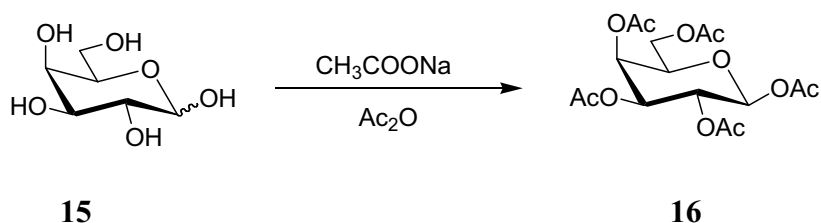
To a soln of compound **11** (1.38 g, 10 mmol) in DMSO (8 mL), KI (3.2 mL, 50 mmol) was added dropwise at room temperature, followed by KOH (4 g, 70 mmol). After addition, the reaction solution was stirred for 5 h. Then the solution was diluted with H₂O (20 mL), extracted with CH₂Cl₂ (3×30 mL), the combined organic layers were washed with sat. aq. Na₂S₂O₃, brine, dried over MgSO₄, evaporated, and purified with column chromatography (petroleum ether: EtOAc=3:1) to afford compound **12** (1.29 g, 78%) as white solid. TLC: *R_f*=0.59(Pet:EtOAc=2:1); ¹H NMR (500 MHz, CDCl₃): δ 2.15 (s, 6H, 2×CH₃), 3.70 (s, 6H, 2×OCH₃), 6.58 (s, 2H, PhH).

1.5.10 Synthesis of compound 14



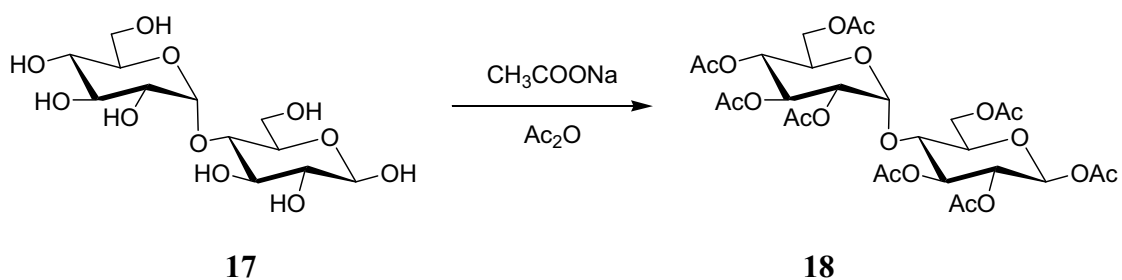
To a solution of compound **13** (5 g, 0.28 mol) in 25 mL of Ac_2O , CH_3COONa (2.3 g, 28 mmol) was added. After addition, the solution was heated to reflux for 2 h, the solution was added to ice water, filtered to give crude product, purified with recrystallization to afford the known compound **14** (8.7 g, 83%) as white solid. TLC: $R_f=0.43$ (Pet:EtOAc=3:1).

1.5.11 Synthesis of compound 16



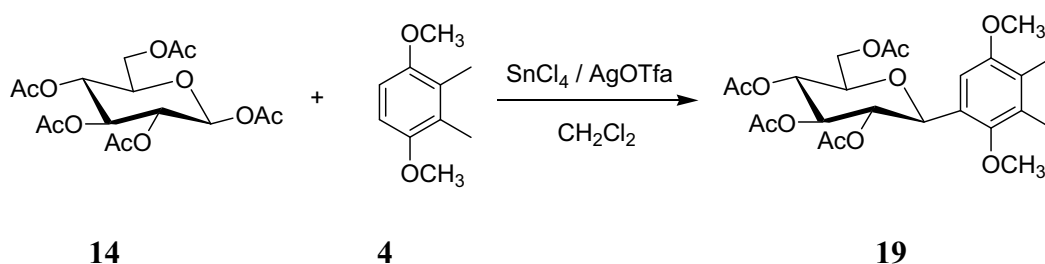
To a solution of compound **15** (5 g, 0.28 mol) in 25 mL of Ac_2O , CH_3COONa (2.3 g, 28 mmol) was added. After addition, the solution was heated to reflux for 2 h, the solution was added to ice water, filtered to give crude product, purified with recrystallization, to afford the known compound **16** (7.5 g, 72%). TLC: $R_f=0.46$ (Pet:EtOAc=3:1).

1.5.12 Synthesis of compound 18



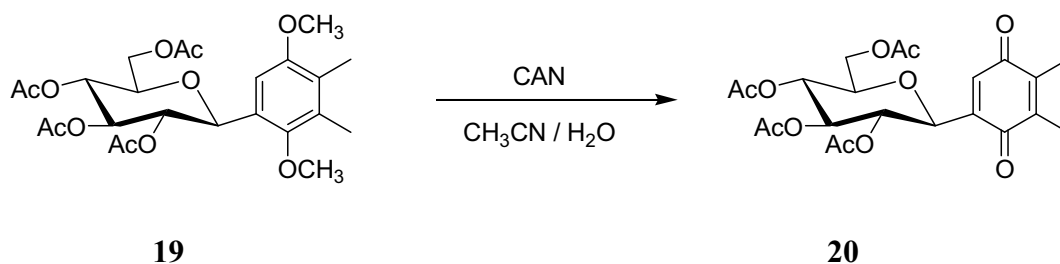
A solution of CH_3COONa (10 g, 0.12 mol) in Ac_2O (110 mL) was heated to reflux for 1 h, compound **17** (20 g, 59 mmol) was added in portions. After addition, the solution was stirred for 3 h at reflux. Then the solution was cooled to r.t, then the solution was extracted with CHCl_3 , dried over MgSO_4 , evaporated to give the known compound **18** (32 g, 81%). mp: 159~160°C.

1.5.13 Synthesis of compound 19



To a solution of compound **14** (985 mg, 2.5 mmol) and compound **4** (830 mg, 5.0 mmol) in 12 mL of CH₂Cl₂, AgOTf (831 mg, 3.75 mmol) was added under Ar. Kept from light, SnCl₄ in CH₂Cl₂ (7.5 mL, 7.5 mmol) was added dropwise over 30 min. After addition, the mixture was stirred at 30°C for 5 h, then diluted with sat.aq NaHCO₃ (40 mL), filtered, extracted with CH₂Cl₂ (3×15 mL). The combined organic layers were washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (Pet:EtOAc=2:1) to afford compound **19** (825 mg, 67%) as white solid. TLC: *R*_f = 0.43 (Pet:EtOAc = 2:1); [α]_D = -20.8 (*c* 0.76, CH₂Cl₂); ¹H NMR (200 MHz, CDCl₃): δ 1.80, 2.03, 2.04, 2.07, 2.12, 2.21 (6s, 18H, 2×CH₃, 4×OAc), 3.72 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.90 (ddd, 1H, *J* = 2.3, 5.0 and 9.7 Hz, H-5'), 4.12 (dd, 1H, *J* = 12.3 and 2.3 Hz, H-6b'), 4.24 (dd, 1H, *J* = 12.3 and 5.0 Hz, H-6a'), 4.90 (d, 1H, *J* = 10.1 Hz, H-1'), 5.24 (t, 1H, *J* = 9.1 and 9.7 Hz, H-4'), 5.38 (t, 1H, *J* = 9.1 Hz, H-3'), 5.52 (t, 1H, *J* = 9.1 and 9.9 Hz, H-2'), 6.71 (s, 1H, ArH-3); ¹³C NMR (50 MHz, CDCl₃): δ 12.2, 12.8, 20.6, 20.7, 20.7, 20.8, 55.8, 62.0, 62.7, 68.9, 70.8, 74.5, 74.9, 76.2, 106.6, 125.3, 128.1, 131.0, 151.2, 154.0, 169.3, 169.6, 170.4, 170.7; Anal. calcd for C₂₄H₃₂O₁₁: C, 58.06; H, 6.50; O, 35.45. found: C, 57.94; H, 6.62; O, 34.90.

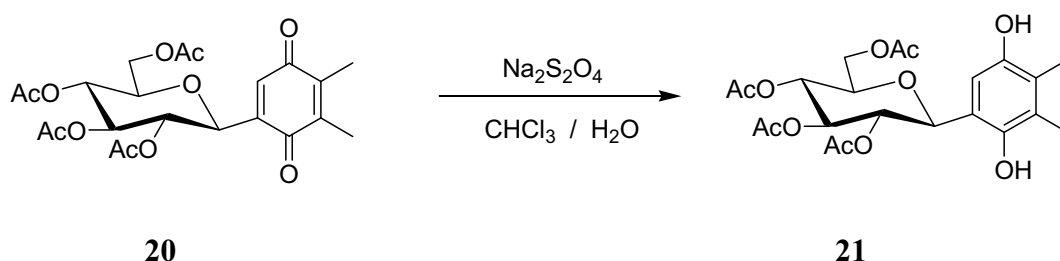
1.5.14 Synthesis of compound 20



To a solution of compound **19** (1.120 g, 2.26 mmol) in 4 mL of CH₃CN, was added CAN (3.72 g, 6.78 mmol) in H₂O (5 mL) at room temperature. After stirring for 30 min, the reaction solution was extracted with CH₂Cl₂ (3×20mL), and the combined organic layers were washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography to afford compound **20** (1.03 g, 97.6%). TLC: *R*_f = 0.45(Pet:EtOAc=2:1); [α]_D²² = -1.2 (*c* 0.8, CH₂Cl₂); IR (KBr): 1760 (C=O, acetyl), 1650 (C=O, benzoquinone); ¹H NMR (200 MHz,

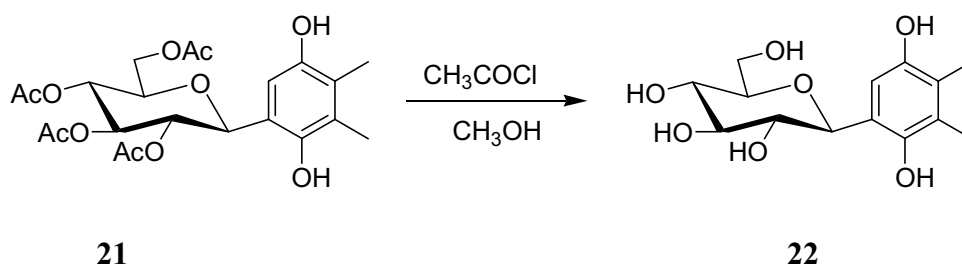
CDCl₃): δ 1.87, 1.98, 1.99, 1.99, 2.02, 2.06.(6s, 18H, 2 \times CH₃, 4 \times OAc), 3.79 (m, 1H, H-5'), 4.10 (dd, 1H, J = 2.3 and 12.4 Hz, H-6'b), 4.20 (dd, 1H, J = 4.7 and 12.4 Hz, H-6'a), 4.66 (dd, 1H, J = 9.7 and 0.8 Hz, H-1'), 4.97 (t, 1H, J = 9.2 and 9.7 Hz, H-2'), 5.11 (t, 1H, J = 9.4 and 10.0 Hz, H-4'), 5.34 (t, 1H, J = 9.2 and 9.4 Hz, H-3'), 6.80 (d, 1H, J = 0.8 Hz, ArH-3); ¹³C NMR (50MHz, CDCl₃): δ 12.2, 12.4, 20.5, 20.6, 20.6, 20.8, 62.0, 68.3, 72.2, 72.3, 73.8, 76.2, 133.4, 140.9, 141.0, 143.4, 169.5, 169.7, 170.1, 170.6, 185.7, 186.9; Anal. calcd for C₂₂H₂₆O₁₁: C, 56.65; H, 5.62; O, 37.73. found: C, 56.56; H, 5.97; O, 36.77.

1.5.15 Synthesis of compound 21



To a solution of compound **20** (932 mg, 2 mmol) in 10 mL of CHCl₃, Na₂S₂O₄ (2.05 g, 12 mmol) in H₂O (10 mL) was added at room temperature. After stirring for 30 min, the solution was extracted with CHCl₃ (3 \times 20mL), the combined organic layers were washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (Pet:EtOAc=2:1) to afford compound **21** (820 mg, 87.6%). TLC: R_f = 0.31 (Pet:EtOAc=2:1); $[\alpha]_D^{25}$ = -37 (c 0.8, CHCl₃); ¹H NMR (200 MHz, CDCl₃): δ 1.86, 2.01, 2.06, 2.12, 2.13, 2.16 (6s, 18H, 2 \times CH₃, 4 \times OAc), 3.89 (m, 1H, H-5'), 4.16 (d, 1H, J = 12.4Hz, H-6b'), 4.32 (dd, 1H, J = 3.8 Hz and 12.4 Hz, H-6a'), 4.52 (br d, 1H, J = 8.0 Hz, H-1'), 4.87 (s, 1H, OH, Ar), 5.23-5.37 (m, 3H, H-2', H-3', H-4'), 6.35 (s, 1H, ArH-3), 6.49 (s, 1H, OH, Ar); ¹³C NMR (50 MHz, CDCl₃): δ 12.1, 12.2, 20.5, 20.6, 20.7, 20.7, 61.7, 68.0, 70.7, 73.9, 76.1, 80.0, 111.7, 117.6, 125.1, 126.6, 146.8, 146.8, 169.0, 169.5, 170.5, 170.8; Anal. calcd for C₂₂H₂₈O₁₁: C, 56.41; H, 6.02; O, 37.57. found: C, 56.15; H, 6.22; O, 37.26.

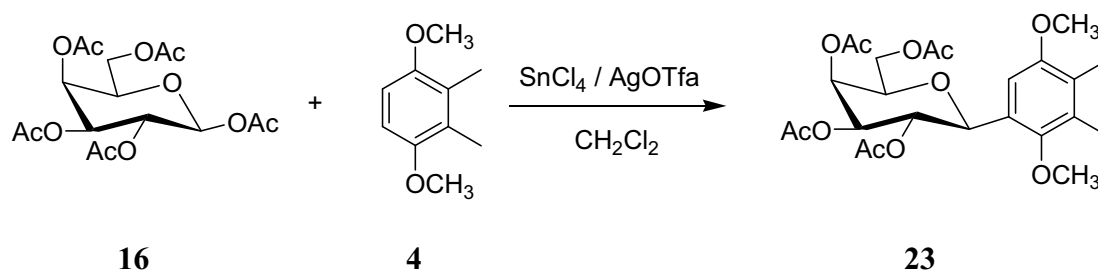
1.5.16 Synthesis of compound 22



To a solution of compound **21** (468 mg, 1 mmol) in 10 mL of MeOH, a freshly prepared

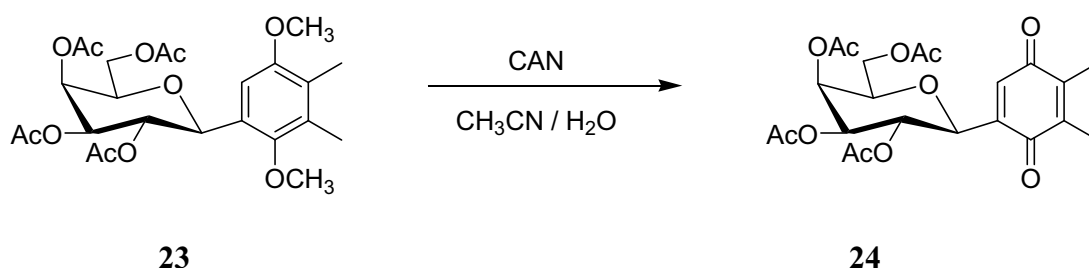
solution of AcCl in MeOH (0.1 M, 2 mL) was added. After addition, the solution was stirred for 72 h, evaporated to afford compound **22** (243 mg, 81%). TLC: $R_f = 0.31$ (CH₃OH:EtOAc = 1:8); ¹H NMR (500 MHz, D₂O): δ 2.08 (2s, 6H, 2×CH₃), 2.19, 3.41-3.74 (m, 3H, H-3', H-4' and H-5'), 3.73-3.90 (m, 3H, H-2', H-6'a and H-6'b), 4.51 (d, $J = 9.8$ Hz, 1H, H-1'), 6.37 (s, 1H, Ar-H); HRESIMS: calcd for [C₁₄H₂₀O₇+Na]⁺: 323.1107. found 323.1093.

1.5.17 Synthesis of compound **23**



To a solution of compound **16** (985 mg, 2.5 mmol) and compound **4** (830 mg, 5.0 mmol) in 12 mL of CH₂Cl₂ was added AgOTf (831 mg, 3.75 mmol) under Ar. Kept from light, SnCl₄ in CH₂Cl₂ (7.5 mL, 7.5 mmol) was added dropwise over 30 min. After addition, the mixture was stirred at 30°C for 5 h, then diluted with sat. aq NaHCO₃ (40 mL), filtered, extracted with CH₂Cl₂ (3×15 mL). The combined organic layers were washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (Pet:EtOAc=2:1) to afford compound **23** (905 mg, 73%). TLC: $R_f = 0.43$ (Pet:EtOAc = 2:1); $[\alpha]_D^{22} = -5.8$ (c 0.80, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 1.80, 2.00, 2.00, 2.12, 2.20, 2.22 (6s, 18H, 2×CH₃, 4×OAc), 3.72 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.08-4.19 (m, 3H, H-5', H-6'a and H-6'b), 4.87 (d, 1H, $J = 10.2$ Hz, H-1'), 5.23 (dd, 1H, $J = 10.0$ and 3.4 Hz, H-3'), 5.54 (d, 1H, $J = 3.4$ Hz, H-4'), 5.69 (t, 1H, $J = 10.0$ and 10.2 Hz, H-2'), 6.76 (s, 1H, ArH-3); ¹³C NMR (75 MHz, CDCl₃): δ 12.5, 13.1, 21.0, 21.0, 21.1, 21.2, 56.1, 62.2, 62.3, 68.4, 68.4, 73.1, 75.2, 75.6, 107.4, 125.9, 128.3, 131.3, 151.6, 154.2, 169.6, 170.5, 170.7, 170.7; Anal. calcd for C₂₄H₃₂O₁₁: C, 58.06; H, 6.50; O, 35.45. found: C, 58.08; H, 6.36; O, 35.63.

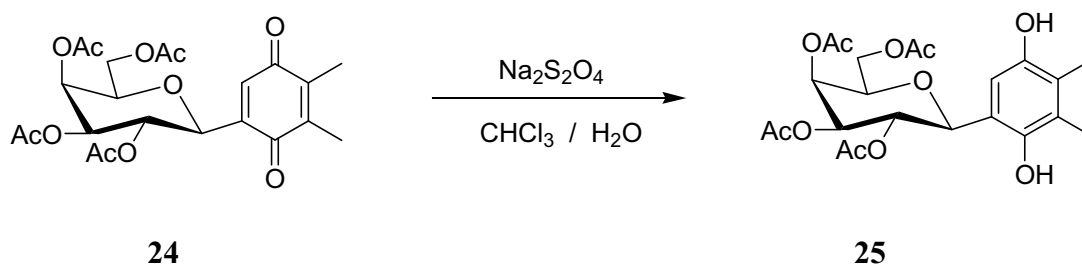
1.5.18 Synthesis of compound **24**



To a solution of compound **23** (932 mg, 2 mmol) in 4 mL of CH₃CN, CAN (3.7 mg, 6.78

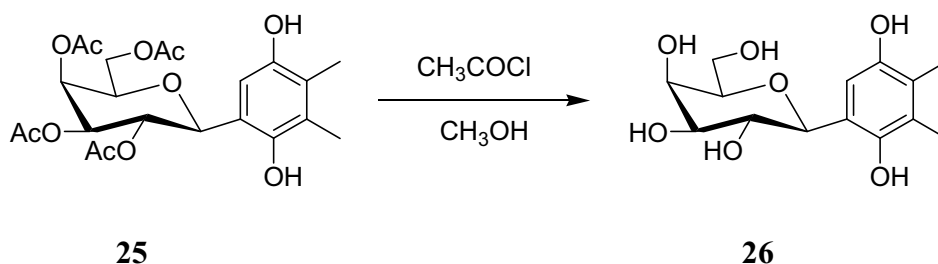
mmol) in H₂O (5 mL) was added at room temperature. After stirring for 30 min, the reaction solution was extracted with CH₂Cl₂ (3×20mL). The combined organic layers were washed with brine, dried over MgSO₄, evaporated, purified with column chromatography to afford compound **24** (904 mg, 97%) as yellow solid. TLC: *R_f* = 0.44 (Pet:EtOAc=1:2); mp 132-133°C (CH₂Cl₂); [α]_D²² = +20.2 (*c* 0.84, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 1.90, 2.00, 2.02, 2.02, 2.04, 2.19 (6s, 18H, 2×CH₃, 4×OAc), 4.02 (m, 1H, H-5'), 4.10 (m, 2H, H-6a', H-6b'), 4.68 (dd, 1H, *J* = 9.2 and 0.8 Hz, H-1'), 5.13 (t, 1H, *J* = 9.2 and 10.0 Hz, H-2'), 5.21 (dd, 1H, *J* = 3.2 and 10.0 Hz, H-3'), 5.50 (d, 1H, *J* = 3.2 Hz, H-4'), 6.91 (d, 1H, *J* = 0.8 Hz, benzoquinone H-3); ¹³C NMR (75 MHz, CDCl₃): δ 12.5, 12.7, 20.9, 21.0, 21.0, 21.1, 62.1, 67.8, 70.3, 72.1, 72.6, 75.0, 133.9, 141.2, 141.3, 144.3, 170.3, 170.3, 170.6, 170.8, 186.2, 187.5; Anal. calcd for C₂₂H₂₆O₁₁: C, 56.65; H, 5.62; O, 37.73. found: C, 56.26; H, 5.56; O, 38.35.

1.5.19 Synthesis of compound **25**



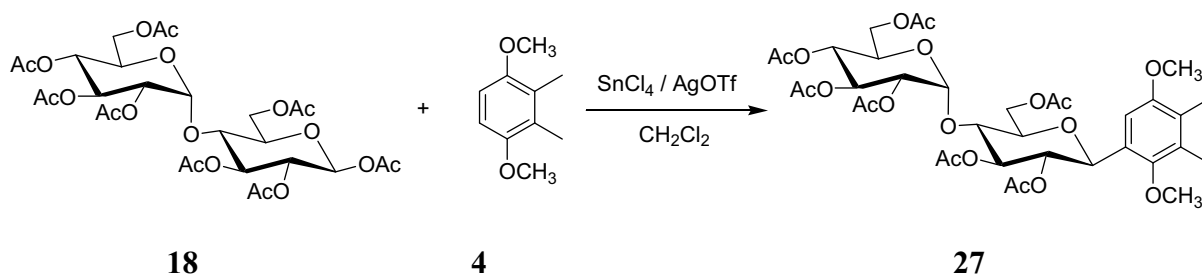
To a solution of compound **24** (932 mg, 2 mmol) in 10 mL CHCl₃, Na₂S₂O₄ (2052 mg, 12 mmol) in H₂O 10 mL was added at room temperature, stirred for 30 min, the solution was extracted with CHCl₃ (3×20mL), the combined organic layers were washed with brine, dried over MgSO₄, evaporated to give crude product, purified with column chromatography (Pet:EtOAc=2:1) to afford compound **25** (824 mg, 88 %). TLC: *R_f* = 0.26 (Pet:EtOAc=2:1); [α]_D²⁵ = -6.32 (*c* 0.87, CHCl₃); ¹H NMR (200 MHz, CDCl₃): δ 1.86, 2.00, 2.05, 2.13, 2.17, 2.23 (6s, 18H, 4×OAc, 2×CH₃), 4.07-4.19 (m, 3H, H-6'a H-6'b and H-5'), 4.39 (d, 1H, *J* = 9.8 Hz, H-1'), 4.73 (s, 1H, Ar-OH, exchanged with D₂O), 5.14 (dd, 1H, *J* = 3.1 and 10.0 Hz, H-3'), 5.54-5.64 (m, 2H, H-2', H-4'), 6.34 (s, 1H, ArH-3), 6.67 (s, 1H, Ar-OH, exchanged with D₂O); ¹³C NMR (50 MHz, CDCl₃): δ 12.1, 12.2, 20.6, 20.7, 20.7, 20.8, 61.7, 67.7, 67.8, 72.0, 74.9, 81.1, 112.1, 117.7, 125.1, 126.4, 146.5, 147.2, 170.0, 170.1, 170.4, 170.5; Anal. calcd for C₂₂H₂₈O₁₁: C, 56.41; H, 6.02; O, 37.57. found: C, 56.15; H, 6.01; O, 37.63.

1.5.20 Synthesis of compound 26



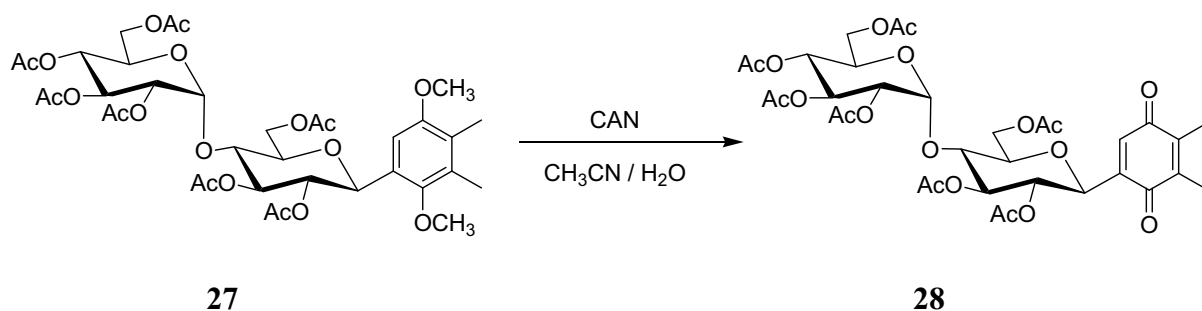
To a solution of compound **25** (468 mg, 1 mmol) in 10 mL of MeOH, was added a freshly prepared CH_3COCl in MeOH (5%) (2 mL). After 72 h's reaction, the reaction mixture was evaporated to give compound **26** (255 mg, 85%). TLC: $R_f = 0.34$ ($\text{CH}_3\text{OH}:\text{EtOAc}=1:6$); ^1H NMR (500 MHz, D_2O): δ 2.19 (2s, 6H, $2\times\text{CH}_3$), 2.24, 3.62 (dd, $J = 9.0$ and 2.4 Hz, 1H, H-3'), 3.68 (m, 1H, H-5'), 3.70-3.75 (m, 2H, H-6'a, H-6'b), 4.05 (d, $J = 2.4$ Hz, 1H, H-4'), 4.09 (t, $J = 9.0$ and 9.5 Hz, 1H, H-2'), 4.61 (d, $J = 9.5$ Hz, 1H, H-1'), 6.25 (s, 1H, Ar-H); HRESIMS: calcd for $[\text{C}_{14}\text{H}_{20}\text{O}_7+\text{Na}]^+$: 323.1119 found 323.1109.

1.5.21 Synthesis of compound 27



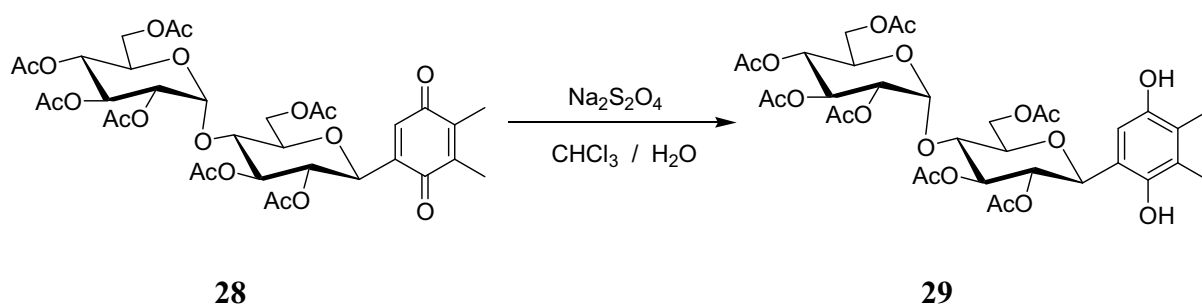
To a solution of compound **18** (1.69 g, 2.5 mmol) and compound **4** (830 mg, 5.0 mmol) in 12 mL of CH_2Cl_2 , was added AgOTf (831 mg, 3.75 mmol) under Ar. Kept from light, SnCl_4 in CH_2Cl_2 (7.5 mL, 7.5 mmol) was added dropwise over 30 min. After addition, the mixture was stirred at 30°C for 5 h, then diluted with sat. aq NaHCO_3 (40 mL), filtered, and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=2:1) to afford compound **27** (1.195 g, 61%). TLC: $R_f = 0.47$ (Pet:EtOAc=3:1); ^1H NMR (200 MHz, CDCl_3): δ 1.77, 2.01, 2.01, 2.03, 2.08, 2.08, 2.09, 2.11, 2.17 (9s, 27H, $2\times\text{ArCH}_3$, $7\times\text{OAc}$), 3.71 (2s, 6H, $2\times\text{OCH}_3$), 3.77-3.90 (m, 1H, H-5' or H-5''), 4.00 (d, 1H, $J = 9.9\text{Hz}$, H-5' or H-5''), 4.07 (d, 1H, $J = 12.6\text{Hz}$, H-6'b or H-6''b), 4.13 (t, 1H, $J = 9.2$ Hz, H-4'), 4.20-4.28 (m, 2H, H-6'ab or H-6''ab), 4.42 (d, 1H, $J = 10.3\text{Hz}$, H-6'a or H-6''a), 4.89 (dd, 1H, $J = 10.4$ Hz, H-2''), 4.90 (d, 1H, $J = 10.4\text{Hz}$, H-1'), 5.08 (t, 1H, $J = 9.2\text{Hz}$, H-2'), 5.33-5.45 (m, 3H, H-3', H-3'', H-4''), 6.63 (s, 1H, Ar-H), 5.47 (d, 1H, $J = 3.9\text{Hz}$, H-1''); HRESIMS: calcd for $[\text{C}_{36}\text{H}_{48}\text{O}_{19}+\text{Na}]^+$: 807.2688 found 807.2647.

1.5.22 Synthesis of compound 28



To a solution of compound **27** (784 mg, 1 mmol) in 10 mL of CH₃CN, CAN (1.64 g, 3 mmol) in H₂O (10 mL) was added at room temperature. After 30 min, the reaction solution was extracted with CH₂Cl₂ (3×20mL), and the combined organic layers were washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **28** (727 mg, 97%) as yellow solid. TLC: *R_f* = 0.50 (Pet:EtOAc=3:1); ¹H NMR (500 MHz, CDCl₃): δ 1.77, 1.93, 1.94, 1.96, 1.96, 2.00, 2.04, 2.06, 2.13 (9s, 27H, 2×CH₃, 7×OAc), 3.66 (m, 1H, H-5' or H-5''), 3.91 (m, 1H, H-5' or H-5''), 4.12-4.20 (m, 3H, H-6'a,b or H-6''a,b, H-4'), 4.20 (dd, 1H, *J*=3.6 and 12.5 Hz, H-6'a or H-6''a), 4.53 (dd, 1H, *J*=2.3 and 12.3 Hz, H-6'a or H-6''a), 4.81 (dd, 1H, *J*=10.5 Hz, H-2''), 4.87 (d, 1H, *J*=10.0 Hz, H-1'), 5.01 (t, 1H, *J*=10.0 and 9.8 Hz, H-4''), 5.23 (t, 1H, *J*=9.2 Hz, H-2'), 5.31 (m, 2H, H-3', H-3''), 5.40 (d, 1H, *J*=4.0 Hz, H-1''), 6.48 (d, 1H, *J*=1.52 Hz, Ar-H); HRESIMS: calcd for [C₃₄H₄₂O₁₉+Na]⁺: 777.2218 found 777.2241.

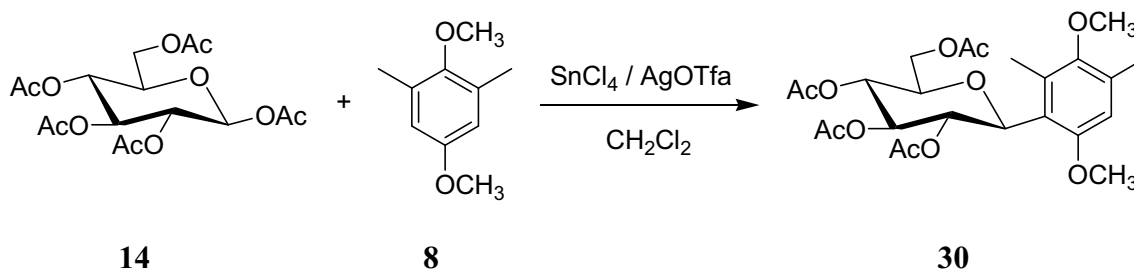
1.5.23 Synthesis of compound 29



To a solution of compound **28** (754 mg, 1 mmol) in 10 mL of HCl₃, Na₂S₂O₄ (1.04 g, 6 mmol) in H₂O (10 mL) was added at room temperature. After 30 min, the reaction solution was extracted with CHCl₃ (3×20mL), and the combined organic layers were washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (Pet:EtOAc=1:1) to afford compound **29** (730 mg, 97%). TLC: *R_f* = 0.41(Pet:EtOAc=2:1); ¹H NMR (200 MHz, CDCl₃): δ 1.84, 2.01, 2.17, 2.02, 2.04, 2.07, 2.11, 2.12, 2.14 (9s, 27H, 2×ArCH₃, 7×OAc); 3.83 (m, 1H, *J*=2.2 and 12.5 Hz, H-6'b or H-6''b), 3.83 (m, 1H, H-5'), 3.95 (m, 1H, H-5''),

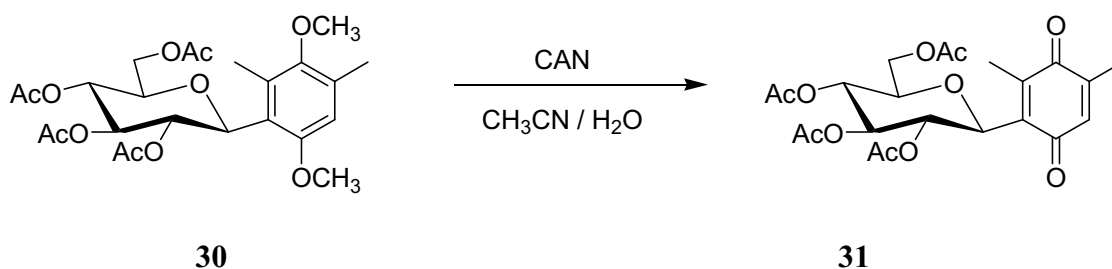
4.04 (dd, 1H, $J = 2.2$ and 12.5 Hz, H-6'b or H-6''b), 4.15 (t, 1H, $J = 9.4$ Hz, H-4'), 4.27 (dd, 1H, $J = 3.5$ and 12.5 Hz, H-6'a or H-6''a), 4.32 (dd, 1H, $J = 3.6$ and 12.3 Hz, H-6'b or H-6''b), 4.48 (dd, 1H, $J = 2.3$ and 12.3 Hz, H-6'a or H-6''a), 4.52 (d, 1H, $J = 10.0$ Hz, H-1'), 4.89 (dd, 1H, $J = 10.5$ Hz, H-2''), 5.08 (t, 1H, $J = 9.8$ Hz, H-2'), 5.15 (t, 1H, $J = 9.7$ Hz, H-4''), 5.37 (m, 2H, H-3', H-3''), 5.47 (d, 1H, $J = 4.0$ Hz, H-1''), 6.31 (s, 1H, ArH), 6.52 (s, 1H, Ar-OH); HRESIMS: calcd for $[C_{34}H_{44}O_{19}+Na]^+$: 779.2375 found 779.2341.

1.5.24 Synthesis of compound 30



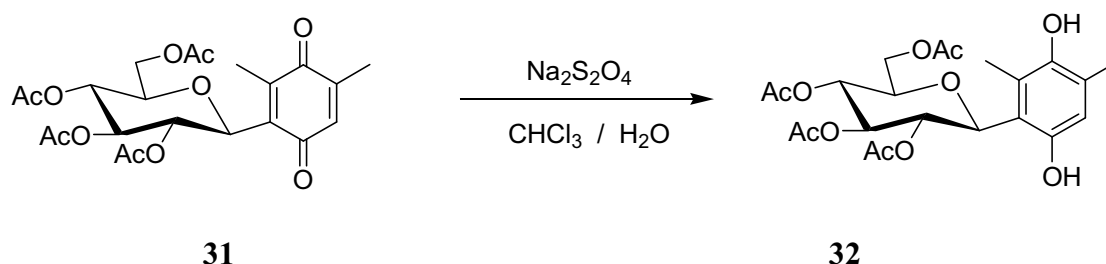
To a solution of compound **14** (985 mg, 2.5 mmol) and compound **8** (830 mg, 5.0 mmol) in 12 mL of CH_2Cl_2 , AgOTf (831 mg, 3.75 mmol) was added under Ar. Kept from light, $SnCl_4$ in CH_2Cl_2 (7.5 mL, 7.5 mmol) was added dropwise over 30 min. After addition, the mixture was stirred at $30^\circ C$ for 5 h, then diluted with sat.aq $NaHCO_3$ (40 mL), filtered, and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, evaporated, and purified with column chromatography (Pet:EtOAc=2:1) to afford compound **30** (909 mg, 74%). TLC: $R_f = 0.40$ (Pet:EtOAc=2:1); $[\alpha]_D^{22} = -10.1$ (c 0.86, CH_2Cl_2); 1H NMR (300 MHz, $DMSO-d_6$, $90^\circ C$): δ 1.69, 1.95, 2.01, 2.03, 2.22, 2.33 (6s, 18H, $6 \times CH_3$), 3.58 (s, 3H, OMe), 3.76 (s, 3H, OMe), 4.00 (m, 1H, H-5'), 4.11 (dd, 1H, $J = 12.4$ and 4.1 Hz, H-6b'), 4.16 (dd, 1H, $J = 12.4$ and 3.4 Hz, H-6a'), 5.05 (dd, 1H, $J = 9.5$ and 10.0 Hz, H-4'), 5.10 (d, 1H, $J = 9.3$ Hz, H-1'), 5.30 (t, 1H, $J = 9.3$ Hz, H-3'), 5.54 (t, 1H, $J = 9.3$ Hz, H-2'), 6.69 (s, 1H, ArH-6); ^{13}C NMR (75 MHz, $DMSO-d_6$, $90^\circ C$): δ 12.5, 16.4, 20.2, 20.5, 20.6, 20.6, 56.9, 59.8, 62.5, 69.2, 70.6, 73.6, 74.7, 75.4, 112.9, 121.7, 131.7, 131.8, 151.3, 154.6, 168.7, 169.5, 169.7, 170.1; Anal. Calcd for $C_{24}H_{32}O_{11}$ (496.19) : C, 58.06; H, 6.50; O, 35.45. found: C, 57.76; H, 6.46; O, 35.95.

1.5.25 Synthesis of compound 31



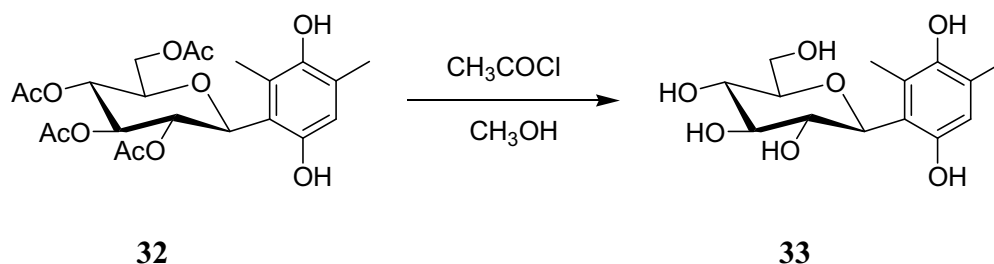
To a solution of compound **30** (932 mg, 2 mmol) in 10 mL of CH₃CN, CAN (1.64 g, 3 mmol) in H₂O (10 mL) was added at room temperature. After 30 min, the reaction solution was extracted with CH₂Cl₂ (3×20mL), and the combined organic layers were washed with brine, dried over MgSO₄, evaporated, purified with column chromatography (Pet:EtOAc=3:1) to afford compound **31** (866 mg, 93 %). Mp: 149~150.5°C(CH₂Cl₂); TLC: *R*_f = 0.43(Pet:EtOAc = 2:1); [α]_D²² = -63 (*c* 0.70, CH₂Cl₂); IR (KBr): 1750 (C=O, acetyl), 1650 (C=O, benzoquinone); ¹H NMR (500 MHz, CDCl₃): δ 2.04 (d, 3H, *J* = 1.5 Hz, Me), 1.87, 2.01, 2.06, 2.08, 2.27 (5s, 15H, CH₃, 4×OAc), 3.76 (m, 1H, H-5'), 4.17 (dd, 1H, *J* = 4.0 and 12.5 Hz, H-6'b), 4.20 (dd, 1H, *J* = 2.6 and 12.5 Hz, H-6'a), 4.96 (d, 1H, *J* = 9.9 Hz, H-1'), 5.20 (t, 1H, *J* = 9.7 Hz, H-4'), 5.31 (t, 1H, *J* = 9.1 and 9.7 Hz, H-3'), 5.43 (t, 1H, *J* = 9.1 and 9.9 Hz, H-2'), 6.56 (d, 1H, *J* = 1.4 Hz, benzoquinone-H-6); ¹³C NMR (50 MHz, CDCl₃): δ 12.7, 16.0, 20.4, 20.6, 20.6, 20.7, 61.9, 68.3, 70.2, 71.9, 74.2, 76.3, 133.0, 136.8, 145.8, 145.9, 169.5, 169.6, 170.1, 170.6, 185.3, 187.7; Anal. Calcd for C₂₂H₂₆O₁₁: C, 56.65; H, 5.62; O, 37.73. found: C, 56.57; H, 5.61; O, 37.50.

1.5.26 Synthesis of compound **32**



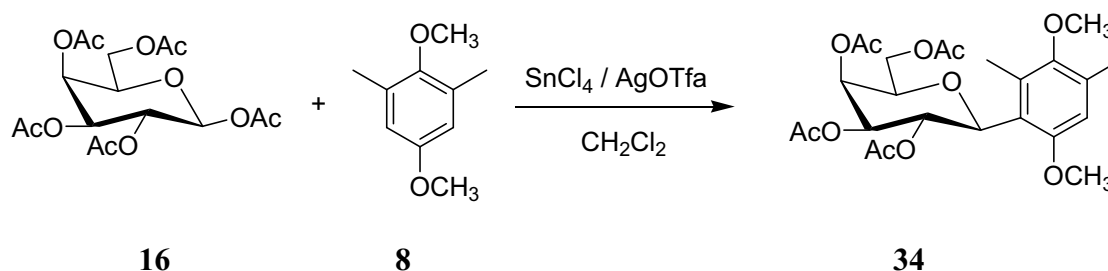
To a solution of compound **31** (932 mg, 2 mmol) in 10 mL of CHCl₃, Na₂S₂O₄ (2.05 g, 12 mmol) in H₂O (10 mL) was added at room temperature. After 30 min, the reaction solution was extracted with CHCl₃ (3×20mL), and the combined organic layers were washed with brine, dried over MgSO₄, evaporated, purified with column chromatography (Pet:EtOAc=1:1) to afford compound **32** (842 mg, 90 %). mp: 198.5~200°C (CH₂Cl₂); TLC: *R*_f = 0.27(Pet:EtOAc=2:1); [α]_D²⁵ = -23.9 (*c* 0.8, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 1.81, 2.01, 2.06, 2.12, 2.17, 2.21 (6s, 18H, 6×CH₃), 3.88 (m, 1H, H-5'), 4.15 (dd, 1H, *J* = 12.5 and 1.4 Hz, H-6'b), 4.25 (s, 1H, exchangeable, OH), 4.32 (dd, 1H, *J* = 2.3 and 12.5 Hz, H-6'a), 4.91 (d, 1H, *J* = 9.9 Hz, H-1'), 5.30-5.37 (2 overlapped triplets, 2H, H-3' and H-4'), 5.50 (t, 1H, *J* = 9.5 Hz, H-2'), 6.58 (s, 1H, Ar-H-6), 6.95 (s, 1H, exchangeable, OH); ¹³C NMR (50 MHz, CDCl₃): δ 12.3, 16.3, 20.3, 20.6, 20.7, 20.7, 61.4, 67.8, 70.4, 73.9, 76.1, 77.0, 117.6, 122.3, 125.3, 125.3, 145.5, 149.4, 168.6, 169.4, 170.4, 170.7; Anal. Calcd for C₂₂H₂₈O₁₁: C, 56.41; H, 6.02; O, 37.57. found: C, 56.03; H, 6.21; O, 37.51.

1.5.27 Synthesis of compound 33



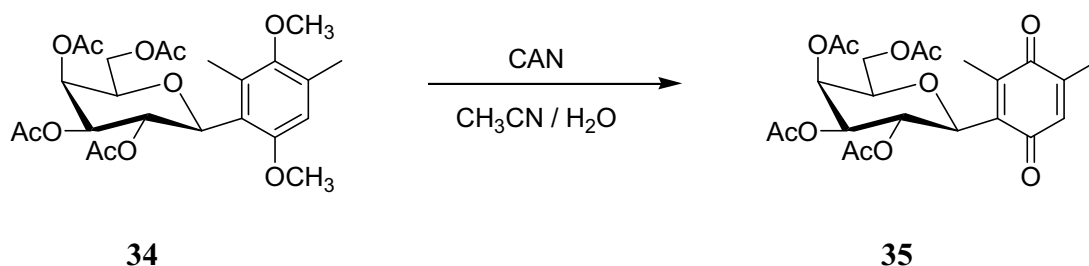
To a solution of compound **32** (468 mg, 1 mmol) in 10 mL of MeOH, was added a freshly prepared solution of CH_3COCl in MeOH (5%, 2 mL). After 72 h, the reaction solution was evaporated to give compound **33** (243 mg, 81%). TLC: $R_f = 0.37(\text{CH}_3\text{OH}:\text{EtOAc}=1:6)$; ^1H NMR (500 MHz, D_2O): δ 2.18, 2.27 (2s, 6H, $2\times\text{CH}_3$), 3.53-3.59 (m, 3H, H-3', H-4' and H-5'), 3.70 (dd, $J = 9.8$ and 8.7 Hz, 1H, H-2'), 3.71-3.84 (m, 2H, H-6'a and H-6'b), 4.59 (d, $J = 10.0$ Hz, 1H, H-1'), 6.86 (s, 1H, Ar-H); HRESIMS: calcd for $[\text{C}_{14}\text{H}_{20}\text{O}_7+\text{Na}]^+$: 323.1107 found 323.1132.

1.5.28 Synthesis of compound 34



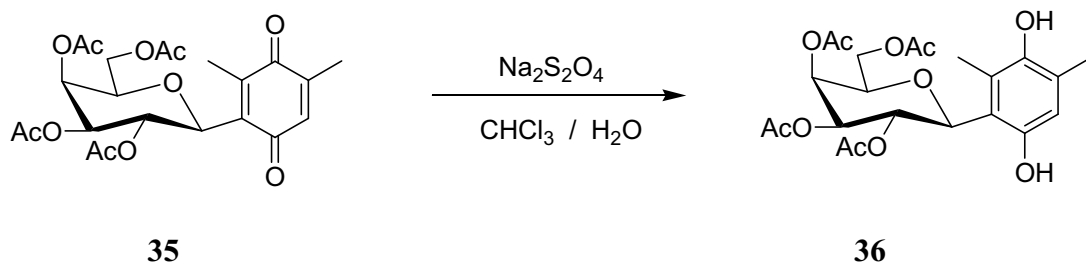
To a solution of compound **16** (985 mg, 2.5 mmol) and compound **8** (830 mg, 5.0 mmol) in 12 mL of CH_2Cl_2 , AgOTf (831 mg, 3.75 mmol) was added under Ar. Kept from light, SnCl_4 in CH_2Cl_2 (7.5 mL, 7.5 mmol) was added dropwise over 30 min. After addition, the mixture was stirred at 30°C for 5 h, then diluted with sat. aq NaHCO_3 (40 mL), filtered, and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **34** (855 mg, 69%). TLC: $R_f = 0.42(\text{Pet}:\text{EtOAc}=2:1)$; ^1H NMR (500MHz, DMSO): δ 1.98, 2.04, 2.07, 2.14, 2.26, 2.31 (6s, 18H, $2\times\text{CH}_3$, $4\times\text{OAc}$), 3.68 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.08-4.26 (m, 3H, H-5', H-6'a and H-6'b), 4.92 (d, 1H, $J = 10.1$ Hz, H-1'), 5.23 (dd, 1H, $J = 9.9$ and 3.6 Hz, H-3'), 5.54 (d, $J = 3.6$ Hz, 1H, H-4'), 5.69 (dd, 1H, $J = 9.9$ and 10.1 Hz, H-2'), 6.69 (s, 1H, Ar-H); HRESIMS: calcd for $[\text{C}_{24}\text{H}_{32}\text{O}_{11} + \text{Na}]^+$: 519.1843 found 519.1825.

1.5.29 Synthesis of compound 35



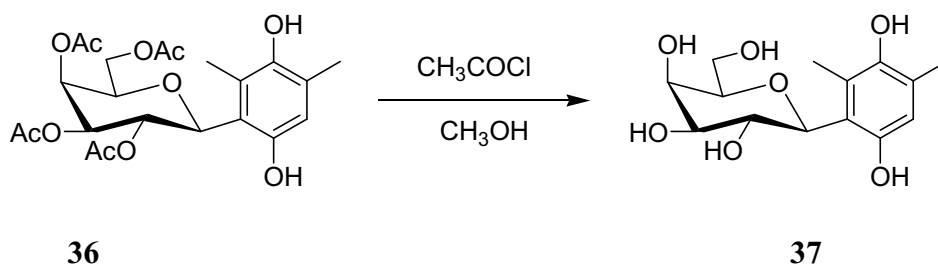
To a solution of compound **34** (932 mg, 2 mmol) in 10 mL of CH₃CN, CAN (1.64 g, 3 mmol) in H₂O (10 mL) was added at room temperature. After 30 min, the reaction solution was extracted with CH₂Cl₂ (3×20mL), the combined organic layers were washed with brine, dried over MgSO₄, evaporated, purified with column chromatography (Pet:EtOAc=2:1) to afford compound **35** (843 mg, 91 %). TLC: $R_f = 0.47$ (Pet:EtOAc=2:1); ¹H NMR (500 MHz, CDCl₃): δ 1.96, 2.02, 2.02, 2.05, 2.06, 2.32 (6s, 18H, 6×CH₃), 4.02-4.10 (m, 3H, H-5', H-6a' and H-6b'), 4.68 (d, $J = 9.6$ Hz, 1H, H-1'), 5.13 (dd $J = 9.6$ and 10.0 Hz, 1H, H-2'), 5.21 (dd, $J = 3.3$ and 10.0 Hz, 1H, H-3'), 5.50 (d, $J = 3.3$ Hz, 1H, H-4'), 6.56 (d, 1H, $J = 0.7$ Hz, benzoquinone-H); HRESIMS: calcd for [C₂₂H₂₆O₁₁+Na]⁺:489.1373 found 489.1391.

1.5.30 Synthesis of compound 36



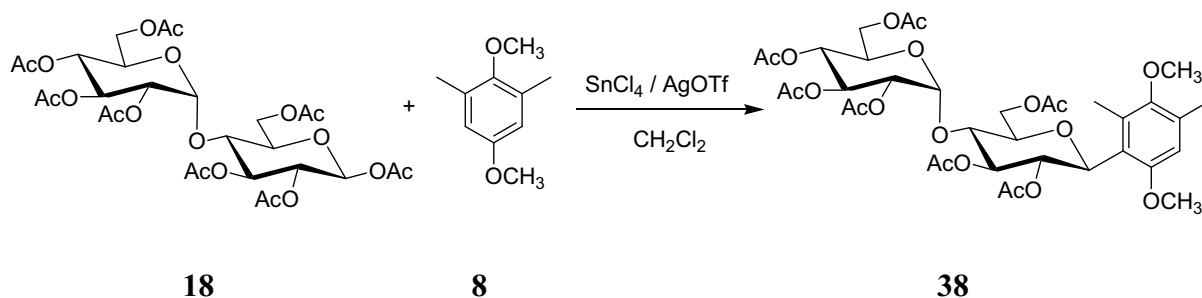
To a solution of compound **35** (932 mg, 2 mmol) in 10 mL CHCl₃ was added Na₂S₂O₄ (2.05 g, 12 mmol) in H₂O (10 mL) at room temperature. After 30 min, the reaction solution was extracted with CHCl₃ (3×20mL), the combined organic layers were washed with brine, dried over MgSO₄, evaporated, purified with column chromatography (Pet:EtOAc=2:1) to afford compound **36** (849 mg, 91 %). TLC: $R_f = 0.29$ (Pet:EtOAc=2:1); ¹H NMR (500 MHz, CDCl₃): δ 1.89, 2.00, 2.03, 2.12, 2.15, 2.21 (6s, 18H, 2×CH₃, 4×OAc), 4.02-4.19 (m, 3H, H-6'a, H-6'b and H-5'), 4.43 (d, $J = 9.8$ Hz, 1H, H-1'), 4.73 (s, 1H, Ar-OH), 5.14 (dd, $J = 3.2$ and 9.9 Hz, 1H, H-3'), 5.43-5.56 (m, 2H, H-2', H-4'), 6.53 (s, 1H, Ar-H), 6.64 (s, 1H, Ar-OH); HRESIMS: calcd for [C₂₂H₂₈O₁₁+Na]⁺:491.1530 found 491.1542.

1.5.31 Synthesis of compound 37



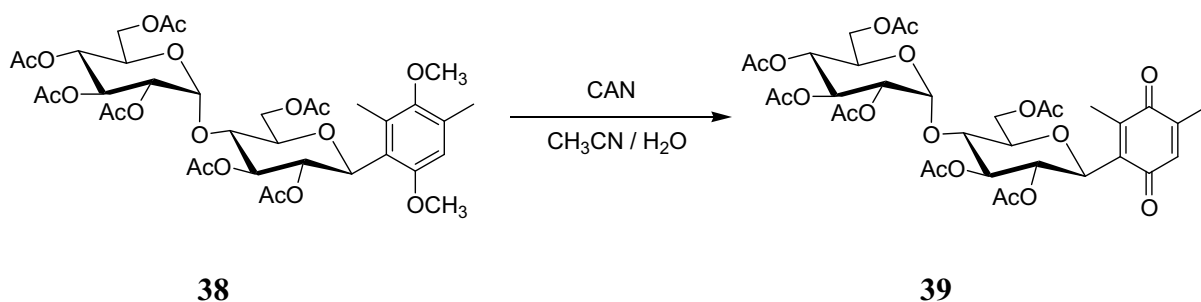
To a solution of compound **36** (468 mg, 1 mmol) in 10 mL MeOH, was added a freshly prepared solution of CH_3COCl in MeOH (5%, 2 mL). After 72 h, the reaction mixture was evaporated to give compound **37** (213 mg, 71%). TLC: $R_f = 0.32$ ($\text{CH}_3\text{OH}:\text{EtOAc}=1:6$); ^1H NMR (500 MHz, D_2O): δ 2.19, 2.24 (2s, 6H, $2\times\text{CH}_3$), 3.62 (dd, $J = 9.0$ and 2.4 Hz, 1H, H-3'), 3.68 (m, 1H, H-5'), 3.70-3.75 (m, 2H, H-6'a, H-6'b), 4.05 (d, $J = 2.4$ Hz, 1H, H-4'), 4.09 (t, $J = 9.5$ Hz, 1H, H-2'), 4.61 (d, $J = 9.5$ Hz, 1H, H-1'), 6.25 (s, 1H, Ar-H); HRESIMS: calcd for $[\text{C}_{14}\text{H}_{20}\text{O}_7 + \text{Na}]^+$: 323.1107 found 323.1119.

1.5.32 Synthesis of compound 38



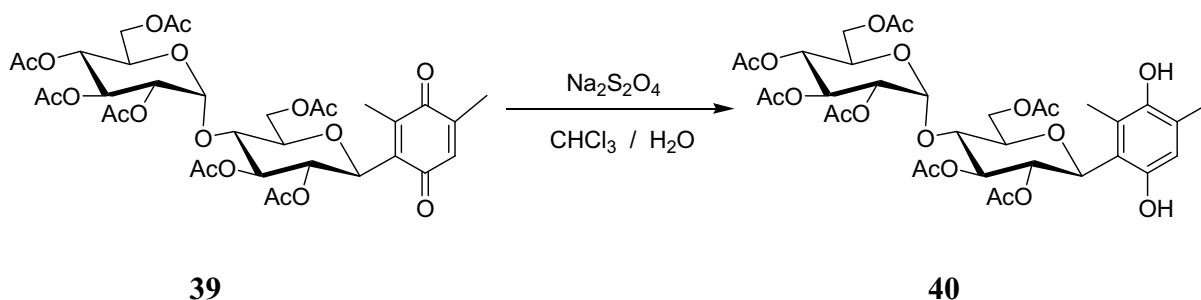
To a solution of compound **18** (678 mg, 1.0 mmol) and compound **8** (332 mg, 2.0 mmol) in 10 mL of CH_2Cl_2 , AgOTf (330 mg, 1.5 mmol) was added under Ar. Kept from light, SnCl_4 (350 μL) in CH_2Cl_2 (3 mL) was added dropwise over 30 min. After addition, the mixture was stirred at 30°C for 5 h, and then diluted with sat. aq NaHCO_3 (40 mL), filtered, and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=4:1) to afford compound **38** (480.8 mg, 61.3 %). TLC: $R_f = 0.37$ (Pet:EtOAc=3:1); ^1H NMR (500 MHz, DMSO): δ 2.00, 2.01, 2.03, 2.04, 2.08, 2.11, 2.12, 2.24, 2.35 (9s, 27H, $2\times\text{CH}_3, 7\times\text{OAc}$), 3.60 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.78 (m, 1H, H-5' or H-5''), 4.00 (m, 1H, H-5' or H-5''), 4.07-4.28 (m, 6H, H-2', H-4', H-6'a,b, H-6''a,b), 4.53 (bd, 1H, $J = 11.6$ Hz, H-1'), 4.90 (t, $J = 10.5$ Hz, 1H, H-2''), 5.09 (t, $J = 9.8$ Hz, 1H, H-4''), 5.39 (m, 2H, H-3', H-3''), 5.51 (d, $J = 3.9$ Hz, 1H, H-1''), 6.53 (s, 1H, Ar-H); HRESIMS : Calcd for $[\text{C}_{36}\text{H}_{48}\text{O}_{19} + \text{Na}]^+$: 807.2688 found 807.2712.

1.5.33 Synthesis of compound 39



To a solution of compound **38** (784 mg, 1 mmol) in 10 mL of CH₃CN, CAN (1.64 g, 3 mmol) in H₂O (10 mL) was added at room temperature. After 30 min, the reaction solution was extracted with CH₂Cl₂ (3×20mL), and the combined organic layers were washed with brine, dried over MgSO₄, evaporated, purified with column chromatography (Pet:EtOAc=3:1) to afford compound **39** (724.1 mg, 96 %). TLC: *R_f* = 0.37(Pet:EtOAc=3:1); ¹H NMR (500 MHz, CDCl₃): δ 1.77, 1.93, 1.94, 1.96, 1.96, 2.00, 2.04, 2.06, 2.13 (9s, 27H, 2×CH₃, 7×OAc), 3.66 (m, 1H, H-5' or H-5''), 3.91 (m, 1H, H-5' or H-5''), 4.12-4.20 (m, 3H, H-6'a,b or H-6''a,b,H-4'), 4.21 (dd, 1H, *J* = 3.6 and 12.5Hz, H-6'a or H-6''a), 4.53 (dd, 1H, *J* = 2.3 and 12.3Hz, H-6'a or H-6''a), 4.81 (dd, 1H, *J* = 10.5 Hz, H-2''), 4.87 (d, 1H, *J* = 10.0 Hz, H-1'), 5.01 (dd, 1H, *J* = 10.0 and 9.8 Hz, H-4'), 5.23 (t, 1H, *J* = 9.2Hz, H-2'), 5.31 (m, 2H, H-3',H-3''), 5.40 (d, 1H, *J* = 4.0 Hz, H-1''), 6.48 (d, 1H, *J* = 1.52Hz, Ar-*H*); HRESIMS: Calcd for [C₃₄H₄₂O₁₉ + Na]⁺: 777.2218 found 777.2241.

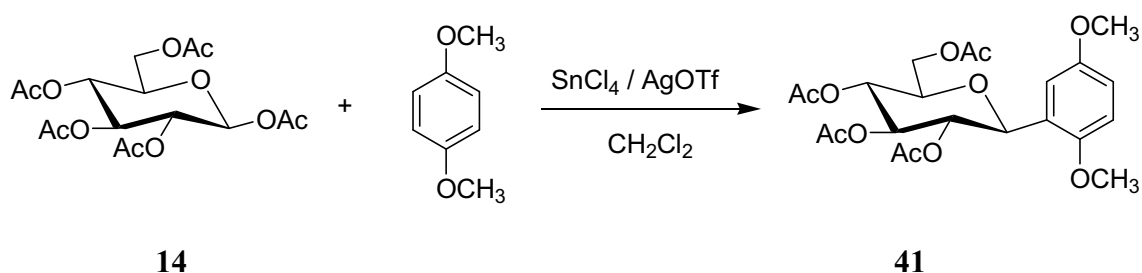
1.5.34 Synthesis of compound 40



To a solution of compound **39** (754 mg, 1 mmol) in 10 mL of CHCl₃, Na₂S₂O₄ (1.04 g, 6 mmol) in H₂O (10 mL) was added at room temperature. The mixture was stirred for 30 min, then extracted with CHCl₃ (3×20mL). The combined organic layers were washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (Pet:EtOAc=1:1) to afford compound **40** (720.0 mg, 95.2%). TLC: *R_f* = 0.32(Pet:EtOAc=1:1); ¹H NMR (CDCl₃, 500 MHz): δ 1.82, 2.00, 2.02, 2.04, 2.08, 2.11, 2.17, 2.17, 2.21 (9s, 27H, 2×CH₃, 7×OAc), 4.03 (dd, 1H, *J* = 2.0 and 12.5 Hz, H-6'b or H-6''b), 4.22 (t, 1H, *J* = 9.37 and 9.18 Hz, H-4'),

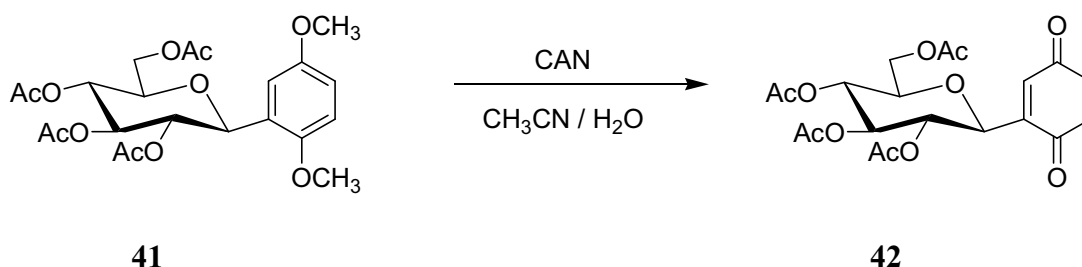
4.27 (dd, 1H, $J = 3.3$ and 12.5 Hz, H-6'a or H-6''a), 4.35 (1s, 1H, Ar-OH), 4.36 (dd, 1H, $J = 2.5$ and 12.1 Hz, H-6'a or H-6''a), 4.46 (dd, 1H, $J = 2.1$ and 12.4 Hz, H-6'a or H-6''a), 4.89 (t, 1H, $J = 10.6$ Hz, H-2''), 4.94 (d, 1H, $J = 9.8$ Hz, H-1'), 5.09 (t, 1H, $J = 9.4$ Hz, H-2'), 5.31-5.45 (m, 3H, H-3', H-3'' H-4''), 5.48 (d, 1H, $J = 3.95$ Hz, H-1''), 6.55 (s, 1H, Ar-H), 8.16 (s, 1H, Ar-OH); HRESIMS : Calcd for $[C_{34}H_{44}O_{19} + Na]^+$: 779.2375 found 779.2394.

1.5.35 Synthesis of compound 41



To a solution of compound **14** (390 mg, 1.0 mmol) and 1,4-dimethoxybenzene (276 mg, 2.0 mmol) in 10 mL of CH_2Cl_2 , AgOTf (330 mg, 1.5 mmol) was added under Ar. Kept from light, $SnCl_4$ (350 μ L) in CH_2Cl_2 (3 mL) was added dropwise over 30 min. After addition, the mixture was stirred at 30 °C for 5 h, then diluted with sat. aq $NaHCO_3$ (40 mL), filtered, and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, evaporated, purified with column chromatography (Pet:EtOAc=3:1) to afford compound **41** (332 mg, 71%). TLC: $R_f = 0.57$ (Pet:EtOAc=3:2); mp:106-107 °C; 1H NMR (500 MHz, $CDCl_3$) δ 1.78 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.06 (s, 3H, OAc), 2.08 (s, 3H, OAc), 3.77 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.80-3.89 (m, 1H, H-5'), 4.14 (dd, 1H, $J = 12.3$ and 2.2 Hz, H-6'b), 4.27 (dd, 1H, $J = 12.3$ and 4.7 Hz, H-6'a), 4.92 (d, 1H, $J = 9.0$ Hz, H-1'), 5.23 (t, 1H, $J = 9.0$ Hz, H-2'), 5.29 (t, 1H, $J = 8.8$ Hz, H-4'), 5.37 (t, 1H, $J = 9.0$ Hz, H-3'), 6.80-6.82 (m, 2H, ArH-5, H-6), 6.95 (d, 1H, $J = 1.9$ Hz, ArH-3).

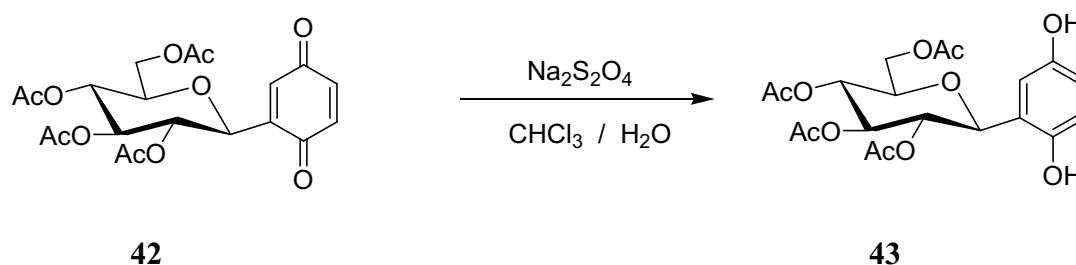
1.5.36 Synthesis of compound 42



To a solution of compound **41** (468 mg, 1 mmol) in 10 mL of CH_3CN , CAN (1.64 g, 3 mmol) in H_2O (10 mL) was added at room temperature. The mixture was stirred for 30 min, then extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried

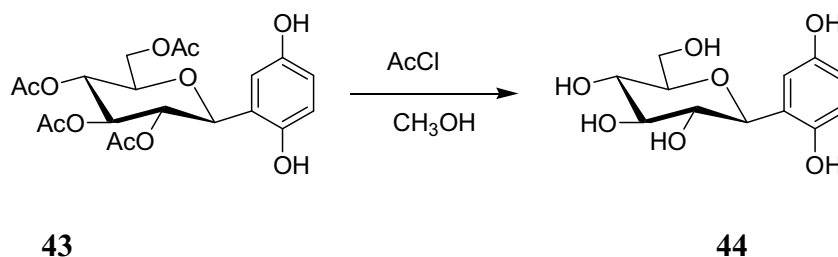
over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **42** (403 mg, 92 %). TLC: $R_f = 0.61$ (Pet:EtOAc=3:2); ^1H NMR (500 MHz, CDCl_3): δ 1.91(s, 3H, OAc), 2.02(s, 3H, OAc), 2.06 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.80 (m, 1H, H-5'), 4.14 (dd, 1H, $J = 2.2$ Hz, H-6'b), 4.26 (dd, 1H, $J = 4.6$ and 12.4 Hz, H-6'a), 4.64 (dd, 1H, $J = 0.8$ and 9.7 Hz, H-1'), 4.98 (t, 1H, $J = 9.5$ Hz, H-2'), 5.15 (t, 1H, $J = 9.8$ Hz, H-4'), 5.37 (t, 1H, $J = 9.4$ Hz, H-3'), 6.77 (d, 2H, $J = 1.2$ Hz, ArH-5, H-6), 6.91 (d, 1H, $J = 0.8$ Hz, ArH-3); ^{13}C NMR (125 MHz, CDCl_3): δ 20.59; 20.60, 20.60, 20.75, 62.00, 68.25, 72.01, 72.54, 73.66, 76.26, 133.73, 136.37, 136.50, 144.06, 169.51, 169.70, 170.05, 170.62, 185.49, 186.93; ESIMS m/e 461.1 $[\text{M}+\text{Na}]^+$ (100%); Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{O}_{11}$: C, 54.80; H, 5.06; O, 40.15. found: C, 54.92; H, 4.95; O, 40.02.

1.5.37 Synthesis of compound 43



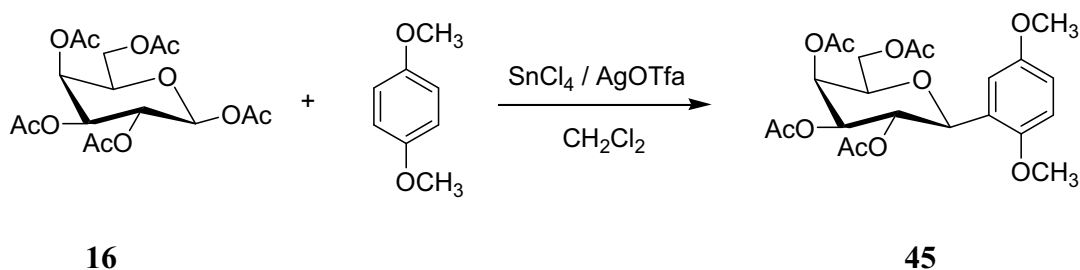
To a solution of compound **42** (438 mg, 1 mmol) in 10 mL of CHCl_3 , $\text{Na}_2\text{S}_2\text{O}_4$ (1.04 g, 6 mmol) in H_2O (10 mL) was added at room temperature. The reaction mixture was stirred for 30 min, extracted with CHCl_3 (3 \times 20mL). The combined organic layers were washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=2:1) to afford compound **43** (396 mg, 90%). TLC: $R_f = 0.30$ (Pet:EtOAc=1:2); $[\alpha]_{\text{D}}^{25} = -23$ (c 0.9, CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 1.86 (s, 3H, OAc), 2.01 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.11 (s, 3H, OAc), 3.89 (m, 1H, H-5'), 4.18 (dd, 1H, $J = 12.6$ and 2.2 Hz, H-6'b), 4.31 (dd, 1H, $J = 12.6$ and 3.8 Hz, H-6'a), 4.60 (d, 1H, $J = 9.8$ Hz, H-1'), 5.27 (t, 1H, $J = 9.8$ Hz, H-4'), 5.31 (t, 1H, $J = 9.8$ Hz, H-2'), 5.36 (t, 1H, $J = 3.4$ Hz, H-3'), 5.71 (s, 1H, OH, exchanged with D_2O), 6.50 (s, 1H, OH, exchanged with D_2O), 6.57 (d, 1H, $J = 2.8$ Hz, ArH-3), 6.68 (dd, 1H, $J = 2.8$ and 8.7 Hz, Ar-H-5), 6.74 (d, 1H, $J = 8.7$ Hz, ArH-6); ^{13}C NMR (125 MHz, CDCl_3): δ 20.83, 21.01, 21.06, 21.09, 62.17, 68.46, 71.33, 74.24, 76.44, 79.28, 115.32, 117.57, 118.71, 121.91, 148.94, 149.54, 169.57, 170.04, 170.96, 171.34; HRESIMS: calcd for $[\text{C}_{20}\text{H}_{24}\text{O}_{11}+\text{H}]^+$: 441.1319 found 441.12890.

1.5.38 Synthesis of compound 44



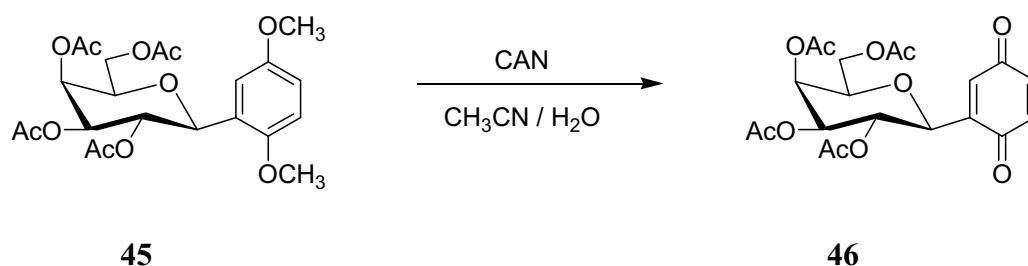
To a solution of compound **43** (100 mg, .227 mmol) in 10 mL of MeOH, was added a freshly prepared solution of CH_3COCl in MeOH (1%, 3 mL). After 72 h, the reaction solution was evaporated to give compound **44** (52 mg, 84%). TLC: $R_f = 0.38$ ($\text{CH}_3\text{OH}:\text{EtOAc} = 1:8$); $[\alpha]_D^{25} = +19.24$ (c 0.8, CH_3OH); $^1\text{H NMR}$ (500 MHz, D_2O): δ 3.53-3.59 (m, 3H, H-3', H-4' and H-5'), 3.70 (dd, 1H, $J = 9.8$ and 8.8 Hz, H-2'), 3.74 (dd, 1H, $J = 4.4$ and 12.3 Hz, H-6'b), 3.84 (d, 1H, $J = 12.3$ Hz, H-6'a), 4.59 (d, 1H, $J = 9.8$ Hz, H-1'), 6.77 (dd, 1H, $J = 2.8$ and 8.8 Hz, ArH-5), 6.82 (d, 1H, $J = 8.8$ Hz, ArH-6), 6.86 (d, 1H, $J = 2.8$ Hz, ArH-3); $^{13}\text{C NMR}$ (125 MHz, D_2O): δ 61.23, 70.13, 73.55, 76.57, 77.93, 80.63, 115.48, 117.27, 117.94, 125.50, 148.30, 149.50; HRESIMS: calcd for $[\text{C}_{12}\text{H}_{16}\text{O}_7 + \text{H}]^+$: 273.0974 found: 273.09759.

1.5.39 Synthesis of compound 45



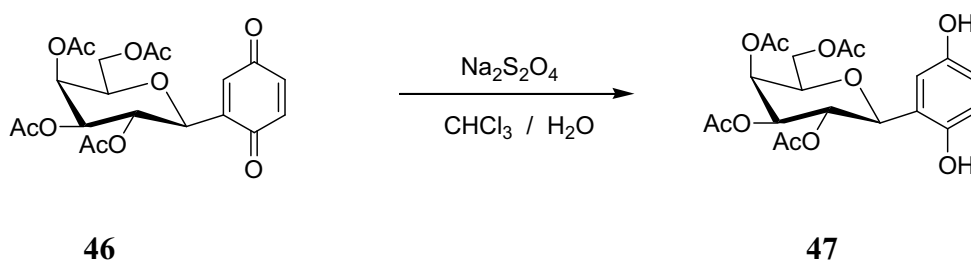
To a solution of compound **16** (390 mg, 1.0 mmol) and 1,4-dimethoxybenzene (276 mg, 2.0 mmol) in 10 mL of CH_2Cl_2 , AgOTf (330 mg, 1.5 mmol) was added under Ar. Kept from light, SnCl_4 (350 μL) in CH_2Cl_2 (3 mL) was added dropwise over 30 min. After addition, the mixture was stirred at 30 $^\circ\text{C}$ for 5 h, and then diluted with sat. aq NaHCO_3 (40 mL), filtered, extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **45** (339 mg, 74%) TLC: $R_f = 0.55$ (Pet:EtOAc=3:2); mp: 86-87 $^\circ\text{C}$; $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 1.80 (s, 3H, OAc), 1.99 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.21 (s, 3H, OAc), 3.78 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.04-4.21 (m, 3H, H-5' and H-6'a,b), 4.91 (d, 1H, $J = 9.9$ Hz, H-1'), 5.21 (dd, 1H, $J = 9.9$ and 3.5 Hz, H-3'), 5.46 (t, 1H, $J = 9.9$ Hz, H-2'), 5.52 (d, 1H, $J = 3.5$ Hz, H-4'), 6.81 (s, 1H, Ar), 6.81 (d, 1H, $J = 2.4$ Hz, Ar), 7.04 (d, 1H, $J = 2.4$ Hz, Ar).

1.5.40 Synthesis of compound 46



To a solution of compound **45** (468 mg, 1 mmol) in 10 mL of CH_3CN , was added CAN (1.64 g, 3 mmol) in H_2O (10 mL) at room temperature. The reaction mixture was stirred for 30 min, then extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **46** (390 mg, 89 %). TLC: $R_f = 0.59$ (Pet:EtOAc=3:2); $[\alpha]_D^{22} = -11.2$ ($c = 0.95$, acetone); IR (KBr): 1740 (C=O, OAc), 1655 (C=O, benzoquinone); ^1H NMR (200 MHz, CDCl_3): δ 1.91 (s, 3H, OAc), 1.99 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.18 (s, 3H, OAc), 3.99–4.21 (m, 3H, H-5', H-6'a, and H-6'b), 4.63 (dd, 1H, $J = 0.8$ and 8.6 Hz, H-1'), 5.11 (dd, 1H, $J = 8.6$ and 10 Hz, H-2'), 5.20 (dd, 1H, $J = 10$ and 3.1 Hz, H-3'), 5.50 (dd, 1H, $J = 0.7$ and 3.1 Hz, H-4'), 6.76 (d, 2H, $J = 1.2$ Hz, Ar-H-5, H-6), 6.98 (d, 1H, $J = 0.8$ Hz, ArH-3); ^{13}C NMR (50 MHz, CDCl_3): δ 20.60, 20.60, 20.70, 20.70, 61.72, 67.45, 70.11, 71.66, 72.08, 74.75, 133.83, 136.35, 136.50, 144.59, 169.94, 170.01, 170.18, 170.42, 185.70, 187.14; HRESIMS Calcd for $[\text{C}_{20}\text{H}_{22}\text{O}_{11}+\text{H}]^+$: 439.1240 found 439.12312.

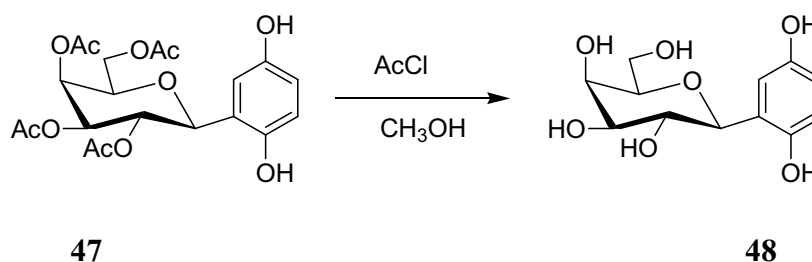
1.5.41 Synthesis of compound 47



To a solution of compound **46** (438 mg, 1 mmol) in 10 mL of CHCl_3 , $\text{Na}_2\text{S}_2\text{O}_4$ (1.04 g, 6 mmol) in H_2O (10 mL) was added at room temperature. After 30 min, the reaction solution was extracted with CHCl_3 (3×20 mL), and the combined organic layers were washed with brine, dried over MgSO_4 , evaporated, purified with column chromatography (Pet:EtOAc=2:1) to afford compound **47** (399 mg, 91%). TLC: $R_f = 0.30$ (Pet:EtOAc=2:1); $[\alpha]_D^{22} = -0.56$ ($c = 0.7$, CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 1.88 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.21 (s, 3H, OAc), 4.08 (t, 1H, $J = 6.3$ Hz, H-5'), 4.18 (m, 2H, H-6'a, and H-6'b), 4.48 (d, 1H, $J = 9.8$ Hz, H-1'), 5.16 (dd, 1H, $J = 2.8$ and 10.1 Hz, H-3'), 5.54 (br s, 1H, H-4'), 5.56

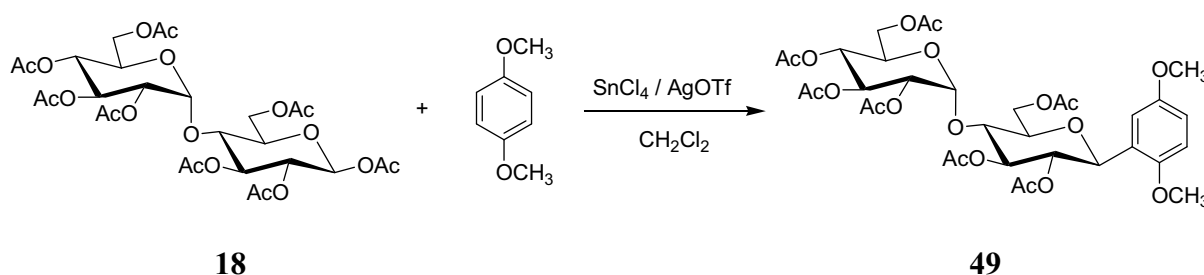
(t, 1H, $J = 10.1$ Hz, H-2'), 6.18 (s, 1H, OH, exchanged with D₂O), 6.55 (d, 1H, $J = 2.8$ Hz, Ar-H-3), 6.63 (s, 1H, OH, exchanged with D₂O), 6.69 (dd, 1H, $J = 2.8$ and 8.5 Hz, ArH-5), 6.77 (d, 1H, $J = 8.5$ Hz, ArH-6); ¹³C NMR (125 MHz, CDCl₃): δ 20.53, 20.68, 20.68, 20.68, 61.71, 67.81, 68.10, 71.92, 74.86, 80.09, 115.20, 117.21, 118.18, 121.76, 148.9, 149.06, 169.26, 170.20, 170.48, 170.72; HRESIMS Calcd for [C₂₀H₂₄O₁₁ +H]⁺: 441.1319. found: 441.12993.

1.5.42 Synthesis of compound 48



To a solution of compound **47** (99 mg, .226 mmol) in 5 mL of MeOH, a freshly prepared solution of CH₃COCl in MeOH (1%, 3 mL) was added. After 72 h, the reaction mixture was evaporated to give compound **48** (50 mg, 81%). TLC: $R_f = 0.33$ (CH₃OH:EtOAc=1:8); mp 209-210.5 °C; $[a]_D^{25} = +31.5$ (c=0.7, MeOH); ¹H NMR (500 MHz, D₂O): δ 3.69-3.78 (m, 4H, H-3', H-5', H-6'a,b), 3.90 (t, 1H, $J = 9.6$ Hz, H-2'), 4.03 (d, 1H, $J = 2.9$ Hz, H-4'), 4.56 (d, 1H, $J = 9.8$ Hz, H-1'), 6.77 (dd, 1H, $J = 2.8$ and 8.8 Hz, ArH-5), 6.82 (d, 1H, $J = 8.8$ Hz, ArH-6), 6.92 (d, 1H, $J = 2.8$ Hz, ArH-3); ¹³C NMR (125 MHz, D₂O): δ 61.59, 69.65, 71.13, 74.62, 76.61, 79.66, 115.28, 117.18, 117.86, 125.74, 148.30, 149.52; HRESIMS Calcd for [C₁₂H₁₆O₇ +H]⁺: 273.0974. found: 273.09722.

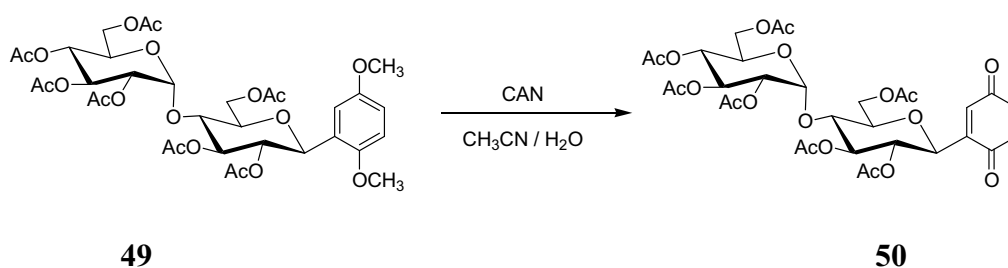
1.5.43 Synthesis of compound 49



To a solution of compound **18** (678 mg, 1.0 mmol) and 1,4-dimethoxybenzene (276 mg, 2.0 mmol) in 10 mL of CH₂Cl₂, AgOTf (330 mg, 1.5 mmol) was added under Ar. Kept from light, SnCl₄ (350 μ L) in CH₂Cl₂ (3 mL) was added dropwise over 30 min. After addition, the mixture was stirred at 30 °C for 5 h, then diluted with sat. aq NaHCO₃ (40 mL), filtered, and extracted with CH₂Cl₂ (3 \times 15 mL). The combined organic layers were washed with brine,

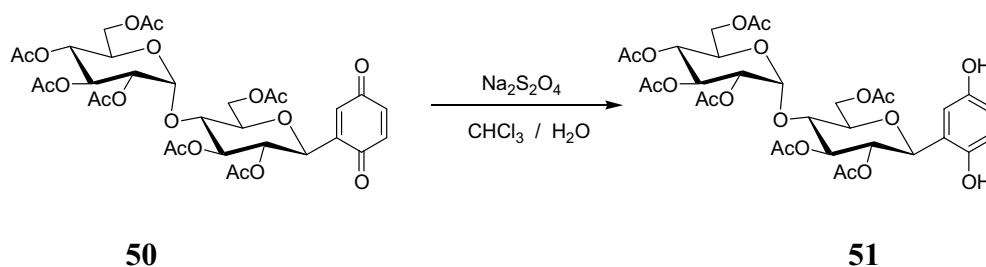
dried over MgSO_4 , evaporated to afford crude product, purified with column chromatography (Pet:EtOAc=4:1) to afford compound **49** (430 mg, 57%). TLC: $R_f = 0.43$ (Pet:EtOAc=3:2); mp:155-156 °C ; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 1.70, 1.92, 1.94, 1.96, 2.00, 2.04, 2.06 (7s, 21H, 7×OAc), 3.67 (s, 3H,OMe), 3.71 (s, 3H, OMe), 3.76 (m, 1H, H-5' or H-5''), 3.93 (m, 1H, H-5' or H-5''), 4.00 (dd, 1H, $J = 12.4$ Hz, H-6'b or H-6''b), 4.05 (t, 1H, $J = 10.4$ Hz, H-4'), 4.16-4.21 (m, 2H, H-6'a,b or H-6''a,b), 4.39 (dd, 1H, $J = 2.0$ and 12.2 Hz, H-6'a or H-6''a), 4.83 (t, 1H, $J = 10.5$ Hz, H-2''), 4.89 (d, 1H, $J = 9.8$ Hz, H-1'), 5.00 (t, 1H, $J = 9.8$ Hz, H-2'), 5.05 (t, 1H, $J = 9.4$ Hz, H-4''), 5.32 (t, 1H, $J = 9.6$ Hz, H-3''), 5.33 (t, 1H, $J = 7.9$ Hz, H-3'), 5.40 (d, 1H, $J = 3.9$ Hz, H-1''), 6.72 (m, 2H, Ar-H-5, H-6), 6.81 (d, 1H, $J = 1.9$ Hz, ArH-3).

1.5.44 Synthesis of compound 50



To a solution of compound **49** (756 mg, 1 mmol) in 10 mL of CH_3CN , was added a solution of CAN (1.64 g, 3 mmol) in H_2O (10 mL) at room temperature. The reaction mixture was stirred for 30 min, then extracted with CH_2Cl_2 (3×20mL). The combined organic layers were washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **50**(660 mg, 91%). TLC: $R_f = 0.55$ (Pet:EtOAc=1:1); mp: 154-156 °C; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 1.81, 1.93, 1.94, 1.97, 2.00, 2.05, 2.08 (7s, 21H, 7×OAc), 3.70 (m, 1H, H-5' or H-5''), 3.91 (m, 1H, H-5' or H-5''), 3.95 (t, 1H, $J = 9.5$ Hz, H-6'b or H-6''b), 4.01 (t, 1H, $J = 10.4$ Hz, H-4'), 4.10-4.21 (m, 2H, H-6'a,b or H-6''a,b), 4.45 (dd, 1H, $J = 2.0$ and 12.2 Hz, H-6'a or H-6''a), 4.60 (t, 1H, $J = 9.3$ Hz, H-2''), 4.80 (d, 1H, $J = 9.8$ Hz, H-1'), 4.81 (t, 1H, $J = 9.8$ Hz, H-2'), 5.05 (t, 1H, $J = 10.0$ Hz, H-4''), 5.32 (t, 1H, $J = 9.6$ Hz, H-3''), 5.34 (t, 1H, $J = 7.3$ Hz, H-3'), 5.38 (d, 1H, $J = 4.0$ Hz, H-1''), 6.68 (m, 2H, Ar-H-5, H-6), 6.72 (d, 1H, ArH-3).

1.5.45 Synthesis of compound 51



To a solution of compound **50** (726 mg, 1 mmol) in 15 mL of CHCl_3 was added $\text{Na}_2\text{S}_2\text{O}_4$ (1.04 g, 6 mmol) in H_2O (10 mL) at room temperature. The reaction mixture was stirred for 30 min, then extracted with CHCl_3 (3×20mL). The combined organic layers were washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=2:1) to afford compound **51** (699 mg, 96 %). TLC: R_f = 0.23 (Pet:EtOAc=1:1); ^1H NMR (500 MHz, CDCl_3): δ 1.84, 2.01, 2.02, 2.04, 2.08, 2.11, 2.15 (7s, 21H, 7×OAc), 3.80 (m, 1H, H-5' or H-5''), 3.97 (m, 1H, H-5' or H-5''), 4.08 (m, 1H, H-6'b or H-6''b), 4.09 (s, 1H, Ar-OH), 4.15 (t, 1H, J = 9.3 Hz, H-4'), 4.26 (dd, 1H, J = 3.3 and 12.6 Hz, H-6'a or H-6''a), 4.31 (dd, 1H, J = 3.4 and 12.3 Hz, H-6'b or H-6''b), 4.49 (d, 1H, J = 12.3 Hz, H-6'a or H-6''a), 4.62 (d, 1H, J = 9.9 Hz, H-1'), 4.89 (dd, 1H, J = 3.9 and 9.5 Hz, H-2''), 5.11 (m, 2H, H-4'', H-2'), 5.40 (m, 2H, H-3', H-3''), 5.47 (d, 1H, J = 3.9Hz, H-1''), 6.55 (d, 1H, J = 2.7Hz, ArH-3), 6.63 (s, 1H, Ar-OH), 6.68 (dd, 1H, J = 2.7 and 8.7 Hz, ArH-4), 6.72 (d, 1H, J = 8.7Hz, ArH-6).

1.5.46 The experimental procedure for tyrosinase test

1) The aim of research

To test the inhibition of samples for tyrosinase.

2) Equipment

ELIASA of American Thermo, CO_2 Incubators

3) Agents and materials

Tyrosinase, L-DOPA (from Sigma), pancreatin, RPMI 1640 Cary-Blair (from Gibco), LDH

4) Cell strain

B16 melanocyte of human being, from Chinese Academy of Science (Shanghai)

5) Procedure

Selected the same generation of cell and digest them with pancreatin, get the solid via centrifugal machine. The filtered cake was added into RPMI 1640 and added different concentration of samples. In 37 °C, 5% CO_2 , after 36h, the solution was added 0.1% L-DOPA 10 mL and detected its absorptivity in 475 nm.

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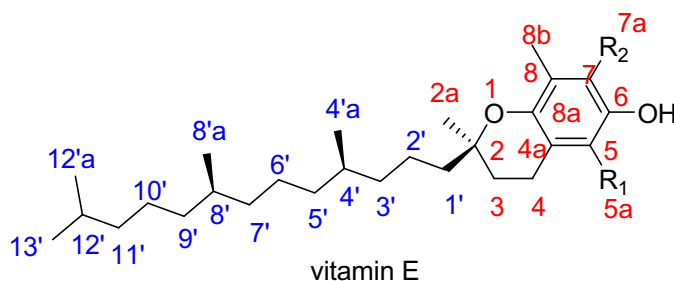
Chapter 2 Synthesis of Aryl C-Glycoside Derivatives of Vitamin E

2.1 Introduction

Research over the past decades has led to many new insights into molecular details of vitamin E action but also to controversies about its usefulness as a dietary supplement. In human physiology, α -tocopherol and its isomers may be involved in the progression of low-density lipoprotein (LDL) oxidation and atherosclerosis, not only through their antioxidant or pro-oxidant properties but also through their ability to regulate gene expression and functional activities of proteins that are critically involved in atherogenesis¹.

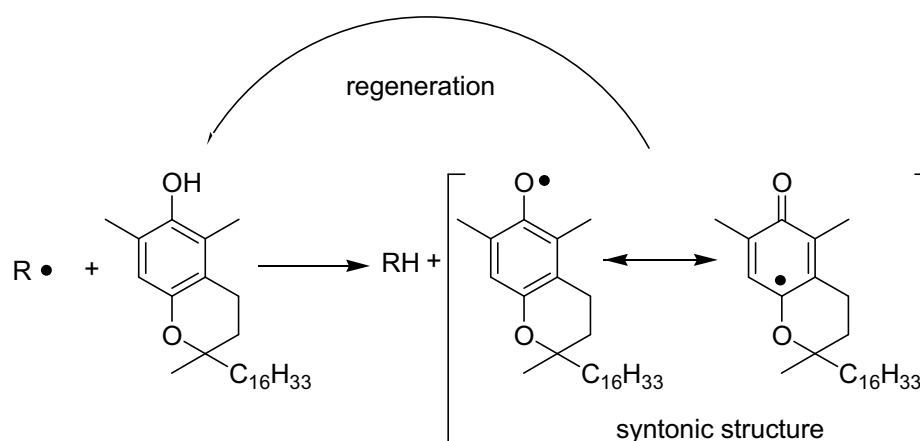
Vitamin E is a kind of outstanding nature antioxidant reagent². Indeed, it is now confidently accepted that R-tocopherol is the most important lipid soluble antioxidant in plasma.³

The term vitamin E is used for a family of eight molecules of related structure. The four tocopherols consist of a chromanol ring with different substitution pattern of methyl groups at positions 5, 7, and 8 of the head group (α -, β -, δ -, and γ -) and a 16-carbon saturated phytanyl rest as a side chain. Tocopherols have three chiral centers at carbons 2, 4', and 8', and the naturally occurring isomers have the R-configuration at all three positions. The tocotrienols have the same substitution pattern on the chromanol ring but an unsaturated C16 isoprenoid side chain with double bonds in the positions 3', 7', and 11'. All of these molecules possess antioxidant activity, although α -tocopherol is chemically and biologically the most active. The other naturally occurring forms of vitamin E (β -, γ -, and δ -tocopherols and the tocotrienols) do not contribute toward meeting the vitamin E requirement because (although absorbed) they are not converted to α -tocopherol by humans, and they are recognized poorly by the α -tocopherol transfer protein in the liver.

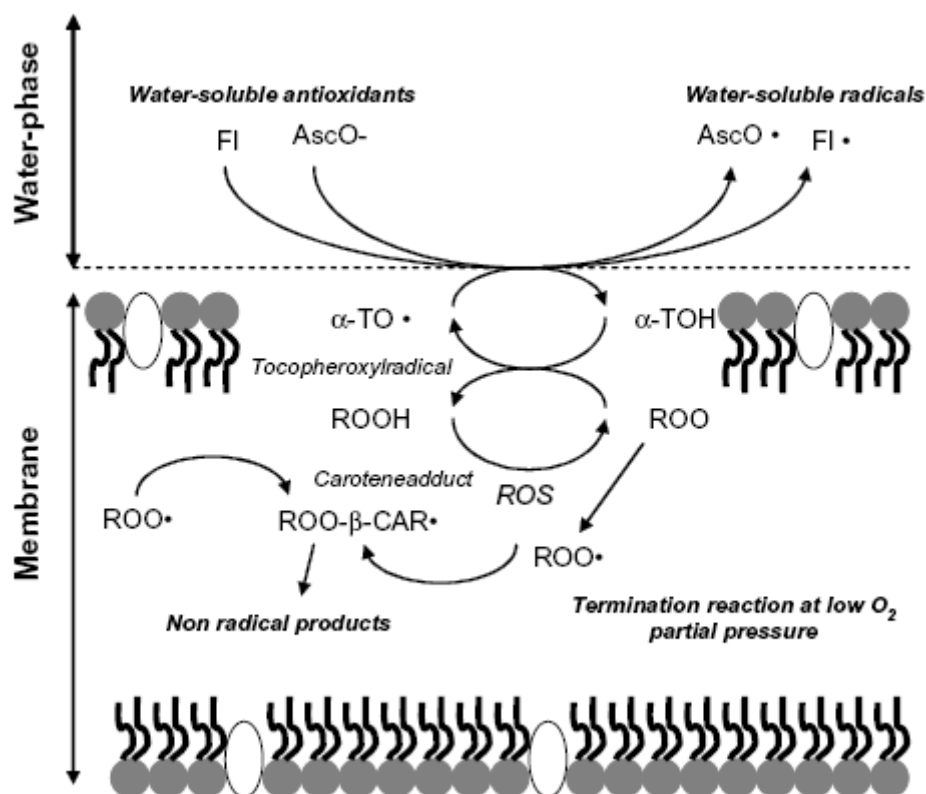


Tocopherol/ tocotrienol	R ₁	R ₂	antioxidation (%)
α	CH ₃	CH ₃	100
β	CH ₃	H	71
γ	H	CH ₃	68
δ	H	H	28

The antioxidant mechanism of vitamin E is to capture free radical and then stop chain reaction. As we know, the OH group is the most important functional group in vitamin E.

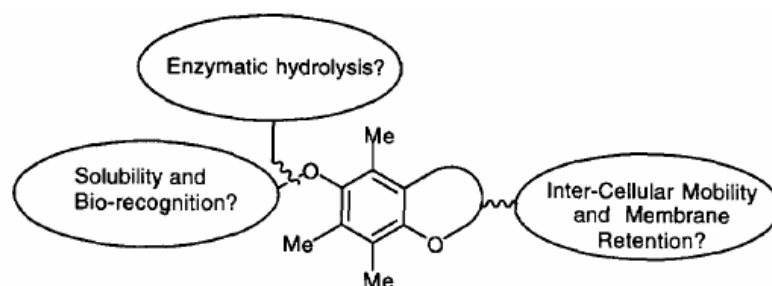


In certain conditions, the syntonic structure of vitamin E and free radical can be reduced by vitamin C to its original structure. In fact, there is a cycle in vitamin E, vitamin C and flavone, it makes the antioxidant system work smoothly. The cycle is as follows:

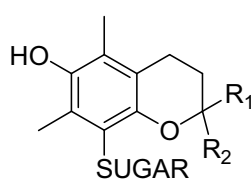


α -tocopherol (α -TOH), ascorbate (AscO⁻) and flavonoid (Fl) during lipid oxidation (ROO[•]) through reactive oxygen species (ROS) and action of β -carotene (β -CAR) in membrane systems.⁴

In order to improve the antioxidant of vitamin E, P. Arya and G. W. Burton thought several very important questions about the vitamin E structure.⁵

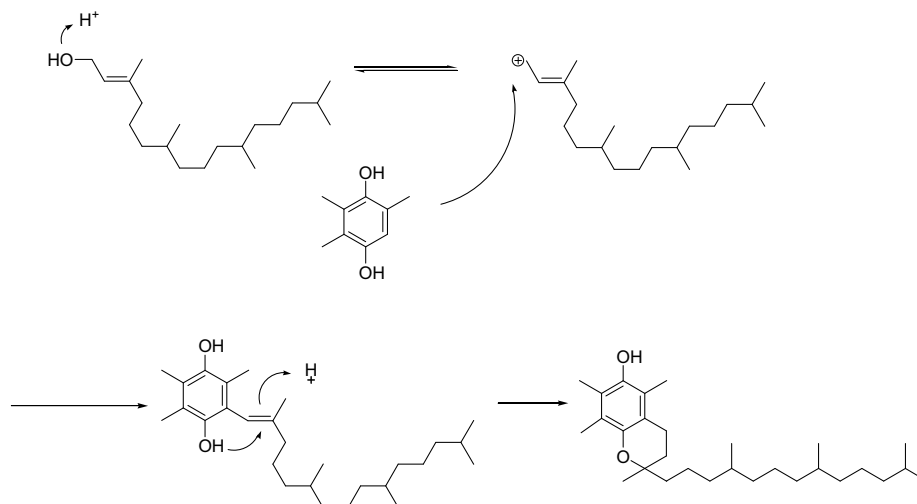


So we designed a series of new C-glycoside analogues of vitamin E, the general structure is as followed:



2.2 Results and discussion

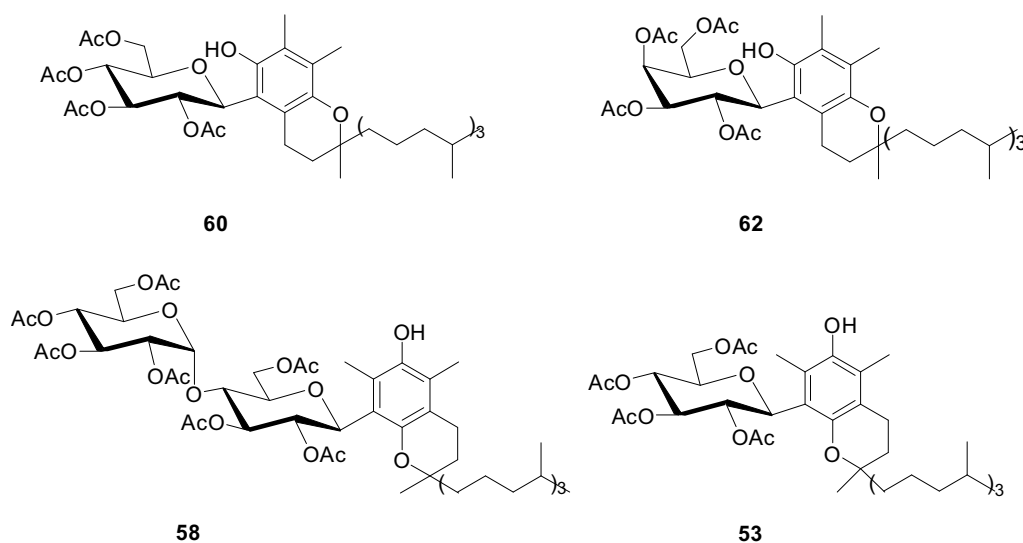
We used phytol and hydroquinone as materials, via Friedel-Craft reaction to synthesize analogues of vitamin E. The mechanism is as followed:



Most common catalysts in this reaction are ZnCl₂, SnCl₄, BF₃.Et₂O, P₂O₅, HCOOH, CH₃COOH, and Ac₂O. We choose ZnCl₂ because it is solid and easy to remove.

Normally, the reaction yield is high at high temperature, so the reaction solution was usually stirred several minutes at 100~200°C. But sugar is unstable at high temperature, so we have chosen CHCl₃ as solvent. The solution had to be stirred for more than 24 h, and the yield is often less than 60%.

In our work, a series of C-glycoside analogues of vitamin E were synthesized, with the structure as followed:



There are at least 3 asymmetric carbon atoms on the aglycon (C₂, C₄, C₈), so there are 8

stereo isomers. It's meaning that every product we obtained is a mixture of several stereoisomers.

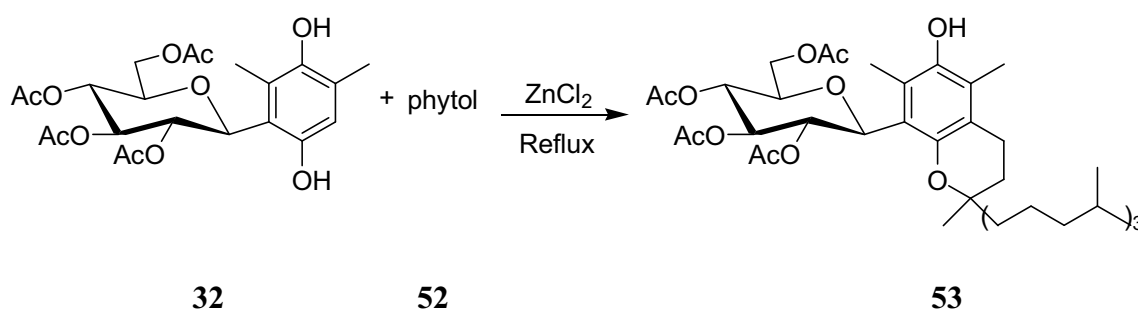
2.3 Conclusion

In this part of work, we tried to modified the structure of vitamin E to improve its antioxidant activity. Based on our previous work, 12 C-glycoside analogues of vitamin E were synthesized, 6 of them are new compounds.

Synthesis of oligo C-glycoside analogues of vitamin E, such as maltose vitamin E analogue, is a new filed of research. Their antioxidant activity has not been confirmed, but the work is valuable for further research of analogue of vitamin E.

2.4 Experimental Section

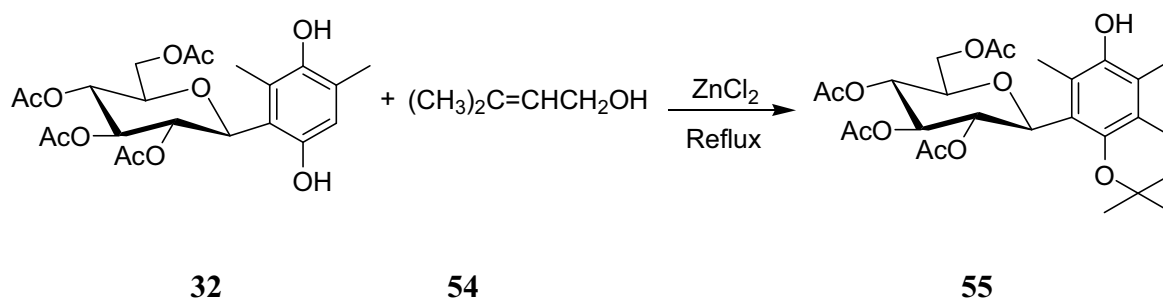
2.4.1 Synthesis of compound 53



To a solution of compound **32** (270 mg, 0.58 mmol) in 5 mL of CHCl_3 , compound **52** (phytol) (0.2 mL, 0.56 mmol) and ZnCl_2 (453.7 mg, 3.34 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq NaHCO_3 and brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **53** (272 mg, 65.6 %). TLC: R_f = 0.26 (Pet:EtOAc=3:1); $[\alpha]_D^{25} = +4.66$ (c 0.88, CH_2Cl_2); $^1\text{H NMR}$ (500 MHz, $\text{DMSO}-d_6$, 120°C): δ 0.87-0.93 (m, 12H, Me13'', 4''a, 8''a, 12''a), 1.12-1.61 (m, 24H, H-1''-12'' and Me2a), 1.71 (2s, 3H, acetyl at C2'), 1.74 (m, 2H, H-3a, H-3b), 1.94, 2.00, 2.02, 2.08, 2.27 (5s, 15H, 2 \times ArCH₃, 3 \times OAc), 2.57 (m, 2H, H-4a, H-4b), 3.86 (m, 1H, H-5'), 4.11 (dd, 1H, J = 4.5 and 12.1 Hz, H-6'b), 4.16 (dd, 1H, J = 3.2 and 12.1 Hz, H-6'a), 5.04-5.10 (m, 1H, H-4'), 5.11 (br signal, 1H, H-1'), 5.23 (2dd, 1H, J = 9.5 and 9.1 Hz, H-3'), 5.64 (br signal, 1H, H-2'), 7.26 (s, 1H, Ar-OH); $^{13}\text{C NMR}$ (125 MHz, $\text{DMSO}-d_6$, 120°C): δ 12.6, 13.3, 20.3, 20.3, 20.3, 20.3, 20.4, 20.4, 20.7, 21.0, 21.0, 21.1, 21.5, 23.1, 23.1, 23.7, 24.0, 24.7, 24.9, 28.2, 31.9, 33.1, 37.6, 37.7, 37.8, 38.2, 39.8, 41.5, 63.4, 63.5, 70.1, 70.2, 71.6, 75.6, 75.7, 76.0, 76.3, 118.4, 118.5, 120.2, 120.4, 125.1, 125.2, 125.3, 125.3, 146.5, 169.1, 169.8, 169.9, 170.1, 170.15, 170.4; HRFABMS: Calcd for

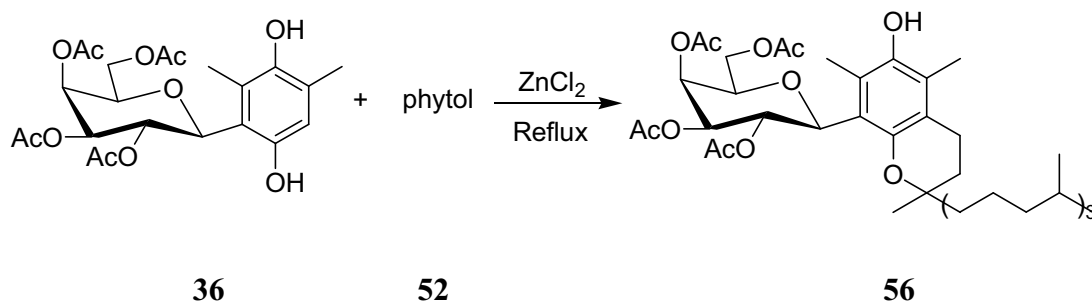
$[C_{42}H_{67}O_{11} + H]^+$: 747.4683. found : 747.46790.

2.4.2 Synthesis of compound 55



To a solution of compound **32** (560 mg, 1.2 mmol) in 5 mL of $CHCl_3$, compound **54** (0.123 mL, 1.19 mmol) and $ZnCl_2$ (979 mg, 7.2 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, evaporated, purified with column chromatography (Pet:EtOAc=3:1) to afford compound **55** (384 mg, 60%). TLC: $R_f = 0.21$ (Pet:EtOAc=2:1); $[\alpha]_D^{25} = -1.1$ (c 0.8, CH_2Cl_2); 1H NMR (500 MHz, $DMSO-d_6$, $120^\circ C$): δ 1.29 (2s, 6H, Me2a, Me2b), 1.33, 1.71, 1.95, 2.00 (4s, 12H, 4 \times OAc), 1.77 (t, 2H, $J = 6.9$ Hz, H-3a, H-3b), 2.03, 2.08 (2s, 6H, Me5a, Me7a), 2.27, 2.58 (t, 2H, $J = 6.9$ Hz, H-4ab), 3.91 (dt, 1H, $J = 9.8$ and 3.8 Hz, H-5'), 4.14 (d, 2H, $J = 3.5$ Hz, H-6'a, H-6'b), 5.07 (t, 1H, $J = 9.5$ and 9.8 Hz, H-4'), 5.11 (br, 1H, H-1'), 5.24 (t, 1H, $J = 9.1$ Hz, H-3'), 5.65 (br triplet, 1H, H-2'), 7.00 (s, 1H, Ar-OH); ^{13}C NMR (125 MHz, $DMSO-d_6$, $120^\circ C$): δ 12.6, 13.3, 20.8, 21.0, 21.0, 21.4, 21.4, 27.0, 27.6, 33.6, 63.4, 70.0, 71.7, 73.5, 74.5, 76.0, 76.0, 118.3, 120.4, 125.1, 125.3, 146.5, 146.8, 169.2, 169.9, 170.2, 170.5; Anal. Calcd for $C_{27}H_{36}O_{11}$: C, 60.44; H, 6.76; O, 32.80. found: C, 60.92; H, 7.05; O, 31.23.

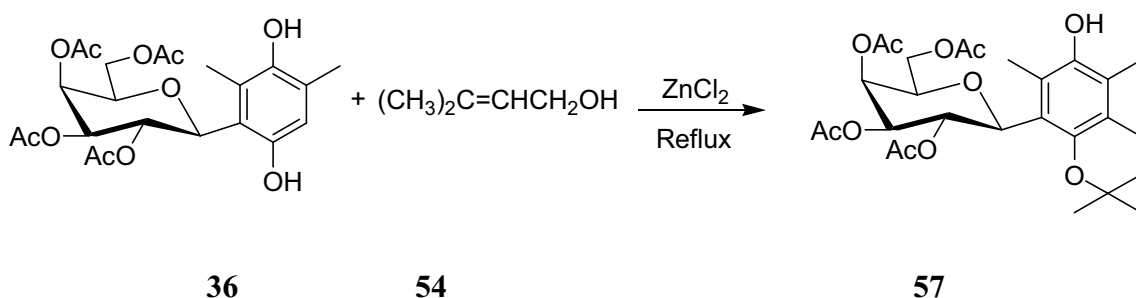
2.4.3 Synthesis of compound 56



To a solution of compound **36** (270 mg, 0.58 mmol) in 5 mL of $CHCl_3$, compound **52** (phytol) (0.2 mL, 0.56 mmol) and $ZnCl_2$ (453.7 mg, 3.34 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq $NaHCO_3$ and brine, dried over $MgSO_4$, evaporated, and purified with column chromatography

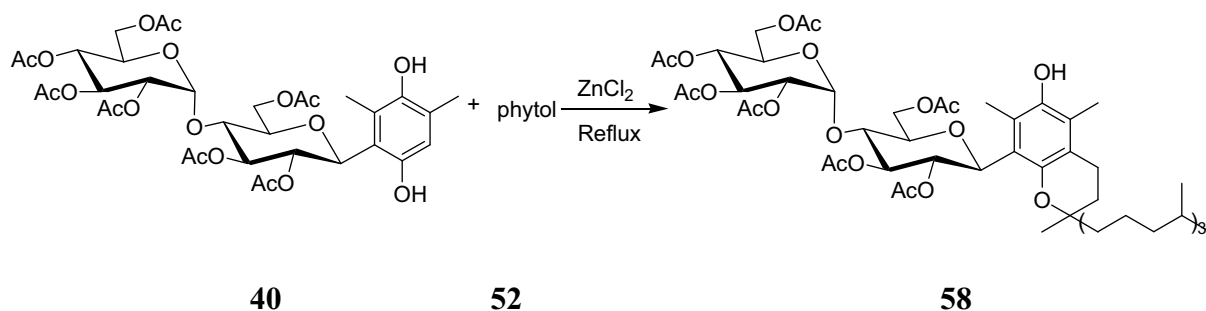
(Pet:EtOAc=3:1) to afford compound **56** (272 mg, 65.6%).

2.4.4 Synthesis of compound **57**



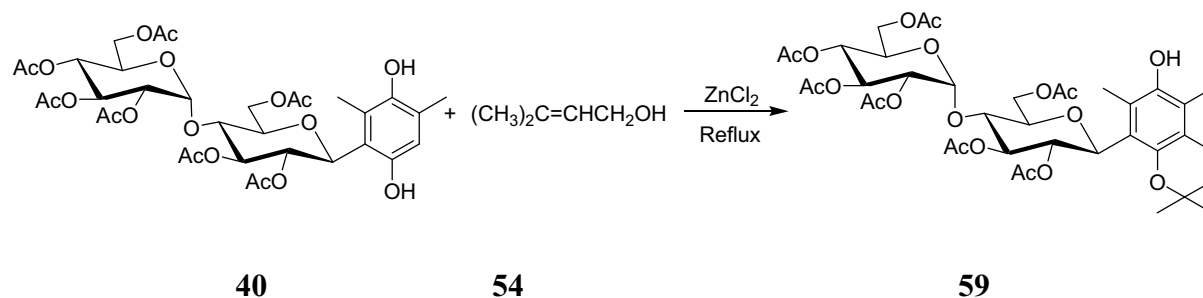
To a solution of compound **36** (560 mg, 1.2 mmol) in 5 mL of CHCl_3 , compound **54** (0.123 mL, 1.19 mmol) and ZnCl_2 (979 mg, 7.2 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq NaHCO_3 and brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **57** (380 mg, 59%).

2.4.5 Synthesis of compound **58**



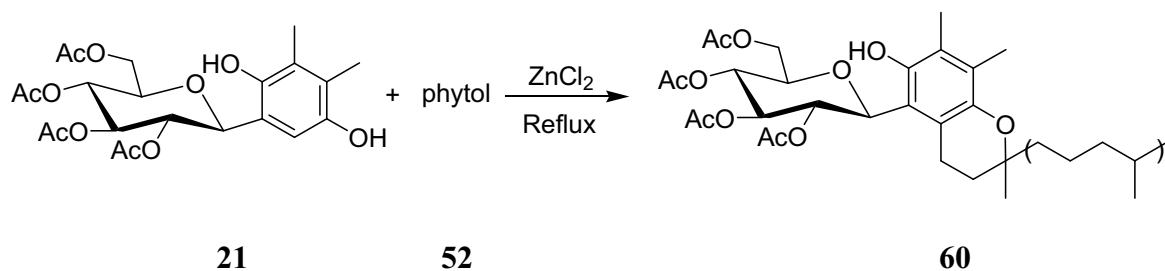
To a solution of compound **40** (756 mg, 1 mmol) in 10 mL of CHCl_3 , compound **52** (phytol) (0.36 mL, 1 mmol) and ZnCl_2 (803 mg, 6 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq NaHCO_3 and brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=2:1) to afford compound **58** (589 mg, 57 %). TLC: $R_f = 0.49$ (Pet:EtOAc=1:1); ^1H NMR (500 MHz, CDCl_3): δ 0.84-0.91 (m, 12H, $4\times\text{CH}_3$), 1.09-1.38 (m, 19H, $3\times\text{CH}$, $8\times\text{CH}_2$), 1.53-2.32 (m, 35H, $2\times\text{CH}_2$, $3\times\text{CH}_3$, $7\times\text{OAc}$), 2.56 (m, 2H, CH_2), 3.78 (m, 1H, H-5' or H-5''), 4.00 (m, 1H, H-5' or H-5''), 4.07-4.28 (m, 6H, H-2', H-4', H-6'a,b, H-6''a,b), 4.53 (bd, 1H, $J = 11.6$ Hz, H-1'), 4.90 (dd, 1H, $J = 10.5$ and 3.6 Hz, H-2''), 5.10 (t, 1H, $J = 9.6$ Hz, H-4''), 5.38 (m, 2H, H-3', H-3''), 5.49 (d, 1H, $J = 3.6$ Hz, H-1''), 7.27 (s, 1H, Ar-OH); HRESIMS: calcd for $[\text{C}_{54}\text{H}_{82}\text{O}_{19}+\text{Na}]^+$: 1057.5348 found 1057.5315.

2.4.6 Synthesis of compound 59



To a solution of compound **40** (756 mg, 1 mmol) in 10 mL of CHCl_3 , compound **54** (0.11 mL, 1 mmol) and ZnCl_2 (803 mg, 6 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq NaHCO_3 and brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=1:1) to afford compound **59** (590.3 mg, 71.6 %), TLC: $R_f = 0.36$ (Pet:EtOAc=1:1); HRESIMS : calcd for $[\text{C}_{39}\text{H}_{52}\text{O}_{19}+\text{Na}]^+$: 847.3001 found 847.3028.

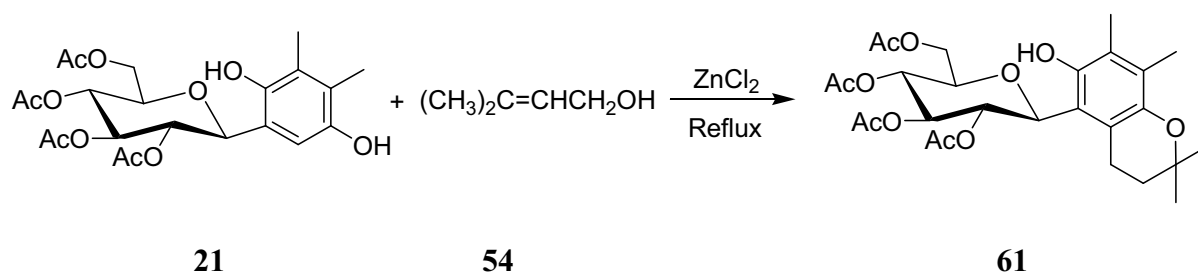
2.4.7 Synthesis of compound 60



To a solution of compound **21** (270 mg, 0.58 mmol) in 5 mL of CHCl_3 , compound **52** (phytol) (0.2 mL, 0.56 mmol) and ZnCl_2 (453.7 mg, 3.34 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered; the filtration was washed with sat. aq NaHCO_3 and brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=2:1), afford compound **60** (272 mg, 65.6 %). TLC: $R_f = 0.20$ (Pet : EtOAc=3:1); mp: 144-146 °C (CH_2Cl_2 /Pet); $[\alpha]_D^{22} = -0.227$ (c 0.88, CH_2Cl_2); ^1H NMR (200 MHz, CDCl_3): δ 0.86-0.89 (m, 12H, Me13'', 4'a, 8''a, 12''a), 1.01-1.60 (m, 24H, H-1''-12'' and H-2a), 1.75 (2H, overlapped, H-3a,b), 1.82, 2.01, 2.06, 2.08, 2.14, 2.14 (6s, 18H, 6 \times CH₃), 2.70 (t, 2H, $J = 6.5$ Hz, H-4a,b), 3.89 (m, 1H, H-5'), 4.15 (d, 1H, $J = 12.4$ Hz, H-6b'), 4.33 (dd, 1H, $J = 2.9$ and 12.4 Hz, H-6a'), 4.86 (d, 1H, $J = 9.9$ Hz, H-1'), 5.30-5.35 (m, 2H, H-3', H-4'), 5.58 (dd, 1H, $J = 7.9$ and 9.9 Hz, H-2'), 6.90, 6.93 (2s, 1H, Ar-OH, exchangeable with D_2O); ^{13}C NMR (50 MHz, CDCl_3): δ 11.9, 12.2, 19.7, 19.8, 20.4, 20.6, 20.6, 20.6, 20.6, 20.7, 20.7, 21.0, 22.6, 22.8, 23.5, 24.5, 24.8, 28.0, 31.7, 32.8, 37.3, 37.4, 37.4, 39.4, 39.4, 61.4, 67.8, 70.3, 74.2, 74.4, 76.2, 76.2, 114.9, 115.6, 124.9, 127.6, 144.9, 146.8, 168.4, 169.3, 170.5, 170.7;; Anal. Calcd

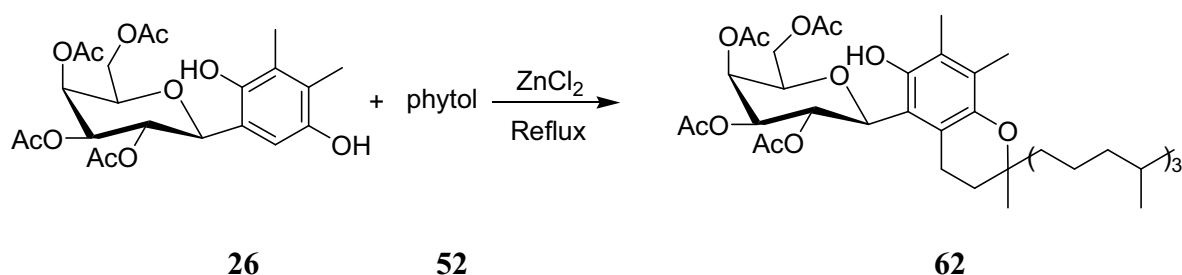
for C₄₂H₆₆O₁₁: C, 67.53; H, 8.91; O, 23.56. found: C, 67.56; H, 8.83; O, 22.67.

2.4.8 Synthesis of compound 61



To a solution of compound **21** (560 mg, 1.2 mmol) in 5 mL of CHCl₃, compound **54** (0.123 mL, 1.19 mmol) and ZnCl₂ (979 mg, 7.2 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq NaHCO₃ and brine, dried over MgSO₄, evaporated to give crude product, purified with column chromatography (Pet:EtOAc=2:1) to afford compound **61** (384 mg, 60%). TLC: *R_f*= 0.23 (Pet :EtOAc=2 :1); mp: 205-206.5 °C (CH₂Cl₂/Pet); [*α*]_D²² = -4.4 (*c* 0.9, CH₂Cl₂); ¹H NMR (200 MHz, CDCl₃): δ 1.23, 1.29 (2s, 6H, Me2a, Me2b), 1.75 (2H, overlapped, H-3a,b), 1.81, 2.01, 2.06, 2.07, 2.14, 2.14 (6s, 18H, 4×OAc, Me7a, Me8b), 2.72 (t, 2H, *J* = 6.7 Hz, H-4a,b), 3.86 (m, 1H, H-5'), 4.14 (dd, 1H, *J* = 2.0 and 12.5 Hz, H-6'b), 4.33 (dd, 1H, *J* = 3.14 and 12.5 Hz, H-6'a), 4.86 (d, 1H, *J* = 10.0 Hz, H-1'), 5.31-5.35 (m, 2H, H-3', H-4'), 5.58 (dd, 1H, *J* = 9.3 and 10.0 Hz, H-2'), 6.93 (s, 1H, Ar-OH); ¹³C NMR (50 MHz, CDCl₃): δ 11.9, 12.2, 20.4, 20.6, 20.7, 20.7, 26.3, 26.9, 20.8, 33.1, 61.4, 72.4, 67.7, 70.3, 74.2, 76.2, 76.2, 114.9, 115.4, 124.9, 127.6, 145.0, 146.9, 168.4, 169.3, 170.5, 170.7; Anal. Calcd for C₂₇H₃₆O₁₁: C, 60.44; H, 6.76; O, 32.80. found: C, 59.98; H, 6.74; O, 33.75.

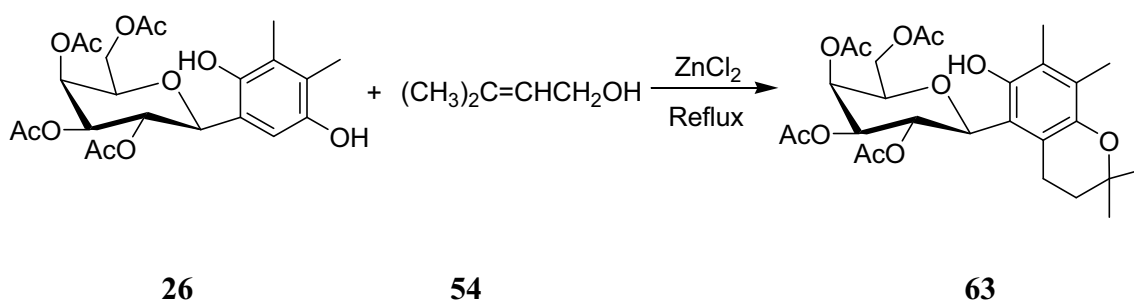
2.4.9 Synthesis of compound 62



To a solution of compound **26** (270 mg, 0.58 mmol) in 5 mL of CHCl₃, compound **52** (phytol) (0.2 mL, 0.56 mmol) and ZnCl₂ (453.7 mg, 3.34 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq NaHCO₃ and brine, dried over MgSO₄, evaporated, and purified with column chromatography (Pet:EtOAc=1:1) to afford compound **62** (291 mg, 69 %). TLC: *R_f* = 0.22(Pet:EtOAc=3:1);

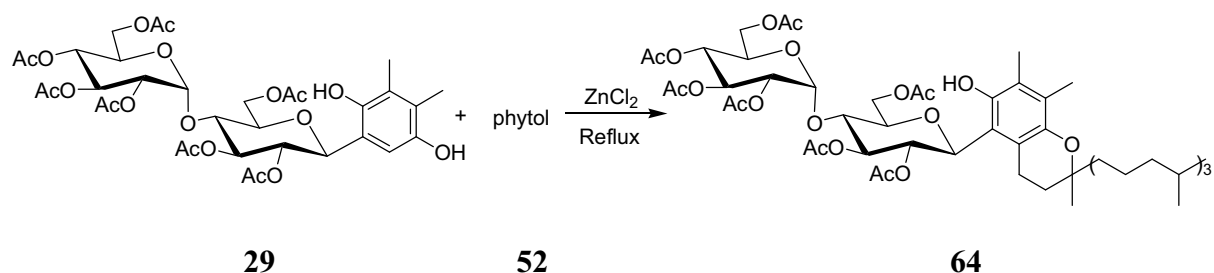
mp: 105.5-107 °C (CH₂Cl₂/Pet); $[\alpha]_D^{22} = +13.2$ (*c* 0.92, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 0.83-0.87 (m, 12H, Me13'', 4''a, 8''a, 12''a), 1.07-1.57 (m, 24H, H-1''-12'' and H-2a), 1.75 (m, 2H, H-3a,b), 1.83, 1.99, 2.05, 2.08, 2.15, 2.26 (6s, 18H, 2×ArCH₃ and 4×OAc), 2.69 (m, 2H, H-4a,b), 4.08 (m, 1H, H-5'), 4.16 (m, 2H, H-6'a, H-6'b), 4.81 (d, 1H, *J* = 10.0 Hz, H-1'), 5.15 (dd, 1H, *J* = 10.0 and 3.0 Hz, H-3'), 5.54 (d, 1H, *J* = 3.0 Hz, H-4'), 5.80 (dt, 1H, *J* = 10.0 and 2.4 Hz, H-2'), 6.93, 6.96 (2s, 1H, Ar-OH, exchangeable with D₂O); ¹³C NMR (CDCl₃, 75 MHz): δ 12.2, 12.5, 20.0, 20.1, 20.1, 20.8, 20.8, 21.0, 21.1, 21.2, 21.4, 23.0, 23.1, 23.9, 24.1, 24.8, 25.2, 28.4, 32.0, 33.2, 37.7, 37.8, 37.9, 39.8, 40.4, 61.9, 68.1, 68.3, 72.7, 74.7, 75.3, 76.7, 115.6, 115.8, 124.9, 127.9, 145.2, 147.4, 168.7, 170.4, 170.7, 170.8; Anal. Calcd for C₄₂H₆₆O₁₁ (746.92): C, 67.53; H, 8.91; O, 23.56. found: C, 67.71; H, 8.91; O, 23.41.

2.4.10 Synthesis of compound 63



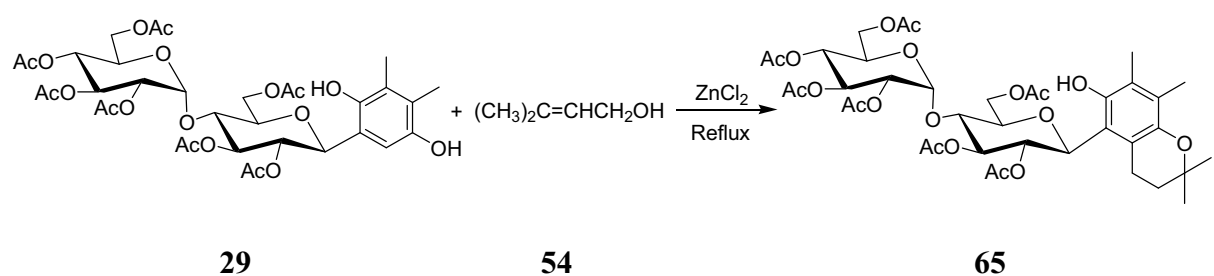
To a solution of compound **26** (560 mg, 1.2 mmol) in 5 mL of CHCl₃, compound **54** (0.123 mL, 1.19 mmol) and ZnCl₂ (980 mg, 7.2 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq NaHCO₃ and brine, dried over MgSO₄, evaporated, and purified with column chromatography (Pet:EtOAc=2:1) to afford compound **63** (399 mg, 62%). TLC: *R_f* = 0.22 (Pet:EtOAc=2:1), mp: 174-176 °C (CH₂Cl₂/PET); $[\alpha]_D^{25} = +7.30$ (*c* 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 1.23, 1.29 (2s, 6H, Me2a,2b), 1.76 (m, 2H, H-3a,b), 1.83, 1.99, 2.05, 2.26 (4s, 12H, 4×OAc), 2.08, 2.15 (2s, 6H, 2×ArCH₃), 2.71 (m, 2H, H-4a,b), 4.07 (m, 1H, H-5'), 4.16 (m, 2H, H-6'a, H-6'b), 4.82 (d, 1H, *J* = 10.0 Hz, H-1'), 5.15 (dd, 1H, *J* = 10.0 and 3.0 Hz, H-3'), 5.54 (d, 1H, *J* = 3.0 Hz, H-4'), 5.80 (t, 1H, *J* = 10.0 Hz, H-2'), 6.96 (s, 1H, Ar-OH, exchangeable with D₂O); ¹³C NMR (75 MHz, CDCl₃): δ 12.0, 12.3, 20.7, 20.8, 20.8, 20.9, 21.0, 26.5, 27.1, 33.3, 61.7, 68.0, 68.2, 72.5, 72.6, 75.2, 76.6, 115.4, 115.4, 124.8, 127.7, 145.1, 147.3, 168.5, 170.2170.5, 170.5; Anal. Calcd for C₂₇H₃₆O₁₁: C, 60.44; H, 6.76; O, 32.80. Found: C, 60.01; H, 6.74; O, 33.24.

2.4.11 Synthesis of compound 64



To a solution of compound **29** (756 mg, 0.58 mmol) in 5 mL of CHCl_3 , compound **52** (phytol) (0.2 mL, 0.56 mmol) and ZnCl_2 (453.7 mg, 3.34 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq NaHCO_3 and brine, dried over MgSO_4 , evaporated to give crude product, purified with column chromatography (Pet:EtOAc=3:1) to afford compound **64** (63.8%). TLC: R_f = 0.42 (Pet:EtOAc=1:1); ^1H NMR (CDCl_3 , 200MHz): δ 0.86-0.89 (m, 12H, Me13'', 4'a, 8''a, 12''a), 1.01-1.60 (m, 24H, H-1''-12'' and H-2a), 1.75 (2H, overlapped, H-3a,b), 1.82, 2.01, 2.06, 2.08, 2.14, 2.14 (6s, 18H, 6 \times CH₃), 2.41 (m, 2H, H-3a,b), 3.86 (m, 1H, H-5' or H-5''), 3.94 (m, 1H, H-5'' or H-5'), 4.01 (dd, 1H, J =2.1 and 12.5Hz, H-6'b or H-6''b), 4.22 (t, 1H, J = 9.2 Hz, H-4'), 4.28 (dd, 1H, J = 3.2 and 12.6Hz, H-6'a or H-6''a), 4.34 (d, 1H, J = 12.0 Hz, H-6'b or H-6''b), 4.46 (d, 1H, J = 12.2 Hz, H-6'a or H-6''a), 4.88 (d, 1H, J = 9.9 Hz, H-1'), 4.89 (dd, 1H, J = 10.7 and 3.9 Hz, H-2''), 5.09 (t, 1H, J = 9.8Hz, H-2'), 5.40 (m, 3H, H-3', H-3'' H-4''), 5.48 (d, 1H, J = 3.9 Hz, H-1''), 6.89, 6.86 (2s, 1H, Ar-OH); HRESIMS: calcd for $[\text{C}_{54}\text{H}_{82}\text{O}_{19}+\text{Na}]^+$:1057.5348 found 1057.5369.

2.4.12 Synthesis of compound 65



To a solution of compound **29** (756 mg, 0.58 mmol) in 5 mL of CHCl_3 , compound **54** (0.11 mL, 1 mmol) and ZnCl_2 (803 mg, 6 mmol) was added under Ar and kept from light, heated to reflux for 24 h. The mixture was filtered, the filtration was washed with sat. aq NaHCO_3 and brine, dried over MgSO_4 , evaporated, and purified with column chromatography (Pet:EtOAc=3:1) to afford compound **65** (612 mg, 74%). TLC: R_f = 0.39 (Pet:EtOAc=2:1); ^1H NMR (200 MHz, CDCl_3): δ 1.15, 1.22 (2s, 6H, Me2a, Me2b), 1.65 (m, 2H, H-3a,b), 1.71, 1.93, 1.94, 1.96, 1.99, 2.00, 2.04, 2.04, 2.11 (9s, 27H, 7 \times OAc, Me7a, Me8b), 2.65 (m, 2H,

H-4a,b), 3.79 (m, 1H, H-5 or H-5'), 3.88 (m, 1H, H-5 or H-5'), 3.95 (dd, 1H, $J = 12.5$ and 2.1 Hz, H-6'b or H-6''b), 4.15 (t, 1H, $J = 9.2$ Hz, H-4'), 4.21 (dd, 1H, $J = 12.5$ and 2.4 Hz, H-6'b or H-6''b), 4.27 (dd, 1H, $J = 12.4$ and 2.7 Hz, H-6'a or H-6''a), 4.39 (dd, 1H, $J = 12.4$ and 2.2 Hz, H-6'a or H-6''a), 4.81 (d, 1H, $J = 9.3$ Hz, H-1'), 4.82 (dd, 1H, $J = 10.4$ and 3.9 Hz, H-2''), 5.02 (t, 1H, $J = 10.4$ Hz, H-2'), 5.32 (m, 3H, H-3', H-3'', H-4''), 5.41 (d, 1H, $J = 3.9$ Hz, H-1''), 6.80 (s, 1H, Ar-OH); HRESIMS: Calcd for $[C_{39}H_{52}O_{19}+Na]^+$: 847.3001 found 847.2994.

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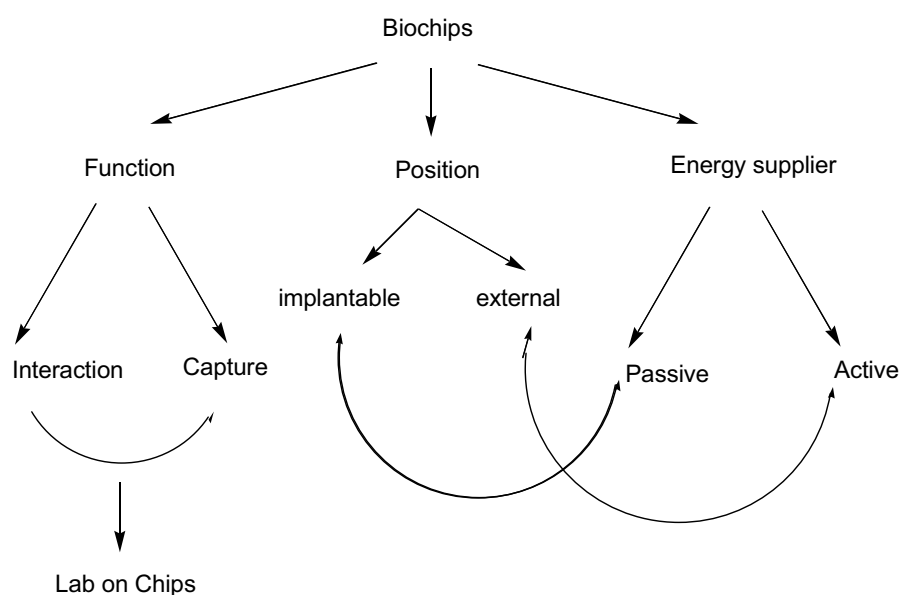
Chapter 3 Synthesis of photolabile sugar molecules as building blocks for carbochips

3.1 Introduction

Biochip, equal bio+chip, bio: stands for any biological entity, such as protein, DNA; chip: a computer chip; so biochip is a mate between biological entity and a computer. It's a marriage between electronics and biology/medicine¹.

Collection of miniaturized test sites of living entities (microarrays) arranged on a solid substrate that permits many tests to be performed at the same time in order to achieve higher throughput, speed, accuracy and smaller size.

Biochips can be classified by its working mechanism and fabrication process. There are many types of biochip, such as gene chip, protein chip, cell chip and tissue chip.



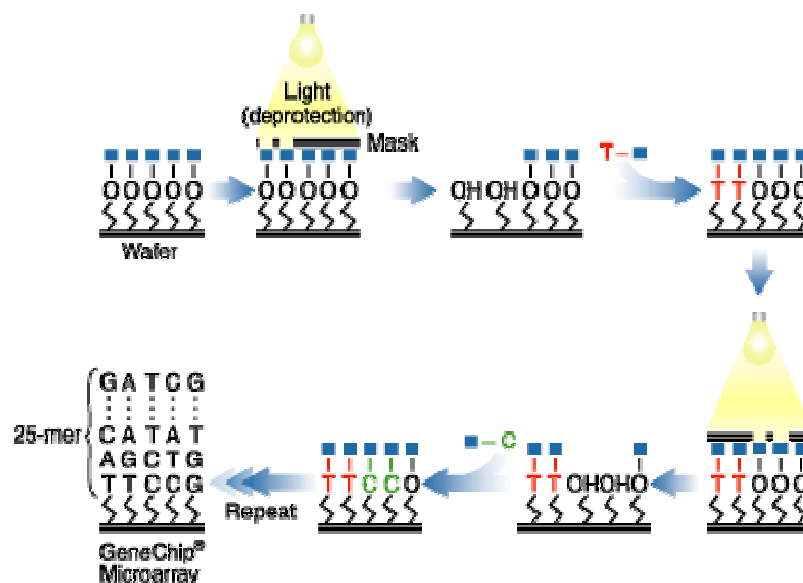
Types of biochips

GeneChip microarrays are a classic Silicon Valley innovation, combining several disciplines to create a new technology and more useful research tool. The integration of semiconductor fabrication techniques, solid phase chemistry, combinatorial chemistry, molecular biology, and sophisticated robotics results in a unique photolithographic manufacturing process that produces GeneChip arrays with millions of probes on a small glass chip.

The photolithographic process begins by coating a 5" x 5" quartz wafer with a light-sensitive chemical compound that prevents coupling between the wafer and the first nucleotide of the DNA probe being created. Lithographic masks are used to either block or transmit light onto specific locations of the wafer surface. The surface is then flooded with a solution containing

either adenine, thymine, cytosine, or guanine, and coupling occurs only in those regions on the glass that have been deprotected through illumination.

The coupled nucleotide also bears a light-sensitive protecting group, so the cycle can be repeated. In this way, the microarray is built as the probes are synthesized through repeated cycles of deprotection and coupling. The process is repeated until the probes reach their full length, usually 25 nucleotides. Commercially available arrays are typically manufactured at a density of over 1.3 million unique features per array. Depending on the demands of the experiment and the number of probes required per array, each quartz wafer can be diced into tens or hundreds of individual arrays.²



The manufacturing process of Genechip

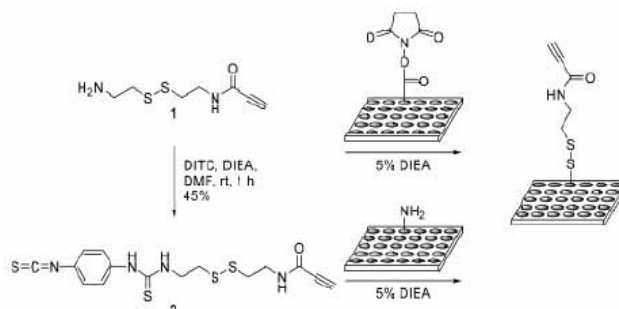
3.1.1 Carbohydrate Microarrays

Glycans in living organisms play a critical role in both normal physiological and detrimental disease processes through their interactions with proteins. Owing to their significance in biological research and biomedical applications, the development of rapid and sensitive methods to elucidate the nature and consequence of glycan-protein interactions has become the target of a number of recent investigations³.

The synthesis of glycoarrays is a challenge for chemists, and more and more chemists have paid attention in this field.

Unlike proteins and nucleic acids, oligosaccharides are difficult to synthesize chemically. This is because some oligosaccharide chains are linear, others are branched. Monosaccharide building blocks are in α or β anomeric configurations and adjacent monosaccharides are linked via different hydroxy groups in their sugar rings. Nevertheless, syntheses of a considerable number of complex oligosaccharides have been achieved.

Usually, carbohydrate microarrays are obtained by immobilization of naturally extracted or synthesized oligo- or polysaccharides on a surface. For example, Chi-Huey Wong reported a new type oligoarray via click chemistry in 2004.⁴



Cleavable linkers can be attached to either NHS- or amine-coated surfaces to give the alkyne-functionalized surface.

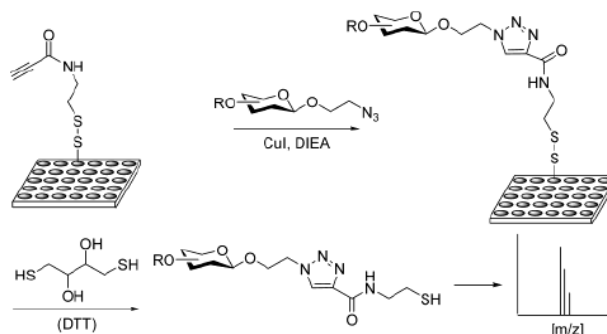
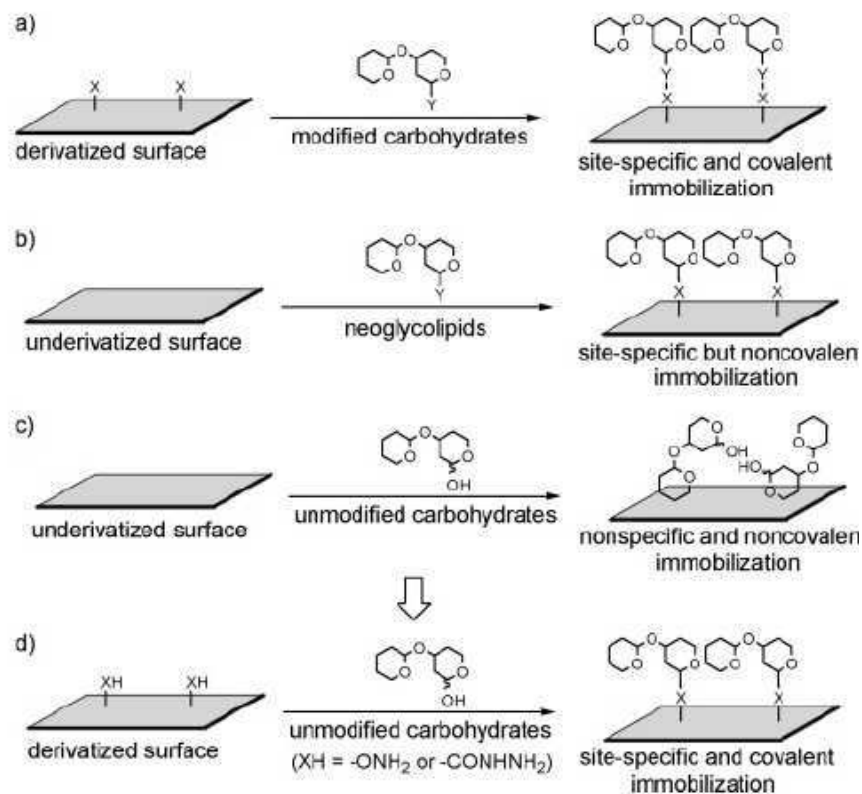


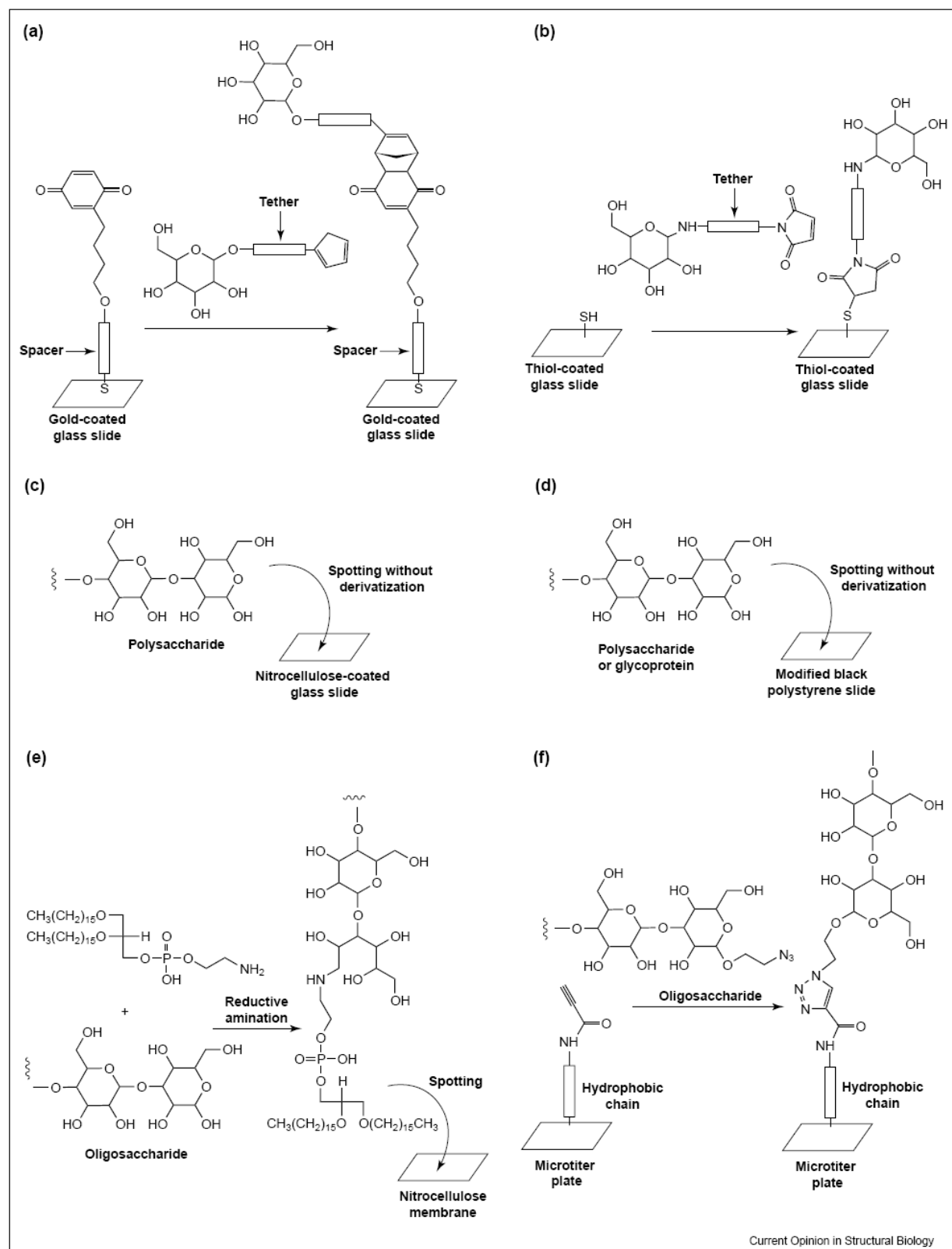
Figure 2. Triazole formation and cleavage by DTT for MS analysis.

General immobilization strategies are shown in the following figure:

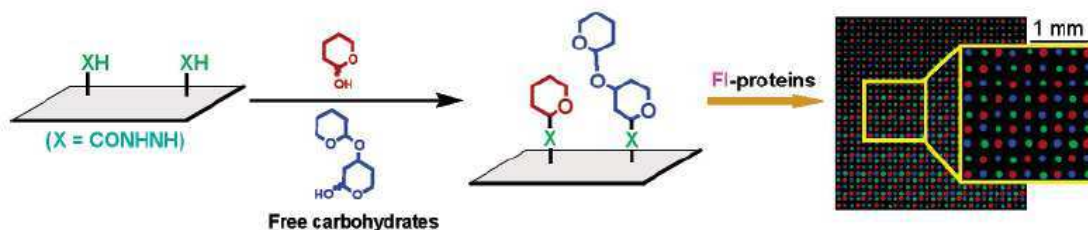


Immobilization strategies for the preparation of carbohydrate microarrays.

Chi-Huey Wong⁵ summarized the recent methods of carbohydrate microarrays preparation as followed:



More recently, Myung-ryul Lee and Injae Shin reported a new method to immobilize the unmodified carbohydrates on Hydrazide-Coated Glass Slides.⁶

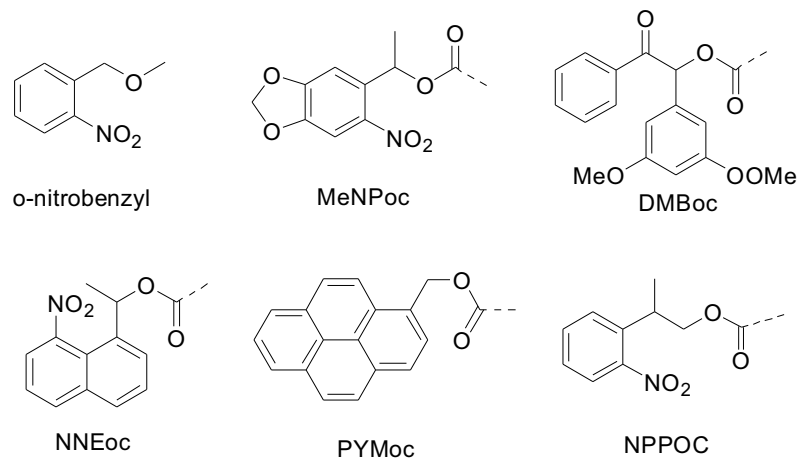


Facile Preparation of Carbohydrate Microarrays by Site-Specific, Covalent Immobilization of Unmodified Carbohydrates on Hydrazide-Coated Glass Slides

However, generation of sugar microarrays through solid-phase oligosaccharides synthesis on chips has never been reported. Usually, solid-phase synthesized oligosaccharides have to be delivered from the solid support, then immobilized on a chip. We then decided to prepare photolabile sugar derivatives so as to study the possibility to generate carbohydrate microarray by the photolithographic process.

3.1.2 Photolabile Protecting Groups

Many photolabile protecting groups have been developed. Mechanism of photo deprotection is related to the substituted group, so it is possible to improve their function by changing the substituted group.^{7,8}



Some photochemically removable protecting groups

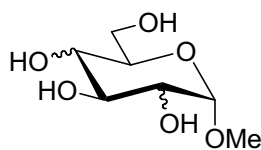
o-Nitrobenzyl group is the most popular photolabile protecting group.⁹⁻¹¹ We decided to prepare various o-nitrobenzyl protected sugar derivatives.

3.1.3 The route of synthesis

3.1.3.1 Sugar

We finally chose glucose, galactose and mannose as the starting materials, considering they are widely existing in nature and they are very cheap. Because the anomeric hydroxyl group is

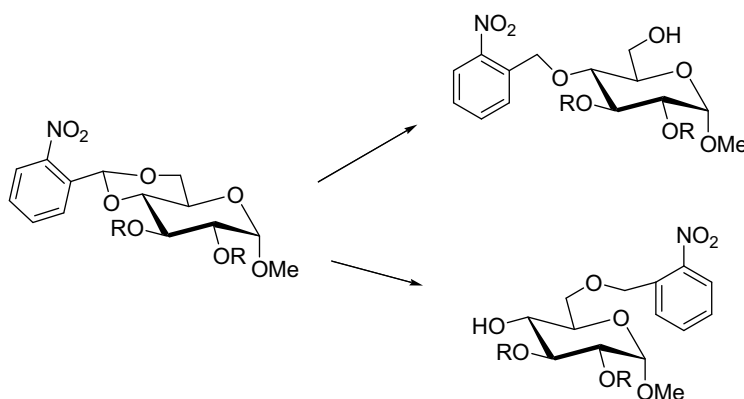
very sensible, so we chose methyl glycosides as starting materials.



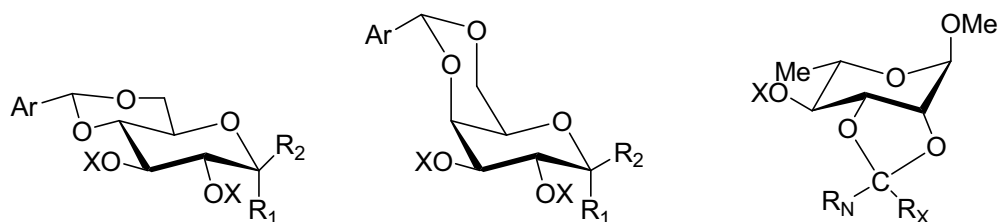
Methyl α -D-glycopyranoside

3.1.3.2 Photolabile group

As photolabile groups, we decided to introduce o-nitrobenzyl group on 4- or 6-position of sugar ring. These compounds can be obtained by regioselective opening of o-nitrobenzylidene ring:



There are many methods to protect vicinal hydroxy groups as benzylidene. Peter M. Collins reported in 1973 the synthesis of various benzylidene-protected sugar derivatives by treating sugars with benzaldehyde in the presence of H_2SO_4 as catalyst:¹²



$R_1 = OMe, R_2 = H, X = H$

$R_1 = OMe, R_2 = H, X = Ac$

$R_1 = OMe, R_2 = H, X = Me$

$R_1 = H, R_2 = OMe, X = H$

$R_1 = H, R_2 = OMe, X = Ac$

$R_1 = OMe, R_2 = H, X = H$

$R_1 = OMe, R_2 = H, X = Ac$

$R_1 = H, R_2 = OMe, X = H$

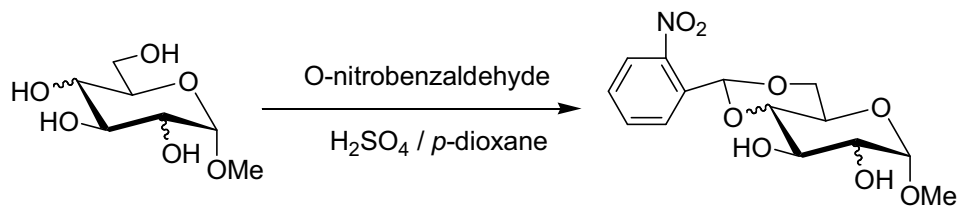
$R_1 = H, R_2 = OMe, X = Ac$

R_X or $R_N = Ar$ or $H, X = H$

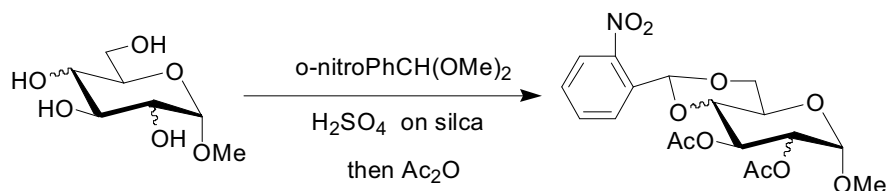
$R_X = Ar, R_N = H, X = Ac$

$R_X = H, R_N = Ar, X = Ac$

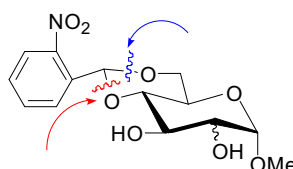
Based on this method, we plan to protect 4,6-hydroxyl groups as o-nitrobenzylidene:



According to the report of Balaram Mukhopadhyay in 2006¹³ who used H_2SO_4 and silica as catalyst in CH_3CN , we have successfully synthesized a series of 4,6-O-o-nitrobenzyl-sugars.



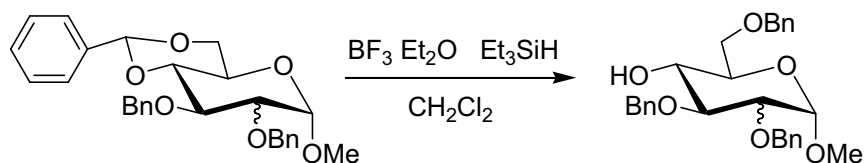
3.1.4 Regioselective Ring Opening



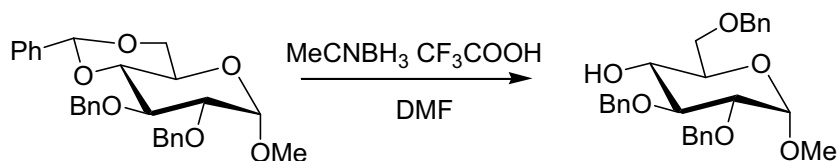
There are many methods about regioselective ring opening of benzylidene acetals:

a. Methods leading to 4-OH free sugars

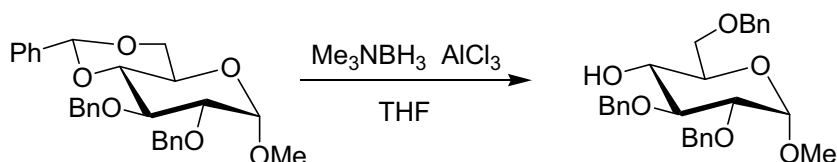
1) $\text{BF}_3\text{Et}_2\text{O}$ and Et_3SiH ¹⁴ in CH_2Cl_2 :



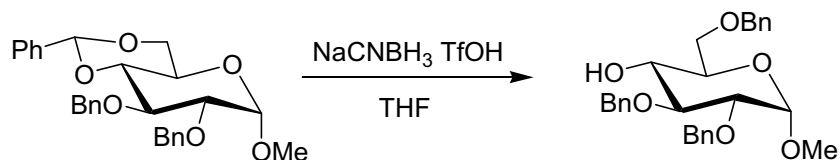
2) MeCNBH_3 and CF_3COOH ^{15,16} in DMF:



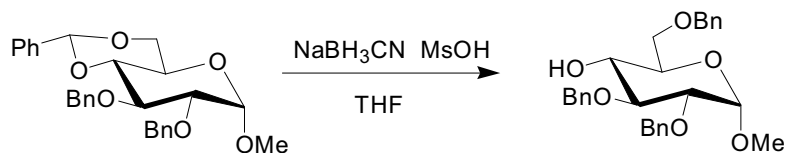
3) Me_3NBH_3 and AlCl_3 ¹⁷ in THF:



4) NaBH_3CN and TfOH ¹⁸ in THF:

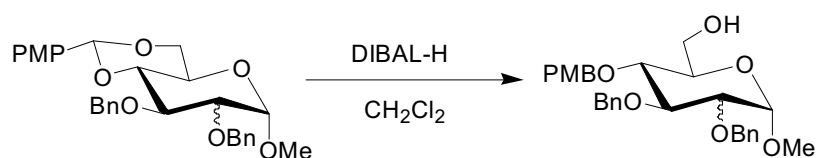


5) NaBH_3CN and MsOH ¹⁹ in THF:

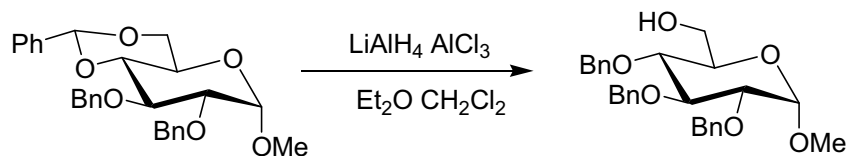


b. Methods leading to 6-OH free sugars

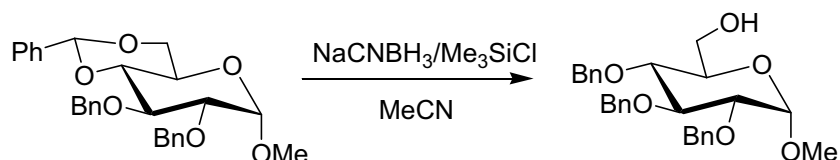
1) DIBAL-H in CH_2Cl_2 ²⁰:



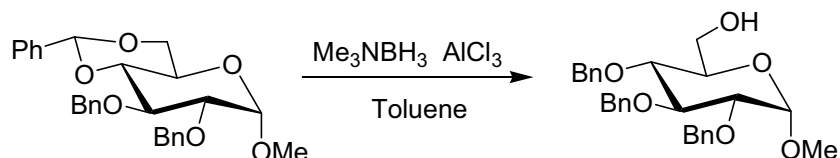
2) $\text{LiAlH}_4/\text{AlCl}_3$ ^{21,22}:



3) NaCNBH_3 and Me_3SiCl in MeCN:²³

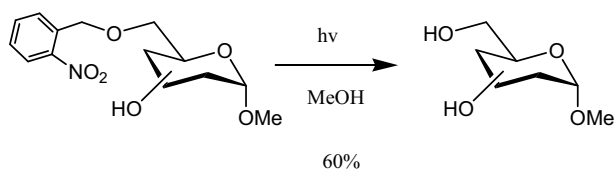


4) Me_3NBH_3 and AlCl_3 in toluene:²⁴



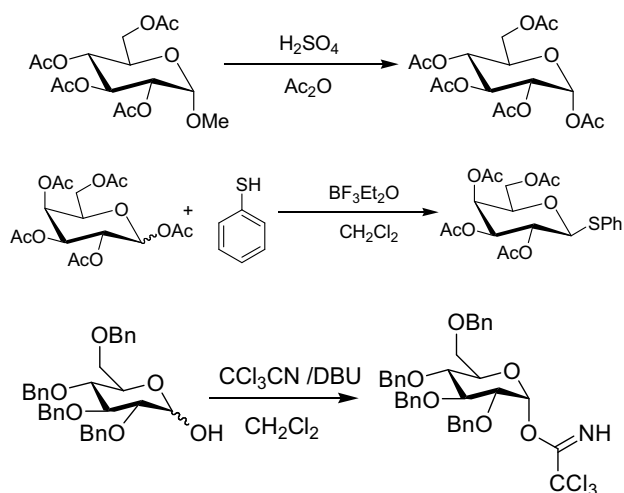
3.1.5 Photo deprotection

As reported by S. Watanabe²⁵ et al., *o*-nitrobenzyl protected methyl- α -D-glycosides can be converted to methyl- α -D-glycosides in 60% yield under 365 nm wave of light.

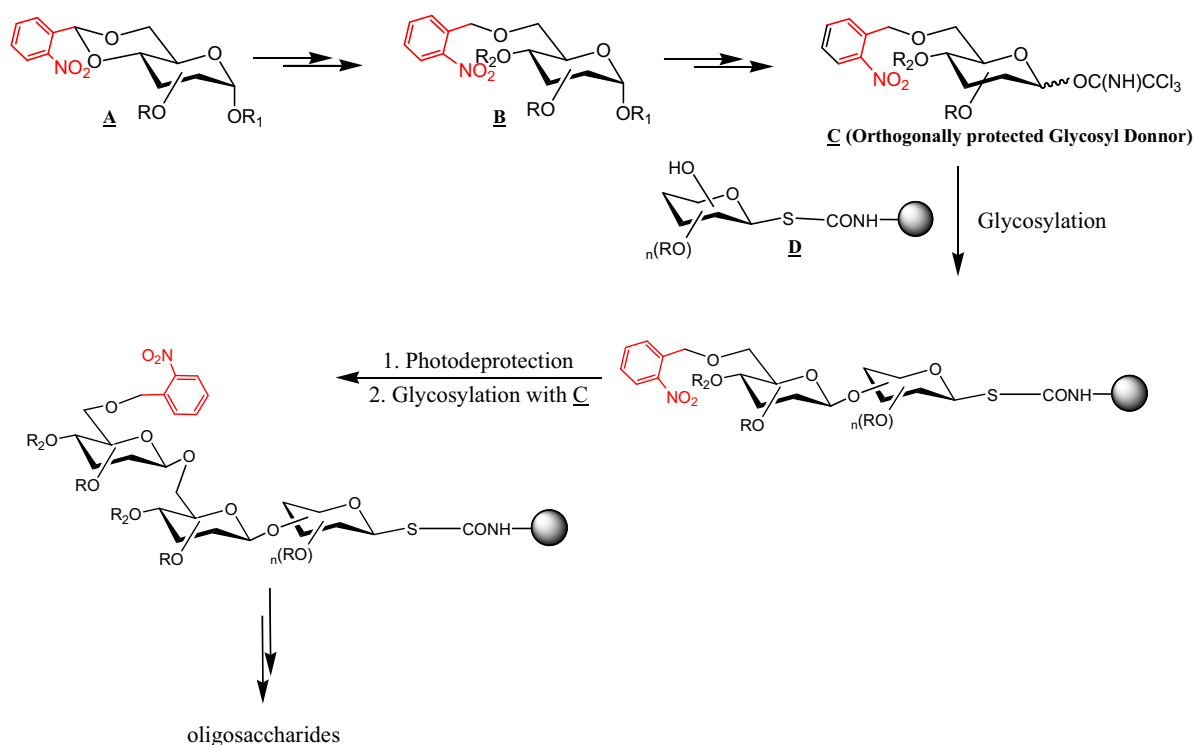


3.1.6 Modification of anomeric methyl group

In order to realize light-controlled oligosaccharide synthesis lately, we planned also to convert the methyl glycoside into thioglycoside or trichloroacetimidate as glycosyl donors with following methods:

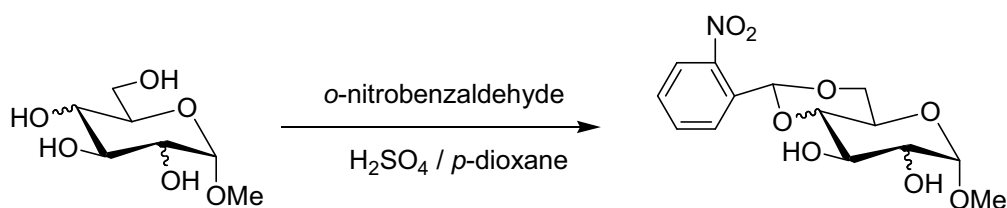


A proposed way to synthesize oligosaccharides is described in the following scheme with o-nitrobenzyl protected sugars:



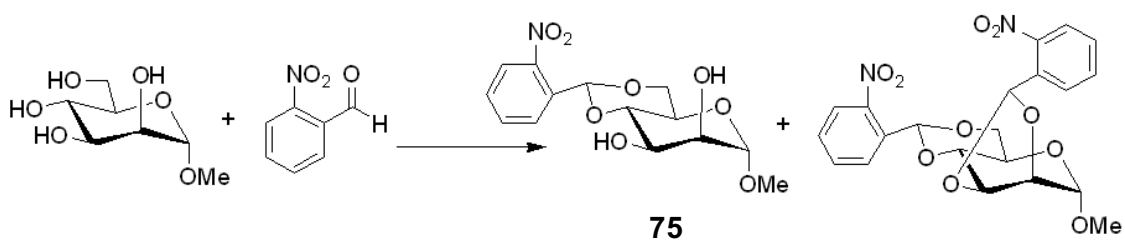
3.2 Results and discussion

3.2.1 Synthesis of 4,6-O-(2'-nitro)benzylidene- α -D-methyl glycopyranoside

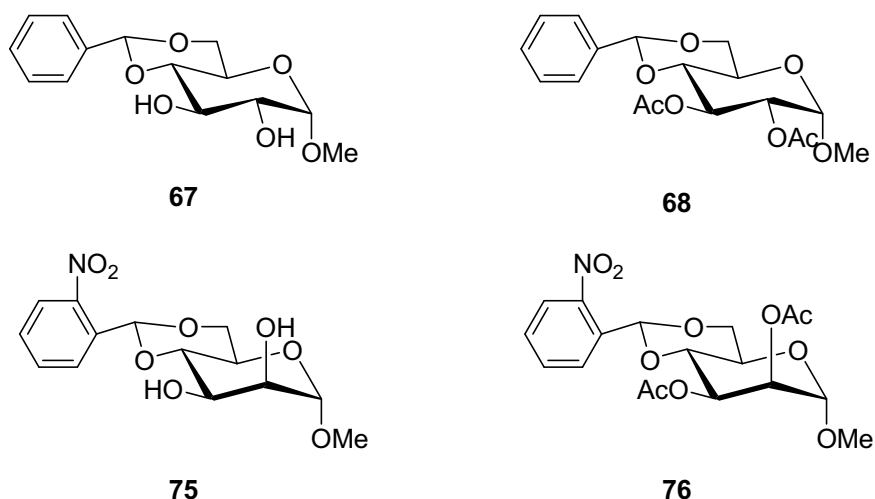


Synthesis of these compounds has already been reported.¹² The product can be used for the next step of acetylation without further purification. But the R_f of NBA (o-nitrobenzaldehyde) on the TLC plate is much closed to that of acetyl sugar, so we often added an excess of sugar to improve the conversion of NBA.

With α -D-methyl glucopyranoside as starting material, the yield of compound **67** is about 68 %; 60% yield has been obtained with β -D-methyl galactopyranoside. When we used α -D-methyl mannopyranoside as starting material, the yield is just 30 % for compound **75** because of easy formation of 2,3-O-benzylidene as by-product:



Acetylation of compounds **67** and **75** led to acetylated derivatives **68** and **76** in good yield. Their NMR ^1H spectra are compared in the following table.

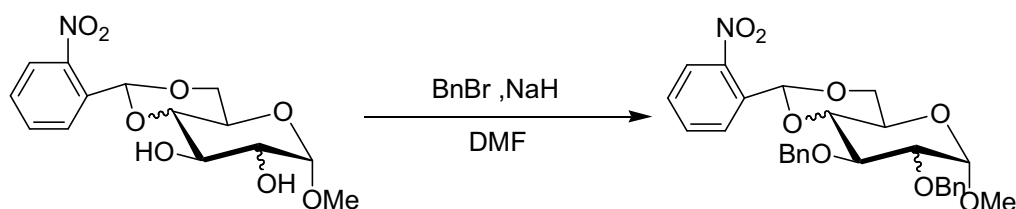


NMR ^1H spectra comparison of compounds **67**, **68**, **75** and **76**:

No./Group	Chemical Shift(ppm)			
	67 ^1H	68 ^1H	75 ^1H	76 ^1H
OMe	3.44	3.39	3.29	3.39
1	4.79	4.93	4.68	4.65
2	3.63	4.85	3.93	5.27
3	3.90	5.48	4.18	5.37
4	3.52	3.64	3.89	4.03
5	4.26	4.30	3.81	4.28
6a	3.76	3.82	3.77	3.88
6b	3.78	3.83	3.79	3.88
7	6.13	6.10	6.10	6.17
ArH-3'	7.90	7.78	7.79	7.80
ArH-4'	7.50	7.46	7.45	7.49
ArH-5'	7.62	7.58	7.71	7.60
ArH-6'	7.86	7.81	7.84	7.81

3.2.2 Protection of 2,3-hydroxyl groups as benzyl ether

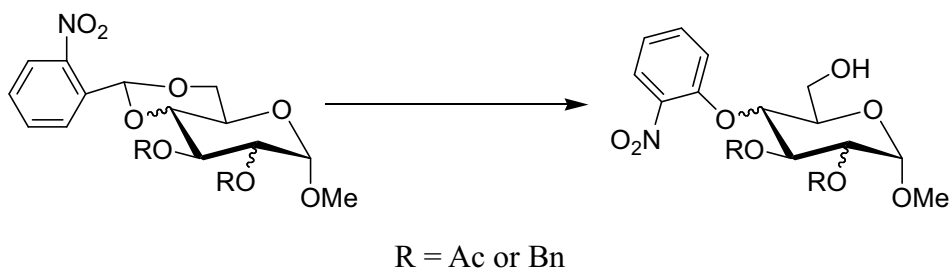
The 2- and 3-hydroxyl function groups of the above 4,6-O-(2'-nitro)benzylidene derivatives were then protected as benzyl ether.



gluco	66	71
galacto	82	84
manno	75	78

We used cyclohexane to wash NaH (60%) before use in the reaction. The yield was improved for about 5 %.

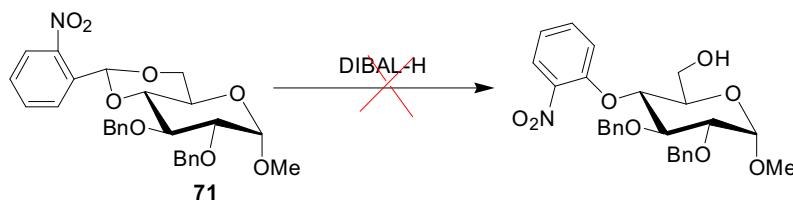
3.2.3 Regioselective ring opening to 4-O-(2'-nitro)benzyl glycosides



1) DIBAL-H in CH₂Cl₂:

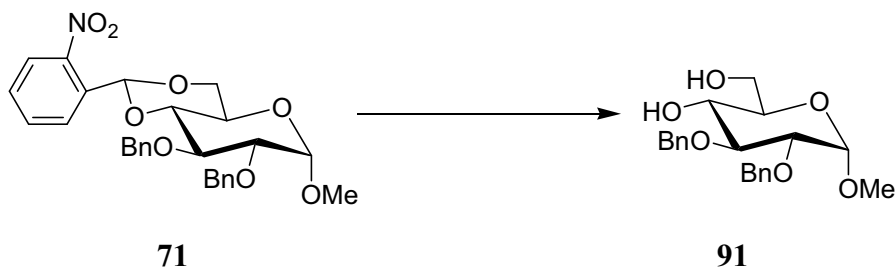
DIBAL-H can also reduce acetyl ester, so we have to use the sugar protected with –OBn as starting material.

We tried to use compound **71** as starting material, DIBAL-H as catalyst, in varying quantities of the reagent, reaction temperature as well as reaction time, to prepare 6-OH free sugar, but all experiments were failed.



DIBAL-H	Solvent	Temperature (°C)	Reaction Time	Result
5 equiv	CH ₂ Cl ₂	-60	6H	no reaction
5 equiv	CH ₂ Cl ₂	r.t	6H	by product
5 equiv	CH ₂ Cl ₂	0	6H	no reaction
2 equiv	CH ₂ Cl ₂	0	64H	yield<5%
3 equiv	CH ₂ Cl ₂	0	13H	by product
4 equiv	CH ₂ Cl ₂	r.t	20H	by product

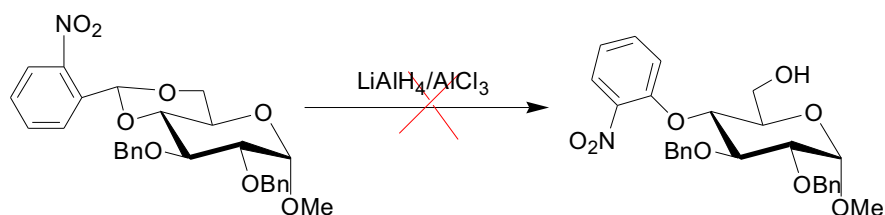
The main reaction is as followed:



We found that treatment with 5 eq of DIBAL-H during 6 h at room temperature afforded the compound **91** in 76% yield. The o-nitrobenzylidene group has been removed from the sugar ring. This represented a new way to afford 4,6-di-OH sugar.

2) LiAlH₄/AlCl₃:

As OAc group can't be used in this condition, we tried with compound **71** which was protected with Bn ether.



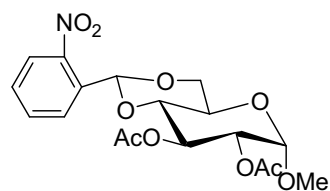
LiAlH₄ / AlCl₃ as catalyst

LiAlH ₄ /AlCl ₃	Solvent	Temperature (°C)	Reaction Time	Result
6eq/6eq	CH ₂ Cl ₂ Et ₂ O	reflux	64h	by product 91
4.7eq/4eq	CH ₂ Cl ₂ Et ₂ O	reflux	8h	by product 91
4.7eq/4eq	CH ₂ Cl ₂ Et ₂ O	r.t	48h	mixture
2eq/2eq	CH ₂ Cl ₂ Et ₂ O	r.t	60h	no reaction

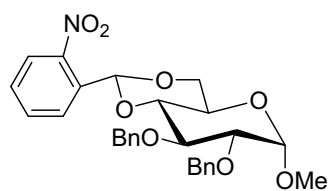
We found in this condition that we can't get the expected product, 6-OH sugar. However, when more than 5 eq of LiAlH₄/AlCl₃ is employed, we could get compound **91** in 72 % yield.

3) NaCNBH₃/Me₃SiCl in MeCN:

Acetyl protected sugar could be used in the presence of NaCNBH₃/Me₃SiCl, so both acetyl and benzyl protected sugars **68** and **71** were used as starting materials. Once again, we did not get the expected product.



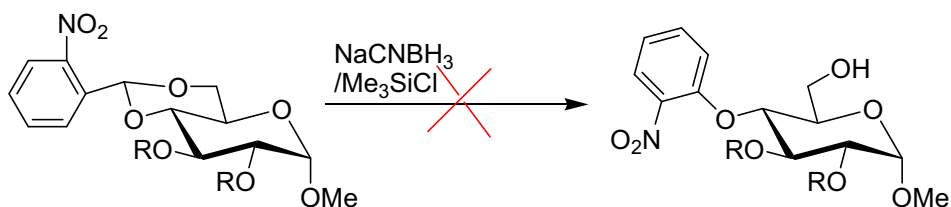
68



71

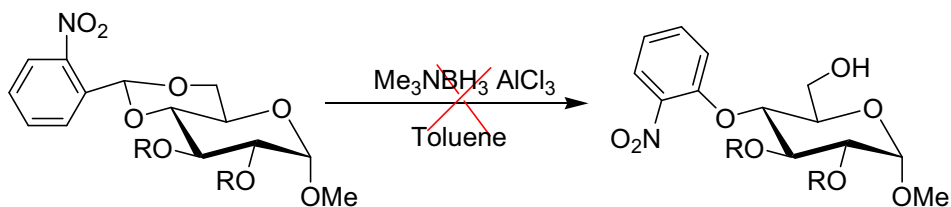
Material	NaCNBH ₃ /Me ₃ SiCl	Solvent	Temperature (°C)	Reaction Time	Result
71	4eq/4eq	MeCN	r.t	24H	no reaction
	6eq/6eq		r.t	24H	no reaction
71	+3eq/3eq	MeCN	r.t	+24H	no reaction
			40	+24H	no reaction

71	12eq/12eq	MeCN	Reflux	48H	yield <10%
	+6eq/6eq			+24H	By product 91
68	6eq/6eq	MeCN	r.t	24H	no reaction
	+3eq/3eq		r.t	13H	no reaction
			40	24H	no reaction

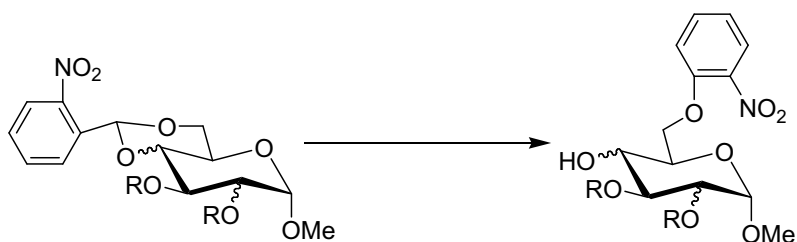


4) $\text{Me}_3\text{NBH}_3 / \text{AlCl}_3$ in toluene:

Material	NaCNBH_3 / Me_3SiCl	Solvent	Temperature (°C)	Reaction Time	Result
68	6eq/6eq	Toluene	r.t	60H	no reaction
68	12eq/6eq	Toluene	r.t	72H	no reaction
68	12eq/12eq	Toluene	100	60H	no reaction
71	12eq/12eq	Toluene	r.t	60H	no reaction
71	12eq/12eq	Toluene	100	72H	no reaction

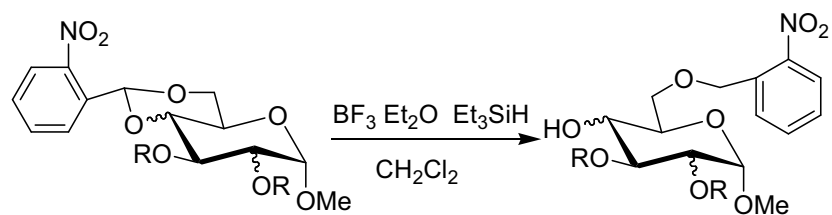


3.2.4 Regioselective ring opening to 6-O-(2'-nitro)benzyl glycosides

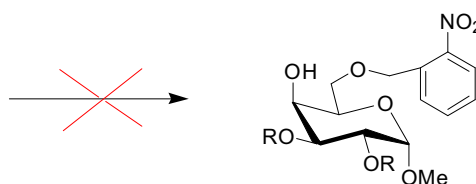
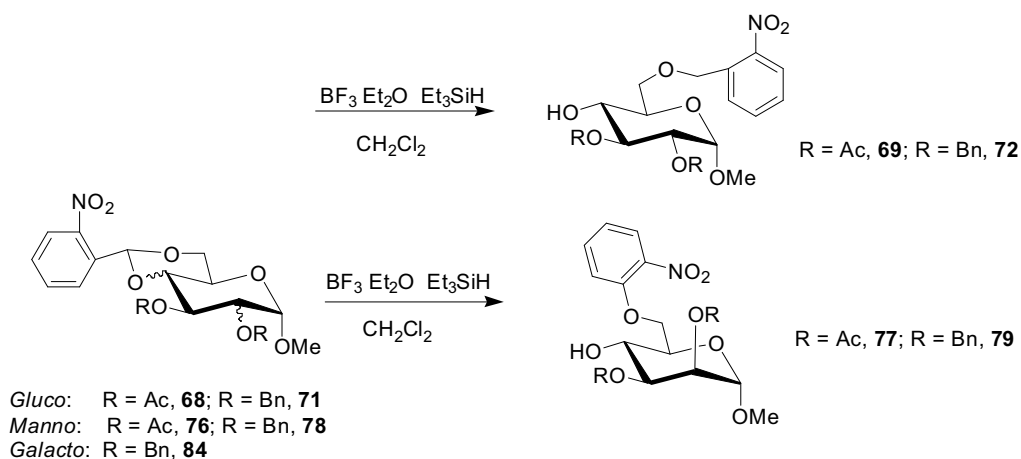


Synthesis of methyl 2,3-di-O-acetyl-6-O-(2'-nitro)benzyl gluco- and manno- α -D-pyranosides have been described by S. Watanabe et al using $\text{BF}_3\text{Et}_2\text{O}$ and Et_3SiH in CH_2Cl_2 .²⁵ We then tried this condition with both acetyl and benzyl protected derivatives.

1) $\text{BF}_3\text{Et}_2\text{O}$ and Et_3SiH in CH_2Cl_2 :

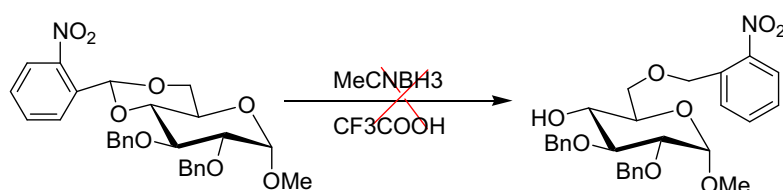


It's pretty good for gluco and mannoside, but it didn't work with the galacto derivative **84**.



Material	BF ₃ Et ₂ O/Et ₃ SiH	Solvent	Temperature (°C)	Reaction Time	Result
68	6eq/12eq	CH ₂ Cl ₂	r.t	20H	69 : 71%
71	3eq/6eq	CH ₂ Cl ₂	r.t	28H	mixture
71	3eq/12eq	CH ₂ Cl ₂	r.t	8H	mixture
71	6eq/12eq	CH ₂ Cl ₂	r.t	14H	72 : 52%
71	6eq/12eq	CH ₂ Cl ₂	r.t	60H	72 : 91%
76	6eq/12eq	CH ₂ Cl ₂	r.t	18H	77 : 73%
78	6eq/12eq	CH ₂ Cl ₂	r.t	18H	79 : 78%

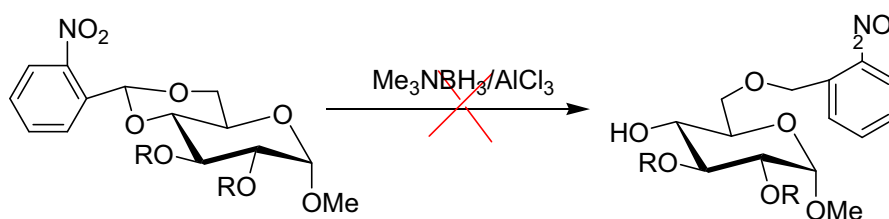
2) MeCNBH₃ and CF₃COOH:



Material	NaCNBH ₃ / CF ₃ COOH	Solvent	Temperature (°C)	Reaction Time	Result
71	5eq/10eq	DMF	r.t	60H	No reaction
	+5eq/10eq			24H	mixture
71	10eq/20eq	DMF	100	48H	No reaction

3) Me₃NBH₃/AlCl₃ in THF:

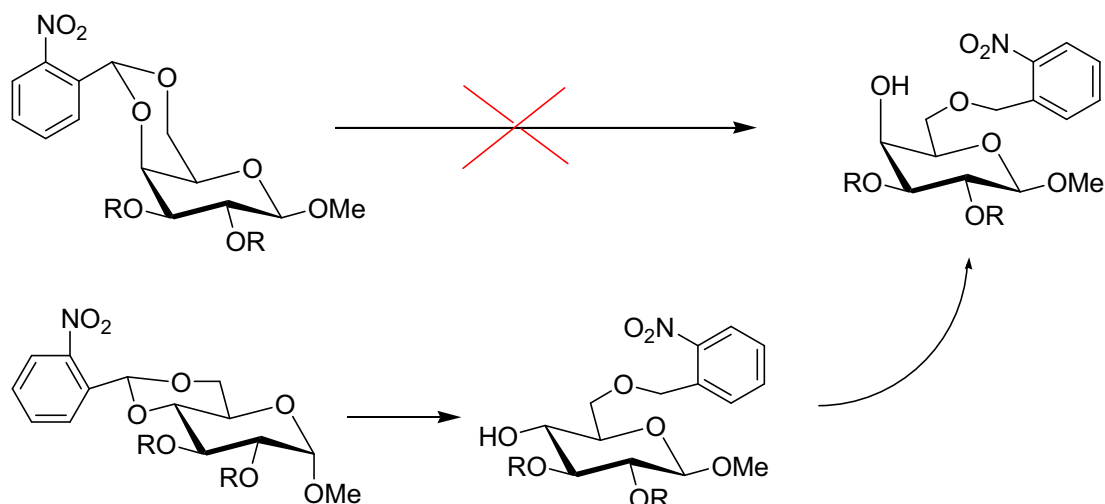
Material	Me ₃ NBH ₃ / AlCl ₃	Solvent	Temperature (°C)	Reaction Time	Result
68	3eq/3eq	THF	r.t	64H	no reaction
	+1.5eq/1.5eq		r.t	24H	no reaction
	+1.5eq /1.5eq		r.t	24H	no reaction
			50	24H	no reaction
68	6eq/6eq	THF	r.t	68H	no reaction
			40	18H	no reaction
68	6eq/6eq	THF	r.t	80H	no reaction
68	12eq/12eq	THF	reflux	48H	no benzene
71	6eq/6eq	THF	r.t	60H	no reaction
			40	26H	no reaction
71	+3eq/3eq	THF	r.t	24H	no reaction
	12eq/12eq		reflux	48H	no reaction



R = Ac or Bn

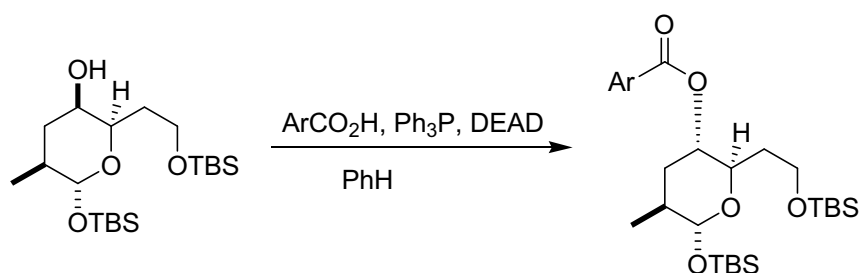
3.2.5 Isomerization

Because the system BF₃Et₂O/Et₃SiH couldn't work with galactopyranoside, so we decided to isomerize the C-4 hydroxy group of the *gluco* compound:

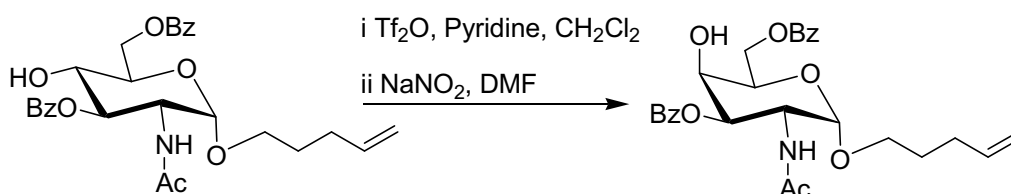


There are several ways to realize isomerization:

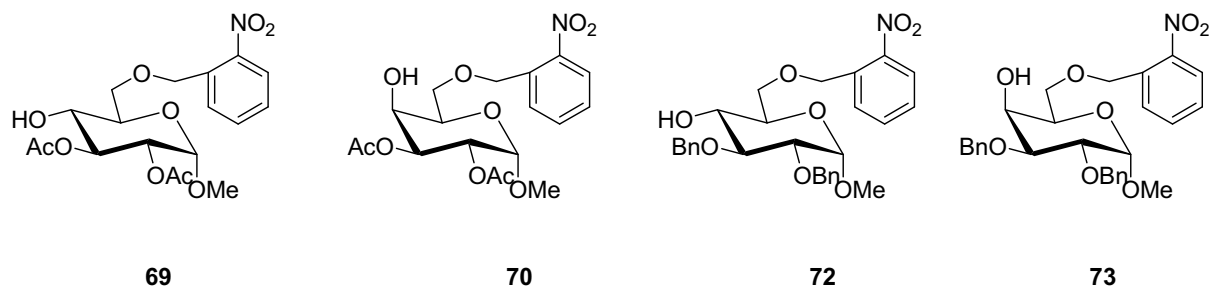
1) with ArCO_2H , Ph_3P and DEAD:²⁶



2) with Tf_2O , NaNO_2 ²⁷



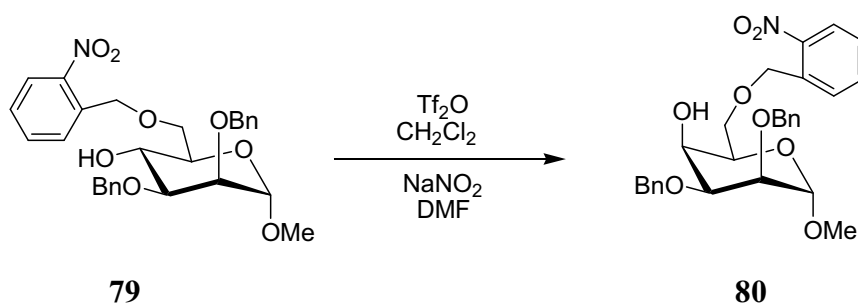
We found that the second method with $\text{Tf}_2\text{O}/\text{NaNO}_2$ is better than the Mitsunobu reaction with $\text{Ph}_3\text{P}/\text{DEAD}$. From compound **69**, we have prepared compound **70** in 97 % yield. Benzylated gluco derivative **72** was also converted to the galacto derivative **73** in 97 % yield.



¹H NMR spectra of gluco- and galacto- derivative

No./Group	Chemical Shift (ppm)			
	69 ¹ H	70 ¹ H	72 ¹ H	73 ¹ H
OAc	2.09	2.11		
OAc	2.11	2.61		
OMe	3.41	3.42	3.40	3.40
1	4.92	5.01	4.65	4.66
2	4.88	5.24	3.54	
3	5.30	5.30	3.83	
4	3.85	4.25	3.74	
5	3.81	4.08	3.62	
6a	3.76	3.83	3.75	3.73
6b	3.78	3.85	3.76	3.73
7a 7b	4.97	4.97	4.94	4.95
ArH-3'	7.77	7.75	7.75	7.75
ArH-4'	7.45	7.45	7.45	7.45
ArH-5'	7.68	7.65	7.65	7.65
ArH-6'	8.06	8.07	8.07	8.07

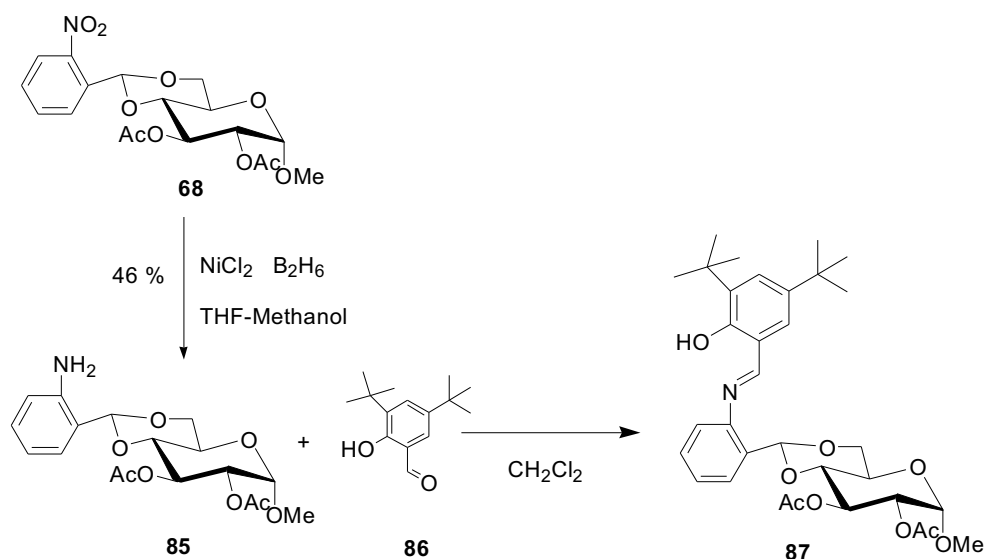
Similarly, the mannopyranoside **79** has been transformed into the talo derivative **80** in 57 % yield.



3.2.6 Synthesis of new photochromic molecule

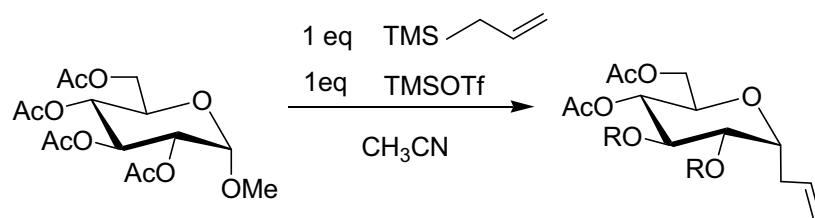
In the field of memory devices, optically active molecular materials open the way to high density information storage with very fast writing and reading rates. The development of such an advanced technology first requires a molecular switch. Photochromic molecules are particularly efficient photo-driven switches, as they can commute upon light excitation between two different molecular species showing large absorption changes. The reversibility and the fast switching rate of the photochromic reaction, associated with the possibility to cycle up to one million “round trip” reactions in some photochromic compounds, make them good candidates for optical switches or rewritable memories.

Schiff's base has been used as photochromic materials. In collaboration with Pr K. Nakatani, we have synthesized a new photochromic molecule **87** in 31 % yield by the condensation of amine function of the benzylidene **85** with the aldehyde **86**. The nitro function can be reduced to amine group with $\text{NiCl}_2/\text{B}_2\text{H}_6$ in a mixture of THF/MeOH.

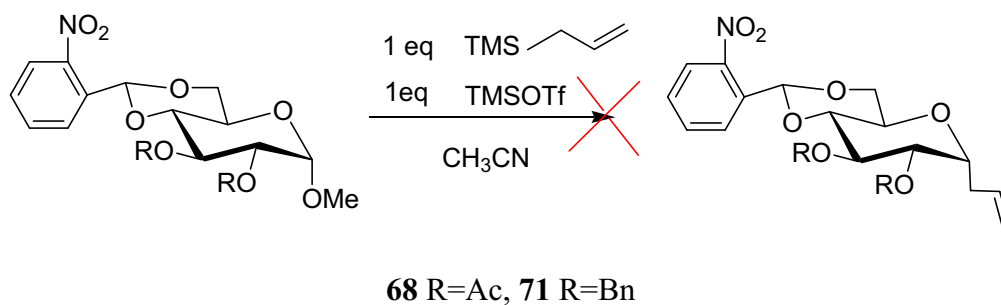


3.2.7 α -C-Allylation of *o*-nitrobenzyl protected glycoside

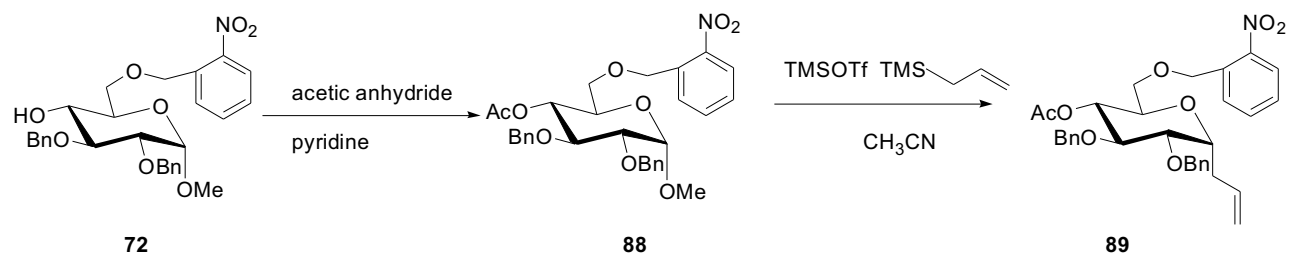
Allyl group is a versatile functional group in organic chemistry, because it can be easily transformed into other functional groups. We have realized the following reaction:



But when we tried to use compounds **68**, **71** as starting materials, unfortunately, the reactions failed.



Finally, we found that when the amount of reagents is more than 5 eq, the reaction could be worked smoothly.



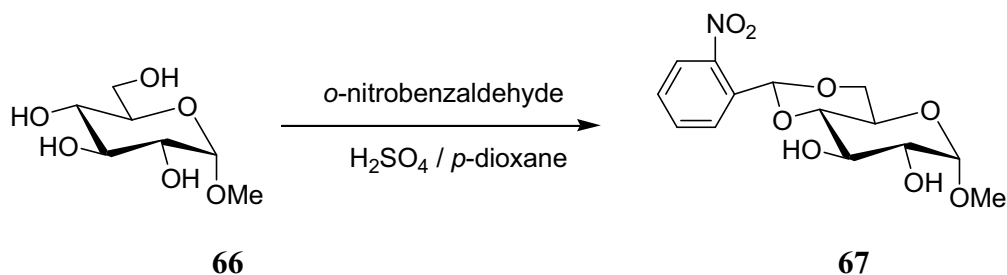
Catalyst		Temperature (°C)	Reaction Time(H)	Result
TMS-allyl	TMSOTf			
1eq/0.2eq		r.t	24	no reaction
+1eq/0.2eq			24	
2eq/1eq		r.t	48	no reaction
4eq/2eq		r.t	72	no reaction
3eq/3eq		r.t	48	no reaction
4eq/4eq		r.t	72	89 : less than 10%
5.1eq/5.1eq		r.t	72	89 : 72%

3.3 Conclusion

This part of work was the basic part of the synthesis of photolabile sugar derivatives which could be used as starting materials for the light-controlled oligosaccharide synthesis. After many attempts with different reaction conditions, finally Et_3SiH and $\text{BF}_3\text{Et}_2\text{O}$ were used to afford a series of benzyl or acetyl-protected 6-O-*o*-nitrobenzyl glucoside and mannosides. Via isomerization, the 6-O-*o*-nitrobenzyl galacto- and talo-pyranosides were prepared successfully from the gluco- and manno- derivative.

3.4 Experimental Section

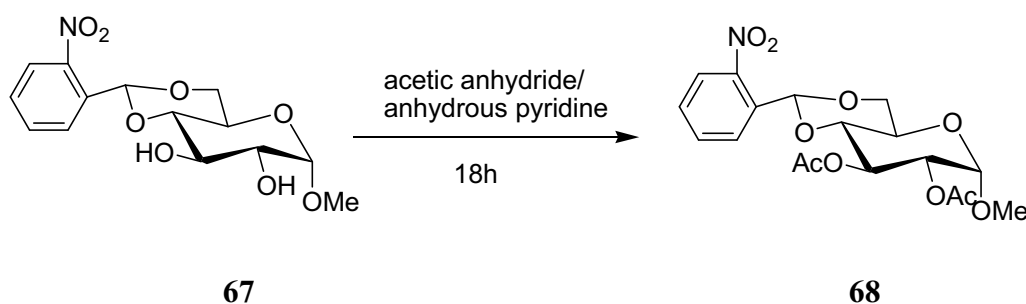
3.4.1 Synthesis of compound 67



To a solution of methyl- α -D-pyranoglucose **66** (4 g, 20 mmol) in *p*-dioxane (20 mL) was added

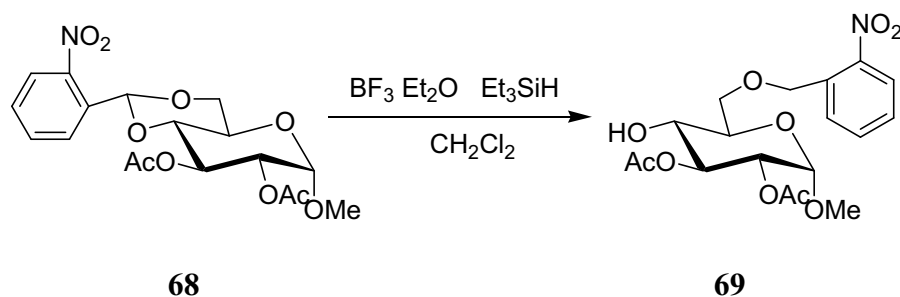
o-nitrobenzaldehyde, NBA 2 g (13 mmol), followed by H₂SO₄ conc (0.8 mL). The reaction mixture was stirred for 6 h at room temperature, then diluted with 30 mL of CH₂Cl₂, neutralised with Na₂CO₃, filtered, and evaporated. The residue was partitioned with CH₂Cl₂ (20 mL×3) and H₂O (20 mL), dried over with MgSO₄, evaporated to afford **67** (2.89 g, 67.9 %). TLC: *R*_f=0.51 (EtOAc); [α]_D = +137 (*c* 0.98 CH₂Cl₂); m.p. 162-163°C (EtOAc); ¹H NMR (300 MHz, CDCl₃): δ 2.36 (br s, 2H, 2xOH), 3.44 (s, 3H, OMe), 3.52 (t, 1H, *J*=9.4 Hz, H-4), 3.63 (dd, 1H, *J*=3.7 and 9.16 Hz, H-2), 3.76-3.78 (m, 2H, H-6a, H-6b), 3.90 (t, 1H, *J*=9.2 Hz, H-3), 4.26 (m, 1H, H-5), 4.79 (d, 1H, *J*=3.7 Hz, H-1), 6.13 (s, 1H, H-7), 7.50 (t, 1H, *J*=8.5 Hz, H-4'), 7.62 (t, 1H, *J*=8.5 Hz, H-5'), 7.85-7.90 (t, 2H, *J*=8.5 Hz, H-3', H-6'); Anal. Calc. for C₁₄H₁₇NO₈: C, 51.7; H, 5.2; N, 4.3. found C, 51.3; H, 5.2; N, 4.1.

3.4.2 Synthesis of compound 68



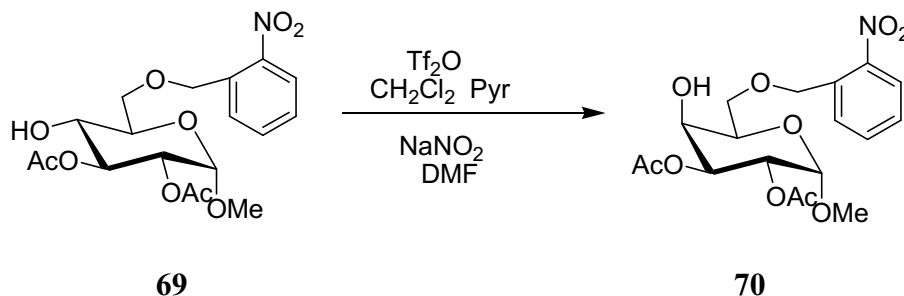
To a solution of compound **67** (3.27 g, 10 mmol) in 20 mL of pyridine was added 8 mL of Ac₂O. The reaction mixture was stirred for 16 h at room temperature, diluted with 30 mL of H₂O, extracted with CH₂Cl₂ (3×20 mL). The combined organic layer was washed with brine, dried over MgSO₄, evaporated, and purified by column chromatography (cyclohexane :EtOAc =4:1) to afford **68** (3.66 g, 89 %) as white solid. TLC: *R*_f=0.77(cyclohexane:EtOAc=1:1); [α]_D = +194 (*c* 0.1 CH₂Cl₂); ¹H NMR(300 MHz, CDCl₃): δ 2.07 (s, 3H, OAc), 2.09 (s, 3H, OAc), 3.39 (s, 3H, OMe), 3.64 (t, 1H, *J*=9.5 Hz, H-4), 3.83 (m, 2H, H-6a, H-6b), 4.30 (dd, 1H, *J*=9.5 Hz, 4.0 Hz, H-5), 4.85 (dd, 1H, *J*=3.7 Hz, 9.9 Hz, H-2), 4.93(d, 1H, *J*=3.7 Hz, H-1), 5.48(t, 1H, *J*=9.9 Hz, H-3), 6.10(s, 1H, H-7), 7.46(t, 1H, *J*=7.4 Hz, H-4'), 7.58(t, 1H, *J*=7.4 Hz, H-5'), 7.78-7.81(d, 2H, *J*=7.7 Hz, H-3', H-6'); ¹³C NMR (75 MHz, CDCl₃): δ 20.6, 20.7, 55.3, 62.0, 68.5, 68.9, 71.2, 79.6, 97.2, 97.5, 124.1, 127.3, 129.6, 130.7, 132.5, 148.3, 170.0, 170.2

3.4.3 Synthesis of compound 69



To a 0 °C solution of compound **68** (2.05 g, 5 mmol) in CH₂Cl₂ (40 mL) was added Et₃SiH (9.63 mL, 60 mmol) and BF₃·Et₂O (1.29 mL, 30 mmol). After addition, the solution was stirred for 4 h. The solution was diluted with 100 mL of CH₂Cl₂, washed with sat. NaHCO₃, dried over MgSO₄, evaporated, and purified with column chromatography (cyclohexane:EtOAc=1:1) to afford the compound **69** (1.45 g, 71 %) as yellow oil. TLC: *R*_f=0.41 (cyclohexane:EtOAc=1:1); ¹H NMR (300 MHz, CDCl₃): δ 2.09 (s, 3H, OAc), 2.11 (s, 3H, OAc), 3.41 (s, 3H, OMe), 3.76-3.87 (m, 4H, H-4, H-5, H-6a, H-6b), 4.88 (dd, 1H, *J* = 3.8 Hz, 6.3 Hz, H-2), 4.92 (d, 1H, *J* = 3.8 Hz, H-1), 4.97 (s, 2H, PhCH₂), 5.30 (t, 1H, *J* = 8.8 Hz, H-3), 7.45 (t, 1H, *J* = 7.6 Hz, H-4'), 7.68 (t, 1H, *J* = 7.6 Hz, H-5'), 7.77 (d, 1H, *J* = 7.6 Hz, H-3'), 8.06 (d, 1H, *J* = 7.6 Hz, H-6'); ¹³C NMR (75 MHz, CDCl₃): δ 20.7, 20.8, 55.2, 69.7, 69.9, 70.2, 70.5, 70.6, 73.4, 96.8, 124.6, 128.0, 128.7, 133.6, 134.5, 147.5, 170.2, 171.7

3.4.4 Synthesis of compound 70

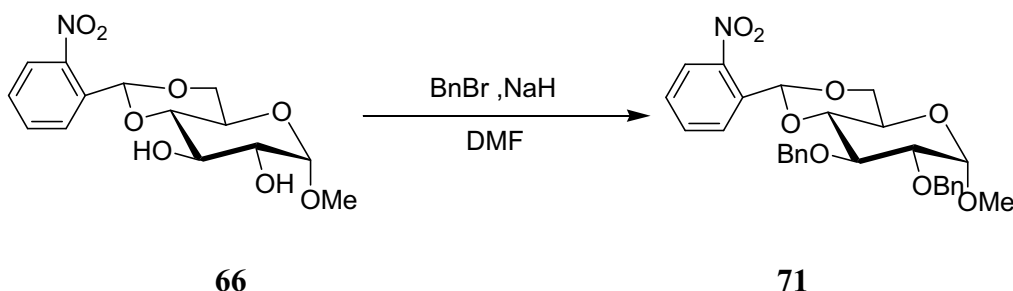


a) To a -15 °C mixture of Tf₂O (36 μL) and pyridine (33 μL) in 1 mL of CH₂Cl₂ was added a solution of compound **69** (53 mg, 0.13 mmol) in CH₂Cl₂ 1 mL under Ar. After the solution was stirred for 2 h, the solution was diluted with 2 mL CH₂Cl₂, washed with 5% HCl, sat NaHCO₃ and brine. The combined organic layers were dried over MgSO₄, evaporated to remove solvents.

b) The residue was dissolved in 2 mL of DMF, followed by addition of NaNO₂ (95 mg), and then stirred for 20h. The solution was diluted with 5 mL of CH₂Cl₂, washed with brine, dried over MgSO₄, evaporated, purified with column chromatography (cyclohexane:EtOAc=3:1) to give compound **70** (51.4 mg, 97%). TLC: *R*_f= 0.34 (EtOAc:cyclohexane=1:2); [α]_D = +129.4 (*c* 0.26, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 2.09 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.61 (s, 1H, 4-OH), 3.42 (s, 3H, OMe), 3.85 (m, 2H, H-6a, H-6b), 4.08 (t, 1H, *J* = 4.7 Hz, H-5), 4.25 (m, 1H, H-4), 4.97 (s, 2H, PhCH₂), 5.01(d, 1H, *J* = 2.6 Hz, H-1), 5.29 (m, 2H, H-2, H-3), 7.45 (t, 1H, *J* = 8.0 Hz, *o*-NO₂-PhH), 7.65 (t, 1H, *J* = 8.0 Hz, *o*-NO₂-PhH), 7.75 (d,

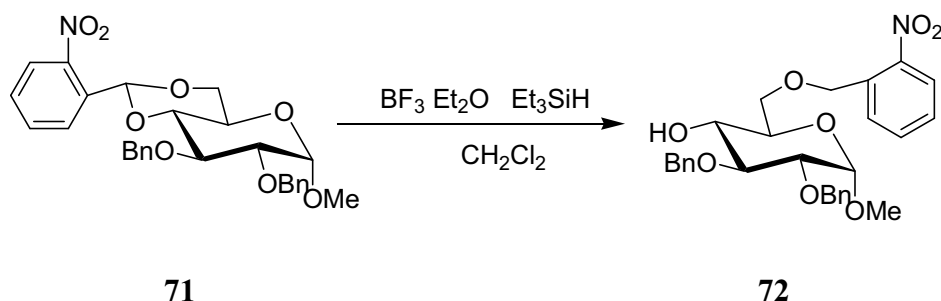
1H, $J = 8.0$ Hz, *o*-NO₂-PhH), 8.07(d, 1H, $J = 8.0$ Hz, *o*-NO₂-PhH); ¹³C NMR (75 MHz, CDCl₃): δ 20.7, 20.8, 55.3, 68.0, 68.2, 68.7, 70.1, 70.2, 70.5, 97.3, 124.7, 128.1, 128.5, 133.6, 134.3, 147.6, 169.9, 170.3. HRESIMS: calcd for C₁₈H₂₃NO₁₀Na: 436.1220; found: m/z 436.1225

3.4.5 Synthesis of compound 71



To a 0 °C solution of compound **66** (2.48 g, 7.6 mmol) in 10 mL of DMF, was added NaH(60%) (790 mg, 19.76 mmol). After 45 min, BnBr (2.17 mL, 19.76 mmol) was added and the solution was stirred for another 16 h. The reaction was quenched with 10 mL of MeOH, and evaporated. The residue was partitioned with CH₂Cl₂ (3×20 mL) and H₂O (20 mL). The combined organic layer was washed with sat NaHCO₃, dried over MgSO₄, evaporated and purified with column chromatography (cyclohexane:EtOAc=3:1) to give compound **71** (2.76 g, 72%) as a yellow oil. TLC: $R_f = 0.67$ (EtOAc:cyclohexane, 1:2); $[\alpha]_D = -31.2$ (c 0.98, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 3.39 (s, 3H, OMe), 3.54 (dd, 1H, $J = 3.7$ and 9.5 Hz, H-2), 3.63 (t, 1H, $J = 9.2$ Hz, H-4), 3.69-3.79 (m, 2H, H-6a, H-6b), 3.99 (t, 1H, $J = 9.2$ Hz, H-3), 4.22 (m, 1H, H-5), 4.57 (d, 1H, $J = 3.7$ Hz, H-1), 4.66 (d, 1H, $J = 12.0$ Hz, CHPh), 4.74 (d, 1H, $J = 11.4$ Hz, CHPh), 4.84 (d, 2H, $J = 12.0$ Hz, 2×CHPh), 6.17 (s, 1H, H-7), 7.27-7.42 (m, 10H, 2×Ph), 7.45 (t, 1H, $J = 8.1$ Hz, *o*-NO₂-PhH), 7.65 (t, 1H, $J = 8.1$ Hz, *o*-NO₂-PhH), 7.75 (d, 1H, $J = 8.1$ Hz, *o*-NO₂-PhH), 8.07 (d, 1H, $J = 8.1$ Hz, *o*-NO₂-PhH); ¹³C NMR (75 MHz, CDCl₃): δ 55.3, 62.0, 69.2, 73.8, 75.1, 78.3, 79.1, 82.3, 97.1, 99.2, 124.2, 127.4, 127.5, 127.8, 128.0, 128.1, 128.2, 128.4, 129.6, 131.2, 138.0, 138.6, 148.3. HRESIMS: calcd for [C₂₈H₂₉NO₈+Na]⁺: 530.1791; found: 530.1798.

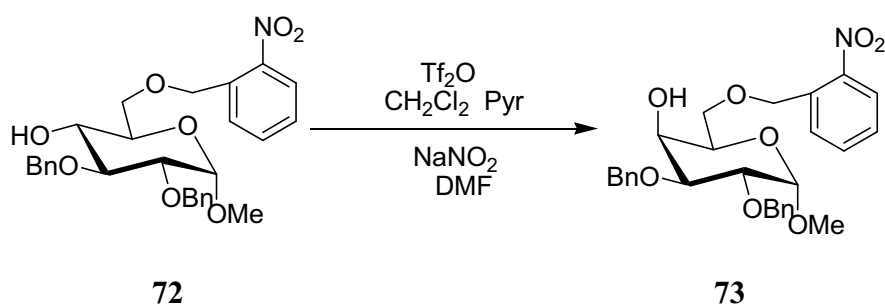
3.4.6 Synthesis of compound 72



To a 0 °C solution of compound **71** (1.42 g, 2.8 mmol) in 20 mL of CH₂Cl₂ was added Et₃SiH (5.32 mL, 33.6 mmol) and BF₃·Et₂O (2.02 mL, 16.8 mmol). After 16 h, the solution was diluted with 20 mL of CH₂Cl₂, washed with sat NaHCO₃ and brine, dried over MgSO₄, evaporated, purified with column chromatography (cyclohexane:EtOAc=4:1) to afford

compound **72** (850 mg, 52%). TLC: $R_f = 0.51$ (EtOAc:cyclohexane=1:2); $[\alpha]_D = +5.8$ (c 0.28, CH_2Cl_2); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 2.29 (d, 1H, $J = 2.2$ Hz, 4-OH), 3.40 (s, 3H, OMe), 3.54 (dd, 1H, $J = 3.7$ Hz, $J = 9.5$ Hz, H-2), 3.62 (m, 1H, H-5), 3.74-3.83 (m, 4H, H-3, H-4, H-6a, H-6b), 4.65 (d, 1H, $J = 3.7$ Hz, H-1), 4.67 (d, 1H, $J = 12.5$ Hz, *CHPh*), 4.73 (d, 1H, $J = 11.4$ Hz, *CHPh*), 4.78 (d, 1H, $J = 12.0$ Hz, *CHPh*), 4.94 (m, 2H, $2 \times \text{CHPh}$), 5.04 (d, 1H, $J = 11.4$ Hz, *CHPh*), 7.27-7.42 (m, 10H, $2 \times \text{Ph}$), 7.45 (t, 1H, $J = 7.4$ Hz, *o*-NO₂-PhH), 7.65 (t, 1H, $J = 7.4$ Hz, *o*-NO₂-PhH), 7.75 (d, 1H, $J = 7.4$ Hz, *o*-NO₂-PhH), 8.07 (d, 1H, $J = 7.4$ Hz, *o*-NO₂-PhH); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 55.2, 70.01, 70.04, 70.07, 70.14, 73.0, 75.4, 79.6, 81.3, 98.1, 124.5, 127.8-128.0, 128.4, 128.5, 128.6, 133.5, 134.9, 137.9, 138.6. HRESIMS: calcd for $[\text{C}_{28}\text{H}_{31}\text{NO}_8 + \text{Na}]^+$: 532.1947; found: 532.1963.

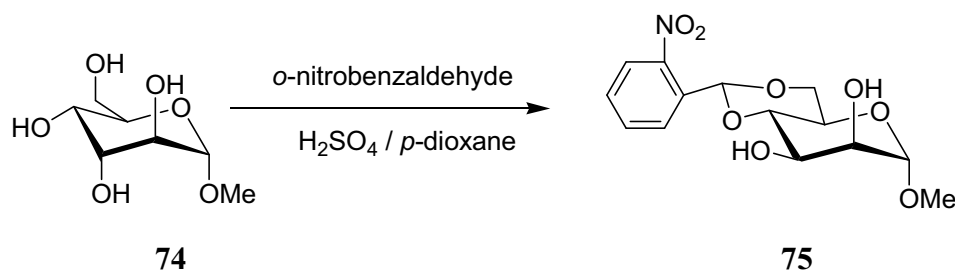
3.4.7 Synthesis of compound **73**



a) To a -15 °C mixture of Tf_2O (27 μL , 0.16 mmol) and pyridine (25 μL) in 1 mL of CH_2Cl_2 was added a solution of compound **72** (52 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) under Ar. After 2 h, the solution was diluted with 2 mL of CH_2Cl_2 , washed with 5% HCl, sat NaHCO_3 and brine. The combined organic layers were dried over MgSO_4 , evaporated to remove solvents.

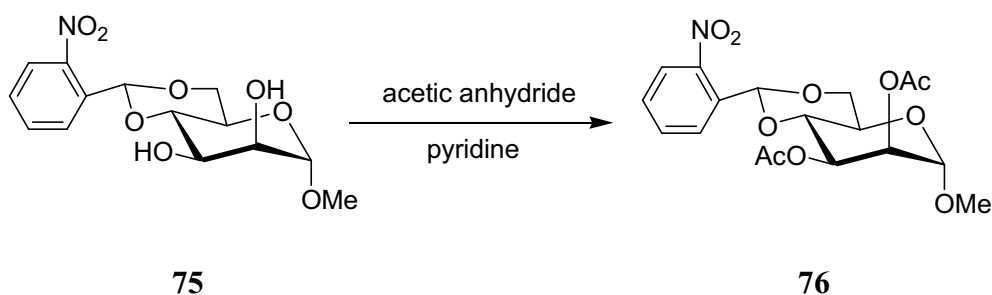
b) The residue was dissolved in 2 mL of DMF, followed by addition of NaNO_2 (73 mg, 1.05 mmol). After 20 h, the solution was diluted with 5 mL of CH_2Cl_2 , extracted with CH_2Cl_2 (3×5 mL), washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (cyclohexane:EtOAc=4:1) to afford compound **73** (27.4 mg, 53%). TLC: $R_f = 0.47$ (EtOAc:cyclohexane, 1:2); $[\alpha]_D = +39.6$ (c 0.60, CH_2Cl_2); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 2.53 (s, 1H, 4-OH), 3.40 (s, 3H, OMe), 3.73-4.06 (m, 6H, H-2, H-3, H-4, H-6a, H-6b, H-5), 4.66 (d, 1H, $J = 3.3$ Hz, H-1), 4.67 (d, 1H, $J = 12.1$ Hz, *CHPh*), 4.72 (d, 1H, $J = 11.7$ Hz, *CHPh*), 4.82 (d, 2H, $J = 12.3$ Hz, $2 \times \text{CHPh}$), 4.95 (s, 2H, $2 \times \text{CHPh}$), 7.30-7.43 (m, 10H, $2 \times \text{Ph}$), 7.45 (t, 1H, $J = 7.4$ Hz, *o*-NO₂-PhH), 7.65 (t, 1H, $J = 7.4$ Hz, *o*-NO₂-PhH), 7.75 (d, 1H, $J = 7.4$ Hz, *o*-NO₂-PhH), 8.07 (d, 1H, $J = 7.4$ Hz, *o*-NO₂-PhH); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 55.3, 67.9, 68.2, 69.9, 70.3, 72.8, 73.5, 75.6, 77.1, 98.5, 124.6, 127.7-128.0, 128.3, 128.4, 128.6, 133.5, 134.8, 138.0, 138.2. HRESIMS: calcd for $\text{C}_{28}\text{H}_{31}\text{NO}_8\text{Na}$: 532.1947; found: m/z 532.1943.

3.4.8 Synthesis of compound 75



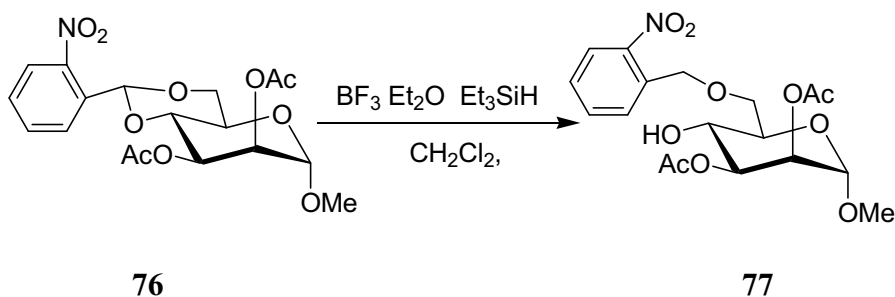
To a solution of compound **74** (4.85 g, 25 mmol) in 20 mL of *p*-dioxane was added NBA (3.04 g, 20 mmol) and conc. H₂SO₄ (1.4 mL) under Ar. After addition, the solution was stirred for 48 h, then diluted with 20 mL of CH₂Cl₂, neutralised with solid Na₂CO₃, and evaporated. The residue was partitioned with CH₂Cl₂ (3×20 mL) and H₂O (20 mL), dried over MgSO₄, evaporated, and purified with column chromatography (cyclohexane:EtOAc=2:1) to give compound **75** (2.04 g, 25%). TLC: R_f = 0.21 (EtOAc: cyclohexane = 1:1); ¹H NMR (300 MHz, CDCl₃): δ 3.29 (s, 3H, OMe), 3.50 (br s, 1H, OH), 3.71 (br s, 1H, OH), 3.77-3.95 (m, 5H, H-2, H-4, H-5, H-6a, H-6b), 4.18 (dd, 1H, *J* = 4.5 and 9.9 Hz, H-3), 4.68 (s, 1H, H-1), 6.10 (s, 1H, H-7), 7.45 (t, 1H, *J* = 7.7 Hz, H-4'), 7.55 (t, 1H, *J* = 7.7 Hz, H-5'), 7.79 (d, 1H, *J* = 7.7 Hz, H-3'), 7.84 (d, 1H, *J* = 7.7 Hz, H-6'); ¹³C NMR (75 MHz, CDCl₃): δ 55.1, 62.6, 68.6, 68.9, 70.7, 79.2, 97.5, 101.2, 124.0, 127.6, 129.8, 131.1, 131.2, 132.7,

3.4.9 Synthesis of compound 76



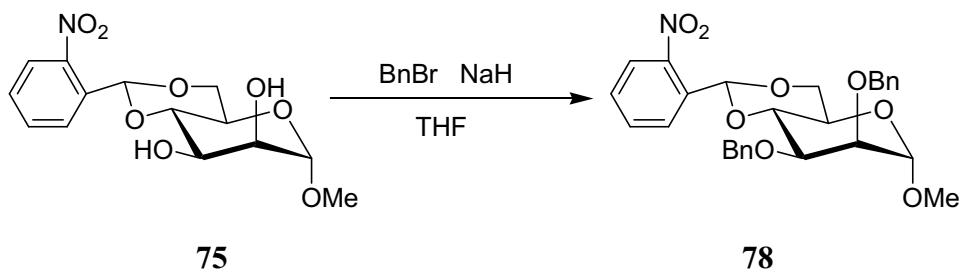
To a solution of compound **75** (156 mg, 0.48 mmol) in 8 mL of pyridine was added 1 mL of Ac₂O. After stirred for 16 h, the solution was extracted with CH₂Cl₂ (3×20 mL), washed with brine, dried over MgSO₄, evaporated and purified with column chromatography (cyclohexane:EtOAc=2:1) to give compound **76** (184 mg, 94%). TLC: R_f = 0.57 (EtOAc: cyclohexane=1:2); ¹H NMR (300.13 MHz, CDCl₃): δ 2.05 (s, 3H, OAc), 2.17 (s, 3H, OAc), 3.39 (s, 3H, OMe), 3.88 (dd, *J* = 2.6 Hz, 6.60 Hz, 2H, H-6a, H-6b), 4.03 (m, 1H, H-4), 4.28 (d, 1H, *J* = 5.5 Hz, H-5), 4.65 (s, 1H, H-1), 5.27 (m, 1H, H-2), 5.37 (dd, 1H, *J* = 3.7 and 10.3 Hz, H-3), 6.17 (s, 1H, H-7), 7.49 (t, 1H, *J* = 6.6 Hz, H-4'), 7.60 (t, 1H, *J* = 6.6 Hz, H-5'), 7.81 (t, 2H, *J* = 6.6 Hz, H-3', H-6'); ¹³C NMR (75 MHz, CDCl₃): δ 20.6, 20.8, 55.1, 63.4, 67.6, 68.8, 70.0, 70.5, 97.3, 99.5, 124.0, 127.4, 130.1, 131.8, 132.6, 148.4, 169.9, 170.8.

3.4.10 Synthesis of compound 77



To a 0 °C solution of compound **76** (200 mg, 0.49 mmol) in 5 mL of CH₂Cl₂ was added Et₃SiH (0.93 mL, 5.84 mmol) and BF₃·Et₂O (0.36 mL, 2.92 mmol). After 16 h, the reaction solution was diluted with 20 mL of CH₂Cl₂, washed with sat NaHCO₃ and brine, dried over MgSO₄, and evaporated. The crude product was purified with column chromatography (EtOAc:cyclohexane=1:2) to afford the compound **77** (146 mg, 73%). TLC: R_f = 0.51 (EtOAc:cyclohexane=1:2); ¹H NMR (300 MHz, CDCl₃): δ 2.08 (s, 3H, OAc), 2.12 (s, 3H, OAc), 3.41 (s, 3H, OMe), 3.83-3.95 (m, 3H), 4.01-4.04 (m, 1H), 4.71 (s, 1H, H-1), 4.99 (s, 2H, PhCH₂), 5.17-5.22 (m, 2H, H-7a, H-7b), 7.45 (t, 1H, *J* = 7.3 Hz, H-4'), 7.64 (t, 1H, *J* = 7.3 Hz, H-5'), 7.78 (d, 1H, *J* = 7.3 Hz, H-3'), 8.04 (d, 1H, *J* = 7.3 Hz, H-6'); ¹³C NMR (75 MHz, CDCl₃): δ 20.8, 20.8, 55.1, 66.3, 69.7, 70.2, 70.3, 71.4, 71.9, 98.6, 124.6, 128.1, 128.7, 133.4, 134.5, 147.5, 169.9, 170.9.

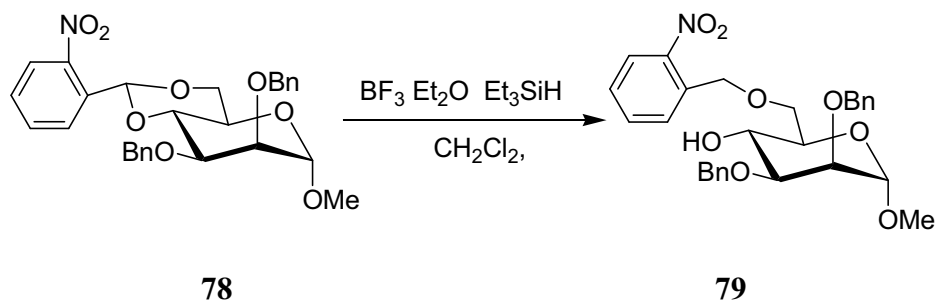
3.4.11 Synthesis of compound 78



To a 0 °C solution of compound **75** (190 mg, 0.58 mmol) in 5 mL of DMF was added NaH(60%) (70 mg, 1.74 mmol). After 45 min, BnBr (208 μL, 1.74 mmol) was added and the solution was stirred for another 32 h, then quenched with 5 mL of MeOH. After evaporation, the residue was partitioned with CH₂Cl₂ (3×10 mL) and H₂O (20 mL). The combined organic layer was dried over MgSO₄, evaporated and purified with column chromatography (EtOAc:cyclohexane=1:3) to afford compound **78** (229 mg, 78%). TLC: R_f = 0.84 (EtOAc:cyclohexane, 2:3); [α]_D = -10.3 (*c* 0.52, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 3.31 (s, 3H, OMe), 3.73 (td, 1H, *J*_{4,5} = *J*_{5,6a} = 9.9 Hz, *J*_{5,6b} = 4.2 Hz, H-5), 3.83 (dd, 1H, *J* = 1.5 and 3.0 Hz, H-2), 3.87-3.93 (m, 2H, H-6a, H-6b), 4.20 (dd, 1H, *J* = 3.6 and 10.2 Hz, H-3), 4.28 (t, 1H, *J* = 9.9 Hz, H-4), 4.59 (d, 1H, *J* = 12.0 Hz, CHPh), 4.68 (d, 1H, *J* = 1.2 Hz, H-1), 4.72 (d, 1H, *J* = 9.3 Hz, CHPh), 4.76 (d, 1H, *J* = 9.3 Hz, CHPh), 4.83 (d, 1H, *J* = 12.3 Hz, CHPh), 6.25 (s, 1H, H-7), 7.28-7.36 (m, 10H, 2×Ph), 7.50 (t, 1H, *J* = 7.4 Hz, *o*-NO₂-PhH), 7.62 (t, 1H, *J* = 7.4 Hz, *o*-NO₂-PhH), 7.87 (m, 2H, 2×*o*-NO₂-PhH); ¹³C NMR (75 MHz, CDCl₃): δ 54.8, 63.8, 69.0, 72.8, 73.6, 76.1, 76.2, 79.4, 97.3, 100.5, 124.3, 127.4-128.3, 129.5, 131.5, 132.5, 138.0, 138.6, 148.4; HRESIMS: calcd for [C₂₈H₂₉NO₈+Na]⁺: 530.1791;

found: 530.1794.

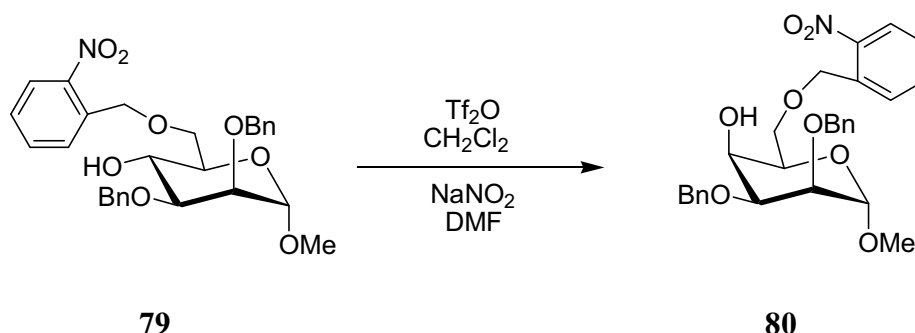
3.4.12 Synthesis of compound 79



To a 0 °C solution of compound **78** (600 mg, 1.18 mmol) in 10 mL of CH₂Cl₂ was added Et₃SiH (2.26 mL, 14.2 mmol) and BF₃·Et₂O (0.88 mL, 7.1 mmol). After 16 h, the solution was diluted with 20 mL of CH₂Cl₂, washed with NaHCO₃ and brine, dried over MgSO₄, evaporated, and purified with column chromatography (EtOAc:cyclohexane=1:4) to afford compound **79** (468 mg, 78%). TLC: R_f= 0.63 (EtOAc:cyclohexane= 2:3); [α]_D = -10.7 (c 0.30, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 3.37 (s, 3H, OMe), 3.69-3.79 (m, 2H, H-4, H-5), 3.81 (dd, 1H, J= 1.8 and 3.0 Hz, H-2), 3.91 (m, 2H, H-6, H-6b), 4.11 (t, 1H, J= 9.5 Hz, H-4), 4.46 (d, 1H, J = 11.8 Hz, CHPh), 4.59 (d, 1H, J=11.7 Hz, CHPh), 4.64 (d, 1H, J =12.3 Hz, CHPh), 4.70 (d, 1H, J=12.3 Hz, CHPh), 4.82 (d, 1H, J= 1.8 Hz, H-1), 5.00 (2d, 2H, PhCH₂), 7.26-7.37 (m, 10H, 2×Ph), 7.40 (t, 1H, J = 8.1 Hz, *o*-NO₂-PhH), 7.58 (t, 1H, J = 8.1 Hz, *o*-NO₂-PhH), 7.86 (d, 1H, J = 8.1 Hz, *o*-NO₂-PhH), 8.06 (d, 1H, J = 8.1 Hz, *o*-NO₂-PhH); ¹³C NMR (75 MHz, CDCl₃): δ 54.8, 66.8, 69.9, 71.56, 71.63, 72.5, 73.6, 79.6, 99.0, 124.4, 127.6-127.7, 128.3, 128.5, 128.6, 133.6, 135.3, 137.9, 138.0. HRESIMS: calcd for [C₂₈H₃₁NO₈+Na]⁺: 532.1947 found: 532.1951.

3.4.13 Synthesis of compound 80

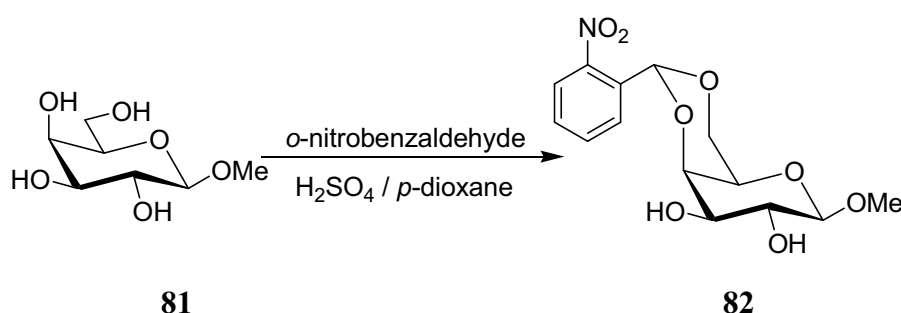
Methyl 2,3-di-*O*-benzyl-6-*O*-(*o*-nitro)benzyl-α-D-talopyranoside



To a -15 °C mixture of Tf₂O (27 μL, 0.16 mmol) and pyridine (25 μL) in 1 mL of CH₂Cl₂ was added a solution of compound **79** (52 mg, 0.1 mmol) in CH₂Cl₂ (1 mL) under Ar. After 2 h, the solution was diluted with 2 mL of CH₂Cl₂, washed with 5% HCl, sat NaHCO₃ and brine. The combined organic layers were dried over MgSO₄, evaporated to remove solvents. The residue was dissolved in 2 mL of DMF, followed by addition of NaNO₂ (73 mg, 1.05 mmol), stirred for 20 h. The solution was diluted with 5 mL CH₂Cl₂, extracted with CH₂Cl₂(3×5

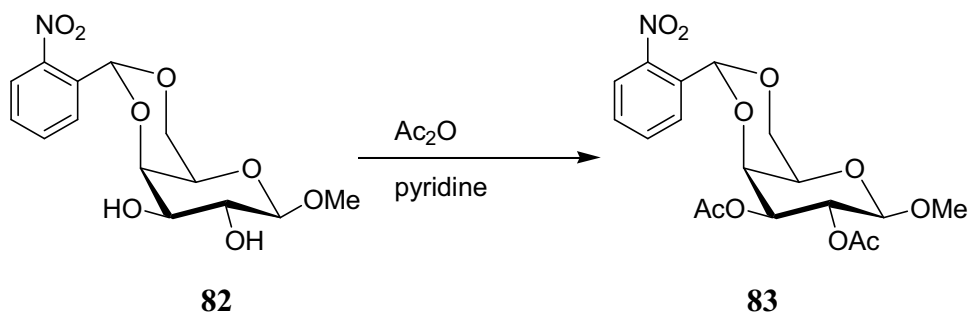
mL), washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (cyclohexane:EtOAc=2:1) to afford compound **80** (43 mg, 57.3 %). TLC: R_f = 0.65 (EtOAc:cyclohexane, 2:3); [α]_D = +37.8 (*c* 2.22, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 3.36 (s, 3H, OMe), 3.77 (m, 1H), 3.88 (m, 2H, H-6a, H-6b), 3.98-4.02 (m, 2H), 4.54 (d, 1H, *J* = 11.7 Hz, CHPh), 4.56 (d, 1H, *J* = 12.1 Hz, CHPh), 4.68 (d, 1H, *J* = 11.7 Hz, CHPh), 4.69 (d, 1H, *J* = 12.1 Hz, CHPh), 4.74 (d, 1H, *J* = 3.8 Hz, H-1), 4.94 (d, 1H, *J* = 12.3 Hz, CHPh), 5.04 (d, 1H, *J* = 12.3 Hz, CHPh), 5.45 (t, 1H, *J* = 9.9 Hz), 7.30-7.39 (m, 10H, 2×Ph), 7.42 (t, 1H, *J* = 8.1 Hz, *o*-NO₂-PhH), 7.55 (t, 1H, *J* = 8.1 Hz, *o*-NO₂-PhH), 7.86 (d, 1H, *J* = 8.1 Hz, *o*-NO₂-PhH), 8.07 (d, 1H, *J* = 8.1 Hz, *o*-NO₂-PhH); ¹³C NMR (75 MHz, CDCl₃): δ 55.3, 68.8, 69.4, 69.8, 72.2, 72.9, 74.4, 77.1, 81.3, 98.9, 124.4, 127.6-128.4, 133.8, 134.9, 137.1, 137.7, 146.5. HRESIMS: calcd for [C₂₈H₃₁NO₈+Na]⁺: 532.1947; found: 532.1962.

3.4.14 Synthesis of compound **82**



To a solution of compound **81** (4 g, 20 mmol) in 20 mL of *p*-dioxane was added NBA (3.04 g, 20 mmol) and conc. H₂SO₄ (1.4 mL) under Ar. After 6 h, the solution was diluted with 30 mL of CH₂Cl₂, neutralised with solid Na₂CO₃, evaporated to remove solvents. The residue was partitioned with CH₂Cl₂ (3×20 mL) and H₂O (20 mL), dried over MgSO₄, evaporated, and purified with column chromatography (cyclohexane:EtOAc=1:1) to afford compound **82** (2.98 g, 59%). TLC: R_f = 0.31 (EtOAc); mp 135-136 °C (EtOAc).

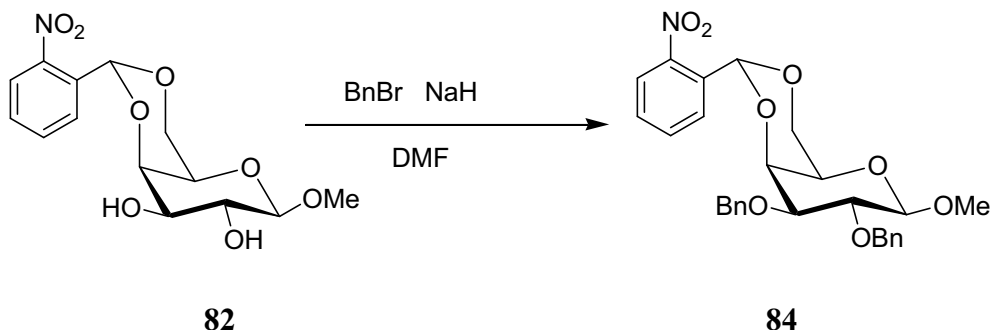
3.4.15 Synthesis of compound **83**



To a solution of compound **82** (201 mg, 0.61 mmol) in 5 mL of pyridine was added 2 mL of Ac₂O. After 16 h, the solution was extracted with CH₂Cl₂ (3×20 mL), washed with brine, dried over MgSO₄, concentrated, and purified with column chromatography (EtOAc:cyclohexane=1:3) to afford compound **83** (152 mg, 61%). TLC: R_f = 0.66 (EtOAc:cyclohexane= 1:1); ¹H NMR (300 MHz, CDCl₃): δ 2.03 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.49 (s, 3H, OMe), 4.09-4.34 (m, 2H, H-6a, H-6b), 4.37-4.42 (m, 3H, H-4, H-1, H-5), 4.98 (dd, 1H, *J* = 3.7 and 10.3 Hz, H-3), 5.58 (dd, 1H, *J* = 10.3 and 8.1 Hz, H-2), 6.13 (s, 1H,

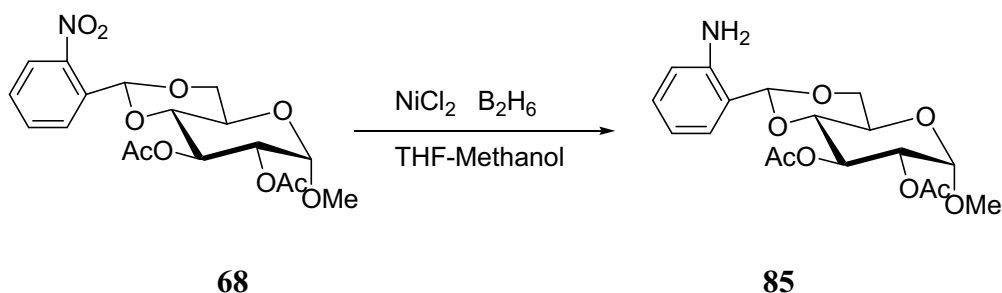
H-7), 7.50 (t, 1H, $J = 8.1$ Hz, H-4'), 7.63 (t, 1H, $J = 8.1$ Hz, H-2'), 7.84 (d, 1H, $J = 8.1$ Hz, H-3'), 7.93 (d, 1H, $J = 8.1$ Hz, H-1').

3.4.16 Synthesis of compound 84



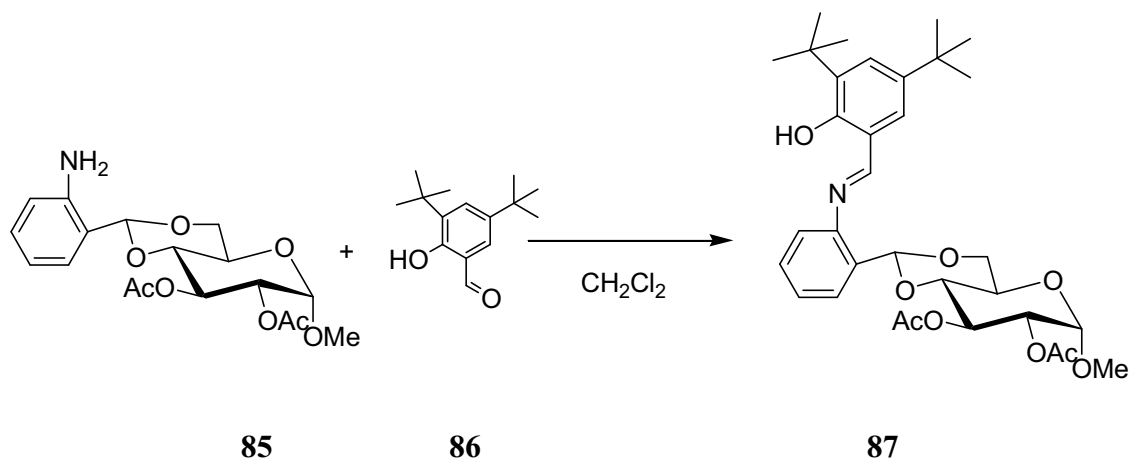
To a 0 °C solution of compound **82** (190 mg, 0.58 mmol) in 5 mL of DMF was added NaH(60%) (70 mg, 1.74 mmol). After 45 min, BnBr (208 μ L, 1.74 mmol) was added and the solution was stirred for another 24 h, then quenched with 5 mL of MeOH, and concentrated. The residue was partitioned with CH₂Cl₂ (3 \times 10 mL) and H₂O(10 mL). The combined organic layers were washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (cyclohexane:EtOAc=3:1) to afford compound **84** (211 mg, 72%). TLC: $R_f = 0.73$ (EtOAc:cyclohexane = 2:3); ¹H NMR (300 MHz, CDCl₃): δ 3.58 (s, 3H, OMe), 3.75 (t, 1H, $J = 7.7$ Hz), 4.09 (d, 1H, $J = 12.4$ Hz), 4.25-4.89 (m, 9H), 6.20(s, 1H, H-7), 7.27-7.37 (10H, Ph), 7.50 (t, 1H, $J = 7.7$ Hz, H-4'), 7.63(t, 1H, $J = 7.7$ Hz, H-2'), 7.84 (d, 1H, $J = 7.7$ Hz, H-3'), 7.93 (d, 1H, $J = 7.7$ Hz, H-1').

3.4.17 Synthesis of compound 85



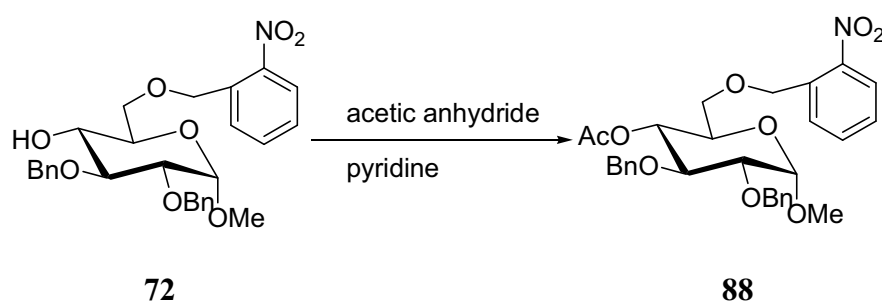
To a solution of compound **68** (54 mg, 0.13 mmol) in THF (3 mL)/MeOH (1 mL) was added NiCl₂·6H₂O (16 mg, 0.066 mmol) and B₂H₆ (1 mL, 1.04 mmol). After 8 h, the reaction solution was evaporated and the residue was partitioned with CH₂Cl₂ and H₂O, dried over MgSO₄, evaporated, purified with column chromatography (cyclohexane:EtOAc=3:1) to afford compound **85** (23 mg, 46 %). TLC: $R_f = 0.32$ (EtOAc:cyclohexane=1:2); ¹H NMR (300 MHz, CDCl₃): δ 2.04 (s, 3H, OAc), 2.10 (s, 3H, OAc), 3.42 (s, 3H, OMe), 3.63-3.97 (m, 3H, H-5, H-6a,6b), 4.32 (t, 1H, $J = 4.77$ Hz, H-3), 4.93 (m, 2H, H-1, H-2), 5.57(m, 2H, H-1, H-7), 6.66-6.76 (m, 2H, *o*-NO₂-PhH), 7.12 (d, 1H, $J = 8.1$ Hz, *o*-NO₂-PhH), 7.21 (d, 1H, $J = 8.1$ Hz, *o*-NO₂-PhH); ¹³C NMR (75 MHz, CDCl₃): δ 20.68, 20.81, 55.17, 61.92, 69.80, 70.65, 71.10, 73.36, 96.72, 128.8-129.5, 135.10, 135.62, 170.24, 171.86, 193.99

3.4.18 Synthesis of compound 87



To a solution of compound **85** (140 mg, 0.34 mmol) in 5 mL of CH_2Cl_2 was added compound **86** (96 mg, 0.41 mmol) and MgSO_4 (20 mg). After 1 week, the solution was washed with H_2O , extracted with CH_2Cl_2 , the combined organic layers were washed with brine, dried over MgSO_4 , concentrated to afford compound **87** (63 mg, 31%). TLC: $R_f = 0.71$ (EtOAc:cyclohexane=1:2); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 1.32 (s, 9H, $3\times\text{CH}_3$), 1.51 (s, 9H, $3\times\text{CH}_3$), 1.69 (s, 3H, OAc), 2.03 (s, 3H, OAc), 3.40 (s, 3H, OMe), 3.68-3.98 (m, 3H, H-5, H-6a,6b), 4.31 (t, 1H, $J = 4.4$ Hz, H-3), 4.85 (dd, 1H, $J = 4.1$ and 3.7 Hz, H-2), 4.92 (d, 1H, $J = 3.7$ Hz, H-1), 5.52 (t, 1H, $J = 4.4$ Hz, H-4), 5.86 (s, 1H, H-7), 7.40-7.78 (m, 6H, Ar-H), 8.58 (s, 1H, $\text{CH}=\text{N}$); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 20.17, 20.62, 29.17, 29.35, 31.22, 31.35, 34.09, 35.09, 55.17, 62.26, 68.80, 71.57, 79.30, 97.52, 98.84, 117.63, 118.24, 119.90, 126.43, 126.48, 126.74, 128.15, 130.15, 130.32, 135.62, 137.14, 140.59, 146.42, 158.41, 158.99, 163.75, 169.90, 170.18.

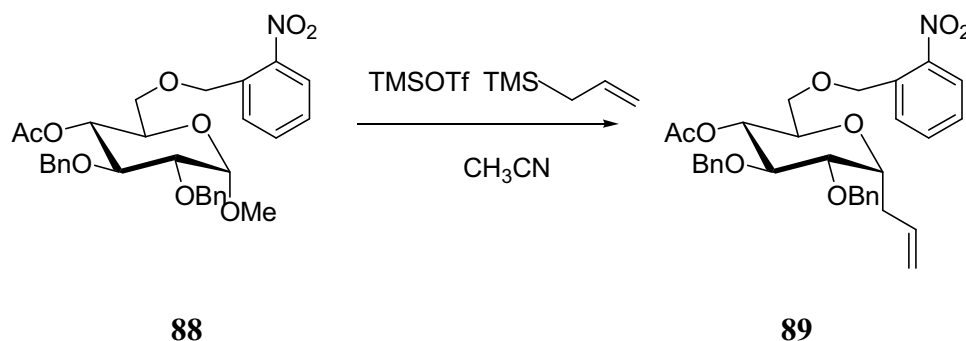
3.4.19 Synthesis of compound 88



To a solution of compound **72** (390 mg, 0.77 mmol) in 8 mL of pyridine, was added 1 mL of Ac_2O . After 16 h, the solution was extracted with CH_2Cl_2 (3×10 mL), washed with brine. The combined organic layers were dried over MgSO_4 , evaporated, purified with column chromatography (EtOAc:cyclohexane=1:5) to afford compound **88** (388 mg, 92%). TLC: $R_f = 0.53$ (EtOAc:cyclohexane, 1:3); $[\alpha]_D = +50.0$ (c 0.53, CH_2Cl_2); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 1.89 (s, 3H, OAc), 3.42 (s, 3H, OMe), 3.58-3.63 (m, 3H, H-2, H-6a,H-6b), 3.84-3.89 (m, 1H, H-5), 3.94 (t, 1H, $J = 9.5$ Hz, H-3), 4.64 (m, 2H, CH_2Ph), 4.68 (d, 1H, $J = 1.2$ Hz, H-1), 4.79-4.96 (m, 4H, $2\times\text{CH}_2\text{Ph}$), 5.07 (dd, 1H, $J = 9.6$ and 9.2 Hz, H-4), 7.27-7.38 (m, 10H, $2\times\text{Ph}$), 7.41 (t, 1H, $J = 8.1$ Hz, *o*- NO_2 -PhH), 7.54 (t, 1H, $J = 8.1$ Hz, *o*- NO_2 -PhH), 7.85 (d, 1H,

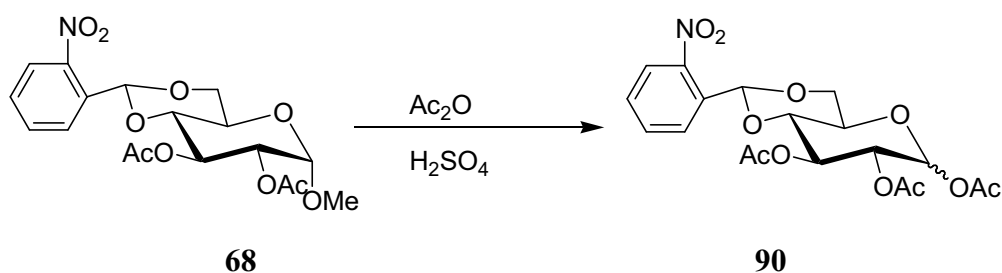
$J = 8.1$ Hz, *o*-NO₂-PhH), 8.05 (d, 1H, $J = 8.1$ Hz, *o*-NO₂-PhH); ¹³C NMR (75 MHz, CDCl₃): $\delta = 20.8, 55.3, 68.6, 69.8, 69.9, 70.2, 73.4, 75.3, 79.2, 79.6, 98.1, 124.4, 127.5, 127.7-128.4, 128.6, 133.7, 134.8, 137.8, 138.5, 146.9, 169.6$; HRESIMS: calcd for [C₃₀H₃₃NO₉+Na]⁺: 574.2053; found: 574.2039.

3.4.20 Synthesis of compound 89



To a solution of compound **88** (52 mg, 0.1 mmol) in 2 mL of CH₃CN, was added TMS Allyl (0.08 mL, 0.5 mmol) and TMSOTf (0.1 mL, 0.5 mmol). After 72 h, the reaction solution was diluted with 5 mL of CH₂Cl₂, extracted with CH₂Cl₂ (2×5 mL), washed with brine, dried over MgSO₄, evaporated, purified with column chromatography (cyclohexane:EtOAc=3:1) to afford compound **89** (34 mg, 71%). TLC: $R_f = 0.59$ (EtOAc:cyclohexane, 1:3); $[\alpha]_D = +48.3$ (*c* 1.21, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 1.93 (s, 3H, OAc), 2.52 (m, 2H, CH₂C=), 3.63 (m, 2H, H-6'a, H-6'b), 3.70-3.85 (m, 3H), 4.07-4.13 (m, 1H), 4.57-4.70 (m, 3H), 4.81-4.88 (m, 3H), 5.00-5.17 (m, 3H, H-4, PhCH₂), 5.76-5.85 (m, 1H, =CH), 7.28-7.34 (m, 10H, 2×Ph), 7.36 (t, 1H, $J = 6.6$ Hz, *o*-NO₂-PhH), 7.41 (t, 1H, $J = 6.6$ Hz, *o*-NO₂-PhH), 7.85 (d, 1H, $J = 6.6$ Hz, *o*-NO₂-PhH), 8.04 (d, 1H, $J = 6.6$ Hz, *o*-NO₂-PhH); ¹³C NMR (75 MHz, CDCl₃): δ 20.9, 30.3, 69.8, 70.2, 70.3, 70.4, 73.0, 73.1, 74.6, 78.2, 78.9, 117.1, 124.4, 127.6, 127.7-127.8, 128.3, 128.4, 128.7, 133.7, 134.3, 135.0, 137.9, 138.2, 146.8, 169.8. HRESIMS: calcd for [C₃₂H₃₅NO₈+Na]⁺: 584.2260

3.4.21 Synthesis of compound 90



To a solution of compound **68** (7.8 mg, 19 μ mol) in 5 mL of Ac₂O, was added a solution of conc. H₂SO₄ (98%, 5 μ L) in 2 mL of H₂O. After 20 h, the reaction was neutralised with solid NaHCO₃, extracted with CH₂Cl₂ (2×5 mL), washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (cyclohexane:EtOAc=3:1) to afford compound **90** as a mixture of α - and β -anomer (2.9 mg, 35%). TLC: $R_f = 0.47$ (EtOAc:cyclohexane, 1:3).

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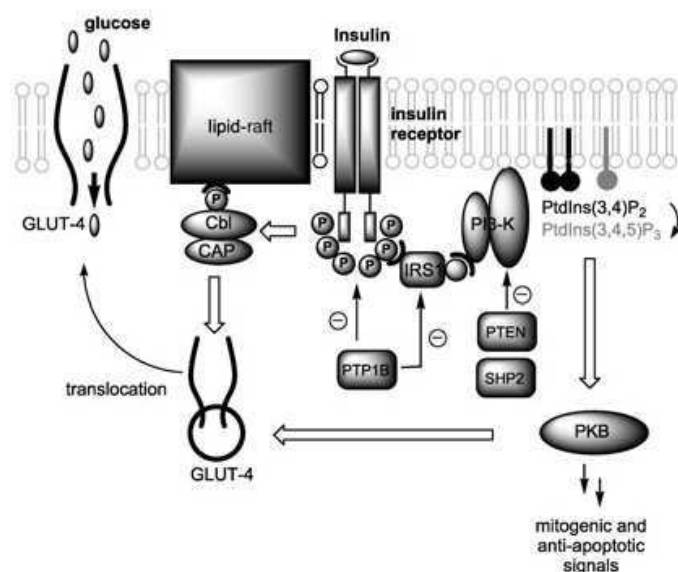
Chapter 4 Synthesis of glycosyl amino acids as potential inhibitors of PTP-1B

4.1 Introduction

Up to the end of 2006, there are already more than 246 million people suffered from diabetes and obesity all over the world. Furthermore, the total patients of diabetes would exceed 380 million if there is not any measure to be taken in future 20 years. And 75% of the obesity patients have the dangerous of suffering from diabetes. Only in 2005, there are about 2.9 million people died from diabetes throughout the world. Diabetes, one of human severe diseases, consists of one fifth reasons of death. Therefore, development of the treatment and high effective drugs for diabetes became more and more urgent.^{1,2}

4.1.1 PTP-1B and non-insulin-dependent diabetes mellitus

Non-insulin-dependent diabetes mellitus (type 2 diabetes), which accounts for 95% of all diabetes cases, is characterized by a deficient insulin cascade and is therefore also termed insulin resistance (IR).³ Recent studies demonstrate that the Protein tyrosine phosphatase 1B (PTP-1B) has close relationship with diabetes and obesity, and plays a key role in the negative regulation of insulin and leptin signaling transduction pathway. Leptin is a peptide hormone that is produced by fat cells and plays a role in body weight regulation by acting on the hypothalamus to suppress appetite and burn fat stored in adipose tissue. PTP1B works as an insulin antagonist through the excess dephosphorylation and inactivation of the insulin receptor for insulin resistance. Furthermore, the over expression of PTP-1B makes the leptin receptor not responsive to leptin signaling and results in obesity (leptin resistance, LR). Therefore, PTP1B has attracted considerable attention as a possible therapeutic target for type 2 diabetes and obesity.^{4,5}



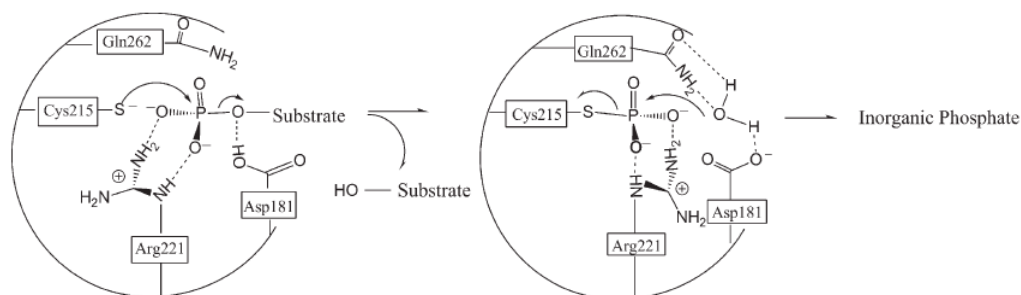
Schematic Illustration of Insulin-dependent Signaling and Relevant Interactions with PTP1B³

Insulin binds the α -chain of the insulin receptor (IR) to cause a conformational change activating the kinase activity of the β -chain and auto-phosphorylating its activation loop. This autophosphorylation further activates the kinase activity to phosphorylate other sites on the β subunit recruiting and phosphorylating different substrates including the insulin receptor substrates (IRSs, for example IRS1). The phosphorylated IRSs recruit phosphatidylinositol 3-kinase (PI3K) resulting in its activation, converting phosphatidyl inositol into 3,4-bis and 3,4,5-trisphosphate which stimulate the activity of phosphoinositide-dependent kinase 1 or 2 (PDK1/2) which in turn activate Akt. Akt is involved in the translocation of GLUT4 transporter to the cell surface for glucose uptake and also promotes glycogen synthesis. In addition to the effects of insulin on glucose metabolism, the insulin-signalling pathway also stimulates transcriptional events: IRS1 forms a complex with Shc and the growth-factor-receptor-binding protein 2 (GRB2) to stimulate the mitogen activated protein kinase (MAPK) pathway. PTP1B has been shown to directly dephosphorylate IR, IRS(s) and Shc.

4.1.2 Structure character of PTP1B⁶⁻⁸

As the novel target for drug development of the diabetes and obesity, recent studies focus on the crystal structure of PTP1B and how inhibitors work. PTP1B consists of 435 amino acids. The active site of PTP1B is defined by residues 214-221 (the P-loop which binds the phosphate group and contains the catalytic Cys215). The mobile WPD loop (Tyr179Pro180Asp181) is responsible to the peptide substrate recognition, by forming one boundary of the binding pocket and contains the general acid/base Asp181, and the Tyr46 and Phe182 define the depth of the pTyr-binding pocket⁹. Other important residues include Arg47, Lys120 and Val 49 which offer electrostatic, hydrogen-bonding and hydrophobic interactions.

It is admitted that the PTP-mediated catalysis proceeds via a two-step process¹⁰.



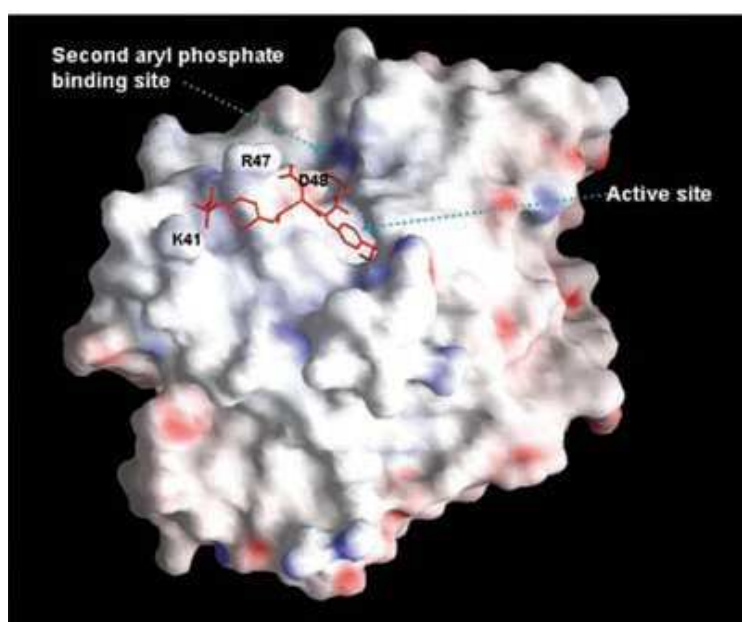
Mechanism for the PTP1B-catalyzed dephosphorylation reaction.

In this mechanism, PTP1B utilizes the active-site cysteine residue (Cys215) as nucleophile to form a covalent thiophosphoryl enzyme intermediate. The phosphoenzyme formation step is assisted by a conserved aspartic acid (Asp181) which protonates the leaving group thereby acting as a general acid catalyst. In the second step, the hydrolysis of the phosphoenzyme intermediate occurs by the nucleophilic attack of a water molecule assisted by Asp181, which functions as a general base, with subsequent release of the free enzyme and inorganic phosphate. A conserved glutamate residue (Gln262) is important for the precise placement of the water nucleophile for phosphoenzyme hydrolysis. The arginine residue (Arg221) mediates substrates binding and transition state stabilisation.

Up to date, various therapeutic strategies have been developed for targeting PTP1B in diabetes^{11,12}. Inhibitors of PTP1B generally fall into two categories: nonhydrolysable phosphotyrosine mimetics (or affinity-based) and covalent inactivators. The first category has received the most attention; numerous phosphotyrosine mimetics have been reported, including difluoromethylphosphonates, cinnamic acid, oxalylamino benzoic acid, isoxazole carboxylic acid, salicylic acid, α -ketocarboxylic acid, etc. The second category of inhibitors consists largely of reactive molecules which modify the active site Cys215, like naphthoquinone as Michael acceptor or oxidant, and halomethyl ketones as alkylating agents¹³. High-affinity inhibitors against PTP1B have been elaborated by industrial and academic laboratories. However, because of the high homology of the PTP family of enzymes, the design of selective inhibitors is a challenging hurdle. Furthermore, many of the reported phosphotyrosine mimics are highly charged, which makes them less attractive as drug candidates.

Recently, two naturally occurring allosteric binding sites have been identified in the PTP1B. The crystal structure of PTP1B/C215S complexed with low molecular weight nonpeptidic substrate revealed the presence of a second aryl phosphate-binding site positioned adjacent to

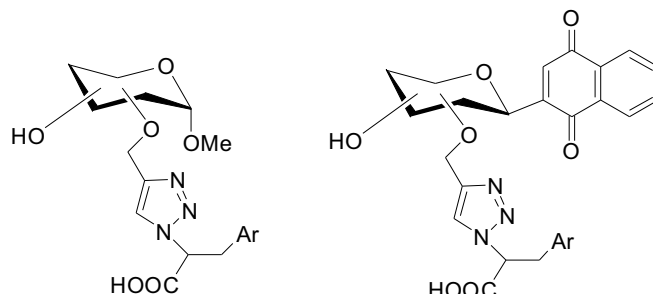
the active site¹⁴. In addition to this second aryl phosphate binding site, a novel allosteric site located ~20 Å from the catalytic site has been discovered from the crystal structure of PTP1B in complex with allosteric inhibitor which block the mobility of the catalytic “WPD” loop, thereby preventing formation of the active form of the enzyme. Discovery of the allosteric sites presents an opportunity for developing more selective inhibitors, as the key residues involved in compound binding are not conserved in most PTP. In addition, the structural adaptability of the allosteric sites may afford increasing flexibility in drug design. A bidentate ligand that binds both the catalytic site and allosteric site should lead to more selective and high-affinity inhibitors. Several potent and remarkable selective bidentate inhibitors of PTP1B have been developed¹⁵⁻¹⁸.



Overall binding mode of an inhibitor with PTP1B

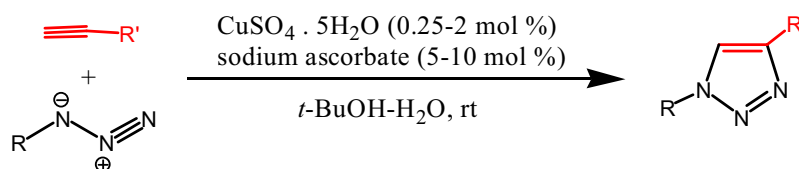
Based on the structure of PTP1B, we decided to develop sugar-based inhibitors for the following reasons: First, sugars are natural compounds containing many functional groups and well-defined stereogenic centers in one molecular unit. Consequently, they are useful building blocks for the design and synthesis of a rich library compounds, including mono- and bidentate inhibitors. Second, a range of glycolipids like glucolipin, caloporoside and woodrosine were identified as micromolar inhibitors of PTPases. Recently, peracetylated β -D-glucopyranosyl-1,4-benzoquinone has also been found to be an inhibitor of PTP1B ($IC_{50} = 4.85 \mu M$).¹⁹ Third, sugar derivatives have already been used to improve the membrane permeability or the cell assimilation of some molecules (e.g. glycosylated enkephalin, toxophores, oligonucleotides, proteins and polymers). Finally, appropriate protection of sugar hydroxyl function might allow controlling the hydrophilic/hydrophobic character of

molecules. Encouraged by the inhibitory activity of β -D-glucopyranosyl-1,4-benzoquinone discovered by Prof. Chen's group in 2005,¹⁹ we decided to prepare glycosylated tyrosine or phenylalanine derivative conjugated with or without 1,4-naphthoquinone moiety as potential inhibitors of PTP1B:



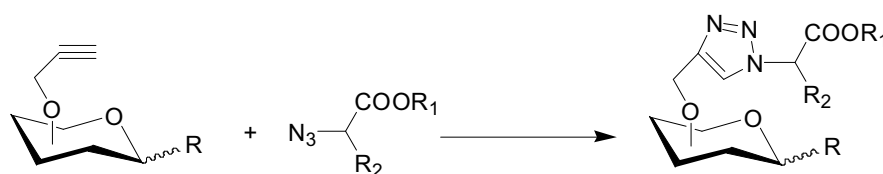
4.1.3 Click chemistry for the connection between amino acids and sugar

Click chemistry, a concept introduced by Sharpless and co-workers in 2001,²⁰ is used to describe almost perfect chemical reactions that share a number of important properties which include very high efficiency in terms of both conversion and selectivity under very mild reaction conditions, and a simple workup. Among these carefully selected reactions, the Cu(I)-catalysed Huisgen 1,3-dipolar cycloadditions of terminal alkynes with organic azides were shown to be the most effective and versatile and have been recently receiving attention as a high efficient and stereo selective reaction associated with excellent functional groups compatibility. In many instances, water is an ideal reaction solvent, providing the best yields and highest rates.

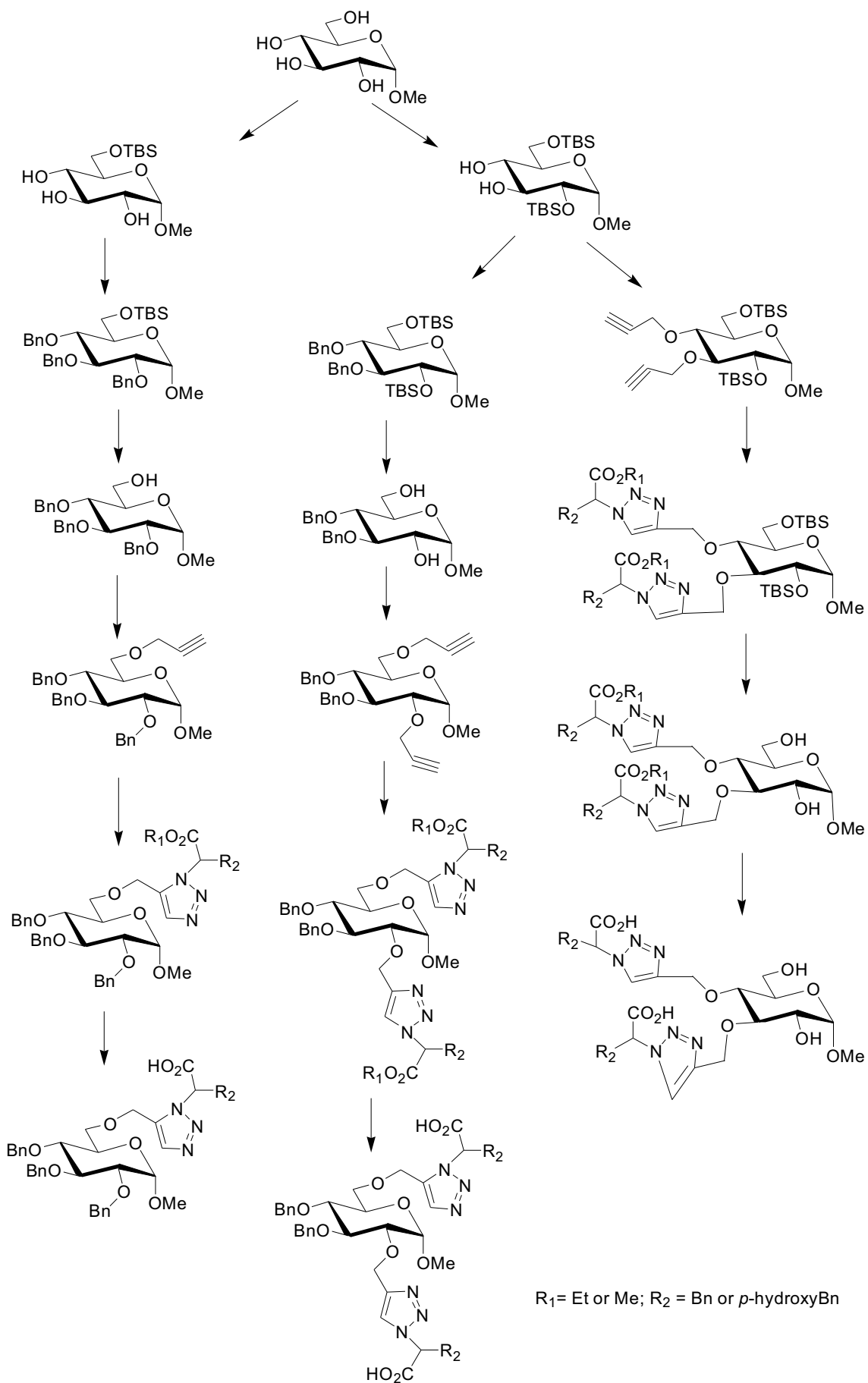


Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition

Because of the convenience of click chemistry, we plan to link amino acid to sugar moiety via click chemistry. The route is as followed:



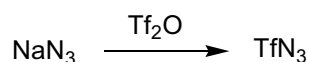
Starting from methyl α -glucopyranoside, the general synthetic way of the target compounds is summarized in the following scheme:



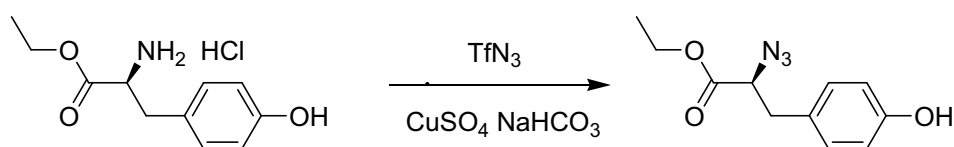
4.2 Results and discussion

4.2.1 Synthesis of azido acids

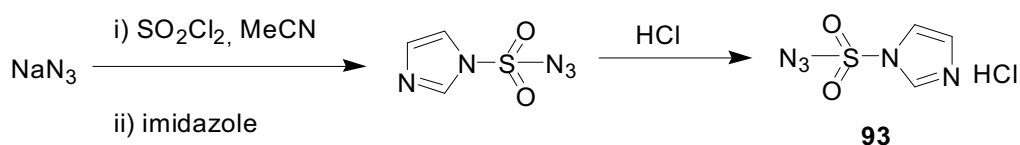
Transformation of amine to azide is usually realized with TfN_3 which could be prepared by reacting sodium azide with triflic anhydride.²¹



We have used TfN_3 to synthesize azido acids from the corresponding amino acids. The yield is more than 69 %.



However, Tf_2O is very expensive and TfN_3 is not easy for use. In 2007, Stick and coll. reported a new solid reagent, the imidazole-sulfonyl azide hydrochloride **93** for the conversion of amine to azide.²² Furthermore, this solid compound is stable enough for deposited a long time.



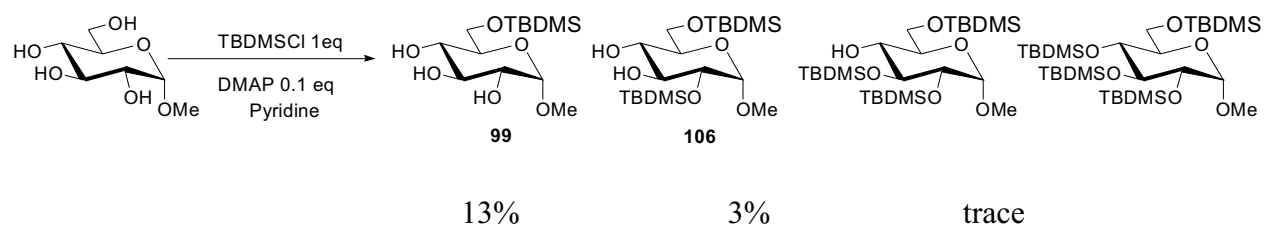
We found that the effects of two reagents are very similar to transform the following amino acids to the corresponding azido acids, so we chose the cheaper compound **93**.

Amino acid	Reagents	
	TfN_3	Imidazole-sulfonyl Azide Hydrochloride 93
Tyr-OEt	74%	71%
Phe-OMe	79%	77%
Val-OMe	69%	63%

4.2.2 Silylation of methyl α -D-glucopyranoside

TBDMS is a popular protecting group. According to the equivalence of TBDMSCl , the reaction would afford different products. We found that reactivity of methyl α -D-glucopyranoside is as follows: 6>2>3>4.

With 1 eq. of TBDMSCl in the presence of 0.1 eq. of DMAP in pyridine, there is mixture of four products, as well as the starting material:

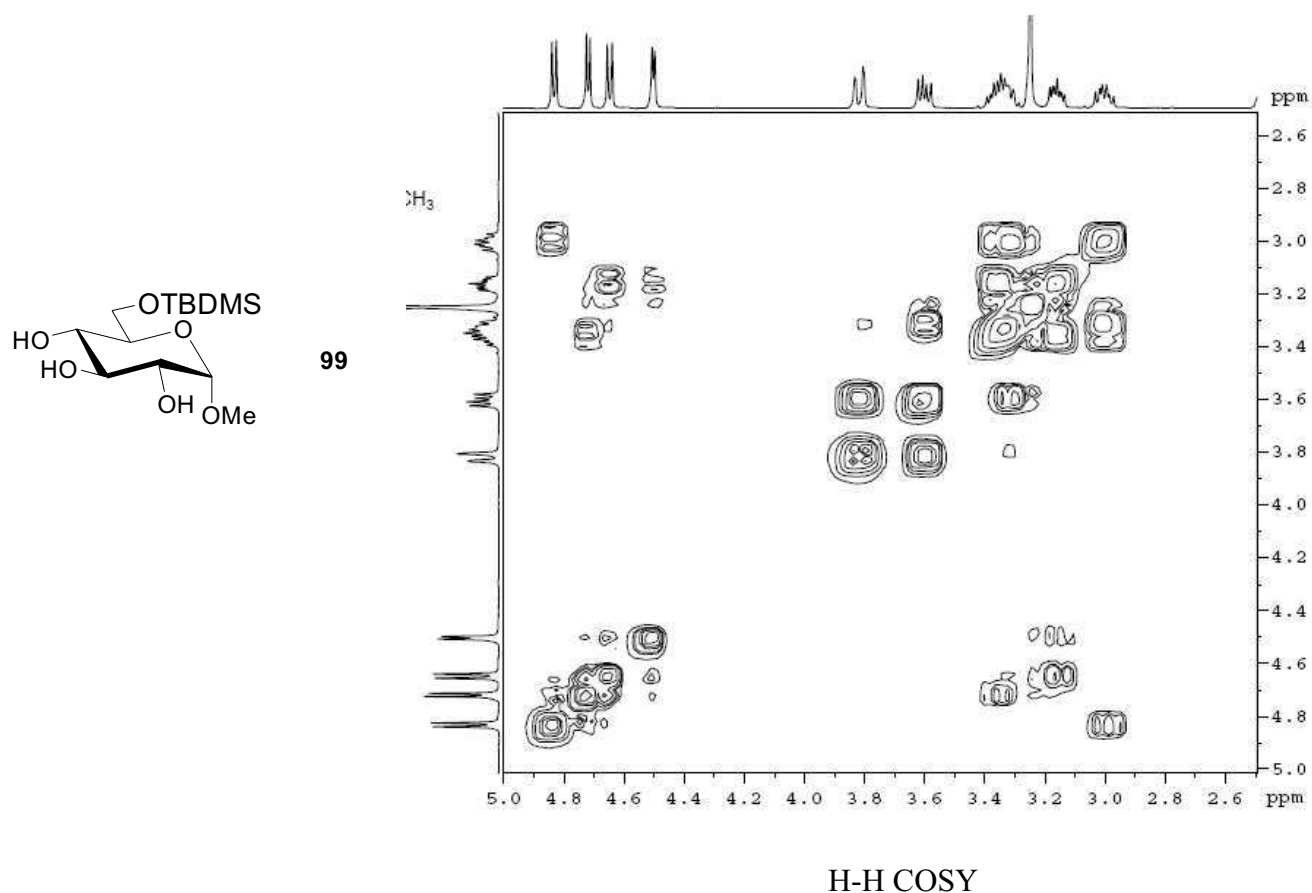


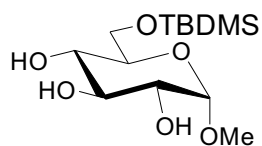
Modification of equiv of TBDMSCl gave the result is as followed:

Different equiv of TBDMSCl afford different product

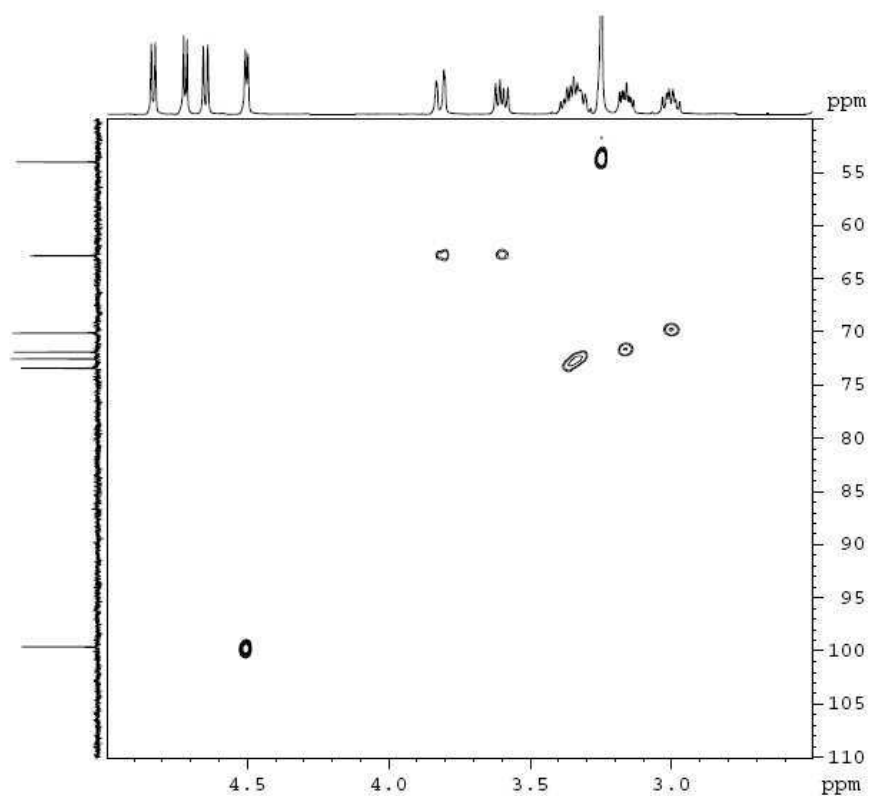
TBDMSCl (equiv)	99 %	106 %	Three TBDMS %	Four TBDMS %
1	78	13	3	
1.5	71	15	3	2
2	56	26	7	4
3	32	55	9	5
3.8	2	71	11	4
5		14	69	14

Consequently, we can selectively prepared mono- and di-silylated compounds **99** and **106** which were used as starting material for the preparation of glycosyl amino acid derivatives. Structure of both compounds has been confirmed by COSY and HSQC analysis.





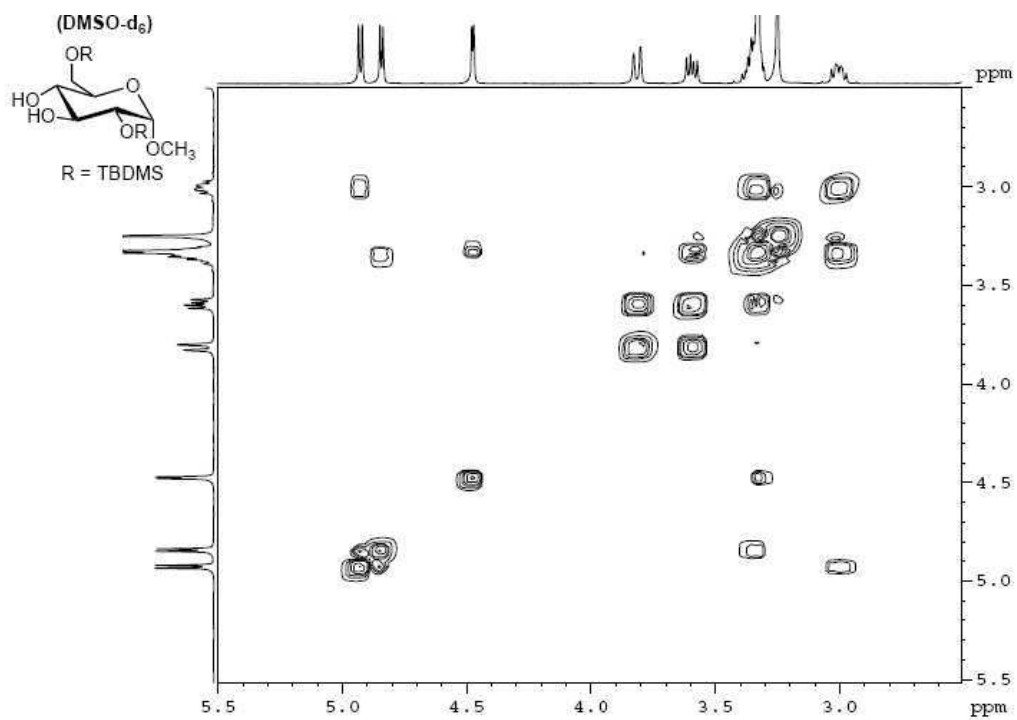
99



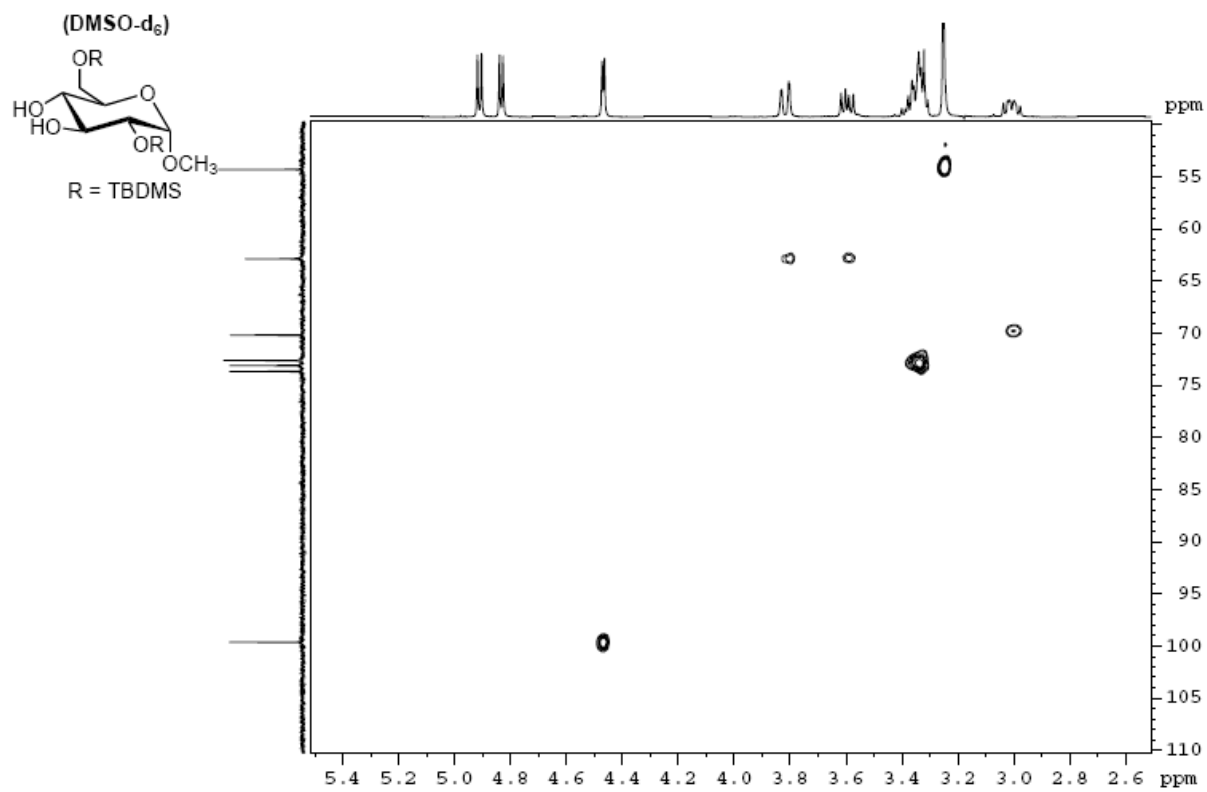
C-H HSQC

The NMR of compound 106

No / Group	Chemical shift (ppm) DMSO	
	¹ H	¹³ C
OMe	3.25	54.3
Si(CH ₃) ₂	0.02-0.03	-5.3, -5.0, -4.4
C(CH ₃) ₃	0.84-0.85	17.9, 25.7
1	4.48	99.6
2	3.34	73.1
3	3.36	72.6
4	3.00	70.2
5	3.31	73.6
6	3.60, 3.82	62.8
OH-3	4.84	
OH-4	4.93	



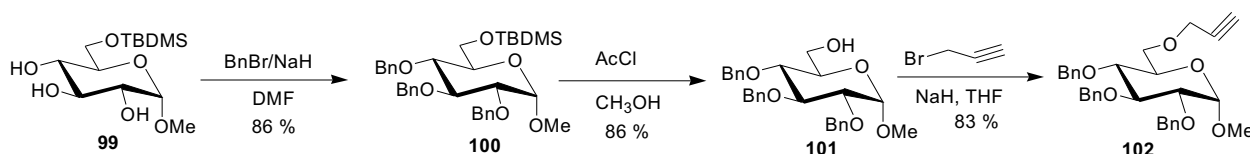
H-H COSY



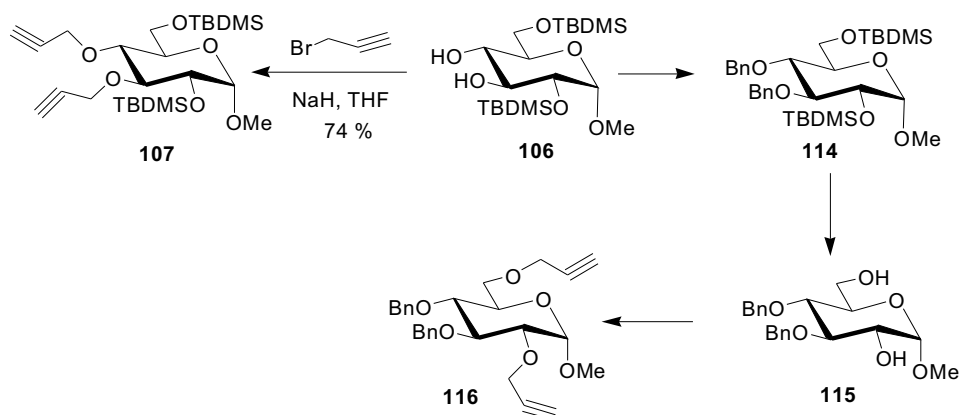
C-H HSQC

4.2.3 Synthesis of glycoside fonctionnalized with propargyl ether

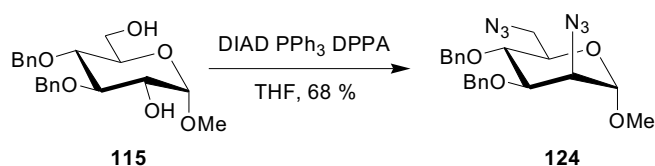
In order to realise the Click reaction with azido esters, we need to introduce the propargyl group on the sugar. For this propose, the free hydroxy group of compounds **99** and **106** were then protected as benzyl ether. After desilylation under acidic condition, propargyl ether can then be introduced. Compound **102** has been easily prepared from **99** in good yield.



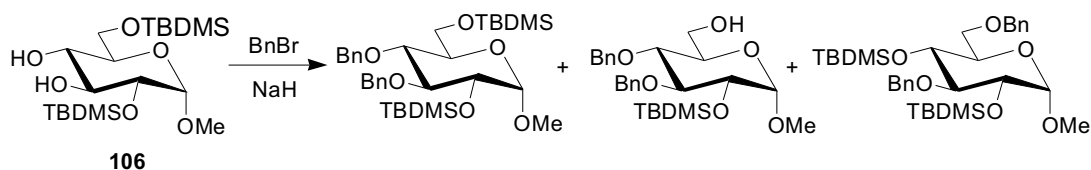
From **106**, it's possible to prepare both 2,6-O-dipropargyl and 3,4-dipropargyl ethers **107** and **116**. Treatment of **106** with propargyl bromide under basic condition afforded compound **107** in 74 % yield.



By the way, compound **115** can also be used to prepare di-azido compound **124** for Click reaction:

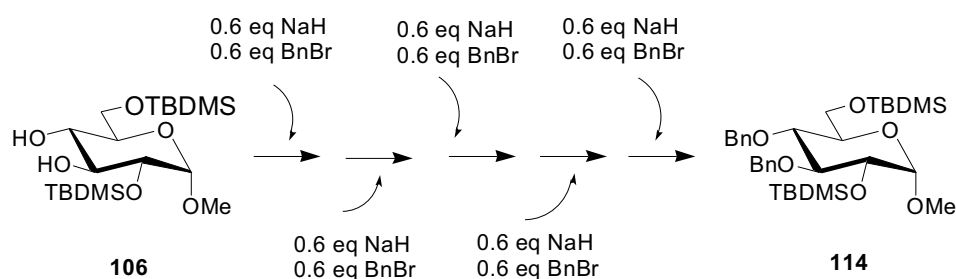


When we tried to protect the OH of compound **106** as benzyl ether under usual condition, TLC showed the presence of several products which are difficult to be separated. According to the NMR spectra, we found that 6-O-silyl group has been partially deprotected:



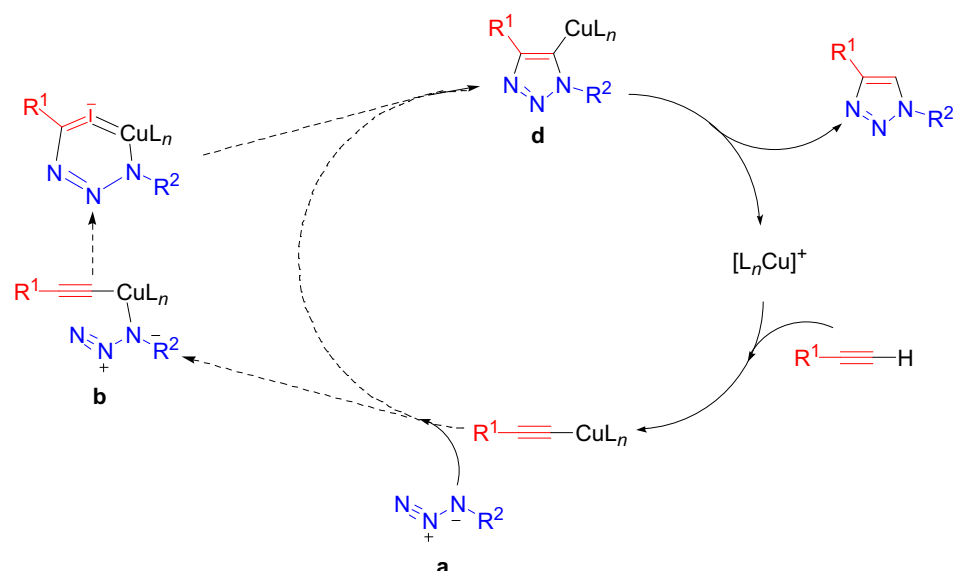
Finally, based on the report of D.Prospéri²³, we added NaH(60%) and BnBr in small portions over 30 min (NaH and BnBr must be added at the same time), the expect product can be obtained in 86%

yield. Successive desilylation and O-propargylation afforded the desired compound **116**.

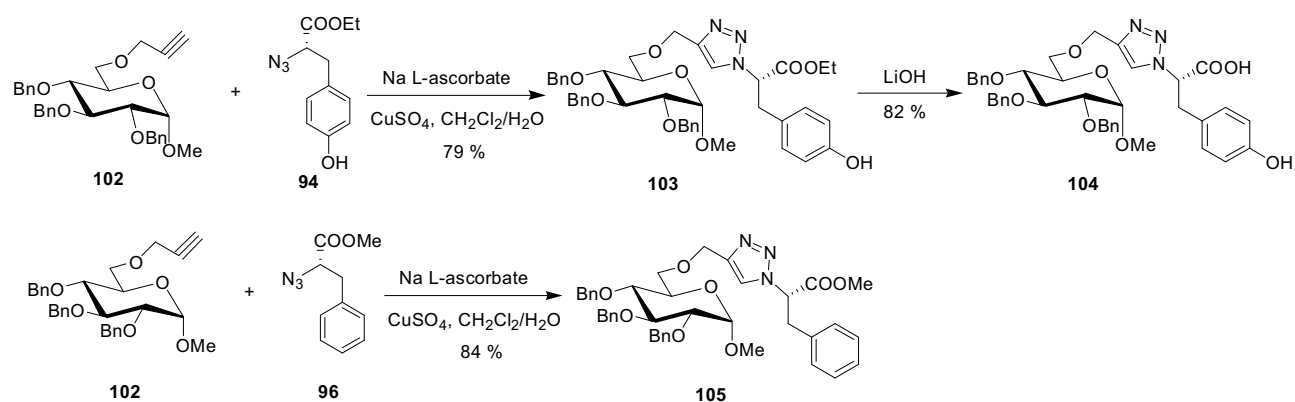


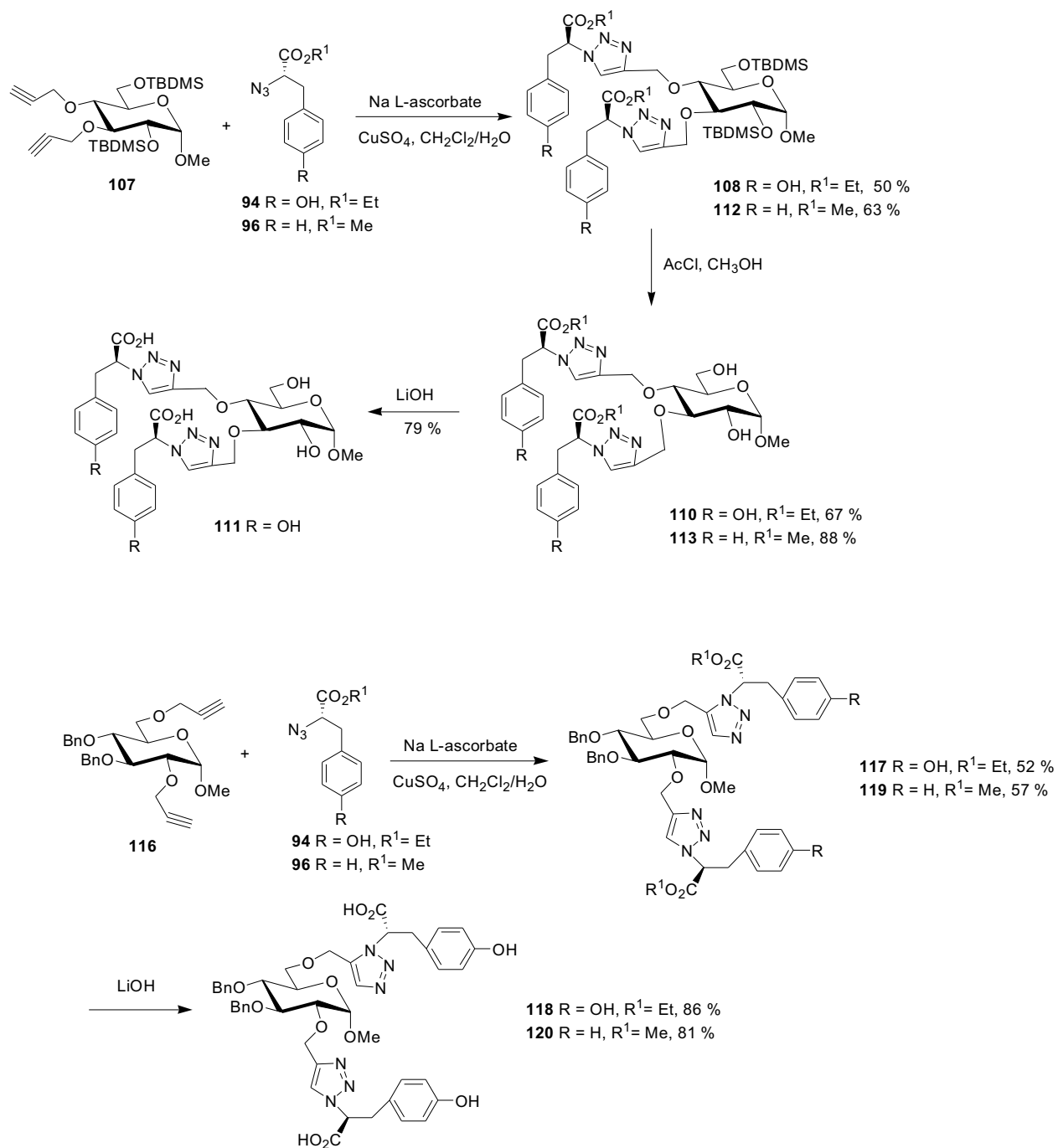
4.2.4 Click reaction

The Cu^I-catalysed Huisgen 1,3-dipolar cycloaddition is a very useful reaction, the mechanism is as followed:

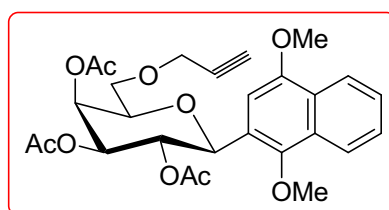
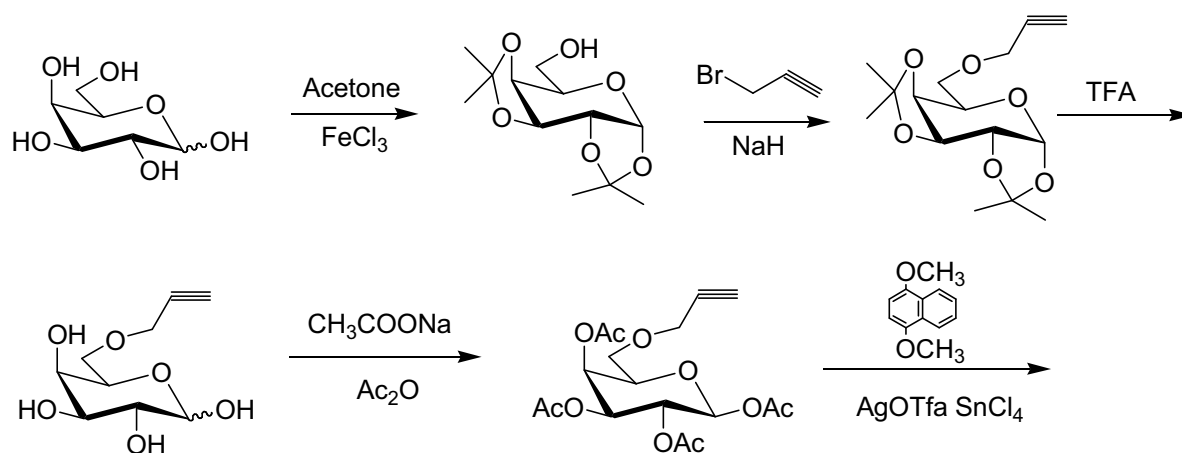


Cycloaddition between different azido esters and alkyne derivatives **102**, **107** and **116** afforded the desired compounds **104**, **105**, **108**, **112**, **117** and **119** in good yield. These compounds have been further desilylated or saponificated to obtain glycosyl azido acids **104**, **111**, **118** and **120**.

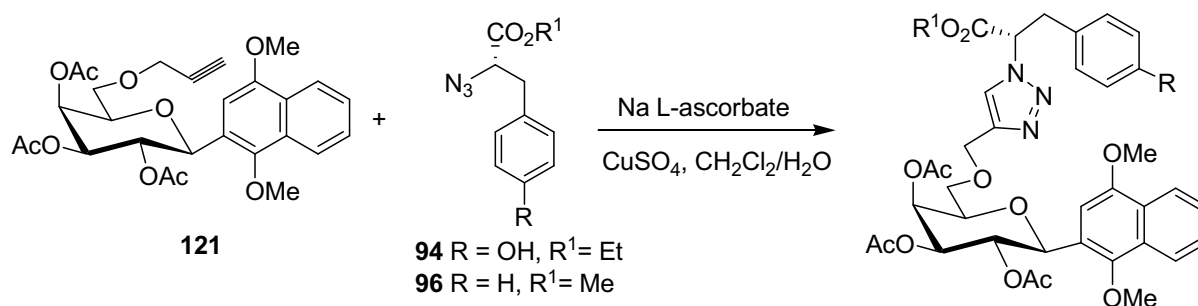




We have also tried the Click reaction on the C-aryl galactoside **121** to lead to compounds **122** and **123**. Unfortunately, we have not time to oxidize the dimethoxynaphthyl group to naphthoquinone derivative.



121



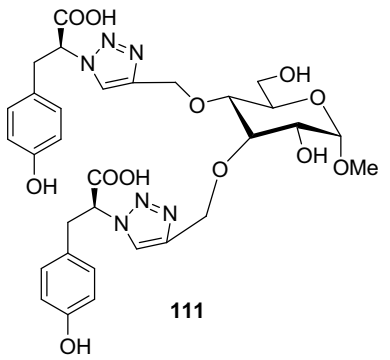
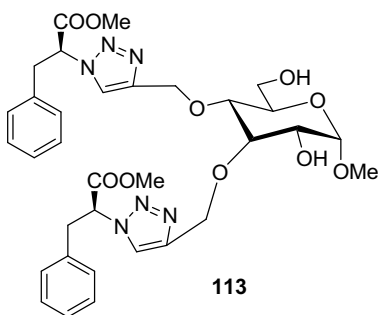
122 R = OH, R¹ = Et, 61 %

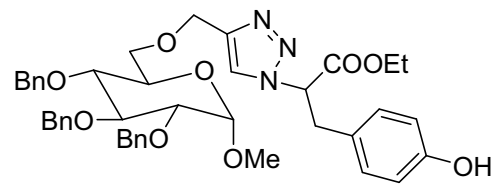
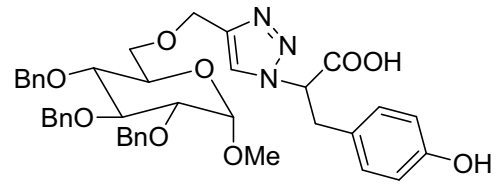
123 R = H, R¹ = Me, 52 %

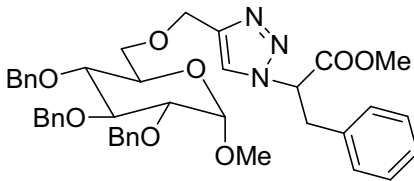
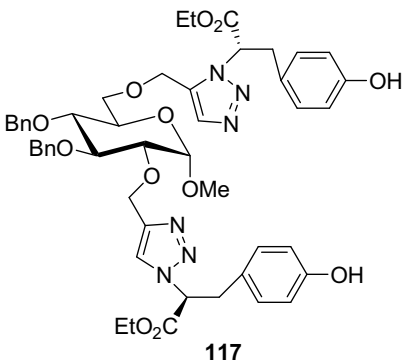
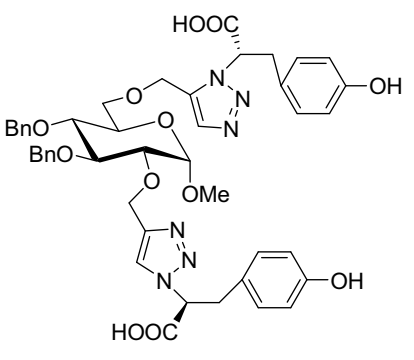
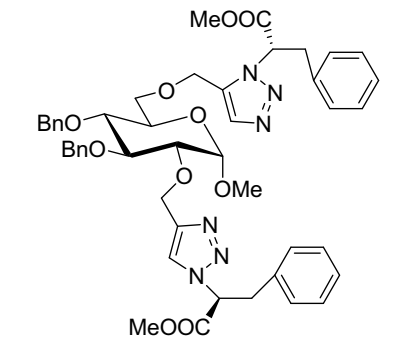
4.2.5 Inhibition test for PTP1B

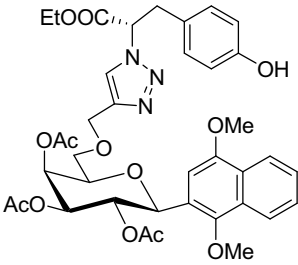
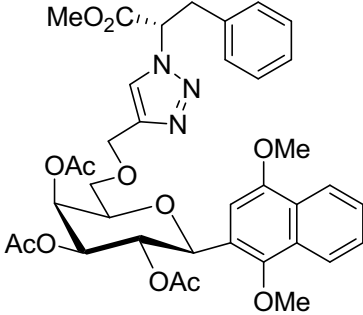
Recombinant human PTP1B catalytic domain was expressed and purified according to procedures described previously.²⁴ The enzymatic activities of PTP1B catalytic domain were determined at 30°C by monitoring the hydrolysis of pNPP. Dephosphorylation of pNPP generates product pNP, which can be monitored at 405 nm. In a typical 100 μ L assay mixture containing 50 mM MOPS, pH 6.5, 2 mM pNPP and recombinant enzymes, PTP1B activities were continuously monitored on a SpectraMax 340 microplate reader at 405 nm for 2 min at 30 °C and the initial rate of the hydrolysis was determined using the early linear region of the enzymatic reaction kinetic curve. For calculating IC₅₀, inhibition assays were performed with 30 nM recombinant enzyme, 2 mM pNPP in 50 mM MOPS at pH 6.5, and the inhibitors diluted around the estimated IC₅₀ values. IC₅₀ was calculated from the nonlinear curve fitting of percent inhibition (inhibition (%)) vs inhibitor concentration [I] by using the following equation inhibition (%) = 100/{1 +(IC₅₀/[I])^k}, where k is the Hill coefficient.

The inhibition for PTP-1B of some compounds

Compd.	inhibition%	
	20 µg/mL	5 µg/mL
 <p>111</p>	99.2	83.4
 <p>113</p>	11.8	

Compd.	inhibition%(20 µg/mL)	IC ₅₀ (µM)
 <p>103</p>	68.3	8.068±0.152
 <p>104</p>	98.9	3.329±0.680

 <p style="text-align: center;">105</p>	45.2	
 <p style="text-align: center;">117</p>	83.6	4.550±0.075
 <p style="text-align: center;">118</p>	45.3	
 <p style="text-align: center;">119</p>	98.4	0.889±0.038

 <p style="text-align: center;">122</p>	11.7	
 <p style="text-align: center;">123</p>	-11.0	

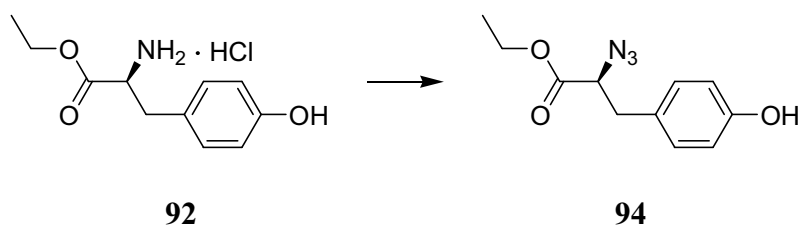
With a concentration of 20 $\mu\text{g/mL}$, compound **111** (99.2% inhibition) showed the best inhibition against PTP1B inhibition, followed by compound **104** (98.9%), compound **119** (98.4%) and compound **103** (68.3%). These compounds inhibited PTP1B with IC_{50} in micromolar range. Comparison of compound **103** ($\text{IC}_{50} = 8.068 \mu\text{M}$) and **104** ($\text{IC}_{50} = 3.329 \mu\text{M}$) showed that presence of $-\text{COOH}$ group improved the inhibition. However, the bis-substituted ester **117** (83.6 % inhibition at 20 $\mu\text{g/mL}$, $\text{IC}_{50} = 4.550 \mu\text{M}$) displayed a better inhibition than the free acid derivative **118** (45.3 % inhibition at 20 $\mu\text{g/mL}$). Because the number of samples is too small, we couldn't obtain a clear conclusion for the moment.

4.3 Conclusion

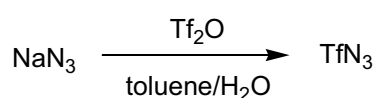
PTP-1B is a new target which aimed to treat type 2 diabetes. Based on the structure of PTP1B, we have designed and synthesized a series of glycosyl amino acids derivatives via click chemistry, so as to find a novel class inhibitor of PTP1B. Amino esters have been transformed into azido esters with imidazole-sulfonyl azide hydrochloride as azide transfer reagent. Mono- and di-propargyl functionalized glucopyranosides have been prepared from mono- and bi-silylated methyl $\alpha\text{-D}$ -glucopyranoside. Click reaction led successfully to the glycosyl amino acid derivatives with one or two amino acid moiety on 6-, 2,6- or 3,4-position of sugars. Some of these conjugated molecules showed obvious inhibition of PTP1B.

4.4 Experimental

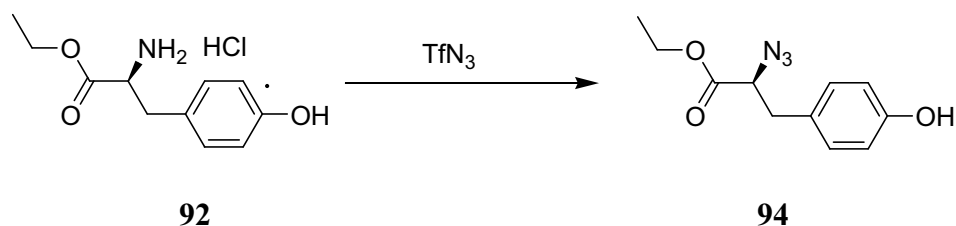
4.4.1 Synthesis of compound **94**



a) preparation of compound **94** with TfN₃

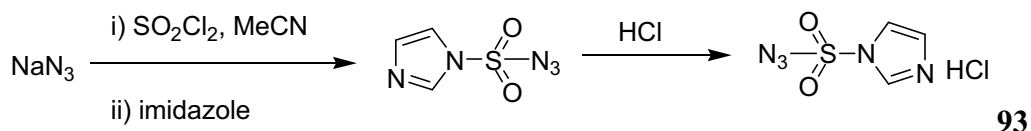


To a 0 °C solution of NaN₃ (546 mg, 8.4 mmol) in H₂O (1.38 mL) was added 1.38 mL of toluene and Tf₂O (898 μL). The solution was stirred at same temperature for 30 min and then stirred at r.t for another 2 h. The solution was neutralised with NaHCO₃ and extracted with toluene (2x1.37 mL).



To a solution of compound **92** (56.5 mg) and NaHCO₃ (78 mg) in H₂O (0.3 mL) was added CuSO₄ 5H₂O (4 mg), followed by the toluene solution of TfN₃ (0.51 mL) obtained above, and MeOH (1.98 mL). After addition, the solution was stirred at r.t overnight. The solution was evaporated to afford a crude product which will be used for next step without further purification.

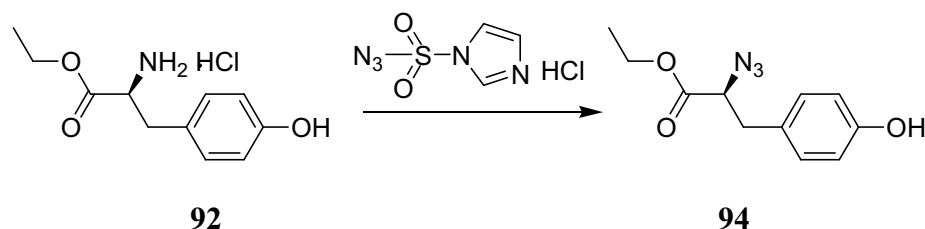
b) preparation of the reagent **93**



To a 0 °C solution of NaN₃ (6.5 g, 100 mmol) in CH₃CN (100 mL) was added SO₂Cl₂ (8 mL, 100 mmol) dropwise. The solution was stirred for 8 h at room temperature, then cooled to 0 °C again, imidazole (13 g, 190 mmol) was added in portions. After addition, the solution was stirred for another 3 h, diluted with EtOAc (200 mL), washed with water (2×200 mL) and sat NaHCO₃ (2×200 mL), dried over MgSO₄. The organic layer was added a freshly prepared solution of HCl in EtOH [AcCl

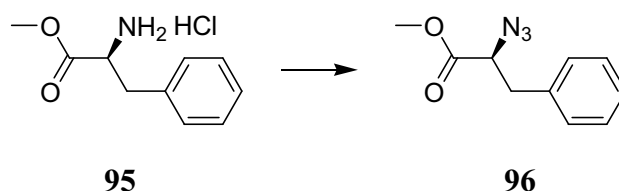
(11.5 mL, 150 mmol) in EtOH (38 mL)] at 0°C. Filtration afforded compound **93** as a white solid. m.p. 101-104°C (lit. 100–102°C); IR ν_{max} . (KBr) 2173, 1384 and 1161 cm^{-1} .

c) synthesis of compound **94** with **93**



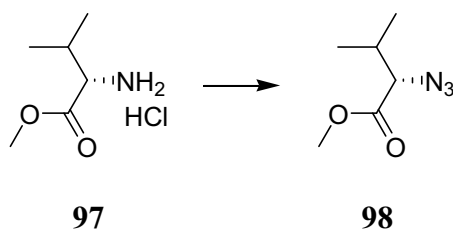
To a solution of compound **92** (245 mg, 1 mmol) in 5 mL of MeOH, was added compound **93** (250 mg, 1.2 mmol), followed by K_2CO_3 (276 mg, 2mmol) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (2.5 mg, 0.01 mmol). After addition, the solution was stirred for 8 h, then diluted with CH_2Cl_2 (10 mL), washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (EtOAc:Pet=1:4) to afford compound **94** (199.75 mg, 85%) as a syrup. TLC: $R_f = 0.69$ (EtOAc:cyclohexane = 1:1); ^1H NMR (300 MHz, CDCl_3): δ 7.12 (d, 2H, $J = 8.5$ Hz, H-3', H-5'), 6.77 (d, 2H, $J = 8.5$ Hz, H-2', H-6'), 5.46 (s, 1H, OH), 4.22 (dd, 2H, $J = 7.0, 14.4$ Hz, CH_2CH_3), 4.02 (dd, 1H, $J = 8.5, 14.0$ Hz, N_3CH), 3.11 (d, 1H, $J = 13.9$ Hz, CHPH), 3.00 (d, 1H, $J = 13.9$ Hz, CHPH), 1.29 (m, 3H, CH_2CH_3).

4.4.2 Synthesis of compound **96**



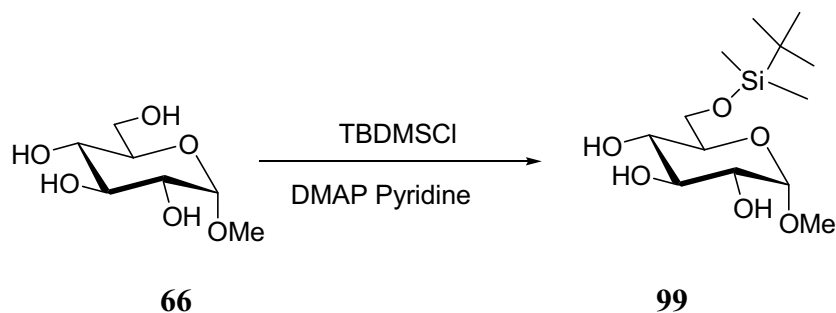
Compound **95** (215 mg, 1 mmol) was treated with compound **93** (250 mg, 1.2 mmol), K_2CO_3 (276 mg, 2mmol) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (2.5 mg, 0.01 mmol) as described for compound **92** to afford compound **96** (168 mg, 82%) as a syrup. TLC: $R_f = 0.81$ (EtOAc : cyclohexane = 1:4); ^1H NMR (400 MHz, CDCl_3): δ 7.24-7.36 (m, 5H, PhH), 4.09 (dd, 1H, $J = 5.2$ Hz and 8.4 Hz, N_3CH), 3.79 (s, 3H, CO_2Me), 3.20 (d, 1H, $J = 14.0$ Hz, CHPh), 3.02 (d, 1H, $J = 14.0$ Hz, CHPh).

4.4.3 Synthesis of compound **98**



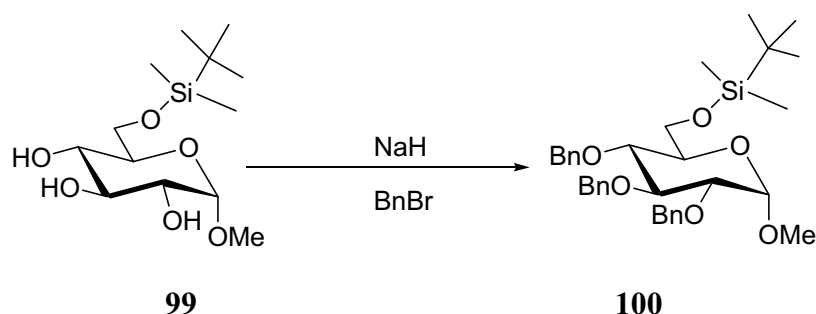
Compound **97** (167 mg, 1 mmol) was treated with compound **93** (250 mg, 1.2 mmol), K_2CO_3 (276 mg, 2mmol) and $CuSO_4 \cdot 5H_2O$ (2.5 mg, 0.01 mmol) as described for compound **92** to afford compound **98** (168 mg, 82%) as yellow syrup. 1H NMR (500 MHz, $CDCl_3$): δ 5.58 (s, 3H, OMe), 2.72 (d, 1H, $J = 5.17$ Hz, N_3CH), 2.16 (m, 1H, CH_3CH), 1.12 (d, 3H, $J = 6.8$ Hz, CH_3), 0.90 (d, 3H, $J = 6.8$ Hz, CH_3).

4.4.4 Synthesis of compound 99



To a $0^\circ C$ solution of compound **66** (1.94 g, 10 mmol) in 10 mL of pyridine, was added TDSMSCl (2.27 g, 15 mmol) and DMAP (242 mg, 2 mmol). After stirred for 16 h. the solution was evaporated, and the residue was partitioned with CH_2Cl_2 and H_2O , dried over $MgSO_4$, evaporated, purified with column chromatography (EtOAc:Pet=1:1) to afford compound **99** (245 mg, 85%) as yellow syrup. TLC: $R_f = 0.27$ (EtOAc:cyclohexane = 1:1). 1H NMR (400 MHz, $DMSO-d_6$): δ 0.02(s, 6H, $Si(CH_3)_2$), 0.86 (s, 9H, $C(CH_3)_3$), 3.00 (m, 1H, H-4), 3.16 (m, 1H, H-2), 3.25 (s, 3H, CH_3), 3.34 (m, 2H, H-3, H-5), 3.60 (dd, 1H, $J = 7.2, 11.2$ Hz, H-6a), 3.82 (d, 1H, $J = 11.2$ Hz, H-6b), 4.50 (d, 1H, $J = 3.6$ Hz, H-1), 4.65 (d, 1H, $J = 7.2$ Hz, OH-2), 4.72 (d, 1H, $J = 5.2$ Hz, OH-3), 4.83 (d, 1H, $J = 6.0$ Hz, OH-4); ^{13}C NMR (100 MHz, $DMSO-d_6$): δ -5.3, 17.9, 25.7, 54.0, 62.9, 70.1, 71.9, 72.5, 73.4, 99.6.

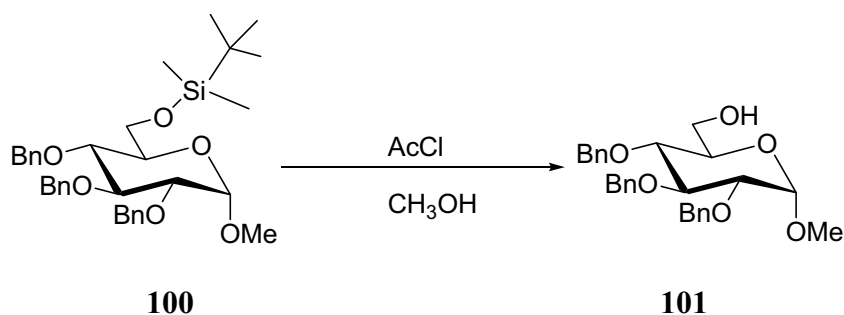
4.4.5 Synthesis of compound 100



To a $0^\circ C$ solution of compound **99** (308 mg, 1 mmol) in 5 mL of DMF, was added $NaH(60\%)$ (200 mg, 5 mmol). After stirring for 45 min, $BnBr$ (598 μL , 5 mmol) was added. After addition, the solution was stirred for 16 h, then quenched $MeOH$, and evaporated. The residue was partitioned with CH_2Cl_2 and H_2O , dried over $MgSO_4$, evaporated, purified with column chromatography

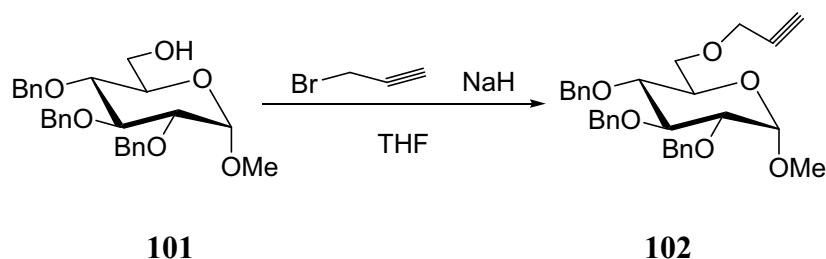
(EtOAc:Pet=1:4) to afford compound **100** (497 mg, 86%) as yellow syrup. TLC: $R_f = 0.42$ (EtOAc:Pet = 1:3). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.27-7.35 (m, 15H, PhH), 4.63-5.00 (m, 6H, 3XPhCH₂), 4.59 (d, 1H, $J = 3.3$ Hz, H-1), 4.17 (dd, 2H, $J = 2.2$ and 10.6 Hz, OCH₂), 3.97 (t, 1H, $J = 9.2$ Hz, H-3), 3.84 (dd, 1H, $J = 3.3$ and 10.2 Hz, H-2), 3.76(m, 1H, H-4), 3.54(m, 1H, H-5), 3.38 (s, 1H, OMe), 0.08 (s, 9H, 3×CH₃), -0.09 (2s, 6H, 2×SiCH₃).

4.4.6 Synthesis of compound **101**



To a solution of compound **100** (578 mg, 1 mmol) in 10 mL of CH_3OH , was added AcCl (40 μL , 0.15 mmol). After 18 h, the mixture was concentrated, and the residue was partitioned with CH_2Cl_2 and H_2O , dried over MgSO_4 , evaporated, purified with column chromatography (EtOAc:Pet=1:5) to afford compound **101** (399 mg, 86%) as a white solid. TLC: $R_f = 0.27$ (EtOAc : cyclohexane = 1:5); m. p.: 64-66°C.

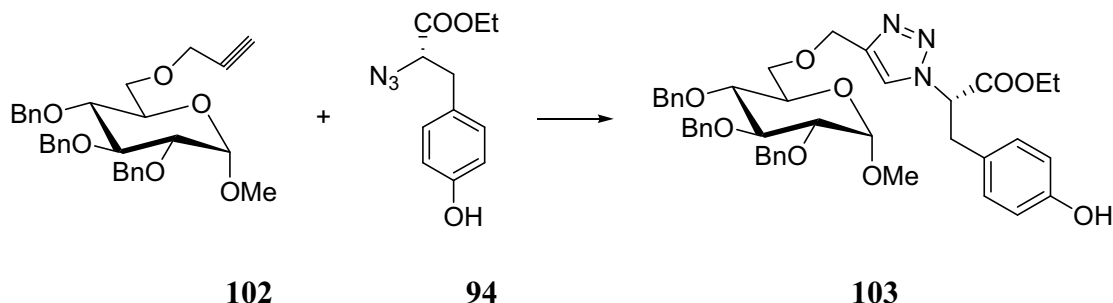
4.4.7 Synthesis of compound **102**



To a solution of compound **101** (374 mg, 1 mmol) in 10 mL of THF was added NaH (60%) (80 mg, 2 mmol). After addition, the solution was stirred for 45 min, followed by addition of 3-bromoprop-1-yne (215 μL , 2 mmol). After stirred for 18 h, the reaction was quenched with MeOH (10 mL), and concentrated. The residue was partitioned with CH_2Cl_2 and H_2O , dried over MgSO_4 , evaporated, and purified with column chromatography (EtOAc:Pet=1:5) to afford compound **102** (417 mg, 83%) as yellow syrup. TLC: $R_f = 0.72$ (EtOAc:cyclohexane = 1:3); $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 2.37 (s, 1H, $\text{C}\equiv\text{CH}$), 3.38 (s, 3H, OMe), 3.52-3.69 (m, 3H, H-5, H-6a,6b), 3.76 (m, 1H, H-4), 3.84 (dd, 1H, $J = 3.3$ Hz and 7.0 Hz, H-2), 3.97 (t, 1H, $J = 9.2$ Hz, H-3), 4.15 (m, 2H, OCH₂C \equiv), 4.59 (d, 1H, $J = 3.3$ Hz, H-1), 4.63-5.00 (m, 6H, 3×CH₂Ph), 7.26-7.35 (m, 15H, PhH); $^{13}\text{C NMR}$

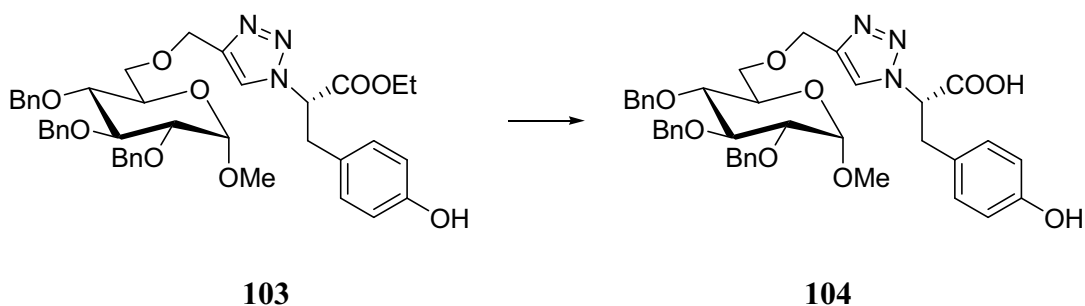
(75 MHz, CDCl₃): δ 55.1, 58.4, 67.9, 69.7, 73.3, 74.8, 74.8, 74.9, 75.6, 79.3, 79.6, 81.9, 98.2, 127.4-128.3(15C), 138.0, 138.3, 138.7.

4.4.8 Synthesis of compound **103**



To a solution of compound **102** (50 mg, 0.1 mmol) in 2 mL of CH₂Cl₂ and 2 mL of H₂O, was added compound **94** (24 mg, 0.1 mmol), followed by Na L-ascorbate (79 mg, 0.4 mmol) and CuSO₄·5H₂O (50 mg, 0.2 mmol). The reaction was stirred for 36 h, then extracted with CH₂Cl₂, washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (EtOAc:Pet=1:1) to afford compound **103** (58 mg, 79%) as yellow syrup. TLC: R_f = 0.22 (EtOAc:cyclohexane = 1:1), ¹H NMR (300 MHz, CDCl₃): δ 1.28 (t, 3H, J = 7.2 Hz, OCH₂CH₃), 3.37 (m, 2H, *p*HO-PhCH₂), 3.38 (s, 3H, OMe), 3.57-3.78 (m, 5H, H-2, H-4, H-5, OCH₂CH₃), 4.04 (t, 1H, J = 9.6 Hz, H-3), 4.26 (m, 2H, OCH₂C=), 4.54-5.04 (m, 9H, 3×CH₂Ph, H-1, H-6a,6b), 5.56 (t, 1H, J = 6.2 Hz, COCH), 6.69 (d, 2H, J = 7.4 Hz, 2× *p*HO-PhH), 6.81 (d, 2H, J = 7.4 Hz, 2× *p*HO-PhH), 7.27-7.48 (m, 15H, 3×PhH), 7.56 (s, 1H, NC=CH); ¹³C NMR (75 MHz, CDCl₃): δ 13.9, 37.9, 55.1, 62.2, 64.0, 64.9, 68.8, 69.9, 73.3, 74.8, 76.0, 77.3, 79.7, 82.1, 98.0, 115.6, 122.8, 125.69, 127.6, 127.86, 128.1, 128.3-128.4, 130.1, 138.0, 138.1, 138.2, 144.6, 155.6, 168.0; HRESIMS: calcd for [C₄₂H₄₇N₃O₉+Na]⁺: 760.3210 found 760.3229.

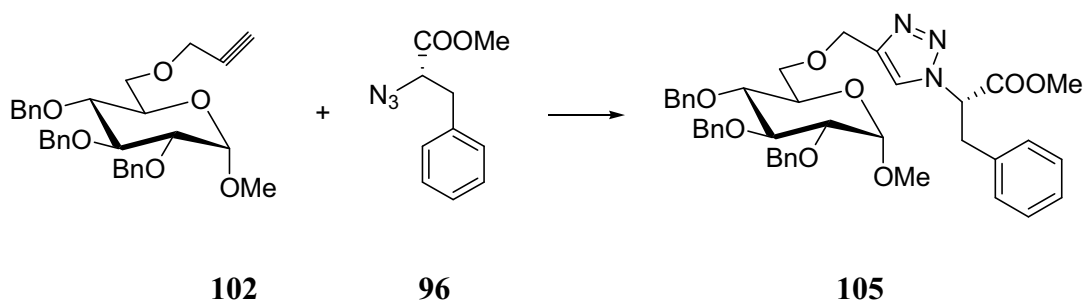
4.4.9 Synthesis of compound **104**



To a solution of compound **103** (113 mg, 0.15 mmol) in a mixture of THF:MeOH: H₂O= 2 mL:2 mL: 2 mL, was added LiOH·H₂O (9 mg, 0.23 mmol). After 8 h, IR 120+ cation exchange resin was added. After filtration, the filtrate was concentrated to afford compound **104** (87 mg, 82%) as yellow syrup.

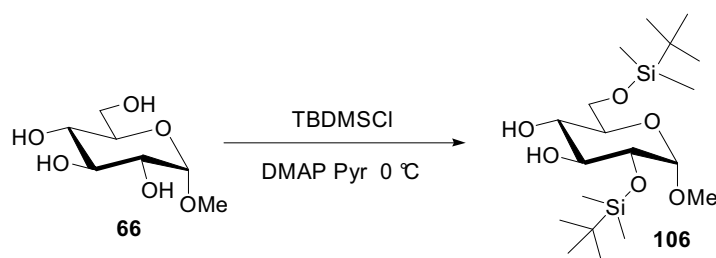
TLC: $R_f = 0.32$ (EtOAc:MeOH = 8:1); $^1\text{H NMR}$ (400 MHz, CD_3OD): δ 3.25 (s, 3H, OMe), 3.45-3.67 (m, 8H, H-6a,6b, H-5, H-4, H-2, *p*HO-PhCH₂, CHCO₂H), 3.86 (t, 1H, $J = 9.3$ Hz, H-3), 4.60-4.96 (m, 9H, 3×CH₂Ph, H-1, OCH₂C=), 5.55 (s, 1H, PhOH), 6.61 (d, 2H, 2× *p*HO-PhH), 6.83 (d, 2H, 2× *p*HO-PhH), 7.23-7.36 (m, 15H, PhH), 7.87 (s, 1H, NC=CH); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 30.8, 55.2, 62.2, 64.1, 64.7, 68.8, 69.9, 75.7, 76.0, 77.3, 79.7, 82.1, 98.0, 115.6, 127.7-239.8, 130.1, 138.0, 138.1, 138.2, 144.6, 155.4, 166.2; HRESIMS: calcd for $[\text{C}_{40}\text{H}_{43}\text{N}_3\text{O}_9+\text{H}]^+$: 710.3078 found: 710.3062.

4.4.10 Synthesis of compound 105



Compound **102** (50 mg, 0.1 mmol) was treated with compound **96** (21 mg, 0.1 mmol), Na L-ascorbate (79.2 mg, 0.4 mmol) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (50 mg, 0.2 mmol) as for the synthesis of **103**. Purified with column chromatography (EtOAc:Pet=1:1) afforded compound **105** (59 mg, 84%) as yellow syrup. TLC: $R_f = 0.53$ (EtOAc : cyclohexane = 1:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 3.31 (m, 2H, H-5, H-6a), 3.37 (s, 3H, OMe), 3.44 (m, 1H, H-6b), 3.56 (m, 1H, H-2), 3.62 (m, 1H, H-4), 3.67 (s, 3H, CO₂Me), 3.73-3.78 (m, 2H, CH₂Ph), 4.00 (t, 1H, $J = 9.2$ Hz, H-3), 4.52-5.00 (m, 9H, 3×OCH₂Ph, H-1, OCH₂C=), 5.50 (m, 1H, COCH), 6.98-7.15 (m, 5H, PhH) 7.27-7.37 (m, 15H, 3×PhH), 7.58 (s, 1H, NC=CH); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 38.64, 38.7, 52.9, 60.3, 63.9, 64.8, 68.8, 69.9, 73.3, 75.0, 75.7, 79.8, 82. 98.1, 122.71, 127.5-128.8, 134.7, 138.1, 138.3, 138.7, 144.8, 168.5; HRESIMS: calcd for $[\text{C}_{41}\text{H}_{45}\text{N}_3\text{O}_8+\text{Na}]^+$: 730.3104 found: 730.3128.

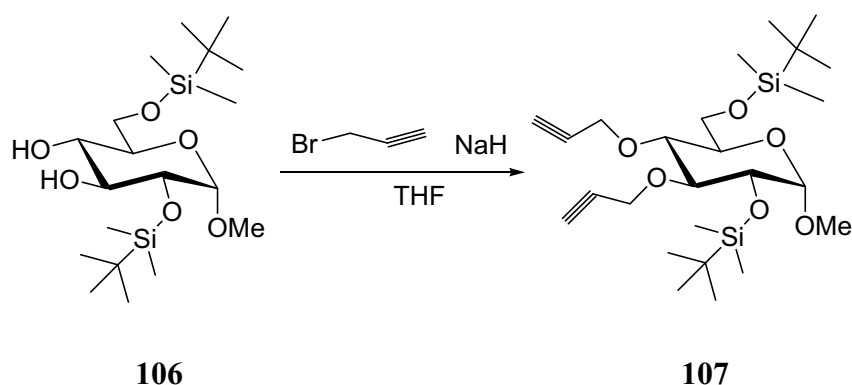
4.4.11 Synthesis of compound 106



To a 0°C solution of compound **66** (970 g, 5 mmol) in 10 mL of pyridine, was added TDSMSCl (2.1 g, 14 mmol) and DMAP (120 mg, 1 mmol). After stirred for 16 h, the solution was evaporated,

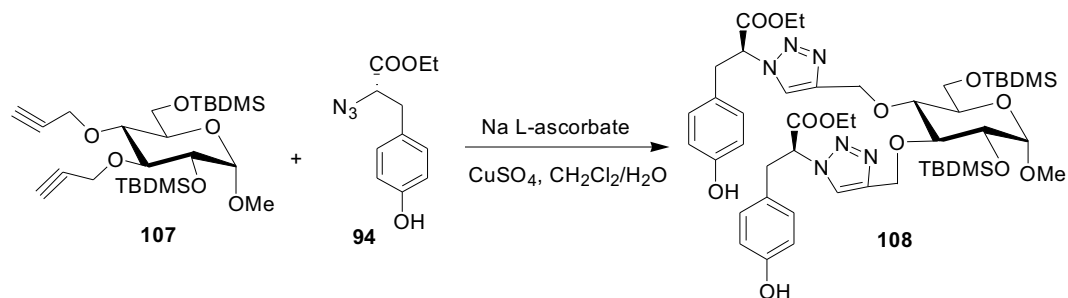
and the residue was partitioned with CH₂Cl₂ and H₂O, dried over MgSO₄, evaporated, purified with column chromatography (EtOAc:Pet=1:1) to afford compound **106** (1.16 g, 55%) as yellow syrup. TLC: *R_f* = 0.57 (EtOAc:cyclohexane = 1:5); ¹H NMR (300 MHz, CDCl₃): δ 0.08 (2s, 12H, 2×Si(CH₃)₂), 0.88 (2s, 18H, 2×C(CH₃)₃), 2.71 (s, 1H, OH), 3.01 (s, 1H, OH), 3.36 (s, 3H, OMe), 3.43-3.60 (m, 3H, H-5, H-6a,6b), 3.75-3.83 (m, 3H, H-2, H-3, H-4), 4.59 (d, 1H, *J* = 3.3 Hz, H-1); ¹³C NMR (75 MHz, CDCl₃): δ -5.5, -5.4, -5.2, -4.5, 18.0, 18.2, 25.3, 25.4, 25.5, 25.6, 25.7, 25.8, 55.0, 63.8, 70.7, 71.5, 73.3, 73.8, 99.8.

4.4.12 Synthesis of compound **107**



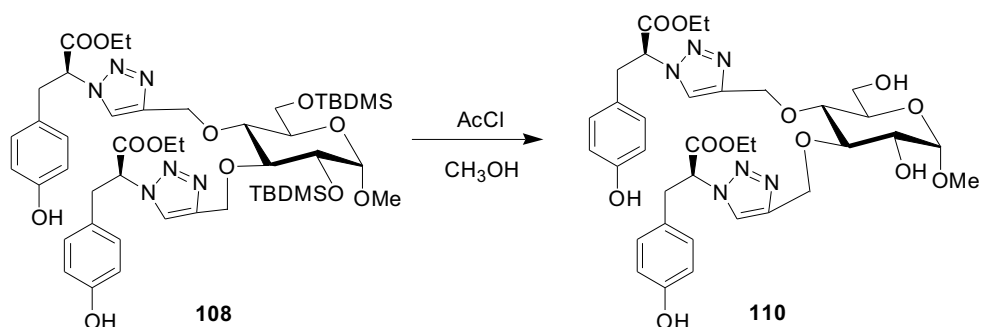
To a solution of compound **106** (422 mg, 1 mmol) in 10 mL of THF, was added TBAI (20 mg), NaH(60%) (200 mg, 5 mmol) and 3-bromoprop-1-yne (50 μL, 5 mmol) in 5 portions over 30 min. After stirred for 20 h, the reaction was quenched with MeOH (10 mL), then concentrated. The residue was partitioned with CH₂Cl₂ and H₂O, dried over MgSO₄, evaporated, purified with column chromatography (EtOAc:Pet=1:10) to afford compound **107** (368 mg, 74%) as yellow syrup. TLC: *R_f* = 0.71 (EtOAc:cyclohexane = 1:10); [α]_D = +64.93 (*c* 3.5 CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 0.06 (m, 12H, 2×Si(CH₃)₂), 0.85 (m, 18H, 2×C(CH₃)₃), 2.44 (m, 2H, 2×C≡H), 3.22 (t, 1H, *J* = 9.3 Hz, H-3), 3.36 (s, 3H, OMe), 3.38 (m, 1H, H-6a), 3.52 (m, 2H, H-5, H-6b), 3.79-3.95 (m, 2H, H-2, H-4), 4.16-4.42 (m, 4H, 2×OCH₂), 4.91 (d, 1H, *J* = 3.7 Hz, H-1); ¹³C NMR (75 MHz, CDCl₃): δ -5.2, -5.14, -5.20 -4.9, 17.9, 18.2, 25.7, 25.7, 25.8, 25.8, 25.9, 25.9, 54.5, 58.3, 59.9, 62.4, 70.8, 73.5, 74.0, 74.5, 78.6, 79.8, 79.9, 80.1, 97.4.

4.4.13 Synthesis of compound 108



To a solution of compound **107** (50 mg, 0.1 mmol) in 2 mL of CH_2Cl_2 and 2 mL of H_2O , was added compound **94** (48 mg, 0.2 mmol), followed by Na L-ascorbate (160 mg, 0.8 mmol) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (100 mg, 0.4 mmol). The reaction was stirred for 36 h, then extracted with CH_2Cl_2 , washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (EtOAc:Pet=1:1) to afford compound **108** (48 mg, 50%) as yellow syrup. TLC: $R_f = 0.77$ (EtOAc:cyclohexane = 1:2); $[\alpha]_D = -21.08$ (c 0.19 CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3): δ 0.10 (m, 12H, $2 \times \text{Si}(\text{CH}_3)_2$), 0.95 (m, 18H, $2 \times \text{C}(\text{CH}_3)_3$), 1.25 (m, 6H, $2 \times \text{CH}_2\text{CH}_3$), 3.03-3.09 (m, 2H, H-2, H-4), 3.18 (s, 3H, OMe), 3.29-3.49 (m, 10H, H-6a,6b, $2 \times \text{CO}_2\text{CH}_2$, $2 \times \text{OCH}_2\text{C}=\text{C}$), 3.81 (m, 2H, H-1, H-5), 3.92 (t, 1H, $J = 9.2$ Hz, H-3), 4.08-4.28 (m, 4H, $2 \times \text{PhCH}_2$), 5.41 (m, 2H, $2 \times \text{CH}=\text{C}$), 6.65-6.87 (m, 8H, $2 \times p\text{-OHPhH}$), 7.37 (s, 1H, $\text{NC}=\text{CH}$), 7.52 (s, 1H, $\text{NC}=\text{CH}$); ^{13}C NMR (75 MHz, CDCl_3): δ -5.4, -5.2, -4.3, -3.9, 13.8, 13.9, 14.1, 17.9, 18.3, 25.8, 37.5, 38.1, 54.5, 60.3, 62.3, 62.4, 63.2, 64.1, 64.3, 64.7, 65.1, 71.1, 73.8, 77.9, 79.0, 97.4, 115.7, 116.4, 123.1, 123.7, 125.6, 125.8, 129.6, 129.9, 144.1, 144.5, 155.7, 156.0, 155.7, 156.0, 167.8, 167.9, 168.1, 170.1, 171.2; HRESIMS: calcd for $[\text{C}_{47}\text{H}_{72}\text{N}_6\text{O}_{12}\text{Si}_2 + \text{H}]^+$: 969.4825 found: 969.4835.

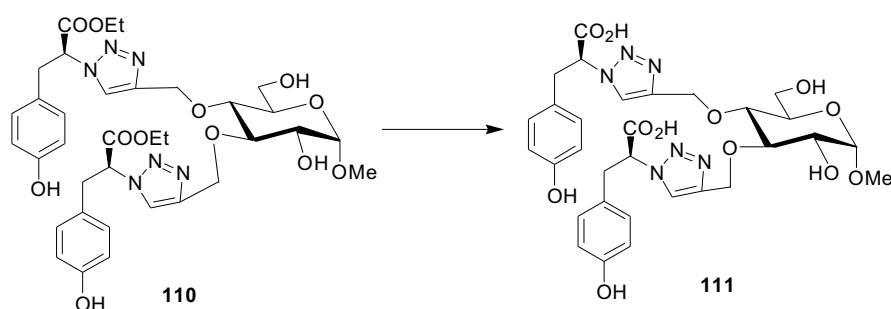
4.4.14 Synthesis of compound 110



To a solution of compound **108** (97 mg, 0.1 mmol) in 5 mL of CH_3OH , was added AcCl (1 μL , 0.015 mmol). After stirred for 24 h, the mixture was concentrated, and the residue was partitioned with CH_2Cl_2 and H_2O , dried over MgSO_4 , evaporated, purified with column chromatography (EtOAc) to afford compound **110** (49 mg, 67%) as yellow syrup. TLC: $R_f = 0.25$ (EtOAc); $[\alpha]_D = -1.72$ (c 0.29 EtOAc); ^1H NMR (300 MHz, CDCl_3): δ 1.32 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 2.82 (t, 1H, $J = 9.9$ Hz, H-3),

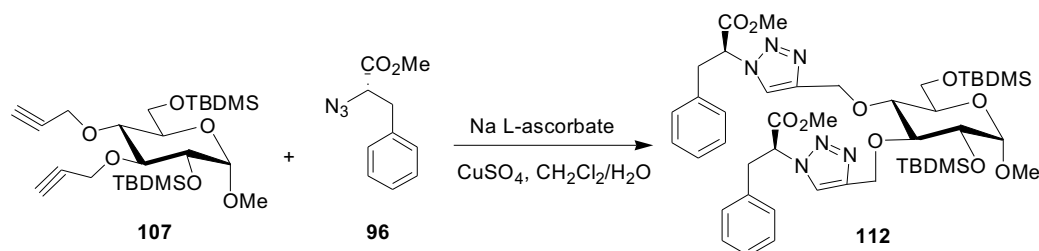
3.07 (dd, 1H, $J = 3.7$ and 9.2 Hz, H-2), 3.32 (m, 2H, H-6a, 6b), 3.37 (s, 3H, OMe), 3.47-3.79 (m, 10H, H-5, H-4, $2 \times \text{OCH}_2$, $2 \times \text{CH}_2\text{CH}_3$), 4.30-5.06 (m, 4H, $2 \times \text{CH}_2\text{Ph}$), 4.79 (d, 1H, $J = 3.3$ Hz, H-1), 5.48, 5.69 (2dd, 2H, $J = 4.8$ and 4.0 Hz, $2 \times \text{COCH}$), 6.56-6.68 (m, 8H, PhH), 7.66 (s, 1H, NC=CH), 7.80 (s, 1H, NC=CH); ^{13}C NMR (75 MHz, CDCl_3): δ 13.96, 13.98, 30.81, 30.82, 37.05, 38.13, 55.07, 60.38, 61.50, 62.58, 62.6, 63.1, 63.3, 64.4, 69.7, 72.1, 73.1, 96.4, 115.6, 115.9, 124.0, 124.3, 124.7, 129.33-129.36, 144.0, 144.3, 156.2, 156.2, 168.0, 168.1.

4.4.15 Synthesis of compound 111



To a solution of compound **110** (74 mg, 0.1 mmol) in a mixture of THF:MeOH: H_2O = 2 mL:2 mL: 2 mL, was added LiOH· H_2O (7 mg, 0.15 mmol). After 8 h, IR 120+ cation exchange resin was added. After filtration, the filtrate was concentrated to afford compound **111** (54 mg, 79%) as yellow syrup. TLC: $R_f = 0.41$ (EtOAc : MeOH = 6:1); HRESIMS: calcd for $[\text{C}_{31}\text{H}_{36}\text{N}_6\text{O}_{12} + \text{H}]^+$: 685.2469 found: 685.2471.

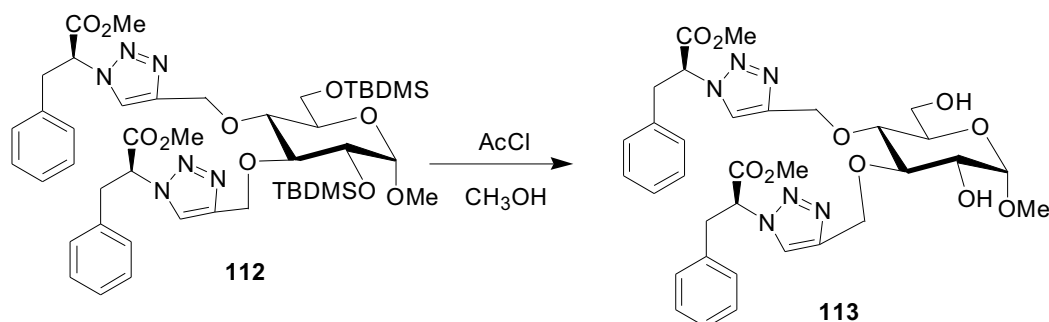
4.4.16 Synthesis of compound 112



To a solution of compound **107** (50 mg, 0.1 mmol) in 2 mL of CH_2Cl_2 and 2 mL of H_2O , was added compound **96** (48 mg, 0.2 mmol), followed by Na L-ascorbate (160 mg, 0.8 mmol) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (100 mg, 0.4 mmol). The reaction was stirred for 36 h, then extracted with CH_2Cl_2 , washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (EtOAc:Pet=1:5) to afford compound **112** (58 mg, 63%) as yellow syrup. TLC: $R_f = 0.44$ (EtOAc:cyclohexane = 1:2), ^1H NMR (400 MHz, CDCl_3): δ 0.01-0.08 (m, 12H, $2 \times \text{Si}(\text{CH}_3)_2$), 0.95 (m, 18H, $2 \times \text{C}(\text{CH}_3)_3$), 3.25 (s, 3H, OMe), 3.36-3.57 (m, 7H, H-5, H-6a,6b, $2 \times \text{OCH}_2\text{C}=\text{C}$), 3.74, 3.76 (2s, 6H, $2 \times \text{CO}_2\text{Me}$), 3.80 (m, 2H, H-2, H-4), 3.94 (t, 1H, $J = 9.2$ Hz, H-3), 4.51 (d, 1H, $J = 3.6$ Hz, H-1), 4.86-4.91 (m, 4H, $2 \times \text{CH}_2\text{Ph}$),

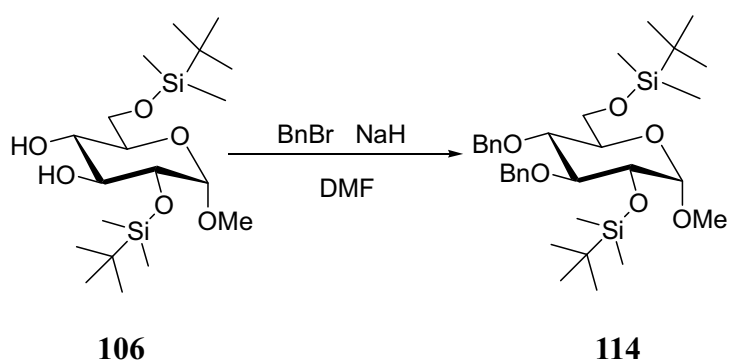
5.55 (m, 2H, 2×COCH), 7.05-7.29 (m, 10H, 2×PhH), 7.55, 7.67 (2s, 2H, 2×NC=CH), ¹³C NMR (100 MHz, CDCl₃): δ 0.01-0.08, 14.19-18.3, 25.9-26.0, 38.71, 38.8, 52.9, 53.0, 54.6, 60.3, 62.27, 63.9, 64.0, 64.5, 66.3, 71.2, 73.6, 79.1, 80.5, 97.5, 121.9, 122.8, 127.5-128.8, 134.7, 134.8, 145.3, 145.4, 168.5, 168.6; HRESIMS: calcd for [C₄₅H₆₈N₆O₁₀Si₂+Na]⁺: 931.4433 found: 931.4434.

4.4.17 Synthesis of compound 113



To a solution of compound **112** (92 mg, 0.1 mmol) in 5 mL of CH₃OH, was added AcCl (1 μL, 0.015 mmol). After stirred for 24 h, the mixture was concentrated. the residue was partitioned with EtOAc and H₂O, dried over MgSO₄, evaporated, and purified with column chromatography (EtOAc) to afford compound **113** (60 mg, 88%) as yellow syrup. TLC: *R_f* = 0.52(EtOAc), ¹H NMR (400 MHz, CDCl₃): δ 3.34 (s, 3H, OMe), 3.43-3.62 (m, 9H, H-5, H-6a,6b, H-2, H-4, 2×OCH₂C=), 3.75, 3.76 (2s, 6H, 2×CO₂Me), 4.09 (t, 1H, *J* = 9.2 Hz, H-3), 4.76-4.95 (m, 5H, H-1, 2×PhCH₂), 5.57 (m, 2H, 2×COCH), 7.04-7.27 (m, 10H, PhH), 7.60, 7.67 (2s, 2H, 2×NC=CH); ¹³C NMR (100 MHz, CDCl₃): δ 38.7, 53.1, 55.1, 61.4, 64.0, 64.2, 65.2, 70.2, 73.5, 79.1, 80.1, 97.5, 122.3, 122.7, 127.6, 128.7-128.9, 134.6, 145.0, 145.4, 168.6, 168.6; HRESIMS: calcd for [C₃₃H₄₀N₆O₁₀+Na]⁺: 703.2704 found: 703.2717.

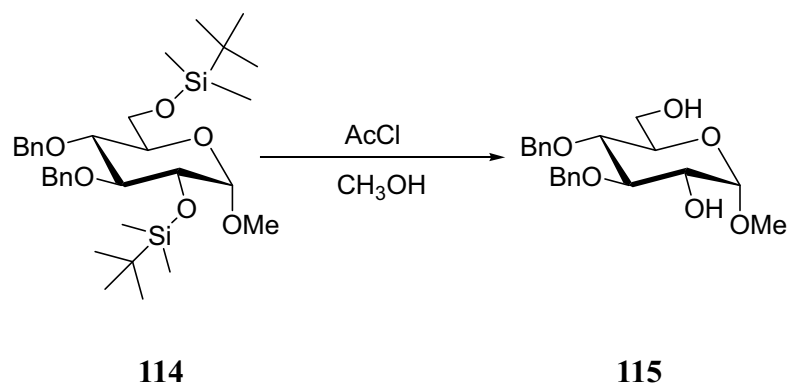
4.4.18 Synthesis of compound 114



To a 0°C solution of compound **106** (422 mg, 1 mmol) in 5 mL of DMF, was added NaH(60%) (200 mg, 5 mmol) and BnBr (120 μL, 5 mmol) in portions over 30 min. After addition, the solution was stirred for 16 h. The reaction was quenched 10 mL of MeOH, then evaporated. The residue was

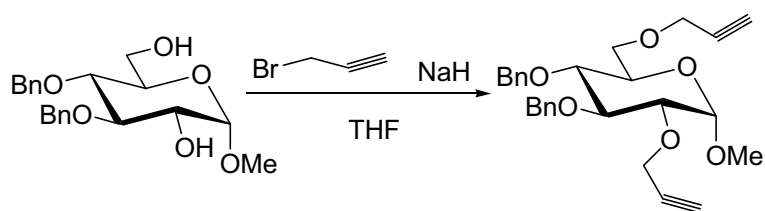
partitioned with CH₂Cl₂ and H₂O, dried over MgSO₄, evaporated, and purified with column chromatography (EtOAc:Pet=1:6) to afford compound **114** (600 mg, 86%) as yellow syrup. TLC: *R_f* = 0.41 (EtOAc:cyclohexane = 1:5); [α]_D=+45.36 (*c* 0.28 CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 0.39 (m, 12H, 2×Si(CH₃)₂), 0.89 (m, 18H, 2×C(CH₃)₃), 3.25 (s, 3H, OMe), 3.26-3.30 (m, 2H, H-6a,6b), 3.55 (m, 1H, H-5), 3.69-3.74 (m, 2H, H-2, H-4), 4.01 (t, 1H, *J* = 9.2 Hz, H-3), 4.42 (d, 1H, *J* = 3.3 Hz, H-1), 4.50-4.87 (m, 4H, 2×CH₂Ph), 7.25-7.33 (m, 10H, PhH); ¹³C NMR (75 MHz, CDCl₃): δ -5.5, -5.2, -4.4, -3.9, 18.0, 18.0, 18.1, 18.2, 25.8, 25.8, 25.9, 25.9, 26.0, 26.0, 54.6, 62.3, 71.3, 73.4, 73.9, 74.6, 79.2, 80.4, 97.8, 127.3, 127.3, 127.4, 127.7, 127.7, 127.8, 127.9, 128.1, 128.1, 128.2, 138.4, 138.5.

4.4.19 Synthesis of compound 115



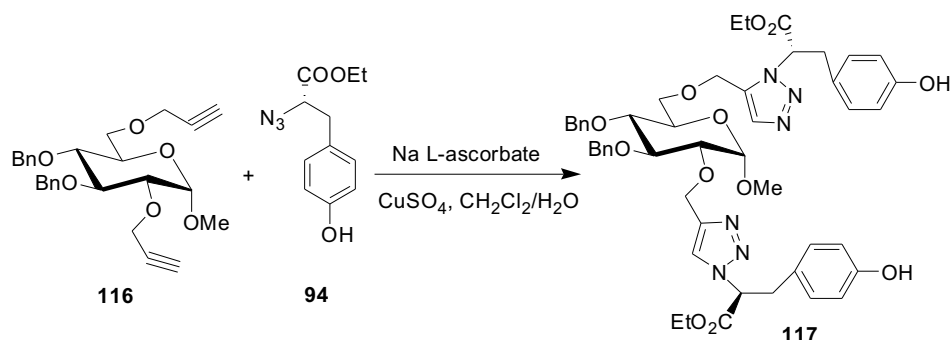
To a solution of compound **114** (602 mg, 1 mmol) in 10 mL of CH₃OH, was added AcCl (10 μL, 0.15 mmol). After stirred for 24 h, the mixture was concentrated, and the residue partitioned with EtOAc and H₂O, dried over MgSO₄, evaporated, purified with column chromatography (EtOAc:cyclohexane = 1:4) to afford compound **115** (236 mg, 63%) as yellow syrup. TLC: *R_f* = 0.21 (EtOAc:cyclohexane = 1:3); [α]_D=+61.95(*c* 0.20 CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃): δ 3.32 (s, 3H, OMe), 3.33-3.37 (m, 2H, H-6a,6b), 3.61-3.77 (m, 3H, H-2, H-4, H-5), 4.10 (t, 1H, *J* = 9.2 Hz, H-3), 4.59 (d, 1H, *J* = 3.3 Hz, H-1), 4.68-4.93 (m, 4H, 2×PhCH₂), 7.25-7.38 (m, 10H, PhH); ¹³C NMR (75 MHz, CDCl₃): δ 55.1, 61.9, 70.1, 73.0, 73.3, 74.4, 77.1, 79.5, 97.4, 127.8, 127.8, 127.9, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 137.8, 138.2.

4.4.20 Synthesis of compound 116



To a solution of compound **115** (374 mg, 1 mmol) in 10 mL of THF, was added NaH(60%) (120 mg, 3 mmol), stirred for 45 min, followed by addition of 3-bromoprop-1-yne (215 μ L, 2 mmol). After stirred for 18 h, the reaction was quenched with MeOH (10 mL), then concentrated. The residue was partitioned with CH_2Cl_2 and H_2O , dried over MgSO_4 , evaporated, and purified with column chromatography (EtOAc:Pet=1:5) to afford compound **116** (423 mg, 94%) as yellow syrup. TLC: R_f = 0.81 (EtOAc:cyclohexane = 1:3); $[\alpha]_D^{25} = +44.08$ (c 3.5 CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3): δ 2.37, 2.38 (2t, 2H, $J = 2.6$ Hz, $2 \times \text{C}\equiv\text{CH}$), 3.34 (s, 3H, OMe), 3.47-3.59 (m, 2H, H-6a,6b), 3.63-3.74 (m, 2H, H-5, H-4), 3.81-3.91 (m, 2H, H-2, H-3), 4.14-4.18 (m, 2H, OCH_2), 4.44-4.97 (m, 7H, OCH_2 , $2 \times \text{PhCH}_2$, H-1), 7.28-7.37 (m, 10H, PhH); ^{13}C NMR (75 MHz, CDCl_3): δ 30.82, 55.0, 58.4, 60.3, 67.8, 69.6, 73.2, 74.0, 74.8, 75.0, 79.3, 79.4, 80.2, 81.6, 98.0, 127.6, 127.7, 128.0, 128.0, 128.1, 128.1, 128.2, 128.3, 128.4, 128.5, 137.9, 138.2.

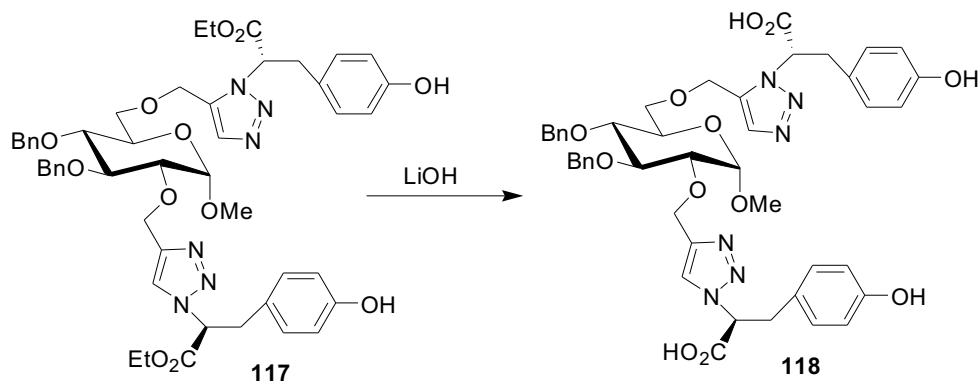
4.4.21 Synthesis of compound 117



To a solution of compound **116** (450 mg, 1 mmol) in 2 mL of CH_2Cl_2 and 2 of mL H_2O , was added compound **94** (470 mg, 2 mmol), followed by addition of Na L-ascorbate (1.6 g, 8 mmol) and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (1 g, 4 mmol). The reaction was stirred for 36 h, then extracted with CH_2Cl_2 (3×10 mL), washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (EtOAc:Pet=1:1) to afford compound **117** (478 mg, 52%) as yellow syrup. TLC: R_f = 0.44 (EtOAc:cyclohexane = 2:1); $[\alpha]_D^{25} = +1.82$ (c 0.17 CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ 1.23 (m, 6H, $2 \times \text{OCH}_2\text{CH}_3$), 3.11-3.21 (m, 1H, H-6a), 3.32 (s, 3H, OMe), 3.38-3.50 (m, 2H, H-5, H-6b), 3.63-3.80 (m, 4H, $2 \times \text{OCH}_2\text{C}=\text{O}$), 3.94 (t, 1H, $J = 9.2$ Hz, H-3), 4.10-4.18 (m, 4H, $2 \times \text{OCH}_2\text{CH}_3$), 4.22-5.13 (m, 11H, $2 \times \text{PhCH}_2$, $2 \times p\text{-OHPhCH}_2$, H-1, H-2, H-4), 5.52-5.54 (m, 2H, $2 \times \text{COCH}$), 6.56-6.70 (m, 8H, $p\text{-OHPhH}$), 7.24-7.36 (m, 10H, PhH), 7.51, 7.69 (2s, 2H, $2 \times \text{NC}=\text{CH}$); ^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 13.9, 38.0, 38.1, 55.1, 60.3, 62.3, 62.4, 63.7, 64.1, 64.7, 65.4, 68.9, 69.7, 73.1, 74.6, 79.7, 81.7, 98.1, 115.5, 115.8, 122.7, 122.9, 124.7, 125.2, 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.3, 128.5, 128.6, 128.8, 128.9, 129.0, 129.1, 129.3, 129.6, 129.8,

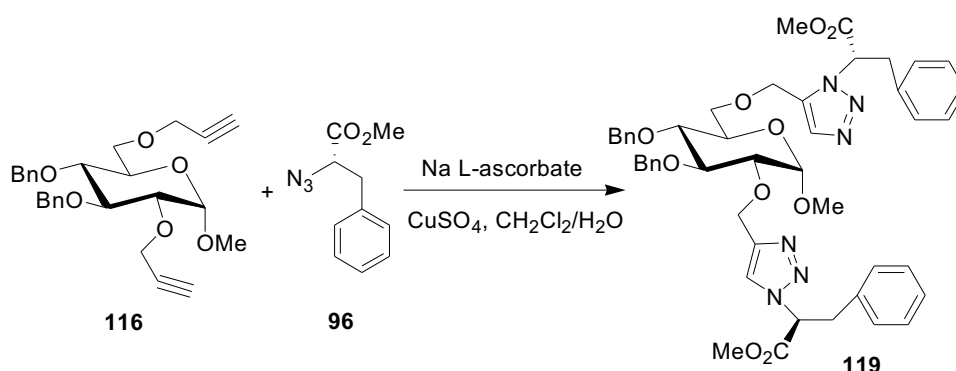
138.0, 144.0, 155.8, 156.3, 168.0, 168.3; HRESIMS: calcd for $[C_{49}H_{56}N_6O_{12}+Na]^+$: 943.3854 found: 943.3861.

4.4.22 Synthesis of compound 118



To a solution of compound **117** (92 mg, 0.1 mmol) in a mixture of THF:MeOH: H₂O=2 mL:2 mL: 2 mL, was added LiOH·H₂O (7 mg, 0.15 mmol). After 8 h, IR 120+ cation exchange resin was added. After filtration, the filtrate was concentrated to afford compound **118** (74 mg, 86%) as yellow syrup. TLC: $R_f = 0.34$ (EtOAc:MeOH = 6:1); ¹H NMR (400 MHz, CDCl₃): δ 3.11-3.21 (m, 1H, H-6a), 3.27 (s, 3H, OMe), 3.31-3.48 (m, 2H, H-5, H-6b), 3.58-3.77 (m, 4H, 2×OCH₂C=), 3.90 (t, 1H, $J=9.2$ Hz, H-3), 4.12-5.07 (m, 11H, 2×PhCH₂, 2×*p*-OHPhCH₂, H-1, H-2, H-4), 5.44-5.51 (m, 2H, 2×COCH), 6.51-6.69 (m, 8H, 2×*p*-OHPhH), 7.20-7.27 (m, 10H, PhH), 7.44, 7.57 (2s, 2H, 2×NC=CH); HRESIMS: calcd for $[C_{45}H_{48}N_6O_{12}+H]^+$: 865.3408 found: 865.3420.

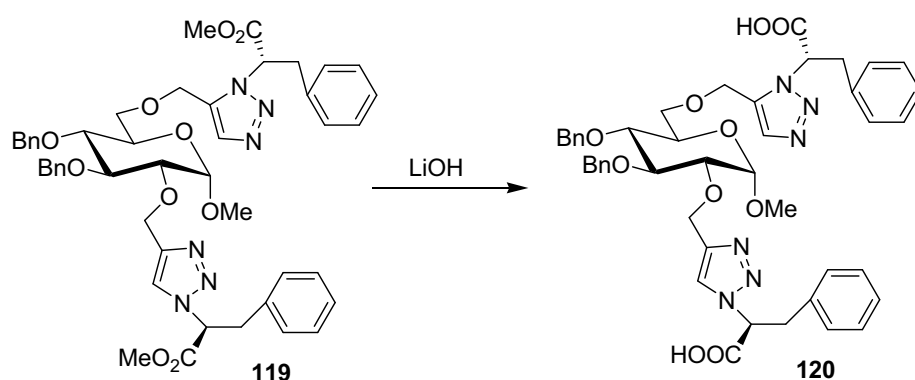
4.4.23 Synthesis of compound 119



To a solution of compound **116** (45 mg, 0.1 mmol) in 2 mL of CH₂Cl₂ and 2 mL of H₂O, was added compound **96** (41 mg, 0.2 mmol), followed by Na L-ascorbate (160 mg, 0.8 mmol) and CuSO₄·5H₂O (100 mg, 0.4 mmol). The reaction was stirred for 36 h, then extracted with CH₂Cl₂ (3×10 mL), washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (EtOAc:Pet=1:1) to afford compound **119** (49 mg, 57%) as yellow syrup. TLC: $R_f = 0.22$ (EtOAc :

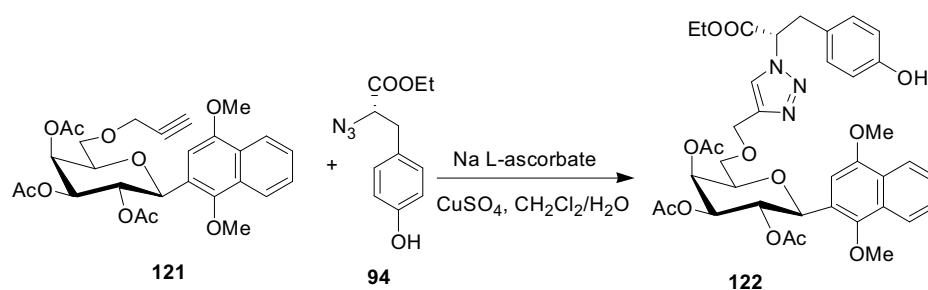
cyclohexane =1:1), ^1H NMR (400 MHz, CDCl_3): δ 3.21-3.28 (m, 1H, H-6a), 3.34 (s, 3H, OMe), 3.41-3.59 (m, 4H, H-2, H-4, H-5, H-6b), 3.61-3.65 (m, 4H, $2\times\text{OCH}_2\text{C}=\text{O}$), 3.68, 3.69 (2s, 6H, $2\times\text{CO}_2\text{Me}$), 3.94 (t, 1H, $J = 9.2$ Hz, H-3), 4.67-5.09 (m, 9H, $4\times\text{PhCH}_2$, H-1), 5.47 (m, 2H, $2\times\text{COCH}$), 7.00-7.38 (m, 20H, PhH), 7.52 (s, 1H, $\text{NC}=\text{CH}$), 7.57 (s, 1H, $\text{NC}=\text{CH}$); ^{13}C NMR (100 MHz, CDCl_3): 38.6, 38.7, 52.9, 53.0, 53.5, 55.2, 63.9, 63.9, 64.9, 66.7, 68.7, 69.8, 73.2, 74.9, 79.6, 81.9, 98.0, 122.4, 122.6, 127.5, 127.6, 127.7, 127.8, 127.9, 127.9, 128.0, 128.1, 128.2, 128.2, 128.4, 128.5, 128.5, 128.6, 128.7, 128.8, 128.9, 134.6, 134.8, 138.2, 138.2, 138.3, 138.3, 138.5, 144.8, 145.5, 168.5, 168.5; HRESIMS: calcd for $[\text{C}_{47}\text{H}_{52}\text{N}_6\text{O}_{10}+\text{Na}]^+$: 883.3643 found: 883.3655.

4.4.24 Synthesis of compound 120



To a solution of compound **119** (86 mg, 0.1 mmol) in a mixture of THF:MeOH: H_2O =2 mL:2 mL: 2 mL, was added LiOH· H_2O (7 mg, 0.15 mmol). After 8 h, IR 120+ cation exchange resin was added. After filtration, the filtrate was concentrated to afford compound **120** (67 mg, 81%) as yellow syrup. TLC: $R_f = 0.22$ (EtOAc:cyclohexane =1:1). I will ask prof. CHEN.

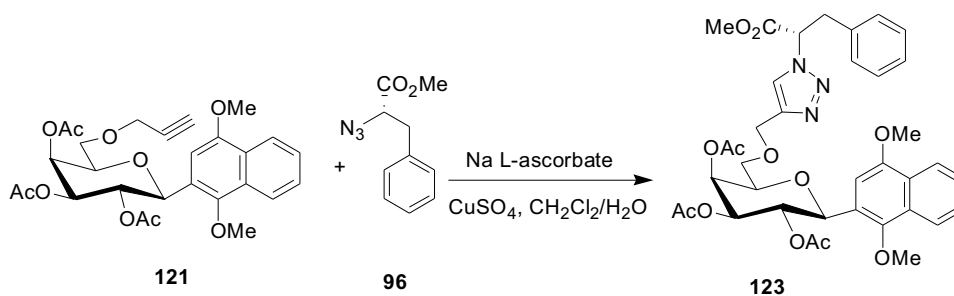
4.4.25 Synthesis of compound 122



To a solution of compound **121** (52 mg, 0.1 mmol) in 2 mL of CH_2Cl_2 and 2 mL of H_2O , was added compound **94** (41 mg, 0.2 mmol), followed by Na L-ascorbate (160 mg, 0.8 mmol) and $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (100 mg, 0.4 mmol). The reaction was stirred for 36 h, then extracted with CH_2Cl_2 (3×10 mL),

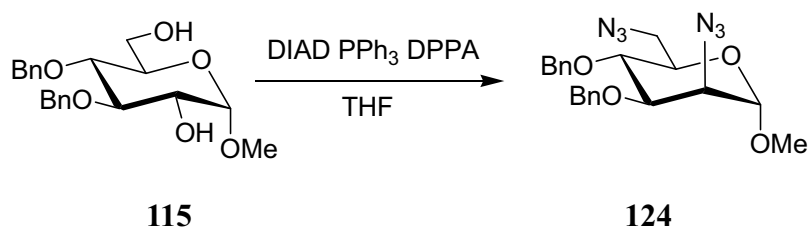
washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (EtOAc:Pet=1:1) to afford compound **122** (46 mg, 61%) as yellow syrup. TLC: $R_f = 0.27$ (EtOAc:cyclohexane 1:1); ^1H NMR (400 MHz, CDCl_3): δ 1.29 (m, 3H, OCH_2CH_3), 1.74, 2.05, 2.27 (3s, 9H, $3\times\text{OAc}$), 3.44 (m, 4H, OCH_2 , H-6a,6b), 3.96, 4.02 (2s, 6H, $2\times\text{ArOMe}$), 4.26 (m, 2H, OCH_2CH_3), 4.54 (m, 2H, H-5, H-4), 5.08 (d, 1H, $J = 10.0$ Hz, H-1), 5.24 (d, 1H, $J = 9.6$ Hz, H-3), 5.47 (m, 2H, CH_2Ph), 5.59 (s, 1H, COCH), 5.74 (t, 1H, $J = 10.0$ Hz, H-2), 6.68-6.82 (m, 5H, naphthylH), 7.36 (1H, m, $\text{NC}=\text{CH}$), 7.54 (m, 2H, benzylH), 8.05 (d, 1H, $J = 8.0$ Hz, benzylH); ^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 20.5, 20.8, 20.9, 29.0, 29.7, 30.9, 30.9, 38.0, 55.7, 56.5, 62.4, 63.4, 64.3, 64.6, 66.2, 67.6, 68.1, 68.3, 72.0, 73.4, 76.0, 115.6, 122.1, 122.5, 123.8, 125.8, 126.2, 128.0, 130.2, 148.5, 152.3, 155.8, 167.9, 169.1, 170.6, 171.2; HRESIMS: calcd for $[\text{C}_{38}\text{H}_{43}\text{N}_3\text{O}_{13}+\text{Na}]^+$: 772.2694 found: 772.2698.

4.4.26 Synthesis of compound 123



To a solution of compound **120** (52 mg, 0.1 mmol) in 2 mL of CH_2Cl_2 and 2 mL of H_2O , was added compound **96** (41 mg, 0.2 mmol), followed by Na L-ascorbate (160 mg, 0.8 mmol) and $\text{CuSO}_4\cdot 5\text{H}_2\text{O}$ (100 mg, 0.4 mmol). The reaction was stirred for 36 h, then extracted with CH_2Cl_2 (3×10 mL), washed with brine, dried over MgSO_4 , evaporated, and purified with column chromatography (EtOAc:Pet=1:1) to afford compound **123** (37 mg, 52%) as yellow syrup. TLC: $R_f = 0.33$ (EtOAc:cyclohexane = 1:1); ^1H NMR (400 MHz, CDCl_3): δ 1.72, 2.01, 2.21 (3s, 9H, $3\times\text{OAc}$), 3.34 (m, 1H, H-5), 3.47 (m, 1H, H-6a), 3.60 (m, 3H, OCH_2 , H-6b), 3.71 (s, 3H, CO_2CH_3), 3.93 (s, 3H, ArOMe), 3.97 (s, 3H, ArOMe), 4.58 (m, 2H, H-7a,7b), 5.08 (d, 1H, $J = 10.0$ Hz, H-1), 5.28 (d, 1H, $J = 9.6$ Hz, H-3), 5.48 (m, 1H, COCH), 5.61 (s, 1H, H-4), 5.72 (t, 1H, $J = 10.0$ Hz, H-2), 6.81-8.23 (m, 11H, ArH, $\text{NC}=\text{CH}$); ^{13}C NMR (100 MHz, CDCl_3): δ 14.2, 20.5, 20.7, 20.9, 21.0, 29.6, 38.6, 53.0, 55.6, 60.4, 63.4, 64.0, 64.8, 68.3, 68.4, 68.5, 74.7, 76.3, 101.9, 122.2, 122.5, 122.7, 123.8, 126.1, 126.7, 127.0, 127.5, 128.1, 128.7, 128.8, 134.7, 144.7, 148.8, 152.1, 168.5, 169.0, 170.3, HRESIMS: calcd for $[\text{C}_{37}\text{H}_{41}\text{N}_3\text{O}_{12}+\text{Na}]^+$: 742.2588 found 742.2607.

4.4.27 Synthesis of compound 124



To a 0°C solution of PPh₃ (452 mg, 1.73 mmol) in 6 mL of THF, was added DIAD (340 μL, 1.72 mmol). After 30 min, a solution of compound **115** (129 mg, 0.35 mmol) in 4 mL of THF was added, followed by DPPA (375 μL, 1.73 mmol). The reaction was stirred for 36 h, then extracted with CH₂Cl₂ (3×10 mL), washed with brine, dried over MgSO₄, evaporated, and purified with column chromatography (EtOAc:Pet=1:1) to afford compound **124** (101 mg, 68%) as yellow syrup. TLC: *R_f* = 0.63 (EtOAc:cyclohexane = 1:6); ¹H NMR (300 MHz, CDCl₃): δ 3.35 (s, 3H, OMe), 3.37-3.49 (m, 4H, H-3, H-5, H-6a,6b), 3.75 (m, 1H, H-2), 4.07 (t, 1H, *J* = 9.2 Hz, H-4), 4.62-4.93 (m, 5H, 2×PhCH₂, H-1), 7.29-7.38 (m, 10H, PhH); ¹³C NMR (75 MHz, CDCl₃): δ 51.3, 55.2, 69.4, 73.0, 73.3, 74.5, 77.9, 79.5, 97.25(C1), 127.8-128.5, 138.04, 137.71.

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