NANYANG TECHNOLOGICAL UNIVERSITY

DEVELOPMENT OF NOVEL STRATEGIES BASED ON LEWIS ACID AND TRANSITION METAL MEDIATED STEREOSELECTIVE *C*-GLYCOSYLATION

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2013

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A thesis submitted to the Nanyang Technological University in partial fulfillment of the requirement for the degree of Doctor of Philosophy

2013

ACKNOWLEDGEMENTS

I would like to express my greatest appreciation to my supervisor, Associate Professor Dr. Liu Xue-Wei, for his constant encouragement, continual guidance and valuable advice throughout my PhD study.

I would also like to express my profound gratitude to Prof. Dr. Chen Anqi, who guided me into the fantastic research area of organic chemistry and introduced me to join the present wonderful research group.

My sincere appreciation is also extended to my senior, Dr. Ma Jimei, for her assistance during the past few years. I would also like to thank all of my lab mates, especially, Cai Shuting, Leow Minli, Xiang Shaohua, Tan Yu Jia, Bai Yaguang, Le Mai Hoang Kim, Dr. Fu Rui, Dr. Seenuvasan Vedachalam, Dr. Wu Junliang and Huang Jie.

I would like to express my appreciation to Dr. Lu Yunpeng and Dr. Rujee Lorpitthaya for their valuable advice and assistance in conducting the computational studies. Special thanks to HPC@NTU for providing the computational resources. In addition, I am grateful to Dr. Li Yongxin and Dr. Rakesh Ganguly for assisting with the X-ray crystallographic analysis, and Ms Goh Ee Ling, Dr. Attapol Pinsa, Ms Zhu Wenwei and Ms Pui Pang Yi for their support on NMR and mass spectroscopy.

I would also like to thank all the CBC staff members, academic and non-academic, for their valuable support.

I would also like to extend my appreciation to Nanyang Technological University for providing the scholarship and laboratory facilities.

Lastly, I am deeply grateful to my beloved family members: my parents, my brother and particularly my wife, for their constant encouragement and support.

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ABSTRACT

The significance of *C*-glycosides has stimulated a wide interest in the development of *C*-glycosylation methods. Among them, Lewis acid and transition metal mediated direct attachment of carbon nucleophiles to sugar anomeric carbon center to produce 2,3-unsaturated glycosides and saturated, fully oxygenated glycosides are probably the most widely used methods. This thesis work focuses on the development of new methodologies in Lewis acid and transition metal mediated stereoselective *C*-glycosylation and application of these methodologies to natural product synthesis.

In the first part, a new method towards 1,2-*cis* and 1,2-*trans* *C*-mannosylation based on $BF_3 \cdot OEt_2$ promoted directed coupling of organotrifluoroborate reagents with mannosyl fluorides is demonstrated. This methodology was also applied into the *α*-*C*-glycosylation for D-glucopyranose, D-galactopyranose, D-mannofuranose and D-arabinofuranose.

In the second part, a highly *β*-selective *C*-glycosylation *via* palladium-catalyzed decarboxylative allylation is introduced. The reaction mechanism was further studied by experimental and DFT calculations. It was found that the reaction proceeded through an ionization-allylation-decarboxylation sequence *via* an outer-sphere mechanism. In addition, the methodology was also applied in normal pyran systems to generate *cis*-2,6-disubstituted tetrahydropyrans in high yields and exclusive selectivity, providing a new facile mode of access to naturally occurring *cis*-2,6-tetrahydropyrans.

Furthermore, the applicability of these methodologies was examined by the total synthesis of (+)-varitriol, (±)-centrolobine, decytospolide A, B and aspergillide A.

INDEX OF ABBREVIATIONS

Δ	chemical shift
ºC	degree centrigrade
Ac	acetyl
acac	acetylacetone
AcCl	acetyl chloride
AcOH	acetic acid
Ac_2O	acetic anhydride
AIBN	azobisisobutyronitrile
aq.	aqueous
BIPHEPHOS	6,6'-{[3,3'-bis(1,1-dimethylethyl)-5,5'-dimethoxy[1,1'-bipheyl]-2,2'-diyl]bis(oxy)}bis{dibenzo[*d*,*f*][1,3,2]dioxaphosphepine}
$BminBF_4$	1-Butyl-3-methylimidazolium tetrafluoroborate
Bn	benzyl
Boc	tert-butoxycarbonyl
Brs	broad singlet
BuLi	butyl lithium
Bz	benzoyl
Brsm	based on recovered starting materidal
calcd.	calculated
CAN	ceric ammonium nitrate
cat.	catalytic
Cbz	benzyloxycarbonyl
$CDCl_3$	deuterated chloroform
CDI	1,1'-carbonyldiimidazole
CSA	camphorsulfonic acid
CH_2Cl_2	dichoromethane
$CHCl_3$	chloroform
cm^{-1}	inverse centimeter
COD	cyclooctadiene
Cy	cyclohexanyl
d	doublet
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]-undec-7-ene
DCM	dichloromethane
DCE	dichloroethane
dd	doublets of doublet
ddd	doublets of doublets of doublet
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	2,3-dihydropyran
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	4-(*N,N*-dimethylamino)-pyridine
DME	dimethoxyethane
DMEDA	*N,N'*-dimethylethylene-diamine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphoryl azide
DPPE	1,3-bis(diphenylphosphino)ethane
DPPP	1,3-bis(diphenylphosphino)propane
dq	doublets of quartet
dt	doublets of triplet
DTBMP	2,6-di-tert-butyl-4-methylpyridine
ee	enantiomeric excess
EDTA	ethylenediaminetetraaceti c acid
EI	electron ionization
equiv.	equivalent
ESI	electronspray ionization
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate

EtOH	ethanol
FTIR	fourier transform infrared spectroscopy
g	gram
h	hour
HPA	*Helix Pomatia* agglutinin
HRMS	high resolution mass spectroscopy
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared
*i*Pr	isopropyl
J	coupling constants
KHMDS	potassium hexamethyl disilazide
M	concentration (mol/L)
M^+	parent ion peak (mass spectrum)
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
μm	micrometer
mm	milimeter
mmol	millimoles
mol	moles
MS	mass spectrum
M.S.	molecular sieves
Ms	methanesulfonyl
*n*Bu	*n*-butyl
NMR	nuclear magnetic resonance
NMP	*N*-methyl-2-pyrrolidone
NOESY	nuclear overhauser enhancement spectroscopy
OTf	trifluoromethanesulfonate
p	para
Pd/C	palladium on carbon
Ph	phenyl
Piv	pivaloyl; 2,2-dimethylpropanoyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pyr	pyridine
q	quartet
rt	room temperature
s	singlet
t	triplet
TBAI	tributylammonium iodide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
*t*Bu	*tert*-butyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	triflate acid
Tf_2O	triflic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMEDA	Tetramethylethylenediamine
Tr	triphenylmethyl
Ts	*p*-toluenesulfonyl
TTBP	2,4,6-tri-tert-butylpyrimidine
V	volume

Chapter 1
Lewis acid and Transition Metal Mediated *C*-Glycosylation

Proteins, nucleic acids, carbohydrates and lipids are the four major classes of biomolecules, each having their own unique characteristic roles and structural differences in biochemistry. Among them, carbohydrates not only have traditionally accepted roles such as energy sources and structural polymers, but also play a crucial role in numerous biological processes. These include viral and bacterial infection, angiogenesis and tumor cell metastasis, toxin interaction, inflammation and immune response, cell growth and proliferation, and many other cell–cell communications. [1] However, when compared to the other three kinds of biomolecules which are generally linear assemblies, carbohydrates remain as the least exploited due to their more complex and diverse structures found in nature. Thus, these complexities hindered the development of practical synthetic and analytical methods for carbohydrate research, which further slow down the pace of development of carbohydrate-based therapeutics.

Most of the naturally occurring carbohydrates are generally not present as monomers in their free forms, but linked to each other or to other compounds (aglycones) by glycosidic bonds to form complex and diverse oligo- and poly-saccharides, glycoproteins, glycolipids and so on. These compounds commonly exist in microheterogeneous forms and are difficult to be isolated from natural sources in acceptable purity and quantity to meet the requirement of biological studies. As such,

these existing difficulties promoted chemists to develop new synthetic pathways toward complex carbohydrate structures. Undoubtedly, glycosylation reaction plays a central role in carbohydrate chemistry as it is the most routine and effective strategy to form glycosidic bonds in specific stereoselectivity, which are widely presented in carbohydrate complexes.

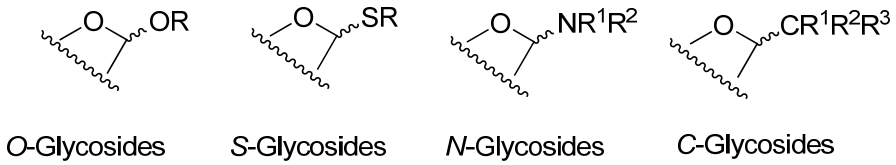


Figure 1.1 *O*-, *S*-, *N*- and *C*-glycosides.

Compounds possessing *O*-, *S*-, *N*- and *C*- glycosidic linkages are correspondingly called *O*-glycosides, *S*-glycosides, *N*-glycosides and *C*-glycosides (**Figure 1.1**). Among them, *O*-glycosides are the most abundant and important glycosides found in nature. However, *C*-glycosides have attracted considerate interest for the past few years due to the following reasons:

1. Unlike *O*-glycosidic bonds which are acid labile and may be susceptible to enzymatic degradation, *C*-glycosidic bonds are chemically and enzymatically stable. This fact implied the potential application of *C*-glycosides in the areas ranging from inhibition of carbohydrate processing enzymes, modulation of immune pathways, lection bindings and the blocking of pathogenesis. In addition, development of *C*-glycosides as stable pharmacophores was also encouraged by the hypothesis that *C*-glycosides have similar activities but better stability as compared to their *O*-glyco parents.[2] One example is shown in **Figure 1.2**.[3] KRN 7000 is a synthetic *O*-glycoside modified from natural agelasphins but has a better activity. Interestingly, it was found that the activity of its *C*-glycoside analogue was 100 times more effective toward

melanoma and 1000 times more protective toward malaria which was partially due to the longer lifetime *in vivo*.

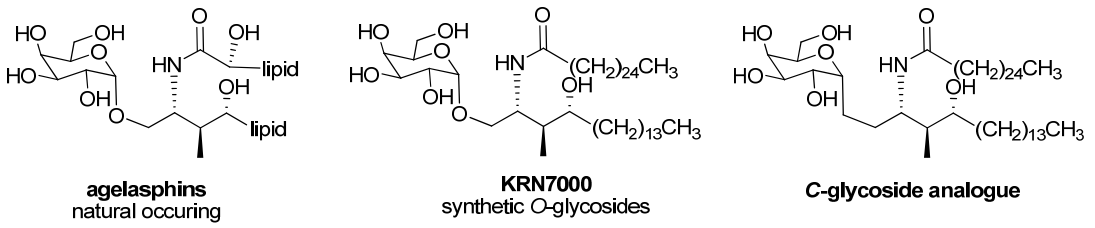


Figure 1.2 Natural and synthetic *O*-glycosides and their *C*-glycoside analogue.

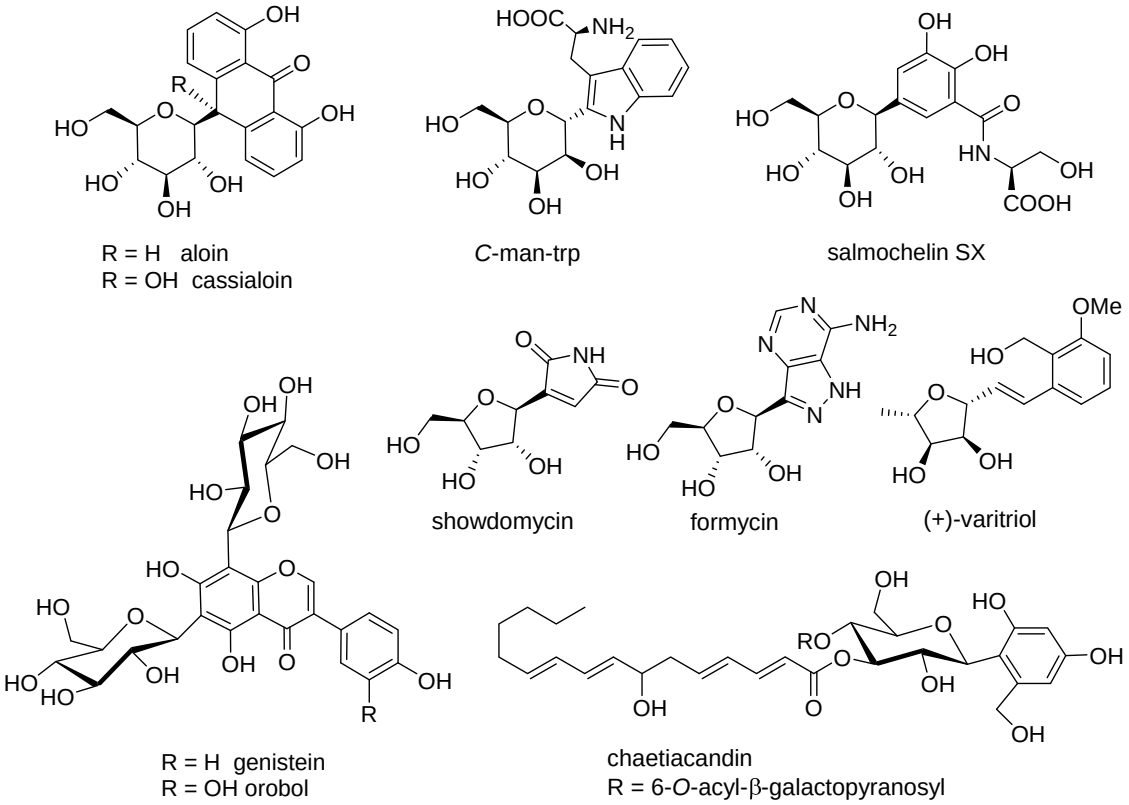


Figure 1.3 Natural occurring *C*-glycosides.

2. *C*-glycosides are widely existed in nature; many of them have been isolated and showed interesting pharmacological and biological properties. Some examples are listed in **Figure 1.3**. These important bio-active natural *C*-glycosides stimulated chemists to look for more *C*-glycosides from nature and to develop their analogues for further pharmacological and biological studies.

3. *C*-glycosides are also architectures to construct a certain amount of natural products (**Figure 1.4**). As a consequence, *C*-glycosides become important chiral building blocks to synthesize diverse natural products as well as some other non-*C*-glycoside containing compounds. Considering of the abundance of availability and the rich of functionality, usage of carbohydrate as chiral building blocks afford one of the most efficient strategy toward total synthesis.

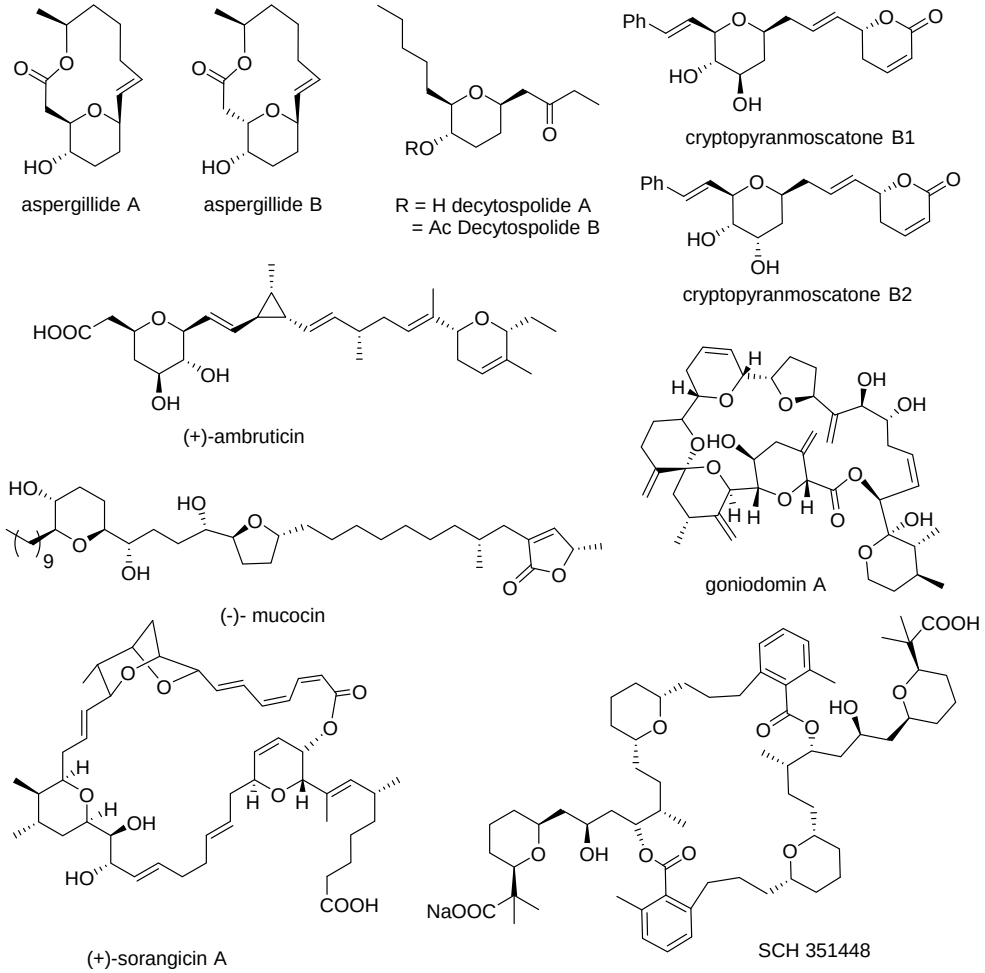
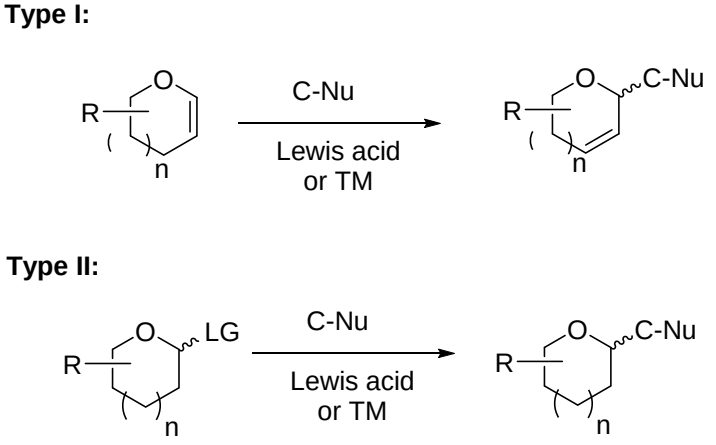


Figure 1.4 Natural products containing *C*-glycoside skeleton.

Undoubtedly, these advantages have attracted considerable interests from carbohydrate chemists to develop efficient and practical glycosylation methods. Although significant effort has been devoted to this area over the past few decades and several reviews have described the advances,[4] stereoselective construction of *C*-

glycosides with high efficiency and diversity still remains a big challenge. This is due to the lack of anomeric effect and the weak neighboring group participation effect, which are the main factors to control the selectivity in *O*-glycosylation.

The most widely developed *C*-glycosylation method is the direct attachment of carbon nucleophiles to sugar anomeric carbon center. In this chapter, we are focus on two types of *C*-glycosylation reaction as shown in **Scheme 1.1**. These two types are also the most commonly used methods for *C*-glycosylation.



Scheme 1.1 Two types of *C*-glycosylation.

1.1 Lewis acid-mediated *C*-glycosylation

Methods used for Lewis acid catalyzed *O*-glycosylation may also be efficient towards Lewis acid catalyzed *C*-glycosylation. The rationality arises from the fact that both reactions proceed through similar mechanism and same oxocarbenium cation intermediate was involved. However, the differences are that: control of the stereoselectivity becomes much more difficult and is completely dominated by other stereoelectronic effect for *C*-glycosylation due to the absence of anomeric effect. Moreover, generating equatorial (generally β) substituted *C*-glycosides is far more

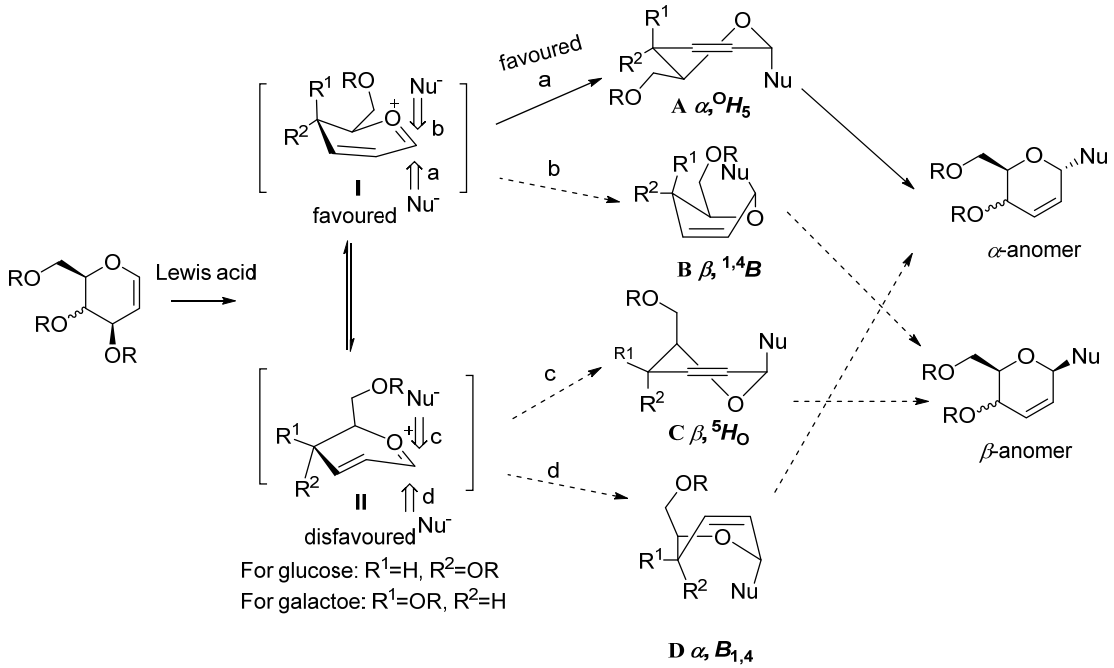
challenged due to the neighboring group participation is not a predominant factor. In addition, slightly more stringent reaction conditions (higher reaction temperature, more catalyst or promoter amount, longer reaction time, *etc*.) were necessary for *C*-glycosylation due to the *C*-nucleophiles suitable for *C*-glycosylation are generally weaker nucleophiles compare to *O*-nucleophiles.

1.1.1 Lewis acid-mediated type I *C*-glycosylation

Lewis acid mediated type I *C*-glycosylation is widely known as Ferrier rearrangement. Argueably, Ferrier rearrangement is one of the most widely used glycosylation methods to generate 2,3-unsaturated sugars which can be used as building blocks to synthesize various forms of sugars or pseudosugars.[5] Although this type of rearrangement was observed early in 1914 by Fischer [6], the synthetic utility of this transformation was only recognized by Ferrier until 1960s.[7] However, most of the applications focused on the formation of *O*-, *S*- or *N*- glycosides until 1980s when *C*-glycosylation captivated much attention. Similar to *O*-glycosylation, Ferrier type *C*-glycosylation also generates oxocarbenium intermediate.

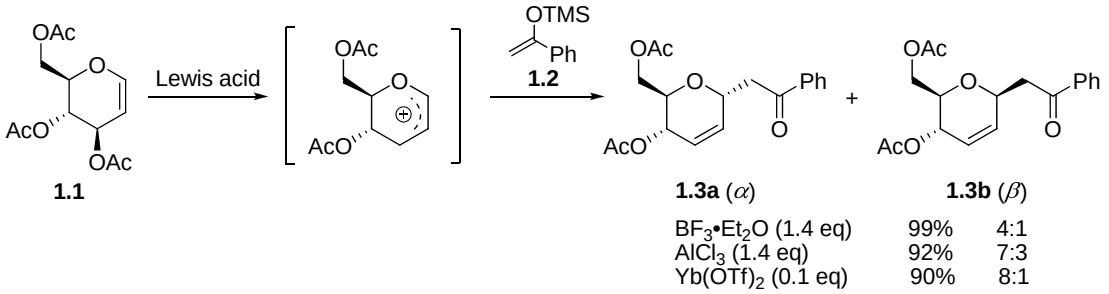
The stereochemistry mainly controlled by the conformation of oxocarbenium intermediate and the attack pathways of nucleophile. Generally, the oxocarbenium cation intermediate favours lower energy conformation **I** other than **II.** The nucleophile could attack from either top face (parthway b) or bottom face (parthway a) of conformer **I**. The top face attack lead to unfavoured boat conformation **B** through higher energy transition state while bottom face attack lead to favoured half chair comformation **A** through a lower energy transition state. As a consequence, α-anomer was produced as a major product. However, it is difficult to avoid the produce of β-anomer in this type of *C*-glycosylation, because, in one hand, the energy gap between

conformation **I** and **II** is not big enough and in another hand, the selectivity is also influenced by other effects such as reaction conditions (reaction temperature, solvent, promoter, etc.) and stereo effect and electronic effect of nucleophile. (**Scheme 1.2**).



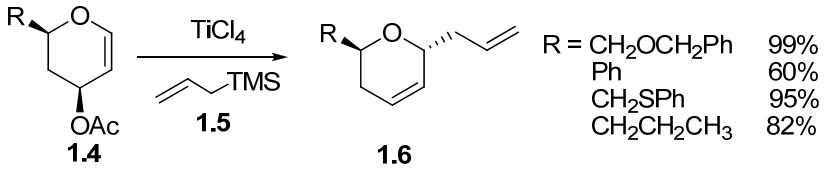
Scheme 1.2 Stereoselectivity of Ferrier rearrangement.

The first example of Lewis acid catalyzed *C*-glycosidation *via* Ferrier rearrangement was reported by Fraser-Reid, B. in 1981 (**Scheme 1.3**).[8] They found that stoichiometric amount of Lewis acid promoted reaction of trimethylsilyl enol ether **1.2** with triacetyl glucal **1.1** to give *C*-glycoside **1.3** in excellent yields with moderate selectivity. A suitable catalyst and solvent is crucial for this reaction. DCM or CH_3CN in combination with $BF_3 \cdot OEt_2$ or $AlCl_3$ gave the best yields and selectivity while other solvents and catalysts systems proved to be not so efficient. They also demonstrated that these Lewis acid-catalyzed condensations are kinetically controlled and α-anomers were favored at low temperature. The catalytic version of this reaction was also achieved while 10% of $Yb(OTf)_2$ was used as catalyst and the selectivity was increased to 8:1.[9]

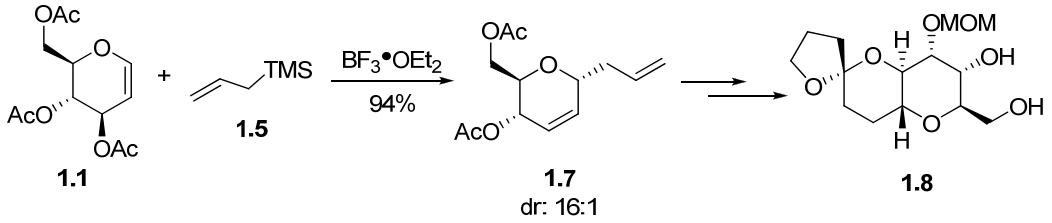


Scheme 1.3 Lewis acid promoted reaction of trimethylsilyl enol ether with glucal.

Inspired by this initial study, Samuel Danishefsky reported a $TiCl_4$ promoted *C*-glycosidation in the same year.[10] In their studies, allyltrimethylsilane **1.4** was chosen to be the nucleophile. Gratifyingly, only α-anomers were observed in excellent yields when the reaction was promoted with stoichiometric amount of $TiCl_4$ (**Scheme 1.4**). Other than $TiCl_4$, a wide range of Lewis acids, including $InCl_3$[10], $InBr_3$[11], $Bi(OTf)_3$[12], $Eu(OTf)_3$[14], $ZrCl_2$[13], $Yb(OTf)_3$[14], $Sc(OTf)_3$[15], $MgClO_4$[16], were also effective to catalyze this reaction. Glycosidation of allyltrimethylsilane to glycals has garnered broad interest partly because of the presence of terminal double bond in the products. This bond is amenable to functionalization, leading to other chiral molecules as well as to carbohydrate mimics. This was showcased by the synthetic studies of okadaic acid.[17,18] In this case, $BF_3 \cdot OEt_2$ was chosen to be the promoter and a 16:1 *dr* ratio was observed (**Scheme 1.5**).

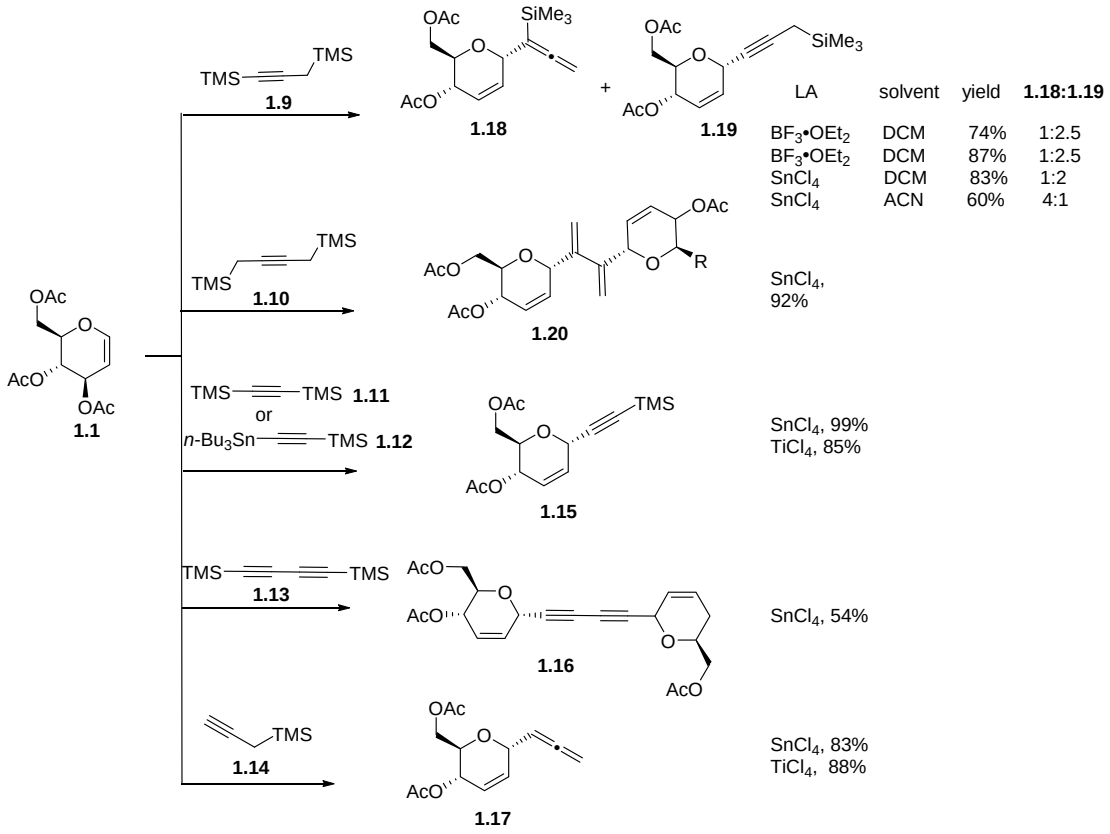


Scheme 1.4 $TiCl_4$ promoted *C*-glycosidation.



Scheme 1.5 Synthetic studies of okadaic acid.

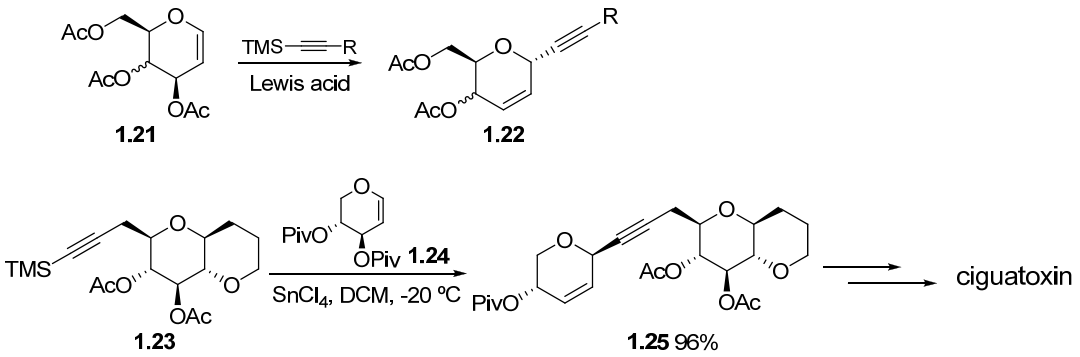
Silyl compounds are also good reaction partners toward Ferrier *C*-glycosylation. Isobe group tested a variety of silyl compounds and obtained a series of interesting *C*-glycosides with extremely good α-selectivity (**Scheme 1.6**).[18]



Scheme 1.6 Ferrier *C*-glycosylation with silyl compounds.

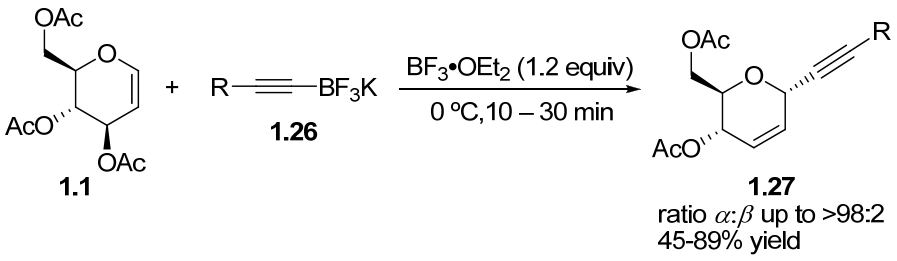
Inspired by these pioneering works, great efforts have been made in the synthesis of sugar acetylenes which are useful building blocks for the synthesis of natural products and pharmaceuticals because of the presence of triple bond which can be easily transformed to other molecules and carbohydrate analogues. In these efforts,

TMS-protected terminal acetylenes were mostly used as glycosyl acceptors and Lewis acid such as I_2[19], $InBr_3$[20], $ZrCl_4$[21], $Er(OTf)_3$[22], $Sc(OTf)_2$[23], *et al*. have been explored. In addition, this methodology has also led to the synthetic study of ciguatoxin (**Scheme 1.7**).[24]



Scheme 1.7 Synthetic study toward ciguatoxin.

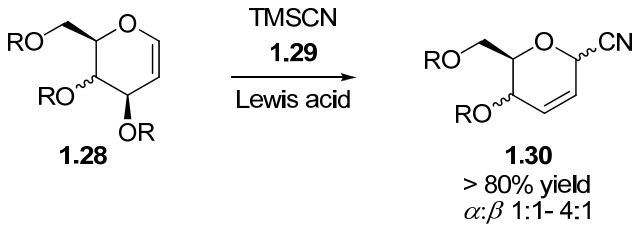
Other types of acetylenes also were explored. In 2008, Stefani *et al*. reported a $BF_3 \cdot OEt_2$ promoted nucleophilic addition of air and moisture stable potassium alkynyltrifluoroborates **1.26** to D-glucals (**Scheme 1.8**).[25] It offered a convenient and highly stereoselective method for alkynylation of glycals which preferentially provides the α-glycosids in good yields.



Scheme 1.8 *C*-glycosylation with alkynyltrifluoroborates.

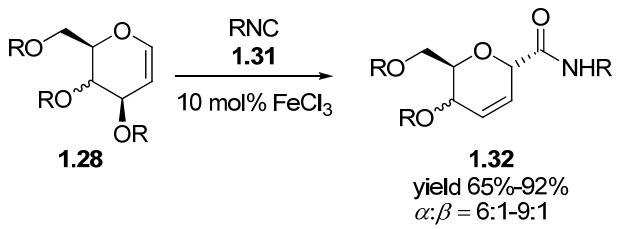
Glycosyl cyanides are versatile building blocks for the synthesis of *C*-glycosyl derivatives because the cyano group can be easily transformed into a variety of other

functional groups. The first synthesis of glycosyl cyanides *via* Ferrier rearrangement was reported by De las Heras F. G. *et al*. in 1983.[26] They found that glycals reacted with trimethylsilylcyanide **1.29** in the presence of $BF_3 \cdot OEt_2$ gave glycosyl cyanides **30** in excellent yields, albeit with poor selectivities. Other Lewis acids such as $ZrCl_2$[20], $Sc(OTf)_3$[22], $InBr_3$[18], I_2[27], $Hg(CN)_2/HgBr_2$[28] were also examined to catalyze this cyanation reaction, unfortunately, most of them only afforded poor to moderate selectivities (**Scheme 1.9**).

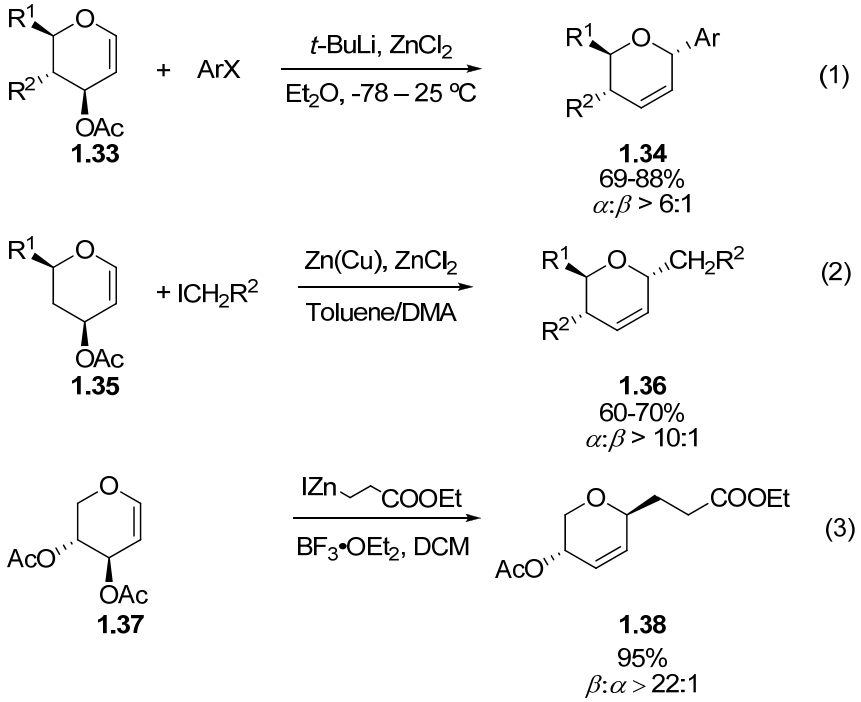


Scheme 1.9 *C*-glycosylation with TMSCN.

Unlike cyanide, the glycosylation reactions with isocyanide **1.31** gave different results and glycosyl amides **1.32** were obtained in good yields with high selectivity (**Scheme 1.10**).[29]



Scheme 1.10 *C*-glycosylation with isocyanide.

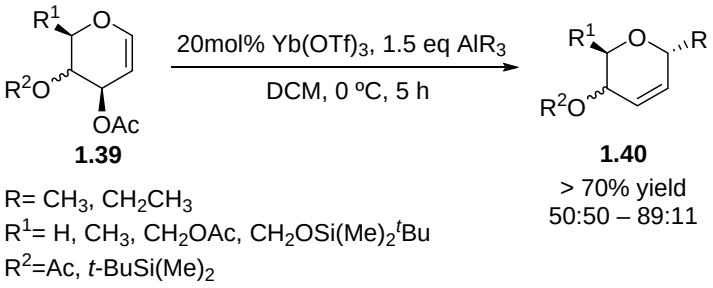


Scheme 1.11 *C*-glycosylation with organozinc reagents.

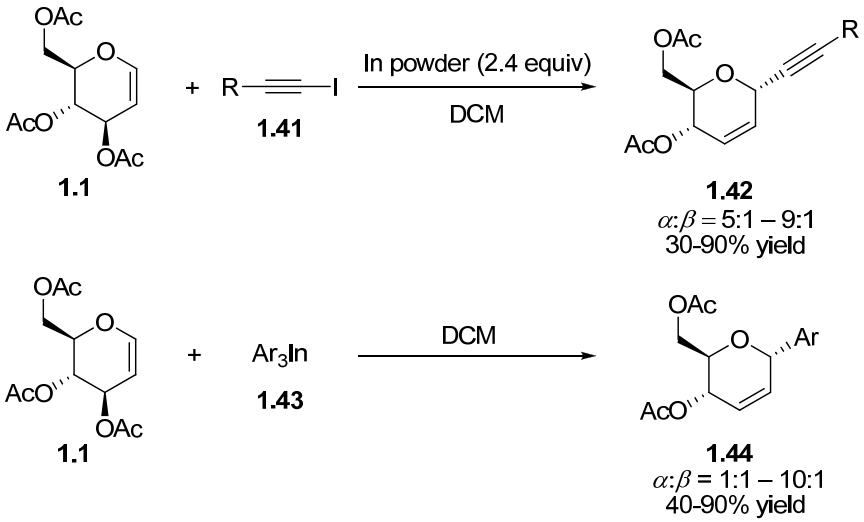
Organometallic reagents also tolerated well in Lewis acid catalyzed Ferrier rearrangement. In 1993, Orsini, F. group reported a reaction of Reformatsky reagent *tert*-butoxycarbonylmethylzinc bromide with acetylated glycal.[30] The reaction was performed in the presence of TMSOTf or $TiCl_4$. However, the reaction was not stereospecific and an *α,β*-mixture was obtained. In 1996, the selectivity of this reaction was improved by Thorn.[31] They demonstrated that the reaction of alkyl organozinc nucleophiles toward a series of glycal derivatives catalyzed by TMSOTf or $BF_3 \cdot OEt_2$ gave the desired glycosides in moderate to good α-anomeric selectivity. However, large amount of excess Lewis acid was necessary in this reaction. These drawbacks were overcome by Du Bois in 2002 (**Scheme 1.11**, eq 1 and 2).[32] It was found that $ZnCl_2$ was an excellent Lewis acid to catalyze both aryl- and alkyl-derived zinc reagents reacted with glycal derivatives. The yields and stereoselectivities were 63-88% and 6:1-10:1 (*α*:*β*) respectively. Even reactions with

pentopyranose-derived D-glycals, excellent yields and selectivity were obtained (**Scheme 1.11**, eq 3).[33]

Trialkylaluminum reagents were also employed into this type of reaction. In 2009, Reutrakul V. group reported that the reaction of trialkylaluminum and glycals catalyzed by 20 mol% $Yb(OTf)_3$ gave *C*-glycosides **1.40** in high yields with moderate to good selectivity (**Scheme 1.12**).[34]



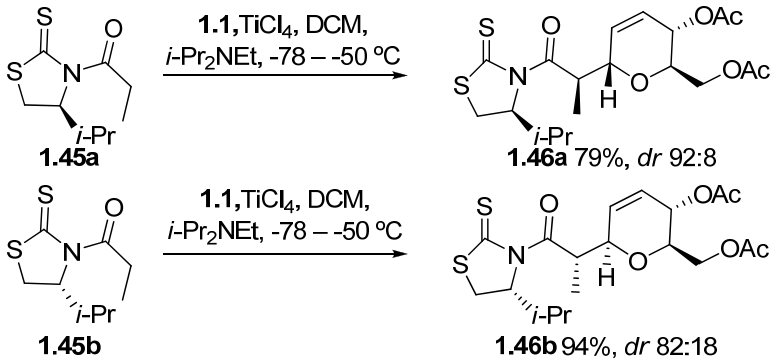
Scheme 1.12 *C*-glycosylation with trialkylaluminum reagents.



Scheme 1.13 *C*-glycosylation with organoindium species.

Another interesting organometallic reagent utilized in *C*-glycosylation is organoindium species which were either preformed (**1.43**) or *in situ* generated (**1.41**).[35] The Lewis acidity of these indium compounds was suggested to catalyze this type of reaction (**Scheme 1.13**).

As we disclosed above, most of Ferrier rearrangement prefer to give the *C*-glycosides with *α*-selectivity and the production of *β*-anomer was highly hampered by the steric factor. This problem was addressed by Rome *et al*. who developed a highly regio- and stereo-selective *C*-glycosylation procedure by employing chiral Evans auxiliaries. In this method, either *α*-, or *β*- *C*-glycosides can be efficiently obtained, depending on the chiral titanium enolates employed (**Scheme 1.14**).[36]

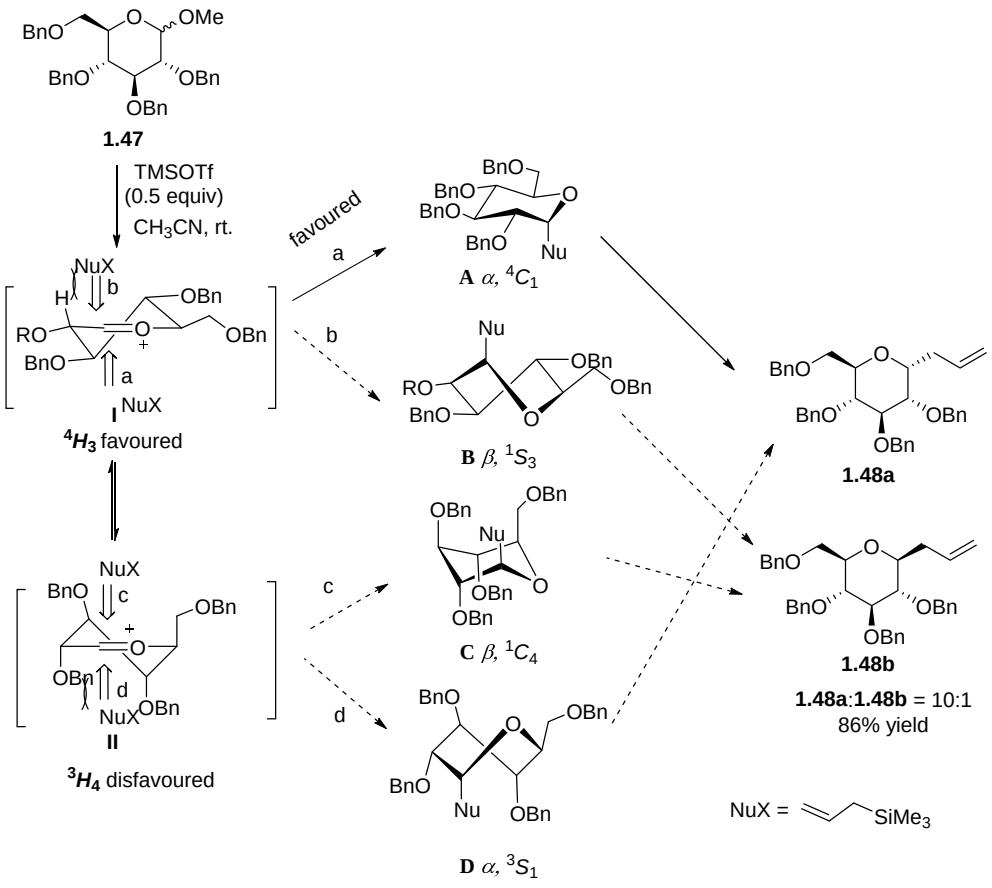


Scheme 1.14 Employing chiral Evans auxiliaries in *C*-glycosylation.

1.1.2 Lewis acid-mediated type II *C*-glycosylation

Obviously, substitution of sugar anomeric leaving group *via* either S_N1 or S_N2 process provides the most direct way to *C*-glycosylation. A Lewis acid is generally used for activating the leaving group and forms the oxonium species. Compared to type II *O*-glycosylation, control of the stereoselectivity of type II *C*-glycosylation is much difficult due to the lack of anomeric effect. Normally, the stereochemistry is mainly dominated by the conformations of oxonium intermediate and the attack pathways of nucleophile. The favoured conformation of oxonium intermediate in this reaction could be $^4H_3$ **I** instead of $^3H_4$ **II**. For both conformation, nucleophile could attack either from top side (pathway b and c) or bottom side (pathway a and d).

However, pathway b for conformation **I** and parthday d for comformation **II** lead to unfavoured twist boat comformations through a energy higher transition states while the pathday a for conformation **I** and parthday c for comformation **II** lead to favoured chair comformations through energy lowered transition states. As a consequence, the favoured pathway a for conformation **I** produced the α-anomer as major product (**Scheme 1.15)**. Other than conformational factors, the differences in steric crowding of two faces also influenced the stereoselectivity. Thus, glucosylation and galactosylation generally produced poorer α-selectivity compared to mannosylation due to the C-2 substituent of glucose and glactose increased the steric hindrance of α-face while that of mannose increased the steric hindrance of β-face.



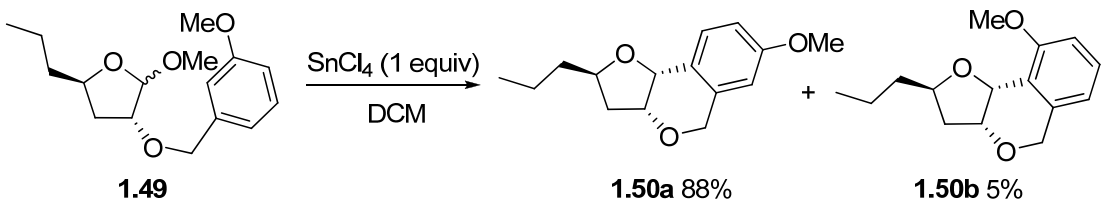
Scheme 1.15 *C*-glycosylation with glycosyl etherate.

Although most of the Lewis acid promoted type-II C-glycosylation proceed through S_N1 mechanism, by carefully choosing the leaving group and reaction conditions, the reaction could proceed through S_N2 like mechanism which makes the *β*-selective glycosylation possible. In addition, in some cases, neighboring group participation plays a big role in forcing the reaction in favour of *β*-selectivity.

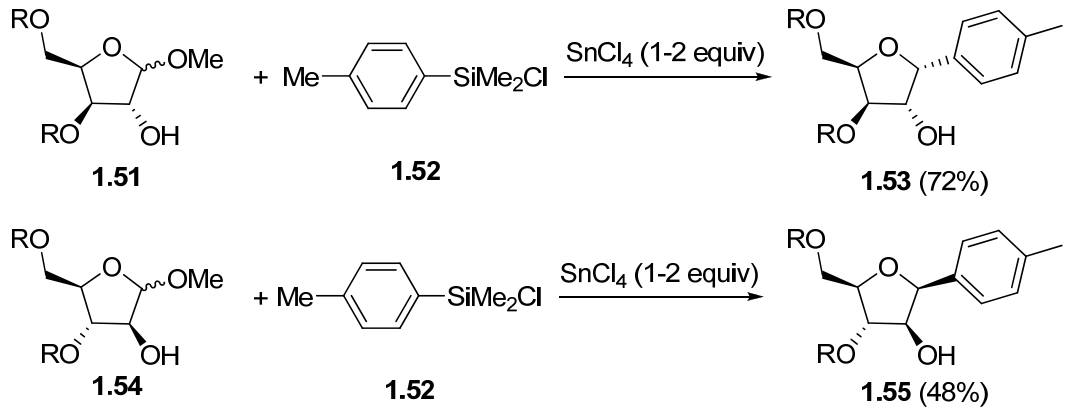
Because *C*-glycosylation generally utilize slightly harsher conditions than *O*-glycosylation, a wider range of leaving groups including those less reactive groups such as ether and acetate could also be applied.

Normally, glycosyl etherate is not an active glycosyl acceptor due to the stable anomeric ether bond. However, Sakurai[37] found that methyl glucopyranoside **1.47** could be activated by catalytic amount of TMSOTf at room temperature to form the oxonium which was further captured by trimethylsilyl compound, producing *C*-glycosides **1.48a** in good yield and selectivity (**Scheme 1.15**).

To prepare *C*-glycofuranoside, methoxy group was also installed on furanose scaffold. The intramolecular reaction of **1.49** promoted by $SnCl_4$ gave two 1,2-*cis* compounds **1.50a** and **1.50b**. This reaction was also applied to the total synthesis of monocerin analogues (**Scheme 1.16**).[38] Similarly, an internal nucleophile delivery strategy could also fulfill the 1,2-*cis* selectivity (**Scheme 1.17**).[39]

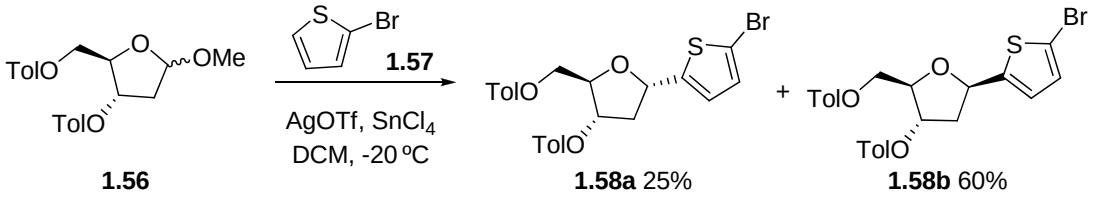


Scheme 1.16 Intramolecular *C*-glycosylation of **1.49**.



Scheme 1.17 1,2-*cis*-*C*-glycosylation *via* internal nucleophile delivery.

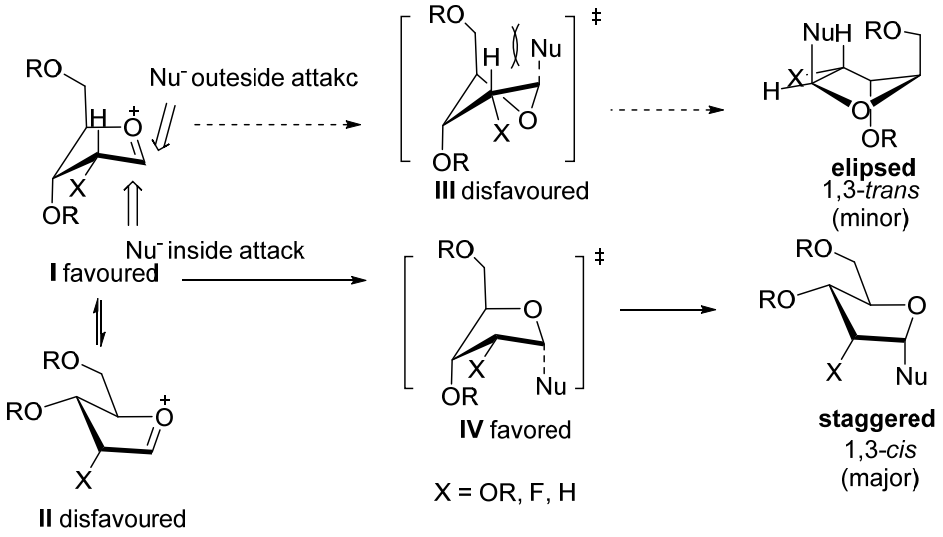
Methoxy group was also installed on 2-deoxyribofuranose to prepare *C*-deoxyribonucleosides based on a Friedel-Crafts-type *C*-glycosidation (**Scheme 1.18**). Interestingly, this reaction gave *β*-anomer as major product[40] which is contrary to Woerpel's observation.



Scheme 1.18 Friedel-Crafts-type *C*-glycosidation.

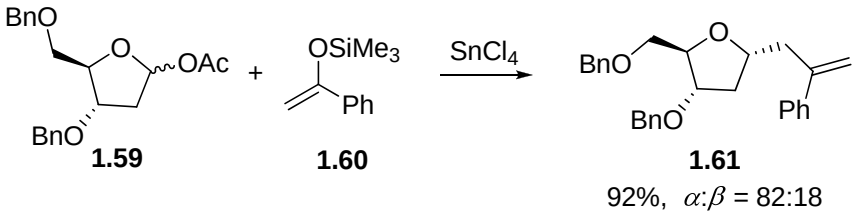
Woerpel et al. carried out a systematic investigation on the electronic effects of five-membered ring oxocarbenium ions.[41] They found that the C-3 alkoxy group generally exerted the most important influence on the selectivity. The lower energy conformer preferred the C-3 alkoxy group to adopt a pseudoaxial orientation, as the partially negative charged alkoxy group was closest to the oxocarbenium ion in this position and this would stabilize the system. In contrast, substituent at C-2 exerted less effect while substituent at C-4 showed no obvious effect. Thus, conformer I was favoured. Subsequent nucleophilic attack preferentially from the inside face of

envelope lead to 1,3-cis product as the major product. Attack from the outside face is disfavored, because eclipsing interactions between the substituents at C-1 and C-2 develop in the transition structure **III** leading to the elipsed 1,3-trans product (**Scheme 1.19**).

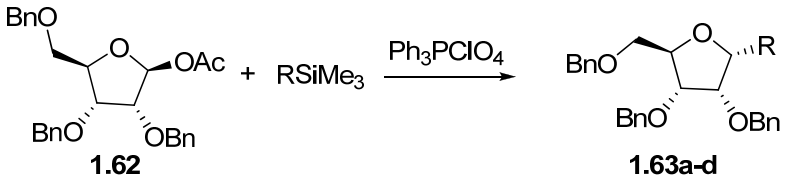


Scheme 1.19 Selectivity of *C*-glycosylation of furanose.

This observation was supported by a lot of reports. For example, the $SnCl_4$ promoted glycosylation of glycosyl acetate **1.59** with **1.60** generated **1.61** with 82:18 α:β-selectivity (**Scheme 1.20**). [42] Kobayashi also reported a triphenylmethyl perchlorate (5% mol) catalyzed reaction of **1.62** with silyl compounds in dimethoxyethane (DME). All of these reactions proceeded smoothly and gave the α-anomer in excellent selectivity except cyanation reaction. However, when the solvent was changed to Et_2O, the selectivity of cyanation reaction was increased to α:β = 93:7 (**Scheme 1.21**).[43]

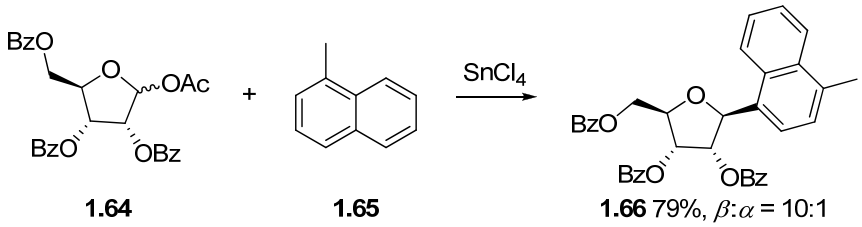


Scheme 1.20 $SnCl_4$ promoted glycosylation of glycosyl acetate **1.59** with **1.60**.



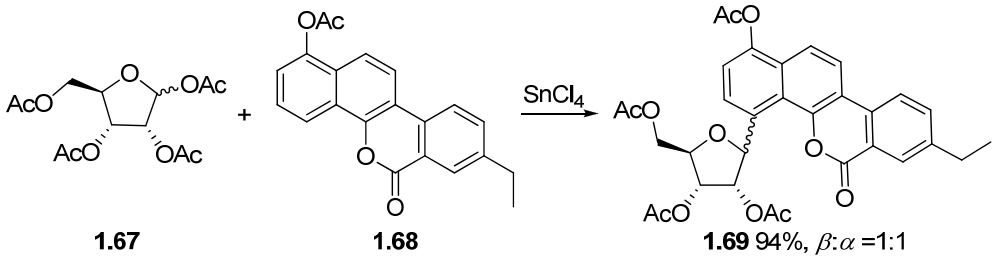
$RSiMe_3$	solvent	yield (%)	α:β
CH_2=C(OSiMe_3)CMe_3	DME	93	99:1
CH_2=C(OSiMe_3)Ph	DME	97	100:0
CH_2=CHCH_2SiMe_3	DME	90	100:0
TMSCN	DME	97	63:37
TMSCN	Et_2O	93	93:7

Scheme 1.21 Triphenylphosphate perchlorate catalyzed *C*-glycosylation.

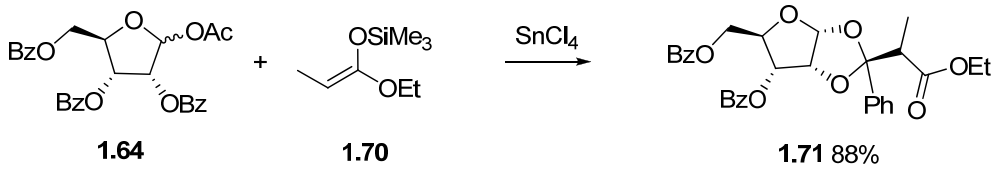


Scheme 1.22 Neighbouring group participation.

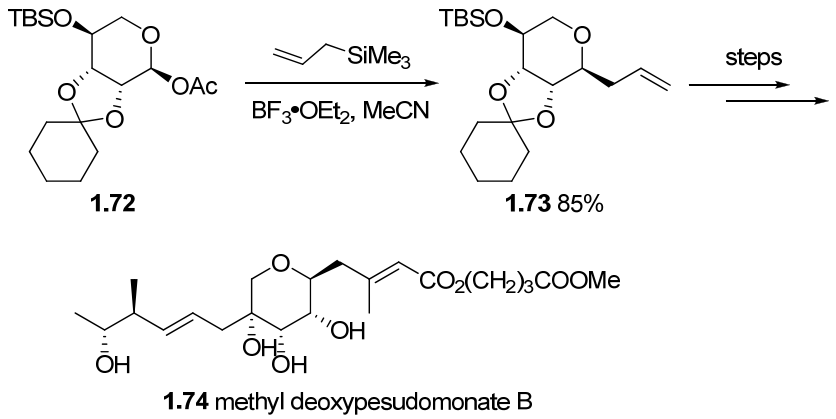
When C-2 hydroxy group was protected by acetate, the $SnCl_4$ promoted reaction of **1.64** and **1.65** gave β-anomer **1.66** as the major product due to the neighbouring group participation (**Scheme 1.22**).[44] However, neighbouring group participation is not always effective in producing β-selectivity. For example, coupling of **1.68** with peracetylated furanose **1.67** only provided a 1:1 mixture of **1.69** (**Scheme 1.23**).[45] Even worse, in some cases, neighbouring group participation did not lead to *C*-glycosylation product and resulted in a side reaction instead (**Scheme 1.24**).[46]



Scheme 1.23 Example of neighbouring group participation was inefficient.



Scheme 1.24 Neighbouring group participation resulted in side reaction.

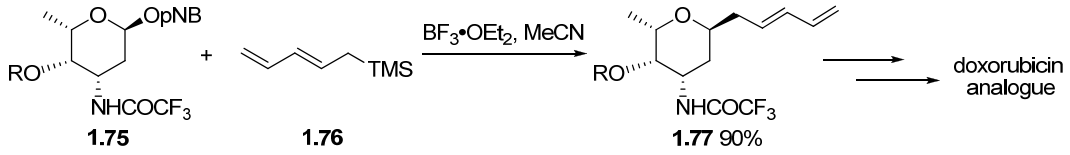


Scheme 1.25 Total synthesis of methyl deoxypesudomonate B.

Glycopyranosyl acetates were also widely exploited in Lewis acid mediated *C*-glycosylation[47] and the stereochemistry was mainly decided by the conformation of oxonium intermediate as shown in **Scheme 1.15**. In the total synthesis of methyl deoxypesudomonate B, Kozikowski developed a $BF_3 \cdot OEt_2$ catalyzed allylation of L-sugar **1.72**, giving the expected product **1.73** in good yield with α-selectivity (**Scheme 1.25**). [48]

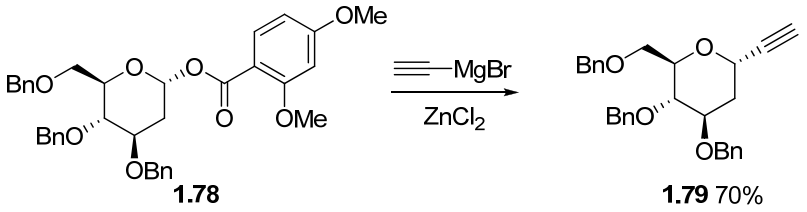
Other than acetyl group, 1-*O*-benzoyl group could also be used as a leaving group. For instance, with 1-*O*-*p*-nitrobenzoyl as the leaving group, **1.75** could react with allyl

trimethylsilane **1.76** in the presence of excess $BF_3{\cdot}OEt_2$ to generate **1.77** as a single isomer, which was the key intermediate for the total synthesis of doxorubicin analogue (**Scheme 1.26**).[49]

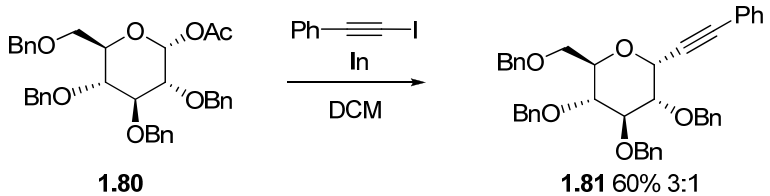


Scheme 1.26 1-*O*-*p*-Nitrobenzoyl used as a leaving group.

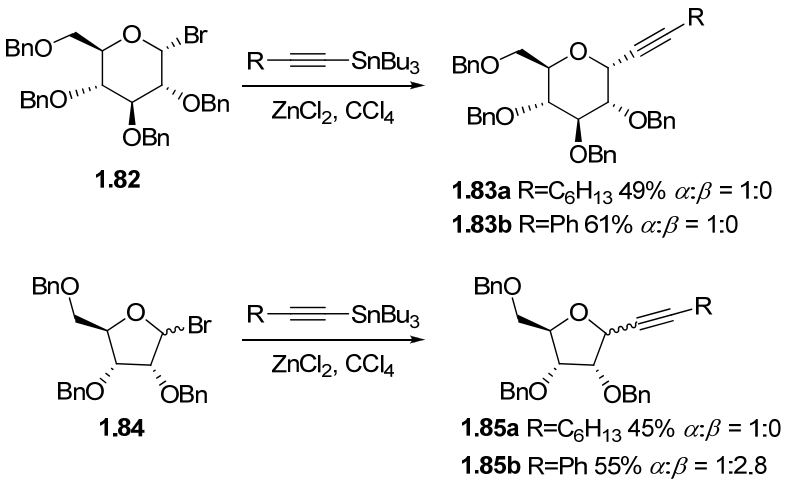
With respect to the nucleophilic *C*-glycosylation, silyl compounds are the most widely used glycosyl acceptors. Other than these compounds, organometallic compounds are also efficient acceptors. Addition of magnesium acetylide to **1.78** in the presence of $ZnCl_2$ produced **1.79** with stereochemistry retention (**Scheme 1.27**).[50] In addition, *in situ* generated alkyl indium compound was also applied, which led to less efficient results (**Scheme 1.28**).[51]



Scheme 1.27 $ZnCl_2$ promoted glycosylation with Grignard reagent.



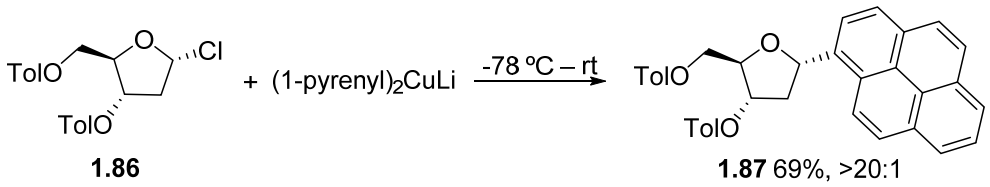
Scheme 1.28 Glycosylation with *in situ* generated indium species.



Scheme 1.29 Glycosylation with tin species.

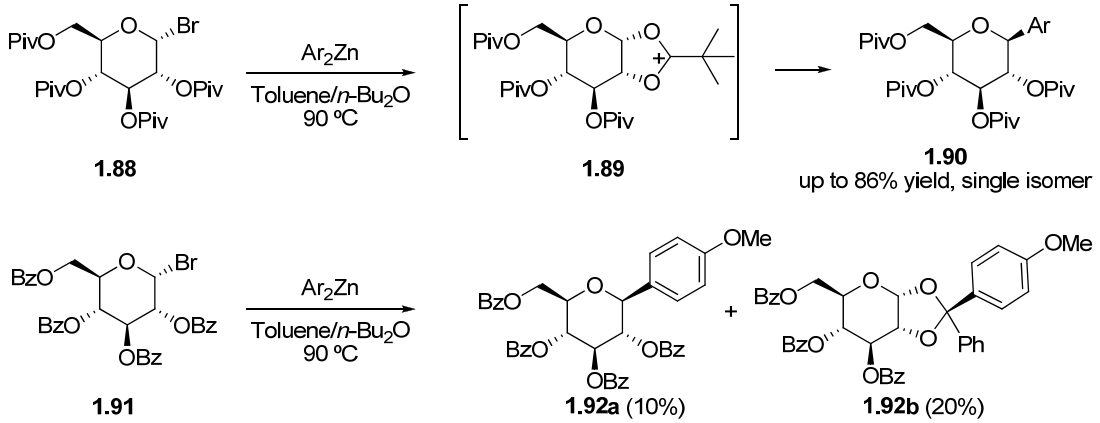
Another type of commonly used electrophilic donor for the *C*-glycosylation is the glycosyl halide. Among glycosyl halides, glycosyl iodide was less frequently used due to its high instability and strong tendency for elimination. Compared to iodide, glycosyl chloride and bromide which combine high reactivity with reasonable stability were widely used as electrophilic donors. Organometallic reagents such as organocuprate, organozinc, organolithium, organotin and Grignard reagents have been utilized for the *C*-glycosylation of glycosyl halides. $ZnCl_2$ catalyzed addition of alkynyltin compound to **1.82** gave α-anomer as a single product. Interestingly, the stereochemistry of the same reaction with furanosyl bromide **1.84** depends on the substituent group of alkyne. With alkanyl substituent, α-anomer was the main product, while with aryl substituent, β-anomer became the major product (**Scheme 1.29**).[52] Other than $ZnCl_2$, $AgBF_4$ can also promote this reaction but the selectivity would become poor.[53]

Arylcuprates reacted rapidly with chlorosugars to deliver *C*-aryl-nucleosides in high yields with excellent selectivities (**Scheme 1.30**). These types of *C*-aryl nucleosides play important roles in studying DNA−DNA and DNA−protein interactions.[54]



Scheme 1.30 Reaction of arylcuprates with chlorosugar.

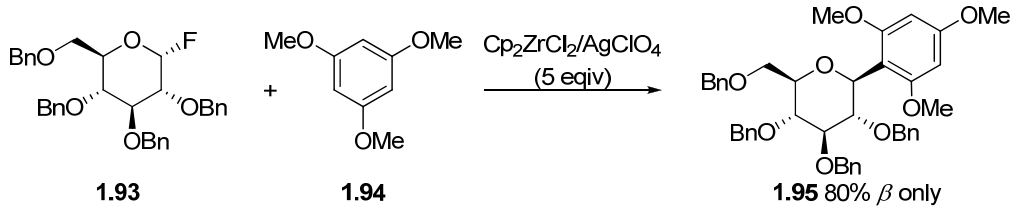
Neighbouring group participation in *C*-glycosylation may sometimes lead to the direct attack of the nucleophile to protecting groups other than the anomeric position. However, a more sterically hindered group was selected as the protecting group could avoid this unwanted side reaction. For example, with pivaloyl (Piv) as the protecting group, glycosyl bromide **1.88** could react with aryl zinc reagent to form the *β*-arylated glycosides in good yields. In contrast, benzoyl-protected **1.91** furnished a mixture of *C*-glycoside **1.92a** and byproduct **1.92b** (**Scheme 1.31**).[55]



Scheme 1.31 Neighbouring group participation in *C*-glycosylation.

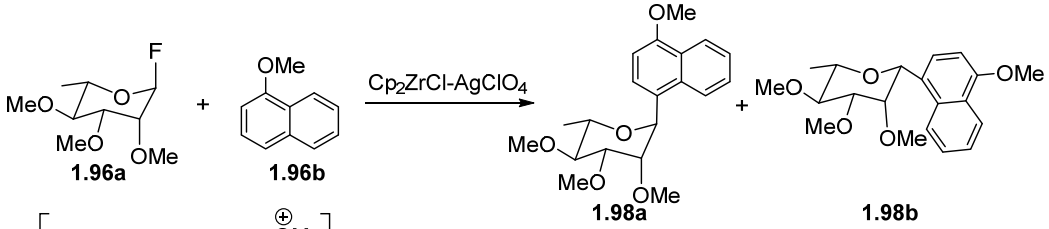
Compared with glycosyl bromides and chlorides, glycosyl fluorides remained less explored until 1980s because C-F bond was generally recognized as too strong to be activated. Since the introduction of *O*-glycosylation by Mukaiyama,[56] glycosyl fluoride has become one of the most frequently used donors due to its increased stability and easy activation by Lewis acids.

Interestingly, in the presence of 5 equiv of Cp_2ZrCl and $AgClO_4$, the Friedel-Crafts type reaction of glycosyl fluoride **1.93** with **1.94** produced sole *β*-anomer (**Scheme 1.32**). Similar reaction could also be carried out in catalytic version, however, it was found that the reaction led to conventional *α*-selectivity. This phenomenon could be explained by the fact that *β*-anomer is thermodynamically favoured. Under the excess amount of Lewis acid conditions, *α*-anomer was *in situ* anomerized to a more stable *β*-anomer through **1.97**. This assumption was supported by the experimental proof that Cp_2ZrCl and $AgClO_4$ could promote the epimerization of preformed *α*-anomer to *β*-anomer (**Scheme 1.33**).[57]



1.93 **1.94** **1.95** 80% *β* only

Scheme 1.32 Friedel-Crafts type reaction of glycosyl fluoride.



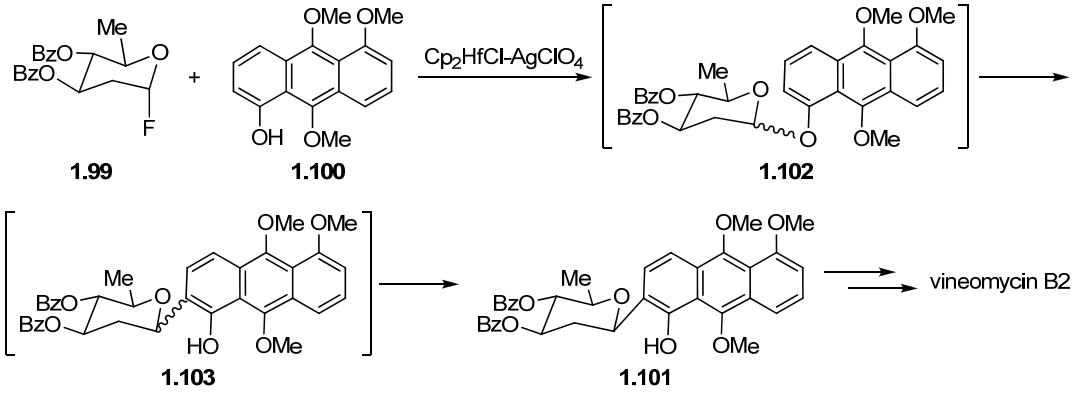
1.96a **1.96b** **1.98a** **1.98b** **1.97**

reagents (equiv)	time	yield (%)	selectivity (*α* : *β*)
5.0	20 min	96	*β*
2.0	45 min	91	1:12
0.3	2 hr	79	2:1

Scheme 1.33 Cp_2ZrCl and $AgClO_4$ promoted *C*-glycosylation.

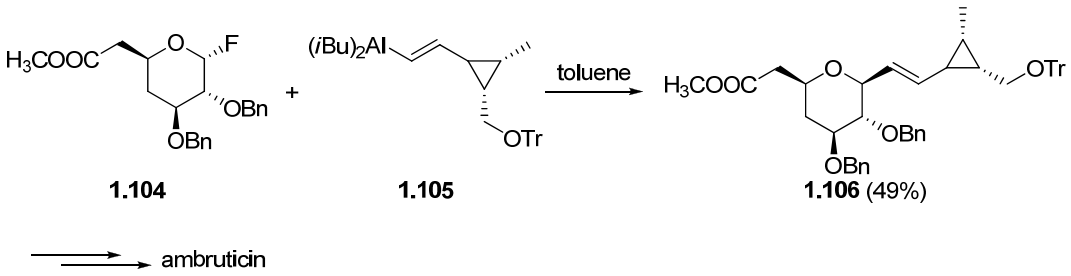
In addition, this reaction was further applied to the synthetic study of vineomycin B2. With phenol **1.100** as nucleophile, the reaction proceeded to produce *β*-*C*-glycosides **1.101**. The reaction was suggested to pass through 3 steps reaction,

namely, *O*-glycosylation, *O*- to *C*-glycoside rearrangement and epimerization (**Scheme 1.34**). [58]



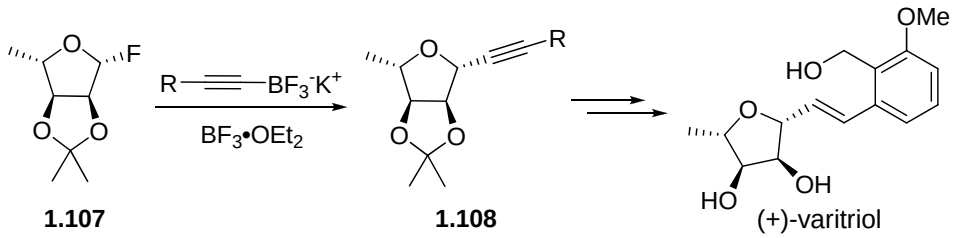
Scheme 1.34 Synthetic study of vineomycin B2.

Aluminum reagents have also been used to react with glycosyl fluorides and this reaction has served as a key step toward the synthesis of ambruticin (**Scheme 1.35**).[59] Although the yield is quite low, the reaction was able to produce good *β*-selectivity with *trans*-product.



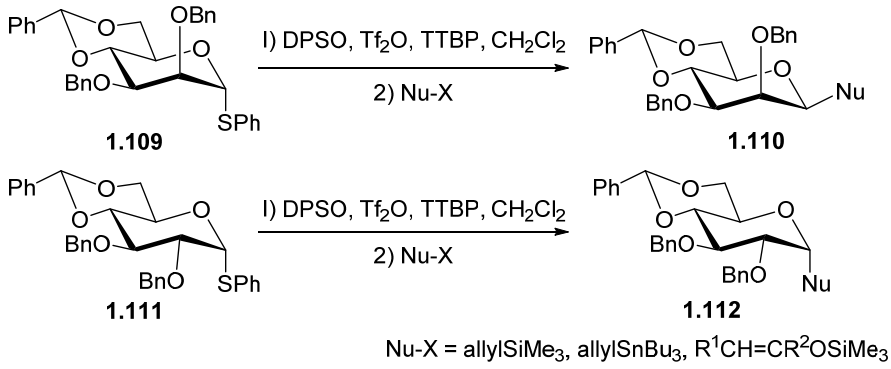
Scheme 1.35 Synthesis of ambruticin.

Apparently, similar to other glycosyl donors, glycosyl halide could also react with silyl compounds and a wide range of Lewis acids could also be used to catalyze these reactions. [60] Besides, alkynyl trifluoroborates are also efficient reaction partners towards *C*-glycosylation. For instance, $BF_3{\cdot}OEt_2$-promoted glycosylation of alkynyl trifluoroborate with glycosyl fluorides produced alkynyl glycosides in good yields with moderate to excellent selectivities. With this methodology, natural product (+)-varitriol was successfully obtained in concise steps (**Scheme 1.36**).[61]



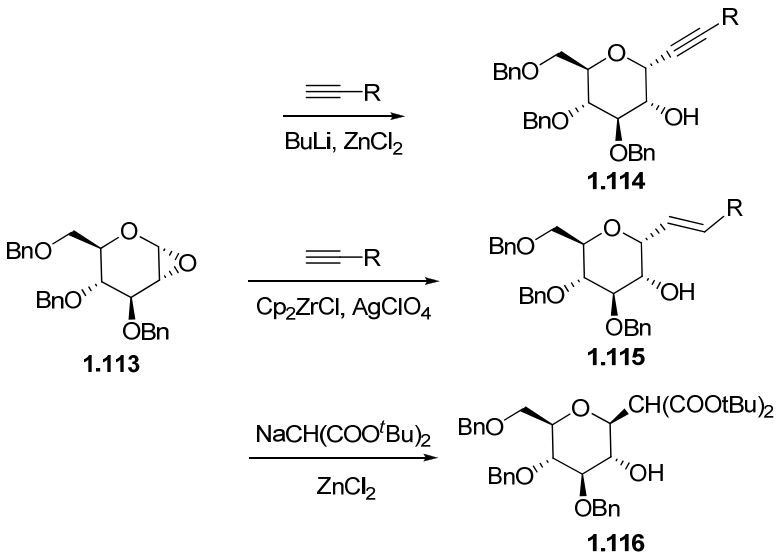
Scheme 1.36 Synthesis of (+)-varitriol.

Glycosyl trichloroimidates are also useful glycosyl donors in *C*-glycosylation especially in aryl *C*-glycosylation.[62] In these reactions, $BF_3 \cdot OEt_2$, TMSOTf and $ZnCl_2$ are commonly used Lewis acids and both α- and β-anomer could be obtained.



Scheme 1.37 *C*-glysosylation with thiol glycoside.

Thiol glycoside is another type of widely used glycosyl donor in *O*-glycosylation, however, it is less employed in *C*-glycosylation.[63] Interestingly, Crich reported that triflic anhydride (Tf_2O) and diphenylsulfoxide (DPSO) promoted glycosylation of 4,6-*O*-benzylidene-protected gluco- and manno-pyranosyl thioglycosides (**1.109** and **1.111)** was highly stereoselective, which produced α-isomer for gluco-system while β-isomer for manno-system (**Scheme 1.37**).[64]



Scheme 1.38 Reaction with 1,2-anhydro sugars.

More labile 1,2-anhydro sugars was also used as glycosyl donors. Early work using 1,2-anhydro sugars focused on the opening of the epoxide ring with organocuprates which resulted in 1,2-*trans* selectivity. Recent work revealed that both 1,2-*trans* and 1,2-*cis* selectivities could be obtained when Lewis acids were employed for this reaction (**Scheme 1.38**).[65]

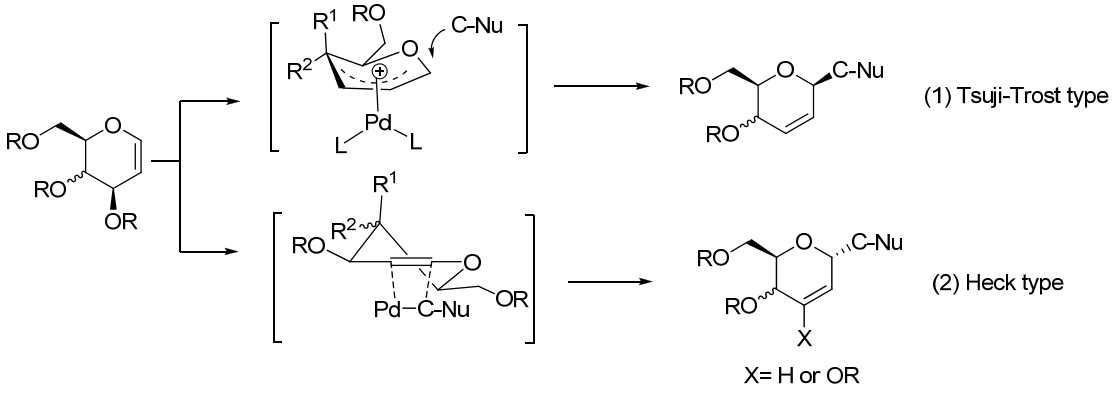
1.2 Transition metal-catalyzed C-glycosylation

Compared to Lewis acid promoted glycosylation, the report of transition metal-catalyzed glycosylation is rare, even in the area of *O*-glycosylation.[66] Although transition metal catalyzed cross-coupling reactions are well developed during the past decades, these methods were not used as the typical methods to form *C*-glycosylation. This is because: (1) the C-1 substituted organometallics are sensitive and prefer *β*-elimination; (2) harsh conditions such as high temperature, generally needed for transition metal catalyzed reactions, are not compatible with carbohydrates. However, the advantages of transition metal catalyzed reaction still prompted chemists to pursue its application in glycosylation. High activity of transition metals eliminates the

necessity to use stoichiometric amount of Lewis acid, which makes glycosylation greener. In addition, the close affinities between transition metal and heteroatoms or unsaturated bonds make it possible to control the anomeric selectivity, especially to generate unusual *β*-selectivity. All these advantages have stimulated the increasing reports on transition metal catalyzed *O*-glycosylation. However, unlike *O*-glycosylation, *C*-glycosylation examples are rare and glycosyl donors are limited to glycals (Type I) and glycosyl halides (Type II) for transition metal catalyzed *C*-glycosylation.

1.2.1 Transition metal catalyzed type I *C*-glycosylation

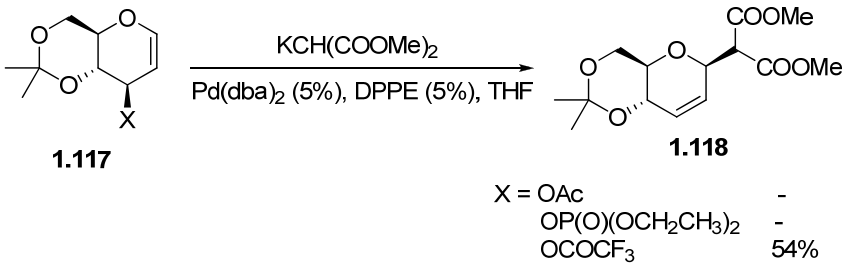
With reference to transition metal catalyzed Type I *C*-glycosylation, the property of olefin was always taken into account. Thus, Tsuji-Trost type reaction (**Scheme 1.39**, eq 1) and Heck type reaction (**Scheme 1.39**, eq 2) were investigated.



Scheme 1.39 Transition metal catalyzed Type I *C*-glycosylation.

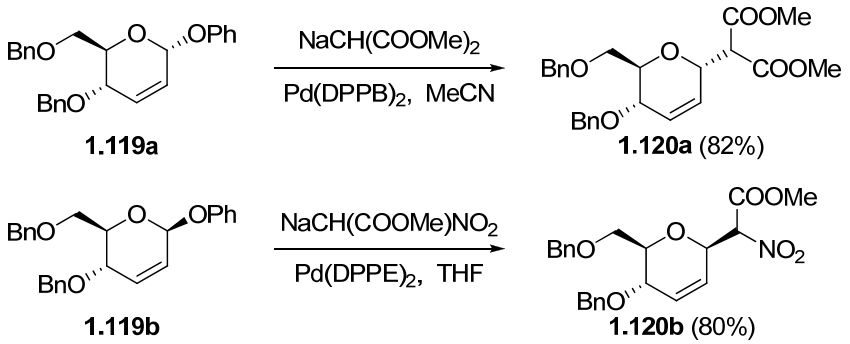
Inspired by the fully explored Tsuji-Trost reaction, the allylic features of glycals stimulated their investigation in carbohydrate chemistry. However, pioneering work done by RajanBabu *et al*. revealed that the formation of Pd π-allyl species in the electron-rich glycal system is difficult, thus, one solution is to use leaving group with

strong electron withdrawing effect, such as trifluoroacetate, at C-3 position (**1.117**). Even then, the reaction was limited to active nucleophiles and generally gave poor yields (**Scheme 1.40**). [67]



Scheme 1.40 Palladium catalyzed *C*-glycosylation with **1.117.**

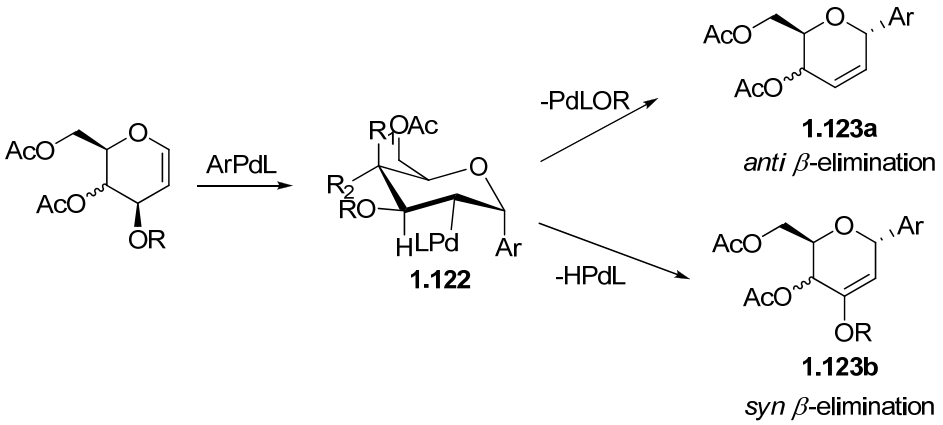
Another solution is to use active pyranose system such as **1.119**, although the results obtained were still not satisfactory.[68] Noteworthily, the stereochemistry was retained which is in agreement with an S_N2 attack by the nucleophile on an allyl-palladium complex. Other optionals included addition of extra additives and the usage of more active pyranose system, however, these reaction was only applicable to *O*-glycosylation so far.[69]



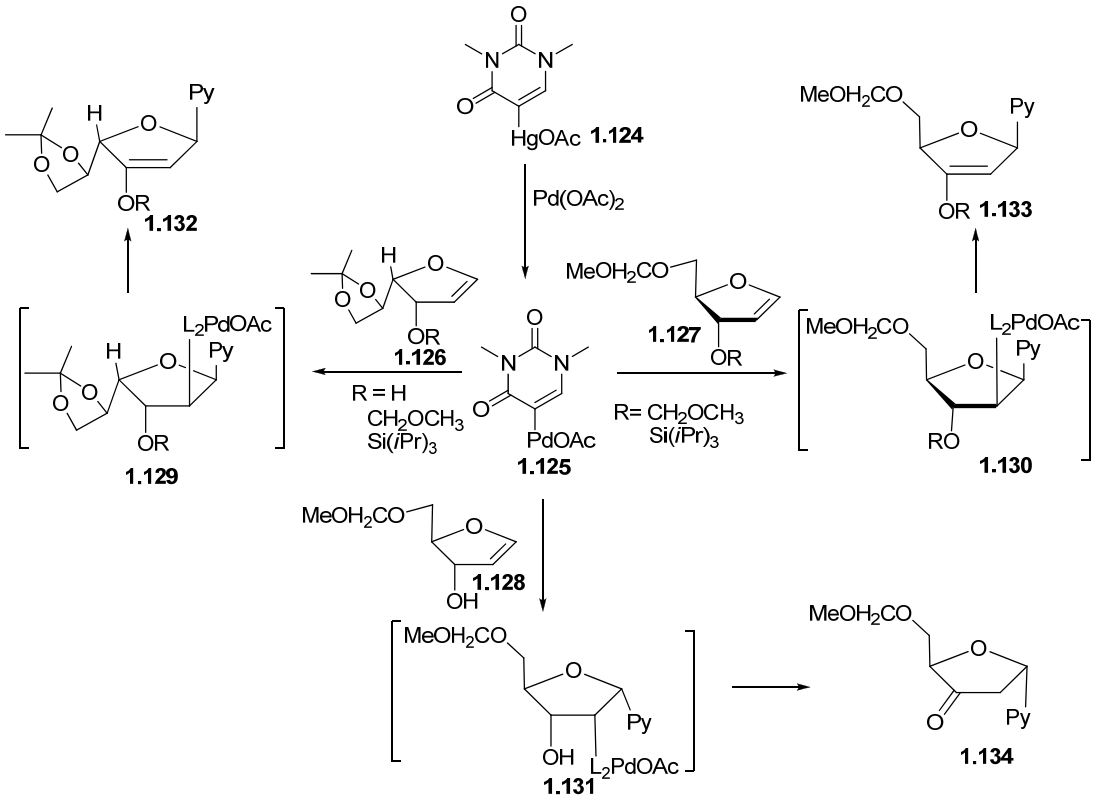
Scheme 1.41 Reaction with active pyranose system.

In contrast, the application of Heck reaction in *C*-glycosylation is more popular. The mechanism involves a *syn* addition of palladium complex to glycal and a

subsequent elimination *via* either *syn* or *anti* manner (**Scheme 1.42**). Since a range of substrates could react with palladium *via* oxidative addition or transmetalation to form organopalladium complex, the substrate scope of Heck type *C*-glycosylation could be further expanded.



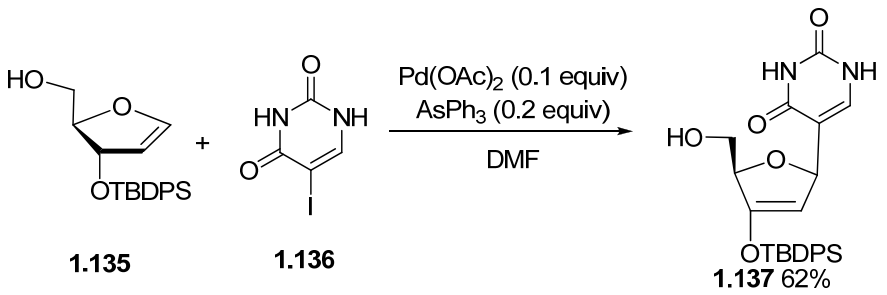
Scheme 1.42 Mechanism of Heck type *C*-glycosylation.



Scheme 1.43 Palladium catalyzed *C*-glycosylation with organomercuric salt.

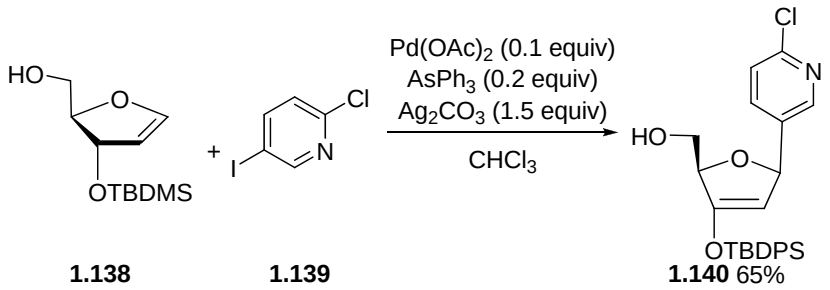
In the effort to prepare *C*-nucleosides, Daves developed a highly regio- and stereo-selective coupling reaction between furanoid glycals and organomercuric salt **1.124** in the presence of Pd (II). The stereochemistry was controlled by C-3 and C-4 substituents, which causes the organopalladium complex **1.125** to approach to the olefin from the less hindered face in a *syn* fashion. This reaction could also be applied to pyranoid glycals. However, stoichiometric amount of palladium and long reaction time (2 days) are required and thus hampered their application (**Scheme 1.43**).[70]

The catalytic version was achieved by using corresponding iodide **1.136**. In the presence of catalytic amount of $Pd(OAc)_2$ and $AsPh_3$, the reaction proceeded smoothly to afford *β*-glycoside **1.137** in 62% yield. This method was successfully applied in the synthesis of formycin analogues (**Scheme 1.44**).[71] Pyridyl iodide could also be used in this type of Heck reaction by using Ag_2CO_3 as additive and base (**Scheme 1.45**).[72]



1.135 **1.136** **1.137** 62%

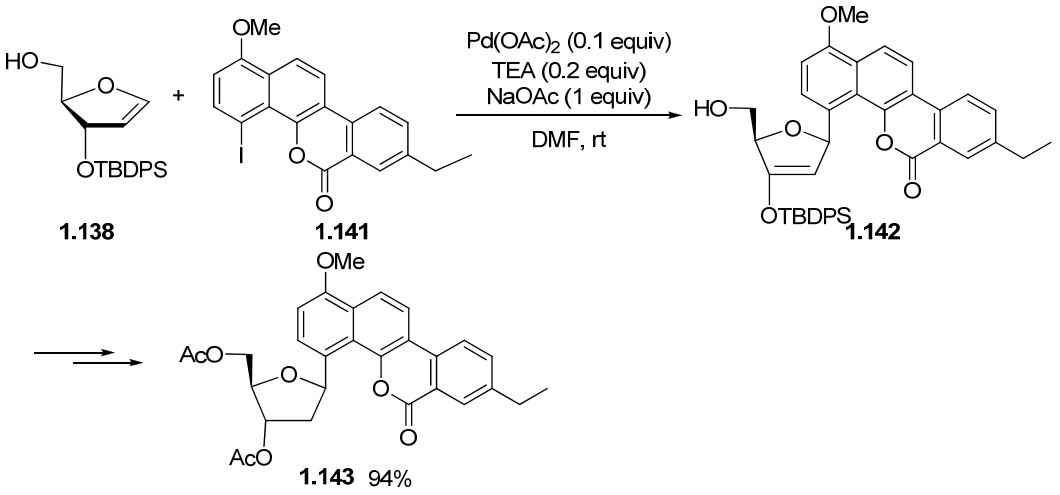
Scheme 1.44 Palladium catalyzed *C*-glycosylation of **1.135**.



1.138 **1.139** **1.140** 65%

Scheme 1.45 Palladium catalyzed *C*-glycosylation with pyridyl iodide.

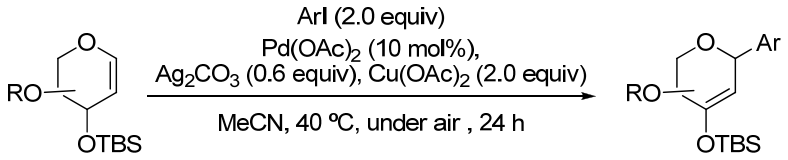
Aryl halides are among the most popular coupling partners used in Heck reaction. Reaction of aryl iodide **1.141** with **1.138** in the presence of 0.1 equiv of $Pd(OAc)_2$ furnished *β*-glycoside **1.142** in good yields. From **1.142,** anthracycline *C*-glycoside **143**, which is a potent antibiotic related to the ravidomycin, gilvocarcin, chrysomycin class, was obtained in a one-pot, three steps sequence (**Scheme 1.46**).[73]



Scheme 1.46 Synthesis of anthracycline *C*-glycoside.

Oxidative Heck-type coupling of glycals with aryl iodides has also been achieved by using catalytic amount of $Pd(OAc)_2$ and excess of Ag_2CO_3 in combination with $Cu(OAc)_2$ as oxidant (**Table 1.1**).[74] The reaction is highly regio- and stereoselective with the formation of a single enol ether coupling product. The stereoselectivity was apparently controlled by the orientation of C-3 substituents of the starting glycals, which resulted in the *syn* addition from the opposite face. In addition, the TBS protecting group of C-3-*O* position played a critical role to the success of this reaction, while other protecting groups such as acetyl or benzyl led to complete failure.

Table 1.1 Oxidative Heck coupling reaction of glycals and aryl iodides.



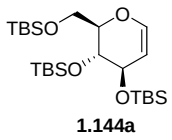
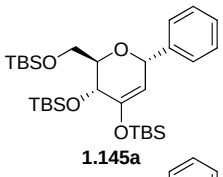
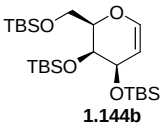
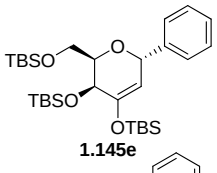
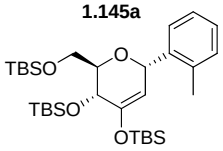
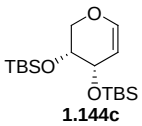
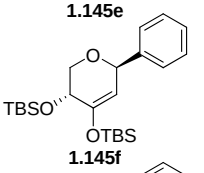
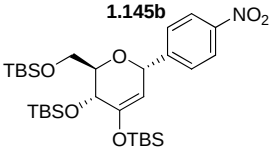
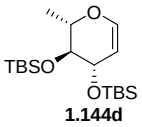
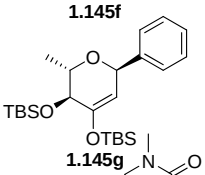
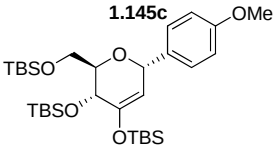
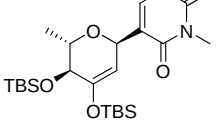
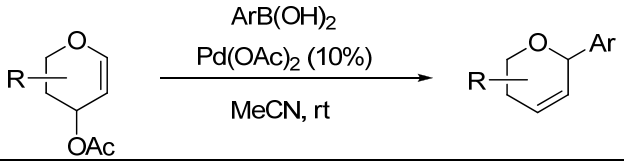
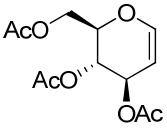
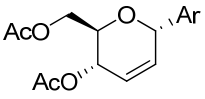
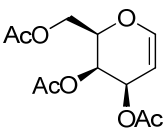
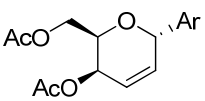
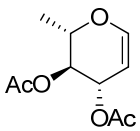
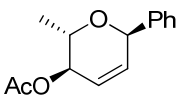
Glycal	Product	Yield	Glycal	Product	Yield
 **1.144a**	 **1.145a**	92%	 **1.144b**	 **1.145e**	94%
	 **1.145b**	99%	 **1.144c**	 **1.145f**	95%
	 **1.145c**	59%	 **1.144d**	 **1.145g**	88%
	 **1.145d**	87%		 **1.145h**	84%

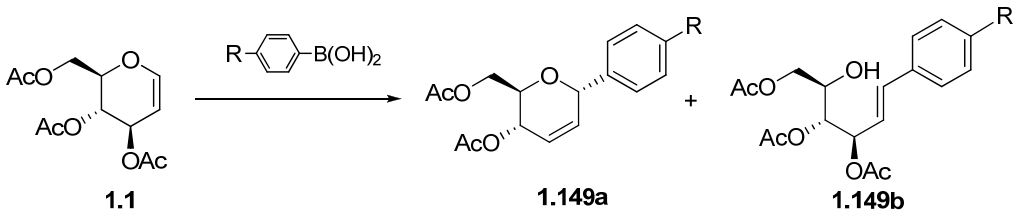
Table 1.2 Palladium catalyzed *C*-glycosylation of glycals with arylboronic acids.



Entry	Glycal Donors	Products		Yield
1	 **1.1**		Ar = Ph **1.146a** 4-MeoPh **1.146b** 2-MePh **1.146c** 4-CF_3Ph **1.146d** 4-ClPh **1.146e**	82% 79% 77% 55% 57%
2	 **1.147**		Ar = Ph **1.146f** 4-MeoPh **1.146g** 2-MePh **1.146h** 4-CF_3Ph **1.146i** 4-ClPh **1.146j**	80% 83% 77% 50% 57%
3	 **1.148**	 **1.146k**		52%

Arylboronic acid is another type of widely used reagents in transition metal catalyzed reaction. Maddaford *et al*. reported a $Pd(OAc)_2$ catalyzed coupling reaction of peracetylated glycals and arylboronic acids (**Table 1.2**).[75] Similarly, *syn* addition of *σ*-aryl-Pd complex to glycal double bond occurred to control the stereoselectivity. However, in the following, *anti β*-OAc elimination happened and *C*-Ferrier type product was generated other than *β*-H elimination to give enol ether product. It was found that the reaction with electron rich arylboronic acids proceeded smoothly and gave good yields. However, electron deficient aryl boronic acids produced lower yields. Subsequently, Figuera *et al*. further found that the reaction with arylboronic acids possessing electron donating groups always lead to ring opening by-products other than the desired *C*-glycosides under the same reaction conditions as reported by Maddaford.[76] When toluene/EtOH was used as the solvent, the ring opening of the glycal could be avoided although moderate yields were obtained (**Table 1.3**).

Table 1.3 Ring opening by-products of palladium catalyzed reaction between glycal and arylboronic acids.



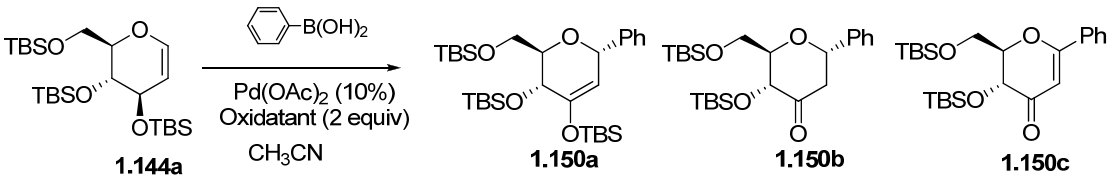
1.1 **1.149a** **1.149b**

R	**1.149a** Yield (%)	**1.149b** Yield (%)
H	80	-
2-Me	77	-
4-MeO	34	59
3-CF_3O	22	23
4-F	51	26
3-Cl	49	25

Oxidant controlled Heck-type coupling of glycals to arylboronic acids has also been reported (**Table 1.4**).[77] By changing the oxidants, three structural motifs could be obtained correspondingly. Employing $Cu(OAc)_2$ in combination with O_2 as oxidant,

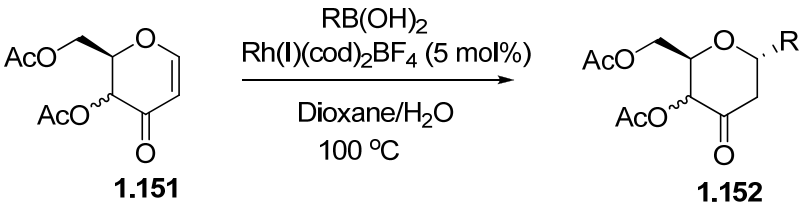
enol ether **1.150a** was obtained with exclusive α-selectivity. By changing the oxidant to benzoquinone (BQ), the reaction did not stop at the β-H elimination step, however, a palladium insertion and desilylation occurred followed by a hydrolysis to give ketone **1.150b**. When 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used as the oxidant, β-H elimination at C-1 position occurred instead of hydrolysis to form **1.150c** in 69% yield. The wide variety of arylboronic acids were compatible with these conditions, however, only TBS-protected glycals could give acceptable yields.

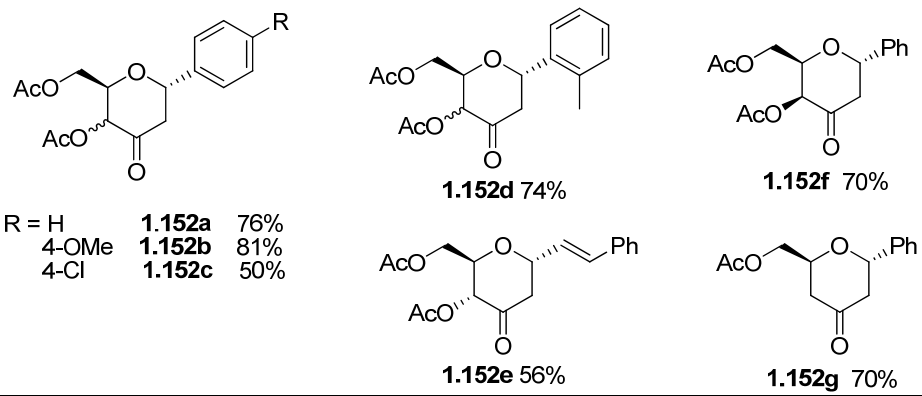
Table 1.4 Oxidant controlled Heck coupling of glycals with arylboronic acids.



Entry	Oxidant	Product	Yield (%)
1	$Cu(OAc)_2$ (2 equiv)/O_2	**1.150a**	94
2	BQ (2 equiv)	**1.150b**	84
3	DDQ (2 equiv)	**1.150c**	69

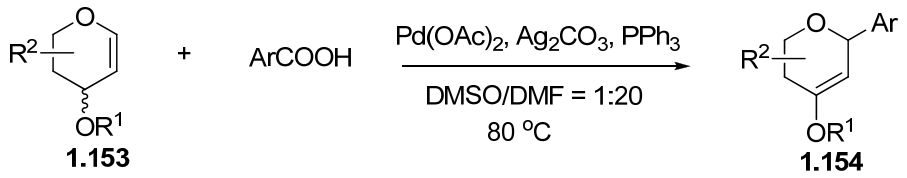
Table 1.5 Rhodium(I) catalyzed 1,4-addition of boronic acids to pyranone.

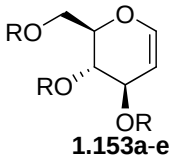
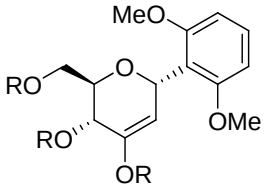
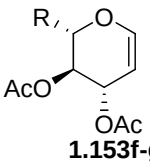
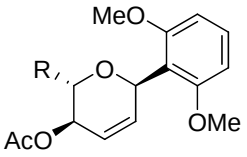
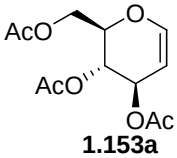
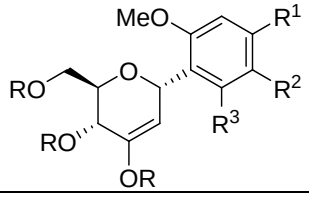




Besides palladium, Maddaford was also interested in rhodium (I) catalyzed addition of arylboronic acids to pyranones. This idea originated from the widely explored rhodium (I) catalyzed 1,4-addition of arylboronic acids to cyclic or acyclic enones. With 5 mol% of $Rh(cod)_2BF_4$ as catalyst, the coupling of pyranone with phenylboronic acids was accomplished in exclusive α-product with 76% yield. A variety of boronic acids including electron-rich and electron-deficient substrates was examined and gave acceptable yields with only α-products (**Table 1.5**).[78]

Table 1.6 Palladium catalyzed decarboxylative Heck-type glycosylation.

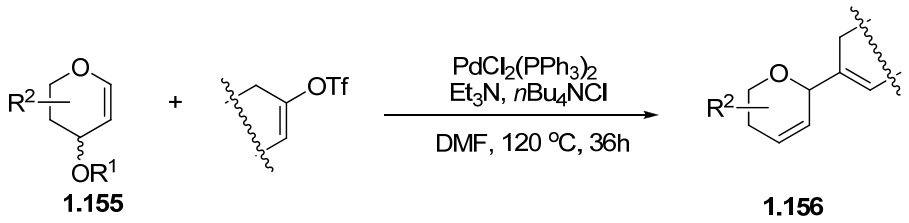


Entry	Glycal donors	Products		Yield
1	 **1.153a-e**		R = Ac **1.154a** Bn **1.154b** TBS **1.154c** Piv **1.154d** Boc **1.154e**	79% 70% 73% 65% 55%
2	 **1.153f-g**		R = H **1.154f** Me **1.154g**	58% 72%
3	 **1.153a**		R^1 = OMe, R^2 = R^3 = H **1.154h** R^1 = R^2 = OMe, R^3 = H **1.154i** R^1 = H, R^2 = Br, R^3 = OMe **1.154j**	45% 48% 43%

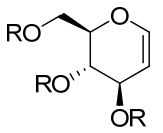
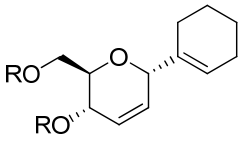
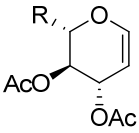
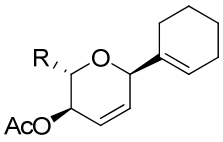
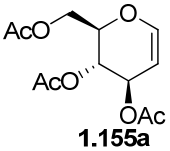
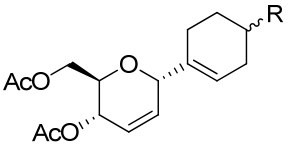
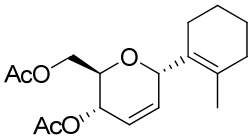
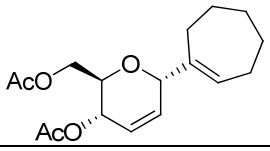
The palladium catalyzed decarboxylative Heck-type glycosylation has been achieved using benzoic acids as coupling partners (**Table 1.6**).[79] The electronic nature of protecting groups on glycal donors has little effect on the reaction. It is clear that the stereoselectivity was controlled by the orientation of C-3 substituents on glycal

donors when comparing the reaction of **1.153a-e** with **1.153f-g**. However, the reaction was limited to benzoic acids with methoxy group at *ortho* position.

Table 1.7 Palladium catalyzed coupling of enol triflates to glycals.



1.155 **1.156**

Entry	Glycal donors	Products		Yield
1	 **1.155a-c**		R = Ac **1.156a** COOEt **1.156b** Piv **1.156c**	78% 80% 25%
2	 **1.155d-e**		R = H **1.156d** Me **1.156e**	49% 52%
3	 **1.155a**		R = Me **1.156f** t-butyl **1.154g**	68% 51%
4			**1.156h**	54%
5			**1.156i**	31%

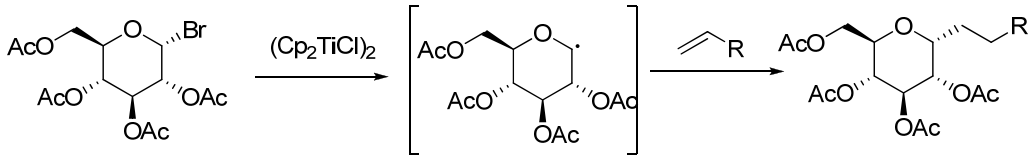
The transition metal catalyzed Heck-type *C*-glycosylation is not only limited to produce aryl *C*-glycosides. Liu *et al* expanded the scope to vinyl *C*-glycosides by coupling enol triflates to glycals (**Table 1.7**).[80] The reaction proceeded smoothly at high temperature and led to exclusive α-selectivity. Et_3N was suggested to reduce Pd (II) to Pd (0) while nBu$_4$NCl was thought to promote the *anti*-β-elimination. A broad

spectrum of glycals possessing good leaving groups was examined to exemplify the flexibility of this reaction and all gave good results. However, only cyclo enol triflates with six or seven membered rings could gave acceptable yields.

1.2.2 Transition metal-catalyzed type II C-glycosylation

Transition metal catalyzed type II *C*-glycosylation remained as the less explored although the transition metal catalyzed coupling reaction of 2º alkyl halides or triflates are fully investigated. This is because C-1 substituted metal complexes always lead to *β*-hydride or *β*-alkoxy elimination.

Most of the *C*-glycosylation methods focused on the generation of electrophilic character at the C-1 center. Considering the radical character at C-1 position may provide an alternative strategy. The typical way of producing glycosyl radical is by subtraction of halogen atom from C-1 position using tin species. However, this method is generally associated with high temperatures, toxic reagents, low yields and moderate stereoselectivities. Schwartz noticed that $(Cp_2TiCl)_2$ could play the same role as tin species to generate glycosyl radicals at or below room temperature. In addition, these glycosyl radicals could be further trapped by unsaturated substrates, which produced *C*-glycosides with good *α*-selectivity (**Scheme 1.47**). [81] Unsatisfactorily, large excess amount of titanium compounds and unsaturated substrates were necessary for this reaction.



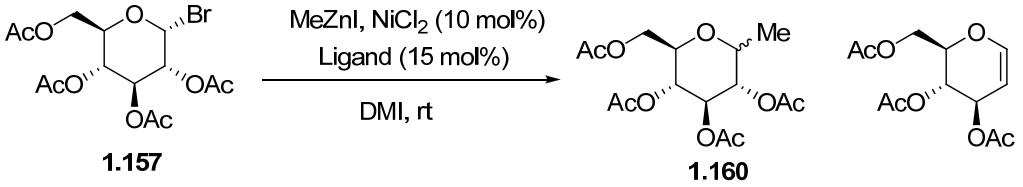
1.157 **1.158**

1.159a R = CO_2Me 55%
1.159b C(O)Me 75%

Scheme 1.47 $(Cp_2TiCl)_2$ promoted radical *C*-glycosylation.

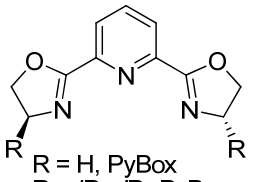
Nickel compounds were used to achieve the radical *C*-glycosylation in a catalytic version. By using 20 mol% of $Ni(tmc)_2(BF_4)_2$, 2 equivalent of Mn and 1 equivalent of PPh_2H, a similar radical reaction to **Scheme 1.47** was implemented with a moderate to good yields. However, trapping of the radical by electron rich acceptors was less successful.[82] The same reaction could also be catalyzed by a chromium (II)-complex $[Cr^{II}EDTA]^{2-}$, the benefit of this reaction is that it could be carried out in an aqueous phase.[83]

Table 1.8 Ligand screening of Ni-catalyzed *C*-alkyl glycosylation.

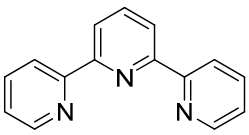


1.157 **1.160**

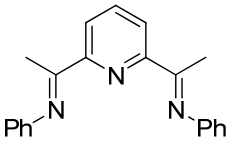
Entry	Ligand	Yield (α:β)	Glucal
1	*S*-*i*Pr-PyBox	50% (1:1.5)	10%
2	*R*-*i*Pr-PyBox	50% (1:1.5)	9%
3	*S*-*s*Bu-PyBox	20% (1:1.5)	trace
4	*S*-Ph-PyBox	trace	NA
5	PyBox	76% (1:2.2)	6%
6	terpy	30% (β-only)	trace
7	Py-bisimine	NR	NA



R = H, PyBox
R = *i*Pr, *i*Pr-PyBox
R = *s*Bu, *s*Bu-PyBox
R = Ph, Ph-PyBox



Terpy

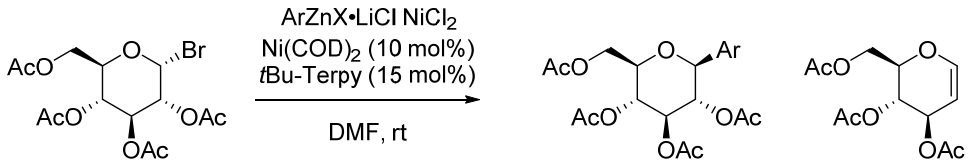


Py-bisimine

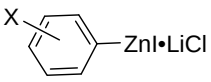
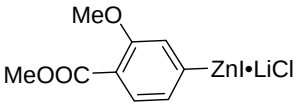
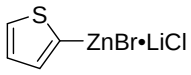
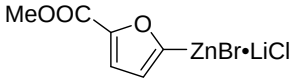
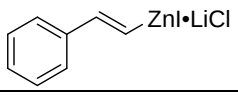
In general, most of the *C*-glycosylation reactions rely on a substrate control to achieve stereoselectivity. Encouraged by Fu and others studies on ligands guided transition metal-catalyzed cross-coupling reaction of alkyl halides with alkyl zinc reagents and the reports on inhibition of *β*-elimination of Ni-catalyzed Negishi cross-coupling by pincer ligands, Gagné *et al* developed the diastereoselective Ni-catalyzed

Negishi cross-coupling approach to saturated, fully oxygenated *C*-alkyl and *C*-aryl glycosides. They presumed that the diastereoselectivity could be controlled by ligands instead of substrates. They commenced their investigation by coupling of glycosyl bromide **1.157** with MeZnI under various conditions. Screening of various ligands revealed that the *β*-elimination could be inhibited and the undesired glucal was only obtained in trace amount. By using PyBox as the ligand, the desired coupling product was obtained in 76% yield with only 1:2.2 diastereoselectivity (**Table 1.8**).[84]

Table 1.9 Ni-catalyzed *C*-aryl glycosylation.



1.157 **1.161**

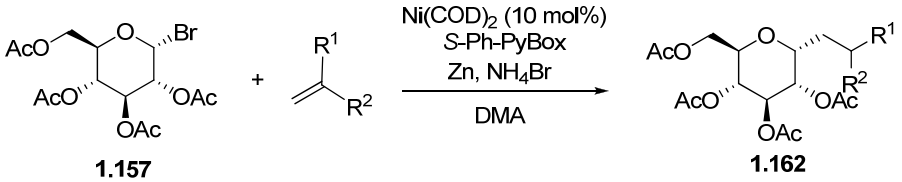
Entry	Zinc reagents	Products	Yield (*α*:*β*)	Glycal
1		**1.161a** X = H **1.161b** X = 4-OMe **1.161c** X = 4-CN **1.161d** X = 4-COOMe **1.161e** X = 3-COOMe **1.161f** X = 3-Cl **1.161g** X = 2-COOMe **1.161h** X = 2-OMe	71% (1:12) 64% (1:13) 79% (1:>12) 66% (1:10) 72% (1:14) 75% (1:13) ND Trace	7% 11% trace trace 8% 5%
2		**1.161i**	82% (1:13)	ND
3		**1.161j**	78% (1:16)	14%
4		**1.161k**	65% (1:14)	trace
5		**1.161l**	60% (1:11)	trace

The reaction was further extended to produce *C*-aryl glycosides. Using $Ni(COD)_2$ as the catalyst and *t*-Bu-TerPy as the ligand, the coupling reactions of glycosyl bromide with various of ArZnX (both electron-rich and electron-poor) resulted in

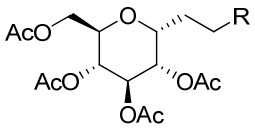
good yielding of *β*-aryl *C*-glycosides (**Table 1.9**).[85] In most cases, only trace amounts of undesired glucal were obtained.

Gagné has also reported a Sn-free, Ni-catalyzed cross-coupling reactions of glycosyl bromide with activated alkenes (**Table 1.10**).[86] By choosing $Ni(COD)_2$ as catalyst, *R*-Ph-Pybox as ligand, Zn as terminal reducing agent and NH_4Br as proton source, the reductive coupling reaction of glycosyl bromide with alkenes produced moderate to good yields of *C*-alkyl glycosides with excellent *α*-selectivity. This methodology overcame the limitations associated with Bu_3SnH participated radical reaction.

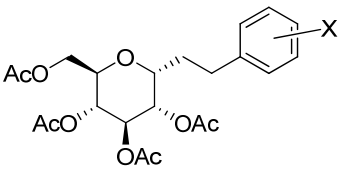
Table 1.10 Ni-catalyzed cross-coupling reaction of glycosyl bromides and activated alkenes.



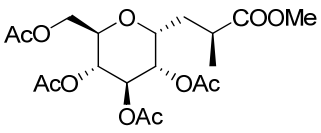
1.157 **1.162**



1.162a R = COOMe 70%
1.162b R = COO^{t}Bu 75%
1.162c R = CN 75%



1.162d X= H trace
1.162e X = 4-OAc 10%
1.162f X = 4-CF_3 45%
1.162g X = 4-COOMe 62%
1.162h X = 3-F 35%
1.162i X = 4-F trace



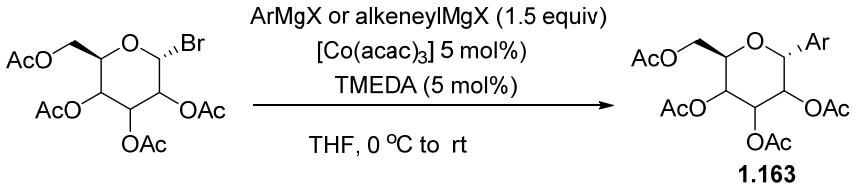
1.162j 80% dr 5:1

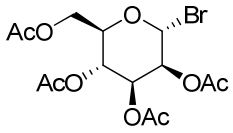
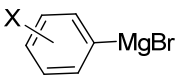
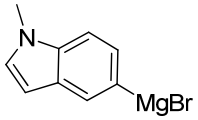
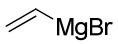
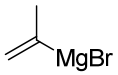
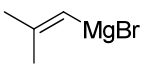
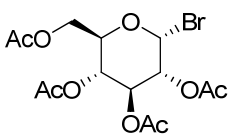
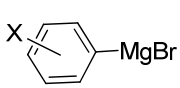
Very recently, Cossy *et. al*. reported a cobalt catalyzed coupling reaction of glycosyl bromide with Grignard reagent (**Table 1.11**).[87] Interestingly, unlike the Ni-catalyzed coupling raction, this reaction favours of *α*-selectivity for both mannose and glucose. The reaction was also proposed to pass through a radical mechanism and this was supported by a model reaction as depicted in **Scheme 1.48**. Coupling of **1.164**

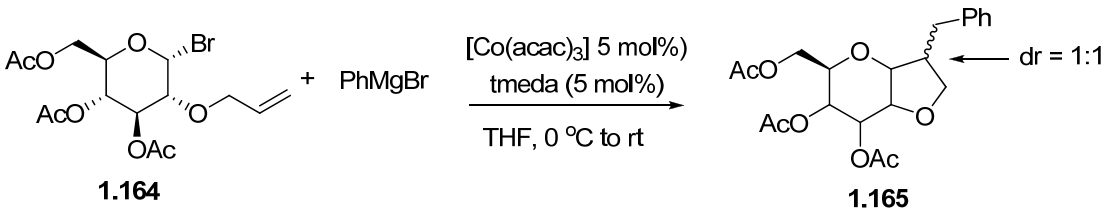
with PhMgBr under the optimized conditions generated an epimeric mixture of bicyclic product **1.165** which resulted from a cascade radical process initiated by an anomeric radical.

Visible light induced radical reaction between glycosyl bromide and alkene was also reported (**Scheme 1.49**).[88] The reaction was initiated by $[Ru^{II}(bpy)_3](BF_4)_2$, which was excited to the MLCT state by visible light and generated a reducing equivalent by Hunig's base. This equivalent reacted with glycosyl bromide to generate a C-1 radical and led to fully saturated *C*-glycosides with exclusive α-selectivity.

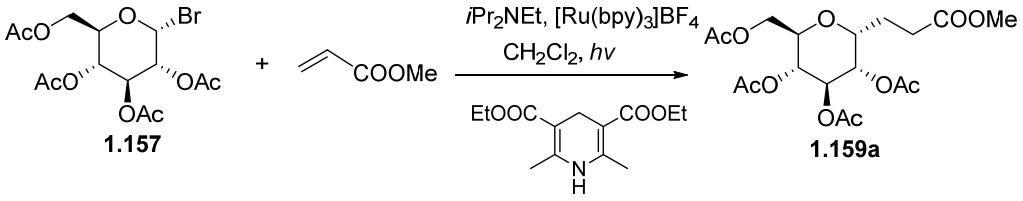
Table 1.11. Cobalt catalyzed cross-coupling reaction.



Entry	Glycosyl bromide	RMgX	Products	Yield (α:β)
1-5			**1.163a** X = H **1.163b** X = 4-OMe **1.163c** X =3-OMe **1.163d** X = 4-F **1.163e** X = 2-Me	76% (>9:1) 70% (>9:1) 82% (>9:1) 83% (>9:1) 72% (>9:1)
6			**1.163f**	53% (>9:1)
7			**1.163g**	-
8			**1.163h**	62% (>9:1)
9			**1.163i**	66% (>9:1)
10-14			**1.163j** X = H **1.163k** X = 4-OMe **1.163l** X =3-OMe **1.163m** X = 4-F	96% (3:1) 83% (2.4:1) 85% (2.3:1) 81% (2:1)



Scheme 1.48 Cross-coupling of glycoside **1.164** with PhMgBr.



Scheme 1.49 Visible light induced radical reaction.

1.3 Conclusion

In the past few decades, the significance of *C*-glycosides has stimulated a wide interest in the development of *C*-glycosylation methods. Considerable efforts have been dedicated to the Lewis acid and transition metal mediated *C*-glycosylation to produce 2,3-unsaturated glycosides (type I) and saturated, fully oxygenated glycosides (type II). Despite these significant advances, stereospecific construction of *C*-glycoside especially for *β*-C-glycoside, in a high efficiency manner is still a big challenge. Judging from the fast growing interest in organic chemistry and organometallic chemistry, new methodologies would undoubtedly be developed to overcome the stringent circumstances.

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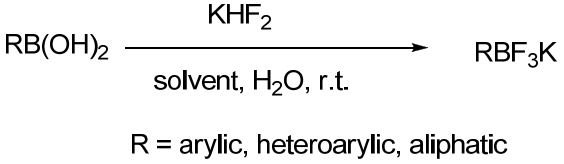
Chapter 2

BF_3·OEt_2 Promoted *C*-Glycosylation of Glycosyl Fluorides with Organotrifluoroborates: Access to 1,2-*cis* and 1,2-*trans C*-Glycosylation

2.1 Introduction

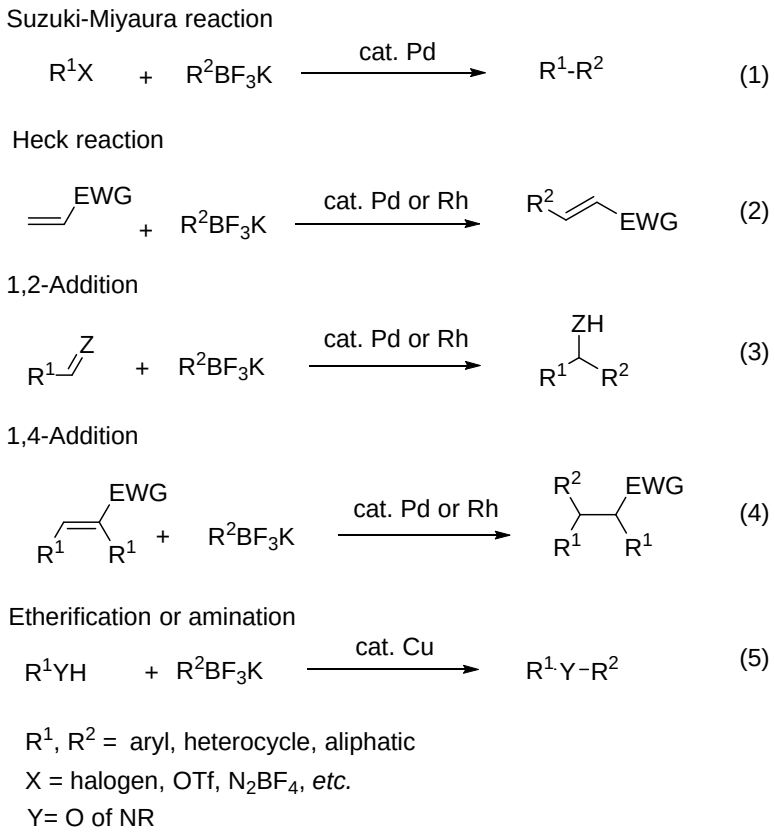
Organoboron compounds exhibit a wide range of utilities in synthetic chemistry.[1] As one of the most stable organoboron reagents, potassium organotrifluoroborates offer various advantages such as easy preparation, exceptional air and moisture stability as well as high nucleophilicity, in contrast to the boronic acids and boronic esters analogues. As such, potassium organotrifluoroborates have gained increasing popularity in the field of C-C bond formation.

Although organotrifluoroborates was discovered in the early 1960s, its synthetic utility has not been fully recognized until recently. It was found that potassium organotrifluoroborates can be obtained by simply treating boronic acids or their derivatives with aqueous solution of KHF_2 (**Scheme 2.1**).[2] This improved and highly efficient procedure brought about advancement to the application of organotrifluoroborates in synthetic organic chemistry.



Scheme 2.1 Preparation of potassium organotrifluoroborates.

Similar to other organoboron reagents, transmetallation of potassium organotrifluoroborates to other organometallic reagents is also feasible. This property enables the application of organotrifluoroborates in transition metal catalyzed reactions such as Suzuki-Miyaura reaction (**Scheme 2.2**, eq 1), Heck reaction (**Scheme 2.2**Scheme 2.2, eq 2), 1,2- and 1,4-addition (**Scheme 2.2**, eq 3 and 4), etherification and amination reaction (**Scheme2.2**, eq 5).[1]

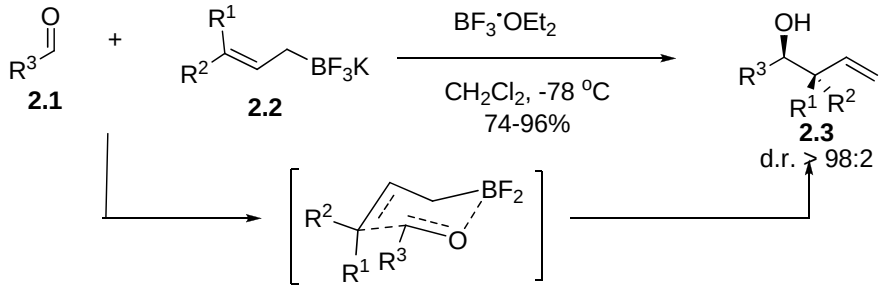


Scheme 2.2 Transition metal catalyzed reaction with organotrifluoroborate.

Since the early days, it was found that organotrifluoroborates can be used as potential precursors of organodifluoroboranes, which are excellent Lewis acids and nucleophiles.[3] This property generated wide interest as Lewis acids such as $BF_3 \cdot OEt_2$ can simply activate organotrifluoroborates to generate organodifluoroboranes *in-situ*.

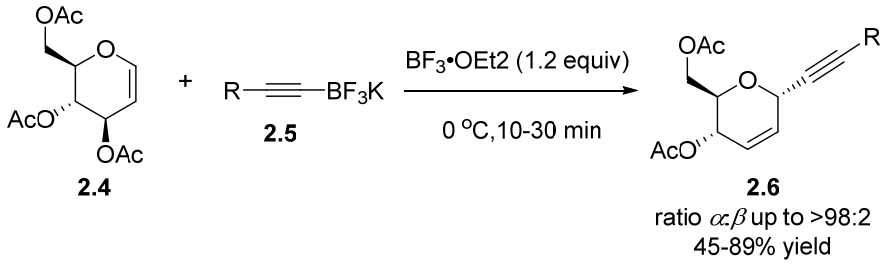
Therefore, new methodologies continue to be developed and a growing number of publications in this area are observed.

Among the reactions involving organotrifluoroborates, addition reaction is one of the most well-explored reactions by researchers. **Scheme 2.3** shows an allylation reaction of aldehyde **2.1** with potassium crotyltrifluoroborate **2.2**. High stereoselectivity control was achieved in this reaction through the formation of a 6-membered ring transition state.[4]



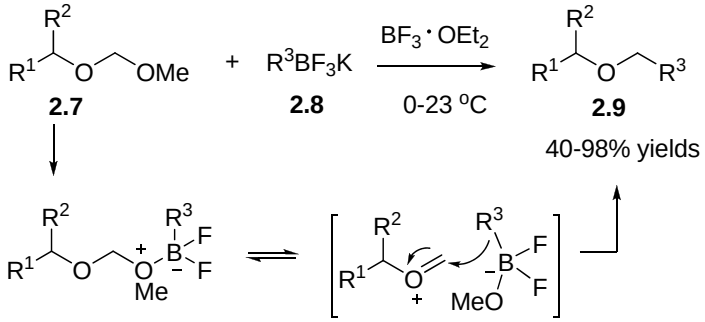
Scheme 2.3 Allylation reaction with allylborate.

Considering the Lewis acidity of organotrifluoroborates, it is not surprising that this reagent has also been utilized in the area of *C*-glycosylation by Stefani in 2008 (**Scheme 2.4**).[5] Lewis acid promoted coupling reaction of glucal **2.4** with alkynyl trifluoroborate **2.5** proceeded through a Ferrier rearrangement to produce α-*C*-glycosides **2.6** in good yields and selectivities. It was suggested that the reaction was initiated by a reaction of $BF_3{\cdot}OEt_2$ with organotrifluoroborate salt to generate the more active organoboron difluoride species, which subsequently reacted with the oxocarbenium cation.[6]



Scheme 2.4 Application of organotrifluoroborates in *C*-glycosylation.

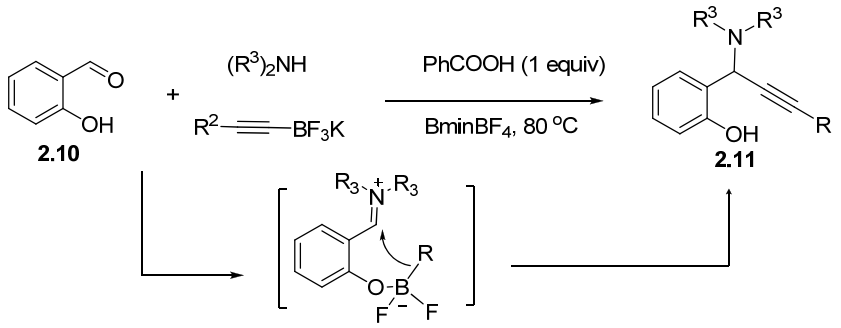
In 2009, Bode reported a direct synthesis of dialkyl ethers from organotrifluoroborates and the corresponding acetals (**Scheme 2.5**, eq 1).[7] This method involved the $BF_3{\cdot}OEt_2$ promoted coupling of stable and easily prepared acetals with ubiquitous potassium aryl-, alkenyl-, and alkynyltrifluoroborates. The driving force is the strong Lewis acidity of organodifluoroborates which promoted the formation of the oxocarbenium.



Scheme 2.5 Reaction of organotrifluoroborates with acetals.

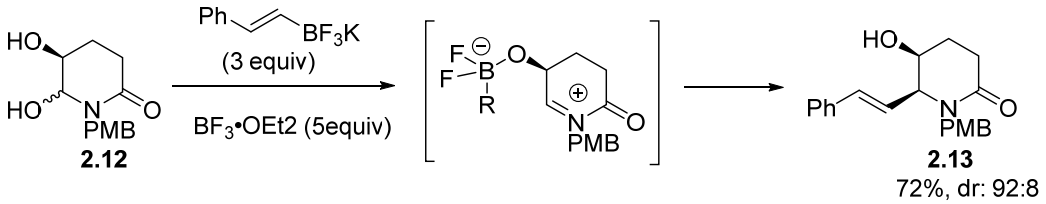
Addition of organotrifluoroborates to iminiums and their derivatives is also possible. This Mannich type reaction is also known as Petasis reaction.[8] An example of this type reaction is shown in **Scheme 2.6**.[9] Reaction of alkynyl trifluoroborate with an amine and salicylaldehyde **2.10** in the presence of 1 equiv of benzoic acid furnished the propargyl amine **2.11** in moderate to good yields. The *o*-hydroxy group played an important role in this reaction, as benzaldehyde derivatives without an *o*-hydroxy group were found to be unreactive. It was suggested that the hydroxyl group

participated the reaction to deliver the organoboron reagents to the iminium functional group due to the strong affinity between oxygen and boron.[10,11]



Scheme 2.6 Addition of organotrifluoroborates to iminiums.

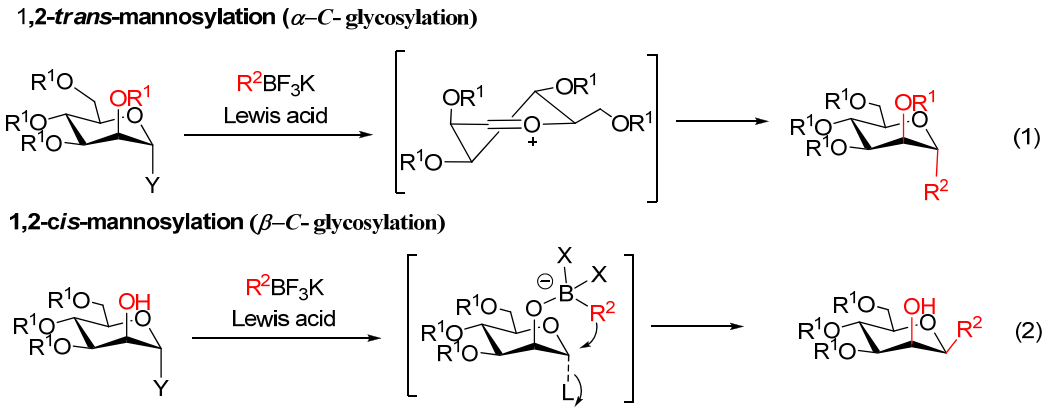
A similar strategy was applied in the synthesis of 5,6-*cis*-piperidinones (**Scheme 2.7**).[12] The hydroxyl mediated delivery of alkenyltrifluoroborate led to a *cis* addition of the alkenyl trifluoroborate.



Scheme 2.7 Synthesis of 5,6-cis-piperidinones.

Proposal

In view of the preceding research conducted on organotrifluoroborates, we hypothesized that they can also be applied to carbohydrate chemistry to synthesize saturated and fully oxygenated *C*-glycosides. We anticipated that the 1,2-*cis*- and 1,2-*trans*-mannosylation could be achieved with or without the use of hydroxy-mediated delivery of organoboron reagents (**Scheme 2.8**).



Scheme 2.8 Strategies on 1,2-*cis* and 1,2-*trans* *C*-glycosylation.

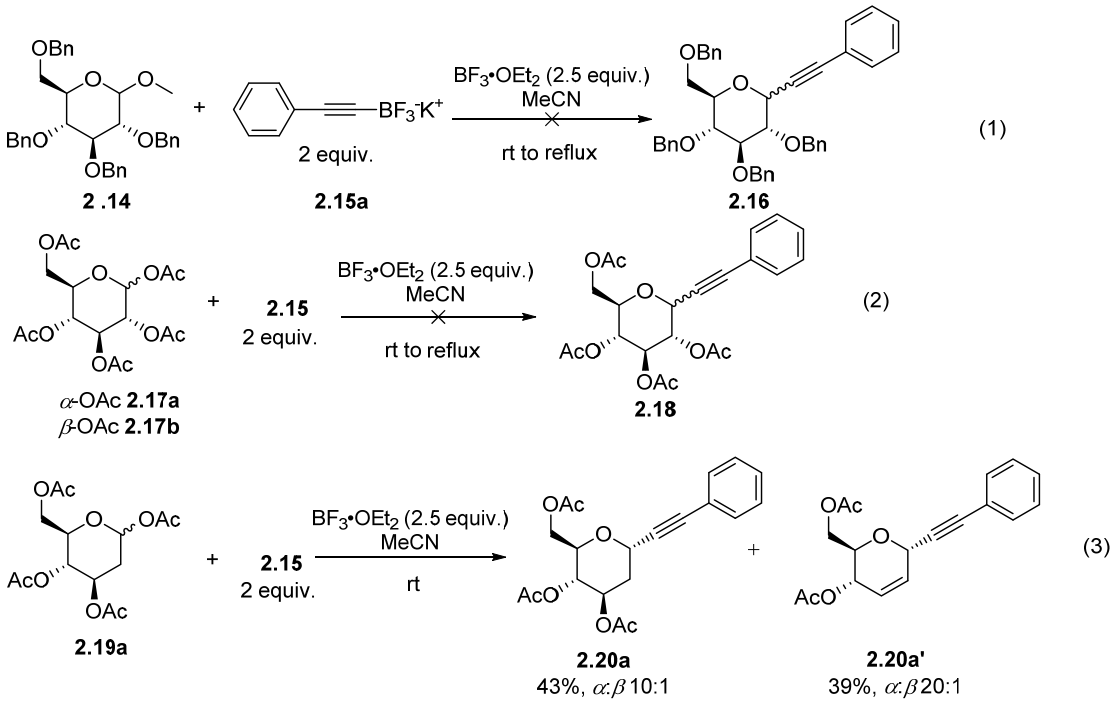
2.2 Access to *α*-*C*-glycosylation

Methyl pyranoside **2.14** was initially subjected to the reported conditions,[7] however, no reaction was observed even under reflux condition (**Scheme 2.9**, eq1). D-Glucopyranose pentaacetate **2.17 (**with better leaving group) was further examined, unfortunately, neither *α*- nor *β*-anomer gave any desired product other than recovered starting material and unwanted byproducts (**Scheme 2.9**, eq 2). We assumed that the acetate group at C-2 position prevented the reaction from occurring.[i] Hence, 2-deoxy-D-glucopyranose **2.19a** was employed. To our delight, the reaction proceeded smoothly. However, other than the desired product **2.20a**, the Ferrier rearrangement product **2.20a'** was also isolated in 39% yield. The diastereoselectivity of both products were excellent and ^{1}H NMR and ^{13}C NMR data spectra of **2.20a** were in agreement with the literature reports,[13] confirming the *α*-stereoselectivity. Further screening of solvents and reaction temperatures could not increase the yield of the desired product.

Extension of this set of reaction condition to other sugar acetates revealed that the yields and diastereoselectivities were substrate dependent. Reaction with mannosyl acetate **2.19c** provided moderate yield with excellent *α*-selectivity. Reaction with

i. See Chapter 1, page 22, Scheme 1.31.

glucosyl acetate **2.19b** gave moderate yield and α-selectivity. In contrast, furanosyl acetate **2.19e** and **2.19d** afforded the desired products in excellent β-selectivities, albeit with poor yields. 2-Deoxy furanose **2.19f** with TBS protecting groups was sensitive to the reaction conditions and decomposed quickly (**Table 2.1**).



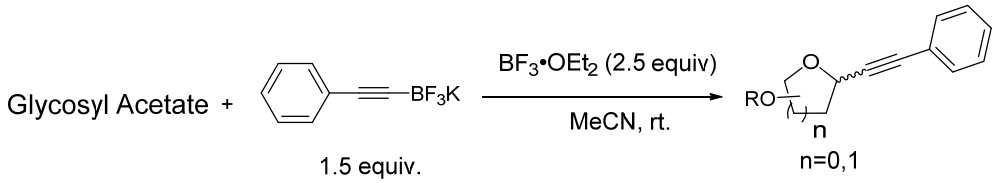
Scheme 2.9 Initial investigation.

Further optimization of the reaction conditions involved screening of the leaving groups, Lewis acids and solvents. To this end, mannose derivatives were chosen as substrates because these compounds gave excellent α-selectivity (generally only α-selectivity was observed due to the β face attack was prevented by C-2 axial substituent) that simplified the isolation and characterization. At the outset, a number of Lewis acids were investigated. $BF_3 \cdot OEt_2$ (1.2 equiv) was proved to be the most efficient, TMSOTf gave moderate yield whereas $TiCl_4$, $SnCl_4$ and $SiHCl_3$ were inferior.

Next, the efficiency of anomeric leaving groups were examined in the presence of $BF_3 \cdot OEt_2$. Good leaving groups such as -STol and trichloroacetimidate afforded better

results than acetal groups, while fluoride leaving groups gave the best results (shortest reaction time and highest yield). Furthermore, an investigation of solvent showed that acetonitrile was the most suitable, as both toluene and DCM gave diminished yields (**Table 2.2**).

Table 2.1 Substrate scope of glycosyl acetates.



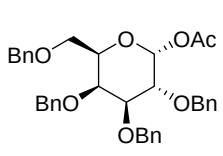
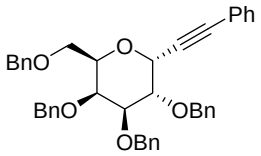
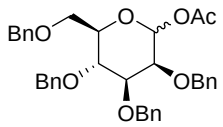
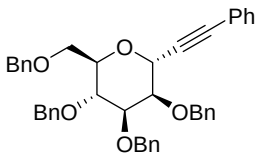
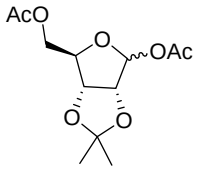
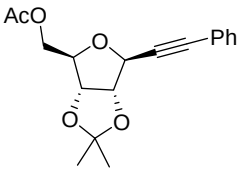
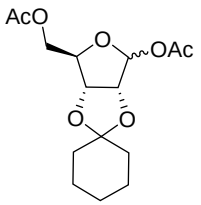
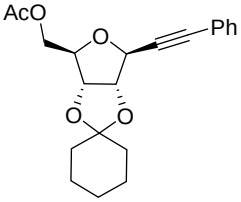
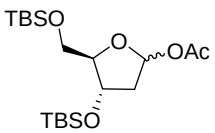
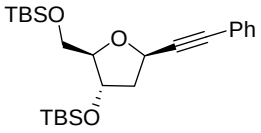
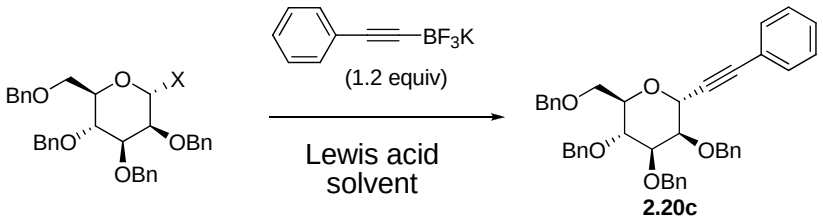
Entry	SM	Product	Time	Yield	α:β
1	 **2.19b**	 **2.20b**	12 h	60%	3.3:1
2	 **2.19c**	 **2.20c**	14 h	61%	>98:2
3	 **2.19d**	 **2.20d**	8 h	26%	<2:98
4	 **2.19e**	 **2.20e**	8 h	33%	<2:98
5	 **2.19f**	 **2.20f**	30 min	decompose	-

Table 2.2 Reaction optimization of *C*-mannosylation.

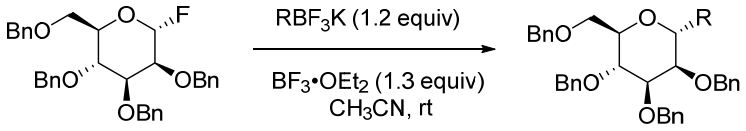


2.20c

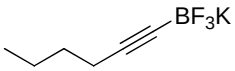
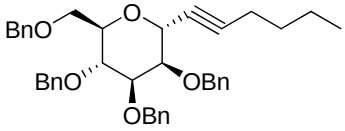
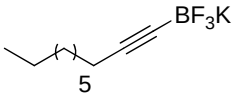
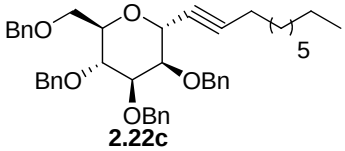
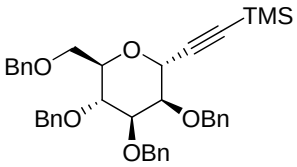
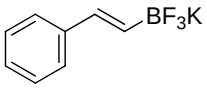
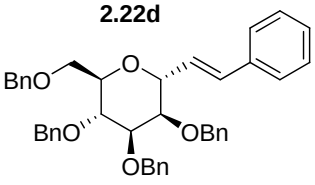
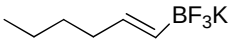
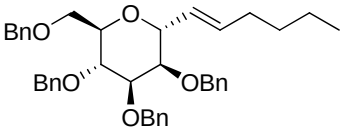
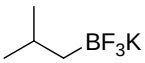
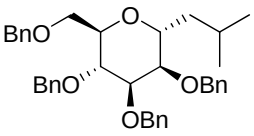
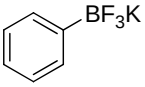
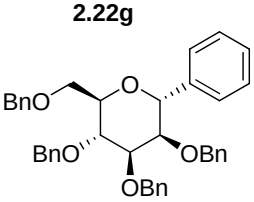
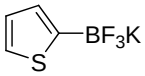
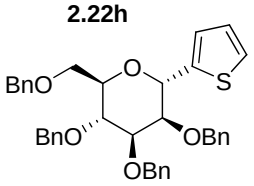
Entry	X	Catalyst (equiv.)	Temp.	Solvent	Time	Yield
1	OAc	$BF_3 \cdot OEt_2$ (2.5)	rt	CH_3CN	14 h	61%
2	OAc	$ZnCl_2$ (1.5)	rt	CH_3CN	12 h	15%
3	OAc	$TiCl_4$ (1.5)	0 ^oC-rt	CH_3CN	12 h	11%
4	OAc	$SnCl_4$ (1.5)	0 ^oC-rt	CH_3CN	14 h	20%
5	OAc	TMSOTf (1.5)	0 ^oC	CH_3CN	2 h	43%
6	OAc	$SiHCl_3$ (1.5)	0 ^oC-rt	CH_3CN	16 h	-
7	STol	$BF_3.OEt_2$ (2)	rt	CH_3CN	4 h	65%
8	$OCNCl_3$	$BF_3.OEt_2$ (2)	rt	CH_3CN	30 min	81%
9	F	$BF_3.OEt_2$ (2)	rt	CH_3CN	20 min	94%
10	F	$BF_3.OEt_2$ (1.3)	rt	CH_3CN	20 min	94%
11	F	$BF_3.OEt_2$ (2)	rt	DCM	30min	71%
12	F	$BF_3.OEt_2$ (2)	rt	toluene	2 h	51%

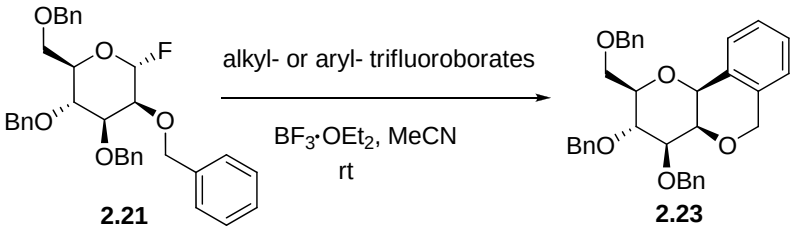
Mannosylation reactions have attracted significant interests in biological and medicinal chemistry because of their roles in numerous physiological processes.[14] Hence, the substrate scope of *C*-mannosylation was further studied. A number of potassium organotrifluoroborates were tested (**Table 2.3**). Among them, alkynyltrifluoroborates possessing either aromatic or aliphatic substituents including long chain substituted alkynyltrifluoroborates provided the desired products in good yields (entry 1-3); Alkenyltrifluoroborates gave lower yields because of the reduced reactivity of sp^2-hybridized bonds (entries 4-5). Unfortunately, preliminary attempts to employ potassium aryl-, alkyl- and heteroaryltrifluoroborates failed to give positive results (entries 6-8). It was found that the anomeric position was intramolecularly arylated by 2-OBn group instead (**Scheme 2.10**). Evidently, the reactivity of alkyl-and aryltrifluoroborates were much lower than the alkynyl trifluoroborates thus, the intramolecular Friedel-Crafts reaction preceded first.

Table 2.3 *C*-Mannosylation with organotrifluoroborates.



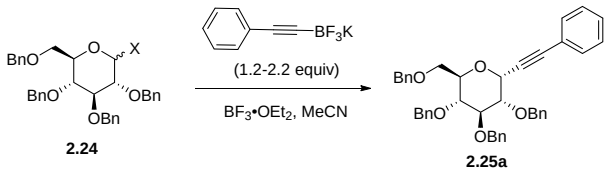
2.21 **2.22**

Entry.	RBF_3K	Product	Yield
1	 **2.15b**	 **2.22b**	85%
2	 **2.15c**	 **2.22c**	76%
3	 **2.15d**	 **2.22d**	92%
4	 **2.15e**	 **2.22e**	82%
5	 **2.15f**	 **2.22f**	70%
6	 **2.15g**	 **2.22g**	-
7	 **2.15h**	 **2.22h**	-
8	 **2.15i**	 **2.22i**	-



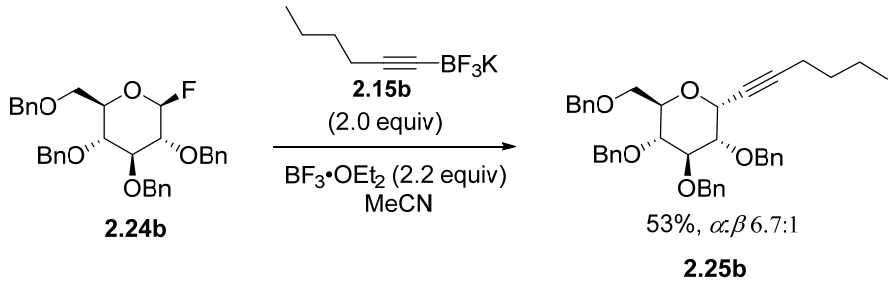
Scheme 2.10 Intramolecular arylation.

Table 2.4 Reaction optimization of *C*-glucosylation.[a]



Entry	X(α:β)	BF_3·OEt_2	Temp.(°C)	Time (h)	Yield	α:β
1[a]	α-$OCNCl_3$ (10:1) **2.24a**	2 equiv.	rt	0.5	76%	2.3:1
2[a]	β-F (5:1) **2.24b**	2 equiv.	rt	0.5	90%	2.6:1
3[b]	β-F (5:1) **2.24b**	2.5 equiv.	-15	5	73%	3.6:1
4[b]	β-F (5:1) **2.24b**	2.5 equiv.	-40	8	67%	5.3:1
5[c]	β-F (5:1) **2.24b**	2.5 equiv.	-40	8	70%	6.9:1
6[c]	β-F (5:1) **2.24b**	4 equiv.	-78	12	23%	ND
7[c]	β-$OCNCl_3$ (2.6:1) **2.24c**	2.5 equiv.	-40	16	32%	3.3:1
8[c]	α-F (6:1) **2.24 d**	2.5 equiv.	-40	8	61%	4.4:1

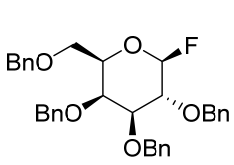
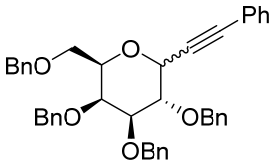
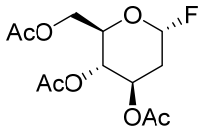
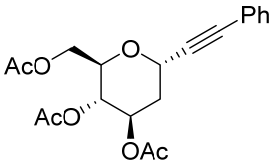
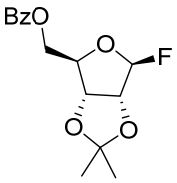
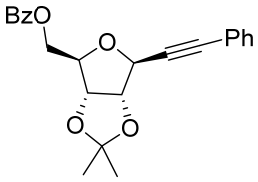
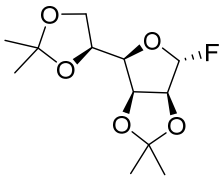
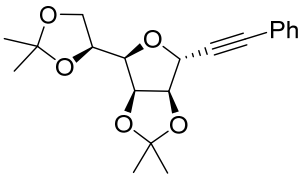
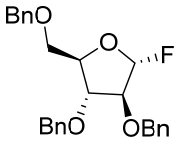
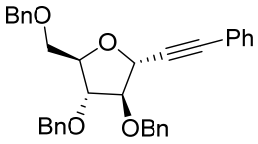
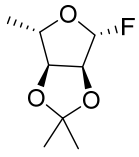
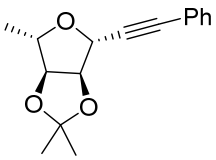
[a] **Procedure A**: To a solution of the corresponding sugar (0.2 mmol) and organo-trifluoroborate (1.2 equiv) in acetonitrile (1 mL) was added BF_3·OEt_2 (1.3 equiv) at rt. [b] **Procedure B**: To a solution of the corresponding sugar (0.2 mmol) and organotrifluoroborate (2.0 equiv) in acetonitrile (1 mL) was added BF_3·OEt_2 (2.2 equiv) at the indicated temperature. [c] **Procedure C**: Premixing of BF_3·OEt_2 (2.2 equiv) and organotrifluoroborate (2.0 equiv) in acetonitrile (1 mL) followed by addition of the corresponding sugar (0.2 mmol) at the indicated temperature.



Scheme 2.11 *C*-glucosylation with **2.15b**.

Encouraged by these results, we further investigated the diastereoselectivity of glucosylation (**Table 2.4**). Compared to mannosylation, it is much difficult to achieve high α-selectivity for glucosylation due to the C-2 substituent of glucose increased the steric hindrance of α face. Both α-glucosyl trichloroacetimidate and β-glucosyl fluoride produced good yields but unfortunately, only slight preference for α-selectivities were detected (2.3:1 and 2.6:1 respectively) (entries 1, 2). With β-glucosyl fluoride, lowering the reaction temperature increased the selectivity; however, diminished yields were observed. At -15 ^{o}C, the selectivity was increased to 3.6:1 (entry 3). At -40 °C, the product was obtained in 67% yield with good α-selectivity (α:β = 5.3:1) (entry 4). Unfortunately, further lowering of the temperature to -78 ^{o}C led to a sharp decrease in yield (entry 6). Interestingly, we found that reversing the sequence of addition (premixing excess potassium organotrifluoroborate and BF_3·OEt_2 in CH_3CN prior to the addition of fluoride) slightly increased the yield and selectivity (70% and 6.9:1 respectively) (entry 5). β-Glucosyl trichloroacetimidate and α-glucosyl fluoride were also examined but both gave inferior results (entry 7, 8). It should be noted that reactions with both α- and β-substrates had an intrinsic α-selectivity, which indicates that the reaction proceeded through an S_N1 mechanism. However, glucosylation reaction with **2.15b** only gave moderate yield although the selectivity was good (**Scheme 2.11**).

Table 2.5 Scope of glycosyl fluorides[a].

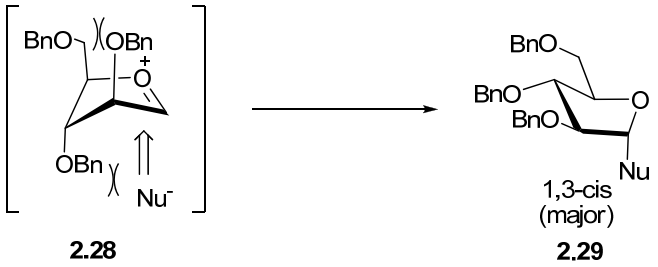
Entry	Glycosyl fluoride	Product	Yield	α:β
1[b]	 **2.26a** α:β 3:5	 **2.27a**	84%	5.6:1
2	 **2.26b** α:β 10:1	 **2.27b**	92%	α only
3	 **2.26c** α:β 1:9	 **2.27c**	89%	β only
4	 **2.26d**	 **2.27d**	69%	α only
5	 **2.26e**	 **2.27e**	81%	3:1
6	 **2.26f**[c]	 **2.27f**	75%	β only

[a] Unless otherwise indicated, the reaction was carried out according to **Procedure A**. [b] Reaction was carried out according to **Procedure C**. [c] Compond **2.26f** is unstable and decomposed quickly.

We further studied the versatility of this $BF_3 \cdot OEt_2$ promoted *C*-glycosylation protocol with other sugar fluorides, using potassium phenylacetylene trifluoroborate as the coupling partner (**Table 2.5**). D-Galactosyl fluoride **2.26a** gave the desired product **2.27a** in good yield with moderate α-selectivity under the optimized conditions. The reaction conditions were also amenable to 2-deoxyglucosyl fluoride **2.27b**, as the α-anomeric product was obtained in excellent yield as a single isomer. It is apparent that the C-2 substituent of glucose exerts a negative effect on the stereoselectivity of *C*-glucosylation when comparing the stereoselectivity of **2.24** to that of **2.27b**. Extension of the glycosylation reaction to furanose was further pursued. Unlike *C*-glycosylation of mannose, glucose and galactose which consistently produced α-selectivity, furanose did not follow the same trend as complex factors influence the stereoselectivity. For fused bicyclic systems **2.26c**, **2.26d** and **2.26f**, 1,2-*trans* selectivity was observed due to the protecting group covered one face and the nucleophile can only attack from the opposite face. But for **2.26e**, 1,3-*cis* selectivity was observed. Thus, reactions with **2.26c** and **2.26f** prefer β selectivity while **2.26d** and **2.26e** are in favor of α-selectivity.

Based on Woerpel's systematic study,[15] the selectivity of **2.26e** is mainly controlled by the C-3 substituent which prefers 1,3-*cis* selectivity (**Scheme 2.12**). This is due to the fact that the C-3 substituent occupies the pseudo-axial position in the preferred conformation **2.28**, placing the partially negative charged OBn group close to the cationic carbon of the oxocarbenium ion and in the process stabilizes the intermediate. However, in this conformation, both the C-2 and C-4 substituents also adopt the pseudo-axial orientation, which creates a *syn*-butanol interaction of approximately 1.8 kcal/mol.[16] This unfavorable interaction destabilized the system and presumably

reduced the 1,3-*cis* selectivity. With respect to fused bicyclic system, the protecting group blocks the α-face, hence only β-attack is possible.

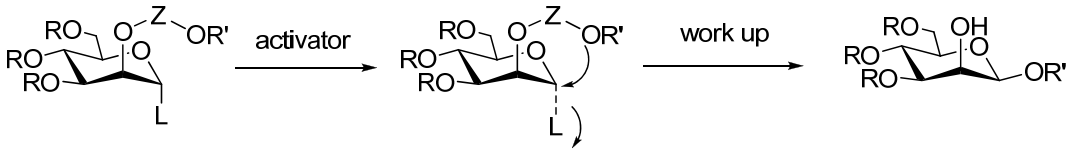


2.28 **2.29**

Scheme 2.12 Favorable conformation of intermediate **2.28**.

2.3 Access to *β-C*-mannosylation

Despite extensive effort being made to stereoselective *C*-glycosylation, 1,2-*cis*-mannosylation, particularly 1,2-*cis*-*C*-mannosylation, remains a challenge to carbohydrate chemists due to two reasons: Firstly, as depicted in chapter I, the electrophilic oxonium cation intermediate prefers the $^4H_3$ conformation which leads to α-selectivity (1,2-*trans* to mannose); Secondly, neighboring group participation of the protecting group also results in α-mannosylation. In addition, steric hindrance of axial C-2 functional group acts an obstruction to prevent attack from β-face.

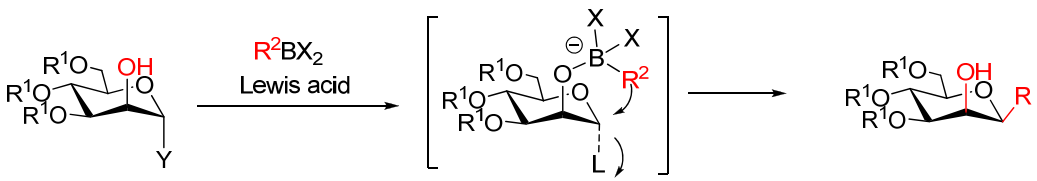


Scheme 2.13 1,2-*cis*-*O*-Mannosylation through IAD reaction.

Several methods have been developed to achieve 1,2-*cis*-*O*-mannosylation, such as: (1) insoluble silver salt mediated S_N2-like reaction with an α-glycosyl halide;[17] (2) inversion of C-2 selectivity of β-D-glucosides;[18] (3) activation of anomeric position

followed by nucleophilic substitution of glycosyl acceptors.[19] Among them, the most successful and attractive way to achieve 1,2-*cis*-*O*-mannosylation is through intramolecular aglycon delivery (IAD) (**Scheme 2.13**).[20]

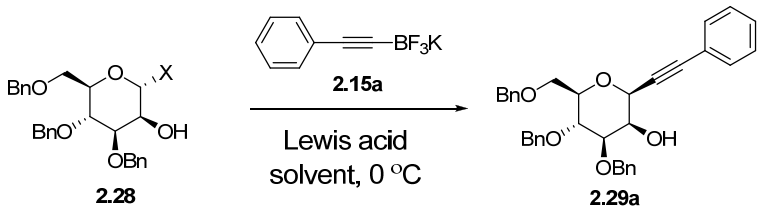
Unfortunately, to the best of our knowledge, limited synthetic methods on 1,2-*cis*-*C*-mannosylation were reported. These methods mainly focused on specific substrates and involved intermolecular reactions.[21] Encouraged by the success of Lewis acid mediated direct *C*-Glycosylation of organotrifluoroborates to achieve 1,2-*trans*-*C*-mannosylation, we anticipated that the free hydroxyl group on C-2 position of mannose might be involved in delivering the boron reagents to the C-1 position, and in the process, achieve 1,2-*cis*-*C*-mannosylation (**Scheme 2.14**).



Scheme 2.14 1,2-cis-*C*-Mannosylation (*β*-*C*-glycosylation).

Our study commenced with optimization of the reaction conditions (Table 2.6). Firstly, the same set of reaction conditions used in 1,2-trans mannosylation was applied to the reaction of mannosyl fluoride 2.28a with 2.15a (entry 1). To our delight, the coupling product 2.29a was obtained as a single isomer albeit with low yield. However, the stereoselectivity was difficult to confirm by 1H NMR due to the overlapping peaks which resulted in difficulties in peak identification. In addition, because of the gauche relationship between H-1 and H-2 protons, the 3JH-1,H-2 coupling constants for both α- and β-mannosides are approximately 1-2 Hz. Consequently, the anomeric configuration of mannoside products could not be determined by simply comparing the $^{3}J_{\text{H-1,H-2}}$ coupling constant, which is usually a

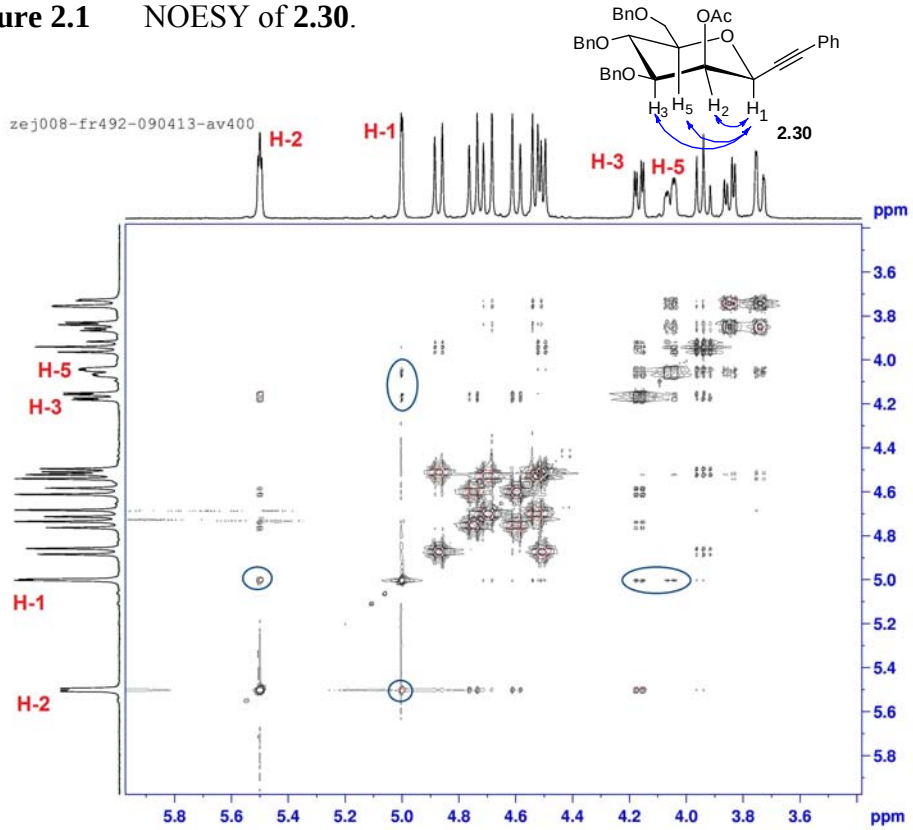
Table 2.6 Reaction optimization of 1,2-*cis*-mannosylation.



Entry	X	**2.15a** (equiv.)	Catalyst (equiv.)	Solvent	Yield[a]
1[b]	F **2.28a**	1.5	$BF_3{\cdot}OEt_2$ (1.5)	CH_3CN	26%
2	F **2.28a**	1.5	$BF_3{\cdot}OEt_2$ (1.5)	CH_3CN	57%
3	F **2.28a**	1.5	$BF_3{\cdot}OEt_2$ (4.0)	CH_3CN	55%
4	F **2.28a**	3.0	$BF_3{\cdot}OEt_2$ (4.0)	CH_3CN	80%
5	F **2.28a**	3.0	$BF_3{\cdot}OEt_2$ (1.5)	CH_3CN	88%
6	OH **2.28b**	3.0	$BF_3{\cdot}OEt_2$ (1.5)	CH_3CN	NR
7	STol **2.28c**	3.0	$BF_3{\cdot}OEt_2$ (1.5)	CH_3CN	NR
8	F **2.28a**	3.0	$TiCl_4$ (1.5)	CH_3CN	trace
9	F **2.28a**	3.o	TESOTf (1.5)	CH_3CN	46%
10	F **2.28a**	3.0	$BF_3{\cdot}OEt_2$ (1.5)	CH_2Cl_2	NR
11	F **2.28a**	3.0	$BF_3{\cdot}OEt_2$ (1.5)	Et_2O	NR
12	F **2.28a**	3.0	$BF_3{\cdot}OEt_2$ (1.5)	CH_3NO_2	NR
13	F **2.28a**	3.0	$BF_3{\cdot}OEt_2$ (1.5)	DMF	NR

[a] Isolated yields. [b] reaction was carried out at rt.

Figure 2.1 NOESY of **2.30**.

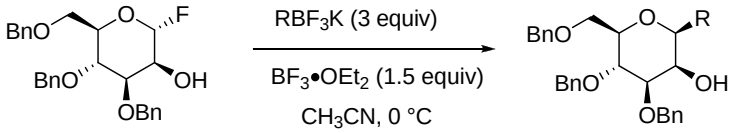


useful way of determining the configuration of *gluco* and *galacto* pyranosides. In this case, we proceeded to determine the configuration at the anomeric carbon by testing Nuclear Overhauster Effect (NOE) of **2.30**, which was derived from **2.29a**. The NOESY of **2.30** (**Figure 2.1**) showed strong signals between H-1 and H-2 and weaker signals between H-1 and H-3. The weak signals between H-1 and H-3 clearly indicate that **2.29a** is the *β*-anomer.

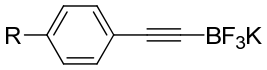
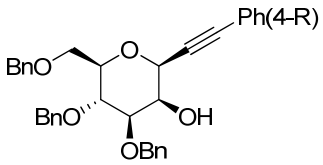
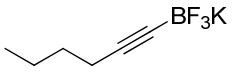
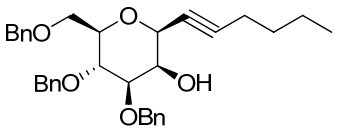
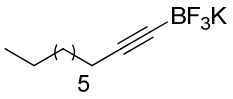
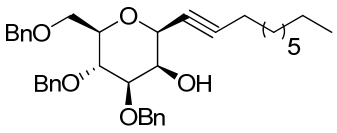
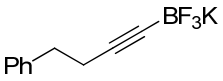
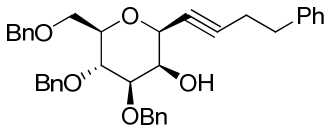
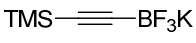
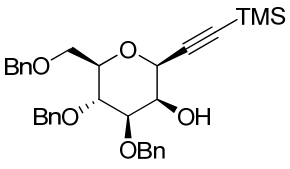
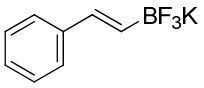
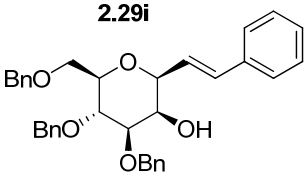
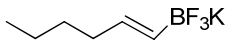
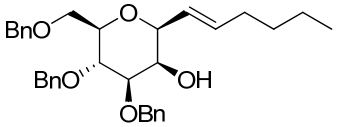
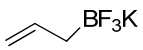
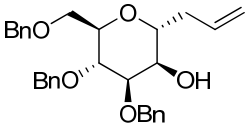
Encouraged by this positive result, we further optimized the reaction by reducing the reaction temperature to 0 ^{o}C. Interestingly, the yield of **2.29a** was increased to 57% (entry 2). Further reduction of the reaction temperature did not lead to an increase in yield but a longer reaction time was required. Increasing the amount of Lewis acid gave rise to a decrease in yield, while 4 equivalents of $BF_3{\cdot}OEt_2$ afforded the desired product in only 55% yield (entry 3). In contrast, adding excess trifluoroborate salt promoted the reaction (entry 4 and 5). The highest yield was obtained with 3 equivalents of **2.15a** and 1.5 equivalents of $BF_3{\cdot}OEt_2$ (entry 5). Similar to the observation in 1,2-*trans*-mannosylation, attempts with other leaving groups, Lewis acids and solvents gave diminished results (entries 6-13).

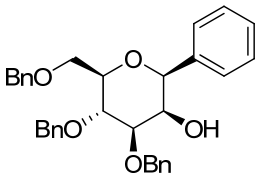
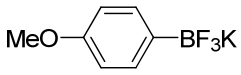
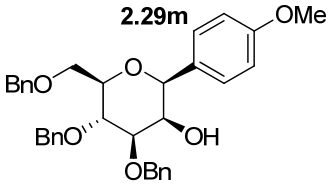
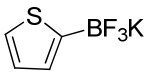
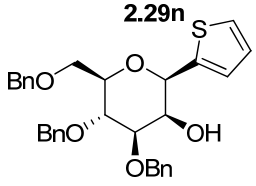
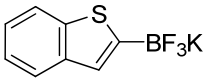
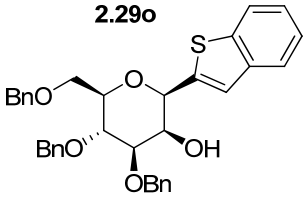
With this optimized conditions in hand, we further investigated the substrate scope (**Table 2.7**). Potassium phenylethynyl trifluoroborates with substituted phenyl rings were tested first (entries 1-4). Reactions with these substrates proceeded smoothly and the desired *β*-mannosides were produced in moderate to good yields. However, the yields obtained were lower than **2.29a**, which might indicate that the electron-donating groups exert a negative effect on the reaction. Attempts to prepare potassium phenylacetylene trifluoroborates possessing electron-withdrawing groups were unsuccessful; hence, the effect of electron-withdrawing groups on this reaction is

Table 2.7 Substrate scope of organotrifluoroborates.



2.28 **2.29**

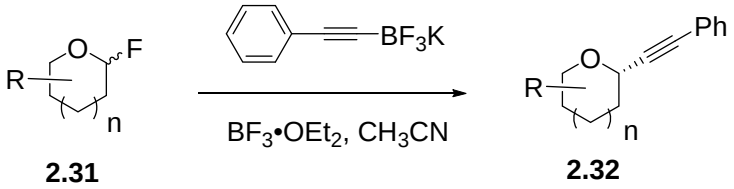
Entry.	RBF_3K		Product	Yield
				
1	R = F	**2.15j**	**2.29b**	87%
2	Me	**2.15k**	**2.29c**	86%
3	*t*-Bu	**2.15l**	**2.29d**	77%
4	OMe	**2.15m**	**2.29e**	60%
5	 **2.15b**		 **2.29f**	86%
6	 **2.15c**		 **2.29g**	82%
7	 **2.15n**		 **2.29h**	80%
8	 **2.15d**		 **2.29i**	55%
9	 **2.15e**		 **2.29j**	67%
10	 **2.15f**		 **2.29k**	69%
11	 **2.15j**		 **2.29l**	70%

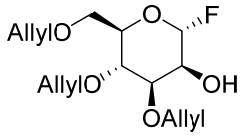
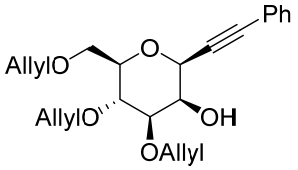
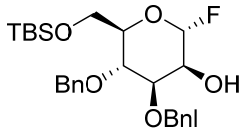
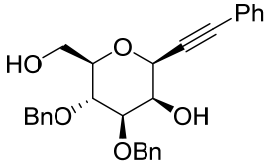
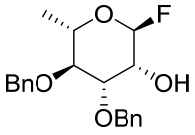
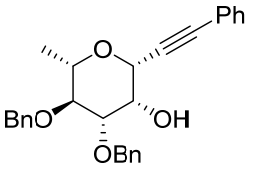
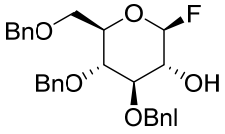
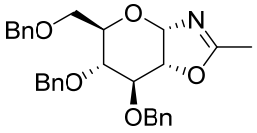
12	$PhBF_3K$ **2.15h**	 **2.29m**	0%
13	 **2.15k**	 **2.29n**	50%
14	 **2.15i**	 **2.29o**	34%
15	 **2.15l**	 **2.29p**	26%

unclear. Reactions with alkynyltrifluoroborates possessing aliphatic substituents such as butyl, phenylethyl and octanyl also provided the desired products in good yields (entries 5-7). When the reaction was carried out with **2.15d** (entry 8), TMS- protected mannoside **2.22i** was obtained only in moderate yield. In addition, the reaction could also be conducted with alkenyltrifluoroborates and the resultant **2.22j** and **2.22k** were produced in 67% and 69% yields respectively (entries 9,10). Similar to what was described for 1,2-*trans*-mannosylation reaction, attempts to employ normal potassium alkyltrifluoroborates were unproductive. However, reaction with potassium allyltrifluoroborate **2.15j** preceded well, but surprisingly, afforded exclusive α-selectivity (entry 11). Similar result was also observed by Cox's group when they use temporary silicon connection as tethering group to deliver allyl group to mannose anomeric position.[22] Potassium phenyltrifluoroborate couldn't participate into the reaction to achieve the *cis*-phenylation (entry 12), however, arylation was occurred

when electron rich potassium 4-methoxyphenyltrifluoroborate were employed (entry 13). Heterocyclic trifluoroborates such as **2.15i** and **2.15l** were also potent coupling partners, although produced poor yields (entries 14,15).

Table 2.8 Substrates scope of sugar scaffold.



Entry	Glycosyl fluoride	Product	Yield
1	 **2.31a**	 **2.32a**	74%
2	 **2.31b**	 **2.32b**	76%
3	 **2.31c**	 **2.32c**	83%
4	 **2.31d**	 **2.32d**	84%

Next, we examined the reactivity of other *sugar*-scaffolds (**Table 2.8**). Allyl-protected mannosyl fluoride **2.31a** reacted smoothly with alkynyl trifluoroboride **2.15a**, furnishing **2.32a** in good yield (entry 1). The TBS-protecting group is sensitive

to this reaction condition and the reaction with **2.31b** produced **2.32b** in 76% yield, with the concurrent deprotection of TBS group (entry 2). L-Rhamnosyl fluoride **2.31c** was also employed in the reaction, generating **2.32c** in 83% yield (entry 3). Unfortunately, attempts to achieve 1,2-*cis*-glucosylation and galactosylation were unsuccessful. Instead of proceeding with the *C*-glycosylation reaction, the solvent was observed to participate in the reaction to generate oxazolines **2.32d** in 84% yield.[23]

2.4 Total synthesis of (+)-varitriol

(+)-Varitriol is a natural product isolated from a marine-derived strain (M75-2) of the fungus *Emericella variecolor* by Barrero *et al* in 2002.[24] The structure of (+)-varitriol was ascertained by detailed NMR studies and was further established *via* total synthesis.[25] This small naturally occurring molecule exhibits significant cytotoxic activity against a variety of tumor cell lines and showed a 100-fold increased potency (over the mean toxicity) toward the RXF 393 (renal cancer), SNB-75 (CNS central nervous system cancer) and T-47D (breast cancer) cell lines. These significant bioactivities but unknown mode of action of (+)-varitriol has undoubtedly driven increasing efforts in the total synthesis of (+)-varitriol and its analogues.[26]

(+)-Varitriol is characterized by a highly substituted tetrahydrofuran ring and a trisubstituted aromatic ring linked to the sugar scaffold by a *trans*-alkene. The reported synthetic strategies mainly focused on connecting the two moieties by means of metathesis,[26f,26h,26i,26j,26l] Heck coupling,[26e] HWE-olefination[26k] and Kocienski-Julia olefination (**Figure 2.2**).[26c] It is apparent that the synthetic challenge lies in the construction of the tetrahydrofuran ring which bears four continuous stereogenic centers. Most of the reports chose to access these tetrahydrofuran synthons from an available chiral pool of materials, particularly carbohydrates such as D-ribose, D-

mannose, D-glucose and D-mannitol. L-Tartrate has also been utilized in these reactions. Unfortunately, as the configuration of stereogenic centers is not consistent

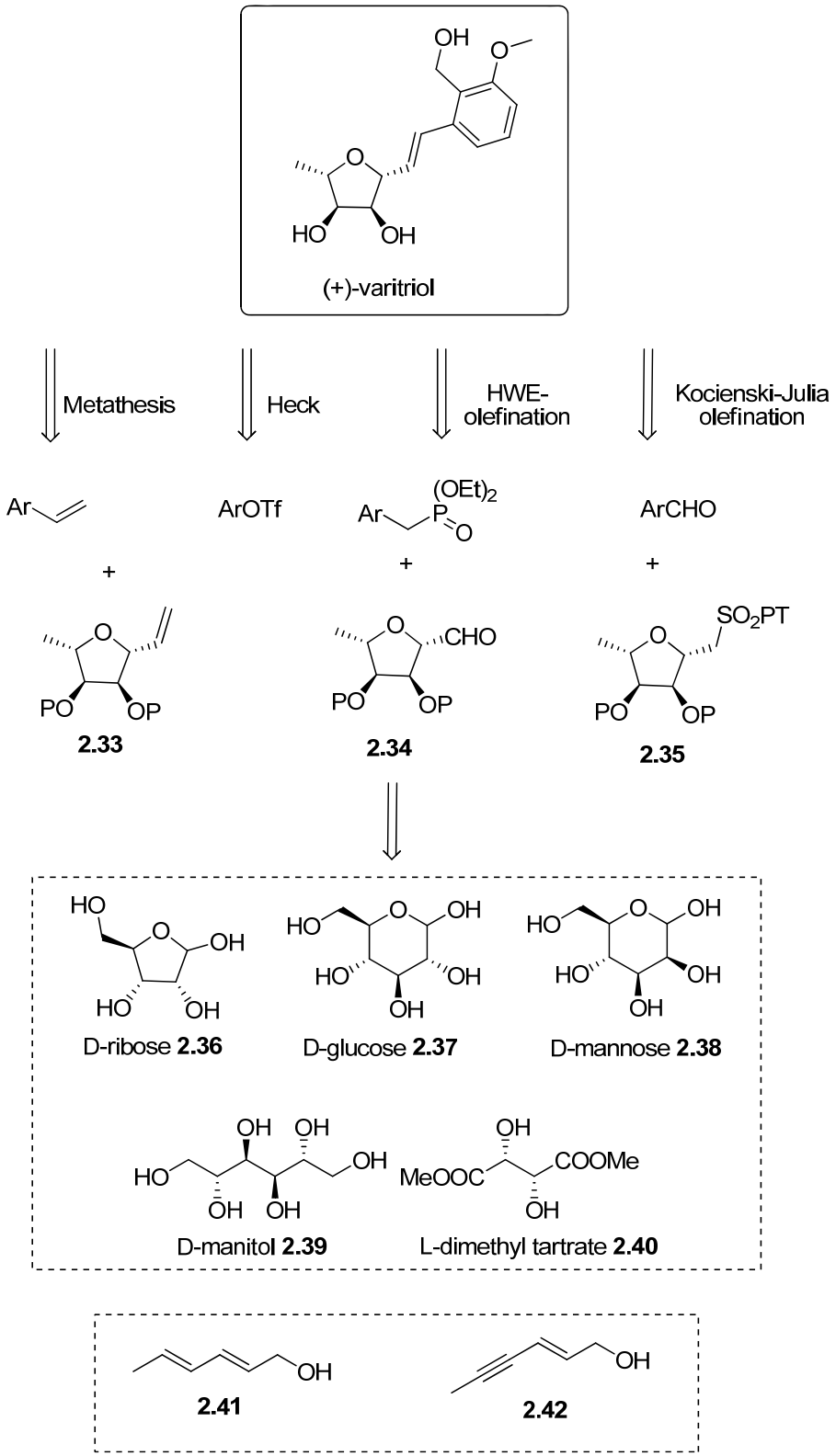
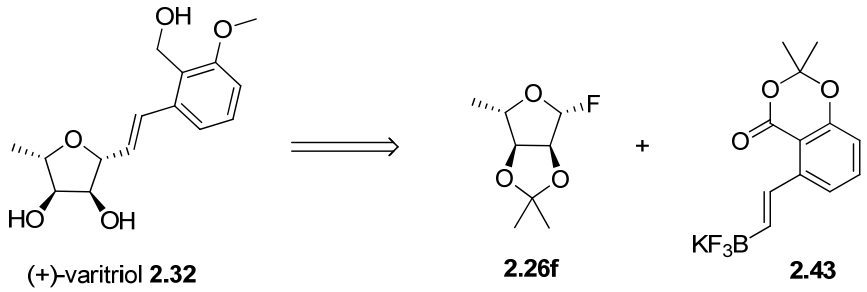


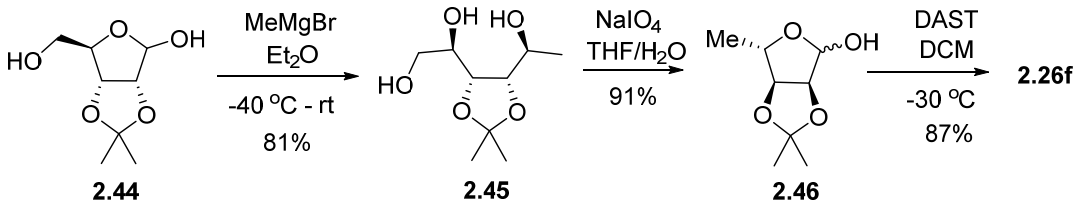
Figure 2.2 Reported synthetic strategies.

with the natural source of materials, several transformation steps are necessary to manipulate the chiral centers. Non-chiral pool syntheses have also been developed by utilizing alcohol **2.41** or **2.42**.



(+)-varitriol **2.32** **2.26f** **2.43**

Scheme 2.15 *C*-glycosylation strategy in the retrosynthesis of (+)-varitriol **2.32**.



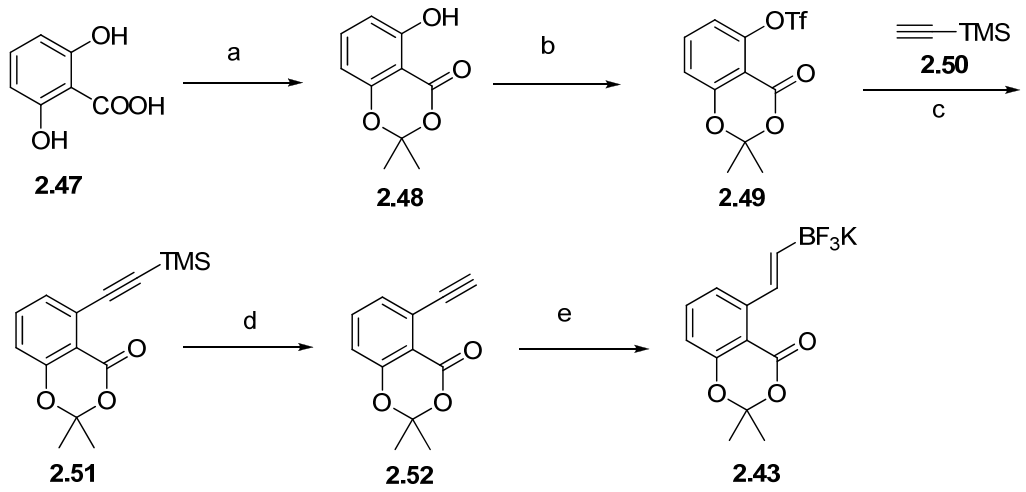
2.44 **2.45** **2.46**

Scheme 2.16 Synthesis of **2.26f**.

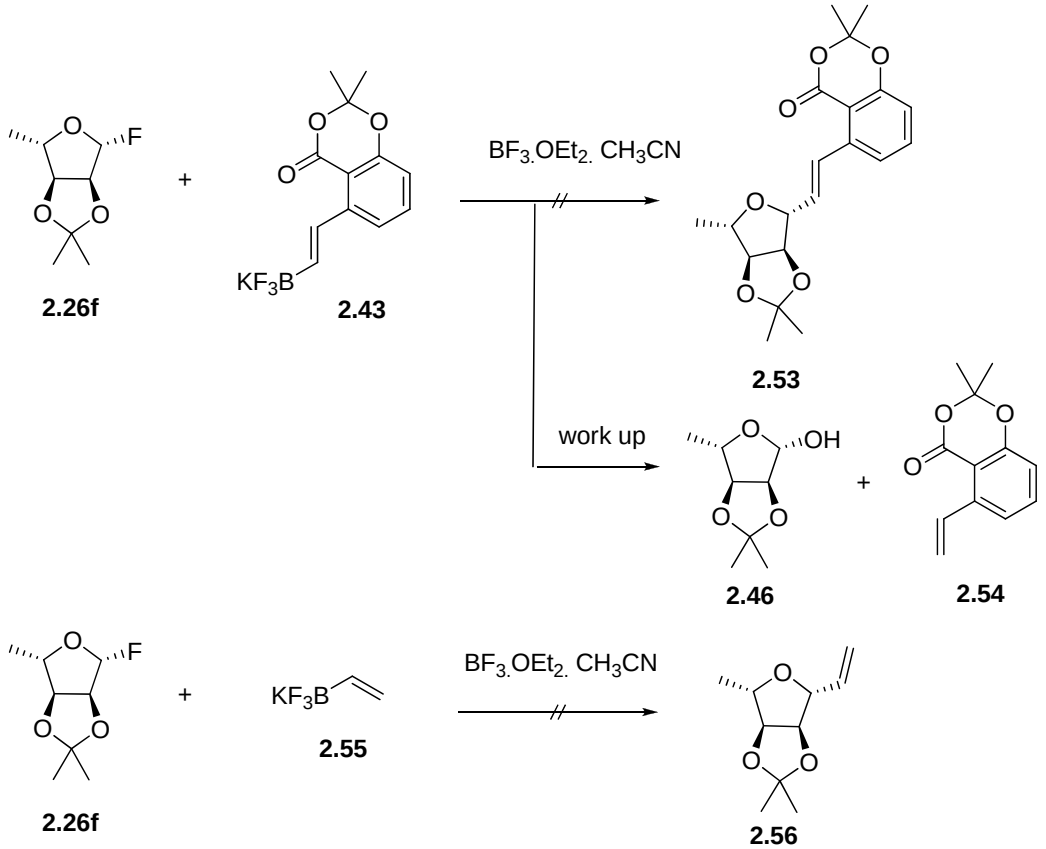
Encouraged by the success of our $BF_3{\cdot}OEt_2$ promoted *C*-glycosylation strategy, we envisaged that this strategy could be further applied to the total synthesis of (+)-varitriol (**Scheme 2.15**). Coupling of glycosyl fluoride **2.26f** and organotrifluoroborate **2.43** is proposed as the key step.

Our synthesis commenced with the preparation of the tetrahydrofuran moiety **2.26f** from D-ribose **2.44**. Treatment of **2.44** with excess methylmagnesium bromide furnished **2.45** with absolute stereo-control. Further oxidation of the 1,2-diol in **2.45** to an aldehyde by $NaIO_4$ led to the formation of lactol **2.46** in excellent yield. Fluorination of **2.46** was achieved by treatment of **2.46** with DAST at -30 ^oC. However, the product **2.26f** was unstable and decomposed during column

chromatography. Therefore, **2.26f** was used in the next step immediately without further purification.



Scheme 2.17 Synthesis of **2.43.** a) $SOCl_2$, acetone, DME, 0 ^oC – rt. 80%; b) Tf_2O, pyr, DCE, 0 ^oC. 94%; c) **2.50**, $Pd(PPh_3)_4$, CuI, DiPEA, DCM, rt. 81%; d) TBAF, THF, rt. 91%; e) $BH_3 \cdot THF$, 2,5-dimetylhexa-2,4-diene, HCHO (37% in H_2O), KHF_2; 63%.

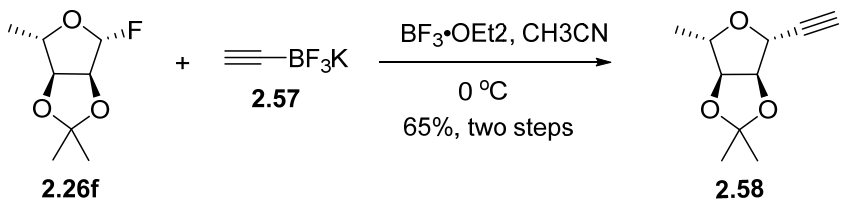


Scheme 2.18 Coupling reaction of **2.26f** with alkenyl trifluoroborate.

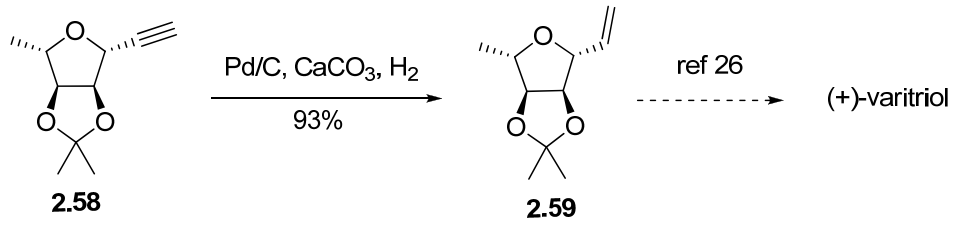
The aromatic moiety **2.43** was synthesized according to the literature procedure.[27] Benzoic acid **2.47** was protected, forming **2.48** in good yield. Subsequent installation of the alkyne group on **2.48** in three steps led to **2.52**. Eventual hydroboration of the terminal alkyne furnished the desired trifluoroborate salt **2.43**.

With **2.26f** and **2.43** in hand, we attempted to link these two moieties under our established reaction conditions (**Scheme 2.18**). Unfortunately, the $BF_3.OEt_2$ promoted coupling reaction was unsuccessful under different reaction temperatures. In addition, by varying the ratio of reagents, we could neither observe the desired product nor recover the starting material; instead, **2.46b** and alkene **2.54** were obtained after work up. Coupling of **2.26f** with a simple vinyl trifluoroborate **2.55** was also unsuccessful. These failures were attributed to the instability of **2.26f** as well as lower reactivity of the alkenyl trifluoroborates.

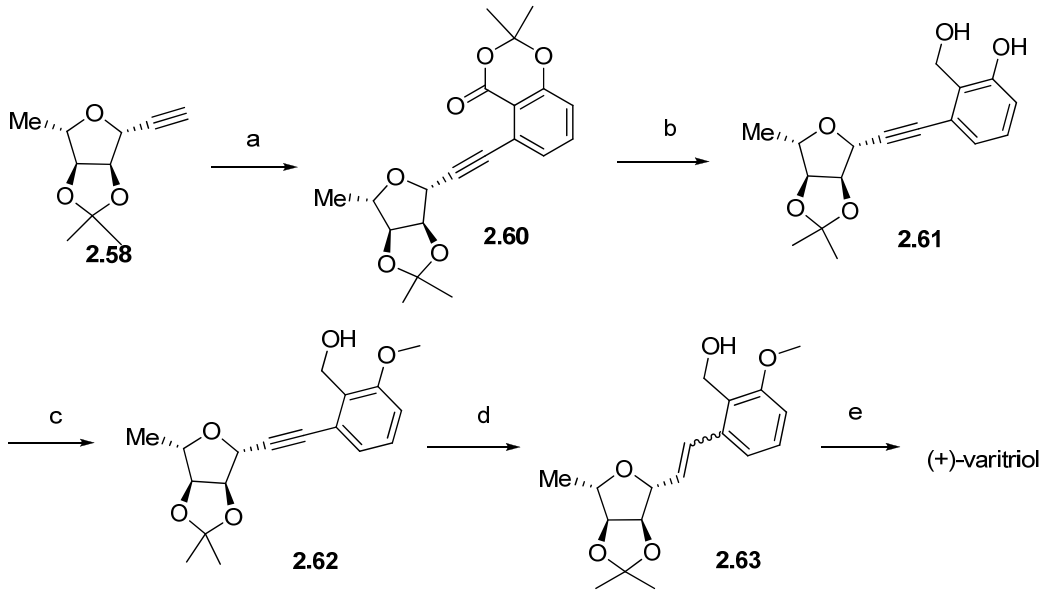
To overcome this problem, alkynyl trifluoroborate **2.57** was used to replace **2.43** or **2.55** as the starting reagent in the coupling reaction. To our delight, the reaction proceeded smoothly at 0 ^{o}C and produced the desired **2.58** in 65% yield over two steps from **2.46** (**Scheme 2.19**). Selective reduction of alkyne to alkene by Lindlar catalyst led to the key intermediate **2.59**. From **2.59**, (+)-varitriol could be synthesized through metathesis or Heck coupling reaction according to literature reports (**Scheme 2.20**).[26]



Scheme 2.19 Coupling reaction of **2.26f** with **2.57**.



Scheme 2.20 Reduction of **2.58** to synthesis of **2.59**.



Scheme 2.21 Total synthesis of (+)-varitriol**.** a) **2.49**, $(PPh_3)_2PdCl_2$, CuI, DMF/Et_3N, 60 ^oC, 91%; b) $LiAlH_4$, THF, -78 ^oC to rt, 89%; c) MeI, K_2CO_3, acetone, reflux, 92%; d) Condition A: Red-Al, THF, -20 ^oC to rt, 89%, *E*:*Z* = 2.8:1.0; Condition B: $LiALH_4$, THF, -20 ^oC to rt, 76%, *E*:*Z* = 2.0:1.0; e) 1 M HCl, rt, then SiO_2, 93%.

As an alternative strategy, we also tried to connect the tetrahydrofuran moiety and the aromatic ring by coupling **2.58** with triflate **2.49** (**Scheme 2.21**). In the reaction catalyzed by $(PPh_3)_2PdCl_2$ and CuI, **2.60** was obtained in 91% yield. Reduction of the ester group by $LiAlH_4$ furnished **2.61** in 89% yield. Further selective methylation of the phenol group of **2.61** produced **2.62** in 92% yield. The partial reduction of the triple bond to a *trans*-alkene was a synthetic challenge. Usually, reduction is achieved by dissolving metal reduction (such as Na/NH_3). In this case, we anticipated that the partial reduction could be conducted by metal hydrides and the chemoselectivity could be controlled by the adjacent hydroxyl group.[28] Unfortunately, reduction of the triple

bond by $LiAlH_4$ gave a 2.0:1.0 *trans* to *cis* selectivity and a moderate yield of 76%. Replacing $LiAlH_4$ with sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) increased the selectivity to 2.8:1 and the yield to 89%. Interestingly, the *Z*-isomer was transformed to give exclusive *E*-product after removing the protecting group of **2.63** under acidic conditions, followed by purification with flash chromatography on silica gel. Thus, we succeeded in the total synthesis of (+)-varitriol from the known compound **2.46**[29] in only seven steps and an overall yield of 42%.

2.5 Conclusion

We have demonstrated a new method towards 1,2-*cis* and 1,2-*trans* *C*-mannosylation based on $BF_3{\cdot}OEt_2$ promoted directed coupling of organotrifluoroborate reagents with mannosyl fluorides. The stereoselectivity was determined by the nature of the C-2 OH group. When the C-2 OH group was protected, 1.2-*trans* selectivity was achieved. In contrast, when C-2 OH group was unprotected, 1,2-*cis*-selectivity was observed.

In addition, this methodology was also applied in the *α*-*C*-glycosylation for D-glucopyranose, D-galactopyranose, D-mannofuranose and D-arabinofuranose in which the C-2 OH groups of these carbohydrates were protected. However, attempts to achieve 1,2-*cis*-*C*-glucosyaltion or 1,2-*cis*-*C*-galactosylation by coupling of organotrifluoroborates with C-2 OH unprotected glucosylfluoride and galactosyl fluoride were unsuccessful.

This methodologie opened a new way to stereoselectively access both *α*- and *β*- C-glycosides, highlighting the synthetic applications to natural products and drug candidates. The applicability of this methodology was examined by the total of (+)-varitriol. By employing the $BF_3{\cdot}OEt_2$ promoted coupling reaction of potassium

ethynyltrifluoroborate with L-furanosyl fluoride as the key step, the naturally occurring (+)-varitriol was obtained in 7 steps from a reported compound **2.46** in 42% yields and in 10 linear steps from D-ribose, which composed one of the most efficient synthetic parthway.

2.6 Experimental section

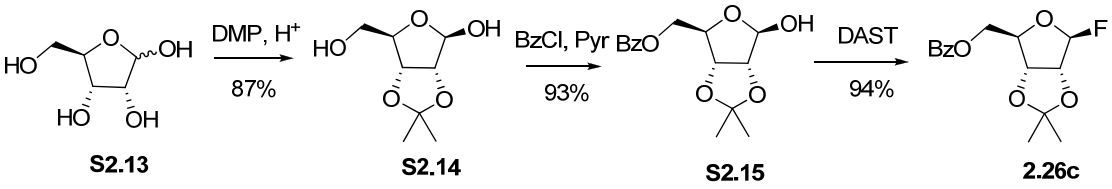
General: All the reactions were carried out in a flame or oven dried glassware under an argon or nitrogen atmosphere with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Organic solutions were concentrated under reduced pressure by rotary evaporation with a water bath (temperature below 40 °C). Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60–F254) using UV light at 254 nm as a visualizing agent and a $KMnO_4$ solution as stain. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ or MeOH on a Schmidt + Haensdch polarimeter with a 1 cm cell (*c* given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu). Analytical HPLC was performed with Shimadzu UFLC HPLC utilizing Prevail C18 5μ and Kromasil 5-CelluCoat columns. NMR spectra were recorded at room temperature on 300 MHz Bruker ACF 300, 400 MHz Bruker DPX 400, 400MHz Bruker BPO 400 NMR spectrometers. Only the data of major isomers were recorded for those compounds contain isomers. The residual solvent signals were taken as the reference (7.26 ppm for 1H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). Sometimes the TMS signal at 0.0 ppm was used an internal standard for ^{1}H NMR spectra. Chemical shift (δ) is reported in ppm, coupling constants (*J*) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal. HR-MS (ESI) spectra were recorded on a Waters Q-Tof premierTM mass spectrometer.

Materials: All solvents were distilled under argon from the following drying agents immediately before use: tetrahydrofuran (THF) was distilled from

sodium/benzophenone ketyl; dichloromethane (DCM) was distilled from calcium hydride. Anhydrous acetonitrile (MeCN) was purchased from commercial suppliers and used without further purification. $BF_3{\cdot}OEt_2$ was distilled from calcium hydride before use. Potassium organotrifluoroborates were purchased from commercial suppliers or synthesized according literature procedures.[30]

2.6.1 Access to *α*-*C*-glycosylation

Synthesis of mannosyl fluoride 2.21. (General procedure)



1-Allyl-2,3,4,6-tetra-*O*-benzyl-D-mannopyranoside (S2.2): To a suspension of NaH (60% in oil, 2.0 g, 50 mmol) in DMF (20 mL) was added dropwise a solution of **S2.1** (2.19 g, 10 mmol) in DMF (20 mL) carefully at 0 °C. The reaction mixture was stirred for 30 min, and then BnBr (5.9 mL, 50 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was carefully quenched with H_2O at 0 °C, diluted with Et_2O (100 mL) and then washed with water (40 mL × 3). The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:10) to afford **S2.2** (5.0 g, 86%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$,) δ 3.67-3.80 (m, 4H), 3.88-4.01 (m, 3H), 4.13 (dd, *J* 5.0, 13.0 Hz, 1H), 4.48 (d, *J* 10.8 Hz, 1H), 4.52 (d, *J* 12.0 Hz, 1H), 4.60 (s, 2H), 4.64 (d, *J* 12.0 Hz, 1H), 4.71 (s, 2H), 4.86 (d, *J* 10.8 Hz, 1H), 4.91 (d, *J* 1.7 Hz, 1H), 5.12 (dd, *J* 1.5, 10.4 Hz, 1H), 5.18 (dd, *J* 1.5, 17.2 Hz, 1H), 5.75-5.87 (m, 1H), 7.12-7.17 (m, 2H), 7.24-7.40 (m, 18H); **^{13}C**

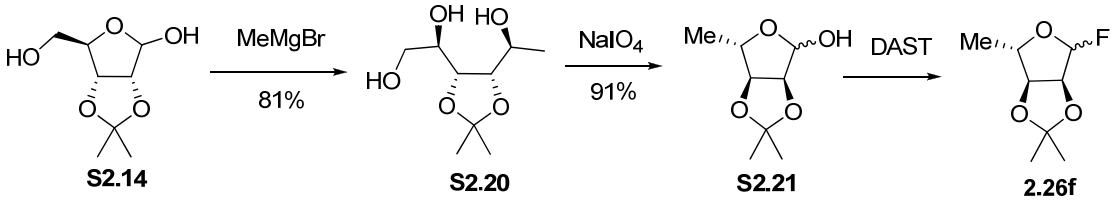
NMR (75 MHz, $CDCl_3$) δ 68.1, 69.6, 72.1, 72.4, 72.8, 73.6, 75.0, 75.23, 75.4, 80.5, 97.4, 117.4, 127.6, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 134.1, 138.6, 138.7, 138.8; **FT-IR** (KBr): *v* 3090, 1630, 1451, 1072, 744, 696 cm^{-1}; **ESI–MS** m/z 603.3 $[M+Na]^+$.

2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (S2.3): A mixture of **S2.2** (580 mg, 1 mmol) and $PdCl_2$ (34 mg, 0.2 mmol) in dry MeOH (6 mL) was stirred vigorously for 6 h at room temperature until consumption of starting material was observed by TLC. The reaction was then diluted with Et_2O, filtered through celite and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:3) to afford **S2.3** (530 mg, 98%) as a corless oil. **^{1}H NMR** (300 MHz, $CDCl_3$,) δ 3.39 (S, 1H), 3.65-3.75 (m, 2H), 3.79-3.81 (m, 1H), 3.86 (t, *J* 9.6 Hz, 1H), 3.97 (dd, *J* 3.0, 9.3 Hz, 1H), 4.02-4.05 (m, 1H), 4.50 (d, *J* 11.3 Hz, 1H), 4.54 (d, *J* 12.2 Hz, 1H), 4.56 (d, *J* 12.2 Hz, 1H), 4.62 (s, 1H), 4.71 (d, *J* 12.4 Hz, 1H), 4.76 (d, *J* 12.4 Hz, 1H), 4.89 (d, *J* 12.3 Hz, 1H), 5.26 (s. 1H). 7.16 -7.18 (m, 2H), 7.25-7.38 (m, 18 H); **^{13}C NMR** (100MHz, $CDCl_3$) 69.6, 71.6, 72.2, 72.7, 73.3, 74.8, 75.1, 75.2, 79.8, 92.8, 127.5, 127.6, 127.7, 127.9, 128.0, 128.3, 128.4, 128.6, 138.0, 138.3, 138.4, 138.5; **FT-IR** (KBr): *v* 3440, 1647, 1450, 1088, 749, 694 cm^{-1}; **ESI–MS** m/z 1103.9 $[2M+Na]^+$.

2,3,4,6-tetra-*O*-benzyl-*α*-D-mannopyranosyl froide (2.21): To a solution of **S2.3** (270 mg, 0.5 mmol) in dry THF (1.5 mL) was added DAST (79.3 μL, 0.6 mmol) in one portion at -30 °C under nitrogen. The reaction mixture was allowed to warm to room temperature and kept for 30 min, then cooled down to -30 °C and treated with methanol (0.5 mL). The mixture was concentrated and the residue was dissolved in DCM (5 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried with

anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:5) to afford **2.21** (230 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ = 23.8 (*c* 3.7, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 3.65 (dd, *J* 1.8, 10.0 Hz, 1H), 3.82 (dd, *J* 4.5, 11.0 Hz, 1H), 3.91-3.98 (m, 3H), 4.12 (dd, *J* 9.3, 9.5 Hz, 1H), 4.56 (d, *J* 12.3 Hz, 1H), 4.57 (d, *J* 10.8 Hz, 1H), 4.65-4.75 (m, 4H), 4.84 (d, *J* 12.3 Hz, 1H), 4.92 (d, *J* 10.8 Hz, 1H), 5.64 (d, *J* 9.6 Hz, 1H), 7.20-7.22 (m, 2H), 7.25-7.38 (m, 18H); **^{13}CNMR** (100MHz, $CDCl_3$) 68.7, 72.3, 73.3, 73.5, 73.7, 74.1 (d, $^2J_{CF}$ 16.2 Hz), 75.2, 79.2, 106.5 (d, $^1J_{CF}$ 220.5 Hz), 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 137.9, 138.1, 138.2, 138.3;**FT-IR** (KBr): *v* 2866, 2088, 1643, 1454, 1099, 736, 696 cm^{-1};**HR/MS (ESI)** calcd for $C_{34}H_{35}O_5FNa$ $[M+Na]^+$ 565.2366, found 565.2359.

Synthesis of glucosyl fluoride 2.24b. (According to the general procedure of preparation of **2.21**)



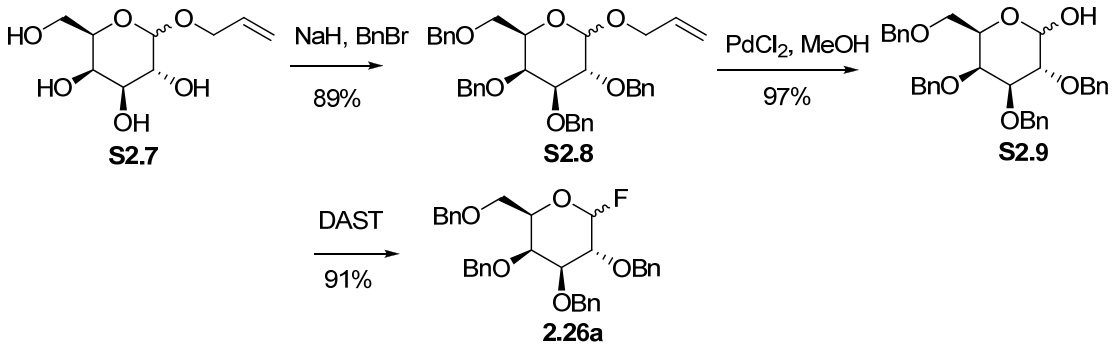
S2.14 S2.20 S2.21 2.26f

1-Allyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (S2.5): (α:β = 2:1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.49-3.71 (m, 6H), 3.98-4.03 (m, 1H), 4.15 (dd, *J* 5.2, 12.7 Hz, 1H), 4.43-4.48 (m, 2H), 4.62-4.65 (m, 2H), 4.67-4.85 (m, 3H), 4.92-5.01 (d, *J* 10.9 Hz, 1H), 5.19-5.37 (m, 2H), 5.90-5.96 (m, 1H),7.12-7.17 (m, 2H), 7.24-7.36 (m, 18H); **^{13}C NMR** (100MH_Z, $CDCl_3$) 68.2, 68.9, 70.3, 73.2, 74.9, 75.9, 77.4, 79.9, 82.1, 84.7, 95.7, 102.7, 118.2, 127.6, 127.7, 127.8, 127.9, 128.0; **FT-IR** (KBr): *v* 3089, 1635, 1454, 1070, 734, 696 cm^{-1}; **ESI–MS** m/z 603.5 $[M+Na]^+$.

2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (S2.6): (α:β = 1.7:1) **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.40-3.72 (m, 4H), 4.00 (dt, *J* 9.2, 9.8 Hz, 1H), 4.01-4.07 (m, 1H), 4.43-4.97 (m, 8H), 5.21 (d, *J* 2.4 Hz, 1H), 7.13-7.35 (m, 20H); **^{13}C NMR** (100MHz, $CDCl_3$): 68.7, 70.2, 73.2, 73.5, 75.1, 75.8, 77.9, 80.1, 81.8, 91.3, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.6, 137.9, 138.0, 138.3, 128.8; **FT-IR** (KBr): *v* 3439, 1645, 1452, 1085, 744, 694 cm^{-1}; **ESI–MS** m/z 1103.7 $[2M+Na]^+$.

2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl fluoride (2.24b): (α:β = 5:1). **^{1}H NMR** (100 MHz, $CDCl_3$) δ 3.57-3.62 (m, 2H), 3.65-3.76 (m, 4H), 4.52-4.97 (m, 8H), 5.26 (dd, *J* 6.6, 52.7 Hz, 1H), 7.13-7.15 (m, 2H), 7.26-7.36 (m, 18H); **^{13}C NMR** (100MHz, $CDCl_3$): 68.4, 73.7, 74.5, 74.9, 75.1, 75.5, 77.0, 81.5 (d, $^2J_{CF}$ 21.5 Hz), 109.9 (d, $^1J_{CF}$ 214.5 Hz), 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 137.8, 137.9, 138.0, 138.4 ppm; **FT-IR** (KBr): *v*, 2869, 2090, 1647, 1450, 1100, 746, 699 cm^{-1}; **HR/MS (ESI)** calcd for $C_{34}H_{35}O_5FNa$ $[M+Na]^+$ 565.2366, found 565.2357.

Synthesis of galactosyl fluoride 2.26a. (According to the general procedure of preparation of 2.21)



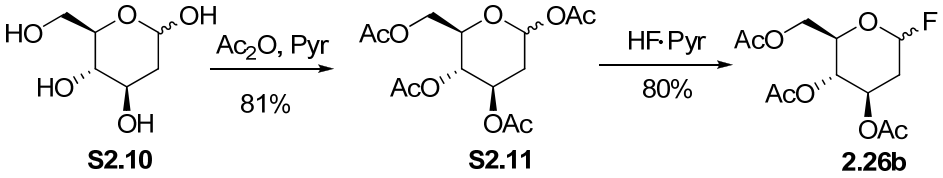
1-Allyl-2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside (S2.8): (α:β = 1.3:1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.52-3.60 (m, 2H), 3.97-3.99 (m, 2H), 4.03-4.04 (m, 1H), 4.14-4.17 (m, 1H), 4.29-4.97 (m, 9H), 5.16-5.20 (m, 1H), 5.26-5.34 (m, 1H), 5.90-5.91 (m,

1H), 7.12-7.17 (m, 2H), 7.24-7.36 (m, 18H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 68.3, 68.9, 69.4, 73.3, 73.4, 73.5, 74.8, 75.2, 76.5, 79.2, 82.3, 96.3, 118. 0, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 134.0, 138.1, 138.6, 138.7, 138.9 ppm; **FT-IR** (KBr): *v* 3079, 1645, 1459, 1071, 735, 699 cm^{-1}; **ESI–MS** m/z 603.2 $[M+Na]^+$.

2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (S2.9): (α:β = 1.7:1) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.08 (s, 1H), 3.41-3.59 (m, 3H), 3.88-3.93 (m, 1H), 4.04(dd, *J* 3.6, 10.9 Hz, 1H), 4.16 (dd, 1H, *J* 6.5, 6.4 Hz), 4.38-4.95 (m, 10H), 5,28 (br s, 1H), 7.13-7.34 (m, 20H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 68.9, 69.5, 72.9, 73.6, 74.7, 76.6, 78.7, 82.2, 91.9, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 137.9, 138.2, 138.4, 138.5, 138.6; **FT-IR** (KBr): *v* 3436, 1640, 1442, 1088, 747, 694 cm^{-1}; **ESI–MS** m/z 1103.5 $[2M+Na]^+$.

2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl fluoride (2.26a) (α:β = 3:5) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.52-3.54 (m,1H), 3.58-3.64 (m, 2H), 3.89-3.97 (m, 2H), 4.01-4.08 (m, 1H), 4.39 (d, *J* 11.7 Hz, 1H), 4.47 (d, *J* 12 Hz, 1H), 4.59 (d, *J* 11.3 Hz, 1H), 4.67-78 (m, 3H), 4.80 (d, *J* 11.3 Hz, 1H), 4.93(d, *J* 11.7 Hz, 1H), 5.17 (dd, *J* 53.1, 6.9 Hz, 1H), 7.17-7.38 (m, 20H); **^{13}C NMR** (75MHz, $CDCl_3$) δ 68.4, 73.1, 73.6, 74.6, 75.0, 78.4, 79.0 (d, $^2J_{CF}$ 20.6 Hz), 81.0, 110.2 (d, $^1J_{CF}$ 214.0 Hz), 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 137.7, 137.8, 138.1, 138.2, 138.4; **FT-IR** (KBr): *v* 3423, 2869, 2083, 1640, 1459, 1097, 738, 698 cm^{-1}; **HR/MS (ESI)** calcd for $C_{34}H_{35}O_5FNa$ $[M+Na]^+$ 565.2366, found 565.2365.

Synthesis of 2-deoxy glucosyl fluoride 2.26b.

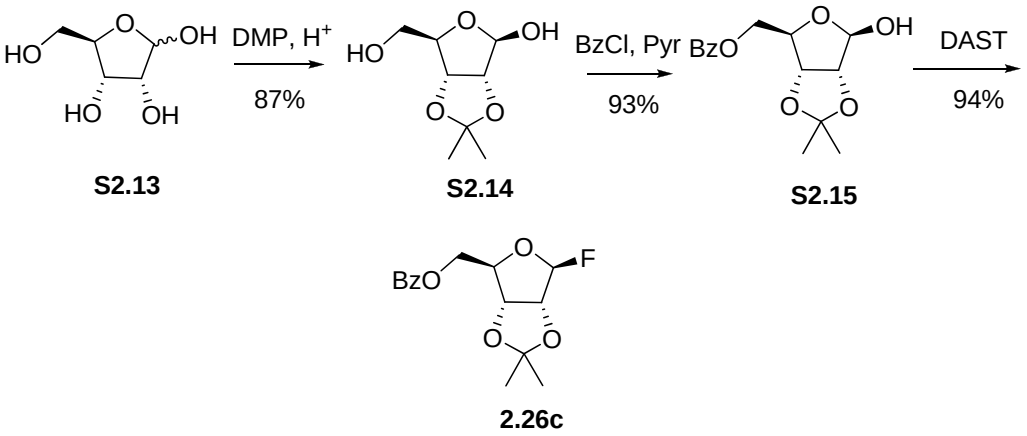


1,3,4,6-Tetra-*O*-acetyl-2-deoxy-D-glucopyranose (S2.11): To a stirred solution of 2-deoxyglucose (164 mg, 1 mmol) in dry pyridine (2 mL) was added dropwise Ac_2O (0.47 mL, 5 mmol) at 0 °C. The reaction mixture was kept at this temperature for 30 min, then allowed to warm to rt and stirred overnight. The reaction mixture was diluted with Et_2O (10 mL), washed with water (3 × 10 mL) and brine, the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **S2.11** (270 mg, 81%) as a white solid. (α:β =2:5). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.81-1.90 (m, 1H), 2.03 (s, 3H), 2.04 (s, 3H), 2.08 (s,3h), 2.11 (s, 3H), 2.34 (ddd, *J* 2.2, 4.7, 12.4 Hz, 1H), 3.74 (ddd, *J* 2.1, 4.7 9.3 Hz, 1H), 4.03-4.11(m, 1H), 4.31 (dd, *J* 4.6, 12.4 Hz, 1H), 4.99-5.10 (m, 2H), 5.79 (dd, *J* 2.2, 9.9 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 20.71, 20.78, 20.87, 20.97, 34.72, 61.93, 68.24, 70.21, 72.86, 91.07, 168.83, 169.78, 170.13, 170.75; **FT-IR** (KBr): ν 2978, 1745, 1645, 1633, 1369, 1226 cm^{-1}; **ESI–MS** m/z 355.0 $[2M+Na]^+$.

3,4,6-Tri-*O*-acetyl-2-deoxy-D-glucopyranosyl fluoride (2.26b)[31]: To a solution of HF·Pyr (70%, 1.4 mL) in dry pyridine (0.5 mL) was added **S2.11** (332 mg, 1 mmol) in toluene (1 mL) at 20 °C. The reaction mixture was stirred at 0 °C for 24h and then poured into a mixture of ether (5 mL) and saturated aqueous potassium fluoride (10 mL). The mixture was extracted with ether (10 mL × 2), the combined organic layers were washed with aqueous potassium fluoride (10 mL), saturated sodium

hydrogencarbonate (10 mL) and brine, dried with anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **2.26b** (234 mg, 80%) as a white solid. (α:β = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.75- 1.91 (m,1H), 1.99 (s, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 2.42-2.48 (m, 1H), 4.06-4.14 (m, 2H), 4.29 (dd, *J* 4.0, 12.1 Hz, 1H), 5.05 (t, *J* 9.8 Hz, 1H), 5.27 (ddd, *J* 5.4, 9.6, 11.5 Hz, 1H), 5.72 (d, *J* 50.9 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 20.6, 20.7, 20.8, 34.5 (d, $^2J_{CF}$ 26.2 Hz), 61.7, 67.9, 68.1, 70.2 (d, $^3J_{CF}$ 2.8 Hz), 105.8 (d, $^2J_{CF}$ 218.4 Hz), 169.7, 170.0, 170.6; **FT-IR** (KBr): ν 2962, 1741, 1732, 1435 cm^{-1}; **ESI–MS** m/z 272.6 $[M-F]^+$; 585.2 $[2M+Na]^+$.

Synthesis of ribofuranosyl fluoride 2.26c.



S2.13 **S2.14** **S2.15** **2.26c**

2,3-*O*-Isopropylidene-*β*-D-ribofuranose (S2.14): A suspension of D-ribose (1.0 g, 6.7 mmol) in dry acetone (20 mL) was treated with 2,2-dimethoxypropane (0.87 mL, 69 mmol) and *p*-toluenesulfonic acid (62.7 mg, 0.2 mmol). After being stirred at rt. for 1h, the clear resulting mixtures was neutralized with $NaHCO_3$, filtered through celite and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 mL), washed with H_2O (20 mL), and extracted with EtOAc (10 mL × 3), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel

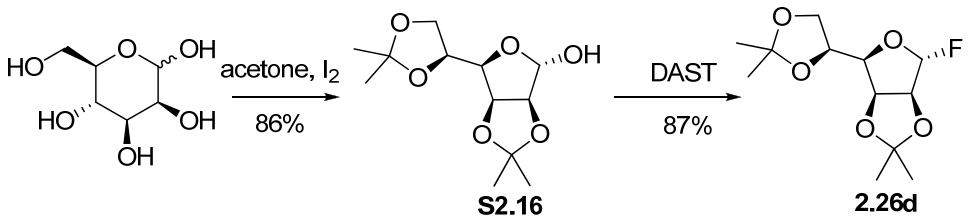
(EtOAc:hexane = 2:1) to afford **S2.14** (1.1 g, 87%) as a colorless oil. (α:β = 1:10). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.46 (s, 3H), 3.67-3.72 (m, 2H), 4.14 (br s, 1H), 4.36 (s, 1H), 4.54 (d, *J* 5.9Hz, 1H), 4.78 (d, *J* 5.9 Hz, 1H), 5.37 (s, 1H), 5.38 (br s, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 24.7, 26.3, 63.5, 81.6, 86.7, 87.6, 102.7, 112.1; **FT-IR** (KBr): *v* 3439, 2991, 2945, 1637, 1381, 1066 cm^{-1};

5-*O*-Benzoyl-2,3-*O*-isopropylidene-*β*-D-ribofuranose (S2.15): To a solution of **S2.14**(560 mg, 2.9mmol) in dry pyridine (5 mL) was added benzoyl chloride (0.38 mL, 3.2 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature, then diluted with diethyl ether (20 mL), washed with water (3 × 10 mL) and brine, the organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:4) to afford **S2.15** (812 mg, 93%) as a white solid. (α:β = 1:10). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.46 (s, 3H), 4.14 (s, 1H), 4.32-4.35 (m, 1H), 4.42-4.50 (m, 2H), 4.65 (d, *J* 5.9 Hz, 1H), 4.78 (d, *J* 5.9 Hz, 1H), 5.49 (s, 1H), 7.37-7.43 (m, 2H), 7.49-7.54 (m, 1H), 8.00-8.02 (m, 2H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 24.9, 26.5, 65.8, 82.1, 84.6, 85.9, 103.1, 112.6, 128.4, 129.8, 129.8, 133.2, 166.5; **FT-IR** (KBr): *v* 3439, 2987, 2943, 1720, 1645, 1452, 1070 cm^{-1}; **ESI–MS** m/z 317.1 $[M+Na]^+$.

4-*O*-Benzoyl-2,3-*O*-isopropylidene-*β*-D-ribofuranosyl fluoride (2.26c): To a solution of **S2.15** (180 mg, 0.6 mmol) in dry THF (2 mL) was added DAST (96.4.3 μL, 0.7 mmol) in one portion at -30 °C under nitrogen. The mixture was allowed to warm to rt. and kept for 30 min, then cooled down to -30 °C and treated with methanol (0.7 mL). The mixture was concentrated and the residue was dissolved in DCM (5 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried with

anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:5) to afford **2.26c** (170 mg, 94%) as a colorless oil. (α:β = 1:9). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.48 (s, 3H), 4.36-4.43 (m, 2H), 4.66-4.69 (m, 1H), 4.86 (d, *J* 5.9 Hz, 2H), 5.82 (d, *J* 61.8 Hz, 1H), 7.44 (t, *J* 7.6 Hz, 2H), 7.56 (t, *J* 7.6 Hz, 1H), 8.06 (d, 7.6 Hz, 2H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 24.9, 26.3, 64.6, 81.0, 85.0 (d, $^2J_{CF}$ 40.5 Hz), 86.4 (d, $^3J_{CF}$ 2.7 Hz), 113.2, 115.3 (d, $^1J_{CF}$ 221.8 Hz), 128.5, 129.6, 129.8, 133.3, 166.1; **FT-IR** (KBr): ν 2989, 2941, 1724, 1635, 1452, 1273, 1093, 711 cm^{-1}; **ESI–MS** m/z 277.0 $[M-F]^+$; 319.1 $[M+Na]^+$.

Synthesis of mannofuranosyl fluoride 2.26d.

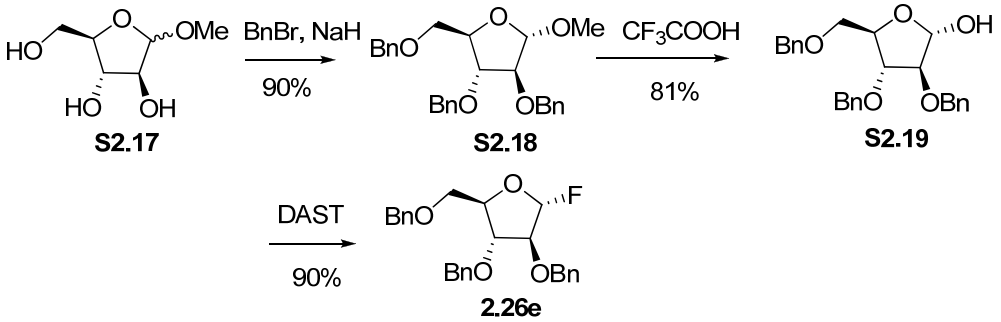


2,3;5,6-Di-*O*-isopropyldene-D-mannofuranose (S2.16): To a solution of D-mannose (540 mg, 3.0 mmol) in acetone (20 mL) was added iodine (154 mg, 0.6 mmol). The mixture was stirred for 2h at rt., and then quenched at 0 °C with aqueous sodiumthiosulfate and sodium bicarbonate. The organic solvent was evaporated, the aqueous solution was extracted with Et_2O (10 mL × 3), the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4 and concentrated. The residue was crystallized from acetone/hexane to produce **S2.16** (670 mg, 86%) as a white solid. (α:β = 8:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.37 (s, 3H), 1.45 (s, 6H), 3.3 (br s, 1H), 4.02-4.09 (m, 2H), 4,17 (dd, *J* 3.6, 7.1 Hz, 1H), 4.40 (dd, *J* 6.0, 12.0 Hz, 1H), 4.60 (d, *J* 5.9 Hz, 1H), 4,80 (dd, *J* 3.8, 5.8 Hz, 1H), 5.37 (d, *J* 2.2 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 24.4, 25.1, 25.8, 26.8, 66.5, 73.3, 79.6, 80.1, 85.5,

101.2, 109.12, 112.6; **FT-IR** (KBr): *v* 3421, 2985, 2945, 1203, 1062 cm^{-1}; **ESI–MS** m/z 283.1 $[M+Na]^+$.

2,3;5,6-Di-*O*-isopropyldene-*α*-D-mannofuranosyl fluoride (2.26d): To a solution of **S2.16** (260 mg, 1.0 mmol) in dry THF (3 mL) was added DAST (0.16 m L, 1.2 mmol) in one portion at 30 °C under nitrogen. The mixture was allowed to warm to room temperature and kept for 30 min, then cooled to 30 °C and treated with methanol (1.0 mL). The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (5 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and then concentrated. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:5) to afford **2.26d** (228 mg, 87%) as a colorless oil. $[\alpha]_D^{20}$ = – 6.8 (c 0.4, $CHCl_3$); **^{1}HNMR** (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.37 (s, 3H), 1.45 (s, 6H), 4.05-4.14 (m, 2H), 4.17 (dd, *J* 3.4, 7.6 Hz, 1H), 4.41 (dd, *J* 6.2, 12.1 Hz, 1H), 4.78 (t, *J* 6.2 Hz, 1H), 4.85 (dd, *J* 3.4, 5.7 Hz, 1H), 5.69 (d, *J* 59.4 Hz, 1H,); **^{13}CNMR** (100 MHz, $CDCl_3$) δ 24.5, 25.2, 25.8, 26.9, 66.7, 72.7, 78.6, 82.6, 84.7 (d, $^2J_{CF}$ 41.5 Hz), 109.4, 113.2, 113.7 (d, $^1J_{CF}$ 220.1 Hz); **FT-IR** (KBr): *v* 2987, 2939, 1373, 1068, 970 cm^{-1}; **ESI–MS** m/z 243.1 $[M-F]^+$; 262.8 $[M+H]^+$.

Synthesis of arabinosyl fluoride 2.26e.



2,3,5-Tri-*O*-benzyl-1-methyl-α-D-arabinofuranoside (S2.18): To a suspension of NaH (60% in oil, 1.6g, 40 mmol) in DMF (20 mL) was added dropwise a solution of **S17** (1.6 g, 10 mmol) in DMF (20 mL) carefully at 0 °C. The reaction mixture was stirred for 30 min, and then BnBr (5.9 mL, 50 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight, then carefully quenched with H_2O at 0 °C, diluted with Et_2O (100 mL) and washed with water (40 mL × 3). The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:10) to afford **S2.18** (3.9 g, 90 %) as a white solid. (α:β = 8:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.59-3.62 (m,2H), 3.88-3.91 (m, 1H), 3.98-3.99 (m, 1H), 4.18-4.22 (m, 1H), 4.43-4.56 (m, 6H), 4.95 (s, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 55.0, 69.9, 71.9, 72.1, 73.4, 80.9, 83.5, 88.1, 107, 3, 127.6, 127.8, 127.8, 127.9, 128.4, 128.4, 128.5, 137.6, 138.9, 138.1; **FT-IR** (KBr): *v* 2929, 2906, 1627, 1496, 1454, 1359, 1087, 734, 696 cm^{-1}; **ESI–MS** m/z 457.1 $[M+Na]^+$.

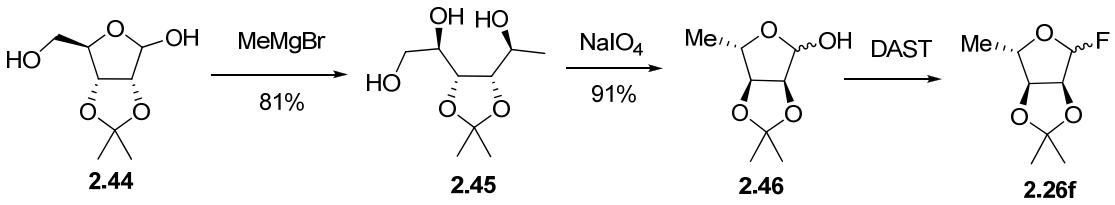
2,3,5-Tri-*O*-benzyl-α-D-arabinofuranoside (S2.19): To a solution of **S2.18** (1.3 g, 3.0 mmol) in MeCN/H_2O (4/1, 21 mL) was added CF_3COOH (0.2 mL, 3 mmol). The reaction mixture was stirred overnight then quenched with aqueous saturated $NaHCO_3$, extracted with dichloromethane, the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:3) to afford **S2.19** (1.0 g, 81 %) as a white solid. (α:β = 10:1). **^{1}H NMR** (400 MHz, CDCl3) δ 3.49-3.54 (m,1H), 3.55-3.63 (m, 1H), 4.02 (dd, *J* 4.5, 4.6 Hz, 1H), 4.09 (dd, *J* 4.3, 8.7 Hz, 1H), 4.17 (t, *J* 4.6 Hz, 1H), 4.44-4.67 (m, 6H), 5.33 (dd, *J* 4.3, 9.9 Hz, 1H), 7.25-7.29 (m, 15H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 70.5, 72.1,

72.3, 73.6, 80.6, 82.1, 82.7, 84.1, 86.4, 96.2, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.4, 128.4, 128.5, 137.0, 137.4, 137.8; **FT-IR** (KBr): *v* 3419, 2866, 1643, 1496, 1454, 1207, 1099, 736, 696 cm^{-1}; **ESI–MS** m/z 443.2 $[M+Na]^+$.

2,3,5-Tri-*O*-benzyl-*α*-D-arabinofuranosyl fluoride 2.26e: (According to the general procedure of preparation of **2.21**) (α:β = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.56-3.62 (m, 2H), 3.96 (d, 3.9 Hz, 1H), 4.14-4.16 (m, 1H), 4.45 (s, 2H), 4.47 (s, 2H), 4.53 (s, 2H), 5.77 (d, *J* 61.5 Hz, 1H), 7.18-7.35 (m, 15H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 69.5, 72.2, 72.2, 73.5, 82.6, 84.2, 86.9 (d, $^2J_{CF}$ 33.4 Hz), 113.6 (d, $^1J_{CF}$ 223.5 Hz) 127.8, 127.8, 127.9, 127.9, 128.1, 128.2, 128.5, 128.5, 128.6, 137.0, 137.5, 138.0;

FT-IR (KBr): *v* 2090, 1724, 1635, 1271, 711 cm^{-1}; **HR/MS (ESI)** calcd for $C_{26}H_{27}O_4FNa[M+Na]^+$ 445.1791, found 445.1797.

Prepare of furanosyl fluoride 2.26f



(R)-1-((4R,5S)-5-((S)-1-Hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (2.45): To a solution of **2.44** (190 mg, 1.0 mmol) in dry diethyl ether (3 mL) was added droppwise MeMgBr (3M in diethyl ether ,1.7 mL, 5 mmol) carefully at -40 °C. The reaction mixture was stirred for 3h at this temperature, then allowed to warm to root temperature and stirred overnight. the reaction mixture was carefully quenched with saturated aqueous NH_4Cl at 0 °C, the precipitate was filtered and the filtrate was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was

purified by flash column chromatography on silica gel (EtOAc:hexane = 2:1) to afford **2.45** (178 mg, 81%) as a colorless oil. $[\alpha]_D^{20}$ = 30.9 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.38 (d, *J* 6.7 Hz, 1H), 3.06 (br s, 1H), 3.67-3.72 (m, 1H), 3.85-3.88 (m, 2H), 3.91-4.03 (m, 2H), 4.10 (dd, *J* 5.2, 9.0 Hz, 1H), 4.53 (br s, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 20.6, 25.4, 28.0, 64.3, 65.9, 69.6, 77.3, 81.7, 108.7; **FT-IR** (KBr): ν 3439, 2989, 1639, 1066cm^{-1}; **ESI–MS** m/z 413.2 $[2M+H]^+$.

4-Deoxy-2,3-*O*-isopropylidene-L-ribofuranose (2.46): To a solution of **2.45** (1.3 g, 5.9 mmol) in THF/H_2O (9/1, 20 mL) was added $NaIO_4$ (1.89g, 8.9 mmol) at 0 °C in portions. The reaction mixture was then allowed to warm to room temperature and stirred for 2h, quenched with aqueous $Na_2S_2O_3$ and extracted with DCM (3 × 10 mL), the combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:2) to afford **2.46** (0.93g, 91%) as a colorless oil. (α:β = 8:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.34 (d, *J* 7.0 Hz, 3H), 1.47 (s, 3H), 3.30 (d, *J* 2.1 Hz, 1H), 4.35 (d, *J* 7.0 Hz, 1H), 4.55 (d, *J* 5.9 Hz, 1H), 4.66 (d, *J* 5.9 Hz, 1H), 5.42 (s, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 21.7, 24.9, 26.3, 83.3, 85.5, 86.4, 103.3; **FT-IR** (KBr): ν 3419, 2983, 2939, 1645, 1375, 1070 cm^{-1}.

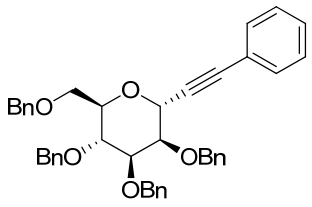
4-Deoxy-2,3-*O*-isopropylidene-L-ribofuranosyl fluoride (2.26f): To a solution of **2.46** (52mg, 0.3 mmol) in dry DCM (1 mL) was added DAST (51 μL, 0.4 mmol) at -30 °C under nitrogen. The mixture was allowed to warm to rt. and kept for 30 min, then cooled to -30 °C and treated with methanol (0.3mL). The r mixture was carefully washed with ice water (0.5 mL) and cold saturated aqueous $NaHCO_3$ and brine, the organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated under

reduced pressure to afford **2.26f** (228 mg, 87%) as a colorless oil which used in the next step immediately without further purification.

Prepare of *C*-glycosides. General procedure A: To a solution of glycosyl fluoride (0.2 mmol) and organotrifluoroborate (1.2 equiv) in acetonitrile (1 mL) was added $BF_3{\cdot}OEt_2$ (1.3 equiv) at rt. The reaction was carried out at rt for 20 min, then quenched with triethylamine (1.5 euiv), filtered and concentrated. The residue was purified by flash column chromatography on silica gel.

General procedure B: To a solution of glycosyl fluoride (0.2 mmol) and organotrifluoroborate (2.0 equiv) in acetonitrile (1 mL) was added $BF_3{\cdot}OEt_2$ (2.2 equiv) at 40 °C. The reaction was carried out at 40 °C for 6h, then quenched with triethylamine (1.5 euiv), filtered and concentrated. The residue was purified by flash column chromatography on silica gel.

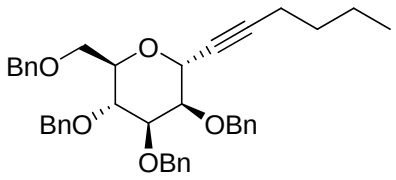
General procedure C: Premixing of $BF_3{\cdot}OEt_2$ (2.2 equiv) and organotrifluoroborate (2.0 equiv) in acetonitrile (1 mL) followed by addition of glycosyl fluoride (0.2 mmol) at 40 ºC, the reaction was carried out at 40 °C for 6 h, then quenched with TEA (1.5 euiv), filtered and concentrated. The residue was purified by flash column chromatography on silica gel.



2.20c

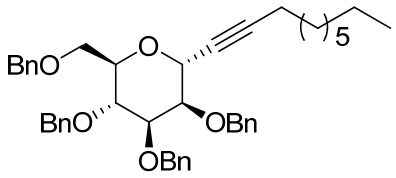
(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(phenylethynyl)tetrahydro-2*H*-pyran (2.20c): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = 77.8 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (300

MHz, $CDCl_3$): δ 3.75 (d, *J* 10.3 Hz, 1H), 3.83 (dd, *J* 3.3, 10.3 Hz, 1H), 3.91 (t, 2.4 Hz, 1H), 4.03 (m, 2H), 4.07-4.10 (m, 2H), 4.54 (d, *J* 10.6 Hz, 1H), 4.55 (d, *J* 12.2 Hz, 1H), 4.64 (s, 2H), 4.66 (d, *J* 12.2 Hz, 1H), 4.70 (d, *J* 12.6 Hz, 1H), 4.80 (d, *J* 12.6 Hz, 1H), 4.90 (d, *J* 10.6 Hz, 1H), 5.04(d, *J* 2.1 Hz, 1H), 7.16-7.19 (m, 2H), 7.23-7.36 (m, 21H), 7.40-7.44 (m, 2H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 66.7, 69.3, 71.9, 72.0, 73.5, 74.9, 75.0, 76.6, 80.0, 83.8, 89.1, 121.9, 127.5, 128.0, 128.2, 128.3, 128.4, 128.8, 131.8, 138.1, 138.3, 138.4; **FT-IR** (KBr): *v* 3421, 2868, 2067, 1637, 1095, 734, 696 cm^{-1}; **HR/MS (ESI)** calcd for $C_{42}H_{40}O_5Na$ $[M+Na]^+$ 647.2773, found 647.2779.



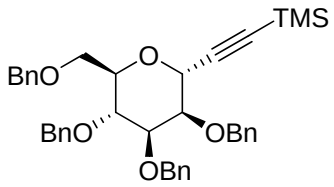
2.22b

(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(hex-1-ynyl)tetrahydro-2*H*-pyran (2.22b): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = 36.8 (*c* 3.24, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* 7.2 Hz), 1.30-1.39 (m, 2H), 1.40-1.47 (m, 2H), 2.15 (t, *J* 6.2 Hz, 2H), 3.72-3.75(m, 1H), 3.79-3.83 (m, 2H), 3.96-4.00 (m, 2H), 4.02- 4.05 (m, 1H), 4.52 (d, *J* 10.6 Hz, 1H), 4.54 (d, *J* 11.9 Hz, 1H), 4.60 (s, 2H), 4.67 (d, *J* 11.9 Hz, 1H), 4.68 (d, 12.6 Hz, 1H), 4.76 (d, *J* 12.6 Hz, 1H), 4.83, (s, 1H), 4.89 (d, *J* 10.6 Hz, 1H), 7.16-7.18 (m, 2H), 7.26-7.36 (m, 16H), 7.37-7.41 (m, 2H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 13.6, 18.5, 22.0, 30.5, 66.4, 69.3, 71.7, 71.9, 73.4, 74.4, 74.8, 75.1, 75.3, 76.7, 80.2, 90.1, 127.5, 127.6, 127.7, 127.8, 127.9 (2C), 128.1, 128.3, 128.4, 128.2, 138.4, 138.5; **FT-IR** (KBr): *v* 3417, 2868, 2085, 1643, 1095, 734, 696 cm^{-1}; **HR/MS (ESI)** calcd for $C_{40}H_{45}O_5$ $[M+H]^+$, 605.3267, found 605.3278.



2.22c

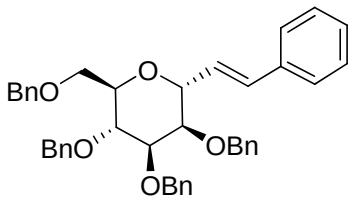
(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(dec-1-ynyl)tetrahydro-2*H*-pyran (2.22c): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = 36.3 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* 6.8 Hz), 1.24-1.32 (m, 10H), 1.40-1.46 (m, 2H), 2.14 (t, *J* 7.2 Hz, 2H), 3.72-3.74(m, 1H), 3.78-3.82 (m, 2H), 3.93-3.98 (m, 2H), 4.00- 4.05 (m, 1H), 4.52 (d, *J* 10.6 Hz, 1H), 4.55 (d, *J* 11.8 Hz, 1H), 4.61 (s, 2H), 4.67 (d, *J* 11.8 Hz, 1H), 4.68 (d, 12.6 Hz, 1H), 4.77 (d, *J* 12.6 Hz, 1H), 4.83, (s, 1H), 4.90 (d, *J* 10.6 Hz, 1H), 7.17-7.20 (m, 2H), 7.26-7.36 (m, 16H), 7.37-7.41 (m, 2H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 14.1, 18.8, 22.6, 28.5, 29.0, 29.1, 29.2, 31.8, 66.3, 71.7, 73.4, 74.4, 75.1, 75.3, 80.3, 90.1, 127.4, 127.6, 127.8, 127.9, 128.1, 128.3, 128.4, 138.2, 128.4, 138.5; **FT-IR** (KBr): *v* 2926, 2856, 2067, 1637, 1454, 1097, 734, 696 cm^{-1}; **HR/MS** (ESI) calcd for $C_{44}H_{53}O_5$ $[M+H]^+$ 661.3893, found 661.3892.



2.22d

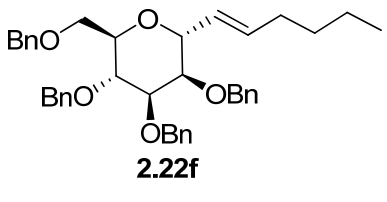
(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(2-trimethylsilylethynyl)tetrahydro-2*H*-pyran (2.22d): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = 45.8 (*c* 3.17, $CHCl_3$); **^{1}H NMR** (400 MHz, CDCl3): δ 0.13 (s, 9H), 3.70-3.73 (m, 3H), 3.79-3.83 (m, 2H), 3.94-3.98(m, 1H), 3.99-4.02 (m, 2H), 4.53 (d, *J* 11.4 Hz, 2H), 4.62 (s, 2H), 4.66 (d, *J* 12.5 Hz, 1H), 4.67 (d, *J* 12.0 Hz, 1H), 4.74 (d, 12.5 Hz, 1H), 4.82 (d, *J* 1.8 Hz, 1H), 4.89 (d, 10.6

Hz, 1H), 7.17-7.19 (m, 2H), 7.23-7.40 (m, 18H); **^{13}C NMR** (100MHz, $CDCl_3$): δ -0.2, 66.7, 69.2, 71.8, 72.1, 73.4, 74.7, 74.9, 75.4, 80.0, 94.5, 100.1, 127.5, 127.6, 127.7, 127.8, 127.9 (2C), 128.2, 128.3, 128.4(2C), 138.2, 138.3, 138.4, 138.5;.**FT-IR** (KBr): *v* 2956, 2167, 1637, 1496, 1097, 844, 696 cm^{-1}; **HR/MS (ESI)** calcd for $C_{39}H_{44}O_5SiNa$ $[M+Na]^+$ 643.2856, found 643.2850.



2.22e

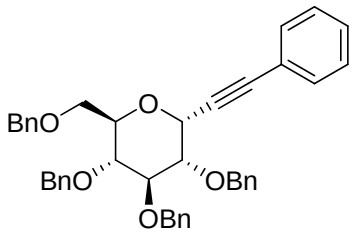
(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-styryltetrahydro-2*H*-pyran (2.22e): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = 36.8 (*c* 1.75, $CHCl_3$); **^{1}H NMR** (400 MHz, CDCl3): δ 3.74-3.82 (m, 4H), 3.93-3.98 (m, 2H), 4.52 (d, *J* 11.0 Hz, *1*H), 4.57 (d, *J* 12.5 Hz, 1H), 4.60 (s, 2H), 4.64 (d, *J* 12.5 Hz, *1*H), 4.70 (d, *J* 10.0 Hz, 2H), 4.73 (d, *J* 5.1 Hz, 1H), 4.77 (d, *J* 11.0 Hz, 1H), 6.13 (dd, *J* 5.1, 16.2 Hz, 1H), 6.52 (d, *J* 16.2 Hz, 1H), 7.16-7.20 (m, 3H), 7.21-7.34 (m, 20H), 7.35-7.40 (m, 2H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 69.4, 71.9, 72.3, 73.4, 73.4, 74.1, 74.4, 75.2, 76.5, 78.3, 125.4, 126.4, 127.5, 127.7, 127.6, 127.8, 127.9, 127.9, 128.0, 128.3, 128.4, 128.4, 128.6, 132. 9, 136.4, 138.3, 138.4; **FT-IR** (KBr): *v* 3420, 2864,2104, 1637, 1494, 1095, 689 cm^{-1}; **HR/MS (ESI)** calcd for $C_{42}H_{42}O_5Na$ $[M+Na]^+$ 649.2930, found 649.2938.



2.22f

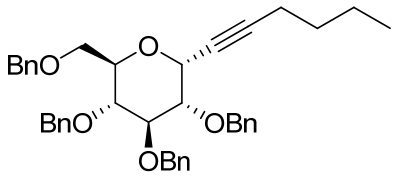
(2*R*,3*R*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-((*E*)-hex-1-enyl)tetrahydro-2*H*-pyran (2.22f): The compound was prepared according to the

general procedure A. $[\alpha]_D^{20}$ = 26.9 (*c* 1.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* 6.7 Hz), 1.26-1.31 (m, 4H), 1.97-1.99 (m, 2H), 3.69 (t, *J* 3.2 Hz, 1H), 3.70-3.76 (m, 3H), 3.80 (m, 1H), 3.92 (t, *J* 8.1 Hz, 1H), 4.50 (d, *J* 11.0 Hz, 1H), 4.53-4.56 (m, 2H), 4.57 (s, 2H), 4.62 (d, *J* 12.2 Hz, 1H), 4.65 (d, *J* 12.4 Hz, 1H), 4.72 (d, *J* 12.4 Hz, 1H), 4.79 (d, *J* 11.0 Hz, 1H), 5.41 (dd, *J* 5.3, 14.4 Hz, 1H), 5.55-5.63 (m, 1H), 7.16-7.18 (m, 2H), 7.24-7.39 (m, 18H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 13.9, 22.2, 31.0, 32.2, 69.5, 71.7, 72.0, 73.3, 73.7, 73.9, 74.6, 75.3, 76.4, 78.6, 125.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 135.3, 138.4, 138.5; **FT-IR** (KBr): *v* 3421, 2926, 2091, 1637, 1454, 1093, 696 cm^{-1}; **HR/MS (ESI)** calcd for $C_{40}H_{46}O_5Na$ [M+Na]+, 629.3243, found 629.3233.



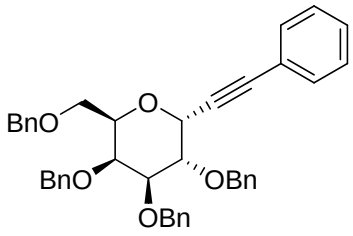
2.25a

(2*R*,3*R*,4*R*,5*S*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(phenylethynyl)tetrahydro-2*H*-pyran (2.25a): The compound was prepared according to the general procedure C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.67-3.82 (m, 4H), 4.02 (d, *J* 9.3 Hz, 1H), 4.06-4.10 (m, 1H), 4.52 (d, *J* 12.1 Hz, 1H), 4.53 (d, *J* 8.7 Hz, 1H), 4.65 (d, *J* 12.1 Hz, 1H), 4.76 (s, 2H), 4.86 (m, 2H), 5.03 (d, 1H, *J* 10.8 Hz), 5.04 (d, *J* 5.4 Hz, 1H), 7.16-7.19 (m, 2H), 7.28-7.42 (m, 21H), 7.46-7.51 (m ,2H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 67,2, 68.7, 72.8, 73.6, 75.3, 75.7, 77.8, 79.3, 83.2, 83.9, 89.4, 122.4, 127.6, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5, 128.7, 132.1, 137.9, 138.0, 138.1, 138.2, 138.3, 138.8; **FT-IR** (KBr): *v* 3032, 2096, 1637, 1452, 1087, 734, 696 cm^{-1}; **HR/MS (ESI)** calcd for $C_{42}H_{40}O_5Na$ $[M+Na]^+$ 647.2773, found 647.2776.



2.25b

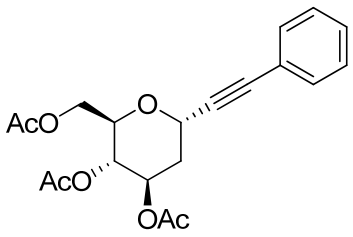
(2*R*,3*R*,4*R*,5*S*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(hex-1-ynyl)tetrahydro-2*H*-pyran (2.25b): The compound was prepared according to the general procedure C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.90 (t, *J* 7.3 Hz, 3H), 1.38-1.46 (m, 2H), 1.47-1.55 (m, 2H), 2.26 (t, *J* 6.9 Hz, 2H), 3.58-3.70 (m, 3H), 3.74 (dd, *J* 3.5, 10.8 Hz, 1H), 3.92 (d, *J* 9.3 Hz, 1H), 3.95-4.00 (m, 1H), 4.48 (d, *J* 11.5 Hz, 2H), 4.60 (d, *J* 12.2 Hz, 1H), 4.69 (m, 2H), 4.79-4.84 (m, 3H), 4.98 (d, *J* 10.9 Hz, 1H), 7.13-7.15 (m, 2H), 7.25-7.37 (m, 18 H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 13.6, 18.7, 22.0, 30.7, 66.8, 68.6, 72.6, 73.2, 73.5, 74.5, 75.2, 75.6, 77.6, 79.3, 83.1, 90.4, 127.6, 127.7, 127.8, 127.9, 128, 128.4, 138.0, 138.2, 138.3, 138.8 ppm; **FT-IR** (KBr): *v* 3419, 2860, 2087, 1640, 1098, 740, 699 cm^{-1}; **HR/MS (ESI)** calcd for $C_{40}H_{44}O_5Na$ $[M+Na]^+$ 627.3086, found 627.3086.



2.27a

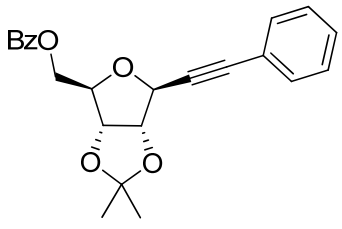
(2*R*,3*S*,4*R*,5*S*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(phenylethynyl)tetrahydro-2*H*-pyran (2.27a): The compound was prepared according to the general procedure A. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.55-3.57 (m, 2H), 3.95 (dd, *J* 2.5, 9.8 Hz, 1H), 3.99 (s, 1H), 4.15 (dd, *J* 5.7, 10.5 Hz, 1H), 4.19-4.21 (m, 1H), 4,41 (d, *J* 11.8 Hz, 1H), 4.49 (d, *J* 11.8 Hz, 1H), 4.59 (d, *J* 11.5 Hz, 1H), 4.75 (d, *J* 11.9 Hz, 1H), 4.78 (s, 1H), 4.84 (d, *J* 11.9 Hz, 1H), 4.95 (d, *J* 11.5 Hz, 1H), 5.04

(d, *J* 5.7 Hz, 1H), 7.24-7.43 (m, 25H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 67.86, 68.76, 7 2.70, 72.86, 73.05, 73.51, 74.90, 75.71, 77.36, 79.84, 84.34, 88.23, 122.58, 127.50, 127.61, 127.75, 127.98, 128.23, 128.25, 128.31, 128.35, 128.41, 128.52, 132.02, 137.92, 138.55, 138.63, 138.74; **FT-IR** (KBr): *v* 3033, 2098, 1647, 1457, 1080, 734, 696 cm^{-1}; **HR/MS (ESI)** calcd for $C_{42}H_{40}O_5Na$ $[M+Na]^+$ 647.2773, found 647.2770.



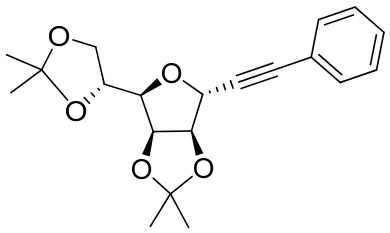
2.27b

(2*R*,3*S*,4*R*,6*S*)-2-(Acetoxymethyl)-6-(phenylethynyl)tetrahydro-2*H*-pyran-3,4-diyl diacetate (2.27b): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = 99.7 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.03 (s, 3H), 2.04-2.08 (m, 1H), 2.08 (s, 3H), 2.33 (ddd, *J* 1.2, 5.0, 12.8 Hz, 1H), 4.09 (dd, *J* 2.0, 12.3 Hz, 1H), 4.22 (ddd, *J* 2.0, 4.2, 9.9 Hz, 1H), 4.33 (dd, *J* 4.2, 12.3 Hz, 1H), 5.00 (t, *J* 9.7 Hz, 1H), 5.06 (d, *J* 4.6 Hz, 1H), 5.42 (ddd, *J* 5.0, 9.5, 11.5 Hz, 1H), 7.29-7.34 (m, 3H), 7.45-7.48 (m, 2H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 20.7, 20.8, 21.0, 35.4, 62.4, 64.5, 69.3, 70.0, 71.2, 84.5, 88.6, 121.8, 128.4, 129.0, 131.9, 169.9, 170.2, 170.8; **FT-IR** (KBr): *v* 3419, 2108, 1744, 1643, 1367, 1228, 692 cm^{-1}; **HR/MS (ESI)** calcd for $C_{20}H_{22}O_7Na$ $[M+Na]^+$ 397.1263, found 397.1263.



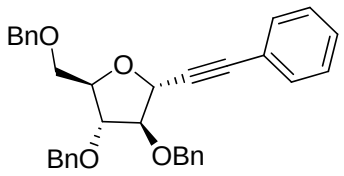
2.27c

((3a*R*,4*R*,6*S*,6*aS*)-2,2-Dimethyl-6-(phenylethynyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl benzoate (2.27c): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = – 61.7 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.57 (s, 3H), 4.48-4.56 (m, 2H), 4.62 (dd, *J* 6, 11.2 Hz, 1H), 4.87 (d, *J* 5.2 Hz, 1H), 4.98 (s, 2H), 7.25-7.32 (m, 3H), 7.37-7.42 (m, 4H), 7.54 (t, 1H, *J* 7.2 Hz), 8.07 (d, 2H, *J* 7.9 Hz); **^{13}C NMR** (100MZ, $CDCl_3$): δ 25.4, 26.9, 64.3, 75.4, 83.0, 83.7, 86.2, 86.5, 87.3, 114.0, 122.0, 128.3, 128.4, 128.7, 129.7, 129.8, 131.7, 133.2, 166.2; **FT-IR** (KBr): *v* 2096, 1720, 1643, 1271, 1070, 711, 696 cm^{-1}; **HR/MS** (ESI) calcd for $C_{23}H_{22}O_5Na$ $[M+Na]^+$ 401.1365, found 401.1369.



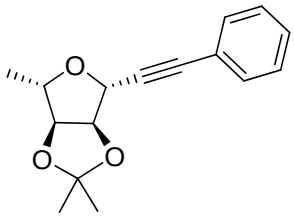
2.27d

(3a*S*,4*R*,6*R*,6a*R*)-4-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-(phenylethynyl)tetrahydrofuro[3,4-*d*][1,3]dioxole (2.27d): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = - 2.9 (c 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 1.50 (s, 3H), 4.00 (dd, *J* 4.2, 10.8 Hz, 1H), 4.06-4.16 (m, 2H), 4.44 (ddd, *J* 6.8, 7.7, 10.3 Hz, 1H), 4.85-4.92 (m, 2H), 4.94 (s, 1H), 7.28-7.34 (m, 3H), 7.40-7.44 (m, 2H); **^{13}CNMR** (100MHz, $CDCl_3$): δ 24.7, 25.2, 25.9, 26.9, 67.0, 73.1, 74.5, 80.5, 81.3, 84.7, 86.4, 87.3, 109.2, 112.9, 122.1, 128.3, 128.8, 131.8; **FT-IR** (KBr): *v* 3410, 2985, 2096, 1635, 1379, 1076, 758 cm^{-1}; **HR/MS (ESI)** calcd for $C_{20}H_{24}O_5Na$ $[M+Na]^+$ 367.1521, found 367.1523.



2.27e

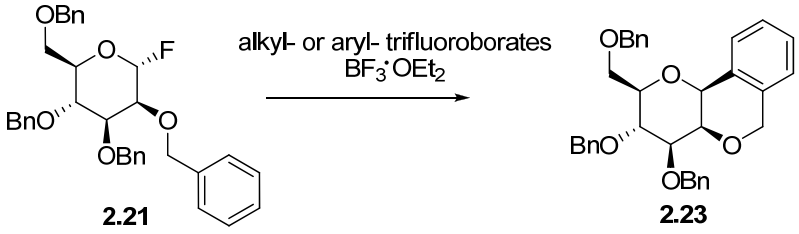
(2*R*,3R,4*R*,5*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-(phenylethynyl)tetrahydrofuran (2.27e): The compound was prepared according to the general procedure A. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.60-3.66 (m, 2H), 4.08 (dd, 1H, *J* 3.5, 5.3 Hz), 4.30-4.33 (m, 2H), 4.50-4.60 (m, 5H), 4.69 (d, *J* 11.8 Hz, 1H), 4.94 (d, *J* 3.5 Hz, 1H), 7.22-7.34 (m, 18 H), 7.40-7.43 (m, 2H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 69.9, 72.1, 72.7, 73.5, 81.5, 84.4, 86.5, 86.8, 88.9, 122.5, 127.6, 127.8, 127.9, 128.3, 128.4, 128.5, 131.8, 137.5, 137.9, 138.1; **FT-IR** (KBr): *v* 3080, 2358, 1635, 1490, 1097, 736, 696 cm^{-1}; **HR/MS** (ESI) calcd for $C_{34}H_{32}O_4Na$ $[M+Na]^+$ 527.2198, found 527.2194.



2.27f

(3a*S*,4*S*,6*R*,6a*R*)-2,2,4-Trimethyl-6-(phenylethynyl)tetrahydrofuro[3,4-*d*][1,3]dioxole (2.27f): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = 69.1 (*c* 1.38, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.42 (d, *J* 6.7 Hz, 3H), 1.54 (s, 3H), 4.19 (dq, *J* 2.9, 6.7 Hz, 1H), 4.51 (dd, *J* 2.9, 6.5 Hz, 1H), 4.79 (d, *J* 3.1 Hz, 1H), 4.91 (dd, *J* 3.1, 6.5 Hz, 1H), 7.29-7.31 (m, 3H), 7.41-7.43 (m, 2H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 19.3, 25.3, 27.0, 74.5, 81.9, 86.3, 86.6, 86.8, 86.9, 114.2, 122.3, 128.3, 128.6, 131.7; **FT-IR** (KBr): *v* 2985, 2096, 1637,

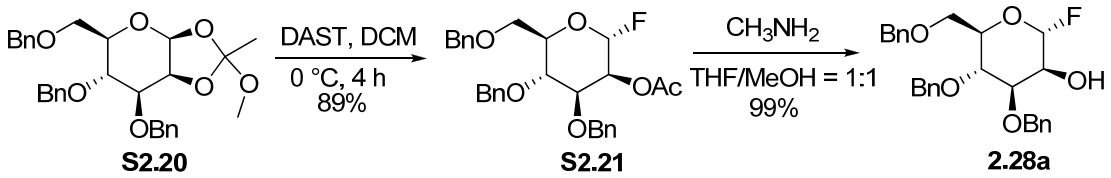
1381, 1074, 758 cm^{-1}; HR/MS (ESI) calcd for $C_{16}H_{19}O_3$ $[M+H]^+$,259.1334, found 259.1336.



(2*R*,3*R*,4*R*,4a*R*,10b*S*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,6,10b-hexahydropyrano[3,2-*c*]isochromene (2.23): The compound was prepared according to the general procedure A. $[\alpha]_D^{20}$ = 31.4 (*c* 0.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.54 (dd, , *J* 2.4, 9.8 Hz, 1H), 3.60-3.65 (m, 2H), 3.68-3.73 (m, 2H), 3.97 (t, *J* 9.6 Hz, 1H), 4.50-4.56 (m, 4H), 4.62-4.66 (m, 3H), 4.88 (d, *J* 10.6 Hz, 1H), 5.19 (s, 1H), 7.18-7.35 (m, 20H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 69.1, 72.1, 72.4, 72.6, 73.5, 74.0, 74.7, 75.3, 79.5, 93.3, 127.6, 127.7, 127.8, 128.0, 128.1, 128.4, 128.5, 137.9, 138.2, 138.3, 138.4; **FT-IR** (KBr): *v* 2916, 1637, 1452, 1103, 734, 696 cm^{-1}; **HR/MS** (ESI) calcd for $C_{34}H_{35}O_5$ $[M+H]^+$ 523.2484, found 523.2482.

2.6.2 Access to 1,2-*cis*-*C*-mannosylation

Synthesis of mannosyl fluoride 2.28a. (General procedure)

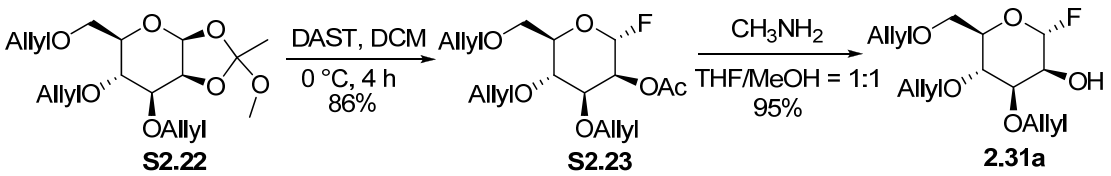


2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-D-mannosyl fluoride (S2.21): Orthoester **S2.20** [32] (858 mg, 1.7 mmol) was dissolved in freshly distilled DCM (8.5 mL). The mixture

was cooled 0°C, and DAST (0.26 mL, 2.0 mmol) was added. The reaction mixture was stirred at 0°C. After 4 h, the reaction was quenched with ice-water and extracted with AcOEt (10 mL×3). The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash column chromatography (AcOEt/Hexane = 1:4) to afford **S2.21** (746 mg, 89%) as a colorless oil. $[\alpha]_D^{20}$ = +13.4 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 3.70 (dd, *J* 11.3, 0.9 Hz, 1H), 3.80 (dd, *J* 11.3, 2.9 Hz, 1H), 3.93-3.98 (m, 3H), 4.49 (d, *J* 10.8, 1H), 4.51 (d, *J* 12.2, 1H), 4.54 (d, *J* 11.2 Hz, 1H), 4.66 (d, *J* 12.2 Hz, 1H), 4.70 (d, *J* 11.2 Hz, 1H), 4.86 (d, *J* 10.8 Hz, 1H), 5.46-5.50 (m, 1H), 5.62 (dd, *J* 49.2, 1.8 Hz, 1H), 7.10-7.20 (m, 2H), 7.22-7.40 (m, 13H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.8, 66.9 ($J_{C,F}$ = 40 Hz), 68.0, 71.9, 73.2, 73.4, 73.6, 75.2, 77.1, 105.4 ($J_{C,F}$ = 219 Hz), 127.6(2C), 127.7, 127.8, 128.0, 128.2, 128.3, 128.4, 137.4, 137.8, 138.0, 169.9 ppm; IR (film) ν_{max}: 1750 cm^{-1};

3,4,6-tri-*O*-benzyl-D-mannosyl fluoride (2.28a): $MeNH_2$ (2.3 mL, 2.27 mmol, 1.0 M in MeOH) was added to the solution of **S2.21** (281 mg, 0.57 mmol) in freshly distilled THF (2.3 mL). The reaction mixture was stirred at rt for 4h. The mixture was concentrated and purified by flash column chromatography (AcOEt/Hexane = 1:3) to afford alcohol **2.28a** (242 mg, 94%) as a colorless oil. $[\alpha]_D^{20}$ = +33.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 2.85 (brs, 1H), 3.75 (dd, *J* 10.8, 1.6 Hz, 1H), 3.83 (dd, *J* 10.8, 3.5 Hz, 1H), 3.90-3.94 (m, 1H), 3.95-4.05 (m, 2H), 4.10-4.15 (m, 1H), 4.52 (d, *J* 10.8 Hz, 1H), 4.54 (d, *J* 12.2 Hz, 1H), 4.71 (d, *J* 11.4 Hz, 1H), 4.72 (d, *J* 12.2 Hz, 1H), 4.76 (d, *J* 11.4 Hz, 1H), 4.89 (d, *J* 10.8 Hz, 1H), 5.70 (dd, *J* 49.5, 1.7 Hz, 1H), 7.15-7.28 (m, 2H), 7.30-7.48 (m, 13H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 67.0 ($J_{C,F}$ = 39 Hz), 68.1, 72.3, 73.2, 73.3, 73.4, 75.1, 79.0, 107.2 ($J_{C,F}$ = 216 Hz), 127.6, 127.7, 127.8 (2C), 127.9, 128.0, 128.3, 128.5, 137.5, 137.9, 138.0 ppm;

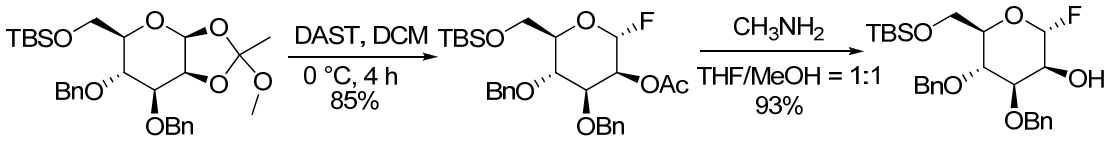
Synthesis of mannosyl fluoride 2.30a. (According to the general procedure of preparation of 2.28a)



2-*O*-Acetyl-3,4,6-tri-*O*-allyl-D-mannosyl fluoride (S2.23): $[\alpha]_D^{20}$ = +20.0 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.65-3.82 (m, 4H), 3.84-3.90 (m, 1H), 3.97-4.08 (m, 2H), 4.08-4.17 (m, 3H), 4.35 (ddt, *J* 12.3, 5.6, 1.2 Hz, 1H), 5.12-5.21 (m, 3H), 5.22-5.29 (m, 2H), 5.31 (dd, *J* 2.5, 1.6 Hz, 1H), 5.33-5.36 (m, 1H), 5.56 (dd, *J* 49.1, 1.6 Hz, 1H), 5.82-5.99 (m, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.9, 67.4 ($J_{C,F}$ = 40 Hz), 68.2, 71.0, 72.5, 73.2, 73.6, 74.1, 76.5, 105.4 ($J_{C,F}$ = 219 Hz), 116.8, 117.2, 117.4, 134.3, 134.5, 134.7, 170.0 ppm; **HRMS** calcd for $C_{17}H_{26}FO_6$ $[M+H]^+$: 345.1713; found: 345.1717.

3,4,5-tri-*O*-allyl-D-mannosyl fluoride (2.31a): $[\alpha]_D^{20}$ = +36.2 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 2.63 (brs, 1H), 3.64-3.77 (m, 4H), 3.81-3.87 (m, 1H), 4.01 (ddt, *J* 12.9, 5.8, 1.4 Hz, 1H), 4.07-4.10 (m, 2H), 4.13 (dt, *J* 5.8, 1.4 Hz, 1H), 4.17 (q, *J* 1.4 Hz, 1H), 4.19 (q, *J* 1.4 Hz, 1H), 4.29 (ddt, *J* 12.4, 5.7, 1.3 Hz, 1H), 5.12-5.36 (m, 6H), 5.64 (dd, *J* 49.5, 1.6 Hz, 1H), 5.85-5.99 (m, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 67.3 ($J_{C,F}$ = 40 Hz), 68.2, 71.3, 72.4, 73.0, 73.3, 73.9, 78.4, 107.2 ($J_{C,F}$ = 216 Hz), 116.9, 117.3, 117.6, 134.2, 134.6, 134.7 ppm; **HRMS** calcd for $C_{15}H_{24}FO_5$ $[M+H]^+$: 303.1608; found: 303.1612.

Synthesis of mannosyl fluoride 2.30b. (According to the general procedure of preparation of 2.28a)

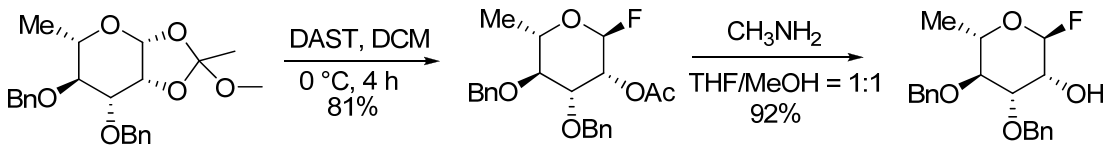


S2.24 **S2.25** **2.31b**

2-*O*-Acetyl-3,4-di-*O*-benzyl-6-*O*-(*tert*-butyl-dimethylsilyl)-D-mannosyl fluoride (S2.25): $[\alpha]_D^{20}$ = +13.6 (*c* 1.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.92 (s, 9H), 2.15 (s, 3H), 3.79 (d, *J* 9.6 Hz, 1H), 3.85 (dd, *J* 11.8, 1.3 Hz, 1H), 3.95-4.04 (m, 2H), 4.07 (t, *J* 9.6 Hz, 1H), 4.59 (d, *J* 11.3 Hz, 1H), 4.69 (d, *J* 10.7 Hz, 1H), 4.73 (d, *J* 11.3 Hz, 1H), 4.92 (d, *J* 10.7 Hz, 1H), 5.45 (t, *J* 2.3 Hz, 1H), 5.57 (dd, *J* 49.5, 1.5 Hz, 1H), 7.27-7.43 (m, 10H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ -5.4, -5.2, 18.2, 20.8, 25.8, 61.4, 67.2 ($J_{C,F}$ = 40 Hz), 72.1, 73.0, 74.8, 75.4, 105.6 ($J_{C,F}$ = 218 Hz), 127.7, 127.9 (2C), 128.1, 128.4 (2C), 137.7, 138.4, 170 ppm; **HRMS** calcd for $C_{28}H_{40}FO_6Si$ $[M+H]^+$: 519.2578; found: 519.2571.

3,4-di-*O*-benzyl-6-*O*-(*tert*-butyl-dimethylsilyl)-D-mannosyl fluoride (2.31b): $[\alpha]_D^{20}$ = +31.4 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 2.53 (dd, *J* 4.2, 2.2 Hz, 1H), 3.75-3.81 (m, 1H), 3.85-3.92 (m, 2H), 3.94-4.03 (m, 2H), 4.09-4.13 (m, 1H), 4.72 (d, *J* 11.5 Hz, 1H), 4.73 (d, *J* 11.1 Hz, 1H), 4.76 (d, *J* 11.5Hz, 1H), 4.88 (d, *J* 11.1 Hz, 1H), 5.64 (dd, *J* 49.7, 1.4 Hz, 1H), 7.27-7.45 (m, 10H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ -5.4, -5.1, 18.3, 25.9, 61.7, 67.3 ($J_{C,F}$ = 40 Hz), 72.4, 73.0, 74.5, 75.2, 79.0, 107.5 ($J_{C,F}$ = 215 Hz), 127.8, 127.9, 128.1, 128.4, 128.6, 137.6, 138.4 ppm; **HRMS** calcd for $C_{26}H_{38}FO_5Si$ $[M+H]^+$: 477.2473; found: 477.2479.

1.3 Synthesis of mannosyl fluoride 2.30c. (According to the general procedure of preparation of 6)

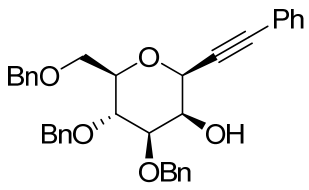


S2.26 **S2.27** **2.31c**

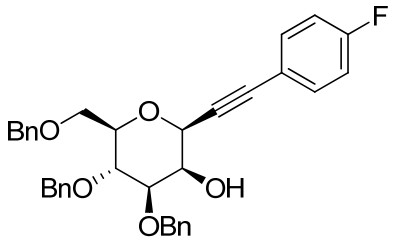
2-*O*-Acetyl-3,4-di-*O*-benzyl-L-rhamnosyl fluoride (S2.27): $[\alpha]_D^{20}$ = –22.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.37 (d, *J* 6.2 Hz, 3H), 2.17 (s, 3H), 3.49 (t, *J* 9.5 Hz, 1H), 3.89-3.98 (m, 2H), 4.57 (d, *J* 11.2 Hz, 1H), 4.64 (d, *J* 10.8 Hz, 1H), 4.72 (d, *J* 11.2 Hz, 1H), 4.94 (d, *J* 10.8 Hz, 1H), 5.49 (t, *J* 2.4 Hz, 1H), 5.52 (dd, *J* =49.2, 1.8 Hz, 1H), 7.27-7.42 (m, 10H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.8, 20.9, 67.3 ($J_{C,F}$ = 40 Hz), 70.3, 72.0, 75.5, 77.0, 78.9, 105.3 ($J_{C,F}$ = 219 Hz), 127.8, 127.9 (2C), 128.1, 128.4 (2C), 137.6, 138.1, 170.0 ppm; **HRMS** calcd for $C_{22}H_{25}FO_5Na$ [M+Na^+]: 411.1584; found: 411.1578.

3,4-di-*O*-benzyl-L-rhamnosyl fluoride (2.31c): $[\alpha]_D^{20}$ = –11.2 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.37 (d, *J* 6.2 Hz, 3H), 2.73 (dd, *J* 4.5, 1.7 Hz, 1H), 3.54 (t, *J* 9.4 Hz, 1H), 3.83-3.89 (m, 1H), 3.89-3.97 (m, 1H), 4.08-4.12 (m, 1H), 4.69 (d, *J* 10.9 Hz, 1H), 4.71 (d, *J* 11.4 Hz, 1H), 4.76 (d, *J* 11.4 Hz, 1H), 4.92 (d, *J* 10.9 Hz, 1H), 5.60 (dd, *J* 49.5, 1.4 Hz, 1H), 7.27-7.43 (m, 10H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.7, 67.3 ($J_{C,F}$ = 40 Hz), 69.9, 72.4, 75.4, 78.8, 79.0, 107.0 ($J_{C,F}$ = 214 Hz), 127.8, 127.9 (2C), 128.1, 128.4, 128.6, 137.5, 138.0 ppm;

General procedure of coupling reaction with organotrifluoroborates: To a solution of glycosyl fluoride (1 equiv) and organotrifluoroborate (3 equiv) in acetonitrile (0.02 M) was added $BF_3{\cdot}OEt_2$ (1.5 equiv) at 0 ºC. The reaction was carried out at 0 ºC for 30 min, then diluted with AcOEt, quenched with saturated aqueous $NaHCO_3$, extracted with AcOEt (3 times), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel.

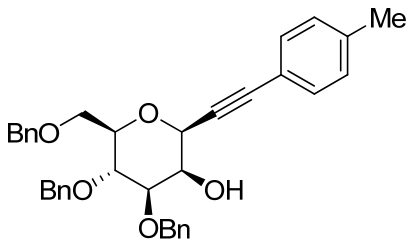


(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(phenylethynyl)tetrahydro-2H-pyran-3-ol (2.29a): $[\alpha]_D^{20}$ = +78.4 (*c* 0.68, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.72 (s, 1 H, OH), 3.72 (dd, *J* 10.8, 1.8 Hz, 1H), 3.80 (*J* 10.8, 4.2 Hz, 1H), 3.91 (t, *J* 9.5 Hz, 1H), 4.01-4.09 (m, 2H), 4.15-4.20 (m, 1H), 4.53 (d, *J* 10.6 Hz, 1H), 4.55 (d, *J* 12.3 Hz, 1H), 4.66 (d, *J* 12.3 Hz, 1H), 4.73 (d, *J* 11.6 Hz, 1H), 4.76 (d, *J* 11.6 Hz, 1H), 4.84 (d, *J* 10.6 Hz, 1H), 5.03 (d, *J* 1.9 Hz, 1H), 7.10-7.21 (m, 2H), 7.24-7.42 (m, 18H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 68.8 (2C), 70.2, 71.9, 73.4, 74.2, 74.4, 75.3, 80.1, 83.2, 88.9, 121.8, 127.5, 127.7, 128.0 (2C), 128.1, 128.2, 128.3(2C), 128.5, 128.8, 131.8, 137.6, 138.0, 138.1 ppm; **HRMS** calcd for $C_{35}H_{35}O_5$ $[M+H]^+$: 535.2484; found: 535.2477.

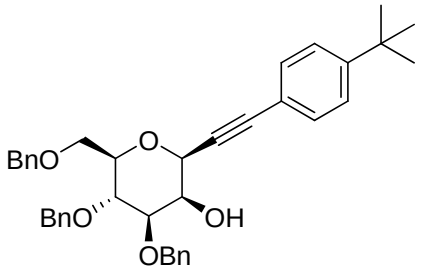


(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-((4-fluorophenyl)ethynyl)tetrahydro-2H-pyran-3-ol (2.29b): $[\alpha]_D^{20}$ = +70.7 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.68 (d, *J* 2.9 Hz, 1H), 3.72 (dd, *J* 10.8, 1.7 Hz, 1H), 3.79 (dd, *J* 10.9, 4.3 Hz, 1H), 3.90 (t, *J* 9.4 Hz, 1H), 3.98-4.06 (m, 2H), 4.14-4.18 (m, 1H), 4.53 (d, *J* 10.6 Hz, 1H), 4.55 (d, *J* 12.2 Hz, 1H), 4.65 (d, *J* 12.2 Hz, 1H), 4.72 (d, *J* 11.6 Hz, 1H), 4.76 (d, *J* 11.6 Hz, 1H), 4.84 (d, *J* 10.6 Hz, 1H), 5.01 (d, *J* 1.8 Hz, 1H), 6.94-7.03 (m, 2H), 7.15-7.21 (m, 2H), 7.22-7.43 (m, 15H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 68.8, 68.9, 70.2, 72.0, 73.5, 74.3, 74.0, 75.4, 80.1, 83.0, 87.9,

115.5, 115.7, 117.9, 127.6, 127.8, 128.0 (2C), 128.1, 128.3, 128.4, 128.6, 133.7, 133.8, 137.7, 138.1, 162.8 ($J_{C,F}$ = 249 Hz) ppm; **HRMS** calcd for $C_{35}H_{34}FO_5$ $[M+H^+]$: 553.2390; found: 553.2379.

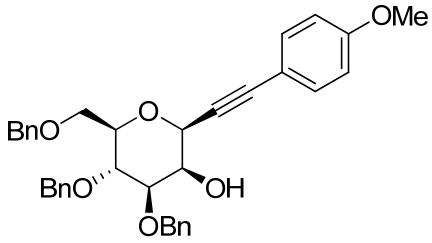


(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(p-tolylethynyl)tetrahydro-2H-pyran-3-ol (2.29c): $[\alpha]_D^{20}$ = +77.1 (*c* 1.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.66 (d, *J* 2.9 Hz, 1H), 3.72 (dd, *J* 10.8, 1.8 Hz, 1H), 3.80 (dd, *J* 10.8, 4.2 Hz, 1H), 3.90 (t, *J* 9.5 Hz, 1H), 4.01-4.09 (m, 2H), 4.14-4.19 (m, 1H), 4.53 (d, *J* 10.6 Hz, 1H), 4.54 (d, *J* 12.2 Hz, 1H), 4.66 (d, *J* 12.2 Hz, 1H), 4.72 (d, *J* 11.6 Hz, 1H), 4.75 (d, *J* 11.6 Hz, 1H), 4.83 (d, *J* 10.6 Hz, 1H), 5.02 (d, *J* 1.9 Hz, 1H), 7.07-7.13 (m, 2H), 7.16-7.21 (m, 2H), 7.22-7.41 (m, 15H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.5, 68.9 (2C), 70.3, 71.9, 73.5, 74.2, 74.4, 75.3, 80.1, 82.5, 89.1, 118.7, 127.5, 127.7, 127.9, 128.0 (2C), 128.3, 128.4, 128.5, 129.0, 131.7, 137.7, 138.2, 139.0 ppm; **HRMS** calcd for $C_{36}H_{37}O_5$ $[M+H]^+$: 549.2641; found: 549.2661.



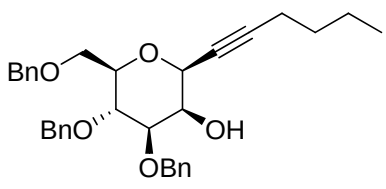
(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-((4-tert-butylphenyl)ethynyl)tetrahydro-2H-pyran-3-ol (2.29d): $[\alpha]_D^{20}$ = +70.4 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.67 (d, *J* 2.0 Hz, 1H), 3.72 (dd,

J 10.7, 1.3 Hz, 1H), 3.79 (dd, *J* 10.8, 4.2 Hz, 1H), 3.90 (t, *J* 9.5 Hz, 1H), 4.01-4.09 (m, 2H), 4.15-4.19 (m, 1H), 4.53 (d, *J* 10.8 Hz, 1H), 4.54 (d, *J* 12.3 Hz, 1H), 4.66 (d, *J* 12.3 Hz, 1H), 4.71 (d, *J* 11.4 Hz, 1H), 4.75 (d, *J* 11.4 Hz, 1H), 4.84 (d, *J* 10.8 Hz, 1H), 5.02 (d, *J* 1.5 Hz, 1H), 7.10-7.20 (m, 2H), 7.23-7.42 (m, 17H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 31.1, 34.8, 68.9, 70.3, 72.0, 73.4, 74.2, 74.4, 75.3, 80.2, 82.6, 89.1, 118.8, 125.3, 127.5, 127.7, 128.0 (3C), 128.3 (2C), 128.5, 131.5, 137.7, 138.1, 138.2, 152.2 ppm; **HRMS** calcd for $C_{39}H_{43}O_5$ $[M+H]^+$: 591.3110; found: 591.3138.

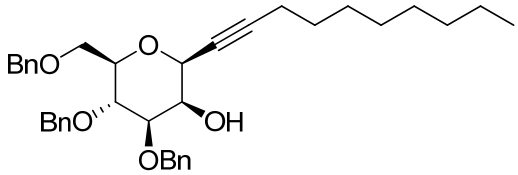


3e

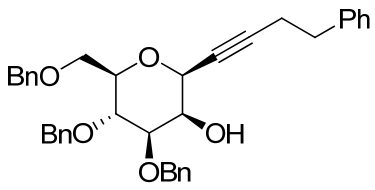
(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-((4-methoxyphenyl)ethynyl)tetrahydro-2H-pyran-3-ol (2.29e): $[\alpha]_D^{20}$ = +64.6 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.61 (s, 1H), 3.72 (dd, *J* 10.8, 1.8 Hz, 1H), 3.78 (d, *J* 4.2 Hz, 1H), 3.80 (s, 3H), 3.90 (t, *J* 9.5 Hz, 1H), 4.01-4.09 (m, 2H), 4.14-4.19 (m, 1H), 4.53 (d, *J* 10.6 Hz, 1H), 4.54 (d, *J* 12.2 Hz, 1H), 4.66 (d, *J* 12.2 Hz, 1H), 4.73 (d, *J* 11.6 Hz, 1H), 4.76 (d, *J* 11.6 Hz, 1H), 4.84 (d, *J* 10.6 Hz, 1H), 5.01 (d, *J* 1.9 Hz), 6.80-6.85 (m, 2H), 7.16-7.21 (m, 2H), 7.24-7.41 (m, 15H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.3, 68.9, 70.0, 70.3, 72.0, 73.5, 74.2, 74.5, 75.4, 80.2, 81.9, 88.9, 113.9, 127.6, 127.8, 128.0 (2C), 128.1 (2C), 128.3, 128.4, 128.6, 133.3, 137.7, 138.2, 160 ppm; HRMS calcd for $C_{36}H_{37}O_6$ $[M+H]^+$: 565.2590; found: 565.2581.



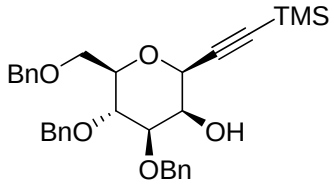
(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(hex-1-ynyl)tetrahydro-2H-pyran-3-ol (2.29f): $[\alpha]_D^{20}$ = +43.2 (*c* 1.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, *J* 7.2 Hz, 3H), 1.31-1.1.50 (m, 4H), 2.18 (td, *J* 6.8, 2.0 Hz, 2H), 2.58 (s, 1H), 3.69 (dd, *J* 10.8, 1.6 Hz, 1H), 3.76 (dd, *J* 10.8, 4.2 Hz, 1H), 3.83 (t, *J* 9.4 Hz, 1H), 3.94-4.02 (m, 2H), 4.04-4.08 (m, 1H), 4.51 (d, *J* 10.7 Hz, 1H), 4.53 (d, *J* 12.1 Hz, 1H), 4.65 (d, *J* 12.2 Hz, 1H), 4.68 (d, *J* 11.5 Hz, 1H), 4.73 (d, *J* 11.5 Hz, 1H), 4.79 (d, *J* 1.7 Hz, 1H), 4.82 (d, *J* 10.7 Hz, 1H), 7.10-7.20 (m, 2H), 7.21-7.40 (m, 13H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.5, 18.4, 21.9, 30.5, 68.5, 68.9, 70.3, 71.8, 73.4, 73.8, 74.3, 74.5, 75.2, 80.3, 90.0, 127.5, 127.7, 127.9 (2C), 128.0, 128.3 (2C), 128.5, 137.8, 138.2, 138.3 ppm; **HRMS** calcd for $C_{33}H_{39}O_5$ $[M+H]^+$: 515.2797; found: 515.2801.



(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(dec-1-ynyl)tetrahydro-2H-pyran-3-ol (2.29g): $[\alpha]_D^{20}$ = +73.0 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.87 (t, *J* 6.1 Hz, 3H), 1.15-1.38 (m, 10H), 1.40-1.53 (m, 2H), 2.17 (td, *J* 7.0, 1.9 Hz, 2H), 2.60 (s, 1H), 3.69 (dd, *J* 10.7, 1.6 Hz, 1H), 3.77 (dd, *J* 10.8, 4.2 Hz, 1H), 3.84 (t, *J* 9.4 Hz, 1H), 3.94-4.01 (m, 2H), 4.04-4.09 (m, 1H), 4.51 (d, *J* 10.7 Hz, 1H), 4.53 (d, *J* 12.2 Hz, 1H), 4.65 (d, *J* 12.2 Hz, 1H), 4.69 (d, *J* 11.4 Hz, 1H), 4.73 (d, *J* 11.4 Hz, 1H), 4.80 (d, *J* 2.0 Hz, 1H), 4.82 (d, *J* 10.7 Hz, 1H), 7.12-7.21 (m, 2H), 7.24-7.41 (m, 13H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.1, 18.7, 22.6, 28.4, 28.9, 19.0, 29.2, 31.8, 68.5, 68.9, 70.3, 71.9, 73.4, 73.7, 74.3, 74.5, 75.3, 80.3, 90.1, 127.5, 127.7, 127.9, 128.0, 128.3 (2C), 128.5, 137.8, 138.2 (2C) ppm; **HRMS** calcd for $C_{37}H_{47}O_5$ $[M+H]^+$: 571.3423; found: 571.3428.

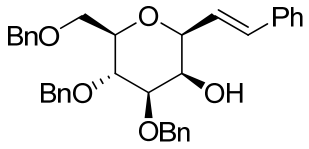


(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(4-phenylbut-1-ynyl)tetrahydro-2H-pyran-3-ol (2.29h): $[\alpha]_D^{20}$ = +32.4 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.49 (td, *J* 7.3, 2.0 Hz, 2H), 2.58 (d, *J* 3.0 Hz, 1H), 2.78 (t, *J* 7.3 Hz, 2H), 3.68 (dd, *J* 10.7, 2.0 Hz, 1H), 3.74 (dd, *J* 10.8, 4.1 Hz, 1H), 3.81 (t, *J* 9.3 Hz, 1H), 3.84-3.91 (m, 2H), 3.99 (dd, *J* 5.0, 2.8 Hz, 1H), 4.50 (d, *J* 10.7 Hz, 1H), 4.52 (d, *J* 12.2 Hz, 1H), 4.61 (d, *J* =11.5 Hz, 1H), 4.63 (d, *J* 12.2 Hz, 1H), 4.65 (d, *J* 11.5 Hz, 1H), 4.77 (q, *J* 2.0 Hz, 1H), 4.81 (d, *J* 10.7 Hz, 1H), 7.15-7.21 (m, 5H), 7.23-7.38 (m, 15H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 20.8, 34.6, 68.4, 68.9, 70.2, 71.8, 73.4, 73.8, 74.4, 75.2, 80.2, 90.0, 126.3, 127.5, 127.7, 127.9 (2C), 128.0, 128.3 (2C), 128.4 (2C), 128.5, 137.8, 138.2, 138.3, 140.2 ppm; **HRMS** calcd for $C_{37}H_{39}O_5$ $[M+H]^+$: 563.2797; found: 563.2799.

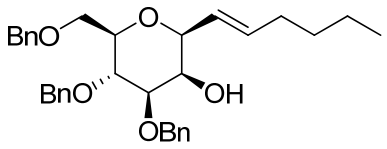


(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-((trimethylsilyl)ethynyl)tetrahydro-2H-pyran-3-ol (3i): $[\alpha]_D^{20}$ = +47.7 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 2.55 (d, *J* 2.8 Hz, 1H), 3.69 (dd, *J* 10.9, 1.7 Hz, 1H), 3.78 (dd, *J* 10.9, 4.2 Hz, 1H), 3.85 (t, *J* 9.4 Hz, 1H), 3.92-3.98 (m, 2H), 4.04-4.08 (m, 1H), 4.51 (s, 1H), 4.54 (s, 1H), 4.65 (d, *J* 12.2 Hz, 1H), 4.70 (d, *J* 12.2 Hz, 1H), 4.73 (d, *J* 12.2 Hz, 1H), 4.79 (d, *J* 2.0 Hz, 1H), 4.82 (d, *J* 10.7 Hz, 1H), 7.17-7.21 (m, 2H), 7.27-7.38 (m, 13H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* -0.2, 68.8 (2C), 70.2, 72.0, 73.4, 74.1, 74.4, 75.4, 79.9, 94.4, 99.5, 127.6, 127.8, 128.0,

128.1, 128.2, 128.3, 128.4, 128.6, 137.7, 128.2 ppm; **HRMS** calcd for $C_{32}H_{39}O_5Si$ $[M+H]^+$: 531.2567; found: 531.2563.

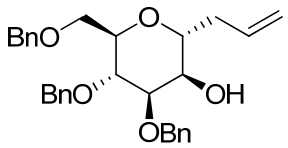


(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-styryltetrahydro-2H-pyran-3-ol (2.29j): $[\alpha]_D^{20}$ = +54.5 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.51 (s, 1H), 3.68-3.76 (m, 2H), 3.77-3.3.84 (m, 1H), 3.85-3.91 (m, 2H), 4.05-4.10 (m, 1H), 4.53 (d, *J* 11.0 Hz, 1H), 4.56 (d, *J* 12.2 Hz, 1H), 4.64 (d, *J* 12.2 Hz, 1H), 4.66-4.73 (m, 3H), 4.78 (d, *J* 11.0 Hz, 1H), 6.18 (dd, *J* 16.3, 5.1 Hz, 1H), 6.57 (dd, *J* 16.3, 1.7 Hz, 1H), 7.10-7.40 (m, 20H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 69.1, 69.7, 72.2, 73.4, 74.5, 74.6, 76.1, 79.4, 124.7, 126.4, 127.6, 127.7, 127.9, 128.0 (2C), 128.1, 128.3, 128.4, 128.6 (2C), 133.5, 136.2, 137.7, 138.0, 138.2 ppm; **HRMS** calcd for $C_{35}H_{37}O_5$ $[M+H^+]$: 537.2641; found: 537.2650.

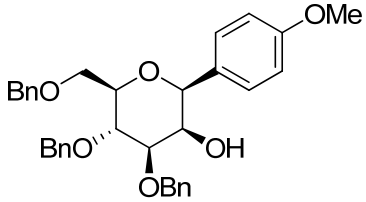


(2S,3R,4R,5R,6R)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)-2-((E)-hex-1-enyl)tetrahydro-2H-pyran-3-ol (2.29k): $[\alpha]_D^{20}$ = +137.0 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J* 7.0 Hz, 3H), 1.20-1.40 (m, 4H), 2.02 (d, *J* 6.6 Hz, 2H), 2.50 (s, 1H), 3.66-3.72 (m, 2H), 3.72-3.80 (m, 2H), 3.84 (t, *J* 8.4 Hz, 1H), 3.95-4.00 (m, 1H), 4.45-4.49 (m, 1H), 4.51 (d, *J* 10.8 Hz, 1H), 4.54 (d, *J* 12.1 Hz, 1H), 4.62 (d, *J* 12.1 Hz, 1H), 4.67 (s, 2H), 4.78 (d, *J* 10.8 Hz, 1H), 5.46 (dd, *J* 15.6, 5.4 Hz, 1H), 5.67 (ddd, *J* 15.6, 6.6, 1.3 Hz, 1H), 7.10-7.40 (m, 15H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.9, 22.2, 31.0, 32.2, 69.2, 69.6, 72.0, 73.0, 73.4, 74.6, 74.7, 76.3, 79.5, 124.9,

127.5, 127.7, 127.8, 128.0 (3C), 128.3, 128.4, 128.5, 135.7, 137.7, 138.1, 138.3 ppm; **HRMS** calcd for $C_{33}H_{41}O_5$ $[M+H]^+$: 517.2954; found: 517.2950.

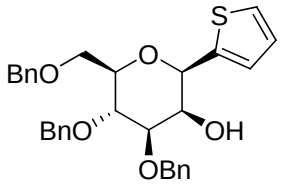


(2*R*,3*R*,4*R*,5*R*,6*R*)-2-Allyl-4,5-bis(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-3-ol (2.29l): $[\alpha]_D^{20}$ = +20.5 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.28-2.43 (m, 2H), 2.44 (s, 1H), 3.65-3.73 (m, 2H), 3.73-3.80 (m, 2H), 3.82 (d, *J* 7.3 Hz, 1H), 3.84-3.87 (m, 1H), 3.92-3.99 (m, 1H), 4.52 (d, *J* 12.2 Hz, 1H), 4.54 (d, *J* 11.2 Hz, 1H), 4.58 (d, *J* 12.2 Hz, 1H), 4.59 (d, *J* 11.6 Hz, 1H), 4.64 (d, *J* 11.6 Hz, 1H), 4.74 (d, *J* 11.2 Hz, 1H), 5.74-5.86 (m, 1H), 7.19-7.23 (m, 2H), 7.26-7.36 (m, 13H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 34.2, 68.3, 68.9, 72.1, 72.9, 73.4, 74.1, 74.2, 74.8, 79.0, 117.3, 127.5, 127.8, 128.0 (2C), 128.1, 128.3, 128.4, 128.6, 134.1, 137.5, 138.1, 138.3 ppm; HRMS calcd for $C_{30}H_{34}NaO_5$ $[M+Na^+]$: 497.2304; found: 497.2304.

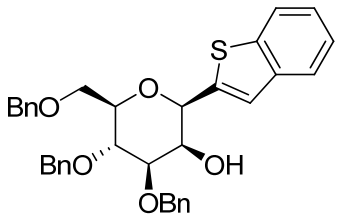


(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(4-methoxyphenyl)tetrahydro-2*H*-pyran-3-ol (2.29n): $[\alpha]_D^{20}$ = +45.6 (*c* 1.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 2.45 (s, 1H), 3.72-3.77 (m, 4H), 3.79 (s, 3H), 3.88-3.97 (m, 1H), 4.33-4.37 (m, 1H), 4.53 (d, *J* 12.2 Hz, 1H), 4.54 (d, *J* 11.2 Hz, 1H), 4.62 (d, *J* 12.2 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.72(d, *J* = 11.7 Hz, 1H), 4.73 (d, *J* = 11.2 Hz, 1H), 4.91 (d, *J* = 4.3 Hz, 1H), 6.80-6.85 (m, 2H), 7.15-7.22 (m, 4H), 7.25-7.37 (m, 13H) pm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 55.3, 68.8, 69.0, 72.6, 73.3 (2C), 74.0, 74.5, 75.8, 78.8, 114.0, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.4, 128.6, 129.5, 137.8,

138.1, 138.3, 159.1 ppm; **HRMS** calcd for $C_{34}H_{36}NaO_6$ [M+Na$^+$]: 563.2410; found: 563.2411.

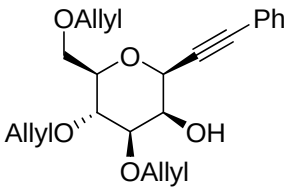


(2*R*,3*S*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-(thiophen-2-yl)tetrahydro-2H-pyran-3-ol (2.29p): $[\alpha]_D^{20}$ = +54.3 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.65 (s, 1H), 3.69-3.74 (m, 1H), 3.75-3.82 (m, 2H), 3.84 (dd, *J* = 8.3, 3.2 Hz, 1H), 3.93 (t, *J* = 8.4 Hz, 1H), 4.39 (t, *J* = 3.0 Hz, 1H), 4.52 (d, *J* = 10.7 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.67 (d, *J* = 12.2 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.77 (d, *J* = 10.7 Hz, 1H), 5.26 (s, 1H), 6.77-6.80 (m, 1H), 6.90-6.94 (m, 1H), 7.15-7.19 (m, 2H), 7.24-7.39 (m, 14H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 68.9, 69.6, 72.5, 73.4, 73.5, 74.4, 74.7 (2C), 79.5, 125.3, 125.5, 126.9, 127.6, 127.7, 127.9 (2C), 128.2, 128.3, 128.4, 128.6, 137.7, 138.1, 138.3, 140.9 ppm; **HRMS** calcd for $C_{31}H_{32}NaSO_5$ [M+Na$^+$]: 539.1868; found: 539.1861.

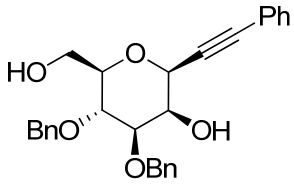


(2*R*,3*S*,4*R*,5*R*,6*R*)-2-(Benzo[b]thiophen-2-yl)-4,5-bis(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-3-ol (2.29q): $[\alpha]_D^{20}$ = +59.4 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.68 (s, 1H), 3.45-3.51 (m, 1H), 3.63 (dd, *J* = 10.6, 2.8 Hz, 1H), 3.75 (dd, *J* = 10.6, 4.8 Hz, 1H), 3.97-4.05 (m, 2H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.49-4.52 (m, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.74 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 11.7 Hz, 1H), 5.31 (d, *J* =

2.4 Hz, 1H), 6.84-6.86 (m, 1H), 7.18-7.23 (m, 2H), 7.25-7.32 (m, 11H), 7.37-7.42 (m, 4H), 7.78-7.83 (m, 1H), 8.16-8.21 (m, 1H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 68.8 (2C), 72.8, 73.4, 73.5, 74.0, 74.5, 74.9, 79.3, 122.4, 123.9, 124.0, 124.3, 124.7, 127.6, 127.7, 127.8, 127.9, 128.3 (2C), 128.4, 128.8, 132.4, 137.8, 138.2 (2C), 138.3, 140.1ppm; **HRMS** calcd for $C_{35}H_{34}NaSO_5$ [M+Na^+]: 589.2025; found: 589.2021.

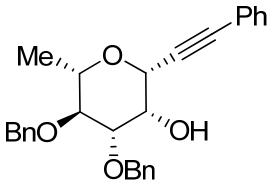


(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(allyloxy)-6-(allyloxymethyl)-2-(phenylethynyl)tetrahydro-2H-pyran-3-ol (2.32a): $[\alpha]_D^{20}$ = +61.9 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.62 (d, *J* 2.8 Hz, 1H), 3.69-3.74 (m, 2H), 3.90 (dd, *J* 9.2, 3.2 Hz, 1H), 3.95-4.06 (m, 2H), 4.08-4.27 (m, 6H), 4.43 (q, *J* 6.0 Hz, 1H), 5.01 (d, *J* 2.0 Hz, 1H), 5.14-5.20 (m, 2H), 5.20-5.27 (m, 2H), 5.28-5.38 (m, 2H), 5.88-6.02 (m, 3H), 7.29-7.36 (m, 3H), 7.39-7.45 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 68.8, 69.0, 70.4, 70.9, 72.5, 74.1, 74.2, 74.3, 79.8, 83.3, 88.9, 117.0, 117.1, 117.4, 121.9, 128.3, 128.8, 131.8, 134.5, 134.8, 134.9 ppm; **HRMS** calcd for $C_{23}H_{29}O_5$ [M+H^+]: 385.2015; found: 385.2014.

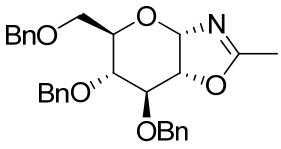


(2*S*,3*R*,4*R*,5*R*,6*R*)-4,5-Bis(benzyloxy)-6-(hydroxymethyl)-2-(phenylethynyl)tetrahydro-2H-pyran-3-ol (2.32b): $[\alpha]_D^{20}$ = +67.4 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.83 (dd, *J* 11.7, 3.2 Hz, 1H), 3.88-3.96 (m, 3H), 4.08 (dd, *J* 8.7, 3.0 Hz, 1H), 4.18 (t, *J* 2.6 Hz, 1H), 4.70 (d, *J* 10.8 Hz, 1H), 4.77 (s, 2H),

4.91 (d, *J* 10.8 Hz, 1H), 5.02 (d, *J* 1.9 Hz, 1H), 7.28-7.48 (m, 15H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 62.0, 68.7, 70.4, 72.1, 74.1, 74.7, 75.4, 80.0, 83.0, 89.0, 121.7, 127.9, 128.1 (2C), 128.3, 128.5, 128.6, 128.9, 131.8, 137.6, 138.1 ppm; **HRMS** calcd for $C_{28}H_{29}O_5$ $[M+H]^+$: 445.2015; found: 445.2015.



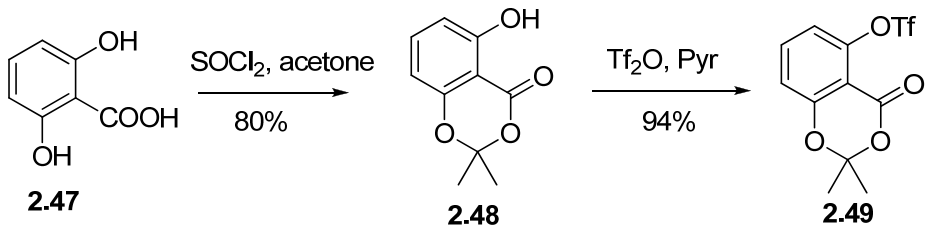
(2*R*,3*S*,4*S*,5*S*,6*S*)-4,5-Bis(benzyloxy)-6-methyl-2-(phenylethynyl)tetrahydro-2H-pyran-3-ol (2.32c): $[\alpha]_D^{20}$ = -60.1 (*c* 1.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.37 (d, *J* 6.2 Hz, 3H), 2.65 (d, *J* 2.2 Hz, 1H), 3.49 (t, *J* 9.3 Hz, 1H), 3.97-4.06 (m, 2H), 4.18 (dd, *J* 5.2, 2.2 Hz, 1H), 4.67 (d, *J* 10.8 Hz, 1H), 4.75 (s, 2H), 4.91 (d, *J* 10.8 Hz, 1H), 4.95 (d, *J* 2.0 Hz, 1H), 7.27-7.43 (m, 15H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.1, 68.5, 70.4, 70.7, 72.1, 75.6, 80.0, 80.2, 83.5, 88.5, 121.9, 127.8, 128.1 (2C), 128.3, 128.4, 128.6, 128.8, 131.8, 137.7, 138.2 ppm; **HRMS** calcd for $C_{28}H_{29}O_4$ $[M+H^+]$: 429.2066; found: 429.2073.



(3a*S*,5*R*,6*R*,7*S*,7a*R*)-6,7-Bis(benzyloxy)-5-(benzyloxymethyl)-2-methyl-5,6,7,7a-tetrahydro-3a*H*-pyrano[2,3-*d*]oxazole (2.32d): $[\alpha]_D^{20}$ = +54.4 (*c* 1.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.51-3.58 (m, 1H), 3.66-3.70 (m, 2H), 3.73-3.82 (m, 2H), 4.42-4.51 (m, 3H), 4.59 (d, *J* 12.1 Hz, 1H), 4.65 (d, *J* 11.6 Hz, 1H), 4.68 (d, *J* 10.2 Hz, 1H), 4.76 (d, *J* 11.6 Hz, 1H), 5.87 (d, *J* 7.4 Hz, 1H), 7.10-7.23 (m, 2H), 7.25-7.43 (m, 13H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.3, 69.5, 71.4, 72.3, 73.5, 73.6, 74.4, 79.8, 80.4, 93.6, 127.6, 127.7, 127.8, 127.9 (2C), 128.0, 128.3 (2C), 128.4,

137.8, 138.0, 168.0 ppm; HRMS calcd for $C_{29}H_{32}NO_5$ [M+H$^+$]: 474.2280; found: 474.2272.

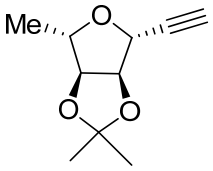
2.6.3 Total synthesis of (+) varitriol



5-Hydroxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (2.48): Acetone (1.8 ml) and $SOCl_2$ (1.87 mL, 26 mmol) were added to a solution of 2,6-dihydroxybenzoic acid (3.1 g, 20 mmol) and DMAP (122 mg, 1 mmol) in anhydrous DME (15 mL) successively. The reaction mixture was allowed to stir at 0 ºC for 1h and rt. for 24h. Then saturated aqueous $NaHCO_3$ was added to the mixture and the aqueous solution was extracted with diethyl ether. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:5) to afford a white solid (3.1 g, 80%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.73 (s, 6H), 6.42 (d. *J* 8.2 Hz, 1H), 6.61 (.d, *J* 8.5 Hz, 1H), 7.40 (dd, *J* 8.2, 8.5 Hz, 1H); **^{13}CNMR** (100MHz, $CDCl_3$): δ 25.6, 93.3, 107.1, 107.3, 110.8, 137.9, 155.6, 161.4, 165.5; **FT-IR** (KBr): ν 3419, 2995, 2943, 1745, 1622, 1579, 1475, 1207 cm^{-1}.

2,2-Dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate (2.49): Anhydrous pyridine (0.3 mL) and trifluoromethansulfonic anhydride (0.21 mL, 1.2 mmol) were successively added to a solution of **2.48** (194 mg, 1.0 mmol) in dichloromethane (2 mL). The mixture was allowed to stir at 0 °C for 1h, the reaction

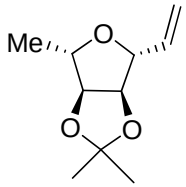
mixture was extracted with ether and the combined organic layers were washed with brine, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:5) to afford a white solid (315 mg, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.74 (s, 6H), 6.62 (d. *J* 8.3 Hz, 1H), 7.07 (.d, *J* 8.4 Hz, 1H), 7.63 (dd, *J* 8.3, 8.4 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 25.5, 106.9, 108.3, 116.6, 117.9, 118.7 (q, $^{3}J_{CF}$ 319.1 Hz), 136.3, 148.6, 157.1, 157.4; **FT-IR** (KBr): *v* 2995, 2943, 1681, 1633, 1587, 1487, 1390, 1209, 1151, 1078 cm^{-1}; **ESI–MS** m/z 326.9 $[M+H]^+$; 349.8 $[M+Na]^+$.



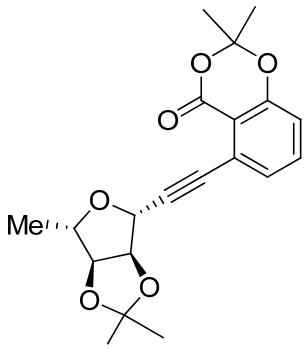
(3a*R*,4*R*,6*S*,6a*S*)-4-Ethynyl-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxole (2.58): To a solution of **2.46** (52mg, 0.3 mmol) in dry dichloromethane (1 mL) was added DAST (51 μL, 0.4 mmol) at -30 °C under nitrogen. The mixture was allowed to warm to rt. and kept for 30 min, then cooled to 30 °C and treated with methanol (0.3 mL). The reaction mixture was carefully washed with ice water (0.5 mL), cold saturated aqueous $NaHCO_3$ and brine, the organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford **2.26f** as colorless oil which was used in the next step immediately without further purification.

To a solution of above fluoride and potassium ethynyl trifluoroborate (59 mg, 0.45 mmol) in acetonitrile (1.5 mL) was added $BF_3{\cdot}OEt_2$ (61.7 μL, 0.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 3h, then quenched with triethylamine (0.1 ml). The mixture was filtered, concentrated under reduced pressure at low temperature (< 20 °C). The residue was purified by flash column chromatography on silica gel

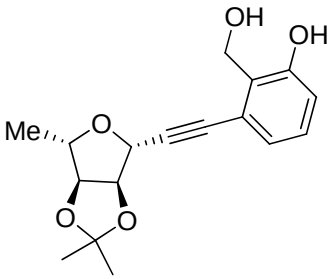
(Et_2O/pentane = 1:5) to afford a colorless oil (36 mg, 65% for two steps). $[\alpha]_D^{20}$ = 32.7 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.36 (d, *J* 6.8 Hz, 1H), 1.50 (s, 3H), 2.53 (d, *J* 2.3 Hz, 1H), 4.15 (dq, *J* 2.8, 6.7 Hz, 1H), 4.46 (dd, *J* 2.8, 6.4 Hz, 1 H), 4.56 (dd, *J* 2.3, 3.0 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 19.2, 25.3, 26.9, 73.7, 74.9, 81.9, 82.1, 86.2, 86.4, 114.1; **FT-IR** (KBr): *v* 3271, 2981, 2937, 1375 cm^{-1} **HR/MS** (ESI) calcd for $C_{10}H_{15}O_3$ $[M+H]^+$ 183.1021, found 183.1019.



(3a*S*,4*S*,6*R*,6a*R*)-2,2,4-Trimethyl-6-vinyltetrahydrofuro[3,4-*d*][1,3]dioxole (2.59):[4] To a solution of **2.58** (64 mg, 0.35 mmol) in EtOAc/Pyr (30/1, 1.8 ml,) was added Lindlar catalyst (12.8 mg). The mixture was stirred at rt under H_2 atmosphere for 2h, then the mixture was filtered and concentrated under reduced pressure at low temperature (< 20 °C). The residue was purified by flash column chromatography on silica gel (Et_2O/pentane = 1:5) to afford a colorless oil (contains 10% of alkane) (63 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32 (d, *J* 6.4 Hz, 3H), 1.34 (s, 3H), 1.55 (s, 3H), 3.96-4.02 (m, 1H), 4.21-4.30 (m, 2H), 4.45 (dd, *J* 5.1, 7.0 Hz, 1H), 5.22 (d, *J* 10.4 Hz, 1H), 5.39 (d, *J* 17.2 Hz, 1H), 5.91 (ddd, *J* 6.4, 10.4, 17.2 Hz, 1H); **^{13}CNMR** (100MZ, $CDCl_3$): δ 18.9, 25.5, 27.3, 80.2, 85.0, 85.3, 86.3, 114.9, 117.3, 136.0; **FT-IR** (KBr): *v* 2980, 2933, 2873, 1456, 1369, 1232 cm^{-1}

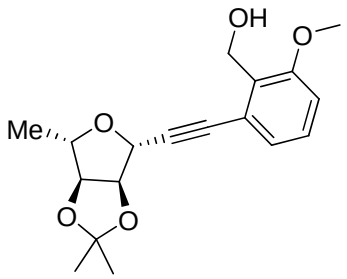


2,2-Dimethyl-5-(((3a*R*,4*R*,6*S*,6a*S*)-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethynyl)-4H-benzo[*d*][1,3]dioxin-4-one (2.60): Under argon, a suspension of **2.58** (74.0 mg, 0.22 mmol), $(PPh_3)_2PdCl_2$ (6.3 mg, 5%) and CuI (5.1 mg, 15%) in degassed Et_3N/DMF (1/5, 0.5 mL) was treated with a solution of **2.49** (34.0 mg, 0.18 mmol) in Et_3N/DMF (1/5, 0.5 mL) at 60 °C and stirred for 3h. the reaction was then cooled down to room temperature, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane = 1:5) to afford a colorless oil (58.6 mg, 91%). $[\alpha]_D^{20}$ = 27.7 (c 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.42 (d, *J* 6.8 Hz, 1H), 1.51 (s, 3H), 4.25 (dq, *J* 2.1, 6.8 Hz, 1H), 4.57 (dd, *J* 2.1, 6.3 Hz, 1H), 4.89 (d, *J* 2.1 Hz, 1H), 5.08 (dd, *J* 2.1, 6.3 Hz, 1H), 6.91 (d, *J* 8.2 Hz, 1H), 7.20 (d, *J* 7.6 Hz, 1H), 7.43 (dd, *J* 6.3, 8.2 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 19.4, 25.3, 25.6, 25.8, 25.9, 74.7, 82.5, 84.2, 86.4, 86.7, 94.0, 105.7, 113.6, 117.7, 124.4, 128.7, 135.0, 156.5; **FT-IR** (KBr): ν 3423, 2987, 2108, 1745, 1643, 1475, 1083, 734, 686 cm^{-1}; **HR/MS** (ESI) calcd for $C_{20}H_{23}O_6$ $[M+H]^+$ 359.1495, found 359.1495.



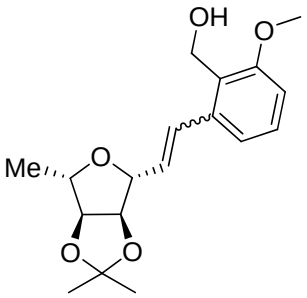
2-(Hydroxymethyl)-3-(((3a*R*,4*R*,6*S*,6a*S*)-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethynyl)phenol (2.61): $LiAlH_4$ (2 M in THF, 80 μL) was added to a solution of **2.60** (42 mg, 0.12 mmol) in THF (0.5 mL) at -78 °C. The mixture was warmed to room temperature and stirred for 2 h, then diluted with diethylether and quenched with wet THF. The organic layer was separated, dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on

silica gel (EtOAc:hexane = 1:1) to afford a colorless oil (8.9 mg, 89%). $[\alpha]_D^{20}$ = 71.6 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.34 (s. 3H), 1.38 (d, *J* 6.7 Hz, 3H), 1.52 (s, 3H), 2.07 (br s, 1H), 4.19 (dq, *J* 2.8, 6.7 Hz, 1H), 4.49 (dd, *J* 2.8, 6.4 Hz, 1H), 4.78 (d, *J* 3.1 Hz, 1H), 4.87 (dd, *J* 3.1, 6.4 Hz, 1H), 5.10 (s, 2H), 6.85 (d, *J* 8.1 Hz, 1H), 6.95 (d, *J* 7.6 Hz, 1H), 7.11 (dd, *J* 7.6, 8.1 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 19.3, 25.4, 27.0, 62.7, 74.5, 81.9. 84.1, 86.3, 86.8, 91.2, 114.3, 117.8, 120.7, 124.3, 125.4, 128.9, 156.6; **FT-IR** (KBr): *v* 3439, 2989, 2100, 1643, 1555, 1454, 1074 cm^{-1}; **HR/MS** (ESI) calcd for $C_{17}H_{21}O_5$ $[M+H]^+$ 305.1389, found 305.1382.



(2-Methoxy-6-(((3a*R*,4*R*,6*S*,6a*S*)-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethynyl)phenyl)methanol (2.62): To a stirred solution of **2.61** (12 mg, 0.04 mmol) in dry acetone (0.5 mL) was added anhydrous K_2CO_3 (11 mg, 0.08 mmol) and iodomethane (4.9 μL, 0.08 mmol). The mixture was allowed to reflux for 6 h, then brought to rt. and concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water, the organic layer was dried, concentrated and purified by flash column chromatography on silica gel (EtOAc:hexane = 1:1) to afford a colorless oil (11.5 mg, 92%). $[\alpha]_D^{20}$ = 63.9 (*c* 0.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.42(d, 6.7 Hz, 3H), 1.55 (s, 3H), 2.51 (br, s, 1H), 3.88 (s, 3H), 4.21 (dq, *J* 2.8, 6.7 Hz, 1H), 4.53 (dd, *J* 2.8, 6.4 Hz, 1H), 4.84 (d, *J* 2.9 Hz, 1H), 4.88 (s, 2H), 4.93 (dd, *J* 2.9, 6.4 Hz, 1H), 6.89 (d, *J* 8.2Hz, 1H), 7.06 (d, *J* 7.6 Hz, 1H), 7.22 (dd, *J* 7.6, 8.2 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 19.3, 25.3, 26.9, 55.6, 59.3, 74.5, 82.0, 84.3, 86.3, 86.8, 90.9, 111.3, 114.1, 122.7, 124.9, 128.8, 130.6, 157.9; **FT-IR** (KBr): *v*

3442, 2358, 2092, 1643, 1577cm^{-1}; **HR/MS** (ESI) calcd for $C_{18}H_{23}O_5$ $[M+H]^+$ 319.1545, found 319.1557.



(2-Methoxy-6-(2-((3a*R*,4*R*,6*S*,6a*S*)-2,2,6-trimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinyl)phenyl)methanol (2.63): To a stirred solution of Red-Al (70% in toluene, 10 μL) in THF (0.5 mL) was added a solution of **2.62** (10 mg, 0.03 mmol) in THF (0.5 ml) at -20 °C. After stirring at rt for 3 h, the reaction mixture was quenched with wet THF and extracted with diethyl ether, the combined organic layers were dried with anhydrous Na_2SO_4, concentrated and purified by flash column chromatography on silica gel (EtOAc:hexane = 1:1) to afford a colorless oil (11.5 mg, 92%) as a *E*, *Z* mixture (*E*:*Z* = 2.8:1). **^{1}H NMR** (400 MHz, $CDCl_3$) (date of *E* isomer): δ 1.30 (d, *J* 6.2 Hz, 3H), 1.36 (s, 3H), 1.37 (s, 3H), 2.3 (br s, 1H), 3.85 (s, 3H), 4.01-4.12 (m, 1H), 4.28-4.36 (m, 1H), 4.43-4.49 (m, 1H), 4.52-4.55 (m, 1H), 4.78 (s, 1H), 6.15 (dd, *J* 6.6, 14.8 Hz, 1H), 6.81-6.93 (m, 1H), 7.04-7.09 (m, 1H), 7.20-7.25 (m, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) (date of *E* isomer): δ 19.1, 25.5, 27.4, 55.6, 56.8, 80.3, 84.8, 85.6, 86.3, 109.8, 115.1, 119.3, 128.8, 129.5, 130.6, 137.3, 158.5; **FT-IR** (KBr): *v* 3442, 2980, 2933, 1597, 1471, 1456, 1283 cm^{-1}; **HR/MS** (ESI) calcd for $C_{18}H_{24}O_5Na$ $[M+Na]^+$ 343.1529, found 343.1521.

(+)-varitriol: To a solution of **2.63** (20 mg, 0.06 mmol) in THF (1 mL) was added aqueous HCl (1 M, 0.5 mL). The reaction mixture was stirred at room temperature for 6h, then quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc, the

combined organic layers were dried with anhydrous Na_2SO_4, concentrated and purified by flash column chromatography on silica gel (DCM:Acetone = 3:2) to afford a white solid (16.3 mg, 93%). $[\alpha]_D^{20}$ = 38.7 (*c* 0.7, MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35 (d, *J* 6.4 Hz, 3H), 2.54 (br s, 1H), 2.81 (br s, 1H), 3.27 (br s, 1H), 3.71-3.77 (m, 1H), 3.87 (s, 3H), 3.89-3.95 (m, 1H), 4.31 (dd, *J* 6.2, 6.4 Hz, 1H), 4.76 (d, *J* 12.0 Hz, 1H), 4.84 (d, *J* 12.0 Hz, 1H), 6.12 (dd, *J* 6.9, 15.7 Hz, 1H), 6.84 (d, *J* 8.1 Hz, 1H), 7.05 (d, *J* 15.7 Hz, 1H), 7.11 (d, *J* 7.8 Hz, 1H), 7.24 (dd, *J* 7.8, 8.1 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$): δ 19.1, 55.7, 56.5, 75.4, 76.2, 79.9, 84.1, 109.9, 119.3, 126.2, 129.0, 129.4, 131.2, 137.7, 158.4; **HR/MS** (ESI) calcd for $C_{15}H_{20}O_5Na$ $[M+Na]^+$ 303.1208, found 303.1210.

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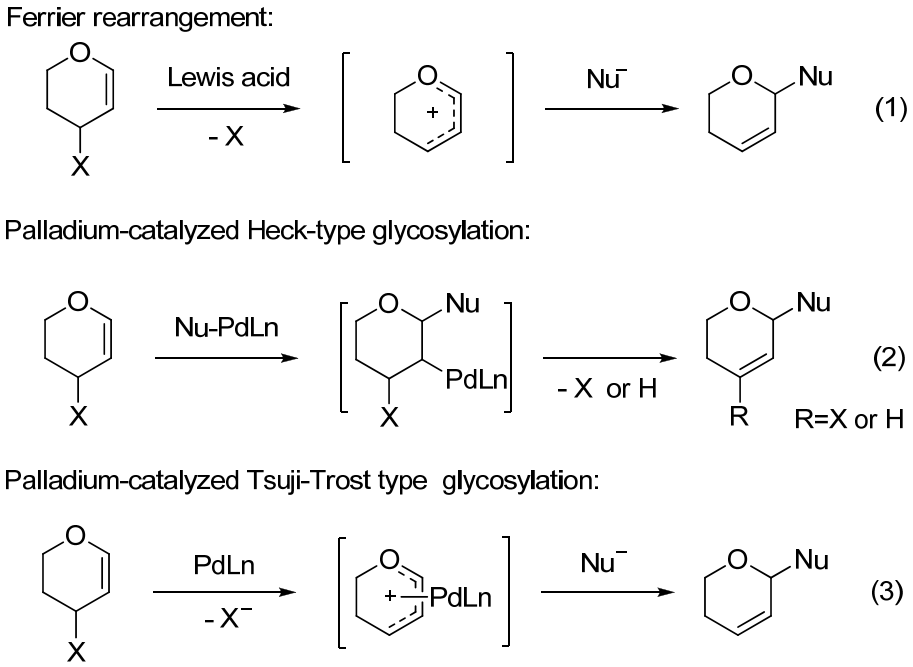
Chapter 3
Stereoselective *β*-*C*-Glycosylation *via* Palladium-Catalyzed Decarboxylative Allylation: Application to Natural Products Synthesis

3.1 Introduction

Synthesis of 2,3-unsaturated *C*-glycosides has received considerable attention in the field of synthetic carbohydrate chemistry, because these unique scaffolds are versatile building blocks for accessing a variety of natural and unnatural compounds with important pharmacological properties. Among the wide variety of methods toward the synthesis of 2,3-unsaturated *C*-glycosides, Lewis acid-promoted Ferrier rearrangement is indubitably the most employed (**Scheme 3.1**, eq 1). However, the strict requisite of glycosyl acceptors generally limits the reaction to specific nucleophiles with strong reactivity, and in some cases, the consumption of stoichiometric Lewis acid is inevitable. In addition, results from Ferrier *C*-glycosylation are often less optimal as only moderate *α*-selectivity can be observed; achieving acceptable *β*-selectivity is almost impossible by means of Ferrier *C*-glycosylation. Consequently, the development of new methods toward the synthesis of 2,3-unsaturated *C*-glycosides is required.

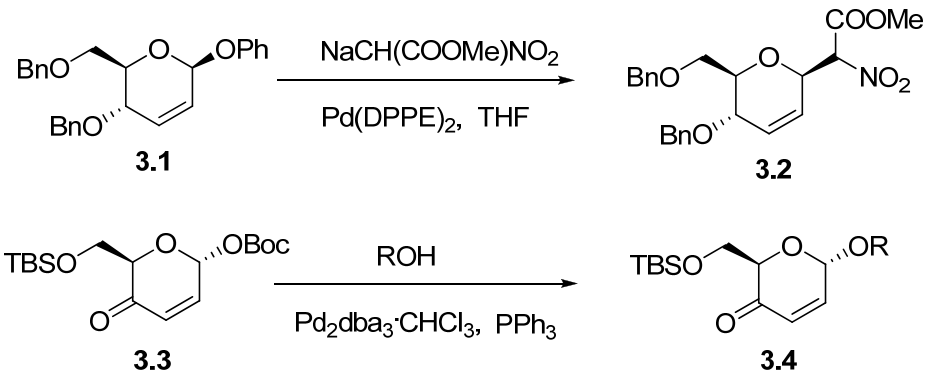
Recent advancements have demonstrated the efficiency of palladium-catalyzed coupling reactions and thus, drawn considerable interest in applying this strategy into carbohydrate chemistry, particularly in the synthesis of 2,3-unsaturated glycosides. Given the vinylic moiety featured in glycals, the Heck-type coupling reaction was intensively studied and successfully applied by using mercury salts,[1] aryl boronic

acids,[2] aryl halides,[3] enol triflates[4] and benzoic acids[5] as coupling partners. However, this strategy is also limited by the α-selectivity of the products (**Scheme 3.1**, eq 2).

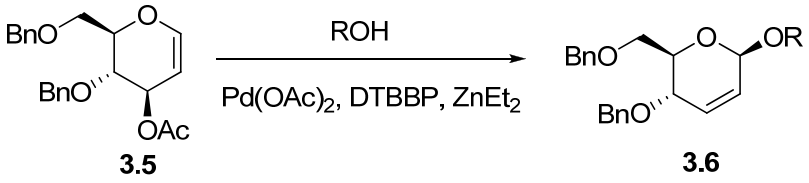


Scheme 3.1 Strategies of 2,3-unsaturated sugar synthesis.

Considering the allylic feature of glycals, palladium-catalyzed allylic alkylation[6] presumably becomes a solution to produce 2,3-unsaturated glycosides with β-selectivity. This is due to the fact that the palladium complex is postulated to approach the π-bound of glycal from the α-face, which leads to nucleophilic attack from the opposite face, resulting in the β-product (**Scheme 3.1**, eq 3). Although this strategy has been investigated 30 years ago, the formation of Pd π-allyl species in glycal system has long been recognized as tedious and difficult.[7] One solution is to generate a more activated pyranose system, such as **3.1** and **3.3** (**Scheme3.2**). In both cases, the stereoselectivities can be retained as the palladium complex coordinates to the pyranose from the less hindered face and the nucleophile attacks from the opposite face. Another solution is to employ the activators such as Et_2Zn in the reaction system (**Scheme 3.3**).[8] However, this method is only applicable in *O*-glycosylation.

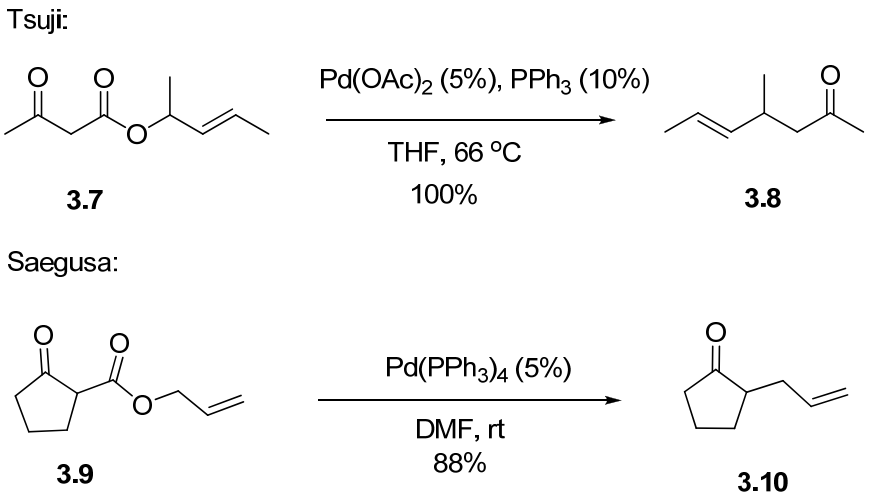


Scheme 3.2 Reaction with active pyranose system.

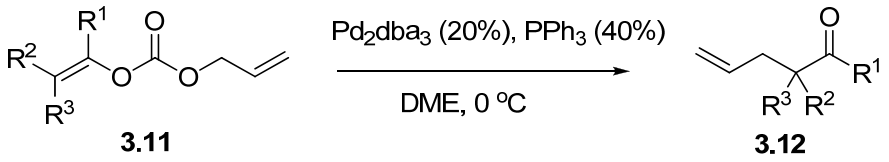


Scheme 3.3 Et_2Zn-activated glycosylation.

In recent years, decarboxylative allylation (DcA) reaction has become a powerful tool for C-C bond formation and has drawn considerable attention due to its high efficiency, mild reaction condition and green feature with CO_2 as the only by-product released.[9] The earliest DcA reactions were disclosed by Tsuji[10] and Saegusa[11] almost simultaneously in 1980 (**Scheme 3.4**). It was found that catalytic amount of Pd promoted the intermolecular transformation of allylic *β*-ketoester (**3.7** or **3.9**) to produce *γ,δ*-unsaturated ketones (**3.8** or **3.9**) in high yield with the release of CO_2. Since the pioneering works established by these authors, DcA reactions have been extensively studied and a wide range of substrates were examined, including allyl enol carbonates (**Scheme 3.5**).[12] In addition, asymmetric DcA has also been achieved by employing chiral ligands in the reaction system (**Scheme 3.6**).[13] In terms of the catalyst, other than Pd, Ru and Ir have also been discovered to facilitate DcA reactions.[14]

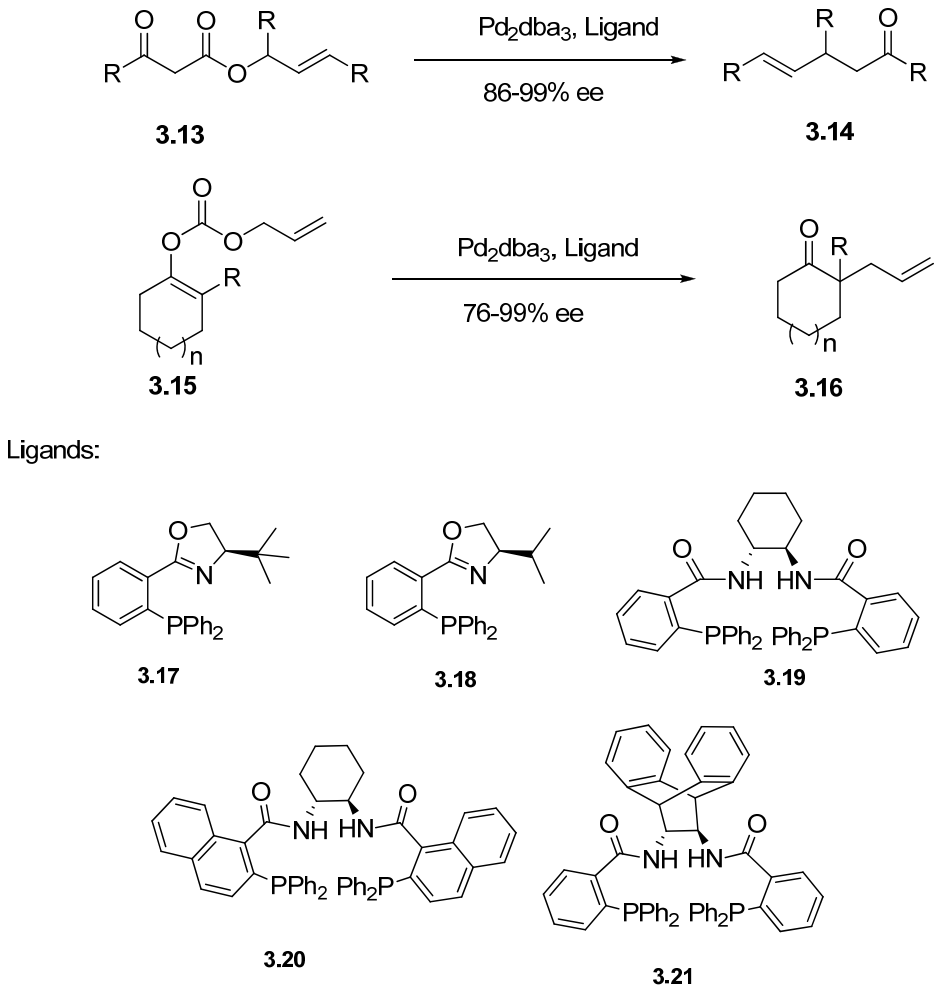


Scheme 3.4 Tsuji-Saegusa decarboxylation allylation.

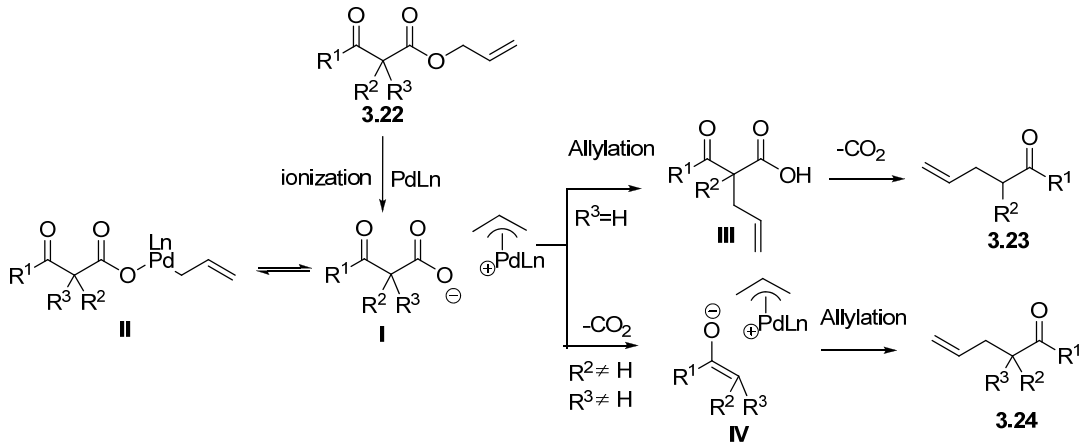


Scheme 3.5 Decarboxylation allylation of allyl enol carbonates.

The mechanism of DcA reactions was proposed to be dependent on the substrate and reaction conditions. Simple modifications to the substrates or reaction conditions in terms of ligands may also lead to a change in the mechanism.[9e] In general, the reaction of DcA for allylic *β*-ketoester involves 3 steps: ionization, allylation and decarboxylation (**Scheme 3.7**). Palladium-induced ionization is the first step commonly for all substrates, and a *π*-allyl palladium carboxylate ion pair is produced. This ion pair is in equilibrium with the neutral *σ*-allyl palladium complex. The sequence of the next two steps is generally dependent on the substrate. For *α*,*α*-disubstituted esters, decarboxylation occurs first to form a reactive site for further allylation. In contrast, for substrates possessing an *α*-hydrogen, it is suggested that allylation precedes decarboxylation.



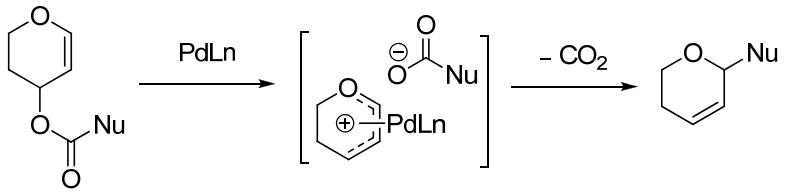
Scheme 3.6 Asymmetric decarboxylation allylation.



Scheme 3.7 Mechanism of decarboxylation allylation reaction.

Inspired by these reports, we envisioned that the palladium-catalyzed decarboxylation of the C-3 ester of glycal would be helpful in the formation of a Pd-π-

allyl intermediate which might accomplish the desired *C*-glycosylation with high stereoselectivity (**Scheme 3.8**).



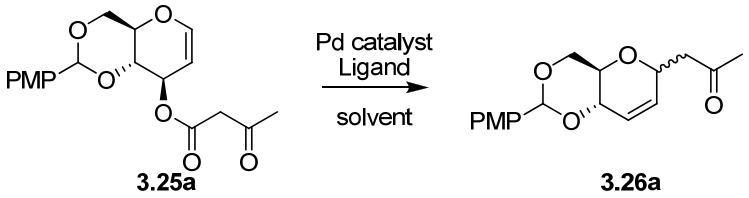
Scheme 3.8 Pd-catalyzed decarboxylative glycosylation.

3.2 Decarboxylative *C*-glycosylation on sugar scaffold

To validate our hypothesis, a decarboxylative coupling reaction of compound **3.25a** was carried out in the presence of catalytic amount of $Pd(PPh_3)_4$ in DMF at 80 °C for 12 h. To our delight, the regiospecific coupling product **3.26a** was obtained in 50% yield with a β/α ratio of 6 to 1 (**Table 3.1**, entry 1). To improve the yield and selectivity, various Pd catalysts were screened in the presence of 1,2-bis(diphenylphosphino)ethane (DPPE) ligand in DMF (**Table 3.1**, entries 2-4). It was found that the reaction catalyzed by $Pd(OAc)_2$ gave better yield and diastereoselectivity (**Table 3.1**, entry 3) than that of $Pd_2(dba)_3$ and $PdCl_2$ (**Table 3.1**, entries 2 and 4). The reaction catalyzed by $Pd(OAc)_2$ and DPPE in toluene was also found to be superior to that in DMF, THF, CH_2Cl_2 and MeCN in terms of diastereoselectivities (**Table 3.1**, entries 5-9). Decreasing the reaction temperature to 60 °C improved the yield to 80% (**Table 3.1**, entry 10). This is due to the fact that the sugar scaffold is prone to decomposition under high temperatures. However, when the temperature was further decreased, the reaction was sluggish and only trace amount of the product was obtained (**Table 3.1**, entry 11). Further ligand screening (**Table 3.1**, entries 12-16) revealed that excellent yield (90%) and exclusive diastereoselectivity

could be obtained when the model reaction was carried out under the optimal conditions, which consist of $Pd(OAc)_2$ and 1,1-bis(diisopropylphosphino)ferrocene (DiPPF) in toluene at 60 °C for 2 h. The stereoselectivity of compound **3.26a** was further confirmed by X-ray structure analysis (**Figure 3.1**).

Table 3.1 Optimization of decarboxylative glycosylation.[a]



3.25a **3.26a**

Entry	Catalyst/Ligand	Solvent	Temp (°C)	Yield (%)[a]	β:α
1	$Pd(PPh_3)_4$	DMF	80	50	6:1
2[b]	$Pd_2(dba)_3$/ DPPE	DMF	80	38	20:1
3[b]	$Pd(OAc)_2$/ DPPE	DMF	80	50	20:1
4[b]	$PdCl_2$/ DPPE	DMF	80	-	-
5[b]	$Pd(OAc)_2$/ DPPE	THF	80	51	>20:1
6[b]	$Pd(OAc)_2$/ DPPE	toluene	80	58	>20:1
7[b]	$Pd(OAc)_2$/ DPPE	CH_2Cl_2	40	-	-
8[b]	$Pd(OAc)_2$/ DPPE	MeCN	80	55	>20:1
9[c]	$Pd(OAc)_2$/ DPPE	toluene	80	68	>20:1
1[c]	$Pd(OAc)_2$/ DPPE	toluene	60	80	>20:1
11[c]	$Pd(OAc)_2$/ DPPE	toluene	40	trace	n.d.
12[c]	$Pd(OAc)_2$/ PPh_3	toluene	60	70	5:1
13[c]	$Pd(OAc)_2$/ DPPP	toluene	60	71	10:1
14[c]	$Pd(OAc)_2$/ PCy_3	toluene	60	-	-
15[c]	$Pd(OAc)_2$/BINAP	toluene	60	15	β-only
16[c]	$Pd(OAc)_2$/DiPPF	toluene	60	90	β -only

[a] Isolated yields.[b] The reaction was conducted for 12 h. [c] The reaction was conducted for 2 h

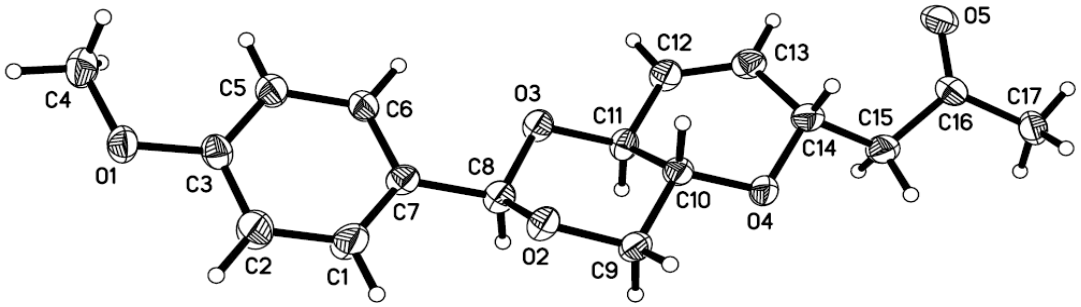


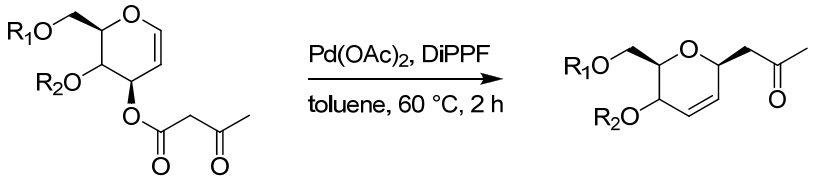
Figure 3.1 X-ray structure of **3.26a**.

This inspiring result motivated us to advance the study of this decarboxylative glycosylation. Gratifyingly, similar results were obtained when other protecting groups were applied and the results are summarized in **Table 3.2**. The protecting groups on glucal, such as benzyl, TBS and PMB groups, did not show any negative effect on the reaction and similar yields and exclusive *β*-anomers were afforded (**Table 3.2**, entries 1-3). Moreover, the decarboxylative glycosylation of 4,6-benzyl galactal derivative gave pure *β*-anomer as the only product as well (**Table 3.2**, entry 4).

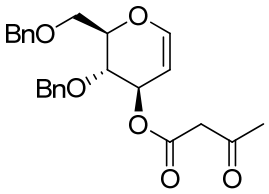
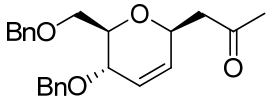
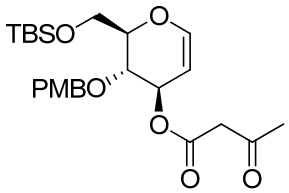
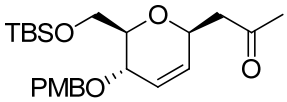
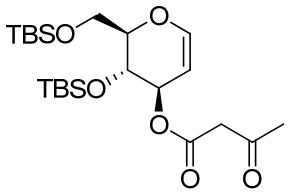
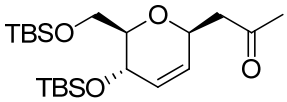
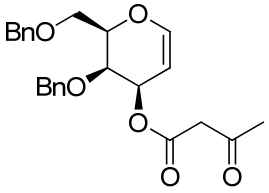
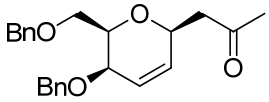
Subsequently, the substituted ketone variants were modified to investigate and broad the application of decarboxylative glycosylation. *γ*-Aliphatic substituted *β*-ketones were found to undergo the decarboxylative coupling under the optimized condition, providing good yields (**Table 3.3**, entries 1-5). From this result, it is noteworthy that sterically hindered and cyclic substituents were able to afford the desired coupling products with exclusive *β*-selectivity (**Table 3.3**, entries 3-5). However, the secondary substituted *β*-ketone substrates provided a mixture due to prochirality of the *α*-carbon (**Table 3.3**, entries 4 and 5). In view of the promising results, the attention was then directed to aromatic substituents. Employing the optimized conditions, an array of *γ*-aromatic substituted *β*-ketones was examined (**Table 3.3**, entries 6-10). The coupling reactions proceeded well with aromatic

ketones bearing electron-withdrawing substituents, which have minor influence on the glycosylation. On the contrary, the reactions of aromatic ketones possessing electron-donating groups required longer time to accomplish and lower yields were obtained.

Table 3.2 Substrate scope of protecting groups. [a,b]

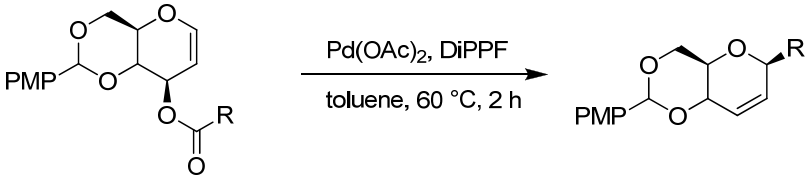


3.25 **3.26**

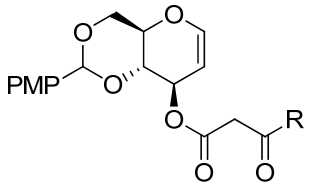
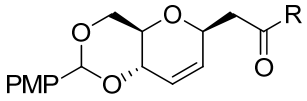
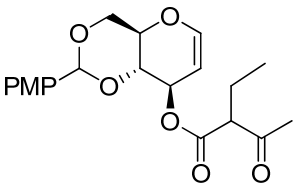
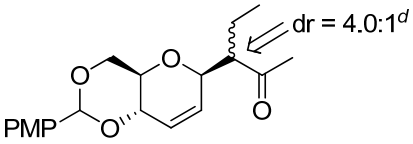
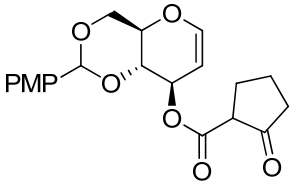
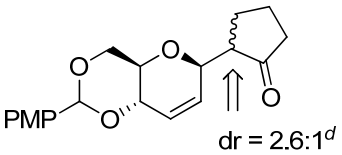
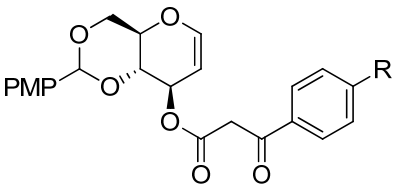
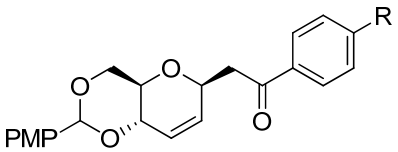
Entry	Starting Material	Product	Yield
1	 **3.25b**	 **3.26b**	86%
2	 **3.25c**	 **3.26c**	83%
3	 **3.25d**	 **3.26d**	80%
4	 **3.25e**	 **3.26e**	90%

[a] Reactions were carried out on a 0.2 mmol scale in the presence of 0.01 mmol of $Pd(OAc)_2$ and 0.02 mmol of DiPPF in 2 mL toluene at 60 °C for 2 h. [b] Isolated yields.

Table 3.3 Substrate scope of *β*-keto esters. [a,b,c]



3.25 **3.26**

Entry	Starting Material	Product	Yield
			
1	R = ethyl **3.25f**	**3.26f**	85%
2	R = *i*-propyl **3.25g**	**3.26g**	75%
3	R = *t*-butyl **3.25h**	**3.26h**	52%
4	 **3.25i**	 dr = 4.0:1[d] **3.26i**	65%
5	 **3.25j**	 dr = 2.6:1[d] **3.26j**	66%
			
6	R = H **3.25k**	**3.26k**	88%
7	R = NO_2 **3.25l**	**3.26l**	82%
8	R = Cl **3.25m**	**3.26m**	71%
9	R = CH_3 **3.25n**	**3.26n**	70%
10	R =OCH_3 **3.25o**	**3.26o**	62%

[a] Reactions were carried out on a 0.2 mmol scale in the presence of 0.01 mmol of $Pd(OAc)_2$ and 0.02 mmol of DiPPF in 2 mL toluene at 60 °C for 2 h. [b] Isolated yields. [c] PMP = 4-Methoxyphenyl. [d] *dr* was determined by ^{1}H NMR.

With the success achieved with minimol scale of *β*-ketone substrates, the reaction was upscaled to examine the possibility of commercial applications. Notably, the reaction proceeded on a gram scale without the reduction of yield (**Scheme 3.9**).

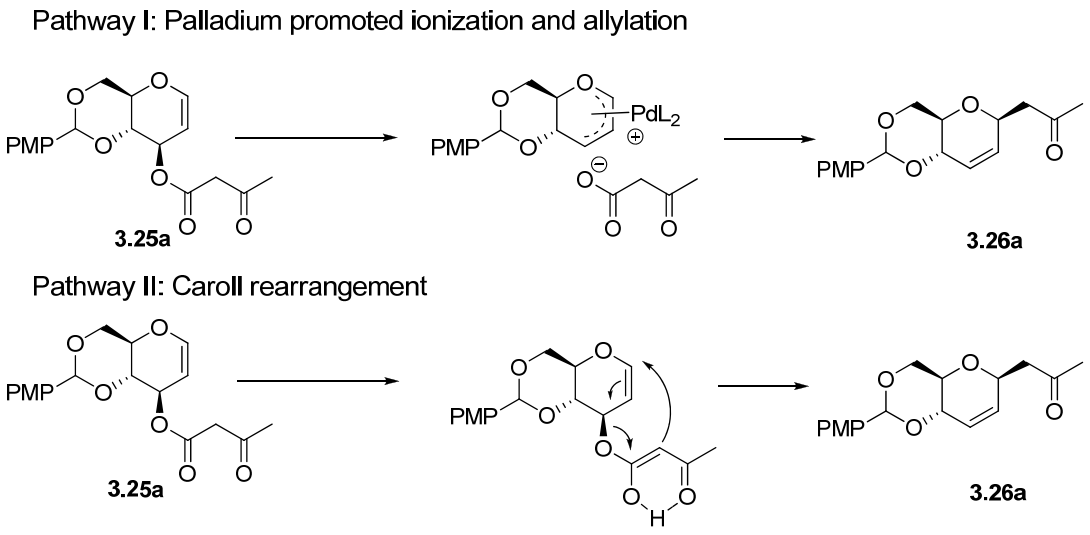
Scheme 3.9 Gram scale synthesis of **3.26k**.

3.3 Mechanism study

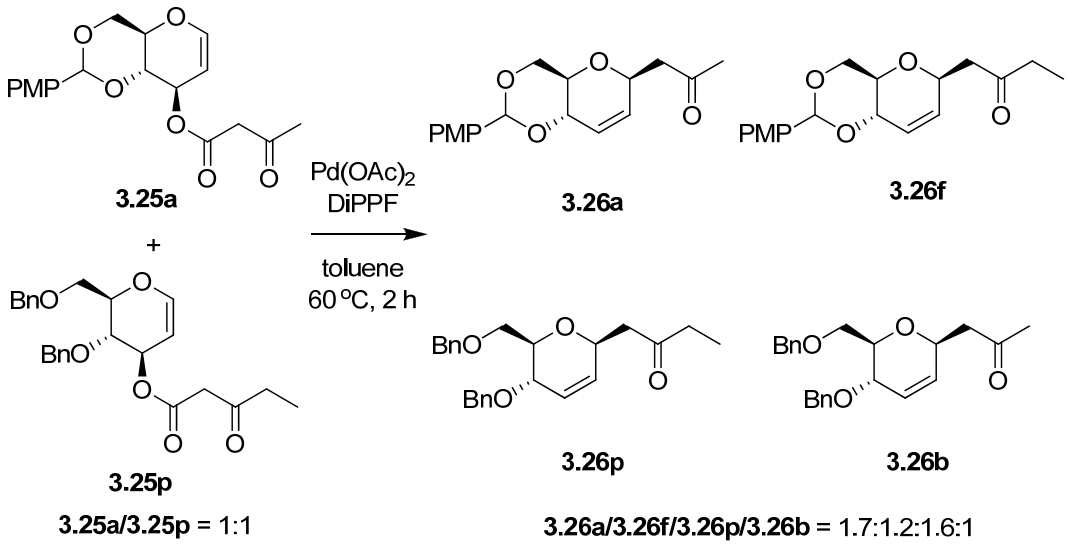
Although the most feasible postulation is that the reaction passes through a palladium catalyzed DcA, an intramolecular rearrangement route (namely Carroll rearrangement) is also possible (**Scheme 3.10**).[15] To identify this possibility, we carried out a crossover decarboxylative coupling reaction. A 1:1 mixture of **3.25a** and **3.25p** was subjected to the optimized reaction conditions. Interestingly, it was found that completely scrambled products were formed in a ratio of 1.7:1.2:1.6:1 (**3.26a**/**3.26f**/**3.26p**/**23.26b**) and only *β*-products were observed. This clearly indicates that the palladium promoted ionization occurred at the beginning of the reaction and an intramolecular rearrangement pathway was not involved.

In addition, the 3,6-*trans* substrate **3.27** was tested under the standard reaction conditions. Interestingly, unlike the 3,6-*cis* substrates, the reaction of 3,6-*trans* substrate **3.27** gave an α/*β* mixture with a 1.2:1 ratio (**Scheme 3.12**). We think it is because the top face of **3.25a** is much bulky than bottom face while the steric environments between top and bottom face of **3.27** are very close. A DFT study[16] revealed that the energy difference between 3,6-*cis*-A and -B is about 1.6

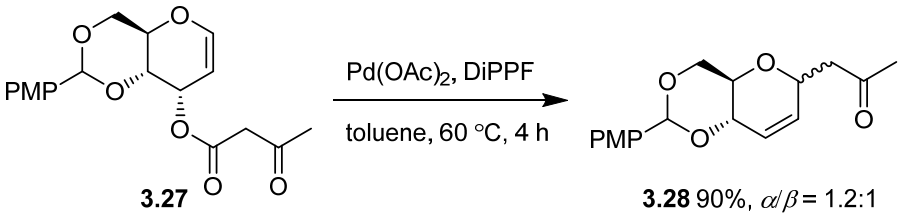
kcal/mmol (**Scheme 3.13**). However, in contrast, the energy difference between 3,6-*trans*-A and -B is smaller. These energy differentials could explain the selectivity differences between 3,6-*cis* and 3,6-*trans* substrates. Furthermore, this phenomenon also implies that the ionization occurred and the ketone enolate anion may attack the allyl group from the opposite face of the Pd complex. Thus, the reaction should pass through an outer-sphere mechanism.[17]



Scheme 3.10 Possible pathways to compound **3.26a**.

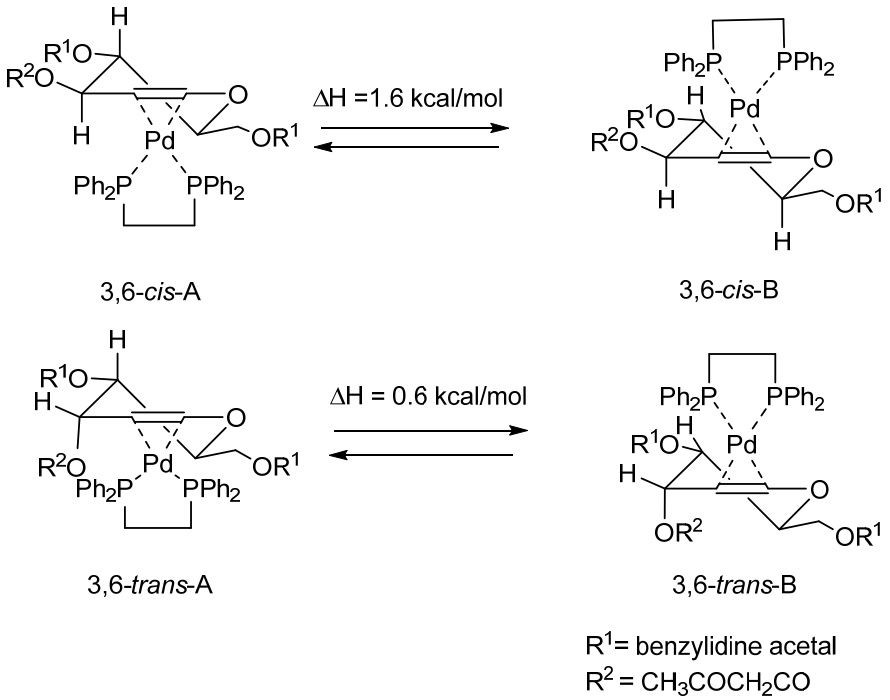


Scheme 3.11 Crossover reaction of compound **3.25a** and **3.25p**.



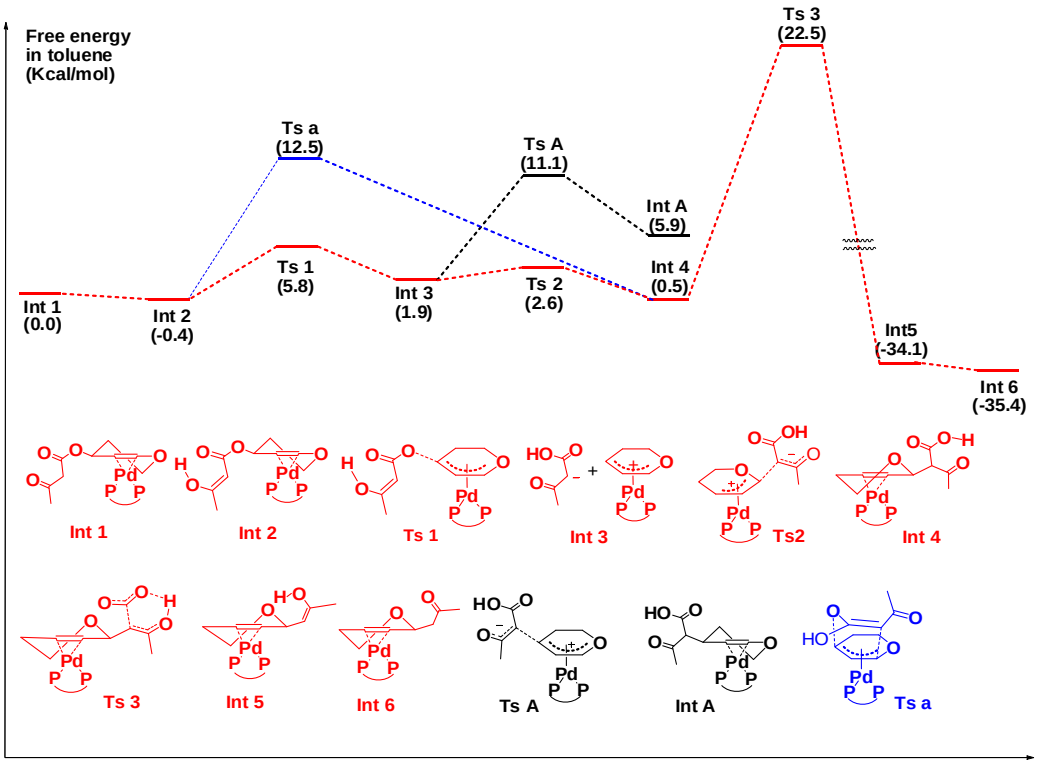
3.27 **3.28** 90%, α/β = 1.2:1

Scheme 3.12 Decarboxylation coupling of compound **3.27**.



Scheme 3.13 Calculated thermal enthalpies of 3,6-*cis* and 3,6-*trans* substrates. Geometry optimization and frequency were performed at the B3LYP level with basic set of 6-31+G(d) for C, H, O and LanL2DZ for Pd and P, solvent effect was not taken into account.

To further investigate the mechanism, a standard DFT calculation was conducted (**Figure 3.2 and 3.3**).[18] The palladium complex **Int 1** was transformed to its enoate form **Int 2** with a 0.4 kcal/mol of energy released. From **Int 2**, palladium induced ionization of the allyl carboxylate produces ion pair **Int 3** through **Ts 1** (5.8 kcal/mol). From **Int 3**, two possible pathways were considered. One possible pathway involves the stabilized enolate attacking the C-3 position of carbohydrate through **Ts A**, producing **Int A**. On the other hand, the negative enolate can attack C-1 through **Ts 2**, which would lead to the formation of **Int 4**. However, from **Int 3**, the transition state



Reaction coordinate: b3lyp/CPCM, basic set = 6-311+G(d,p) for C, H, O, P and SDD for Pd

Figure 3.2 DFT study of mechanism.

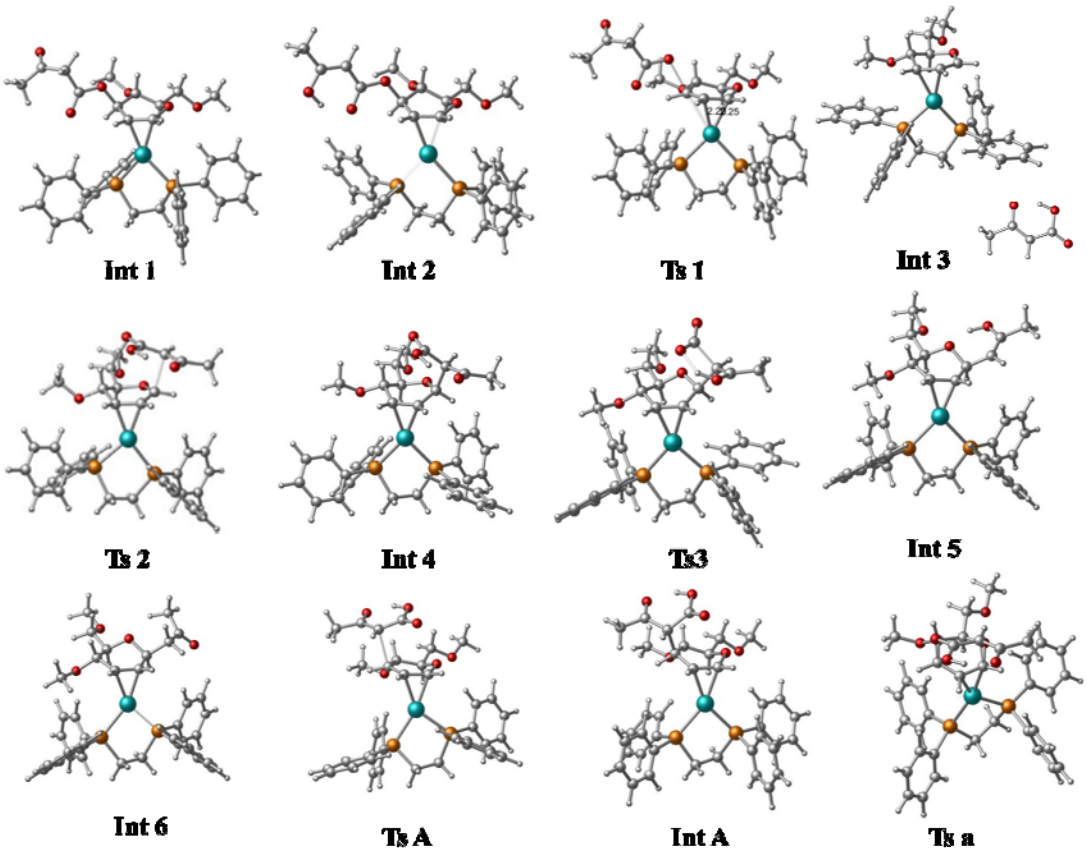


Figure 3.3 Optimized structures.[19]

Ts A resulting from the C-3 attack has a much higher energy level than that of the C-1 attack. In an orbital point of view, C-1 position of LUMO has a larger coefficient than that of C-3 position (**Figure 3.4)** which indicates that the C-1 attack pathway is much more accessible. Subsequently, the release of CO_2 from **Int 4** through **Ts 3** produces the decarboxylative product **Int 5** From **Int 4** to **Ts 3**, the free energy increases with a variance of 22.5 kcal/mol. Thus, decarboxylation is the rate-determinating step in the catalytic cycle. Finally, the enolate **Int 5** transforms to a more stable ketone **Int 6**. The possibility of intramolecular rearrangement *via* a boat transition state[17c] **Ts a** to **Int 4** was also considered. However, the energy barrier from **Int 2** to **Ts a** is much higher than that of ionization, suggesting that the intramolecular rearrangement is unlikely. Thus, this reaction was suggested to pass through a Pd-coordination, ionization, allylation and decarboxylation in sequence, which is in agreement with the DcA reaction of precedent literature reports.

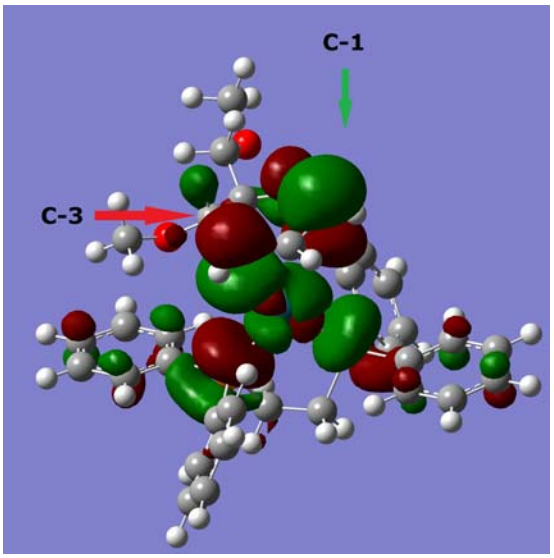


Figure 3.4 LUMO 0f oxocarbenium cation (cataion part of Int 3)

3.4 DcA on normal pyran system

This palladium-catalyzed decarboxylative coupling reaction could obviously be further expanded to normal pyran system to produce *cis*-2,6-pyrane. Due to the abundance of *cis*-2,6-tetrahydropyrane motifs in natural products (**Figure 3.5**), great efforts have been made to achieve the efficient stereoselective synthesis of *cis*-2,6-disubstitued pyrans.[20] Of particular importance are Prins cyclization,[21] intramolecular oxa-cyclization,[22] oxa-Diels-Alder reaction[23] and Japp-Maitland reaction[24] *et. al*.. Given the high efficiency of palladium-catalyzed decarboxylative coupling reaction, application of this method to the normal pyran system could provide a practical access to the synthesis of natural products.

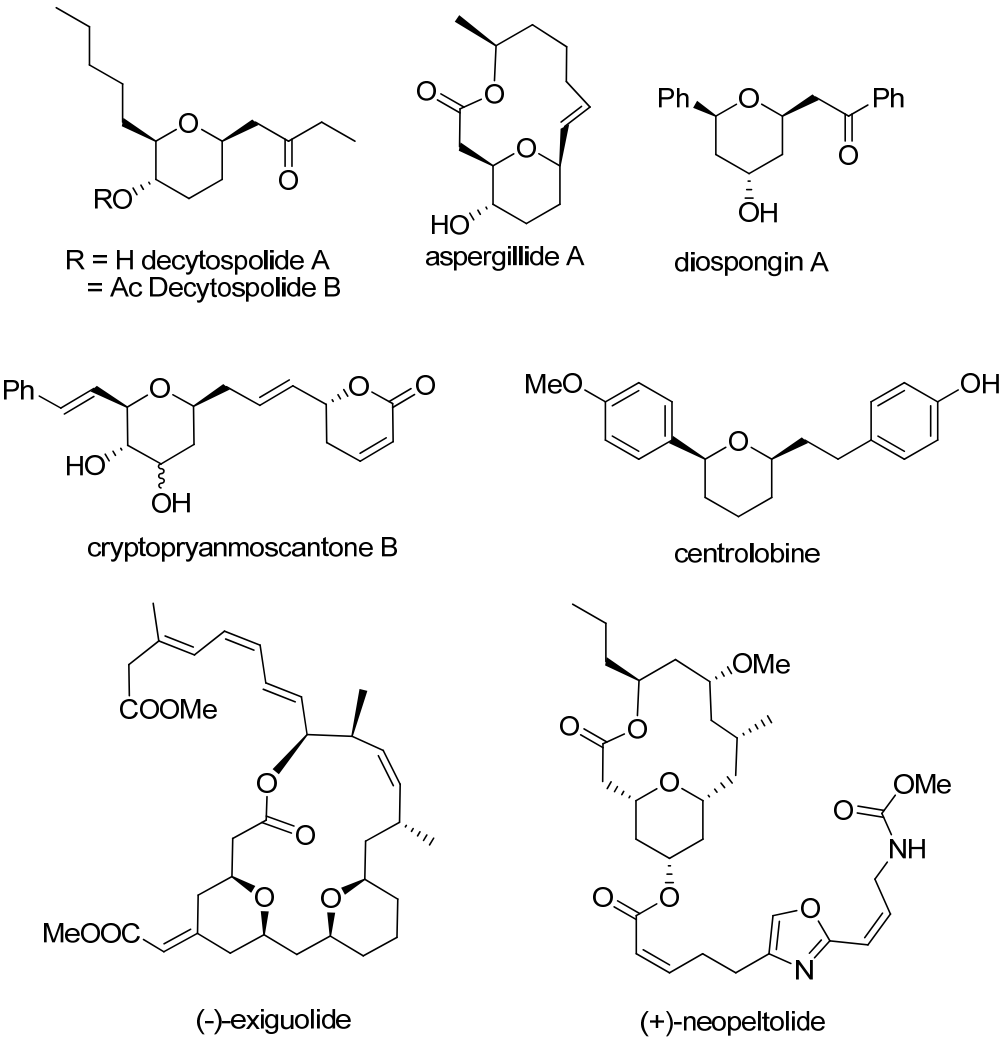


Figure 3.5 Naturally occurring 2,6-*cis*-THPs.

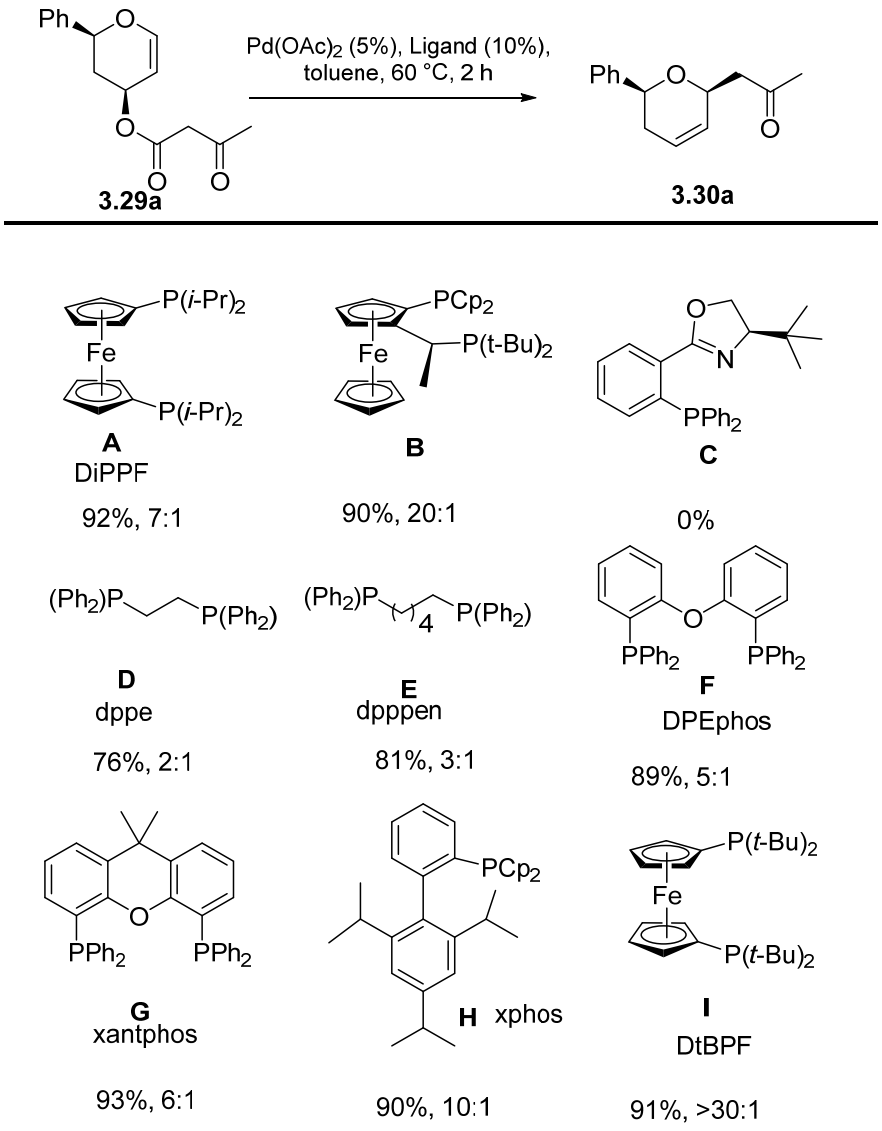
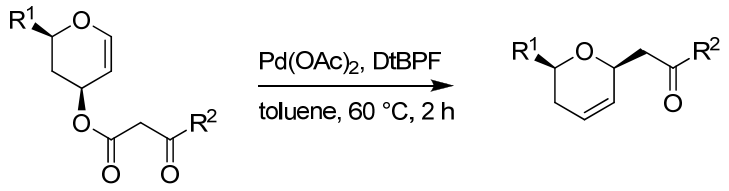


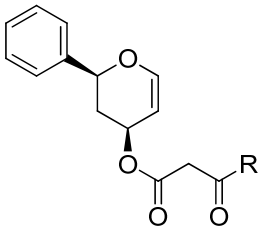
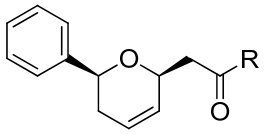
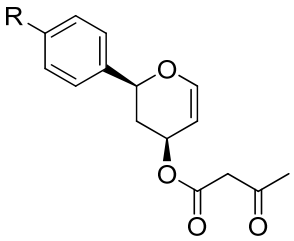
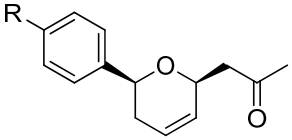
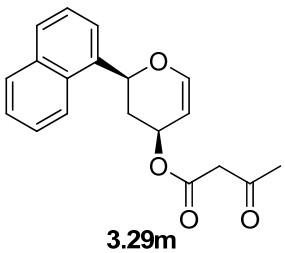
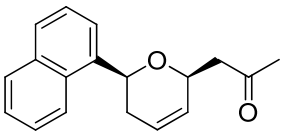
Figure 3.6 Screening of ligands.

Our investigation commenced with the decarboxylative coupling reaction of **3.29a** under the optimized reaction conditions established previously ($Pd(OAc)_2$ 2.5% mol, DiPPF 10 % mol, toluene, 60 °C) (**Figure 3.6**). After 3 h, the starting material was consumed and the desired product **3.30a** was obtained in 92% yield. However, only 7:1 *cis* to *trans* selectivity was observed. Further screening of ligands revealed that bulky ligands could increase the diastereoselectivity. Among them, ligand **B** enhanced the selectivity to 20:1 while ligand **I** gave only the *cis* product in 91% yield. Other ligands such as dppe **D** and dpppen **E** gave poor selectivity, while xanphos **G** and

Table 3.4 Substrate scope.[a]



3.29 **3.30**

Entry	Starting Material		Product	Yield[b]
				
1	R = ethyl	**3.29b**	**3.30b**	85%
2	R = *n*-propyl	**3.29c**	**3.30c**	78%
3	R = *i*-propyl	**3.29d**	**3.30d**	86%
4	R = *t*-butyl	**3.29e**	**3.30e**	89%
5	R = Ph	**3.29f**	**3.30f**	94%
6	R = (4-OMe)Ph	**3.29g**	**3.30g**	86%
				
7	R =Me	**3.29h**	**3.30h**	82%
8	R = OMe	**3.29i**	**3.30i**	83%
9	R =Br	**3.29j**	**3.30j**	86%
10	R = NO_2	**3.29k**	**3.30k**	87%
11	R =COOMe	**3.29l**	**3.30l**	88%
12	 **3.29m**		 **3.30m**	91%

[a] Reactions were carried out on a 0.2 mmol scale in the presence of 0.01 mmol of $Pd(OAc)_2$ and 0.02 mmol of DtPPF in 2 mL toluene at 60 °C for 2 h. [b] Isolated yields..

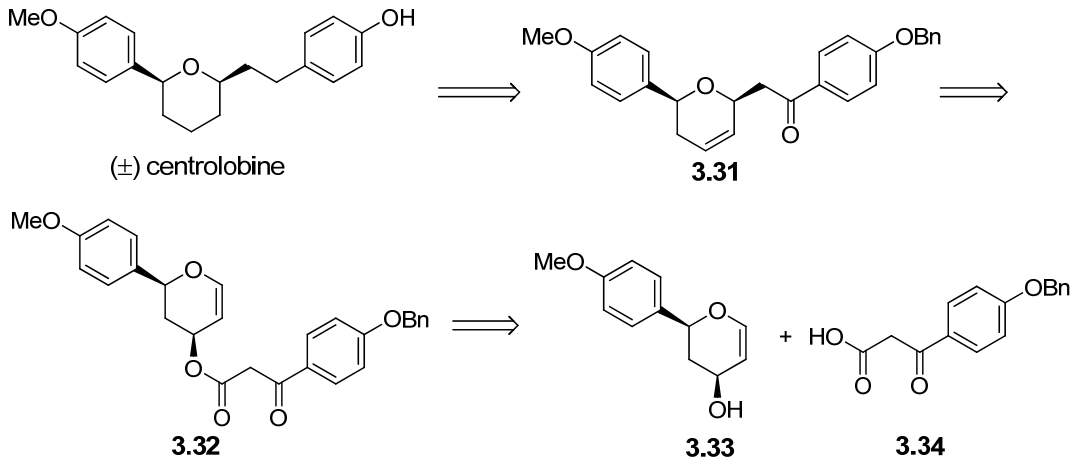
xphos **H** gave moderate selectivity, albeit with good yields. Interestingly, ligand **C** could not promote this decarboxylative coupling reaction.

The substrate scope was further examined as depicted in **Table 3.4**. Gratifyingly, in all cases, good to excellent yields and sole *cis* selectivity were obtained. A variety of functional groups at the α-position of ketone was tolerated. Interestingly, sterically hindered substituents such as isopropyl and tertiary butyl gave slightly higher yields. The reaction of substrates possessing aromatic substituents at the *α*-position of ketone proceeded very well and gave higher yields than that of aliphatic substituents. R^1 group was also modified to investigate and broaden the applications of the decarboxylative coupling reaction. Both electron rich and electron deficient aromatic substituents at the R^1 position could participate in this decarboxylative coupling reaction and gave good to excellent yields.

3.5 Application to natural product synthesis

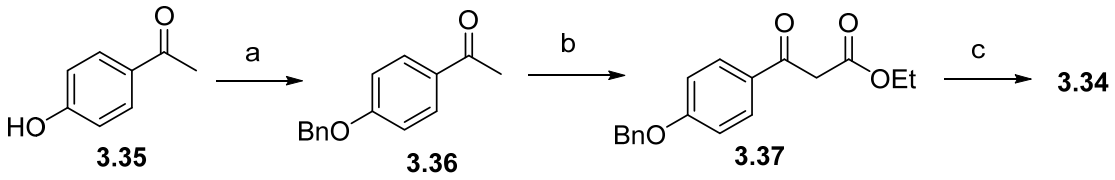
3.5.1 Total synthesis of (±)-centrolobine

Centrolobine is a tetrahydropyranyl diarylheptanoids type of natural compound possessing 2,6-*cis* disubstituents. (-)-Centrolobine was isolated from the heartwood of *Centrolobium robustum* and the stem of *Brosinium potabile*, while the (+)-enantiomer was isolated from *Centrolobium tomentosum*.[25] Although the basic structure was elucidated in 1964,[25a] the absolute structure of (-)-centrolobine was only confirmed in 2002 by Colobert *et al*. Centrolobines have been found to exhibit anti-inflammatory, anti-bacterial, and anti-leishmanial characteristic.[26] The excellent bioactivities and relatively simple structure have drawn considerable interests toward the total synthesis of centrolobine, both in racemic and optically pure forms.[27]



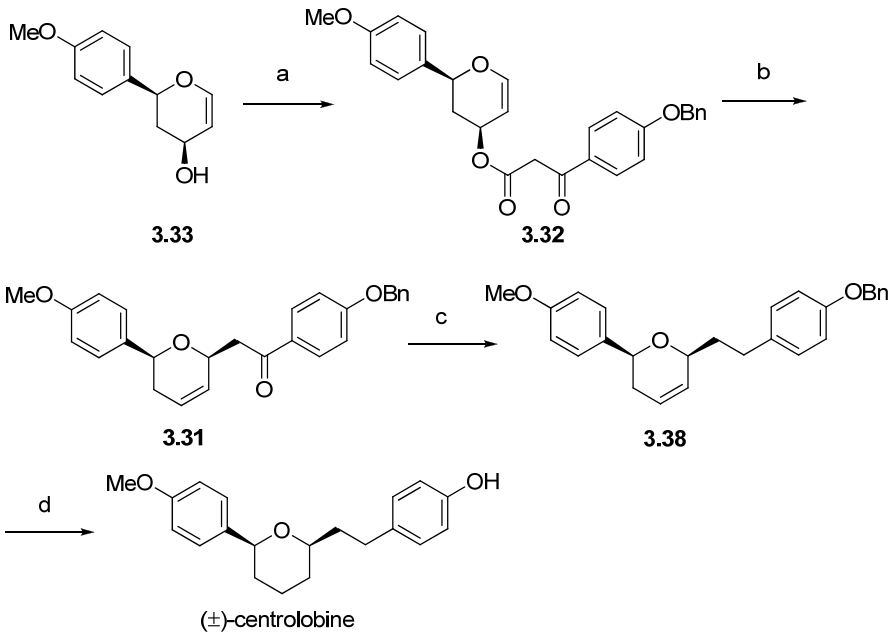
Scheme 3.14 Retro-synthetic analysis.

Based on our development of decarboxylative coupling reaction, we envisioned that centrolobine could be obtained by the decarboxylative allylation reaction of compound **3.32,** which could be assembled from allyl alcohol **3.33** and acid **3.34** (**Scheme 3.14**).



Scheme 3.15 Synthesis of **3.34**. (a) BnBr, K_2CO_3, acetone, 93%; (b) $CO(OEt)_2$, NaH, THF, 82%; (c) KOH, $EtOH/H_2O$, 87%.

Our synthesis started from the preparation of *β*-keto acid **3.34** (**Scheme 3.15**). Protection of commercially available compound **3.35** with BnBr in the presence of K_2CO_3 gave **3.36** in 93% yield. Compound **3.36** was further transformed to *β*-ketoester **3.37** in 82% yield. Hydrolysis of the ester under strong basic conditions furnished acid **3.34** in 87% yield. It is worthy of note that *β*-keto acid **3.37** is unstable, which should be handled at low temperatures and used in the next step immediately.

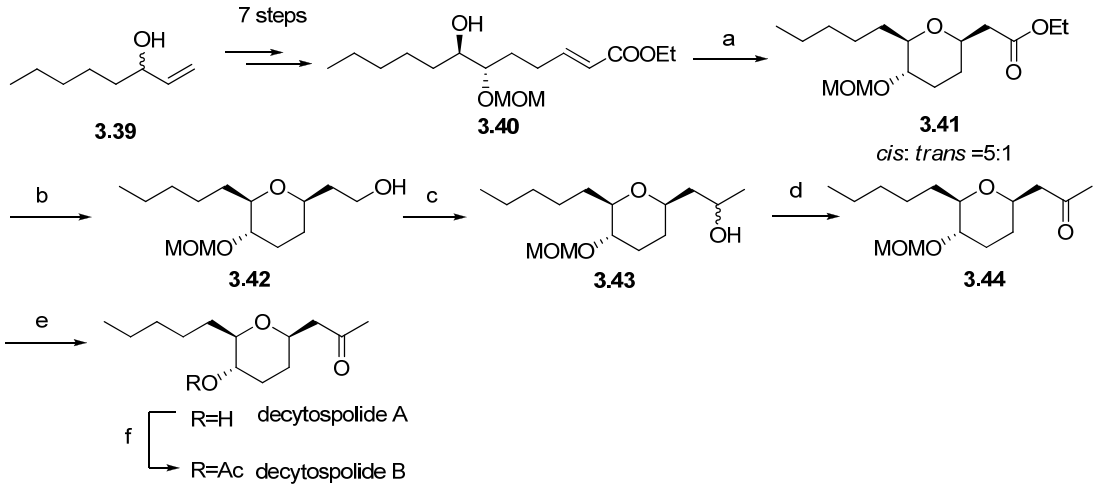


Scheme 3.16 Total synthesis of centrolobine. (a) DCC, DMAP, CH_2Cl_2, **3.34**, 91%; (b) $Pd(OAc)_2$, DtBMP, toluene, 94%, (c) 1) $LiBH_4$, Et_2O; 2) TFA, Et_3SiH. 84%; (d) Pd/H_2, EtOH/EtOAc, 2 M HCl, 76%.

Esterification of known compound **3.33** with **3.34** produced **3.32** in good yield. Subjecting **3.32** to our standard decarboxylative coupling reaction led to **3.31** in 94% yield with exclusive *cis* selectivity. Further reduction of the ketone by $LiBH_4$ and TFA/Et_3SiH in two steps furnished **3.38** in 84% yield. However, attempts to reduce the double bond by routine hydrogenation led to low yield of the desired product due to the unexpected ring opening.[28] Fortunately, hydrogenation under acidic conditions removed both the double bond and the protecting group and offered (±)-centrolobine in 76% yield (**Scheme 3.16**). In conclusion, based on our strategy, the total synthesis of (±)-centrolobine was successfully achieved in 5 steps starting from known compound **3.33** with a total yield of 55% .

3.5.2 Total synthesis of (+)-decytospolide A and B

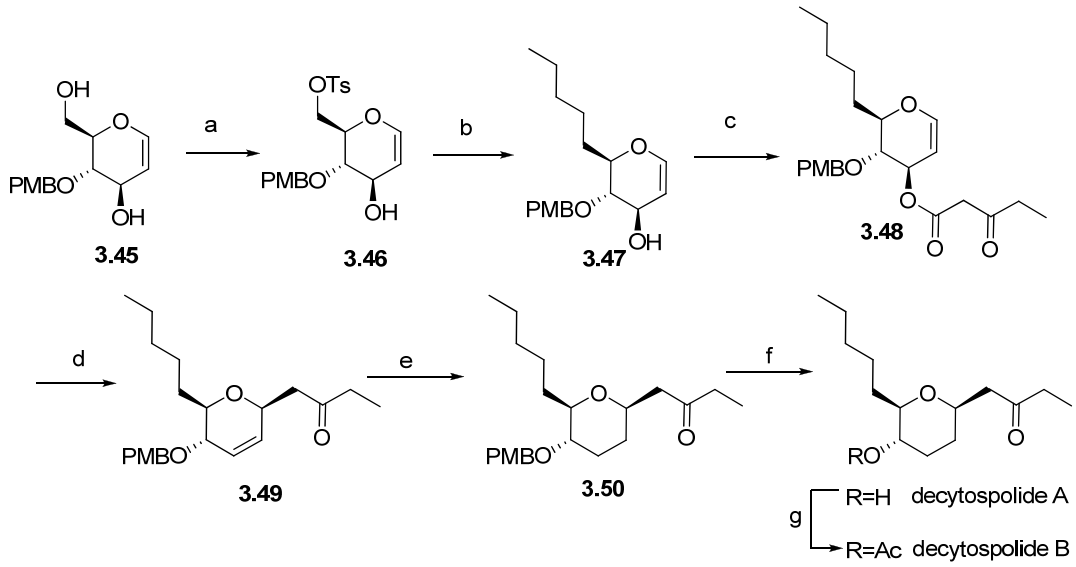
To further examine the synthetic utility of the novel DcA strategy, (+)-decytospolide A was chosen as our target. (+)-Decytospolide A was isolated from the *Cytospora sp.*, an endophytic fungus from *Ilex canariensis*, by Zhang and co-workers recently.[29] So far, only one research group has reported the total synthesis of decytospolide **A** and **B** (**Scheme 3.17**).[30] The synthesis involved Sharpless kinetic resolution and intramolecular oxa-Michael addition as the key steps. Starting from racemic allyl alcohol **3.39**, the total synthesis of decytospolide **A** and **B** were accomplished in 4.12% (13 steps) and 3.38% yield (14 steps) respectively.



Scheme 3.17 Reported total synthesis of decytopolide A and B. (a) DBU, toluene, reflux 72 h, 80%; (b) DIBAL-H, CH_2Cl_2, -78 ^oC, 90%; (c) 1. DMP, CH_2Cl_2; 2. EtMgBr, Et_2O, 75%; (d) DMP, CH_2Cl_2, 80%; (e) PMA-silica, 85%; (g) Ac_2O. pyridine, CH_2Cl_2, 82%.

Our synthesis started from the commercial available glucal **3.45**. Transformation of the primary alcohol of **3.45** to butyl group in two steps afforded **3.47** in good yield. Coupling of **3.47** with propionyl acetic acid generated γ-ketoester **3.48** in 86% yield. Again, our methodology of decarboxylative coupling worked well on substrate **3.48**, leading to 2,6-*cis*-dihydropyran **3.49** in high yield. However, the same problem as that

in our synthesis of centrolobine was encountered when we attempted to reduce the double bond by conventional hydrogenation. Even when the reaction was subjected to the acidic hydrogenation conditions as in the synthesis of centrolobine, low yield was obtained. Fortunately, the hydrogenation reaction catalyzed by Wilkinson's catalyst produced the desired product in excellent yield. Finally, removal of the PMB protecting group finished the total synthesis of decytospolide A in a total of 6 steps with 35% yield. Decytospolide B was obtained in 91% yield by protecting of the free OH group of decytospolide A with Ac_2O/pyr (**Scheme 3.18**).



Scheme 3.18 Total synthesis of decytospolide A and B. (a) TsCl (1.2 equiv), Pyridine, 0 ^{o}C - rt, 87%; (b) BuMgBr (4 equiv), CuI (2 equiv), THF, 0 ^{o}C - rt, 65%; (c) Propionyl acetic acid (1.5 equiv), *N,N'*-diisopropylcarbodiimide (DIC) (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 ^{o}C - rt, 86%; (d) $Pd(OAc)_2$ (0.05 equiv), DtBPF (0.1 equiv), toluene, 60 ^{o}C, 87%; (e) Wilkinson's catalyst (0.1 equiv), H_2, toluene, 50 ^{o}C, 95%; (f) DDQ (2.0 equiv), CH_2Cl_2/H_2O, 89%; (g) Ac_2O, Pyr. 91%.

3.5.3 Formal total synthesis of (+)-aspergillide A

Aspergillide A, B and C (**Figure 3.7**) were isolated from a marine-derived fungus, *Aspergillus ostianus* strain cultivated in a bromine-modified medium by Kusumi and co-workers in 2008.[31] These compounds showed significant cytotoxicity against mouse lymphocytic leukemia cells (L1210) (LD_{50} values: 2.1, 71.0 and 2.0 μg/mL, respectively).[28] In terms of structure, Aspergillide A, B and C are intriguing 14-membered macrolides, comprising of a 2,5,6-trisubstituted pyran ring fused with a 12-membered lactone ring. Their absolute stereochemistry was determined by total synthesis[32] and X-ray crystallographic analysis.[33]

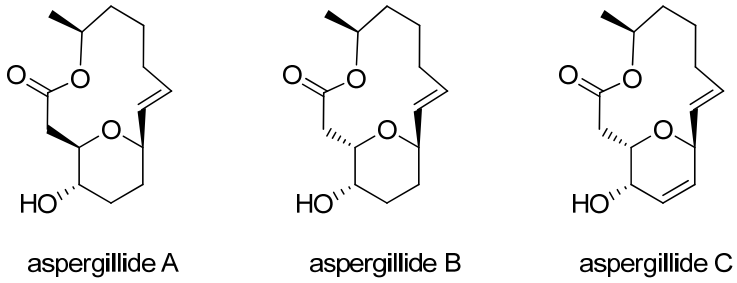
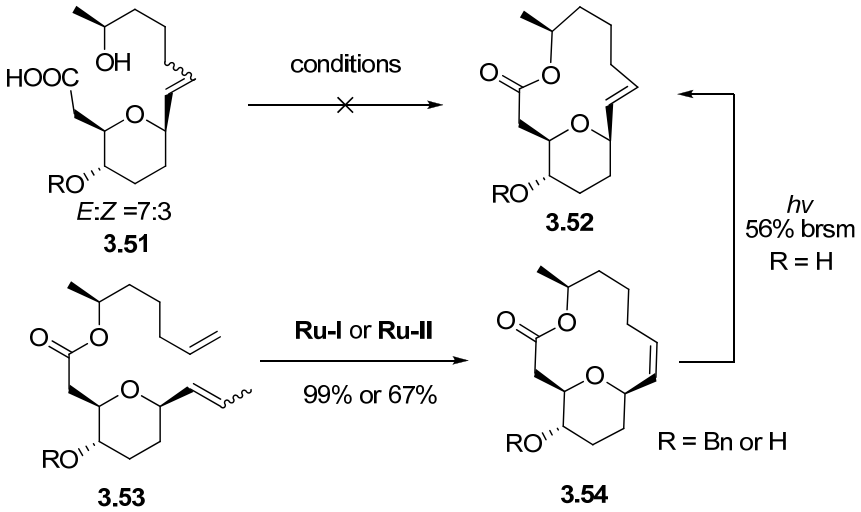


Figure 3.7 Aspergillide A, B and C.

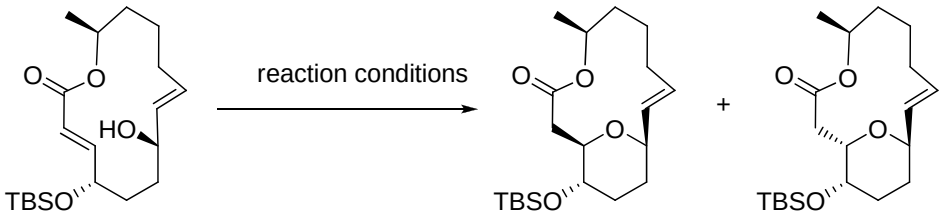
The synthetic challenges of aspergillides include the stereoselective construction of 2,6-substituents on tetrahydropyran ring and the building of macrolactone ring.[34] For the former, intramolecular oxa-Michael reaction and Lewis acids promoted *C*-glycosylation are found to be the solutions which produced good 2,6-*cis* or *trans* selectivity. To build the macrolactone ring, intramolecular lactonization and ring-closing metathesis (RCM) turned out to be the optimal choice. Both strategies worked well in the synthesis of aspergillide B and C, unfortunately, diminished results were obtained when these methods were applied to the synthesis of aspergillide A (**Scheme 3.19**).[35] Macrolactonization of **3.51** under Yamaguchi condition did not provide the desired *E* isomer **3.52**. Instead, only the *Z* isomer **3.51** underwent cyclization to give Z isomer **3.54** in 28% yield. Attempts to close the ring with first- and second-generation

ruthenium catalyst **Ru-I** and **Ru-II** also failed to produce the desired *E* isomer **3.52**. However, the *Z* isomer **3.54** was obtained in good yield. This is probably due to the fact that the *Z* isomer is more thermodynamically stable than the *E* isomer (15 kcal/mol) and the 2,6-*cis* tetrahydropyran ring may increase the conformational restraints which make the formation of *E*-isomer kinetically disfavored.[33] Notably, about 56% of *E*-isomer **3.52** was obtained by irradiation of the *Z* isomer **3.54**.



Scheme 3.19 Building of the macrolactone ring of aspergillide A.

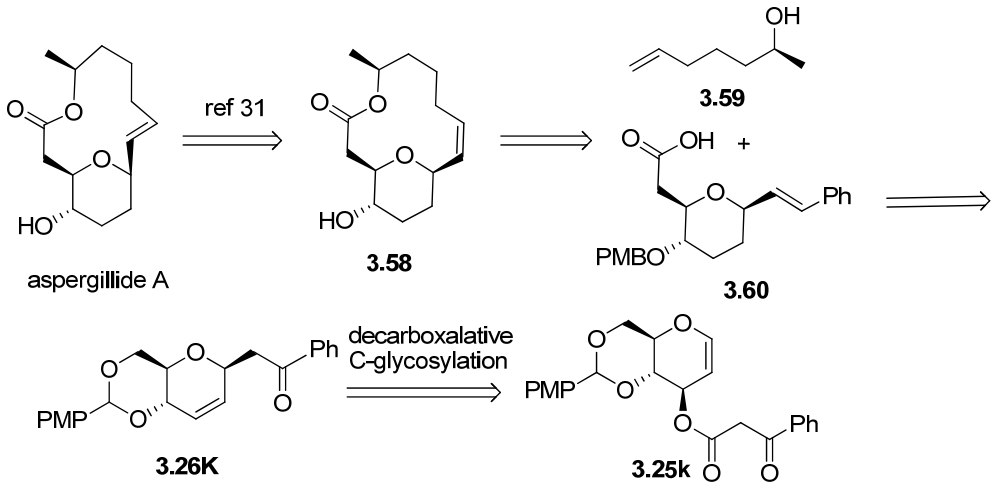
To overcome the difficulty, Shishido *et al.* developed a new strategy, in which, the 14-membered macrolactone ring was assembled first followed by a pyran moiety formation through a base-mediated transannular oxa-Michael reaction.[36] Interestingly, depending on the reaction conditions, both 2,6-*trans* pyran and 2,6-*cis* pyan could be obtained in high yields and selectivity (**Scheme 3.20**). Based on this methodology, aspergillide A and B were synthesized from the same intermediate.



Reaction conditions	Yield	3.56/3.57
1. DBU (10 equiv), LiCl (10 equiv), CH_3CN, rt, 1.5 h	quant	1:0
2. KH (1.1 equiv), [18]crow-6 (5 equiv), THF, 0 ^oC, 0.5 h	96%	0:1

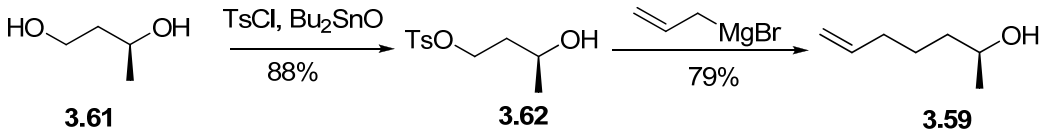
Scheme 3.20 Transannular oxa-Michael reaction.

In our previous study, we obtained a 2,6-*cis* compound **3.26k** through the decarboxylative *C*-glycosylation methodology. We envisioned that aspergillide A could be obtained from **3.26k** in concise steps as depicted in **Scheme 3.21**.



Scheme 3.21 Retro-synthetic analysis.

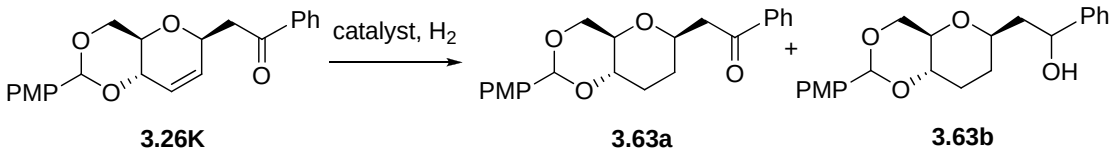
Our synthesis started from the preparation of alcohol **3.59** from commercially available **3.61** in 2 steps. Bu_2SnO catalyzed selective sulfonylation of primary alcohol of **3.61** led to **3.62** in 88% yield.[37] Further coupling of allylmagnesium bromide with monotosylate **3.62** afforded **3.59** in 79% yield.



3.61 **3.62** **3.59**

Scheme 3.22 Synthesis of **3.59**.

With **3.59** in hand, we started to synthesize tetrahydropyran moiety **3.60**. First, we tried to reduce the alkene to alkane by hydrogenation (**Scheme 3.22**). Interestingly, Pd/C catalyzed hydrogenation not only reduced the alkene to alkane but also reduced the ketone to alcohol. Replacing the catalyst with Raney Ni increased the yield of fully reduced product **3.63b** to 90% yield. The reaction catalyzed by Wilkinson's catalyst ($RhCl(PPh_3)_3$) at room temperature did not proceed and only the starting material was recovered. However, by increasing the temperature to 50 ^oC, the partially reduced product **3.63a** was obtained in 90% yield.



3.26K **3.63a** **3.63b**

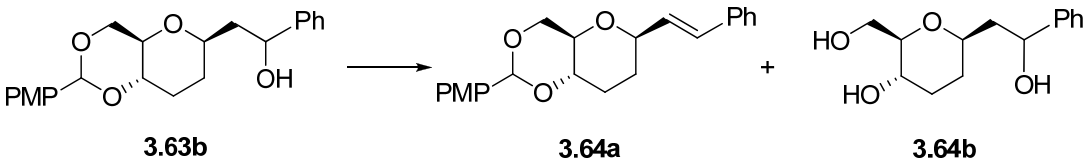
Conditions	Product (yield)
1. Pd/C, EtOAc, rt.	**3.63b** (82%)
2. Raney Ni, EtOH/EtOAc, rt.	**3.63b** (90%)
3.$RhCl(PPh_3)_3$, DCM, rt.	no reaction
4. $RhCl(PPh_3)_3$, toluene, 50 ^oC	**3.63a** (90%)

Scheme 3.23 Hydrogenation reaction of **3.26k**.

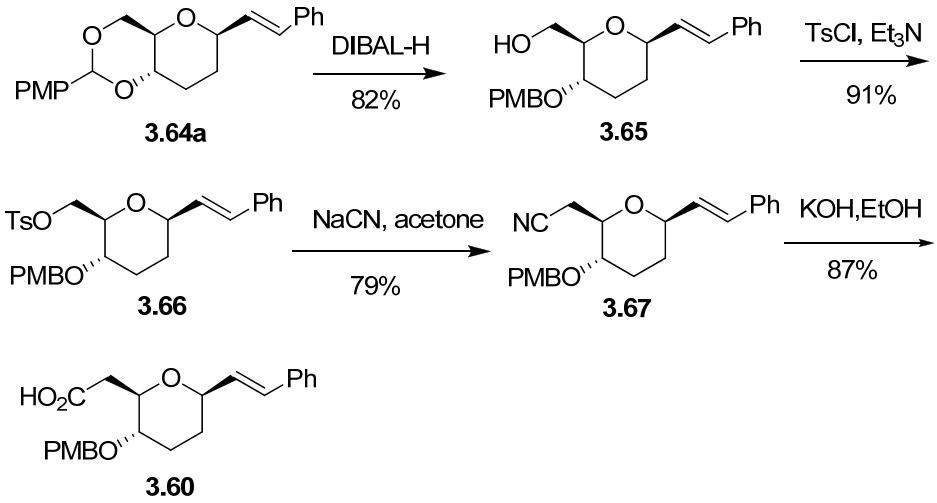
The next step was the elimination of alcohol **3.63b** to produce alkene **3.64a** (**Table 3.5**). However, the reaction did not proceed under alkaline conditions (entries 1, 2). Treatment of **3.63b** with camphor-10-sulfonic acid (CSA) or H_3PO_4 also failed to generate **3.64a**, instead, the protecting group on **3.64b** was removed (entries 3, 4). Next, we tried to activate the alcohol first before elimination under alkaline conditions. However, treatment of **3.63b** with MsCl/Et_3N or Tf_2O/DBU afforded **3.64a** in trace

amounts only (entries 5, 6). Using a stronger base, the yield of **3.64a** was increased. With 2,6-lutidine, **3.64a** was obtained in 50% yield, while with DTBMP, 83% yield of **3.64a** was achieved.

Table 3.5 Elimination reaction of **3.63b**.



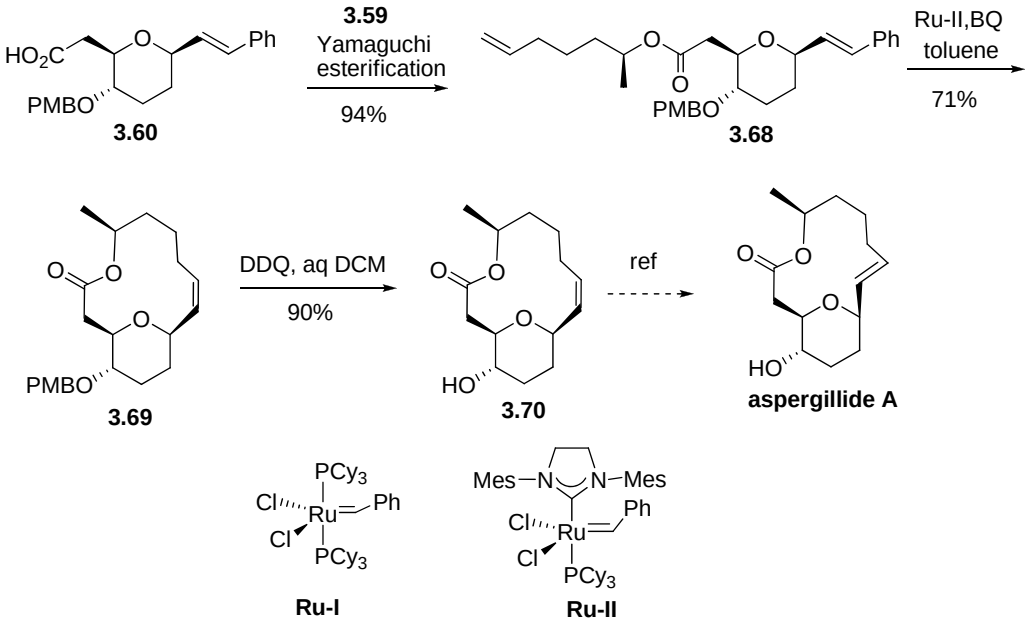
Entry	Conditions	Product (yield)
1	DBU, toluene, reflux	No reaction
2	NaOH, THF/H_2O, rt - 60 ^oC	No reaction
3	CSA, toluene, reflux	**3.64b** (60%)
4	85% H_3PO_4, THF, reflux	**3.64b** (50%)
5	MsCl, Et_3N, DCM, 0 ^oC - rt	**3.64a** (trace)
6	Tf_2O, DBU, DCM, 0 ^oC - rt	**3.64a** (trace)
7	Tf_2O, 2,6-lutidine, DCM, 0 ^oC - rt	**3.64a** (50%)
8	Tf_2O, DTBMP, DCM, 0 ^oC - rt	**3.64a** (83%)



Scheme 3.24 Synthesis of **3.60**.

It was found that the choice of solvent is crucial to the selective reduction of PMB acetal by DIBAL-H (1 M in toluene). The reaction was carried out in DCM and only 20% of desired product **3.65** was obtained in combination with the recovered starting

material. Subjecting the reaction to high concentrations in toluene produced **3.65** in 82% yield successfully. Tosylation of **3.65** and subsequent cyanation resulted in the formation of **3.67** in 72% yield. Subjecting cyanide **3.67** to a strong alkaline condition led to acid **3.60** in 87% yield.



Scheme 3.25 Formal synthesis of aspergillide A.

With the two key building blocks **3.59** and **3.60** in hand, the esterification reaction was carried out using Yamaguchi's condition,[38] providing **3.68** in 94% yield. Unfortunately, attempts to achieve the ring-closing metathesis (RCM) of **3.68** with **Ru-I** in DCM or toluene failed to give either *Z* or *E* alkene. Thus, a stronger condition (Ru-II, BQ, toluene, 100 ^{o}C)[39] was applied to the RCM reaction, which furnished *Z*-alkene **3.69** in 71% yield. Further deprotection of **3.69** by DDQ in aqueous DCM produced known compound **3.70** in 90% yield. Notably, compound **3.70** has been reported to have the best cytotoxic activity among the naturally occurring aspergilides and their analogues.[31k] Following the literature procedure, irradiation of **3.70** resulted in isomerization of the double bond to form aspergillide A. Thus, we successfully

achieved the formal total synthesis of aspergillide A by using the decarboxylative *C*-glycosylation product **3.26k** as the starting material. The longest linear step is only 12 steps from commercial available glucal, providing one of the most concise total syntheses of aspergillide A.

3.6 Conclusion

In conclusion, a mild Pd-catalyzed decarboxylative *C*-glycosylation from readily available glycal derivatives was developed. The versatility and flexibility of this methodology were displayed through an extensive array of substrate scope. Remarkably, high yields, exclusive regioselectivity and diastereoselectivity were obtained, demonstrating the tolerance of the reaction. In addition, the reaction could be conducted on gram scale, highlighting the possibility of extending this methodology to industrial applications.

The reaction mechanism was further studied by experimental and DFT calculations. It was found that the reaction proceeded through an ionization-allylation-decarboxylation sequence *via* an outer-sphere mechanism. Essentially, this transformation is a tandem sequence of rearrangement and decarboxylation on the sugar scaffold.

The methodology was also applied in normal pyran systems to generate *cis*-2,6-disubstituted tetrahydropyrans in high yields and exclusive selectivity, providing a new and facile mode of access to naturally occurring *cis*-2,6-tetrahydropyrans. This was demonstrated by the concise total synthesis of (±)-centrolobine, decytospolide A, B and aspergillide A.

3.7 Experimental section

General: All reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich, Merck, Strem and Alfa Asear) and used without further purification unless stated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010-0.063 mm). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using a basic solution of potassium permanganate. Technical grade solvents were used for chromatography and were distilled prior to use. Optical rotations were measured in $CHCl_3$ on a Schmidt + Haensdch polarimeter with a 1 cm cell (c given in g/100 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 400 MHz Bruker DPX 400 NMR spectrometers. The residual solvent signals were taken as the reference (7.26 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). Chemical shift (δ) is reported in ppm, coupling constants (J) are given in Hz. The following abbreviations classify the multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved. HRMS (ESI) spectra were recorded on a Waters Q-Tof premier^{TM} mass spectrometer. X-ray crystallographic data was collected by using a Bruker X8Apex diffractometer with Mo K/α radiation (graphite monochromator).

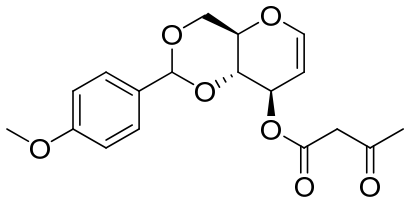
3.7.1 Decarboxylative *C*-glycosylation on sugar scaffold

General procedure A for the preparation of glycal-derived β-ketoesters:

A mixture of 4,6-protected-D-glycal (0.4 mmol, 1 equiv) and *β*-ketoesters (0.8 mmol, 2 equiv) was refluxed overnight in the presence of DMAP (48.9 mg, 0.4 mmol, 1 equiv) and molecular sieves (400 mg) in toluene (4 mL) under N_2 atmosphere. The suspension was filtered through a pad of Celite and the filtrate was concentrated. The crude compound was purified by column chromatography on silica gel (Ethyl acetate/hexanes).

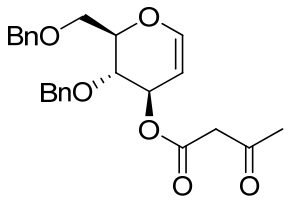
General procedure B for the decarboxylative glycosylation:

A mixture of glycal-derived *β*-ketoesters (0.1 mmol, 1 equiv), palladium acetate (1.1 mg, 0.005 mmol, 0.05 equiv) and DPPF (5.5 mg, 0.01 mmol, 0.1 equiv) in anhydrous toluene (2 mL) was heated to 60 °C under N_2 in a Schlenk tube. The reaction was stirred for 2-18 h. The product was purified by flashing column chromatography on silica gel (Ethyl acetate/hexanes).

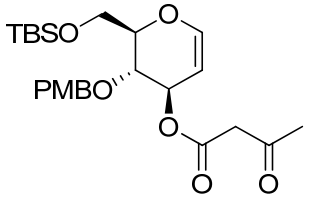


3-*O*-(3-Oxobutanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25a): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1:8) as a white solid (119.8 mg, 86%). **Mp** 134-135 °C; $[\alpha]_D^{20} = -98.5$ (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.40 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.40 (d, *J* = 6.0 Hz, 1H), 5.59 (d, *J* = 7.0 Hz, 1H), 5.54 (s, 1H), 4.82 (dd, *J* = 6.0, 1.5 Hz, 1H), 4.37 (dd, *J* = 10.7, 4.4 Hz, 1H), 3.85-3.80 (m containing s, 4H), 3.46 (s, 2H), 2.25 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 200.2, 166.9, 160.2, 145.8, 129.3, 127.5, 113.7, 101.6, 100.1, 69.8, 68.8, 68.2, 55.3,

50.2, 30.0; **IR** (neat): ν 3019, 1746, 1715, 1643, 1520, 1215, 754 cm^{-1}; **HRMS (ESI)**: calcd. for $C_{18}H_{20}O_7Na$ $[M+Na]^+$, 371.1107; found, 371.1118.

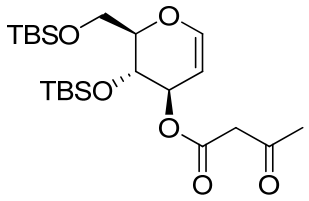


3-*O*-(3-Oxobutanoyl)-4,6-di-*O*-benzyl-D-glucal (3.25b): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1:6) as a colorless oil (85.4 mg, 52%). $[\alpha]_D^{20} = -18.6$ (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 10H), 6.46 (d, *J* = 6.0 Hz, 1H), 5.48 (dd, *J* = 6.0, 1.4 Hz, 1H), 4.77 (dd, *J* = 6.0, 2.9 Hz, 1H), 4.66 (d, *J* = 11.4 Hz, 1H), 4.63-4.61 (m, 2H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.12-4.08 (m, 1H), 3.95(dd, *J* = 8.7, 6.3 Hz, 1H), 3.82 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.75 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.35 (s, 2H), 2.22 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.0, 166.7, 146.2, 137.9, 137.8, 128.4(2C), 127.9, 127.8(2C), 98.6, 76.8, 73.5(2C), 73.1, 72.0, 68.0, 50.1, 30.1; **IR** (neat): ν 3030, 2870, 1746, 1715, 1645, 1454, 1240, 1107, 741 cm^{-1}; **HRMS** (ESI): calcd. for $C_{24}H_{26}O_6Na$ $[M+Na]^+$, 433.1627; found, 433.1625.



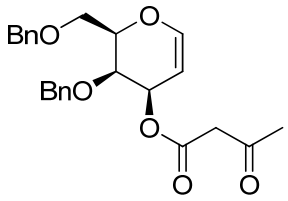
3-*O*-(3-Oxobutanoyl)-4-*O*-(4-methoxybenzyl)-6-*O*-*tert*-butyl-dimethylsilyl-D-glucal (3.25c): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 6) as a white solid (94.8 mg, 51%). **Mp** 65-66 °C; $[\alpha]_D^{20} = -16.1$ (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz,

$CDCl_3$): δ 7.26 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.42 (d, J = 6.0 Hz, 1H), 5.47-5.44 (m, 1H), 4.73 (dd, J = 6.0, 2.8 Hz, 1H), 4.65 (dd, J = 14.5, 11.2 Hz, 2H), 3.96-3.85 (m, 4H), 3.80 (s, 3H), 3.38 (s, 2H), 2.25 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.1, 166.8, 159.3, 146.2, 130.3, 129.6, 113.8, 98.3, 78.1, 73.3, 72.3, 72.1, 61.3, 55.3, 50.2, 30.1, 25.9, 18.3, -5.2, -5.4; **IR** (neat): ν 2930, 2847, 1746, 1717, 1651, 1514, 1250, 1107, 837 cm^{-1}; **HRMS** (ESI): calcd. for $C_{24}H_{36}O_7NaSi$ $[M+Na]^+$, 487.2128; found, 487.2129.

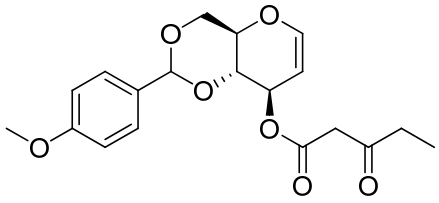


3-*O*-(3-Oxobutanoyl)-4,6-di-*O*-*tert*-butyl-dimethylsilyl-D-glucal (3.25e):

Compound was prepared following the general procedure A (0.2 mmol) and obtained by flashing column chromatography (EA/hexanes = 1: 20) as a colorless oil (57.8 mg, 63%). $[\alpha]_D^{20}$ = −35.4 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.39 (d, J = 6.2 Hz, 1H), 5.25-5.23 (m, 1H), 4.71 (dd, J = 6.2, 2.6 Hz, 1H), 4.06 (dd, J = 9.0, 6.6 Hz, 1H), 3.91-3.83 (m, 2H), 3.79-3.76 (m, 1H), 3.44 (d, J = 2.6 Hz, 2H), 2.27 (s, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.1, 167.0, 146.1, 98.2, 79.3, 74.5, 66.4, 61.3, 50.1, 30.1, 25.9, 25.7, 18.4, 18.0, -4.6, -5.0, -5.1, -5.3; **IR** (neat): ν 2955, 2930, 2857, 1746, 1721, 1651, 1472, 1254, 1125, 837, 758 cm^{-1}; **HRMS** (ESI): calcd. for $C_{22}H_{42}O_6Si_2Na$ $[M+Na]^+$, 481.2418; found, 481.2418.

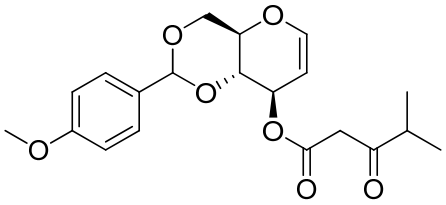


3-*O*-(3-Oxobutanoyl)-4,6-di-*O*-benzyl-D-galactal (3.25e): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 7) as a colorless oil (91.9 mg, 56%). $[\alpha]_D^{20}$ = −36.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.28 (m, 10H), 6.44 (d, *J* = 6.1 Hz, 1H), 5.54 (t, *J* = 4.0 Hz, 1H), 4.77 (dd, *J* = 6.1, 3.6 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 2H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.31 (quintet, *J* = 3.6 Hz, 1H), 4.04 (t, *J* = 3.6 Hz, 1H), 3.76 (dd, *J* = 10.4, 7.7 Hz, 1H), 3.62 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.38 (d, *J* = 1.4 Hz, 2H), 2.17 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 200.0, 166.6, 146.0, 137.8, 137.6, 128.4(2C), 127.9, 127.8(2C), 127.7, 97.8, 75.3, 73.3, 73.2, 70.8, 67.4, 65.8, 50.0, 30.0; **IR** (neat): ν 3032, 2926, 2874, 1746, 1715, 1645, 1454, 1234, 1094, 752 cm^{-1}; **HRMS** (ESI): calcd. for $C_{24}H_{26}O_6Na$ $[M+Na]^+$, 433.1627; found, 433.1635.

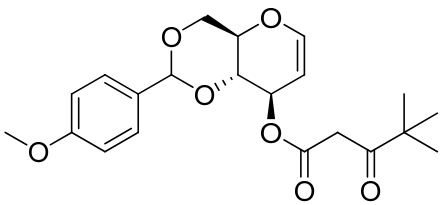


3-*O*-(3-Oxopentanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25f): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 6) as a white solid (120.3 mg, 83%). Mp 112-113 °C; $[\alpha]_D^{20}$ = −84.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 7.40 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.40 (dd, *J* = 6.1, 1.2 Hz, 1H), 5.59 (d, *J* = 7.5 Hz, 1H), 5.54 (s, 1H), 4.83 (dd, *J* = 6.1, 2.0 Hz, 1H), 4.37 (dd, *J* = 10.4, 4.6 Hz, 1H), 4.04-3.95 (m, 2H), 3.85-3.80 (m containing s, 4H), 3.45 (d, *J* = 2.0 Hz, 2H), 2.54

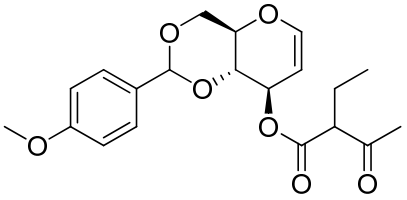
(q, J = 7.2 Hz, 2H), 1.04 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 202.9, 167.1, 160.2, 145.7, 129.3, 127.5(2C), 113.6, 101.5, 100.1, 69.8, 68.8, 68.2, 55.3, 49.1, 36.1, 7.4; **IR** (neat): ν 2905, 1742, 1707, 1637, 1518, 1254, 1034, 827, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{19}H_{22}O_7Na$ $[M+Na]^+$, 385.1263; found, 385.1293.



3-*O*-(4-Methyl-3-oxopentanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25g): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 7) as a white solid (126.5 mg, 84%). **Mp** 100-101 °C; $[\alpha]_D^{20}$ = −113.2 (c = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.40 (d, J = 6.1 Hz, 1H), 5.56 (dd, J = 17.6, 7.1 Hz, 1H), 5.54 (s, 1H), 4.84 (d, J = 6.1 Hz, 1H), 4.37 (dd, J = 10.4, 4.0 Hz, 1H), 4.06-3.95 (m, 2H), 3.86-3.80 (m, 1H), 3.80 (s, 3H), 3.52 (dd, J = 21.5, 15.6 Hz, 1H), 2.71 (septet, J = 6.8 Hz, 1H), 1.11 (d, J = 6.8 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.2, 184.1, 172.7, 167.2, 160.2, 145.7, 145.4, 129.4, 129.3, 127.5(2C), 113.6, 101.6, 101.5, 100.8, 100.2, 86.7, 69.7, 68.9, 68.8, 68.4, 68.2, 55.3, 47.3, 41.0, 33.8, 19.6, 17.9; **IR** (neat): ν 2972, 1748, 1715, 1643, 1520, 1234, 1094, 997, 835, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{20}H_{24}O_7Na$ $[M+Na]^+$, 399.1420; found, 399.1432.

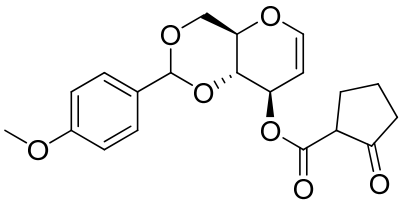


3-*O*-(4,4-Dimethyl-3-oxopentanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25h): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 7) as a white solid (131.2 mg, 84%). **Mp** 114-115 °C; $[\alpha]_D^{20}$ = −118.8 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.2 (s, 0.5H), 7.41 (dd, *J* = 8.6, 2.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.39 (d, *J* = 6.1 Hz, 1H), 5.60-5.59 (m, 1H), 5.55 (d, *J* = 7.2 Hz, 1H), 5.08 (s, 0.5H), 4.86 (dq, *J* = 6.1, 1.5 Hz, 1H), 4.39-4.35 (m, 1H), 4.07-3.94 (m, 2H), 3.86-3.80 (m,1H), 3.80 (s, 3H), 3.57 (dd, *J* = 29.2, 15.7 Hz, 1H), 1.15 (d, *J* = 3.6 Hz, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.7, 186.4, 173.0, 167.5, 160.2(2C), 145.5(2C), 129.4(2C), 127.5(2C), 113.6(2C), 101.6, 101.5, 100.8, 100.3, 85.6, 76.9, 69.7, 68.6(2C), 68.5, 68.2, 55.3, 44.7, 44.0, 36.7, 27.4, 26.1; **IR** (neat): ν 3019, 2970, 1748, 1705, 1643, 1614, 1518, 1215, 1096, 1009, 756 cm^{-1}; **HRMS** (ESI): calcd. for $C_{21}H_{26}O_7Na$ $[M+Na]^+$, 413.1576; found, 413.1575.

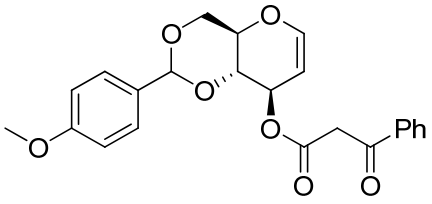


3-*O*-(2-Ethyl-3-oxobutanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25i): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 6) as a white solid (102.4 mg, 68%). **Mp** 93-94 °C; $[\alpha]_D^{20}$ = −100.2 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.35 (m, 2H), 6.88 (dd, *J* = 8.8, 2.8 Hz, 2H), 6.40 (d, *J* = 6.0 Hz, 1H), 5.64-5.60 (m, 1H), 5.54 (s, 1H), 4.76 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.40-4.36 (m, 1H), 4.05-3.96 (m, 1H), 3.86-3.82 (m, 1H), 3.80 (s, 3H), 3.34 (dd, *J* = 17.2, 7.6 Hz, 1H), 2.18 (d, *J* = 16.4 Hz, 3H), 1.95-1.82 (m, 2H), 0.93 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ

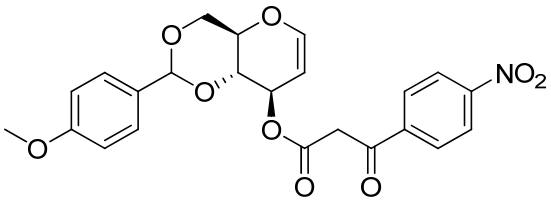
202.8, 202.6, 169.7, 169.6, 160.1(2C), 145.8, 129.3, 129.2, 127.3, 127.2, 113.6(2C), 101.4, 101.3, 100.1, 100.0, 76.8, 69.5(2C), 68.8, 68.1, 61.5, 61.3, 55.2, 28.7, 28.2, 21.4, 11.7(2C); **IR** (neat): ν 2970, 2936, 1738, 1715, 1643, 1614, 1520, 1371, 1254, 1096, 827, 743 cm^{-1}; **HRMS** (ESI): calcd. for $C_{20}H_{24}O_7Na$ $[M+Na]^+$, 399.1420; found, 399.1435.



3-*O*-(2-Oxocyclopentanecarbonyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25j): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 4) as a white solid (109.3 mg, 73%). **Mp** 152-153 °C; $[\alpha]_D^{20} = -58.9$ (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.39 (d, *J* = 6.1 Hz, 1H), 5.56 (d, *J* = 10.1 Hz, 1H), 5.54 (s, 1H), 4.81 (dd, *J* = 6.1, 1.4 Hz, 1H), 4.36 (dd, *J* = 10.5, 5.1 Hz, 1H), 4.11-4.06 (m, 1H), 3.98 (dt, *J* = 10.1, 5.1 Hz, 1H), 3.83 (t, *J* = 10.5 Hz, 1H), 3.80 (s, 3H), 3.19 (t, *J* = 9.0 Hz, 1H), 2.38-2.21 (m, 4H), 2.17-2.11 (m, 1H), 1.90-1.81 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.0, 169.2, 160.2, 145.6, 129.4, 127.5, 113.6, 101.5, 100.4, 76.7, 69.7, 68.7, 68.2, 55.3, 54.6, 38.0, 27.1, 20.8; **IR** (neat): *v* 3019, 1749, 1728, 1641, 1518, 1217, 1094, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{20}H_{22}O_7Na$ $[M+Na]^+$, 397.1263; found, 397.1272.

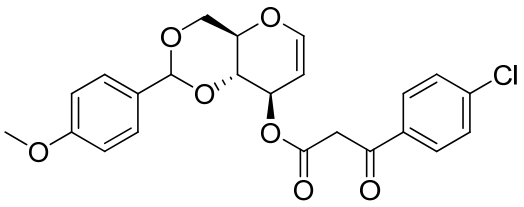


3-*O*-(3-Oxo-phenylpropanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25k): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 8) as a white solid (124.8 mg, 76%). **Mp** 134-136 °C; $[\alpha]_D^{20} = -107.8$ (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.1 Hz, 2H), 7.56-7.36 (m, 5H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.37 (d, *J* = 6.2 Hz, 1H), 5.61 (d, *J* = 6.0 Hz, 1H), 5.47 (s, 1H), 4.82 (d, *J* = 6.2 Hz, 1H), 4.36-4.32 (m, 1H), 4.12-3.92 (m, 3H), 3.87-3.78 (m containing s, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 192.2, 167.3, 160.1, 145.7, 133.7, 129.4, 128.8, 128.5, 127.5, 126.1, 113.7, 101.5, 100.2, 87.4, 69.9, 68.9, 68.2, 55.3, 46.1; **IR** (neat): ν 3018, 1744, 1684, 1518, 1215, 1096, 756 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{22}O_7Na$ $[M+Na]^+$, 433.1263; found, 433.1269.

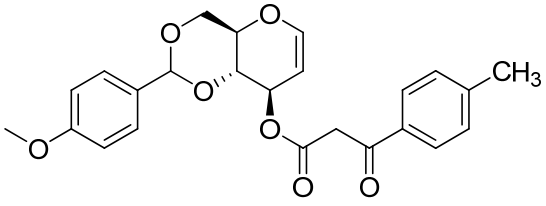


3-*O*-(3-(4-Nitrophenyl)-3-oxopropanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25l): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 4) as a light yellow solid (118.4 mg, 65%). **Mp** 163-165 °C; $[\alpha]_D^{20} = -190.6$ (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.39 (s, 0.5 H), 8.26 (d, *J* = 8.6 Hz, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.44 (d, *J* = 6.1 Hz, 0.5H), 6.40 (d, *J* = 6.1 Hz, 0.5H), 5.79 (s, 0.5H), 5.69 (d, *J* = 7.4 Hz, 0.5H), 5.62 (d, *J* = 6.8 Hz, 0.5H), 5.57 (s, 0.5H), 4.87 (d, *J* = 6.0 Hz, 0.5H), 4.79 (d, *J* = 6.0 Hz, 0.5H), 4.42-4.33 (m, 1H), 4.12-4.05 (m, 1H), 4.04 (s, 1H), 3.97-3.93 (m, 0.5H), 3.86-3.77 (m containing s,

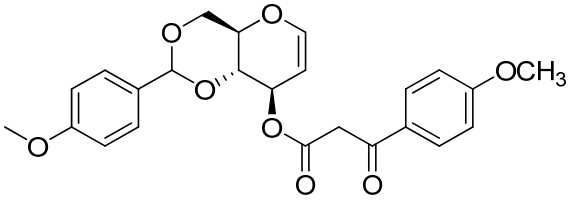
4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.7, 172.4, 168.8, 166.5, 160.4, 160.3, 150.6, 149.3, 146.0, 145.9, 140.1, 139.2, 129.5, 129.3, 129.1, 127.6, 127.5, 127.4, 127.0, 123.9, 123.8, 113.7, 101.7, 101.6, 100.3, 99.8, 90.2, 76.8, 70.2, 69.4, 68.9, 68.8, 68.2, 68.1, 55.3, 46.5; **IR** (neat): ν 3019, 1742, 1641, 1526, 1348, 1215, 1094, 756 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{21}NO_9Na$ $[M+Na]^+$, 478.1114; found, 478.1105.



3-*O*-(3-(4-Chlorophenyl)-3-oxopropanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25m): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 8) as a white solid (138.9 g, 78%). **Mp** 116-118 °C**;** $[\alpha]_D^{20}$ = −91.4 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.38 (d, *J* = 6.1 Hz, 1H), 5.62-5.60 (m, 1H), 5.47 (s, 1H), 4.80 (dd, *J* = 6.1, 1.9 Hz, 1H), 4.34 (dd, *J* = 6.8, 3.6 Hz, 1H), 3.97-3.91 (m, 4H), 3.82-3.77 (m containing s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.9, 170.6, 167.0, 160.3, 145.8, 140.3, 134.2, 129.9, 129.1, 127.6, 113.7, 101.6, 100.1, 87.6, 76.7, 70.0, 68.9, 68.2, 55.3, 46.1; **IR** (neat): ν 2938, 1738, 1694, 1520, 1252, 1094, 989, 833, 756 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}ClH_{21}O_7Na$ $[M+Na]^+$, 467.0874; found, 467.0871.

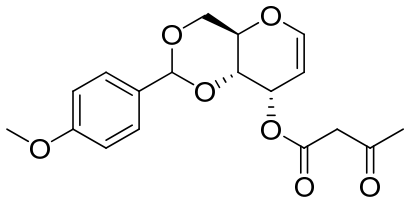


3-*O*-(3-(4-Methylphenyl)-3-oxopropanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25n): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 8) as a white solid (132.4 mg, 78%). **Mp** 111-113 °C; $[\alpha]_D^{20}$ = −99.3 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.38 (d, *J* = 6.2 Hz, 1H), 5.63-5.61 (m, 2H), 5.50 (s, 1H), 4.84 (dd, *J* = 6.2, 1.8 Hz, 1H), 4.37-4.34 (m, 1H), 4.09-3.94 (m, 3H), 3.85-3.78 (m containing s, 4H), 2.37 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.8, 167.5, 160.2, 145.7, 144.7, 133.5, 129.5, 128.6, 127.6, 126.1, 113.7, 101.5, 100.3, 86.6, 69.8, 68.8, 68.2, 55.3, 46.1, 21.7; **IR** (neat): ν 2934, 1746, 1682, 1520, 1252, 1094, 998, 833, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{24}H_{24}O_7Na$ $[M+Na]^+$, 447.1420; found, 447.1436.

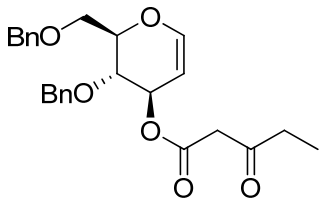


3-*O*-(3-(4-Methoxyphenyl)-3-oxopropanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-glucal (3.25o): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 5) as a yellow solid (132.1 g, 75%). **Mp** 122-124 °C; $[\alpha]_D^{20}$ = −113.8 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.87 (dd, *J* = 8.8, 3.6 Hz, 4H), 6.38 (d, *J* = 6.1 Hz, 1H), 5.61-5.60 (m, 1H), 5.49 (s, 1H), 4.82 (dd, *J* = 6.1, 1.8 Hz, 1H), 4.35 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.99-3.95 (m, 4H), 3.83-3.78 (m containing 2s, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.6, 167.5, 164.0, 160.2, 145.7, 130.9, 129.4, 129.0, 127.5, 113.9, 113.7, 101.5, 100.3, 69.8, 68.8, 68.2, 55.5, 55.3,

46.0; **IR** (neat): ν 2936, 2839, 1742, 1682, 1601, 1518, 1258, 1173, 1094, 988, 833, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{24}H_{24}O_8Na$ $[M+Na]^+$, 463.1369; found, 463.1369.

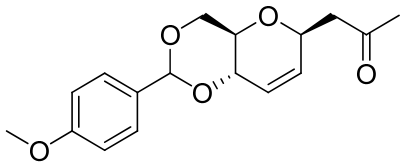


3-*O*-(3-Oxobutanoyl)-4,6-di-*O*-(4-methoxybenzylidene)-D-allal (3.27): Compound was prepared following the general procedure A (0.1 mmol scale) and obtained by flashing column chromatography (EA/hexanes = 1: 6) as a white solid (29.3 mg, 84%). **Mp** 74-75 °C; $[\alpha]_D^{20}$ = +232.7 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.51 (d, *J* = 6.0 Hz, 1H), 5.57 (s, 1H), 5.47 (dd, *J* = 6.0, 3.9 Hz, 1H), 5.01 (t, *J* = 6.0 Hz, 1H), 4.44 (dd, *J* = 10.6, 5.2 Hz, 1H), 4.11 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.99 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.82 (t, *J* = 10.3 Hz, 1H), 3.80 (s, 3H), 3.45 (s, 2H), 2.19 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.3, 166.6, 160.2, 147.8, 129.4, 127.4, 113.6, 101.5, 97.8, 75.8, 68.4, 65.0, 63.1, 55.3, 50.3, 30.0; **IR** (neat): ν 2936, 2864, 1744, 1715, 1634, 1520, 1244, 1090, 831, 758 cm^{-1}; **HRMS** (ESI): calcd. for $C_{18}H_{20}O_7Na$ $[M+Na]^+$, 371.1107; found, 371.1104.

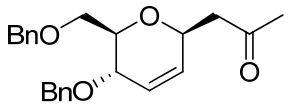


3-*O*-(3-Oxopentanoyl)-4,6-di-*O*-benzyl-D-glucal (3.25p): Compound was prepared following the general procedure A and obtained by flashing column chromatography (EA/hexanes = 1: 7) as a white solid (100.2 mg, 59%). **Mp** 52-53 °C; $[\alpha]_D^{20}$ = −21.9 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 10H), 6.46 (d, *J* = 6.1

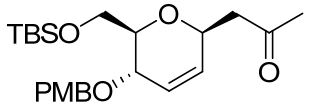
Hz, 1H), 5.47 (dd, *J* = 6.1, 1.6 Hz, 1H), 4.77 (dd, *J* = 6.1, 2.9 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 11.4 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.11-4.07 (m, 1H), 3.95(dd, *J* = 8.7, 6.1 Hz, 1H), 3.82 (dd, *J* = 10.8, 4.6 Hz, 1H), 3.75 (dd, *J* = 10.8, 2.9 Hz, 1H), 3.35 (s, 2H), 2.51 (q, *J* = 7.3 Hz, 2H), 1.05 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 202.8, 166.9, 146.2, 137.9, 137.8, 128.4(2C), 127.9, 127.8, 127.7, 98.6, 76.8, 73.5(2C), 73.1, 72.0, 68.0, 49.0, 36.3, 7.5; **IR** (neat): ν 2932, 2878, 1744, 1713, 1651, 1458, 1242, 1103, 741 cm^{-1}; **HRMS** (ESI): calcd. for $C_{25}H_{28}O_6Na$ $[M+Na]^+$, 447.1784; found, 447.1805.



1-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-*β*-D-erythro-hex-2-enopyranosyl)-2-propanone (3.26a): Compound was prepared following the general procedure B and obtained by flashing column chromatography (EA/hexanes = 1: 3) as a white solid (27.4 mg, 90%). **Mp** 79-81 °C; $[\alpha]_D^{20}$ = +81.8 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.97 (d, *J* = 10.2 Hz, 1H), 5.70 (d, *J* = 10.2 Hz, 1H), 5.54 (s, 1H), 4.78-4.76 (m, 1H), 4.27 (dd, *J* = 10.2, 4.5 Hz, 1H), 4.16-4.14 (m, 1H), 3.80 (s, 3H), 3.73 (t, *J* = 10.2 Hz, 1H), 3.63-3.57 (m, 1H), 2.73 (dd, *J* = 16.2, 7.6 Hz, 1H), 2.57 (dd, *J* = 16.2, 5.6 Hz, 1H), 2.18 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 205.9, 160.1, 130.2, 129.9, 127.5, 127.2, 113.7, 101.9, 75.0, 72.2, 70.9, 69.3, 55.3, 48.5, 30.9; **IR** (neat): ν 2855, 1715, 1614, 1518, 1250, 1098, 831 cm^{-1}; **HRMS** (ESI): calcd. for $C_{17}H_{20}O_5Na$ $[M+Na]^+$, 327.1208; found, 327.1194.

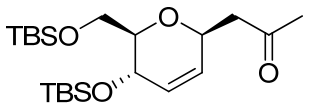


1-(4,6-di-*O*-benzyl-2,3-dideoxy-*β*-D-erythro-hex-2-enopyranosyl)-2-propanone (3.26b): Compound was prepared following the general procedure B and obtained by flashing column chromatography (EA/hexanes = 1: 5) as a colorless oil (31.5 mg, 86%). $[\alpha]_D^{20}$ = +109.7 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.24 (m, 10H), 5.93 (d, *J* = 10.3 Hz, 1H), 5.77 (d, *J* = 10.3 Hz, 1H), 4.62-4.53 (m, 4H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.06-4.04 (m, 1H), 3.74-3.70 (m, 1H), 3.67-3.61 (m, 2H), 2.76 (dd, *J* = 16.0, 7.1 Hz, 1H), 2.55 (dd, *J* = 16.0, 7.1 Hz, 1H), 2.19 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.5, 138.3, 138.0, 130.6, 128.4, 128.3, 127.9, 127.8, 127.5, 126.8, 77.2, 73.3, 71.4, 71.2, 70.3, 69.5, 48.8, 31.0; **IR** (neat): ν 3030, 2864, 1715, 1454, 1361, 1092, 737 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{26}O_4Na$ $[M+Na]^+$, 389.1729; found, 389.1731.

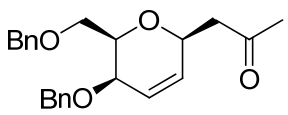


1-(4-*O*-4-Methoxybenzyl-6-*O*-*tert*-butyl-dimethylsilyl-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)-2-propanone (3.26c): Compound was prepared following the general procedure B (18 h) and obtained by flashing column chromatography (EA/hexanes = 1: 8) as a colorless oil (34.9 mg, 83%). $[\alpha]_D^{20}$ = +88.1 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.88 (d, *J* = 10.3 Hz, 1H), 5.71 (d, *J* = 10.3 Hz, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.57-4.55 (m, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.01 (d, *J* = 7.2 Hz, 1H), 3.83 (d, *J* = 11.6 Hz, 1H), 3.80 (s, 3H), 3.76 (dd, *J* = 11.6, 4.8 Hz, 1H), 3.44-3.41 (m, 1H), 2.65 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.50 (dd, *J* = 15.6, 5.5 Hz, 1H), 2.18 (s, 3H), 0.89 (s, 9H),

0.05 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.8, 159.3, 130.4, 130.3, 129.5, 127.4, 113.8, 78.3, 71.3, 71.0, 69.5, 63.0, 55.2, 48.9, 31.0, 25.9, 18.4, -5.2, -5.3; **IR** (neat): *v* 2928, 2855, 1715, 1613, 1514, 1250, 1088, 837 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{36}O_5SiNa$ $[M+Na]^+$, 443.2230; found, 443.2231.

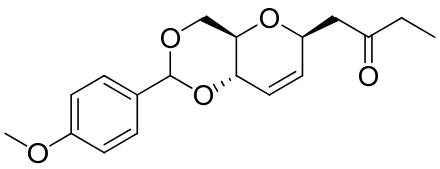


1-(4,6-di-*O*-*tert*-butyl-dimethylsilyl-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)-2-propanone (3.26d): Compound was prepared following the general procedure B and obtained by flashing column chromatography (EA/hexanes = 1: 20) as a colorless oil (33.2 mg, 80%). $[\alpha]_D^{20}$ = +85.3 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.71 (d, *J* = 10.3 Hz, 1H), 5.63 (d, *J* = 10.3 Hz, 1H), 4.56-4.54 (m, 1H), 4.22 (d, *J* = 7.2 Hz, 1H), 3.82 (dd, *J* = 11.4, 1.6 Hz, 1H), 3.74 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.30-3.27 (m, 1H), 2.65 (dd, *J* = 15.7, 7.7 Hz, 1H), 2.49 (dd, *J* = 15.7, 5.5 Hz, 1H), 2.18 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.04 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.8, 130.8, 129.3, 80.0, 71.3, 63.3, 62.6, 49.0, 31.0, 25.9, 25.8, 18.4, 18.0, -4.3, -4.9, -5.1, -5.3; **IR** (neat): ν 2930, 2857, 1717, 1472, 1256, 1092, 837, 777 cm^{-1}; **HRMS** (ESI): calcd. for $C_{21}H_{42}O_4Si_2Na$ $[M+Na]^+$, 437.2519; found, 437.2520.

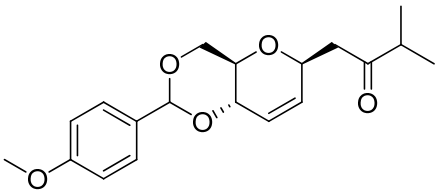


1-(4,6-di-*O*-benzyl-2,3-dideoxy-β-D-threo-hex-2-enopyranosyl)-2-propanone (3.26e): Compound was prepared following the general procedure B and obtained by

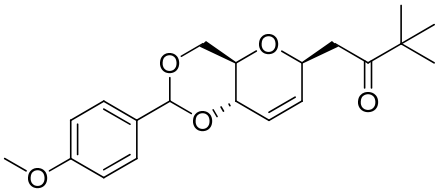
flashing column chromatography (EA/hexanes = 1: 4) as a colorless oil (33.0 mg, 90%). $[\alpha]_D^{20}$ = −99.4 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.25 (m, 10H), 5.99 (ddd, *J* = 10.2, 4.6, 1.6 Hz, 1H), 5.94 (d, *J* = 10.2 Hz, 1H), 4.62 (dd, *J* = 12.0, 7.7 Hz, 2H), 4.56-4.55 (m, 1H), 4.54 (dd, *J* = 12.0, 3.6 Hz, 2H), 3.82-3.68 (m, 4H), 2.85 (dd, *J* = 16.2, 7.1 Hz, 1H), 2.61 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.20 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.5, 138.6, 138.2, 134.0, 128.3, 128.2, 127.8, 127.7, 127.6, 124.6, 73.5, 71.5, 70.8, 69.7, 68.1, 48.4, 30.0; **IR** (neat): ν 3030, 2864, 1715, 1454, 1362, 1090, 736 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{26}O_4Na$ $[M+Na]^+$, 389.1729; found, 389.1742.



1-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)-2-butanone (3.26f): Compound was prepared following the general procedure B and obtained by flashing column chromatography (EA/hexanes = 1: 6) as a white solid (27.1 mg, 85%). **Mp** 99-100 °C; $[\alpha]_D^{20}$ = +65.2 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.96 (d, *J* = 10.4 Hz, 1H), 5.70 (d, *J* = 10.4 Hz, 1H), 5.54 (s, 1H), 4.79-4.77 (m, 1H), 4.27 (dd, *J* = 10.2, 4.5 Hz, 1H), 4.16-4.14 (m, 1H), 3.80 (s, 3H), 3.72 (t, *J* = 10.2 Hz, 1H), 3.62-3.56 (m, 1H), 2.72 (dd, *J* = 16.0, 7.6 Hz, 1H), 2.54 (dd, *J* = 16.0, 7.6 Hz, 1H), 2.48 (q, *J* = 7.3 Hz, 2H), 1.07 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 208.6, 160.1, 130.3, 130.0, 127.5, 127.1, 113.7, 101.9, 75.0, 72.4, 70.9, 69.4, 55.3, 47.3, 36.9, 7.5; **IR** (neat): ν 3017,1709, 1623, 1518, 1250, 1098, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{18}H_{22}O_5Na$ $[M+Na]^+$, 341.1365; found, 341.1375.

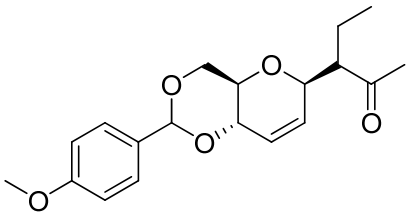


1-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)-3-methyl-2-butanone (3.26g): Compound was prepared following the general procedure B and obtained by flashing column chromatography (EA/hexanes = 1: 6) as a white solid (24.9 mg, 75%). **Mp** 84-85 °C; $[\alpha]_D^{20}$ = +76.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.96 (d, *J* = 10.4 Hz, 1H), 5.71 (d, *J* = 10.4 Hz, 1H), 5.54 (s, 1H), 4.81-4.74 (m, 1H), 4.26 (dd, *J* = 10.2, 4.5 Hz, 1H), 4.16-4.14 (m, 1H), 3.80 (s, 3H), 3.72 (t, *J* = 10.2 Hz, 1H), 3.62-3.56 (m, 1H), 2.79 (dd, *J* = 16.4, 7.2 Hz, 1H), 2.65-2.54 (m, 2H), 1.11 (s, 3H), 1.10 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.7, 160.1, 130.5, 130.0, 127.5, 127.0, 113.7, 101.9, 75.1, 72.4, 70.9, 69.4, 55.3, 45.3, 41.5, 17.9; **IR** (neat): ν 2970, 2874, 1713, 1614, 1518, 1385, 1250, 1099, 831 cm^{-1}; **HRMS** (ESI): calcd. for $C_{19}H_{24}O_5Na$ $[M+Na]^+$, 355.1521; found, 355.1546.

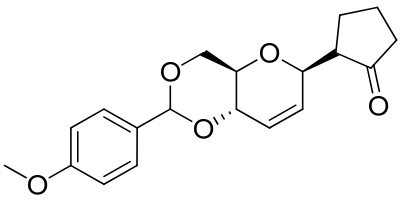


1-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)-3,3-dimethyl-2-butanone (3.26h): Compound was prepared following the general procedure B (18 h) and obtained by flashing column chromatography (EA/hexanes = 1: 8) as a colorless oil (18.2 mg, 52%). $[\alpha]_D^{20}$ = +40.1 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.95 (d, *J* = 10.4 Hz, 1H), 5.73 (d, *J* = 10.4 Hz, 1H), 5.54 (s, 1H), 4.82-

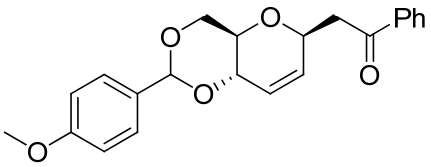
4.80 (m, 1H), 4.27 (dd, *J* = 10.2, 4.5 Hz, 1H), 4.16-4.14 (m, 1H), 3.80 (s, 3H), 3.71 (t, *J* = 10.2 Hz, 1H), 3.62-3.55 (m, 1H), 2.89 (dd, *J* = 17.0, 6.7 Hz, 1H), 2.55 (dd, *J* = 17.0, 6.7 Hz, 1H), 1.14 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.8, 160.1, 130.7, 130.0, 127.5, 126.8, 113.7, 101.9, 75.1, 72.5, 70.8, 69.4, 55.3, 44.3, 41.9, 26.1, 1.00; **IR** (neat): ν 2968, 2870, 1705, 1614, 1518, 1250, 1096, 1034, 831, 756 cm^{-1}; **HRMS** (ESI): calcd. for $C_{20}H_{27}O_5Na$ $[M+Na]^+$, 369.1678; found, 369.1681.



3-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)-2-pentanone (3.26i): Compound was prepared following the general procedure B (18 h) and obtained by flashing column chromatography (EA/hexanes = 1: 6) as a colorless oil (21.6 mg, 65%). $[\alpha]_D^{20}$ = +82.2 (*c* = 1.0, $CHCl_3$); major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.00 (d, *J* = 10.4 Hz, 1H), 5.67 (dt, *J* = 10.4, 2.1 Hz, 1H), 5.5 (s, 1H), 4.54-4.52 (m, 1H), 4.27 (dd, *J* = 10.3, 4.6 Hz, 1H), 4.12-4.10 (m, 1H), 3.80 (s, 3H), 3.74 (t, *J* = 10.3 Hz, 1H), 3.59-3.54 (m, 1H), 2.66-2.62 (m, 1H), 2.19 (s, 3H), 1.82-1.76 (m, 1H), 1.60-1.56 (m, 1H), 0.90 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 209.9, 160.1, 129.9, 128.6, 127.8, 127.5, 113.7, 101.9, 76.5, 75.0, 70.9, 69.4, 58.5, 55.3, 31.1, 20.1, 12.0; **IR** (neat): ν 2967, 2876, 1713, 1620, 1518, 1250, 1099, 831 cm^{-1}; **HRMS** (ESI): calcd. for $C_{19}H_{24}O_5Na$ $[M+Na]^+$, 355.1521; found, 355.1530.

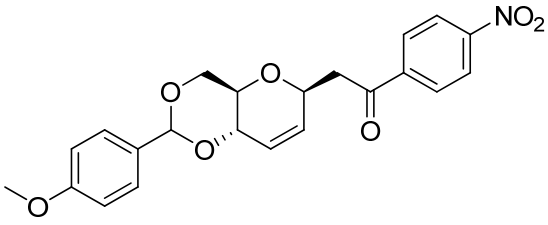


2-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)- cyclopetanone (3.26j): Compound was prepared following the general procedure B (18 h) and obtained by flashing column chromatography (EA/hexanes = 1: 5) as a white solid (21.9 mg, 66%). Major isomer: **Mp** 105-107 °C; $[\alpha]_D^{20}$ = +21.7 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.02 (d, *J* = 10.2 Hz, 1H), 5.67 (d, *J* = 10.2 Hz, 1H), 5.53 (s, 1H), 4.80-4.78 (m, 1H), 4.25 (dd, *J* = 9.9, 4.5 Hz, 1H), 4.15-4.13 (m, 1H), 3.80 (s, 3H), 3.68 (t, *J* = 10.4 Hz, 1H), 3.60-3.53 (m, 1H), 2.33-2.11 (m, 3H), 2.07-1.73 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 218.5, 160.2, 130.0, 129.7, 128.5, 128.0, 127.6, 113.7, 101.9, 75.9, 75.1, 74.8, 70.8, 70.5, 69.4, 55.3, 52.6, 52.3, 39.1, 25.1, 23.6, 20.8, 20.6; **IR** (neat): ν 2965, 2876, 1738, 1614, 1518, 1250, 1098, 831, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{19}H_{22}O_5Na$ $[M+Na]^+$, 353.1365; found, 353.1367.

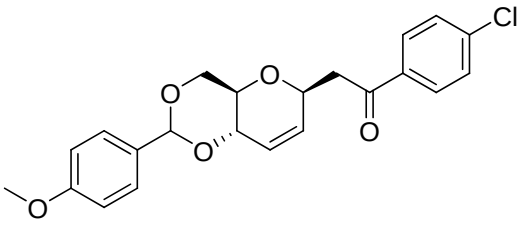


2-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)- 1-phenylethanone (3.26k): Compound was prepared following the general procedure B and obtained by flashing column chromatography (EA/hexanes = 1: 8) as a white solid (32.2 mg, 88%). **Mp** 94-95 °C; $[\alpha]_D^{20}$ = +115.8 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.00 (d, *J* = 10.5

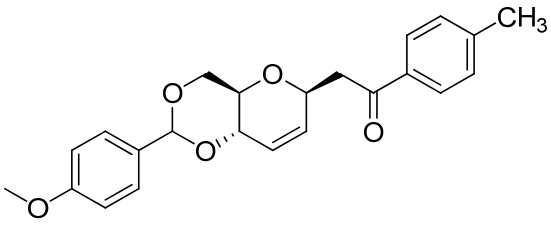
Hz, 1H), 5.84 (d, *J* = 10.5 Hz, 1H), 5.55 (s, 1H), 5.00-4.98 (m, 1H), 4.29 (dd, *J* = 10.0, 4.3 Hz, 1H), 4.19-4.16 (m, 1H), 3.80 (s, 3H), 3.73 (t, *J* = 10.0 Hz, 1H), 3.67-3.62 (m, 1H), 3.36 (dd, *J* = 16.6, 6.6 Hz, 1H), 3.09 (dd, *J* = 16.6, 6.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.1, 160.1, 136.9, 133.3, 130.5, 130.0, 128.6, 128.2, 127.5, 127.1, 113.7, 101.9, 75.1, 72.5, 70.9, 69.4, 55.3, 43.8; **IR** (neat): ν 3013, 2864, 1682, 1614, 1518, 1248, 1099, 752 cm^{-1}; **HRMS** (ESI): calcd. for $C_{22}H_{23}O_5$ $[M+H]^+$, 367.1545; found, 367.1560.



2-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)- 1-(4-nitrophenyl)ethanone (3.26l): Compound was prepared following the general procedure B and obtained by flashing column chromatography (EA/hexanes = 1: 3) as a white solid (33.7 mg, 82%). Mp 150-152 °C; $[\alpha]_D^{20}$ = +96.7 (*c* = 1.0, $CHCl_3$); **1H NMR** (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.03 (d, *J* = 10.4 Hz, 1H), 5.81 (dt, *J* = 10.4, 2.0 Hz, 1H), 5.54 (s, 1H), 4.99-4.97 (m, 1H), 4.26 (dd, *J* = 9.5, 3.8 Hz, 1H), 4.17-4.15 (m, 1H), 3.80 (s, 3H), 3.70-3.61 (m, 2H), 3.37 (dd, *J* = 16.5, 7.1 Hz, 1H), 3.11 (dd, *J* = 16.5, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 160.2, 150.4, 141.3, 129.9, 129.3, 127.7, 127.5, 123.8, 113.7, 102.0, 74.9, 72.4, 71.0, 69.3, 55.3, 44.2; **IR** (neat): ν 2835, 1688, 1518, 1344, 1250, 1101, 995, 750 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{21}NO_9Na$ $[M+Na]^+$, 478.1114; found, 478.1105.

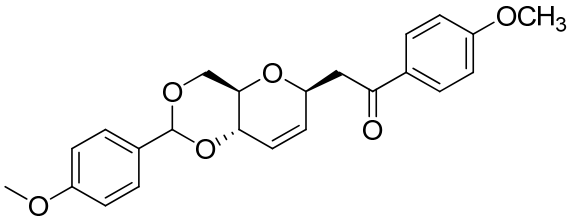


2-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)- 1-(4-chlorophenyl)ethanone (3.26m): Compound was prepared following the general procedure B and obtained by flashing column chromatography (EA/hexanes = 1: 7) as a white solid (28.5 mg, 71%). **Mp** 119-121 °C; $[\alpha]_D^{20}$ = +89.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.6 Hz, 2H), 7.46-7.41 (m, 4H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.01 (d, *J* = 10.4 Hz, 1H), 5.82 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.54 (s, 1H), 4.98-4.96 (m, 1H), 4.27 (dd, *J* = 9.8, 4.2 Hz, 1H), 4.17-4.15 (m, 1H), 3.80 (s, 3H), 3.71 (t, *J* = 10.1 Hz, 1H), 3.66-3.61 (m, 1H), 3.31 (dd, *J* = 16.5, 6.8 Hz, 1H), 3.04 (dd, *J* = 16.5, 6.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.0, 160.1, 139.8, 135.2, 130.3, 129.9, 129.6, 128.9, 127.5, 127.3, 113.7, 101.9, 75.0, 72.4, 70.9, 69.3, 55.3, 43.7; **IR** (neat): ν 3020, 1731, 1619, 1518, 1250, 1098, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{22}H_{21}ClO_5Na$ $[M+Na]^+$, 423.0975; found, 423.0987.

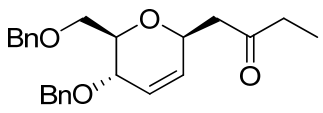


2-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)- 1-(4-methylphenyl)ethanone (3.26n): Compound was prepared following the general procedure B (18 h) and obtained by flashing column chromatography (EA/hexanes = 1: 8) as a white solid (26.6 mg, 70%). **Mp** 132-133 °C; $[\alpha]_D^{20}$ = +101.2 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.2

Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.99 (d, *J* = 10.4 Hz, 1H), 5.55 (s, 1H), 4.98-4.97 (m, 1H), 4.28 (dd, *J* = 10.1, 4.3 Hz, 1H), 4.19-4.16 (m, 1H), 3.80 (s, 3H), 3.73 (t, *J* = 10.1 Hz, 1H), 3.67-3.61 (m, 1H), 3.33 (dd, *J* = 16.5, 6.6 Hz, 1H), 3.06 (dd, *J* = 16.5, 6.6 Hz, 1H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.7, 160.1, 144.2, 134.5, 130.7, 130.0, 129.3, 128.3, 127.5, 127.0, 113.7, 101.9, 75.1, 72.6, 70.9, 69.4, 55.3, 43.7, 21.6; **IR** (neat): ν 2972, 2872, 1680, 1516, 1246, 1101, 808, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{24}O_5Na$ $[M+Na]^+$, 403.1521; found, 403.1529.

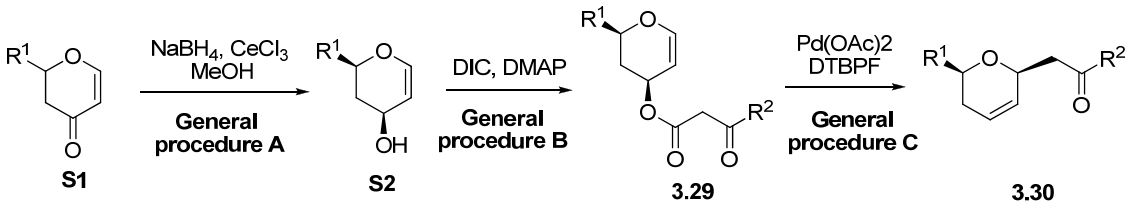


2-((4,6-di-*O*-(4-Methoxybenzylidene)-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)- 1-(4-methoxyphenyl)ethanone (3.26o): Compound was prepared following the general procedure B (18 h) and obtained by flashing column chromatography (EA/hexanes = 1: 5) as a white solid (24.6 mg, 62%). **Mp** 136-137 °C; $[\alpha]_D^{20}$ = +103.3 (*c* = 0.84, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.98 (d, *J* = 10.4 Hz, 1H), 5.83 (d, *J* = 10.4 Hz, 1H), 5.54 (s, 1H), 4.98-4.96 (m, 1H), 4.28 (dd, *J* = 10.0, 4.3 Hz, 1H), 4.18-4.16 (m, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.73 (t, *J* = 10.2 Hz, 1H), 3.67-3.61 (m, 1H), 3.30 (dd, *J* = 16.3, 6.6 Hz, 1H), 3.03 (dd, *J* = 16.3, 6.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.6, 163.7, 160.1, 130.7, 130.5, 130.0(2C), 127.5, 126.9, 113.7(2C), 101.9, 75.1, 72.7, 70.9, 69.4, 55.5, 55.3, 43.5; **IR** (neat): ν 2839, 1667, 1603, 1518, 1252, 1175, 1022, 820, 754 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{24}O_6Na$ $[M+Na]^+$, 419.1471; found, 419.1477.



1-(4,6-Di-*O*-benzyl-2,3-dideoxy-β-D-erythro-hex-2-enopyranosyl)-2-butanone (3.26p): A mixture of **3.25a** (34.8 mg, 0.1 mmol) and **3.25p** (42.4 mg, 0.1 mmol), palladium acetate (2.3 mg, 0.01 mmol) and 1,2-bis(diphenylphosphino)ethane (8.4 mg, 0.02 mmol) in anhydrous toluene (2 mL) was heated to 60 °C for 4 h in a Schlenk tube filled with N_2. Compound **3.26p** was purified by flashing column chromatography on silica gel (Ethyl acetate/hexanes = 1: 8) as a colorless oil (19.2 mg, 25%). $[\alpha]_D^{20}$ = +109.9 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.24 (m, 10H), 5.93 (d, *J* = 10.3 Hz, 1H), 5.78 (d, *J* = 10.3 Hz, 1H), 4.62-4.59 (m, 3H), 4.54 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.06-4.04 (m, 1H), 3.73-3.70 (m, 1H), 3.66-3.60 (m, 2H), 2.75 (dd, *J* = 15.8, 7.1 Hz, 1H), 2.52 (dd, *J* = 15.8, 6.3 Hz, 1H) 2.48 (q, *J* = 7.3 Hz, 2H), 1.05 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 209.1, 138.3, 138.0, 130.8, 128.4, 128.3, 127.9, 127.7, 127.5, 126.7, 77.2, 73.3, 71.5, 71.1, 70.3, 69.5, 47.7, 37.0, 7.5; **IR** (neat): ν 3032, 2870, 1713, 1450, 1366, 1096, 741 cm^{-1}; **HRMS** (ESI): calcd. for $C_{24}H_{28}O_4Na$ $[M+Na]^+$, 403.1885; found, 404.1885.

3.7.2 Decarboxylative allylation on normal pyran system



General procedure A: Reduce of pyran-4-one to pyran-4-ol with $NaBH_4$ and $CeCl_3$.

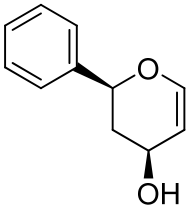
To a solution a ketone **S1** (5 mmol, 1equiv) and $CeCl_3.7H_2O$ (1.88g, 5.1 mmol, 1.1 equiv) in methanol (10 mL) was added $NaBH_4$ (0.19 g, 5.1 mmol, 1.1 equiv) in portions at -30 ^oC. the reaction mixture was stirred at -30 ^oC from 30 min. to 2 h, then quenched with saturated aqueous NH_4Cl. The mixture was then extracted with ethyl acetate (3 x 10 mL), the combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was used in the next step without further purification.

General procedure B: Coupling of pyran-4-ol with *β*-ketoacid.

To a stirred solution of pyran-4-ol **S2** (1 mmol, 1 equiv), β-ketoacid (1.5 mmol, 1.5 equiv) and DMAP (cat.) in DCM (3 mL) at 0 ^oC, DCC (0.31 g, 1.5 mmol, 1.5 equiv) was added slowly. The reaction mixture was stirred at 0 ^oC for 1h and then allowed to warm to r.t.. The stirring was continued from 3 to 12 hours. The mixture was filtrated through a pad of cellite and the resultant filtrate was evaporated and purified by column chromatography on silica gel (silica gel was deactivated by water in advance).

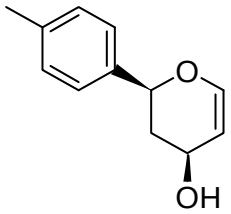
General procedure C: palladium catalyzed decarboxalative coupling reaction.

A mixture of **3.29** (0.1 mmol, 1 euiv), palladium acetate (2.2 mg, 0.005 mmol, 5% equiv) and 1,1′-Bis(di-*tert*-butylphosphino)ferrocene (4.7 mg, 0.01 mmol, 0.1 equiv) in anhydrous toluene (1.0 mL) was heated to 60 °C under N_2 in a Schlenk tube. The reaction was stirred for 3 - 12 h. The product was purified by flashing column chromatography on silica gel to give **3.30.**



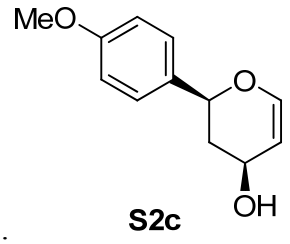
S2a

2-Phenyl-3,4-dihydro-2*H*-pyran-4-ol (**S2a**): According to general procedure A, the title compound was obtained in 97% yield as white solid. **Mp** 54 - 55 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25-7.40 (m, 5H), 6.51 (d, J = 6.2 Hz, 1H), 4.99 (dd, J = 2.0, 11.8 Hz, 1H), 4.86 (dt, J = 1.9, 6.2 Hz, 1H), 4.59 (t, J = 7.8 Hz, 1H), 2.33-2.40 (m, 1H), 1.93-2.04 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.3, 140.3, 128.6, 128.1, 126.0, 105.8 76.8, 63.5, 39.9 ppm. **IR** (neat): ν 3371, 1640, 1567, 1037 cm^{-1}; **HRMS** (ESI): calcd. for $C_{11}H_{13}O_2$ $[M+H]^+$, 177.0916; found, 177.0913.



S2b

2-*p*-Tolyl-3,4-dihydro-2*H*-pyran-4-ol (**S2b**): According to general procedure A, the title compound was obtained in 93% yield as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.17 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 6.41 (d, J = 6.2 Hz, 1H), 4.86 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 6.2 Hz, 1H), 4.47-4.51 (m, 1H), 2.24 (s, 3H), 2.22-2.26 (m, 1H), 1.85-1.96 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.4, 137.9, 137.4, 129.3, 126.1, 105.7, 76.8, 63.5, 39.9, 21. ppm. **IR** (neat): ν 3400, 1630, 1513 cm^{-1}; **HRMS** (ESI): calcd. for $C_{12}H_{14}O_2Na$ $[M+Na]^+$, 213.0891; found, 213.0897.



S2c

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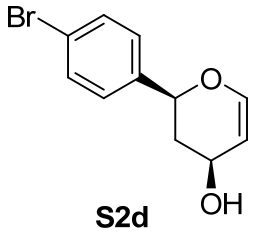
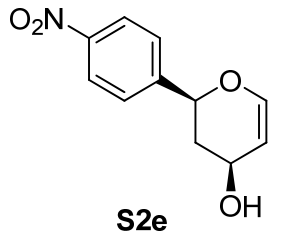
2-(4-Methoxyphenyl)-3,4-dihydro-2*H*-pyran-4-ol (**S2c**): According to general procedure A, the title compound was obtained in 95% yield as yellow solid. **Mp** 71 - 72 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.28 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.48 (d, J = 6.2 Hz, 1H), 4.92 (d, J = 11.8 Hz, 1H), 4.83(d, J = 6.2 Hz, 1H), 3.77-3.80 (m, 1H), 3.79 (s, 3H), 2.29-2.35 (m, 1H), 1.93-2.00 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.4, 145.4, 132.4, 127.5, 114.0, 105.7, 76.6, 63.6, 55.3, 39.8 ppm. **IR** (neat): v 3417, 1643, 1516 cm^{-1}; **HRMS** (ESI): calcd. for $C_{12}H_{13}O_2$ $[M\text{-}OH]^+$, 189.0916; found, 189.0912.



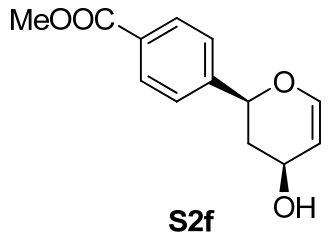
S2d

2-(4-Bromophenyl)-3,4-dihydro-2*H*-pyran-4-ol (**S2d**): According to general procedure A, the title compound was obtained in 92% yield as yellow solid. **Mp** 63 - 65 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.41 (d, J = 6.2 Hz, 1H), 4.85 (d, J = 11.7 Hz, 1H), 4.77 (d, J = 6.2 Hz, 1H), 4.48-4.52 (m, 1H), 2.22-2.27 (m, 1H), 1.82-1.96 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.1, 139.4, 131.7, 127.7, 121.9, 105.9, 76.1, 63.3, 39.9 ppm. **IR** (neat): v 3409, 1623, 1509 cm^{-1}; **HRMS** (ESI): calcd. for $C_{11}H_{10}O^{79}Br$ $[M\text{-}OH]^+$, 236.9915; found, 236.9917.



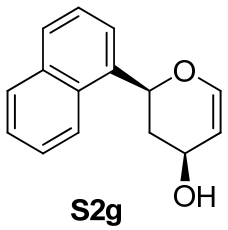
S2e

2-(4-Nitrophenyl)-3,4-dihydro-2*H*-pyran-4-ol (**S2e**): According to general procedure A, the title compound was obtained in 92% yield as yellow solid. **Mp** 99 - 101 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.16 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 6.46 (d, J = 5.8 Hz, 1H), 5.03 (d, J = 11.6 Hz, 1H), 4.85 (d, J = 5.8 Hz, 1H), 4.56-4.58 (m, 1H), 2.32-2.36 (m, 1H), 1.82-1.90 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.7, 144.8, 126.6, 123.8, 106.2, 75.7, 62.9, 60.4, 39.9 ppm; **IR** (neat): v 3226, 1637, 1526, 1367 cm^{-1}; **HRMS** (ESI): calcd. for $C_{11}H_{10}NO_3$ $[M\text{-}OH]^+$, 204.0661; found, 204.0659.



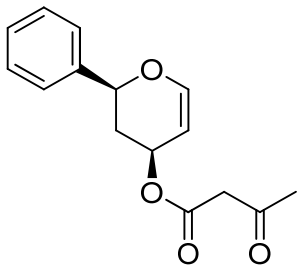
S2f

Methyl 4-(4-hydroxy-3,4-dihydro-2*H*-pyran-2-yl)benzoate (S2f): According to general procedure A, the title compound was obtained in 90% yield as yellow solid. **Mp** 58 - 59 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.95 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 6.42 (d, J = 6.1 Hz, 1H), 4.94 (d, J = 11.6 Hz, 1H), 4.79(d, J = 6.1 Hz, 1H), 4.50-4.54 (m, 1H), 3.83 (s, 3H), 2.25-2.31 (m, 1H), 1.80-1.89 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 166.9, 145.6, 144.9, 129.9, 129.7, 125.9, 106.1, 76.3, 63.1, 52.2, 39.9, 29.7 ppm; **IR** (neat): v 3230, 1721, 1620, 1543 cm^{-1}; **HRMS** (ESI): calcd. for $C_{13}H_{13}O_3$ $[M\text{-}OH]^+$, 217.0865; found, 217.0860.

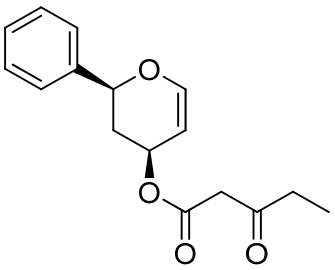


S2g

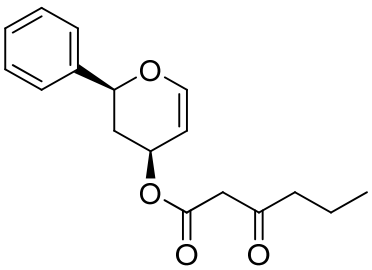
2-(Naphthalen-1-yl)-3,4-dihydro-2*H*-pyran-4-ol (S2g):According to general procedure A, the title compound was obtained in 90% yield as yellow solid. **Mp** 75 - 76 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.87 (d, J = 8.3 Hz, 1H), 7.69-7.78 (m, 3H), 7.52 (d, J = 7.1 Hz, 1H), 7.33-7.43 (m, 3H), 6.50 (d, J = 6.2 Hz, 1H), 5.59 (d, J = 11.8 Hz, 1H), 4.82(d, J = 6.2 Hz, 1H), 4.59-4.64 (m, 1H), 2.41-2.46 (m, 1H), 1.98-2.05 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.6, 135.8, 133.8, 130.3, 129.0, 128.7, 126.3, 125.7, 125.5, 123.4, 122.8, 105.2, 74.1, 63.9, 39.2 ppm; **IR** (neat): v 3310, 1634, 1532 cm^{-1}; **HRMS** (ESI): calcd. for $C_{15}H_{13}O$ $[M\text{-}OH]^+$, 209.0966; found, 209.0965.



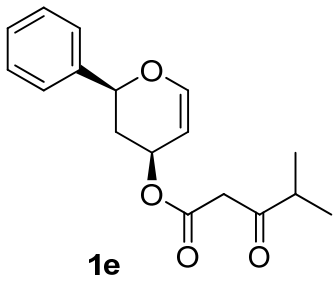
2-Phenyl-3,4-dihydro-2*H*-pyran-4-yl 3-oxobutanoate (3.29a): According to general procedure B, the title compound was obtained in 85% yield as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.23-7.36 (m, 5H), 6.59 (d, J = 6.1 Hz, 1H), 5.60-5.65 (m, 1H), 5.04 (dd, J = 11.7, 2.0 Hz, 1H), 4.83-4.87 (m, 1H), 3.39 (s, 2H), 2.45-2.51 (m, 1H), 2.22 (s, 3H), 2.04-2.13 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.3, 166.9, 147.3, 139.8, 128.6, 128.2, 125.9, 100.9, 76.5, 67.1, 50.2, 35.3, 30.2 ppm; **IR** (neat): v 3030, 1740, 17124, 1655, 1223 cm^{-1}; **HRMS** (ESI): calcd. for $C_{15}H_{16}O_4Na$ $[M+Na]^+$, 283.0946; found, 283.0941.



2-Phenyl-3,4-dihydro-2*H*-pyran-4-yl 3-oxopentanoate (3.29b): According to general procedure B, the title compound was obtained in 83% yield as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25-7.39 (m, 5H), 6.59 (d, J = 6.3 Hz, 1H), 5.60-5.65 (m, 1H), 5.04 (d, J = 11.8 Hz, 1H), 4.85 (d, J = 6.3 Hz, 1H), 3.39 (s, 2H), 2.46-2.55 (m, 3H), 2.04-2.13 (m, 1H), 1.06 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.1, 167.1, 147.2, 139.9, 128.6, 128.2, 125.9, 100.9, 76.5, 67.0, 49.0, 36.3, 35.3, 7.5 ppm; **IR** (neat): v 3027, 1737, 1719, 1649, 1223 cm^{-1}; **HRMS** (ESI): calcd. for $C_{16}H_{18}O_4Na$ $[M+Na]^+$, 297.1103; found, 297.1102.

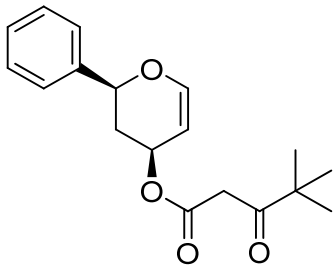


2-Phenyl-3,4-dihydro-2*H*-pyran-4-yl 3-oxohexanoate (3.29c): According to general procedure B, the title compound was obtained in 82% yield as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.26-7.39 (m, 5H), 6.61 (d, J = 6.2 Hz, 1H), 5.63 (dd, J = 8.4, 7.5 Hz, 1H), 5.04 (d, J = 11.6 Hz, 1H), 4.85 (d, J = 6.2 Hz, 1H), 3.38 (s, 2H), 2.45-2.52 (m, 3H), 2.04-2.16 (m, 1H), 1.61 (q, J = 7.4 Hz, 2H), 0.92 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 202.6, 167.1, 147.2, 139.9, 128.6, 128.2, 125.9, 100.9, 76.5, 67.0, 49.3, 44.9, 35.3, 16.9, 13.6 ppm; **IR** (neat): v 3020, 1739, 1720, 1644, 1228 cm^{-1}; **HRMS** (ESI): calcd. for $C_{17}H_{20}O_4Na$ $[M+Na]^+$, 311.1259; found, 311.1259.



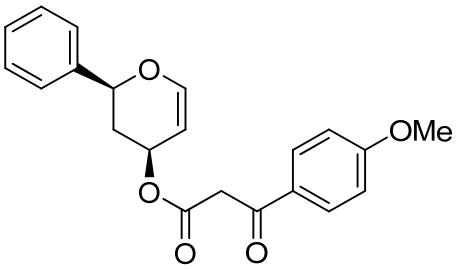
1e

2-Phenyl-3,4-dihydro-2*H*-pyran-4-yl 4-metnyl-3-oxopentanoate (3.29d): According to general procedure B, the title compound was obtained in 79% yield as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.26-7.39 (m, 5H), 6.60 (d, J = 6.2 Hz, 1H), 5.63 (dt, J = 8.7, 7.3 Hz, 1H), 5.04 (dd, J = 11.8, 2.0 Hz, 1H), 4.84-4.87 (m, 1H), 3.45 (s, 2H), 2.65-2.74 (m, 1H), 2.46-2.52 (m, 1H), 2.02-2.14 (m, 1H), 1.12 (d, J = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 202.3, 167.3, 147.2, 139.9, 128.5, 128.2, 125.9, 101.0, 76.5, 67.0, 47.1, 41.2, 35.3, 17.9 ppm; **IR** (neat): v 3008, 1740, 1719, 1648, 1238 cm^{-1}; **HRMS** (ESI): calcd. for $C_{17}H_{20}O_4Na$ $[M+Na]^+$, 311.1259; found, 311.1256.

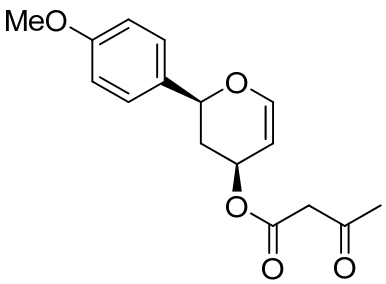


2-Phenyl-3,4-dihydro-2*H*-pyran-4-yl 4,4-dimethyl-3-oxopentanoate (3.29f): According to general procedure B, the title compound was obtained in 84% yield as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25-7.36 (m, 5H), 6.60 (d, J = 6.2 Hz, 1H), 5.61-5.67 (m, 7.3 Hz, 1H), 5.04 (d, J = 11.7, 1H), 4.84-4.87 (m, 1H), 3.50 (s, 2H), 2.46-2.52 (m, 1H), 2.08-2.13 (m, 1H), 1.15 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.9, 167.7, 147.1, 139.9, 128.5, 128.1, 125.9, 101.0, 85.6, 76.5, 67.0,

44.7, 35.7, 26.1 ppm; **IR** (neat): *v* 3012, 1736, 1722, 1649, 1238 cm^{-1}; **HRMS** (ESI): calcd. for $C_{18}H_{22}O_4Na$ $[M+Na]^+$, 325.1416; found, 325.1412.

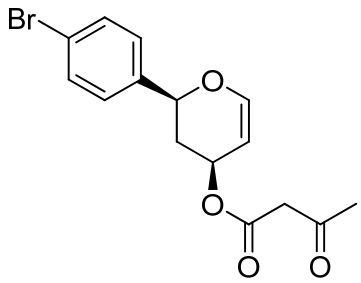


2-Phenyl-3,4-dihydro-2*H*-pyran-4-yl 3-(4-methoxyphenyl)-3-oxopropanoate (3.29g): According to general procedure B, the title compound was obtained in 78% yield as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.88 (d, J = 8.7 Hz, 2H), 7.31-7.38 (m, 5H), 6.92 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 6.2 Hz, 1H), 5.63-5.68 (m, 7.3 Hz, 1H), 5.01 (d, J = 11.9 Hz, 1H), 4.84 (d, J = 6.2 Hz, 1H), 3.89 (s, 2H), 3.85 (s, 3H), 2.44-2.51 (m, 1H), 2.00-2.12 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.8, 167.6, 164.0, 147.1, 139.9, 130.8, 129.0, 128.1, 125.9, 126.2, 113.9, 101.0, 76.5, 67.1, 55.5, 45.8, 35.3 ppm; **IR** (neat): *v* 3031, 1739, 1720, 1644, 1228 cm^{-1}; **HRMS** (ESI): calcd. for $C_{20}H_{18}O_4Na$ $[M+Na]^+$, 345.1103; found, 345.1101.

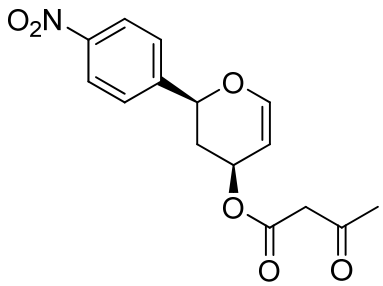


2-(4-Methoxyphenyl)-3,4-dihydro-2*H*-pyran-4-yl 3-oxopentanoate (3.29i): According to general procedure B, the title compound was obtained in 84% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.59 (d, J = 6.2 Hz, 1H), 5.61-5.65 (m, 1H), 4.97 (d, J = 11.5, 1H), 4.83 (d, J

= 6.3 Hz, 1H), 3.80 (s, 3H), 3.42 (s, 2H), 2.42-2.48 (m, 1H), 2.13 (s, 3H), 1.95-2.11 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.3, 167.0, 159.5, 131.9, 127.4, 113.9, 100.8, 76.3, 67.3, 55.3, 50.2, 35.2, 30.2 ppm; **IR** (neat): ν 3020, 1733, 1718, 1634, 1228 cm^{-1}; **HRMS** (ESI): calcd. for $C_{21}H_{20}O_5Na$ $[M+Na]^+$, 375.1208; found, 375.1207.

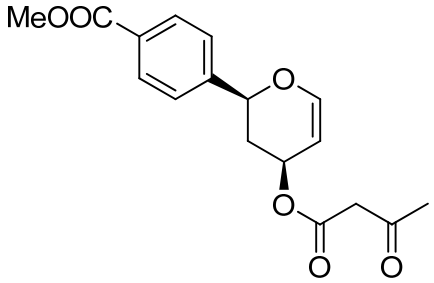


2-(4-Bromophenyl)-3,4-dihydro-2*H*-pyran-4-yl 3-oxopentanoate (3.29j): According to general procedure B, the title compound was obtained in 86% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 6.2 Hz, 1H), 5.51-5.55 (m, 1H), 4.94 (d, J = 11.5, 1H), 4.79 (d, J = 6.2 Hz, 1H), 3.33 (s, 2H), 2.37-2.43 (m, 1H), 2.16 (s, 3H), 1.87-1.98 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.2, 166.9, 147.0, 138.9, 131.7, 127.6, 121.9, 101.0, 75.7, 66.7, 50.1, 35.2, 30.2 ppm; **IR** (neat): ν 3021, 1733, 1711, 1634, 1238 cm^{-1}; **HRMS** (ESI): calcd. for $C_{15}H_{15}O_4{}^{79}BrNa$ $[M+Na]^+$, 361.0051; found, 361.0054.

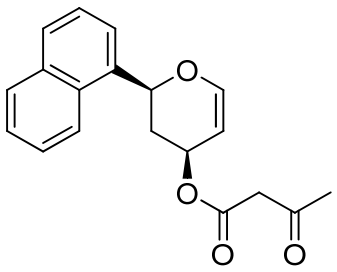


2-(4-Nitrophenyl)-3,4-dihydro-2*H*-pyran-4-yl 3-oxopentanoate (3.29k): According to general procedure B, the title compound was obtained in 81% yield as colorless oil.

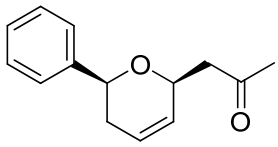
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 6.3 Hz, 1H), 5.58-5.62 (m, 1H), 5.17 (d, J = 11.2, 1H), 4.90 (d, J = 6.2 Hz, 1H), 3.38 (s, 2H), 2.51-2.56 (m, 1H), 2.21 (s, 3H), 1.99-2.07 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.2,166.8, 147.6, 147.1, 146.7, 126.7, 123.8, 101.4, 75.1, 66.2, 50.0, 35.2, 30.2, 21.3 ppm; **IR** (neat): v 3019, 1734, 1713, 1633, 1338 cm^{-1}; **HRMS** (ESI): calcd. for $C_{15}H_{15}NO_6Na$ $[M+Na]^+$, 328.0797; found, 328.0794.



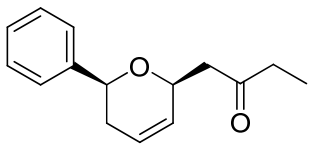
2-(4-Methoxycarbonylphenyl)-3,4-dihydro-2*H*-pyran-4-yl 3-oxopentanoate (3.29l): According to general procedure B, the title compound was obtained in 83% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 6.56 (d, J = 6.2 Hz, 1H), 5.52-5.27 (m, 1H), 5.04 (d, J = 11.4, 1H), 4.81 (d, J = 6.2 Hz, 1H), 3.85 (s, 3H), 3.32 (s, 2H), 2.11-2.50 (m, 1H), 2.11 (s, 3H), 1.95-2.01 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.2, 166.9, 166.7, 147.0, 145.0, 129.9, 125.8, 101.1, 75.8, 66.6, 52.2, 50.1, 35.2, 30.9 ppm; **IR** (neat): v 3028, 1733, 1724, 1719, 1644, cm^{-1}; **HRMS** (ESI): calcd. for $C_{17}H_{18}O_6Na$ $[M+Na]^+$, 341.1001; found, 341.0999.



2-(Naphthalen-1-yl)-3,4-dihydro-2*H*-pyran-4-yl 3-oxopentanoate (3.29m): According to general procedure B, the title compound was obtained in 83% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.4 Hz, 1H), 7.80 (J = 7.8 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H),7.38-7.49 (m, 3H), 6.64 (d, J = 6.2 Hz, 1H), 5.67-5.72 (m, 2H), 4.84-4.88 (m, 1H), 3.33 (s, 2H), 2.57-2.63 (m, 1H), 2.13 (s, 3H), 2.11-2.15 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.3, 166.9, 147.5, 135.2, 133.8, 130.1, 129.0, 128.8, 126.5, 125.8, 125.4, 123.5, 122.7, 101.3, 73.9, 67.4, 50.2, 34.5, 30.2 ppm; **IR** (neat): v 3019, 1738, 1715, 1645, 1234 cm^{-1}; **HRMS** (ESI): calcd. for $C_{19}H_{18}O_4Na$ $[M+Na]^+$, 333.1103; found, 333.1102.

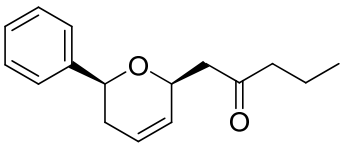


6-(2-Oxopropyl)-2-phenyl-3,6-dihydro-2*H*-pyran (3.30a): According to general procedure C, the title compound was obtained in 91% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17-7.27 (m, 5H), 5.84-5.88 (m, , 1H), 5.73 (d, J = 10.4 Hz, 1H), 4.68-4.71 (m, 1H), 4.56 (dd, J = 5.2, 8.6 Hz, 1H), 2.74 (dd, J = 7.4, 15.4 Hz, 1H), 2.56 (dd, J = 5.7, 15.4 Hz, 1H), 2.18-2.23 (m, 2H), 2.16 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.2, 142.4, 129.2, 128.3, 127.4, 125.7, 125.5, 75.7, 72.4, 49.2, 32.8, 31.2 ppm; **IR** (neat): v 1721, 1622, 1515, 1247 cm^{-1}; **HRMS** (ESI): calcd. for $C_{14}H_{16}O_2Na$ $[M+Na]^+$, 239.1048; found, 239.1050.

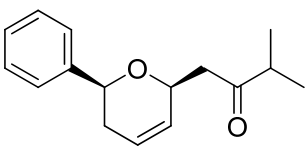


6-(2-Oxobutane-1-yl)-2-phenyl-3,6-dihydro-2*H*-pyran (3.30b): According to general procedure C, the title compound was obtained in 85% yield as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.27 (m, 5H), 5.84-5.88 (m, 1H), 5.67 (d, J = 10.4 Hz, 1H), 4.69-4.71 (m, 1H), 4.55 (dd, J = 5.7, 8.4 Hz, 1H), 2.74 (dd, J = 7.4, 15.3 Hz, 1H), 2.52 (dd, J = 5.9, 15.3 Hz, 1H), 2.46 (q, J = 7.3 Hz, 2H), 2.18-2.21 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 209.7, 142.5, 129.4, 128.3, 127.4, 125.6, 125.4, 75.7, 72.5, 48.0, 37.2, 32.8, 7.6 ppm; **IR** (neat): v 1719, 1625, 1525, 1251 cm^{-1}; **HRMS** (ESI): calcd. for $C_{15}H_{18}O_2Na$ $[M+Na]^+$, 253.1204; found, 253.1194.

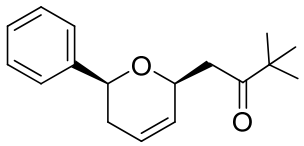


6-(2-Oxopentan-1-yl)-2-phenyl-3,6-dihydro-2*H*-pyran (3.30c): According to general procedure C, the title compound was obtained in 78% yield as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.18-7.29 (m, 5H), 5.82-5.87 (m, 1H), 5.67 (dd, J = 1.5, 10.2 Hz, 1H), 4.70-4.71 (m, 1H), 4.55 (dd, J = 6.0, 8.0 Hz, 1H), 2.74 (dd, J = 7.3, 15.4 Hz, 1H), 2.51 (dd, J = 6.0, 15.4 Hz, 1H), 2.16-2.21 (m, 2H), 1.48-1.61 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 209.3, 142.5, 129.4, 128.3, 127.4, 125.6, 125.4, 75.7, 72.4, 48.3, 45.9, 32.8, 17.0, 13.7 ppm; **IR** (neat): v 1728, 1612, 1523, 1241 cm^{-1}; **HRMS** (ESI): calcd. for $C_{16}H_{20}O_2Na$ $[M+Na]^+$, 267.1361; found, 267.1362.

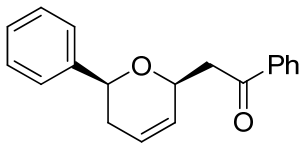


6-(3-Methyl-2-oxobutane-1-yl)-2-phenyl-3,6-dihydro-2*H*-pyran (3.30d): According to general procedure C, the title compound was obtained in 86% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.17-7.27 (m, 5H), 5.82-5.87 (m, 1H),

5.68 (dd, *J* = 1.6, 10.0 Hz, 1H), 4.71-4.74 (m, 1H), 4.56 (dd, *J* = 5.5, 8.3 Hz, 1H), 2.84 (dd, *J* = 7.0, 15.9 Hz, 1H), 2.62 (q, *J* = 6.9 Hz, 1H), 2.84 (dd, *J* = 6.4, 15.9 Hz, 1H), 2.17-2.22 (m, 2H), 1.05 (t, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.7, 142.6, 129.6, 128.3, 127.3, 125.6, 125.3, 75.7, 72.4, 45.9, 41.6, 32.9, 17.9 ppm. **IR** (neat): *v* 1721, 1612, 1520, 1249 cm^{-1}; **HRMS** (ESI): calcd. for $C_{16}H_{20}O_2Na$ $[M+Na]^+$, 267.1361; found, 267.1362.

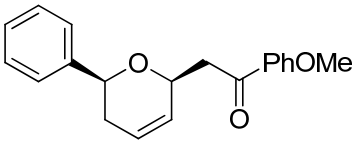


6-(3,3-Dimethyl-2-oxobutane-1-yl)-2-phenyl-3,6-dihydro-2*H*-pyran (3.30e): According to general procedure C, the title compound was obtained in 89% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24-7.35 (m, 5H), 5.89-5.93 (m, 1H), 5.75 (d, *J* = 10.2 Hz, 1H), 4.82-4.84 (m, 1H), 4.63 (dd, *J* = 5.1, 8.9 Hz, 1H), 3.03 (dd, *J* = 6.5, 16.8 Hz, 1H), 2.58 (dd, *J* = 7.0, 15.9 Hz, 1H), 2.25-2.27 (m, 2H), 1.15 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 213.6, 142.6, 129.8, 128.3, 127.3, 125.7, 125.2, 75.8, 72.4, 44.35, 42.4, 33.0, 26.1 ppm. **IR** (neat): *v* 1719, 1625, 1525, 1237 cm^{-1}; **HRMS** (ESI): calcd. for $C_{17}H_{22}O_2Na$ $[M+Na]^+$, 281.1517; found, 281.1516.

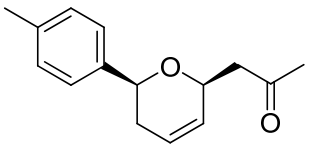


6-(2-Oxo-2-phenylethyl)-2-phenyl-3,6-dihydro-2*H*-pyran (3.30f): According to general procedure C, the title compound was obtained in 94% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.3 Hz, 2H), 7.48-7.51 (m, 1H), 7.37-7.41 (m, 2H), 7.15-7.23 (m, 5H), 5.86-5.90 (m, 1H), 5.80 (d, *J* = 10.4 Hz, 1H), 4.90-4.94 (m, 1H), 4.60 (dd, *J* = 5.4, 8.7 Hz, 1H), 3.39 (dd, *J* = 6.2, 16.0 Hz, 1H), 3.07 (dd, *J* =

7.1, 16.0 Hz, 1H), 2.20-2.23 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.3, 142.5, 137.3, 133.1, 129.6, 128.5, 128.4, 128.3, 127.3, 125.7, 125.4, 75.8, 72.6, 44.4, 32.9 ppm. **IR** (neat): *v* 1724, 1623, 1518, 1233 cm^{-1}; **HRMS** (ESI): calcd. for $C_{19}H_{18}O_2Na$ $[M+Na]^+$, 301.1204; found, 301.1200.

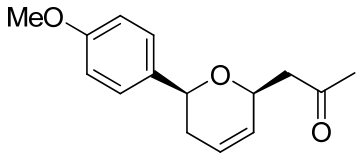


6-(2-Oxo-2-(4-methoxyphenyl)ethyl)-2-phenyl-3,6-dihydro-2*H*-pyran (3.30g): According to general procedure C, the title compound was obtained in 95% yield as colorless oil. **1H NMR** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.23-7.31 (m, 5H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.92-5.95 (m, 1H), 5.87 (d, *J* = 10.4 Hz, 1H), 4.95-4.97 (m, 1H), 4.66 (dd, *J* = 5.2, 8.8 Hz, 1H), 3.87 (s, 3H), 3.41(dd, *J* = 6.2, 16.0 Hz, 1H), 3.07 (dd, *J* = 7.1, 15.8 Hz, 1H), 2.27-2.30 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.7, 163.5, 142.5, 130.7, 130.5, 129.8, 128.3, 127.3, 125.7, 125.2, 113.7, 75.8, 72.7, 55.5, 44.0, 32.9 ppm. **IR** (neat): *v* 1728, 1620, 1525, 1237 cm^{-1}; **HRMS** (ESI): calcd. for $C_{20}H_{20}O_3Na$ $[M+Na]^+$, 331.1310; found, 331.1299.

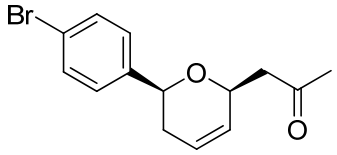


2-(4-Methylphenyl)-6-(2-oxopropyl)-3,6-dihydro-2*H*-pyran (3.30h): According to general procedure C, the title compound was obtained in 82% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.90-5.96 (m, 1H), 5.72 (ddd, *J* = 1.2, 1.3, 10.1 Hz, 1H), 4.74-4.77 (m, 1H), 4.59 (dd, *J* = 4.2, 9.7 Hz, 1H), 2.80 (dd, *J* = 7.4, 15.4 Hz, 1H), 2.61 (dd, *J* = 5.8, 15.4 Hz, 1H), 2.28 (s, 3H), 2.22-2.27 (m,2H), 2.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.3,

139.5, 137.1, 129.1, 129.0, 125.7, 125.6, 75.6, 72.4, 49.2, 32.7, 31.2, 21.1 ppm. **IR** (neat): *v* 1726, 1625, 1520, 1241 cm^{-1}; **HRMS** (ESI): calcd. for $C_{15}H_{18}O_2Na$ $[M+Na]^+$, 253.1204; found, 253.1204

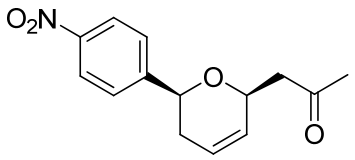


2-(4-Methoxyphenyl)-6-(2-oxopropyl)-3,6-dihydro-2*H*-pyran (3.30i): According to general procedure C, the title compound was obtained in 83% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.91-5.95 (m, 1H), 5.72 (ddd, *J* = 1.1, 1.3, 10.1 Hz, 1H), 4.74-4.77 (m, 1H), 4.57 (dd, *J* = 3.7, 10.2 Hz, 1H), 3.80 (s, 3H), 2.80 (dd, *J* = 7.3, 15.5 Hz, 1H), 2.61 (dd, *J* = 5.8, 15.5 Hz, 1H), 2.23-2.30 (m,2H), 2.25 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.2, 158.9, 134.6, 129.1, 127.0, 126.9, 126.8, 125.6, 113.7, 113.6, 75.4, 72.3, 55.3, 49.2, 32.7, 31.1 ppm; **IR** (neat): *v* 1712, 1612, 1514, 1247 cm^{-1}; **HRMS** (ESI): calcd. for $C_{15}H_{18}O_3Na$ $[M+Na]^+$, 269.1154; found, 269.1150.

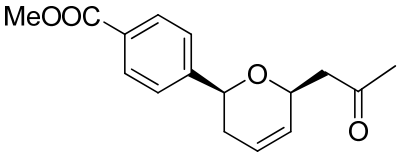


2-(4-Bromophenyl)-6-(2-oxopropyl)-3,6-dihydro-2*H*-pyran (3.30j): According to general procedure C, the title compound was obtained in 86% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 5.84-5.87 (m, 1H), 5.66 (d, *J* = 10.2 Hz, 1H), 4.68-4.71 (m, 1H), 4.52 (dd, *J* = 5.8, 8.2 Hz, 1H), 2.74 (dd, *J* = 7.6, 15.6 Hz, 1H), 2.54 (dd, *J* = 5.6, 15.6 Hz, 1H), 2.15-2.18 (m,2H), 2.16 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.0, 141.5, 131.4, 129.2,

127.4, 125.3, 121.2, 75.0, 72.3, 49.1, 32.7, 31.1 ppm; **IR** (neat): *v* 1714, 1621, 1512, 1237 cm^{-1}; **HRMS** (ESI): calcd. for $C_{14}H_{15}O_2{}^{79}BrNa$ $[M+Na]^+$, 371.0; found, 371.0152.

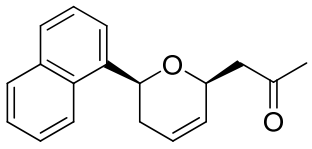


2-(4-Nitrophenyl)-6-(2-oxopropyl)-3,6-dihydro-2*H*-pyran (3.30k): According to general procedure C, the title compound was obtained in 87% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 5.91-5.96 (m, 1H), 5.76 (d, *J* = 10.2 Hz, 1H), 4.80-4.82 (m, 1H), 4.73 (dd, *J* = 3.5, 10.5 Hz, 1H), 2.84 (dd, *J* = 7.7, 15.8 Hz, 1H), 2.63 (dd, *J* = 5.5, 15.8 Hz, 1H), 2.15-2.34 (m,2H), 2.22 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.6, 149.7, 157.2, 129.3, 126.3, 124.8, 123.6, 74.6, 72.2, 48.9, 32.7, 31.1 ppm; **IR** (neat): *v* 1714, 1600, 1518, 1348 cm^{-1}; **HRMS** (ESI): calcd. for $C_{14}H_{15}NO_4Na$ $[M+Na]^+$, 284.0899; found, 284.0904.



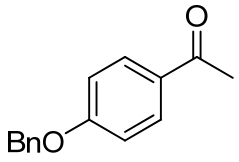
2-(4-Methoxycarbonylphenyl)-6-(2-oxopropyl)-3,6-dihydro-2*H*-pyran (3.30l): According to general procedure C, the title compound was obtained in 88% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 5.90-5.95 (m, 1H), 5.74 (d, *J* = 10.3 Hz, 1H), 4.77-4.79 (m, 1H), 4.68 (dd, *J* = 4.0, 9.8 Hz, 1H), 3.90 (s, 3H); 2.82 (dd, *J* = 7.6, 15.6 Hz, 1H), 2.62 (dd, *J* = 5.6, 15.6 Hz, 1H), 2.23-2.28 (m,2H), 2.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.0,

167.0, 129.7, 129.2, 129.1, 125.5, 125.2, 75.2, 72.3, 52.1, 49.1, 32.7, 31.1, 29.7 ppm ; **IR** (neat): *v* 1733, 1717, 1617, 1511, 1237 cm^{-1}; **HRMS** (ESI): calcd. for $C_{16}H_{18}O_4Na$ $[M+Na]^+$, 297.1103; found, 297.1098.



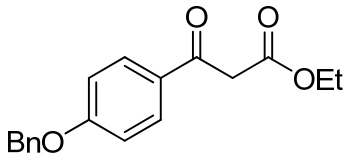
2-(Naphthalen-1-yl)-6-(2-oxopropyl)-3,6-dihydro-2*H*-pyran (3.30m): According to general procedure C, the title compound was obtained in 91% yield as colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 6.7 Hz, 1H), 5.91-5.96 (m, 1H), 5.74 (d, *J* = 10.2 Hz, 1H), 5.25 (dd, *J* = 3.5, 10.3 Hz, 1H), 4.83-4.89 (m, 1H), 2.80 (dd, *J* = 7.4, 15.6 Hz, 1H), 2.60 (dd, *J* = 5.6, 15.6 Hz, 1H), 2.38-2.63 (m,2H), 2.15 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.2, 137.8, 133.8, 130.5, 129.2, 128.8, 128.1, 125.9, 125.8, 125.5, 123.6, 123.1, 73.5, 72.6, 49.2, 31.9, 31.1 ppm; **IR** (neat): *v* 1711, 1619, 1510, 1243 cm^{-1}; **HRMS** (ESI): calcd. for $C_{18}H_{18}O_2Na$ $[M+Na]^+$, 289.1204; found, 289.1208.

3.7.3 Total synthesis of centrolobine.

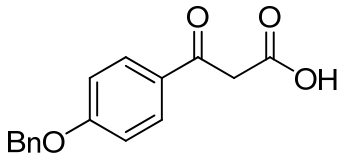


1-(4-(Benzyloxy)phenyl)ethanone (3.36): To a suspension of K_2CO3 (1.5 g, 10.9 mmol), NaI (219.6 mg, 1.5 mmol) and 4'-hydroxyacetophenone (1.0 g, 7.4 mmol) in acetone (10 mL) was added dropwise BnBr (0.96 mL, 8.1 mmol). The mixture was

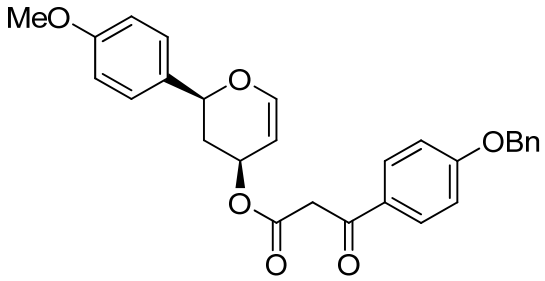
stirred overnight, then diluted with Et_2O (40 mL), washed with water. The organic phase was dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (EA/Hex = 1:10) to give a colorless liquid (1.6 g, 94%). **Mp**: 93 – 94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.26-7.36 (m, 5H), 6.93 (d, J = 8.8 Hz, 2H), 5.05 (s, 2H), 2.47 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.8, 162.6, 136.2, 130.6, 130.5, 128.7, 128.3, 127.5, 114.6, 70.1, 26.4 ppm; **IR** (neat): v 3053, 1676, 1600, 1419, 1265 cm^{-1}.



Ethyl 3-(4-(benzyloxy)phenyl)-3-oxopropanoate (3.37): A suspension of diethyl carbonate (0.58 mL, 4.8 mmol) and NaH (160 mg, 4 mmol) in THF (5 mL) was heated to 60 °C. To the suspension, **3.26** (452.2 mg, 2 mmol) in THF (5 mL) was added dropwise in 1 hour. After being stirred for another 3 hours, the reaction mixture was cooled and added to ice cold aqueous HOAc (30%, 20 mL), then extracted with Et_2O (3 X 10 mL), The combined organic phase washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (EA/Hex = 1:10) to give a wite solid (536.9 mg, 90%). **Mp**: 58 – 59 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.7 Hz, 2H), 7.38-7.43 (m, 5H), 7.02 (d, J = 8.7 Hz, 2H), 5.12 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.94 (s, 2H), 1.26 (t, J = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 191.0, 167.8, 163.1, 136.0, 130.9, 129.3, 128.7, 128.3, 127.5, 114.8, 70.2, 61.4, 45.8, 14.1 ppm; **IR** (neat): v 3043, 1721, 1686, 1610, 1489 cm^{-1}.

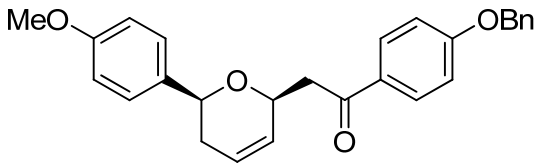


3-(4-(benzyloxy)phenyl)-3-oxopropanoic acid (3.34): To **3.37** (149 mg, 0.5 mmol) was added a freshly prepared aqueous KOH solution (5%, 2.5 mL), the reaction mixture was stirred at room temperature for 40 h. Then the solution was extracted with ether and the ether layer was discarded. The aqueous layer was cooled to 0 °C, and acidified to pH = 4 with cold 1 M H_2SO_4, extracted with cold ether, dried, concentrated under reduced pressure at 20 °C to give a white solid (102 mg, 76%). The crude acid was used in the next step immediately without further purification.

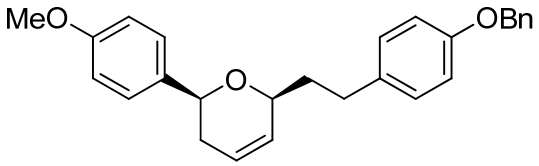


2-(4-Methoxyphenyl)-3,4-dihydro-2*H*-pyran-4-yl 3-(4-(benzyloxy)phenyl)-3-oxopropanoate (3.32): To a solution of corresponding alcohol (38.1 mg, 0.18 mmol), acid (74.7 mg, 0.28 mmol) and DMAP (5 mg) in DCM (0.5 mL) was added dropwise DIC (42.9 μL, 0.28 mmol) at 0 °C. the reaction mixture was stirred for 4 hours at this temperature then diluted with DCM (3 mL), washed with water, dried and concentrated. The residue was purified by column chromatography (EA/Hex = 1:4) on silica gel (deactivated by water in advance) to give a yellow oil (60.8 mg, 76%). **1H NMR** (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.7 Hz, 2H), 7.25-7.42 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.56 (d, J = 6.3 Hz, 1H), 5.63-5.68 (m, 1H), 5.28 (s, 2H), 5.11 (d, J = 8.4 Hz, 1H), 4.82 (d, J = 6.2 Hz, 1H), 3.91 (s, 2H), 3.79 (s, 3H), 2.44 (dd, J = 6.8, 12.0 Hz, 1H), 2.02-2.11 (m, 1H); **^{13}C NMR** (100 MHz,

$CDCl_3$): δ 190.8, 167.7, 163.2, 159.5, 147.2, 136.0, 132.0, 130.9, 129.2, 128.7, 128.3, 127.8, 127.6, 127.4, 126.2, 114.8, 113.8, 101.0, 76.3, 70.2, 67.3, 55.3, 45.8, 35.1, 32.4 ppm; **IR** (neat): ν 1735, 1678, 1598, 1514 cm^{-1}; **HRMS** (ESI): calcd. for $C_{28}H_{26}O_6Na$ $[M+Na]^+$, 481.1627; found, 481.1624.

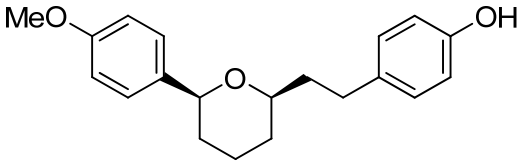


6-(2-Oxo-2-(4-benzyloxyphenyl)ethyl)-6-(4-methoxyphenyl)-5,6-dihydro-2*H*-pyran (3.31): A mixture of **3.32** (62 mg, 0.13 mmol), palladium acetate (3.0 mg, 0.013 mmol) and [1,1′-Bis(di-*tert*-butylphosphino)ferrocene (12.8 mg, 0.027 mmol) in anhydrous toluene (1.3 mL) was heated to 60 °C under N_2 in a Schlenk tube. The reaction was stirred for 6 h. The product was purified by flashing column chromatography on silica gel (EA/Hex = 1:4) to give a colorless oil (51 mg, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.7 Hz, 2H), 7.32-7.43 (m, 5H), 7.24 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.90-5.94 (m, 1H), 5.83-5.86 (m, 1H), 5.12 (s, 2H), 4.94 (br s, 1H), 4.60 (dd, J = 3.6, 10.2 Hz, 1H), 3.78 (s, 3H), 3.39 (dd, J = 6.0, 15.9 Hz, 1H), 3.07 (dd, J = 7.3, 15.9 Hz, 1H), 2.18-2.30 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 196.7, 162.7, 158.9, 136.2, 134.8, 130.7, 130.6, 129.7, 128.7, 128.3, 127.5, 127.1, 125.3, 114.5, 113.7, 75.5, 72.7, 70.1, 55.3, 44.1, 32.8 ppm; ; **IR** (neat): ν 1674, 1599, 1514 cm^{-1}; **HRMS** (ESI): calcd. for $C_{27}H_{26}O_4Na$ $[M+Na]^+$, 437.1729; found, 437.1732.



1.1

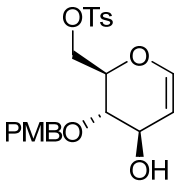
6-(4-(benzyloxy)phenethyl)-2-(4-methoxyphenyl)-3,6-dihydro-2*H*-pyran (3.38): To a stirred solution of **3.31** (27 mg, 0.065 mmol) in dry Et_2O (0.5 mL) was added $LiBH_4$ (2.2 mg, 0.1 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2h, then cooled to 0 °C and added Et_3SiH (0.1 mL, 0.65 mmol) and TFA (0.1 mL, 1.3 mmol). The solution was warmed to rt and stirred for 1h, then quenched with saturated aqueous $NaHCO_3$, extracted with Et_2O, dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (EA/Hex = 1:5) to give a colorless oil (21 mg, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.44 (m, 7H), 7.13 (d, J = 8.6 Hz, 2H), 6.88-6.92 (m, 4H), 5.88-5.93 (m, 1H), 5.69-5.73 (m, 1H), 5.02 (s, 2H), 4.56 (dd, J = 3.7, 10.2 Hz, 1H), 4.32 (br s, 1H), 3.81 (s, 3H), 2.73-2.78 (m, 2H), 2.22-2.30 (m, 2H), 1.85-1.92 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.9, 157.0, 137.3, 135.3, 134.8, 130.3, 129.5, 128.7, 128.6, 127.9, 127.5, 127.3, 127.0, 125.0, 114.7, 113.7, 75.2, 74.6, 70.1, 55.3, 37.4, 33.2, 30.3 ppm; **IR** (neat): ν 1612, 1510, 1246 cm^{-1}; **HRMS** (ESI): calcd. for $C_{27}H_{28}O_3Na$ $[M+Na]^+$, 423.1936; found, 423.1933.



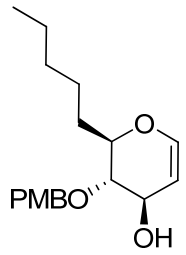
(±)-centrolobine: To a solution of **3.38** (10 mg, 0.026 mmol) in EtOH/EtOAc/20% HCl (5/1/1, 0.5 mL) was added Pd/C (1 mg). The reaction mixture was stirred under H_2 atmosphere at rt for 1 h, then filtered, concentrated and purified by column chromatography (EA/Hex = 1:5) to give a white solid (6.2 mg, 76%). **^{1}H NMR** (400

MHz, $CDCl_3$): δ 7.31 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.88 (dd, J =2.0, 6.8 Hz, 2H), 6.73 (dd, J = 1.9, 6.5 Hz, 2H), 4.29 (dd, J = 1.9, 11.1 Hz, 1H), 3.80 (s, 3H), 3.41-3.45 (m, 1H), 2.64-2.72 (m, 2H), 1.80-1.94 (m, 3H), 1.64-1.75 (m, 1H), 1.47-1.63 (m, 2H), 1.37-1.26 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.7, 153.4, 135.9, 134.7, 129.6, 127.1, 115.1, 113.6, 79.1, 77.2, 55.3, 38.3, 33.3, 31.3, 30.8, 24.1 ppm; **IR** (neat): ν 3451, 1612, 1520 cm^{-1}; **HRMS** (ESI): calcd. for $C_{20}H_{24}O_3Na$ $[M+Na]^+$, 335.1623; found, 335.1627.

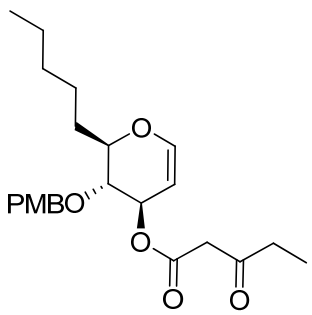
3.7.4 Total synthesis (+)-decytospolide A and B



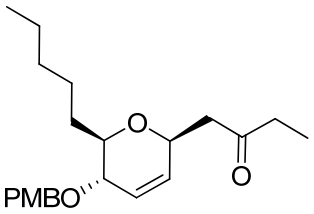
4-*O*-(*p*-Methoxybenzyl)-6-*O*-tosyl-D-glucal (3.46): To a solution of **3.45** (266 mg, 1.0 mmol) in DCM (5 mL) was added triethylamine (0.17 mL, 1.2 mmol) and TsCl (269.7 mg, 1.1 mmol) at 0 ^oC. The reaction mixture was stirred under N_2 atmosphere at rt for overnight. The reaction mixture was washed with H_2O, dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (EA/Hex = 1:3) to give a colorless oil (365 mg, 87%) which was used in the next step immediately. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.22 (d, J = 6.0 Hz, 1H), 4.73 (d, J = 11.1 Hz, 1H), 4.68 (dd, J = 2.4, 6.0 Hz, 1H), 4.62 (d, J = 11.1 Hz, 1H), 4.26-4.37 (m, 2H), 3.91-3.96 (m, 1H), 3.81 (s, 3H), 3.55 (dd, J = 6.9, 9.5 Hz, 1H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.5, 144.9, 143.9, 132.8, 129.9, 129.8, 129.6, 128.1, 114.0, 103.2, 75.7, 74.7, 73.6, 69.5, 68.0, 55.3, 21.7 ppm.



(2*R*,3*S*,4*R*)-3-(4-methoxybenzyloxy)-2-pentyl-3,4-dihydro-2*H*-pyran-4-ol (3.47): To a flame dried RBF was added **3.46** (84 mg, 0.2 mmol) and CuI (76 mg, 0.4 mmol). Anhydrous THF (0.5 mL) was added and the solution was cooled down to -30 ^{o}C. Then BuMgBr (2 M in THF, 0.5 mL) was added drop wise. The reaction mixture was stirred for 1h then warmed to rt and stirred overnight. Then quenched with saturated aqueous NH_4Cl , extracted with extracted with Et_2O, dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (EA/Hex = 1:4) to give a white solid (79.7mg, 65%). $[\alpha]_D^{20}$ = +13.4 (*c* 0.61, $CHCl_3$); **Mp** 65 - 66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.33 (d, *J* = 5.8 Hz, 1H), 4.72 (d, *J* = 4.6 Hz, 1H), 4.67 (dd, *J* = 2.5, 6.1 Hz, 1H), 4.30-4.33 (m, 1H), 3.80 (s, 3H), 3.76 (dt, *J* = 2.9, 9.1 Hz, 1H), 3.31 (dd, *J* = 6.8, 9.4 Hz, 1H), 1.82-1.90 (m, 1H), 1.73-1.76 (m, 1H), 1.54-1.63 (m, 1H), 1.47-1.51 (m, 1H), 1.25-1.39 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): 159.4, 144.7, 130.4, 129.7, 114.0, 102.8, 80.4, 77.6, 73.8, 70.1, 55.3, 31.8, 30.9, 24.7, 22.6, 14.1 ppm; **IR** (neat): *v* 3410, 3030, 1613, 1513 cm^{-1}; **HRMS** (ESI): calcd. for $C_{18}H_{26}O_4Na$ $[M+Na]^+$, 329.1729; found, 329.1726.

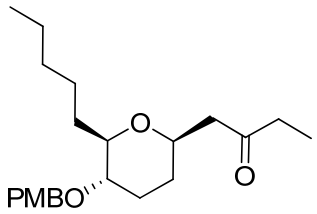


(2*R*,3*R*,4*R*)-3-(4-methoxybenzyloxy)-2-pentyl-3,4-dihydro-2*H*-pyran-4-yl 3-oxopentanoate (3.48): To a solution of **3.47** (50.0 mg, 0.16 mmol), 3-oxopentanoic acidc (28.5 mg, 0.24 mmol) and DMAP (5 mg) in DCM (0.8 mL) was added dropwise DIC (37.6 μL, 0.24 mmol) at 0 °C. the reaction mixture was stirred for 4 hours at this temperature then diluted with DCM (3 mL), washed with water, dried and concentrated. The residue was purified by column chromatography (EA/Hex = 1:4) on silica gel (deactivated by water in advance) to give a white solid (55.6 mg, 86%). $[\alpha]_D^{20}$ = -17.7 (*c* 1.0, $CHCl_3$); **Mp** 48 - 50 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.42 (d, *J* = 6.0 Hz, 1H), 5.40-5.43 (m, 1H), 4.75 (dd, *J* = 3.1, 6.0 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 3.90-3.96 (m, 1H), 3.80 (s, 3H), 3.57 (dd, *J* = 5.7, 7.8 Hz, 1H), 3.42 (s, 2H), 2.54 (q, *J* = 7.2 Hz, 2H), 1.70-1.78 (m, 1H), 1.60-1.66 (m, 2H), 1.41-1.47 (m, 1H), 1.23-1.37 (m, 4H), 1.07 (t, *J* = 7.3 Hz, 1H), 0.88 (t, *J* = 6.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): 202.9, 166.9, 159.4, 146.3, 130.0, 129.6, 113.8, 98.2, 77.5, 75.9, 72.9, 71.7, 55.3, 49.1, 36.4, 31.7, 30.4, 24.9, 22.6, 14.0, 7.5 ppm; **IR** (neat): *v* 1741, 1716, 1647, 1519 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{32}O_6Na$ $[M+Na]^+$, 427.2097; found, 427.2099.



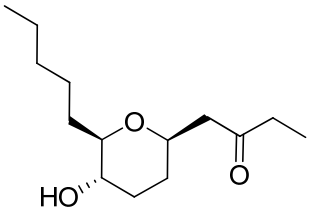
1-((2*S*,5*S*,6*R*)-5-(4-methoxybenzyloxy)-6-pentyl-5,6-dihydro-2*H*-pyran-2-yl)butan-2-one (3.49): A mixture of 23 (50 mg, 0.12 mmol), palladium acetate (2.8 mg, 0.012 mmol) and [1,1′-Bis(di-*tert*-butylphosphino)ferrocene (11.7 mg, 0.024 mmol) in anhydrous toluene (1.2 mL) was heated to 60 °C under N_2 in a Schlenk tube. The reaction was stirred for 6 h. The product was purified by flashing column

chromatography on silica gel (EA/Hex = 1:4) to give a colorless oil (37.6 mg, 87%). $[\alpha]_D^{20}$ = -18.2 (*c* 0.38, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.88 (d, *J* = 10.3 Hz, 1H), 5.73 (d, *J* = 10.3 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.48-4.55 (m, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.69-3.72 (m, 1H), 3.34 (dt, *J* = 2.5, 8.4 Hz, 1H), 2.63 (dd, *J* = 8.0, 15.2 Hz, 1H), 2.42-2.51 (m, 3H), 1.74-1.81 (m, 1H), 1.21-1.44 (m, 7H), 1.04 (t, *J* = 7.3 Hz, 1H), 0.87 (t, *J* = 6.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): 209.4, 159.3, 130.9, 130.3, 129.6, 127.1, 113.8, 74.3, 70.8, 55.3, 47.9, 37.0, 32.4, 31.8, 25.0, 22.6, 14.0, 7.5 ppm; **IR** (neat): *v* 1712, 1647, 1612, 1524 cm^{-1}; **HRMS** (ESI): calcd. for $C_{22}H_{32}O_4Na$ $[M+Na]^+$, 383.2198; found, 383.2199.

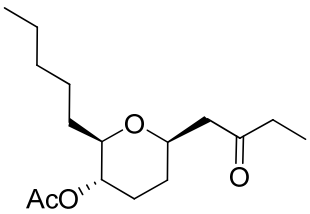


1-((2*R*,5*S*,6*R*)-5-(4-methoxybenzyloxy)-6-pentyltetrahydro-2*H*-pyran-2-yl)butan-2-one (3.50): To a solution of **3.49** (16 mg, 0.044 mmol) in toluene (1 mL) was added Wilknsin's catalyst (4.0 mg, 0.0044 mmol). The reaction mixture was stirred at 50 ^oC for 10 h under H_2 atmosphere. Then the mixture was concentrated and purified by flashing column chromatography on silica gel (EA/Hex = 1:4) to give a colorless oil (15 mg, 95%). $[\alpha]_D^{20}$ = +42.3 (*c* 0.97, $CHCl_3$) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.71-3.74 (m, 1H), 3.12-3.17 (m, 1H), 2.98-3.05 (m, 1H), 2.63 (dd, *J* = 8.0, 15.0 Hz, 1H), 2.43-2.51 (m, 2H), 2.37 (dd, *J* = 4.8, 15.0 Hz, 1H), 2.18-2.23 (m, 1H), 1.81-1.87 (m, 1H), 1.74-1.78 (m, 1H), 1.22-1.46 (m, 9H), 1.03 (t, *J* = 7.3 Hz, 1H), 0.87 (t, *J* = 6.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): 210.1, 159.2,

130.6, 129.4, 113.8, 80.9, 74.1, 70.6, 55.3, 48.5, 37.0, 32.1, 31.9, 31.1, 29.3, 25.0, 22.7, 14.1, 7.5 ppm; **IR** (neat): *v* 1714, 1637, 1610, 1534 cm^{-1}; **HRMS** (ESI): calcd. for $C_{22}H_{34}O_4Na$ $[M+Na]^+$, 385.2355; found, 385.2357.



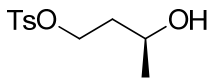
(+)-Decytospolide A: To a solution of **3.50** (14 mg, 0.039 mmol) in DCM/H2O (5/1, 0.6 mL) was added DDQ (17.5 mg, 0.077 mmol), the reaction mixture was stirred for 2h at rt, then cextracted with DCM, dried and concentrated. The residue was purified by column chromatography (EA/Hex = 1:2) on silica gel to give colorless syrup (8.3 mg, 89%). $[\alpha]_D^{20}$ = +18.6 (*c* 0.60, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.70-3.77 (m, 1H), 3.22-3.29 (m, 1H), 2.99-3.04 (m, 1H), 2.65 (dd, *J* = 8.0, 15.0 Hz, 1H), 2.41-2.55 (m, 2H), 2.38 (dd, *J* = 4.8, 15.0 Hz, 1H), 2.05-2.11 (m, 1H), 1.73-1.82 (m, 2H), 1.27-1.48 (m, 9H), 1.03 (t, *J* = 7.3 Hz, 1H), 0.87 (t, *J* = 6.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): 210.1, 82.1, 74.1, 70.5, 48.4, 37.1, 32.9, 31.9, 31.8, 31.3, 25.0, 22.6, 14.0, 7.5 ppm; **IR** (neat): *v* 3440, 1715, 1669, 1451, 1344 cm^{-1}; **HRMS** (ESI): calcd. for $C_{14}H_{26}O_3Na$ $[M+Na]^+$, 265.1780; found, 265.1783.



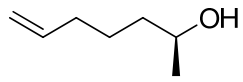
(+)-Decytospolide B: To a solution of decytospolide A (7.0 mg, 0.029 mmol) in Pyr (0.3 mL) was added Ac_2O (5.5 μL, 0.058 mmol) at 0 °C, the reaction mixture was stirred overnight, then diluted with DCM (2mL), washed with H_2O and 1M HCl, dried and concentrated. The residue was purified by column chromatography (EA/Hex = 1:4)

on silica gel to give colorless oil (7.5 mg, 91%). $[\alpha]_D^{20}$ = +27.6 (*c* 0.59, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.41-4.48 (m, 1H), 3.74-3.81 (m, 1H), 3.20-3.26 (m, 1H), 2.67 (dd, *J* = 8.0, 15.2 Hz, 1H), 2.42-2.54 (m, 2H), 2.38 (dd, *J* = 4.9, 15.2 Hz, 1H), 2.11-2.16 (m, 1H), 2.03 (s, 3H), 1.73-1.77 (m, 1H), 1.21-1.55 (m, 10H), 1.04 (t, *J* = 7.3 Hz, 1H), 0.87 (t, *J* = 6.9 Hz, 1H); **^{13}C NMR** 100 MHz, $CDCl_3$): 209.9, 170.3, 79.3, 74.2, 72.0, 48.2, 37.2, 31.9, 31.7, 30.8, 29.3, 24.8, 22.6, 21.2, 14.0, 7.5 ppm; **IR** (neat): *v* 1661, 1638, 1451, 1344 cm^{-1}; **HRMS** (ESI): calcd. for $C_{16}H_{28}O_4Na$ $[M+Na]^+$, 307.1885; found, 307.1889.

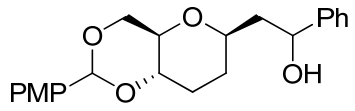
3.7.5 Total synthesis of aspergerllide A



(*S*)-3-Hydroxybutyl 4-methylbenzenesulfonate (3.62): To a solution of (s)-1,3-butandiol (430 mg, 4.8 mmol), triethyl amine (0.67 mL, 4.8 mmol) and Bu_2SnO (119.5 mg, 0.48 mmol) in CH_2Cl_2 (10 mL) was added p-TsCl (910.8 mg, 4.8 mmol) in portion wise. The reaction mixture was stirred overnight at room temperature. The reaction mixture was washed with H_2O, saturated aqueous NaCl. The organic phase was dried over Na_2SO_4, filtered, evaporated and purified by column chromatography (EA/Hex = 1:2) to give a colorless oil (949 mg, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.16-4.22 (m, 1H), 4.05-4.11 (m, 1H), 3.88-3.91 (m, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.06-4.04 (m, 1H), 3.73-3.70 (m, 1H), 3.66-3.60 (m, 2H), 2.41 (s, 3H), 2.10 (br s, 1H), 1.73-1.79 (m, 1H), 1.65-1.71 (m, 1H), 1.14 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 144.8, 132.8, 129.8, 127.7, 67.8, 63.9, 37.7, 23.4, 21.8.

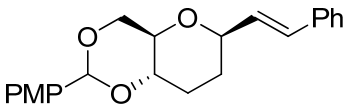


(*S*)-Hept-6-en-2-ol (3.59): Allylmangesium bromide (1M in THF, 2.5 mL, 2,5 mmol) was added to a solution of above monotosylate (122 mg, 0.5 mmol) in THF at 0 °C. After 20 minutes of stirring, the reaction mixture was warmed to reflux for 3 h and then partitioned between 10% HCl and Et_2O. The organic phase was washed with aq. $NaHCO_3$, NH_4Cl and dried over Na_2SO_4, filtered, concentrated at low temperature and purified by column chromatography (EA/Hex = 1:2) to give a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.76-5.87 (m, 1H), 4.94-5.03 (m, 2H), 3.78-3.84 (m, 1H), 2.05-2.10 (m, 2H), 1.39-1.62 (m, 4H), 1.19 (d, J = 6.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.7, 114.6, 68.1, 38.7, 33.7, 25.0, 23.5.

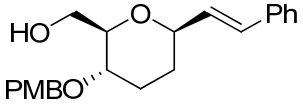


3.63b: A suspension of compound **3.30k** (0.80 g) and Raney Ni (~100 mg) in EtOH/EA (20 ml/10ml) was stirred for 4 h under H_2 pressure. The suspension was filtered through a pad of Celite. The filtrate was concentrated and flashed by column chromatography (EA/Hex = 1:5 to 1:3) to give a white solid (0.77 g, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (d, J = 7.2 Hz, 2H), 7.37-7.35 (m, 4H), 7.28-7.26 (m, 1H), 6.90 (d, J = 7.2 Hz, 2H), 5.53 (d, J = 2.9 Hz, 1H), 4.99-4.93 (m, 1H), 4.28 (dd, J = 10.4, 4.8 Hz, 1H), 3.80 (s, 3H), 3.77-3.69 (m, 2H), 3.57-3.50 (m, 1.5H), 3.48-3.38 (m, 1H), 3.01 (d, J = 4.8 Hz, 0.5H), 2.01-2.08 (m, 1H), 2.05-1.90 (m, 1H), 1.81-1.55 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.1, 144.5, 144.1, 130.1, 130.0, 128.4, 127.4, 127.2, 125.7, 125.5, 113.6, 101.7, 78.4, 78.2, 77.9, 75.3, 73.7, 73.5, 71.0, 69.3, 69.2, 55.3, 44.9, 43.9, 31.2, 30.9, 28.7, 28.5; **IR** (neat): ν 3485, 2941, 2870, 1614, 1518,

1250, 1096, 829, 758, 702 cm^{-1}; **HRMS** (ESI): calcd. for $C_{22}H_{27}O_5$ $[M+H]^+$, 371.1858; found, 371.1865.

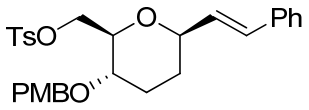


3.64a: DTBMP (0.60 g, 2.88 mmol) was added to a solution of compound **3.63b** (0.30 g, 0.8 mmol) in 15 ml of dry CH_2Cl_2 at 0 °C under N_2. Tf_2O (0.16 mL, 0.96 mmol) was then added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for another 2 h. The resulting mixture was diluted with CH_2Cl_2 and washed with NH_4Cl solution and brine. The organic phase was dried over Na_2SO_4, filtered, evaporated and purified by column chromatography (EA/Hex = 1:30 to 1:10) to give a white solid (0.24 g, 83%). **Mp** 154-155 °C; $[\alpha]_D^{20}$ = +36.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.34-7.30 (m, 2H), 7.26-7.25 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.20 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.55 (s, 1H), 4.32 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.18-4.15 (m, 1H), 3.81 (s, 3H), 3.76 (t, *J* = 10.4 Hz, 1H), 3.61-3.51 (m, 2H), 2.20-2.16 (m, 1H), 1.99-1.95 (m, 1H), 1.82-1.59 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.1, 136.5, 131.1, 130.2, 128.9, 128.5, 127.7, 127.4, 126.5, 113.7, 101.7, 78.2, 78.1, 73.5, 69.4, 55.3, 31.4, 28.8; **IR** (neat): ν 2936, 2835, 1682, 1599, 1252, 968, 816, 745, 692 cm^{-1}; **HRMS** (ESI): calcd. for $C_{22}H_{25}O_4$ $[M+H]^+$, 353.1753; found, 353.1758.



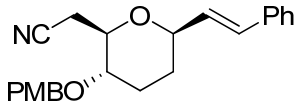
3.65: DIBAL-H (3.0 mL, 1.0 M in toluene) was added dropwise to a solution of compound **3.64a** (0.28 g, 0.79 mmol) in 2 mL of CH_2Cl_2 at -15 °C under N_2. After 30 mins, the mixture was allowed to warm to room temperature and stirred for another 2

h. Potassium sodium tartrate solution was then added to quench the reaction. The mixture was stirred for 30 min. The resulting solution was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (EA/Hex = 1:20 to 1:4) to give a colorless oil (0.23 g, 82%). $[\alpha]_D^{20}$ = +87.0 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.33-7.24 (m, 5H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.19 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.60 (d, *J* = 11.2 Hz, 1H), 4.43 (d, *J* = 11.2 Hz, 2H), 4.06-4.05 (m, 1H), 3.93-3.89 (m, 1H), 3.81 (s, 3H), 3.78-3.74 (m, 1H), 3.43-3.38 (m, 2H), 2.34-2.31 (m, 1H), 2.20 (t, *J* = 6.4 Hz, 1 H), 1.90-1.87 (m, 1H), 1.58-1.54 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.3, 136.6, 130.6, 130.2, 129.4, 129.3, 128.5, 127.6, 126.4, 113.8, 80.4, 77.7, 73.4, 70.5, 63.2, 55.2, 31.1, 29.0; **IR** (neat): ν 3460, 2936, 2866, 1612, 1514, 1248, 1093, 820, 750 cm^{-1}; **HRMS** (ESI): calcd. for $C_{22}H_{26}O_4Na$ $[M+Na]^+$, 377.1729; found, 377.1730.



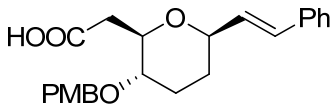
3.66: Et_3N (0.47 mL, 3.39 mmol) and DMAP (6.9 mg, 0.06 mmol) were added to a solution of compound **3.65** (0.40 g, 1.13 mmol) in dry CH_2Cl_2 (20 mL) under N_2 at 0 °C. Then TsCl (0.43 g, 2.26 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight. The resulting mixture was diluted with C CH_2Cl_2 and washed with aq. $NaHCO_3$, NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (EA/Hex = 1:8 to 1:5) to give a white solid (0.56 g, 91%). **Mp** 126-127 °C; $[\alpha]_D^{20}$ = +69.7 (*c* = 2.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.36-7.24 (m, 7H),

7.21 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.51 (d, *J* = 16.1 Hz, 1H), 6.09 (dd, *J* = 16.1, 5.8 Hz, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.35 (d, *J* = 10.9 Hz, 1H), 4.31-4.27 (m, 2H), 3.95-3.93 (m, 1H), 3.82 (s, 3H), 3.50-3.48 (m, 1H), 3.39-3.33 (m, 1H), 2.37 (s, 3H), 2.33-2.31 (m, 1H), 1.87-1.79 (m, 1H), 1.60-1.43 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.3, 144.5, 136.7, 133.1, 130.3, 130.0, 129.6, 129.4, 129.2, 128.5, 128.0, 127.6, 126.4, 113.8, 78.1, 77.7, 71.9, 70.5, 69.8, 55.3, 30.8, 29.0, 21.5; **IR** (neat): ν 2938, 2864, 1514, 1362, 1177, 1096, 966, 816, 750 cm^{-1}; **HRMS** (ESI): calcd. for $C_{29}H_{33}O_6S$ $[M+H]^+$, 509.1998; found, 509.2000.

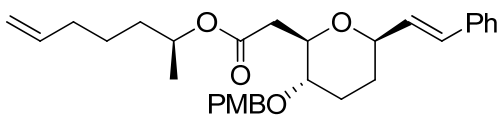


3.67: KCN (0.13 g, 2.0 mmol) was added to a solution of compound **3.66** (0.51 g, 1.0 mmol) in DMSO (20 mL). The mixture was heated to 50 °C and stirred for 6 h under N_2. The mixture was cooled to room temperature and quenched by water. The resulting solution was extracted with Et_2O (3×30 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (EA/Hex = 1:8 to 1:6) to give a white solid (0.29 g, 79%). **Mp** 106-107 °C; $[\alpha]_D^{20}$ = +87.7 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.28-7.23 (m, 3H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.60 (d, *J* = 16.0 Hz, 1H), 6.17 (dd, *J* = 16.0, 5.8 Hz, 1H), 4.61 (d, *J* = 11.0 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 4.08-4.05 (m, 1H), 3.81 (s, 3H), 3.55-3.52 (m, 1H), 3.33-3.30 (m, 1H), 2.78 (dd, *J* = 16.8, 3.5 Hz, 1H), 2.69 (dd, *J* = 16.8, 5.8 Hz, 1H), 2.38-2.35 (m, 1H), 1.02-1.89 (m, 1H), 1.60-1.51 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.4, 136.6, 130.7, 129.8, 129.5, 128.7, 128.5, 127.7, 126.5, 117.6, 114.0, 78.1, 75.8, 75.3, 70.5, 55.3, 30.8, 28.6, 21.5;

IR (neat): ν 2938, 2866, 1611, 1514, 1248, 1092, 822, 750 cm^{-1}; **HRMS** (ESI): calcd. for $C_{23}H_{26}NO_3$ $[M+H]^+$, 364.1913; found, 364.1922.

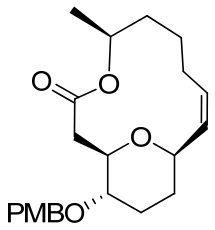


3.60: To a solution of compound **3.67** (26 mg, 0.07 mmol) in EtOH (0.5 mL) was added KOH (118 mg, in 0.8 mL H_2O). The resulting mixture was refluxed overnight then cooled to 0 °C. 10% HCl was slowed added to adjust pH to 4. The mixture was extracted with EtOAc and dried over Na_2SO_4, filtered, concentrated and purified by column chromatography (EA/Hex = 1:1) to give a colorless oil (23 mg, 87%). $[\alpha]_D^{20}$ = +55.5 (*c* = 0.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.6 Hz, 2H), 7.18-7.30 (m, 5H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 16.0 Hz, 1H), 6.14 (dd, *J* = 16.0, 5.7 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.38 (d, *J* = 11.1 Hz, 1H), 4.05-4.11 (m, 1H), 3.79 (s, 3H), 3.75-3.81 (m, 1H), 3.15-3.21 (m, 1H), 2.91 (dd, *J* = 15.6, 3.7 Hz, 1H), 2.51 (dd, *J* = 15.6, 8.0 Hz, 1H), 2.29-2.32 (m, 1H), 1.83-1.89 (m, 1H), 1.50-1.59 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 176.2, 159.3, 136.7, 130.6, 130.0, 129.5, 129.2, 128.5, 127.6, 126.5, 113.9, 77.9, 75.9, 70.4, 55.3, 38.0, 31.0. 28.9; **HRMS** (ESI): calcd. for $C_{23}H_{26}O_5Na$ $[M+Na]^+$, 405.1678; found, 405.1673.



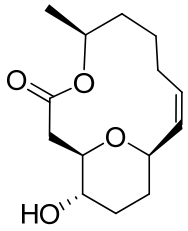
3.68: A solution of compound **3.60** (10 mg, 0.026 mmol) in dry THF (0.2 mL) was cooled to 0 °C under N_2, Then triethylamine (9 μL, 0.065 mmol) and 2,4,6-trichlorobenzoyl chloride (8 μL, 0.052 mmol) were added dropwise sequentially. The reaction mixture was stirred at rt for 2 h, then a solution of (s)-hept-6-en-2-ol (3.6 mg, 0.031 mmol) and DMAP (7.9 mg, 0.065 mmol) in THF (0.5 mL) was added. The

resulting reaction mixture was fiurther stirred at rt for 16 h. The mixture was concentrated and purified by column chromatography (EA/Hex = 1:5) to give a colorless oil (11.7 mg, 94%). $[\alpha]_D^{20}$ = +18.9 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18-7.35 (m, 7H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.14 (dd, *J* = 16.0, 5.6 Hz, 1H), 5.69-5.75 (m, 1H), 4.86-4.99 (m, 3H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.39 (d, *J* = 11.1 Hz, 1H), 4.01-4.05 (m, 1H), 3.80 (s, 3H), 3.76-3.83 (m, 1H), 3.17-3.23 (m, 1H), 2.88 (dd, *J* = 14.9, 3.8 Hz, 1H), 2.41 (dd, *J* = 14.9, 8.6 Hz, 1H), 2.29-2.32 (m, 1H), 1.95-2.01 (m, 2H), 1.86-1.89 (m,1H), 1.31-1.61 (m, 6H), 1.18 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.3, 159.3, 138.6, 136.9, 130.3, 129.6, 129.4, 128.5, 127.5, 126.4, 114.6, 113.8, 77.8, 77.6, 76.1, 70.8, 70.3, 55.3, 38.7, 35.4, 33.5, 31.2, 29.1, 24.6, 20.0; **HRMS** (ESI): calcd. for $C_{30}H_{38}O_5Na$ $[M+Na]^+$, 501.2617; found, 501.2616.



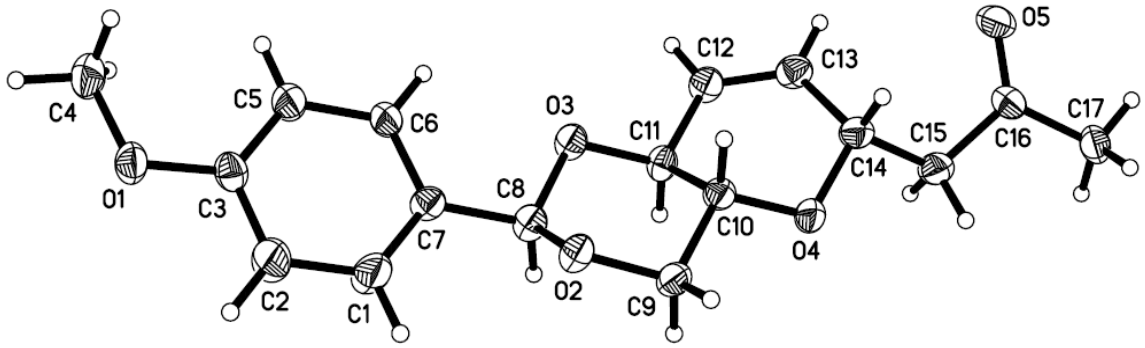
3.69: To a solution of diene **3.68** (5.2 mg, 0.011 mmol) and 1,4-benzoquinone (1 mg, 0.1 mmol) in degassed toluene (3 mL) at 100 °C was added a solution of **Ru-II** (3.1 mg, 0.003 mmol) in toluene (1 mL) over a period of 3 h by syringe pump. The resulting solution was stirred at 100 °C for a further 12 h under argon and overnigh at rt under air. The mixture was concentrated and purified by prepare TLC to give a colorless oil (2.9 mg, 71%). $[\alpha]_D^{20}$ = +47.3 (*c* = 0.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.58-5.65 (m, 1H), 5.17 (dd, *J* = 11.1, 2.4 Hz, 1H) 5.00-5.04 (m, 1H), 5.57 (d, *J* = 11.4 Hz, 1H), 4.36 (d, *J* = 11.4 Hz, 1H), 4.04-4.08 (m, 1H), 3.80 (s, 3H), 3.66-3.72 (m, 1H), 3.09-3.16 (m, 1H),

2.86 (dd, *J* = 11.8, 2.4 Hz, 1H), 2.17-2.29 (m, 3H), 1.78-1,82 (m, 1H), 1.39-1.65 (m,7H), 1.24 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.4, 159.2, 135.5, 130.4, 129.3, 128.2, 113.8, 80.0, 76.1, 75.0, 70.2, 69.6, 55.3, 39.2, 34.5, 31.8, 29.7, 29.5, 28.0, 25.9, 20.9; **HRMS** (ESI): calcd. for $C_{22}H_{30}O_5Na$ $[M+Na]^+$, 397.1991; found, 397.2005.



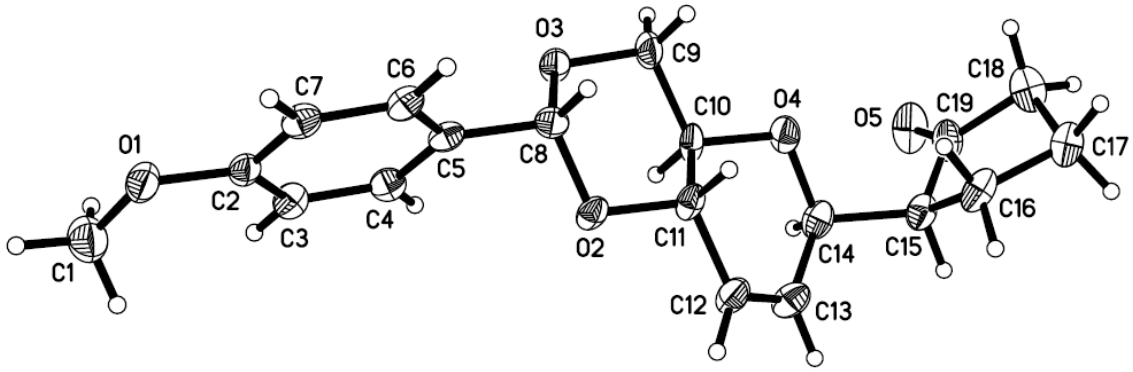
3.70: A solution of diene **3.69** (4 mg, 0.011 mmol) in aqueous dichloromethane (DCM:H_2O 0.5mL :0.1 mL) was was treated with DDQ (27.5 mg, 0.055 mmol) at rt. The resulting solution was stirred for 12 hr. The mixture was concentrated and purified by prepare TLC to give a colorless oil (2.8 mg, 90%). $[\alpha]_D^{20}$ = +41.1 (*c* = 0.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.63-5.66 (m, 1H), 5.19 (dd, *J* = 11.1, 2.8 Hz, 1H), 5.00-5.05 (m, 1H), 4.06 (dd, 1H, *J* = 11.4, 2.2 Hz), 3.56 (dt, 1H, *J* = 10.3, 2.5 Hz), 3.35-3.39 (1H, m), 2.85 (dd, *J* = 11.8, 2.5 Hz, 1H), 2.35 (t, *J* = 11.6 Hz, 1H), 2.20 (*q*, *J* = 10 Hz, 1H), 2.12-2.16 (m, 1H), 1.77-1.82 (m, 1H), 1.40-1.64 (m, 7H), 1.27 (d, J=6.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 173.5, 135.7, 128.1, 81.6, 74.9, 70.2, 69.8, 39.1, 34.5, 33.7, 32.0, 28.1, 25.9, 20.9; **HRMS** (ESI): calcd. for $C_{14}H_{22}O_4Na$ $[M+Na]^+$, 277.1416; found, 277.1414.

3.7.6 : X-ray structure and data



Crystal data and structure refinement for 3.30a.

Empirical formula	C17 H20 O5	
Formula weight	304.33	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 4.5114(5) Å	α= 90°.
	b = 17.2328(15) Å	β= 90°.
	c = 19.301(2) Å	γ = 90°.
Volume	1500.5(3) $Å^3$	
Z	4	
Density (calculated)	1.347 Mg/m^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	648	
Crystal size	0.40 x 0.10 x 0.06 mm^3	
Theta range for data collection	2.11 to 32.90°.	
Index ranges	-6<=h<=3, -26<=k<=26, -24<=l<=29	
Reflections collected	8496	
Independent reflections	3184 [R(int) = 0.0512]	
Completeness to theta = 25.00°	99.9 %	
Absorption correction	Semi-emp**IR**ical from equivalents	
Max. and min. transmission	0.9941 and 0.9616	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3184 / 0 / 201	
Goodness-of-fit on F^2	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0607, wR2 = 0.1544	
R indices (all data)	R1 = 0.1189, wR2 = 0.2119	
Largest diff. peak and hole	0.355 and -0.281 $e.Å^{-3}$	



Crystal data and structure refinement for 3.30j.

Empirical formula	C19 H22 O5
Formula weight	330.37
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)
Unit cell dimensions	a = 5.4648(3) Å = 90°. b = 34.821(2) Å = 91.115(3)°. c = 17.6086(11) Å = 90°.
Volume	3350.1(3) $Å^3$
Z	8
Density (calculated)	1.310 Mg/m^3
Absorption coefficient	0.094 mm^{-1}
F(000)	1408
Crystal size	0.40 x 0.14 x 0.12 mm^3
Theta range for data collection	1.64 to 28.96°.
Index ranges	-6<=h<=7, -47<=k<=46, -23<=l<=23
Reflections collected	35371
Independent reflections	8924 [R(int) = 0.0681]
Completeness to theta = 28.96°	98.9 %
Absorption correction	Semi-emp**IR**ical from equivalents
Max. and min. transmission	0.9888 and 0.9633
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8924 / 1 / 869
Goodness-of-fit on F^2	1.019
Final R indices [I>2sigma(I)]	R1 = 0.0722, wR2 = 0.1779
R indices (all data)	R1 = 0.1237, wR2 = 0.2111
Largest diff. peak and hole	0.533 and -0.366 $e.Å^{-3}$

3.7.7 Computational section

1. Computational Method

All DFT calculations were performed with the Gaussian09 program package. Geometry optimizations were done by employing density functional theory B3LYP method. A combined basis set was used, in which Pd and P atoms were described by LANL2DZ basis set and effective core potential implemented and 6-31+G(d) was used for other atoms. Frequency analysis was done at the same level of theory to verify that these optimized structures are real minima or saddale point on the potential energy surface, and to get the thermodynamic corrections. Intrinsic reaction coordinate (IRC) calculations were used to confirm that the transition states fond connected the relacted reactants and products. On the optimized structures, single point energy calculations were performed using SDD for Pd and 6-311+G(d, p) for the rest. Solvation effects were computed by the conducter-like polarizable continuum model (CPCM) with radii and nonelectrostatic terms for the SMD salvation model as implemented in Gaussian 09. Toluene was used as the solvent to model the reaction medium. Single point energies in solution including all computed corrections were appended with the correction to Gibbs free energy from B3LYP/6-31+G(d) + LANL2DZ frequencies computed for 1 mol/L solution at 298.15 K. to describe reaction energetics, as reflected by the relative Gibbs free energy in Figure 1.

2. Standard orientations of optimized structures

3,6-cis-A

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.563912	0.733659	-2.187250
2	1	0	-0.450926	1.775010	-2.474216
3	6	0	0.284046	-0.228873	-2.790694
4	1	0	0.960327	0.001925	-3.603430
5	8	0	-0.098171	-1.610875	-2.864014
6	8	0	-3.019057	1.022590	-2.419447
7	8	0	-3.042058	-1.557383	-0.612770
8	6	0	-1.326891	-3.464241	-1.877789
9	1	0	-1.823392	-3.646960	-2.841809
10	1	0	-0.463210	-4.121410	-1.779723
11	8	0	-2.222142	-3.802251	-0.766438
12	6	0	-3.400204	-2.961824	-0.723505
13	1	0	-3.940627	-3.087853	-1.679002
14	6	0	-3.314743	2.321888	-2.139560
15	8	0	-2.725779	2.996928	-1.280752
16	6	0	-4.432501	2.824896	-3.035748
17	1	0	-3.962126	3.373510	-3.865098
18	1	0	-4.974755	1.973619	-3.447923
19	6	0	-5.429698	3.749308	-2.329363
20	8	0	-6.605747	3.385170	-2.182604
21	6	0	-4.932235	5.093553	-1.863897
22	1	0	-4.078774	4.958831	-1.190744
23	1	0	-4.576652	5.683664	-2.719217
24	1	0	-5.736877	5.632686	-1.361209
25	6	0	-1.912074	0.357603	-1.615337
26	1	0	-2.055615	0.702257	-0.590848
27	6	0	-2.208870	-1.131667	-1.740824
28	1	0	-2.753389	-1.299891	-2.681398
29	6	0	-0.942344	-1.995119	-1.746246
30	1	0	-0.384935	-1.836083	-0.812909
31	46	0	1.109140	0.373585	-0.852213
32	15	0	1.121296	1.526025	1.368848
33	15	0	3.184506	-0.707431	-0.080135
34	6	0	2.849796	1.118973	2.102752
35	1	0	3.563666	1.813587	1.644371
36	1	0	2.848911	1.293661	3.184445
37	6	0	3.256034	-0.333987	1.807643
38	1	0	2.566579	-1.034562	2.292840
39	1	0	4.265678	-0.524812	2.188105
40	6	0	-0.036699	0.853851	2.704672
41	6	0	-0.060574	1.378730	4.007536
42	6	0	-0.906375	-0.195952	2.372565
43	6	0	-0.933539	0.851268	4.964791
44	1	0	0.584697	2.211437	4.271903
45	6	0	-1.784191	-0.722527	3.329345
46	1	0	-0.909799	-0.594628	1.363721
47	6	0	-1.795617	-0.200878	4.626917
48	1	0	-0.947646	1.265504	5.968414
49	1	0	-2.459798	-1.524557	3.050662
50	1	0	-2.477263	-0.604040	5.369393
51	6	0	0.979416	3.391947	1.587268
52	6	0	1.852832	4.150547	2.383803
53	6	0	-0.060169	4.042013	0.896967
54	6	0	1.689148	5.537886	2.492248
55	1	0	2.664968	3.672661	2.922021
56	6	0	-0.225757	5.425959	1.015336
57	1	0	-0.737407	3.475051	0.264022

58	6	0	0.648197	6.177215	1.810985
59	1	0	2.372540	6.113898	3.108876
60	1	0	-1.034130	5.914211	0.480396
61	1	0	0.520983	7.251944	1.896388
62	6	0	3.417109	-2.572614	-0.159308
63	6	0	4.096179	-3.313801	0.822513
64	6	0	2.854611	-3.245411	-1.258554
65	6	0	4.221729	-4.703551	0.701460
66	1	0	4.523722	-2.818101	1.688301
67	6	0	2.989938	-4.633121	-1.382457
68	1	0	2.294190	-2.684946	-2.001440
69	6	0	3.673710	-5.364232	-0.403595
70	1	0	4.744710	-5.266276	1.468562
71	1	0	2.556887	-5.141491	-2.238380
72	1	0	3.772476	-6.441104	-0.497277
73	6	0	4.835043	0.006850	-0.662322
74	6	0	6.062793	-0.650933	-0.486908
75	6	0	4.815476	1.267390	-1.282639
76	6	0	7.253111	-0.052057	-0.915388
77	1	0	6.093606	-1.635960	-0.032608
78	6	0	6.007444	1.869501	-1.703747
79	1	0	3.863553	1.765564	-1.445007
80	6	0	7.228227	1.210602	-1.520307
81	1	0	8.196551	-0.572227	-0.780521
82	1	0	5.979423	2.844187	-2.180872
83	1	0	8.152373	1.672941	-1.852748
84	6	0	-4.244743	-3.348665	0.461291
85	6	0	-4.191897	-4.653569	0.973289
86	6	0	-5.123135	-2.413736	1.030975
87	6	0	-5.011378	-5.018931	2.046566
88	1	0	-3.501936	-5.365049	0.536563
89	6	0	-5.940432	-2.783518	2.104441
90	1	0	-5.151215	-1.404076	0.639073
91	6	0	-5.887969	-4.086606	2.613782
92	1	0	-4.962685	-6.029469	2.440210
93	1	0	-6.615557	-2.054482	2.541474
94	1	0	-6.524306	-4.372402	3.445706

3,6-cis-B

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.651150	0.030669	-2.211894
2	1	0	0.296324	0.743448	-2.949029
3	6	0	0.177999	-1.306671	-2.297186
4	1	0	-0.487038	-1.620696	-3.095509
5	8	0	0.963491	-2.425422	-1.837390
6	8	0	1.997121	1.421804	-0.587383
7	8	0	4.051331	-0.661074	-0.765491
8	6	0	3.063718	-3.320886	-1.047996
9	1	0	2.580293	-3.511121	-0.078480
10	1	0	3.025889	-4.223761	-1.657171
11	8	0	4.481454	-3.010984	-0.861609
12	6	0	4.678575	-1.789647	-0.105610
13	1	0	4.181095	-1.919112	0.873194
14	6	0	1.805217	2.707623	-0.995652
15	8	0	1.578081	3.023327	-2.174227
16	6	0	1.882458	3.658746	0.182983
17	1	0	0.867613	3.745275	0.599334
18	1	0	2.518512	3.223756	0.955059
19	6	0	2.403220	5.057409	-0.150217
20	8	0	3.432774	5.474294	0.402945
21	6	0	1.612018	5.898650	-1.118591
22	1	0	1.585876	5.403589	-2.095481
23	1	0	0.570917	5.994555	-0.784121
24	1	0	2.065517	6.887662	-1.203946
25	6	0	2.012079	0.339109	-1.627003

26	1	0	2.700758	0.691566	-2.402863
27	6	0	2.611847	-0.862159	-0.919262
28	1	0	2.147003	-0.978161	0.070609
29	6	0	2.385994	-2.139194	-1.736736
30	1	0	2.809411	-2.000882	-2.741059
31	46	0	-1.005650	-0.323712	-0.802963
32	15	0	-2.639523	-1.812342	0.304216
33	15	0	-2.026785	1.481320	0.593491
34	6	0	-3.611459	0.673520	1.337156
35	1	0	-3.957461	1.258779	2.196148
36	1	0	-4.381765	0.718918	0.558230
37	6	0	-3.359148	-0.780780	1.760500
38	1	0	-4.290191	-1.234938	2.117206
39	1	0	-2.623202	-0.826434	2.571647
40	6	0	-1.122289	2.028190	2.163686
41	6	0	-1.488040	3.160117	2.910997
42	6	0	-0.040821	1.242036	2.596143
43	6	0	-0.787969	3.494151	4.076544
44	1	0	-2.307101	3.790697	2.580260
45	6	0	0.652903	1.571885	3.766938
46	1	0	0.265714	0.387063	2.001326
47	6	0	0.280575	2.698651	4.508596
48	1	0	-1.074321	4.374877	4.643125
49	1	0	1.487583	0.957814	4.089851
50	1	0	0.823755	2.960926	5.410882
51	6	0	-2.699350	3.086469	-0.132604
52	6	0	-3.871658	3.712837	0.324978
53	6	0	-1.990640	3.664882	-1.200762
54	6	0	-4.320377	4.900657	-0.266348
55	1	0	-4.445459	3.280142	1.138031
56	6	0	-2.436520	4.855970	-1.786449
57	1	0	-1.099943	3.177438	-1.585638
58	6	0	-3.601599	5.476316	-1.319911
59	1	0	-5.228925	5.372327	0.095169
60	1	0	-1.880223	5.288042	-2.612165
61	1	0	-3.950661	6.396051	-1.778496
62	6	0	-4.208211	-2.270528	-0.646261
63	6	0	-5.083796	-3.291393	-0.244009
64	6	0	-4.504541	-1.529596	-1.802707
65	6	0	-6.243642	-3.558455	-0.980598
66	1	0	-4.857327	-3.891021	0.631540
67	6	0	-5.669137	-1.791868	-2.534578
68	1	0	-3.812442	-0.759339	-2.132257
69	6	0	-6.540768	-2.806547	-2.123958
70	1	0	-6.911037	-4.354278	-0.664304
71	1	0	-5.887520	-1.212094	-3.425983
72	1	0	-7.440297	-3.015970	-2.694281
73	6	0	-2.094345	-3.405489	1.140274
74	6	0	-2.694163	-3.916457	2.304424
75	6	0	-1.011274	-4.094703	0.566001
76	6	0	-2.227756	-5.105494	2.878710
77	1	0	-3.520623	-3.392187	2.774131
78	6	0	-0.553372	-5.287544	1.138606
79	1	0	-0.515705	-3.687259	-0.311037
80	6	0	-1.159924	-5.795358	2.293424
81	1	0	-2.697066	-5.489688	3.779196
82	1	0	0.280572	-5.814719	0.685655
83	1	0	-0.799982	-6.717892	2.738089
84	6	0	6.152508	-1.523978	0.040694
85	6	0	6.616523	-0.209904	0.202411
86	6	0	7.062982	-2.590678	0.064416
87	6	0	7.981464	0.032976	0.386767
88	1	0	5.909175	0.609918	0.167132
89	6	0	8.427137	-2.343131	0.249188
90	1	0	6.698855	-3.601039	-0.076951
91	6	0	8.889669	-1.032069	0.412524
92	1	0	8.334288	1.052576	0.505979
93	1	0	9.127328	-3.172701	0.261337

94	1	0	9.948866	-0.841575	0.555799

3,6-trans-A

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.380101	-0.243019	-2.484752
2	1	0	0.113405	0.353041	-3.247841
3	6	0	0.180708	-1.521788	-2.213792
4	1	0	0.977486	-1.945332	-2.814202
5	8	0	-0.595360	-2.593291	-1.672079
6	8	0	-2.232743	1.244224	-1.578448
7	8	0	-3.901062	-0.934513	-1.329474
8	8	0	-3.904590	-2.971169	-0.071819
9	6	0	-2.219058	1.367517	-0.217547
10	8	0	-1.861642	0.497475	0.583562
11	6	0	-2.691840	2.754066	0.170289
12	1	0	-2.859834	2.752815	1.252153
13	1	0	-1.900388	3.477222	-0.049155
14	6	0	-3.956879	3.218759	-0.554789
15	8	0	-3.990299	4.334846	-1.096085
16	6	0	-5.151260	2.297797	-0.530773
17	1	0	-4.918499	1.351987	-1.033548
18	1	0	-5.425321	2.044836	0.501522
19	1	0	-5.996858	2.781257	-1.023513
20	6	0	-2.606485	-1.260183	-1.918395
21	1	0	-2.773049	-1.845835	-2.839949
22	46	0	1.069250	-0.177528	-0.797911
23	15	0	1.841270	1.874911	0.470871
24	15	0	2.841216	-1.350487	0.451132
25	6	0	-1.865316	0.016827	-2.350334
26	1	0	-2.266048	0.324333	-3.320286
27	6	0	0.840698	3.090337	1.519963
28	6	0	0.763105	4.461608	1.225828
29	6	0	0.093210	2.583104	2.598801
30	6	0	-0.028109	5.312852	2.008623
31	1	0	1.317552	4.871014	0.388810
32	6	0	-0.685631	3.436915	3.387113
33	1	0	0.092450	1.518740	2.811130
34	6	0	-0.746522	4.805641	3.096461
35	1	0	-0.079826	6.369651	1.766070
36	1	0	-1.250202	3.030588	4.220689
37	1	0	-1.355018	5.466887	3.705102
38	6	0	3.042418	2.982000	-0.477976
39	6	0	3.897519	3.901850	0.153737
40	6	0	3.094448	2.852193	-1.875047
41	6	0	4.790245	4.673369	-0.598286
42	1	0	3.861413	4.028891	1.231398
43	6	0	3.988000	3.624019	-2.628939
44	1	0	2.434118	2.141416	-2.363136
45	6	0	4.837600	4.534238	-1.991427
46	1	0	5.444822	5.381415	-0.099443
47	1	0	4.017728	3.514284	-3.708455
48	1	0	5.530517	5.133194	-2.574017
49	6	0	4.186280	-2.347298	-0.422255
50	6	0	4.922224	-3.358693	0.213761
51	6	0	4.459696	-2.040401	-1.765653
52	6	0	5.922554	-4.047836	-0.482465
53	1	0	4.710692	-3.616556	1.246340
54	6	0	5.464899	-2.724468	-2.458670
55	1	0	3.876647	-1.272353	-2.266595
56	6	0	6.197656	-3.730409	-1.817741
57	1	0	6.484003	-4.831303	0.017328
58	1	0	5.667885	-2.479004	-3.496509
59	1	0	6.972559	-4.266985	-2.356217
60	6	0	2.306593	-2.476733	1.864276
61	6	0	2.873319	-2.459555	3.148502

62	6	0	1.257710	-3.374795	1.591527
63	6	0	2.403062	-3.326877	4.143931
64	1	0	3.679689	-1.774165	3.388401
65	6	0	0.797637	-4.247113	2.583147
66	1	0	0.799621	-3.379662	0.606067
67	6	0	1.367554	-4.223748	3.862316
68	1	0	2.846884	-3.300192	5.134445
69	1	0	-0.009905	-4.937622	2.360619
70	1	0	1.003854	-4.895261	4.633627
71	6	0	3.887309	0.026011	1.277967
72	1	0	4.543574	0.401873	0.484488
73	1	0	4.533835	-0.390956	2.057516
74	6	0	3.010205	1.154951	1.829597
75	1	0	2.365016	0.793046	2.637485
76	1	0	3.629055	1.962051	2.235818
77	6	0	-2.612401	-3.391198	-0.622006
78	1	0	-2.139342	-3.993213	0.153621
79	1	0	-2.763258	-4.008013	-1.520287
80	6	0	-1.797956	-2.150783	-0.968724
81	1	0	-1.526118	-1.587167	-0.074678
82	6	0	-4.658497	-2.136837	-0.974141
83	1	0	-4.850207	-2.694777	-1.906000
84	6	0	-5.927154	-1.704682	-0.300701
85	6	0	-5.918285	-1.347964	1.056374
86	6	0	-7.117529	-1.616156	-1.034129
87	6	0	-7.094933	-0.910082	1.670639
88	1	0	-4.993648	-1.428865	1.615131
89	6	0	-8.294479	-1.174377	-0.419293
90	1	0	-7.124551	-1.891559	-2.085077
91	6	0	-8.284179	-0.820816	0.934440
92	1	0	-7.086323	-0.640359	2.722101
93	1	0	-9.213258	-1.109142	-0.993300
94	1	0	-9.196568	-0.480330	1.414200

3,6-trans B

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.347347	0.013340	-2.392848
2	1	0	0.057251	0.733792	-3.152235
3	6	0	-0.287087	-1.251145	-2.394542
4	1	0	-1.000969	-1.547971	-3.152874
5	8	0	0.319692	-2.409400	-1.802276
6	8	0	2.739771	0.132837	-2.870972
7	8	0	3.416046	-0.848346	-0.415087
8	6	0	2.145065	-3.407889	-0.565940
9	1	0	1.513058	-3.407118	0.334512
10	1	0	2.081245	-4.380702	-1.053055
11	8	0	3.554748	-3.227406	-0.203705
12	6	0	3.816276	-1.958679	0.444347
13	1	0	3.224492	-1.903489	1.372349
14	6	0	3.901488	0.867749	-2.831690
15	8	0	4.917541	0.440783	-3.381201
16	6	0	3.849330	2.256382	-2.187117
17	1	0	4.635367	2.833233	-2.685285
18	1	0	2.885766	2.735551	-2.374560
19	6	0	4.116941	2.289934	-0.676692
20	8	0	3.220706	2.637199	0.111586
21	6	0	5.504369	1.931902	-0.221420
22	1	0	5.793365	0.952725	-0.616205
23	1	0	6.227756	2.663636	-0.604633
24	1	0	5.547535	1.914561	0.868347
25	6	0	2.011969	-0.922791	-0.811036
26	1	0	1.373626	-0.820504	0.079098
27	6	0	1.741483	-2.269450	-1.492662
28	1	0	2.322398	-2.307670	-2.420413
29	46	0	-1.260256	0.014345	-0.905140

30	15	0	-3.341391	-0.883244	0.065475
31	15	0	-1.577542	1.904134	0.701951
32	6	0	-3.451185	1.784366	1.130136
33	1	0	-3.676957	2.446331	1.973839
34	1	0	-4.009804	2.136995	0.255211
35	6	0	-3.846307	0.338809	1.470214
36	1	0	-4.925568	0.274079	1.645485
37	1	0	-3.330321	0.005107	2.377340
38	6	0	-0.829676	1.647224	2.420628
39	6	0	-0.774744	2.671927	3.379060
40	6	0	-0.343561	0.372168	2.753234
41	6	0	-0.243469	2.423417	4.649712
42	1	0	-1.133341	3.665994	3.131938
43	6	0	0.181052	0.121978	4.027245
44	1	0	-0.375181	-0.419412	2.009490
45	6	0	0.232931	1.148045	4.977113
46	1	0	-0.200016	3.224621	5.381076
47	1	0	0.551547	-0.868466	4.273102
48	1	0	0.645435	0.957789	5.962992
49	6	0	-1.300368	3.741335	0.399830
50	6	0	-2.348157	4.672325	0.314681
51	6	0	0.023031	4.178695	0.197722
52	6	0	-2.080621	6.018839	0.032030
53	1	0	-3.376536	4.362578	0.465467
54	6	0	0.285801	5.524918	-0.073502
55	1	0	0.853154	3.479437	0.251416
56	6	0	-0.764130	6.448579	-0.159618
57	1	0	-2.901070	6.727012	-0.033132
58	1	0	1.311661	5.848167	-0.219392
59	1	0	-0.557083	7.491978	-0.375920
60	6	0	-4.869897	-0.832178	-1.046438
61	6	0	-6.038141	-1.567137	-0.791148
62	6	0	-4.819591	0.004488	-2.174385
63	6	0	-7.142377	-1.457634	-1.644684
64	1	0	-6.085896	-2.237321	0.060650
65	6	0	-5.927669	0.120669	-3.022068
66	1	0	-3.904264	0.548753	-2.391800
67	6	0	-7.091447	-0.610414	-2.758145
68	1	0	-8.038523	-2.036136	-1.441877
69	1	0	-5.876455	0.770752	-3.890000
70	1	0	-7.948598	-0.527996	-3.419044
71	6	0	-3.412202	-2.557314	0.919116
72	6	0	-4.280872	-2.850867	1.984707
73	6	0	-2.518060	-3.545649	0.470403
74	6	0	-4.265584	-4.116564	2.583566
75	1	0	-4.967520	-2.097203	2.357912
76	6	0	-2.509703	-4.812309	1.066864
77	1	0	-1.818483	-3.315457	-0.328699
78	6	0	-3.383189	-5.100279	2.122041
79	1	0	-4.939466	-4.331796	3.407139
80	1	0	-1.817095	-5.568707	0.711367
81	1	0	-3.372484	-6.081588	2.586004
82	6	0	1.699612	0.215602	-1.779319
83	1	0	1.788597	1.184801	-1.290663
84	6	0	5.289078	-1.853187	0.700386
85	6	0	5.777618	-1.754375	2.009024
86	6	0	6.186418	-1.860330	-0.380323
87	6	0	7.154903	-1.664310	2.243712
88	1	0	5.082773	-1.747826	2.844162
89	6	0	7.560992	-1.769142	-0.144564
90	1	0	5.802295	-1.924932	-1.391973
91	6	0	8.047601	-1.672187	1.166753
92	1	0	7.526725	-1.588763	3.260625
93	1	0	8.251599	-1.773483	-0.981698
94	1	0	9.116115	-1.603088	1.345934

Int 1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.298183	-0.863946	-1.637670
2	1	0	-1.627100	-0.044457	-2.270146
3	6	0	-0.166492	-1.614138	-2.028007
4	1	0	0.326373	-1.502956	-2.984965
5	8	0	0.034171	-2.934376	-1.538110
6	8	0	-3.658985	-1.614943	-1.520507
7	8	0	-2.551254	-3.138954	1.075794
8	6	0	-0.220709	-4.605205	0.167601
9	1	0	-0.886226	-4.915703	0.982964
10	1	0	-0.378565	-5.259107	-0.702854
11	6	0	-3.992563	-3.314416	1.182075
12	1	0	-4.175477	-3.633745	2.208845
13	1	0	-4.534213	-2.382079	0.989581
14	1	0	-4.349049	-4.082997	0.483777
15	8	0	1.163541	-4.671936	0.605741
16	6	0	1.561870	-6.003131	1.009918
17	1	0	2.592952	-5.924186	1.357093
18	1	0	0.931019	-6.379342	1.828881
19	1	0	1.511570	-6.711189	0.170061
20	6	0	-4.447448	-0.517955	-1.675811
21	8	0	-4.174922	0.608002	-1.228629
22	6	0	-5.708708	-0.850711	-2.454726
23	1	0	-5.662822	-0.307380	-3.407541
24	1	0	-5.744635	-1.922139	-2.648441
25	6	0	-6.979476	-0.439154	-1.697839
26	8	0	-7.703316	-1.305796	-1.186440
27	6	0	-7.287409	1.033879	-1.620204
28	1	0	-6.415574	1.576318	-1.237951
29	1	0	-7.496465	1.427323	-2.624232
30	1	0	-8.155495	1.201335	-0.980530
31	6	0	-2.349647	-1.459828	-0.740262
32	1	0	-2.599077	-0.816255	0.105035
33	6	0	-2.043906	-2.891504	-0.263100
34	1	0	-2.508516	-3.590115	-0.974684
35	6	0	-0.533182	-3.172579	-0.211472
36	1	0	-0.052898	-2.489768	0.502764
37	46	0	0.440909	-0.008164	-0.654324
38	15	0	0.092182	1.836331	1.008733
39	15	0	2.847847	0.373583	-0.253125
40	6	0	1.855629	2.535781	1.342777
41	1	0	2.077616	3.248399	0.540059
42	1	0	1.862388	3.075213	2.296368
43	6	0	2.896205	1.405655	1.364381
44	1	0	2.681348	0.696054	2.171872
45	1	0	3.900279	1.803910	1.546821
46	6	0	-0.413156	1.322978	2.759496
47	6	0	-0.822626	2.248082	3.733495
48	6	0	-0.354282	-0.040126	3.091385
49	6	0	-1.158056	1.816006	5.021568
50	1	0	-0.894227	3.302392	3.485475
51	6	0	-0.684794	-0.471722	4.382124
52	1	0	-0.061402	-0.761912	2.334802
53	6	0	-1.086522	0.456021	5.349092
54	1	0	-1.478378	2.538780	5.765925
55	1	0	-0.638147	-1.528866	4.623343
56	1	0	-1.349420	0.122658	6.348244
57	6	0	-0.935395	3.383281	0.694670
58	6	0	-0.513172	4.678654	1.039182
59	6	0	-2.182402	3.214069	0.066209
60	6	0	-1.324839	5.786671	0.763564
61	1	0	0.447142	4.836143	1.519350
62	6	0	-2.994124	4.322185	-0.200087
63	1	0	-2.521152	2.224424	-0.225830
64	6	0	-2.567875	5.610055	0.146257

65	1	0	-0.985404	6.782655	1.031688
66	1	0	-3.953762	4.174320	-0.684943
67	1	0	-3.196428	6.469152	-0.067030
68	6	0	4.125623	-0.971939	0.088571
69	6	0	5.479681	-0.683689	0.328135
70	6	0	3.690007	-2.306188	0.098722
71	6	0	6.386710	-1.716703	0.585637
72	1	0	5.834781	0.341965	0.297220
73	6	0	4.601945	-3.338531	0.355445
74	1	0	2.651752	-2.549967	-0.101052
75	6	0	5.947469	-3.047228	0.600741
76	1	0	7.431879	-1.485346	0.767886
77	1	0	4.252171	-4.365214	0.353177
78	1	0	6.652977	-3.849158	0.796284
79	6	0	3.713589	1.498110	-1.503611
80	6	0	4.603088	2.527084	-1.154052
81	6	0	3.437465	1.275886	-2.864100
82	6	0	5.209252	3.312489	-2.143262
83	1	0	4.829851	2.730838	-0.112651
84	6	0	4.048194	2.054008	-3.853093
85	1	0	2.733939	0.497086	-3.142193
86	6	0	4.936004	3.075358	-3.494442
87	1	0	5.892184	4.106471	-1.856655
88	1	0	3.825665	1.867856	-4.899127
89	1	0	5.405806	3.684114	-4.260536

Int 2

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.328617	-1.079813	-1.464062
2	1	0	-1.780187	-0.300810	-2.071227
3	6	0	-0.154866	-1.712049	-1.926829
4	1	0	0.276112	-1.531676	-2.903308
5	8	0	0.197091	-3.014226	-1.479174
6	8	0	-3.604739	-1.994163	-1.198586
7	8	0	-2.253882	-3.581793	1.204233
8	6	0	0.192869	-4.733608	0.190740
9	1	0	-0.380240	-5.131533	1.036843
10	1	0	0.047003	-5.380482	-0.687019
11	6	0	-3.672161	-3.863664	1.354941
12	1	0	-3.782541	-4.290951	2.352802
13	1	0	-4.279808	-2.955605	1.278769
14	1	0	-4.014500	-4.585227	0.601122
15	8	0	1.604599	-4.660158	0.530146
16	6	0	2.242541	-5.956179	0.609432
17	1	0	3.290446	-5.767362	0.846604
18	1	0	1.794935	-6.580935	1.396804
19	1	0	2.176932	-6.491713	-0.348487
20	6	0	-4.514489	-0.980843	-1.174089
21	8	0	-4.299658	0.108919	-0.556162
22	6	0	-6.734004	-0.333212	-1.958308
23	6	0	-8.023038	-0.530455	-2.687305
24	1	0	-8.068500	-1.512539	-3.162025
25	1	0	-8.865395	-0.426466	-1.993779
26	1	0	-8.141842	0.244580	-3.453235
27	6	0	-2.266323	-1.785580	-0.511748
28	1	0	-2.477935	-1.200358	0.384280
29	6	0	-1.817928	-3.207207	-0.130436
30	1	0	-2.236059	-3.905499	-0.870813
31	6	0	-0.286700	-3.334757	-0.136986
32	1	0	0.143533	-2.615983	0.574201
33	46	0	0.379370	-0.058190	-0.573247
34	15	0	-0.090925	1.861288	0.966235
35	15	0	2.770112	0.506104	-0.198684
36	6	0	-5.729635	-1.260799	-1.898446
37	1	0	-5.828151	-2.212103	-2.399870

38	8	0	-6.649788	0.879702	-1.348824
39	1	0	-5.760100	0.954235	-0.885561
40	6	0	2.732888	2.182283	0.740807
41	1	0	3.698105	2.367600	1.223849
42	1	0	2.572894	2.964259	-0.010443
43	6	0	1.608791	2.214683	1.787833
44	1	0	1.588826	3.191225	2.284777
45	1	0	1.769278	1.441821	2.548702
46	6	0	3.805333	-0.566897	0.967627
47	6	0	5.040580	-0.139599	1.483209
48	6	0	3.317814	-1.834512	1.316027
49	6	0	5.765354	-0.959595	2.354119
50	1	0	5.450453	0.824969	1.197686
51	6	0	4.043880	-2.655652	2.188889
52	1	0	2.388085	-2.197987	0.895232
53	6	0	5.263993	-2.218318	2.713290
54	1	0	6.719140	-0.620487	2.747233
55	1	0	3.644342	-3.630351	2.447499
56	1	0	5.826601	-2.852915	3.391411
57	6	0	3.975869	0.847473	-1.612381
58	6	0	4.822221	1.966372	-1.664987
59	6	0	4.012276	-0.084112	-2.664598
60	6	0	5.690646	2.149643	-2.749196
61	1	0	4.812167	2.704065	-0.869664
62	6	0	4.886160	0.093924	-3.741731
63	1	0	3.349542	-0.944381	-2.639392
64	6	0	5.726988	1.213015	-3.787211
65	1	0	6.337104	3.021577	-2.779127
66	1	0	4.905548	-0.635322	-4.545672
67	1	0	6.400970	1.355049	-4.626216
68	6	0	-0.428779	3.531938	0.143428
69	6	0	-0.269219	3.631125	-1.248241
70	6	0	-0.810563	4.669652	0.872650
71	6	0	-0.474094	4.853896	-1.900090
72	1	0	0.004013	2.745921	-1.816012
73	6	0	-1.020606	5.889757	0.220392
74	1	0	-0.958748	4.601532	1.946074
75	6	0	-0.849650	5.984626	-1.166626
76	1	0	-0.348319	4.918493	-2.976481
77	1	0	-1.320781	6.762465	0.792513
78	1	0	-1.015092	6.931390	-1.671455
79	6	0	-1.296276	1.857651	2.412979
80	6	0	-0.938859	2.203636	3.726248
81	6	0	-2.618574	1.456529	2.145389
82	6	0	-1.887885	2.153844	4.756339
83	1	0	0.075320	2.509418	3.960264
84	6	0	-3.565090	1.417392	3.174416
85	1	0	-2.912178	1.164594	1.140691
86	6	0	-3.202900	1.764756	4.481994
87	1	0	-1.597564	2.420371	5.768161
88	1	0	-4.581340	1.107526	2.952056
89	1	0	-3.937573	1.727155	5.280372

Ts 1

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.965185	0.889352	-2.018259
2	1	0	1.146270	0.084575	-2.722444
3	6	0	-0.206910	1.685227	-2.132162
4	1	0	-0.840790	1.666400	-3.008124
5	8	0	-0.300651	2.930048	-1.489376
6	8	0	3.790954	1.705391	-1.987438
7	8	0	2.127875	2.276829	1.211019
8	6	0	0.318264	4.477409	0.242308
9	1	0	1.003347	4.623627	1.088656
10	1	0	0.642691	5.105110	-0.600425

11	6	0	3.561726	2.104364	1.464807
12	1	0	3.658758	2.061390	2.550011
13	1	0	3.941168	1.180908	1.017383
14	1	0	4.126551	2.957382	1.070451
15	8	0	-1.039034	4.812437	0.633998
16	6	0	-1.192425	6.200498	1.017524
17	1	0	-2.235409	6.324566	1.312073
18	1	0	-0.541876	6.456390	1.866469
19	1	0	-0.966339	6.875631	0.179981
20	6	0	4.665931	0.776389	-1.759706
21	8	0	4.473454	-0.272985	-1.051107
22	6	0	6.050768	0.990432	-2.421021
23	1	0	6.141652	0.249301	-3.226203
24	1	0	6.082701	1.995057	-2.842829
25	6	0	7.196310	0.821009	-1.435131
26	8	0	7.792006	1.810851	-0.972954
27	6	0	7.550981	-0.589843	-1.032165
28	1	0	6.641485	-1.089104	-0.679092
29	1	0	7.917501	-1.152296	-1.901658
30	1	0	8.320351	-0.579311	-0.257500
31	6	0	1.866826	1.133251	-0.965828
32	1	0	2.577788	0.379437	-0.656177
33	6	0	1.769052	2.433436	-0.190375
34	1	0	2.465305	3.132130	-0.674539
35	6	0	0.346355	3.020522	-0.163548
36	1	0	-0.259571	2.436931	0.541548
37	46	0	-0.526594	0.028905	-0.647036
38	15	0	-0.078808	-1.819908	0.965813
39	15	0	-2.901810	-0.387230	-0.235003
40	6	0	-1.810253	-2.617072	1.178262
41	1	0	-1.993177	-3.246191	0.299886
42	1	0	-1.820050	-3.258609	2.065771
43	6	0	-2.891532	-1.530654	1.301517
44	1	0	-2.692255	-0.877893	2.158908
45	1	0	-3.876161	-1.983356	1.458001
46	6	0	0.400975	-1.457650	2.754639
47	6	0	0.394365	-2.468994	3.730624
48	6	0	0.775593	-0.153944	3.112008
49	6	0	0.738328	-2.175279	5.053539
50	1	0	0.139716	-3.490125	3.461475
51	6	0	1.119258	0.136843	4.439938
52	1	0	0.832601	0.628814	2.362330
53	6	0	1.096968	-0.868653	5.411019
54	1	0	0.733381	-2.963057	5.800466
55	1	0	1.407698	1.148629	4.706428
56	1	0	1.364828	-0.641211	6.438083
57	6	0	1.045063	-3.243875	0.466860
58	6	0	0.669416	-4.592003	0.588483
59	6	0	2.312948	-2.926156	-0.052170
60	6	0	1.549710	-5.608604	0.196725
61	1	0	-0.304970	-4.862104	0.982761
62	6	0	3.191618	-3.944938	-0.435758
63	1	0	2.633911	-1.895865	-0.170527
64	6	0	2.812136	-5.286860	-0.313945
65	1	0	1.247878	-6.647196	0.291896
66	1	0	4.164277	-3.676414	-0.833853
67	1	0	3.492889	-6.075920	-0.617597
68	6	0	-4.088013	0.991767	0.240318
69	6	0	-5.406018	0.742616	0.658681
70	6	0	-3.616639	2.312806	0.186581
71	6	0	-6.238917	1.803553	1.027914
72	1	0	-5.791982	-0.271408	0.690329
73	6	0	-4.452849	3.372749	0.559456
74	1	0	-2.608555	2.527220	-0.150056
75	6	0	-5.761809	3.120515	0.980897
76	1	0	-7.256279	1.603569	1.349642
77	1	0	-4.067084	4.385252	0.516961
78	1	0	-6.410177	3.941970	1.269416

79	6	0	-3.800333	-1.408598	-1.542134
80	6	0	-4.829342	-2.316160	-1.241395
81	6	0	-3.416446	-1.235529	-2.882331
82	6	0	-5.465953	-3.031523	-2.262648
83	1	0	-5.141537	-2.479104	-0.215021
84	6	0	-4.055855	-1.946346	-3.904059
85	1	0	-2.609256	-0.549761	-3.119910
86	6	0	-5.082507	-2.845760	-3.595655
87	1	0	-6.258279	-3.731397	-2.016302
88	1	0	-3.748458	-1.801880	-4.934781
89	1	0	-5.576628	-3.400993	-4.386390

Int 3- enoate t

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	8	0	2.410077	-0.860549	0.000391
2	6	0	1.364352	-0.206280	0.000143
3	8	0	1.416693	1.155440	-0.000263
4	6	0	-1.122304	0.012923	-0.000540
5	6	0	-2.487357	-0.675344	0.000169
6	1	0	-2.418852	-1.768366	-0.004020
7	1	0	-3.058398	-0.358832	0.882401
8	1	0	-3.062439	-0.352013	-0.876868
9	6	0	0.026168	-0.772740	-0.000405
10	1	0	-0.043106	-1.855082	-0.001086
11	8	0	-1.146184	1.295525	0.000331
12	1	0	0.452961	1.459610	-0.000308

Int 3 Pd-complex

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.024813	0.731286	-3.065260
2	1	0	-0.365448	-0.041790	-3.717472
3	6	0	-0.821168	1.769414	-2.675853
4	1	0	-1.854942	1.838730	-2.988824
5	8	0	-0.397074	2.909500	-2.066230
6	8	0	2.986555	1.832267	-1.049947
7	6	0	1.362561	4.368136	-1.296344
8	1	0	2.420660	4.405702	-1.001638
9	1	0	1.244223	4.859111	-2.273675
10	6	0	4.283311	1.373987	-1.536219
11	1	0	4.937863	1.381616	-0.665781
12	1	0	4.229374	0.355026	-1.936058
13	1	0	4.674171	2.052248	-2.305643
14	8	0	0.529696	4.999036	-0.296289
15	6	0	0.769958	6.426306	-0.158911
16	1	0	0.096539	6.772409	0.625016
17	1	0	1.808939	6.628843	0.134646
18	1	0	0.548143	6.957635	-1.093920
19	6	0	1.339584	0.667392	-2.500558
20	1	0	2.031570	-0.075767	-2.882095
21	6	0	1.959208	1.989031	-2.060904
22	1	0	2.400482	2.485110	-2.944037
23	6	0	0.935239	2.919799	-1.383847
24	1	0	0.752878	2.539957	-0.373307
25	46	0	-0.068458	-0.045411	-0.976226
26	15	0	-1.997862	-0.418126	0.508247
27	15	0	1.215633	-1.353074	0.621377
28	6	0	0.092884	-1.421676	2.172387
29	1	0	0.469941	-2.198395	2.845258
30	1	0	0.192317	-0.459660	2.686199
31	6	0	-1.363101	-1.695289	1.786306
32	1	0	-2.007536	-1.674168	2.670224

33	1	0	-1.467896	-2.682860	1.325139
34	6	0	1.354780	-3.153971	0.120895
35	6	0	1.734452	-4.142517	1.046784
36	6	0	1.048162	-3.526369	-1.197793
37	6	0	1.803657	-5.483474	0.654598
38	1	0	1.987168	-3.873909	2.067927
39	6	0	1.117622	-4.869641	-1.587897
40	1	0	0.754092	-2.766210	-1.915474
41	6	0	1.495079	-5.848431	-0.662279
42	1	0	2.098722	-6.239847	1.374073
43	1	0	0.879628	-5.148061	-2.609108
44	1	0	1.549885	-6.889087	-0.963369
45	6	0	2.887845	-0.849464	1.300216
46	6	0	4.033352	-1.635846	1.103303
47	6	0	2.991963	0.366314	1.996984
48	6	0	5.267614	-1.217642	1.617048
49	1	0	3.969997	-2.572119	0.560437
50	6	0	4.224343	0.776936	2.513308
51	1	0	2.123425	1.004188	2.127106
52	6	0	5.364625	-0.015314	2.326161
53	1	0	6.147302	-1.834659	1.466643
54	1	0	4.294116	1.713434	3.056309
55	1	0	6.319960	0.303056	2.729738
56	6	0	-2.473766	1.070766	1.540000
57	6	0	-2.075555	2.347861	1.112647
58	6	0	-3.200510	0.938883	2.737404
59	6	0	-2.383109	3.478428	1.879006
60	1	0	-1.533177	2.473859	0.182933
61	6	0	-3.511686	2.070888	3.498051
62	1	0	-3.534649	-0.036314	3.078124
63	6	0	-3.099236	3.340793	3.072465
64	1	0	-2.052561	4.452934	1.537201
65	1	0	-4.073799	1.961303	4.419506
66	1	0	-3.337813	4.215214	3.668622
67	6	0	-3.587317	-1.181054	-0.130561
68	6	0	-3.511670	-2.412840	-0.805239
69	6	0	-4.828423	-0.542951	0.010190
70	6	0	-4.669721	-3.006163	-1.316488
71	1	0	-2.554058	-2.909718	-0.938458
72	6	0	-5.984864	-1.138664	-0.509454
73	1	0	-4.899800	0.410368	0.521823
74	6	0	-5.908865	-2.369657	-1.168968
75	1	0	-4.604829	-3.959698	-1.830055
76	1	0	-6.941593	-0.640035	-0.395188
77	1	0	-6.806558	-2.829478	-1.568108

Ts 2

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.910994	0.654086	-1.127651
2	1	0	1.810579	1.300591	-1.992068
3	6	0	2.665259	1.173995	-0.025620
4	1	0	2.658046	2.228765	0.210332
5	8	0	2.962188	0.423034	1.059737
6	8	0	5.462459	-0.717486	-0.636623
7	8	0	1.740543	-2.933646	-0.117323
8	6	0	3.749808	-1.679386	1.920562
9	1	0	3.692911	-2.774091	1.826380
10	1	0	4.719281	-1.335447	1.540766
11	6	0	2.508288	-4.126325	-0.459653
12	1	0	1.824684	-4.965993	-0.323016
13	1	0	2.853456	-4.093020	-1.500300
14	1	0	3.375634	-4.254248	0.198729
15	8	0	3.545897	-1.296842	3.306236
16	6	0	4.656996	-1.646709	4.163817
17	1	0	4.395728	-1.293104	5.162498

18	1	0	4.818882	-2.734938	4.194223
19	1	0	5.586096	-1.161160	3.833916
20	6	0	5.031851	0.190467	-1.382926
21	6	0	4.437821	2.602235	-1.840073
22	8	0	4.058497	2.372667	-3.049348
23	6	0	4.458000	4.039851	-1.364729
24	1	0	4.619717	4.124574	-0.286176
25	1	0	5.262903	4.580596	-1.877706
26	1	0	3.519037	4.534395	-1.638020
27	6	0	1.690554	-0.754280	-1.227979
28	1	0	1.484663	-1.179122	-2.206398
29	6	0	2.463506	-1.664389	-0.299814
30	1	0	3.444391	-1.883303	-0.739884
31	6	0	2.646197	-1.047363	1.100374
32	1	0	1.693775	-1.114925	1.634271
33	8	0	4.683903	-0.102935	-2.678605
34	1	0	4.373577	0.744576	-3.138682
35	6	0	4.774732	1.555837	-0.931516
36	1	0	5.199313	1.808552	0.031861
37	46	0	-0.112874	0.120933	-0.425443
38	15	0	-1.922200	-1.532600	-0.247125
39	15	0	-1.827935	1.775573	0.298256
40	6	0	-3.522007	-0.471426	-0.260352
41	1	0	-3.674500	-0.129250	-1.290484
42	1	0	-4.379876	-1.088697	0.028722
43	6	0	-3.390975	0.724650	0.693259
44	1	0	-3.286075	0.380313	1.728447
45	1	0	-4.283773	1.355938	0.630143
46	6	0	-2.115109	-2.470592	1.378135
47	6	0	-2.997718	-3.554150	1.512555
48	6	0	-1.364078	-2.051726	2.487364
49	6	0	-3.132225	-4.203645	2.744653
50	1	0	-3.567711	-3.901183	0.656215
51	6	0	-1.502361	-2.699615	3.721053
52	1	0	-0.662762	-1.229969	2.379745
53	6	0	-2.386854	-3.775897	3.850739
54	1	0	-3.812931	-5.044099	2.839172
55	1	0	-0.912004	-2.370373	4.569975
56	1	0	-2.489796	-4.283735	4.804528
57	6	0	-2.225903	-2.834196	-1.565648
58	6	0	-3.470521	-3.032941	-2.184501
59	6	0	-1.128669	-3.625796	-1.949898
60	6	0	-3.617708	-4.013406	-3.174819
61	1	0	-4.329267	-2.431023	-1.906885
62	6	0	-1.282550	-4.608225	-2.933355
63	1	0	-0.163538	-3.459968	-1.478928
64	6	0	-2.525723	-4.803226	-3.548742
65	1	0	-4.583178	-4.157360	-3.649887
66	1	0	-0.431088	-5.215112	-3.224988
67	1	0	-2.640628	-5.561681	-4.316649
68	6	0	-1.683403	2.879579	1.814344
69	6	0	-2.784530	3.240393	2.610254
70	6	0	-0.405386	3.341237	2.170472
71	6	0	-2.609243	4.054954	3.735615
72	1	0	-3.780657	2.886649	2.365024
73	6	0	-0.230913	4.158732	3.292303
74	1	0	0.453881	3.045669	1.576739
75	6	0	-1.333270	4.517492	4.076557
76	1	0	-3.466973	4.324406	4.343944
77	1	0	0.762943	4.504357	3.557457
78	1	0	-1.198302	5.146686	4.950435
79	6	0	-2.463131	2.909716	-1.072730
80	6	0	-3.252205	4.044196	-0.825386
81	6	0	-2.134738	2.576244	-2.397435
82	6	0	-3.714118	4.827028	-1.889730
83	1	0	-3.494857	4.330029	0.192925
84	6	0	-2.603494	3.356176	-3.461536
85	1	0	-1.501075	1.714692	-2.589649

86	6	0	-3.394251	4.482505	-3.208786
87	1	0	-4.318330	5.706229	-1.688394
88	1	0	-2.341568	3.089824	-4.480536
89	1	0	-3.751817	5.092649	-4.032121

Int 4

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.818120	-0.734091	-1.282436
2	1	0	2.056147	-0.143213	-2.164471
3	6	0	2.903582	-0.768163	-0.239005
4	1	0	3.112350	0.243688	0.127569
5	8	0	2.608566	-1.560836	0.931510
6	8	0	4.120609	-3.713954	-0.842663
7	8	0	-0.327586	-3.588171	-0.171364
8	6	0	1.773110	-3.564520	1.936013
9	1	0	1.025202	-4.363745	1.837957
10	1	0	2.765670	-3.953253	1.671017
11	6	0	-0.646651	-4.602775	-1.160608
12	1	0	-1.567100	-5.078843	-0.817508
13	1	0	-0.812007	-4.167261	-2.154643
14	1	0	0.151031	-5.355187	-1.229100
15	8	0	1.767357	-3.045841	3.294502
16	6	0	2.188603	-4.021216	4.273387
17	1	0	2.143470	-3.523707	5.243843
18	1	0	1.524376	-4.899142	4.284030
19	1	0	3.217505	-4.362406	4.086260
20	6	0	4.163795	-2.661130	-1.484880
21	6	0	4.964870	-0.223505	-1.631952
22	8	0	4.791685	-0.163807	-2.874702
23	6	0	5.785068	0.819119	-0.922796
24	1	0	5.256218	1.209025	-0.044993
25	1	0	6.718034	0.368641	-0.558403
26	1	0	6.024525	1.635654	-1.605725
27	6	0	0.882571	-1.793538	-1.381492
28	1	0	0.443790	-2.029736	-2.347264
29	6	0	0.967168	-2.931339	-0.389038
30	1	0	1.671373	-3.699816	-0.743337
31	6	0	1.415171	-2.431800	0.994823
32	1	0	0.593424	-1.845716	1.421009
33	8	0	4.002915	-2.661059	-2.839461
34	1	0	4.140535	-1.747886	-3.217847
35	6	0	4.327627	-1.307831	-0.797114
36	1	0	4.909812	-1.472816	0.112726
37	46	0	-0.099989	-0.000272	-0.583862
38	15	0	-2.568013	0.061095	-0.348916
39	15	0	-0.177928	2.325909	0.267384
40	6	0	-2.957385	1.943347	-0.401794
41	1	0	-2.799245	2.278852	-1.433658
42	1	0	-4.008478	2.114225	-0.142135
43	6	0	-2.047821	2.716473	0.564679
44	1	0	-2.257508	2.424587	1.599743
45	1	0	-2.218643	3.794093	0.471193
46	6	0	-3.362288	-0.414797	1.299178
47	6	0	-4.754817	-0.433359	1.481853
48	6	0	-2.523601	-0.740904	2.376034
49	6	0	-5.298800	-0.765069	2.727419
50	1	0	-5.415609	-0.204587	0.650974
51	6	0	-3.068390	-1.069513	3.623970
52	1	0	-1.447679	-0.749187	2.232542
53	6	0	-4.455957	-1.081083	3.801000
54	1	0	-6.376558	-0.781005	2.858526
55	1	0	-2.408611	-1.323490	4.447344
56	1	0	-4.879727	-1.341132	4.766062
57	6	0	-3.763412	-0.670738	-1.605698
58	6	0	-4.711867	0.079270	-2.318730

59	6	0	-3.663516	-2.053122	-1.846796
60	6	0	-5.548543	-0.543032	-3.255870
61	1	0	-4.808388	1.147292	-2.155648
62	6	0	-4.505757	-2.673617	-2.773426
63	1	0	-2.918907	-2.633250	-1.309752
64	6	0	-5.450083	-1.919133	-3.482322
65	1	0	-6.275947	0.048743	-3.803198
66	1	0	-4.421545	-3.741851	-2.947591
67	1	0	-6.099468	-2.400086	-4.207002
68	6	0	0.571550	2.771864	1.935272
69	6	0	0.187442	3.906539	2.672987
70	6	0	1.516797	1.888994	2.485165
71	6	0	0.754727	4.163892	3.926462
72	1	0	-0.559614	4.589464	2.279797
73	6	0	2.082532	2.146938	3.740133
74	1	0	1.788816	0.984027	1.949931
75	6	0	1.706683	3.286310	4.459748
76	1	0	0.449675	5.042733	4.486209
77	1	0	2.803128	1.449844	4.155330
78	1	0	2.142938	3.484531	5.433752
79	6	0	0.337020	3.701465	-0.922725
80	6	0	0.851989	4.945158	-0.525144
81	6	0	0.190630	3.431176	-2.295400
82	6	0	1.197109	5.907106	-1.483113
83	1	0	0.999999	5.165062	0.526152
84	6	0	0.524665	4.397060	-3.250982
85	1	0	-0.163253	2.453180	-2.610516
86	6	0	1.027903	5.639014	-2.846076
87	1	0	1.599904	6.863180	-1.162636
88	1	0	0.405461	4.174200	-4.306714
89	1	0	1.296071	6.386383	-3.586167

Ts 3

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.834082	-0.477609	-1.327292
2	1	0	2.061091	0.317956	-2.030273
3	6	0	2.908377	-0.779064	-0.296878
4	1	0	2.792602	-0.117402	0.574303
5	8	0	2.860975	-2.157083	0.183978
6	8	0	5.514019	-2.876601	-1.082657
7	8	0	-0.433670	-3.415235	-0.873481
8	6	0	1.755779	-4.115753	0.968032
9	1	0	0.894345	-4.765928	0.763813
10	1	0	2.663881	-4.566899	0.543115
11	6	0	-1.140201	-3.726342	-2.103104
12	1	0	-2.019671	-4.301336	-1.808537
13	1	0	-1.463741	-2.818520	-2.624524
14	1	0	-0.513435	-4.332280	-2.772536
15	8	0	1.906517	-3.920609	2.400450
16	6	0	2.321353	-5.116444	3.097621
17	1	0	2.398749	-4.846179	4.152104
18	1	0	1.587052	-5.928923	2.983717
19	1	0	3.298440	-5.471630	2.739514
20	6	0	4.752074	-2.134487	-1.683536
21	6	0	4.791340	0.417548	-1.655782
22	8	0	4.237446	0.442956	-2.875874
23	6	0	5.876024	1.417945	-1.436657
24	1	0	5.430701	2.412105	-1.288601
25	1	0	6.463909	1.175960	-0.549272
26	1	0	6.525867	1.482979	-2.314816
27	6	0	0.870924	-1.448698	-1.694296
28	1	0	0.441771	-1.393481	-2.692522
29	6	0	0.894556	-2.822213	-1.058423
30	1	0	1.480589	-3.511084	-1.691480
31	6	0	1.535276	-2.758109	0.332519

32	1	0	0.907169	-2.144455	0.992140
33	8	0	4.109525	-2.077434	-2.769410
34	1	0	3.876101	-0.500824	-3.079077
35	6	0	4.401306	-0.572386	-0.726522
36	1	0	5.036840	-0.616333	0.154344
37	46	0	-0.106193	0.109989	-0.501104
38	15	0	-2.551508	-0.077797	-0.087278
39	15	0	-0.262430	2.259611	0.742529
40	6	0	-3.046785	1.698699	0.454267
41	1	0	-3.055340	2.294572	-0.466039
42	1	0	-4.065845	1.713804	0.854452
43	6	0	-2.047393	2.275582	1.464927
44	1	0	-2.019166	1.670454	2.378159
45	1	0	-2.325128	3.295581	1.750330
46	6	0	-3.156016	-1.157603	1.338135
47	6	0	-4.129053	-0.751514	2.267145
48	6	0	-2.574577	-2.432496	1.467505
49	6	0	-4.516085	-1.603786	3.309366
50	1	0	-4.592764	0.226507	2.192843
51	6	0	-2.969396	-3.283486	2.506690
52	1	0	-1.813192	-2.753990	0.760875
53	6	0	-3.937671	-2.872005	3.429998
54	1	0	-5.266066	-1.275688	4.022766
55	1	0	-2.510758	-4.262976	2.597733
56	1	0	-4.235987	-3.531237	4.239331
57	6	0	-3.806097	-0.387759	-1.465079
58	6	0	-3.416776	-0.074990	-2.778705
59	6	0	-5.092281	-0.899696	-1.235629
60	6	0	-4.306197	-0.253933	-3.844327
61	1	0	-2.412525	0.297506	-2.962209
62	6	0	-5.978728	-1.086930	-2.303525
63	1	0	-5.401074	-1.161631	-0.228941
64	6	0	-5.589702	-0.761012	-3.608002
65	1	0	-3.994834	-0.006811	-4.854597
66	1	0	-6.970341	-1.487249	-2.115478
67	1	0	-6.278382	-0.907003	-4.434299
68	6	0	0.772461	2.625265	2.278616
69	6	0	0.887007	1.594443	3.230047
70	6	0	1.467197	3.825923	2.488854
71	6	0	1.661384	1.772033	4.380458
72	1	0	0.385654	0.644771	3.063561
73	6	0	2.250182	3.998807	3.638108
74	1	0	1.404637	4.626726	1.760623
75	6	0	2.344683	2.976954	4.588330
76	1	0	1.739434	0.967506	5.104758
77	1	0	2.783334	4.932808	3.787903
78	1	0	2.951095	3.113004	5.478167
79	6	0	-0.233389	3.853502	-0.265375
80	6	0	-0.731074	5.078841	0.211918
81	6	0	0.291537	3.792965	-1.566698
82	6	0	-0.701882	6.220678	-0.597021
83	1	0	-1.137583	5.151282	1.216133
84	6	0	0.321991	4.935070	-2.376580
85	1	0	0.664289	2.844209	-1.941000
86	6	0	-0.174486	6.150287	-1.892515
87	1	0	-1.089323	7.161026	-0.217278
88	1	0	0.728187	4.873001	-3.381232
89	1	0	-0.153606	7.036072	-2.519552

Int 5

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.651198	-0.308712	-1.904427
2	1	0	1.688004	0.459451	-2.674570
3	6	0	2.920192	-0.461824	-1.073129
4	1	0	2.723123	-0.224763	-0.013943

5	8	0	3.327662	-1.900260	-1.056911
6	8	0	0.036145	-3.516137	-0.915783
7	6	0	2.888750	-4.114607	-0.276911
8	1	0	2.101950	-4.832736	-0.009043
9	1	0	3.403644	-4.467525	-1.183753
10	6	0	-1.057013	-3.874973	-1.801375
11	1	0	-1.737748	-4.488989	-1.209571
12	1	0	-1.590646	-2.988873	-2.161335
13	1	0	-0.689859	-4.457881	-2.658889
14	8	0	3.837576	-3.958622	0.809706
15	6	0	4.572476	-5.166569	1.115872
16	1	0	5.249522	-4.912867	1.932537
17	1	0	3.900473	-5.977017	1.435282
18	1	0	5.157557	-5.511165	0.250878
19	6	0	5.372485	0.058632	-1.262578
20	8	0	5.753362	-1.028434	-0.496809
21	6	0	6.555567	0.872488	-1.692447
22	1	0	7.234716	0.266408	-2.304014
23	1	0	6.250370	1.752058	-2.265118
24	1	0	7.125030	1.200450	-0.814218
25	6	0	0.779867	-1.414095	-2.093468
26	1	0	0.167341	-1.417484	-2.993938
27	6	0	1.134913	-2.794723	-1.570207
28	1	0	1.459118	-3.416479	-2.425241
29	6	0	2.269394	-2.757208	-0.537623
30	1	0	1.888594	-2.341730	0.406321
31	1	0	4.992402	-1.661830	-0.408229
32	6	0	4.089103	0.337048	-1.578225
33	1	0	3.875726	1.185650	-2.219021
34	46	0	-0.141532	0.034177	-0.724470
35	15	0	-2.357800	-0.406897	0.307433
36	15	0	-0.254851	2.214520	0.472366
37	6	0	-2.934215	1.325548	0.908736
38	1	0	-3.256776	1.854715	0.004389
39	1	0	-3.810696	1.239501	1.559634
40	6	0	-1.802957	2.089823	1.609690
41	1	0	-1.491233	1.566853	2.521087
42	1	0	-2.140289	3.094970	1.886514
43	6	0	-2.392547	-1.458719	1.873800
44	6	0	-3.180608	-1.158825	2.997913
45	6	0	-1.563873	-2.595572	1.901060
46	6	0	-3.144461	-1.980738	4.131547
47	1	0	-3.825910	-0.286308	3.003805
48	6	0	-1.535853	-3.418250	3.033670
49	1	0	-0.940998	-2.832588	1.041704
50	6	0	-2.322633	-3.113066	4.150445
51	1	0	-3.755632	-1.735328	4.994830
52	1	0	-0.891717	-4.291942	3.043555
53	1	0	-2.292687	-3.748956	5.029840
54	6	0	-3.884930	-0.962288	-0.659601
55	6	0	-4.966402	-1.640310	-0.076841
56	6	0	-3.922878	-0.665770	-2.033105
57	6	0	-6.071873	-2.008238	-0.854266
58	1	0	-4.945239	-1.890556	0.978650
59	6	0	-5.031458	-1.025554	-2.807585
60	1	0	-3.076281	-0.163525	-2.493667
61	6	0	-6.108703	-1.698801	-2.218765
62	1	0	-6.901435	-2.536058	-0.393610
63	1	0	-5.049561	-0.788964	-3.867048
64	1	0	-6.966416	-1.984992	-2.819433
65	6	0	1.070214	2.875121	1.638944
66	6	0	0.785838	3.464573	2.882174
67	6	0	2.411554	2.742911	1.239178
68	1	0	-0.239661	3.571697	3.219528
69	6	0	3.446889	3.199257	2.061596
70	1	0	2.648840	2.270841	0.290753
71	6	0	3.154797	3.786545	3.298492
72	1	0	4.477018	3.083903	1.740507

73	1	0	3.958283	4.133323	3.940553
74	6	0	-0.702423	3.724363	-0.577698
75	6	0	-0.736031	5.027764	-0.056465
76	6	0	-1.026732	3.517435	-1.927933
77	6	0	-1.098810	6.105888	-0.871321
78	1	0	-0.464091	5.206778	0.979340
79	6	0	-1.395360	4.595951	-2.742228
80	1	0	-0.976866	2.511230	-2.335415
81	6	0	-1.432358	5.891269	-2.214752
82	1	0	-1.116764	7.110654	-0.460214
83	1	0	-1.644235	4.424438	-3.784976
84	1	0	-1.712034	6.728977	-2.845994
85	6	0	1.823464	3.916186	3.707911
86	1	0	1.589834	4.366031	4.668091

Int 6

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.520693	-0.456996	-2.059149
2	1	0	1.572195	0.315513	-2.824788
3	6	0	2.818714	-0.724422	-1.301330
4	1	0	2.738847	-0.397965	-0.254507
5	8	0	3.107583	-2.165510	-1.283831
6	8	0	-0.293588	-3.520006	-0.966534
7	6	0	2.525462	-4.339493	-0.471060
8	1	0	1.681276	-4.998711	-0.225992
9	1	0	3.016682	-4.709622	-1.384325
10	6	0	-1.460854	-3.783831	-1.788716
11	1	0	-2.156463	-4.339288	-1.157639
12	1	0	-1.937900	-2.855628	-2.120978
13	1	0	-1.193265	-4.394573	-2.663612
14	8	0	3.473718	-4.296202	0.626558
15	6	0	4.062153	-5.582629	0.925671
16	1	0	4.743175	-5.420861	1.762484
17	1	0	3.297784	-6.319703	1.214692
18	1	0	4.626095	-5.977859	0.067728
19	6	0	5.245552	-0.049491	-1.011903
20	8	0	5.500700	0.959878	-0.325598
21	6	0	6.056830	-1.314046	-0.902683
22	1	0	5.403955	-2.126413	-0.557733
23	1	0	6.438846	-1.614238	-1.886618
24	1	0	6.888683	-1.169145	-0.210754
25	6	0	0.550363	-1.486671	-2.193756
26	1	0	-0.114048	-1.439273	-3.055320
27	6	0	0.823567	-2.889606	-1.680577
28	1	0	1.054315	-3.538680	-2.546134
29	6	0	2.011324	-2.934710	-0.707477
30	1	0	1.711015	-2.490221	0.251841
31	6	0	4.044833	-0.048719	-1.947254
32	1	0	3.796299	0.993599	-2.172656
33	1	0	4.265978	-0.575043	-2.882665
34	46	0	-0.157220	0.028502	-0.775242
35	15	0	-2.333237	-0.232514	0.388907
36	15	0	-0.023290	2.217603	0.422754
37	6	0	-2.740226	1.543881	0.999645
38	1	0	-3.065061	2.090140	0.106105
39	1	0	-3.587070	1.531717	1.693892
40	6	0	-1.518396	2.221746	1.634418
41	1	0	-1.202052	1.683552	2.535171
42	1	0	-1.761710	3.252261	1.916374
43	6	0	-2.337996	-1.262566	1.969109
44	6	0	-3.014664	-0.887900	3.142344
45	6	0	-1.601954	-2.461810	1.955197
46	6	0	-2.958671	-1.696877	4.284496
47	1	0	-3.587336	0.033179	3.180349
48	6	0	-1.554280	-3.270769	3.096947

49	1	0	-1.066296	-2.758065	1.056360
50	6	0	-2.229103	-2.890666	4.262924
51	1	0	-3.482142	-1.393260	5.186032
52	1	0	-0.981428	-4.192554	3.075112
53	1	0	-2.183098	-3.516172	5.149055
54	6	0	-3.957641	-0.686398	-0.465449
55	6	0	-4.077673	-0.384827	-1.833191
56	6	0	-5.034138	-1.296549	0.196322
57	6	0	-5.261392	-0.670350	-2.522750
58	1	0	-3.237328	0.062673	-2.357223
59	6	0	-6.215243	-1.590835	-0.496497
60	1	0	-4.950747	-1.551349	1.247502
61	6	0	-6.333260	-1.274814	-1.854781
62	1	0	-5.342710	-0.429675	-3.578322
63	1	0	-7.040339	-2.066239	0.025215
64	1	0	-7.249789	-1.503111	-2.389777
65	6	0	1.405894	2.772098	1.518106
66	6	0	1.232315	3.400096	2.763643
67	6	0	2.710419	2.512868	1.064804
68	6	0	2.344694	3.762060	3.534574
69	1	0	0.237648	3.605979	3.145536
70	6	0	3.822593	2.872379	1.833252
71	1	0	2.870029	2.017678	0.113953
72	6	0	3.639190	3.499433	3.071352
73	1	0	2.197228	4.244400	4.496302
74	1	0	4.813181	2.638091	1.459723
75	1	0	4.498455	3.774534	3.675071
76	6	0	-0.408270	3.749944	-0.619337
77	6	0	-0.283679	5.056853	-0.121342
78	6	0	-0.851422	3.558499	-1.937761
79	6	0	-0.608928	6.154046	-0.926668
80	1	0	0.082921	5.221628	0.887130
81	6	0	-1.181670	4.656516	-2.742283
82	1	0	-0.924215	2.547310	-2.329222
83	6	0	-1.061813	5.955733	-2.237242
84	1	0	-0.504098	7.160867	-0.533973
85	1	0	-1.523044	4.496455	-3.760442
86	1	0	-1.311679	6.808302	-2.861078

Ts A

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.664725	0.235717	-1.710178
2	1	0	-1.377942	0.753028	-2.618891
3	6	0	-1.275894	-1.125639	-1.545097
4	1	0	-0.903256	-1.717802	-2.369099
5	8	0	-1.938239	-1.944001	-0.621609
6	8	0	-3.925047	-1.207372	-3.288582
7	8	0	-2.857116	0.806872	1.614622
8	6	0	-3.384145	-2.285455	1.251523
9	1	0	-3.938035	-1.774355	2.054071
10	1	0	-4.094593	-2.638054	0.491353
11	6	0	-3.836768	1.840041	1.935462
12	1	0	-3.648408	2.112539	2.974955
13	1	0	-3.707416	2.728021	1.303276
14	1	0	-4.859112	1.465148	1.818284
15	8	0	-2.622905	-3.388751	1.805818
16	6	0	-3.466179	-4.438799	2.338352
17	1	0	-2.794612	-5.203272	2.732227
18	1	0	-4.106815	-4.066125	3.151346
19	1	0	-4.102537	-4.876045	1.556598
20	6	0	-4.603863	-0.621830	-2.428794
21	6	0	-5.451346	1.517225	-1.360003
22	8	0	-6.175265	0.903805	-0.480703
23	6	0	-5.557111	3.025098	-1.438326
24	1	0	-5.537952	3.455777	-0.431457

25	1	0	-4.764306	3.471444	-2.045368
26	1	0	-6.523549	3.296449	-1.881669
27	6	0	-2.607950	0.819623	-0.839258
28	1	0	-2.708020	1.897511	-0.810993
29	6	0	-3.115418	0.061989	0.371807
30	1	0	-4.199713	-0.075080	0.286465
31	6	0	-2.427196	-1.301045	0.610531
32	1	0	-1.561011	-1.130088	1.261200
33	8	0	-5.422105	-1.334260	-1.568072
34	1	0	-5.943618	-0.687235	-0.996699
35	6	0	-4.544780	0.827914	-2.210698
36	1	0	-4.050350	1.381593	-2.998850
37	46	0	0.282181	0.096853	-0.601945
38	15	0	2.167716	-1.395975	-0.151002
39	15	0	1.680917	1.908482	0.420335
40	6	0	3.414633	-0.339433	0.864136
41	1	0	3.096512	-0.410207	1.910310
42	1	0	4.415555	-0.776475	0.779807
43	6	0	3.437542	1.122959	0.402221
44	1	0	3.802569	1.199962	-0.628100
45	1	0	4.110097	1.713337	1.033245
46	6	0	3.187275	-1.881622	-1.664193
47	6	0	4.106130	-2.942833	-1.659733
48	6	0	3.014077	-1.130408	-2.838833
49	6	0	4.850846	-3.236050	-2.808118
50	1	0	4.230339	-3.554309	-0.772519
51	6	0	3.764341	-1.419900	-3.984623
52	1	0	2.275260	-0.333579	-2.857051
53	6	0	4.685576	-2.473027	-3.970193
54	1	0	5.553404	-4.063530	-2.796075
55	1	0	3.618671	-0.834481	-4.887042
56	1	0	5.261737	-2.705122	-4.860207
57	6	0	2.000660	-2.953663	0.880055
58	6	0	3.060402	-3.470902	1.647782
59	6	0	0.753680	-3.599788	0.899869
60	6	0	2.878207	-4.629115	2.411350
61	1	0	4.026014	-2.974866	1.662230
62	6	0	0.576201	-4.757181	1.667651
63	1	0	-0.086412	-3.200824	0.340928
64	6	0	1.635754	-5.275593	2.418889
65	1	0	3.701358	-5.021082	3.000876
66	1	0	-0.398223	-5.231168	1.681863
67	1	0	1.494708	-6.171529	3.015457
68	6	0	2.023238	3.592664	-0.357468
69	6	0	1.772705	4.802067	0.308835
70	6	0	2.485198	3.629007	-1.685768
71	6	0	1.993124	6.025351	-0.337597
72	1	0	1.406353	4.794428	1.329349
73	6	0	2.712341	4.850614	-2.326607
74	1	0	2.657839	2.703669	-2.228540
75	6	0	2.467476	6.053771	-1.652863
76	1	0	1.794582	6.953207	0.189863
77	1	0	3.073137	4.862678	-3.350346
78	1	0	2.639364	7.002346	-2.151275
79	6	0	1.410246	2.259802	2.249166
80	6	0	2.397096	2.848266	3.060659
81	6	0	0.181569	1.887845	2.820010
82	6	0	2.161284	3.056228	4.423796
83	1	0	3.348033	3.154436	2.635036
84	6	0	-0.049938	2.096171	4.186521
85	1	0	-0.596365	1.438544	2.208722
86	6	0	0.936753	2.677482	4.989290
87	1	0	2.929773	3.510919	5.041224
88	1	0	-0.999774	1.796873	4.617807
89	1	0	0.756066	2.834857	6.048023

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Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.672806	-0.021931	-1.618832
2	1	0	-1.515575	0.646191	-2.462725
3	6	0	-1.125016	-1.317518	-1.707165
4	1	0	-0.647780	-1.709676	-2.594947
5	8	0	-1.714400	-2.376774	-0.966554
6	8	0	-3.789380	-1.339692	-3.637302
7	8	0	-3.165079	-0.242270	1.610280
8	6	0	-2.776346	-3.214777	1.008855
9	1	0	-3.411168	-2.909575	1.854187
10	1	0	-3.389002	-3.758484	0.274820
11	6	0	-4.348076	0.468457	2.060695
12	1	0	-4.166469	0.709993	3.108661
13	1	0	-4.504613	1.403201	1.506297
14	1	0	-5.247914	-0.152249	1.970596
15	8	0	-1.695729	-4.054116	1.490261
16	6	0	-2.163214	-5.300894	2.057908
17	1	0	-1.277345	-5.832905	2.407033
18	1	0	-2.839171	-5.126990	2.908486
19	1	0	-2.685535	-5.911771	1.307978
20	6	0	-4.419116	-1.033206	-2.628367
21	6	0	-5.406305	0.885343	-1.236758
22	8	0	-6.274631	0.155337	-0.695360
23	6	0	-5.541655	2.383989	-1.207985
24	1	0	-6.342818	2.677255	-0.527595
25	1	0	-4.601976	2.863864	-0.911017
26	1	0	-5.781246	2.747243	-2.216666
27	6	0	-2.961930	0.204450	-0.847547
28	1	0	-2.928402	1.187411	-0.362463
29	6	0	-3.231480	-0.843753	0.276414
30	1	0	-4.229883	-1.280198	0.147278
31	6	0	-2.190679	-1.981120	0.351418
32	1	0	-1.334606	-1.610549	0.931599
33	8	0	-5.338525	-1.885814	-2.073048
34	1	0	-5.888502	-1.420568	-1.384516
35	6	0	-4.186047	0.301462	-1.908845
36	1	0	-3.834957	1.000393	-2.672812
37	46	0	0.259801	-0.012985	-0.600230
38	15	0	1.116190	2.047827	0.563141
39	15	0	2.469911	-0.976799	-0.018796
40	6	0	2.955338	1.659049	0.980283
41	1	0	3.543093	1.902765	0.087833
42	1	0	3.290472	2.302653	1.801169
43	6	0	3.136136	0.181230	1.356375
44	1	0	2.556327	-0.066363	2.253094
45	1	0	4.185925	-0.035991	1.582411
46	6	0	0.439243	2.443691	2.288334
47	6	0	0.891727	3.537969	3.044808
48	6	0	-0.532585	1.588637	2.830988
49	6	0	0.390419	3.765864	4.330767
50	1	0	1.624139	4.224104	2.630217
51	6	0	-1.028146	1.814576	4.122796
52	1	0	-0.919050	0.760841	2.245476
53	6	0	-0.567538	2.899952	4.874689
54	1	0	0.744778	4.616331	4.905454
55	1	0	-1.772569	1.139871	4.534139
56	1	0	-0.952807	3.074977	5.874573
57	6	0	1.242962	3.748838	-0.248729
58	6	0	2.336420	4.615751	-0.083313
59	6	0	0.180145	4.150931	-1.075597
60	6	0	2.360638	5.861644	-0.723203
61	1	0	3.178533	4.327630	0.537234
62	6	0	0.200044	5.397612	-1.709547
63	1	0	-0.654668	3.474269	-1.232699
64	6	0	1.291366	6.256800	-1.533982
65	1	0	3.213844	6.519394	-0.588249
66	1	0	-0.628010	5.693175	-2.346459

67	1	0	1.311496	7.221756	-2.030533
68	6	0	2.770695	-2.685938	0.719971
69	6	0	4.048656	-3.124452	1.105938
70	6	0	1.668362	-3.538025	0.885100
71	6	0	4.220818	-4.396422	1.661004
72	1	0	4.914159	-2.484893	0.961182
73	6	0	1.844634	-4.812518	1.439877
74	1	0	0.676455	-3.223989	0.579045
75	6	0	3.116501	-5.242546	1.829823
76	1	0	5.212045	-4.728175	1.955213
77	1	0	0.982790	-5.460002	1.557031
78	1	0	3.251408	-6.231466	2.257493
79	6	0	3.791408	-0.844724	-1.366054
80	6	0	5.115096	-0.438132	-1.132247
81	6	0	3.408920	-1.183512	-2.675792
82	6	0	6.038685	-0.377213	-2.183890
83	1	0	5.439757	-0.162451	-0.134182
84	6	0	4.332374	-1.131122	-3.725214
85	1	0	2.382809	-1.479848	-2.870526
86	6	0	5.650379	-0.726937	-3.481405
87	1	0	7.057831	-0.058167	-1.987453
88	1	0	4.021212	-1.399009	-4.730026
89	1	0	6.366427	-0.680470	-4.295854

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Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.096891	-2.686814	0.829248
2	6	0	2.298955	-1.307444	1.477717
3	6	0	3.279901	-1.349757	2.628486
4	8	0	2.806450	-0.318252	0.507349
5	6	0	1.562166	-2.602788	-0.582164
6	8	0	3.411867	-3.358158	-1.442718
7	6	0	1.466961	-1.382306	-1.254778
8	1	0	1.079921	-3.483516	-0.984737
9	6	0	2.087522	-0.223706	-0.697168
10	1	0	1.183389	-1.371335	-2.301927
11	1	0	2.441884	0.600912	-1.293996
12	6	0	3.805248	-2.529460	-2.351881
13	6	0	4.319908	-1.241882	-2.062256
14	8	0	3.617873	-2.887479	-3.657095
15	1	0	4.511871	-0.994467	-1.030351
16	1	0	1.326010	-0.950339	1.838275
17	1	0	4.307998	-1.402064	2.241788
18	1	0	3.076858	-2.245933	3.232773
19	1	0	3.036933	-3.248700	0.788627
20	8	0	1.155410	-3.373500	1.720069
21	6	0	1.208076	-4.828006	1.649368
22	1	0	2.210168	-5.195804	1.903714
23	1	0	0.483305	-5.186601	2.380998
24	1	0	0.934781	-5.199240	0.654840
25	8	0	3.096822	-0.157876	3.434247
26	6	0	3.981615	-0.102900	4.579997
27	1	0	3.734181	0.815535	5.113712
28	1	0	3.826972	-0.963925	5.246367
29	1	0	5.036409	-0.076093	4.271953
30	8	0	4.562718	-0.625141	-4.348723
31	1	0	3.959690	-2.124408	-4.244692
32	6	0	4.709480	-0.349775	-3.094013
33	6	0	5.320607	0.989709	-2.736970
34	1	0	6.373653	1.004338	-3.044528
35	1	0	4.816434	1.786592	-3.295060
36	1	0	5.267125	1.201833	-1.665192
37	46	0	-0.093701	-0.089996	-0.315824
38	15	0	-2.542895	-0.555157	0.022622
39	15	0	-0.609857	2.200031	0.367415

40	6	0	-3.282087	1.173288	0.421724
41	1	0	-3.500706	1.654497	-0.537983
42	1	0	-4.224715	1.054922	0.966963
43	6	0	-2.305609	2.028639	1.242535
44	1	0	-2.092145	1.561689	2.210712
45	1	0	-2.733023	3.016539	1.446532
46	6	0	-3.060909	-1.561595	1.537204
47	6	0	-4.401500	-1.652834	1.947948
48	6	0	-2.069345	-2.233165	2.268614
49	6	0	-4.744394	-2.391738	3.084621
50	1	0	-5.184928	-1.163496	1.376924
51	6	0	-2.415287	-2.970612	3.409519
52	1	0	-1.032895	-2.202862	1.948212
53	6	0	-3.749330	-3.048774	3.820642
54	1	0	-5.783384	-2.458213	3.392381
55	1	0	-1.638155	-3.480723	3.969779
56	1	0	-4.015948	-3.620692	4.703966
57	6	0	-3.674785	-1.183315	-1.348116
58	6	0	-4.982494	-0.711607	-1.549954
59	6	0	-3.166056	-2.171665	-2.207352
60	6	0	-5.768375	-1.225128	-2.589057
61	1	0	-5.396372	0.060214	-0.909148
62	6	0	-3.953536	-2.689265	-3.241231
63	1	0	-2.148264	-2.525571	-2.072630
64	6	0	-5.256892	-2.216403	-3.433801
65	1	0	-6.776342	-0.850219	-2.737333
66	1	0	-3.546908	-3.451491	-3.898066
67	1	0	-5.866534	-2.612751	-4.239439
68	6	0	0.388605	3.235594	1.581773
69	6	0	0.038056	4.559938	1.895023
70	6	0	1.507097	2.650568	2.194973
71	6	0	0.791839	5.287200	2.821407
72	1	0	-0.808643	5.033967	1.408675
73	6	0	2.258599	3.383006	3.123330
74	1	0	1.809757	1.638665	1.951957
75	6	0	1.902991	4.697693	3.439104
76	1	0	0.516332	6.310731	3.056226
77	1	0	3.121720	2.917094	3.585932
78	1	0	2.488888	5.264804	4.155854
79	6	0	-0.979304	3.364344	-1.071383
80	6	0	-2.015039	4.313428	-1.052637
81	6	0	-0.169627	3.266309	-2.215888
82	6	0	-2.231925	5.151235	-2.153793
83	1	0	-2.664048	4.406353	-0.187926
84	6	0	-0.381928	4.106935	-3.313888
85	1	0	0.620711	2.523186	-2.250166
86	6	0	-1.414446	5.051470	-3.284760
87	1	0	-3.037993	5.877869	-2.126534
88	1	0	0.252349	4.018046	-4.189869
89	1	0	-1.583836	5.700135	-4.138124

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