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Glycosylation Formelle de Quinones à partir d'*exo*-Glycals par Transfert d'Atome d'Hydrogène. Application à la synthèse de *C*,*C*-aryl glycosides *via* un réarrangement de type Fries

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Table of Contents

Abbreviations

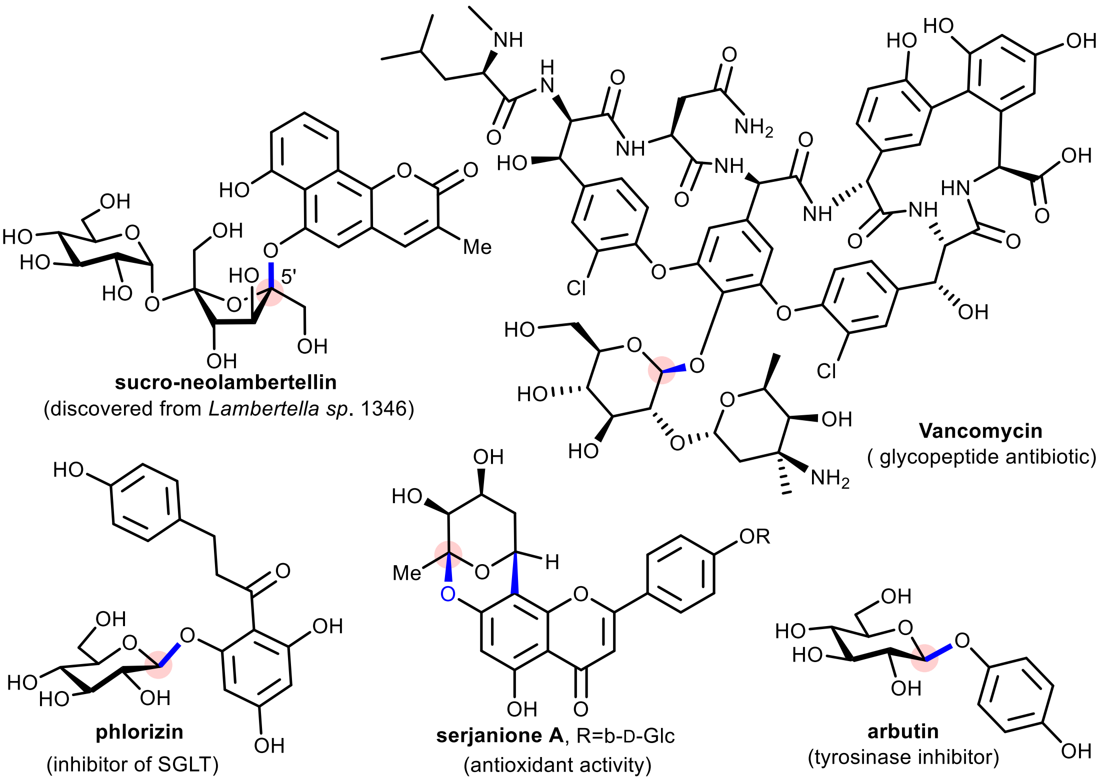
Acac	Acetylacetone
AcOH	Acetic acid
Ac$_2$O	Acetic anhydride
ADDP	1,1'-(Azodicarbonyl)dipiperidine
All	Allyle
AlBN	Azobisisobutyronitrile
Bn	Benzyl
Bz	Benzoyle
CAN	Ceric ammonium nitrate
cat.	Catalyst
CMBP	Cyanomethylenetributylphosphorane
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dba	dibenzylideneacetone
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DCC	*N*,*N'*-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DEC	Diethyl carbonate
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMAP	4-Dimethylaminopyridine
DMPU	*N,N'*-Dimethylpropyleneurea
DMDO	Dimethyldioxirane
DIAD	Diisopropyl azodicarboxylate
dibm	diisobutyrylmethane
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
HBPin	Pinacolborane
HFIP	Hexafluoro-2-propanol
HMPA	Hexamethylphosphoramide
iPr$_2$NH	*N*-(Propan-2-yl)propan-2-amine
IsoQ	Isoquinoline
KO-*t*-Bu	Potassium *tert*-butoxide
LDA	Lithium diisopropylamide
LiTMP	Lithium tetramethylpiperidide
LiHMDS	Lithium bis(trimethylsilyl)amide
***m*-CPBA**	*meta*-Chloroperoxybenzoic acid
MEMCl	Methoxyethoxymethyl Chloride
MOMCl	Chloromethyl methyl ether
***n*-BuBr**	1-Bromobutane
***n*-Bu**	*n*-Butyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide

NaHMDS	Sodium bis(trimethylsilyl)amide
NMO	*N*-Methylmorpholine *N*-oxide
NR	no reaction
Nu	Nucleophile
***o*-Tol**	*o*-tolyl
$PdCl_2$(dppf)	1,1'-Bis(diphenylphosphino)ferrocenepalladium(II)dichloride dichloromethane
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
Pr	Propyle
Py	Pyridine
TBAF	Tetra-*n*-butylammonium fluoride
TBAB	Tetrabutylammonium bromide
***t*-Bu**	*Tert*-butyle
TBS	*Tert*-butyldimethylsilyl
TEA	Triethylamine
TES	Triethylsilane
THF	Tetrahydrofurane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TMSBr	Bromotrimethylsilane
TMSCN	Trimethylsilyl cyanide
TMEDA	Tetramethylethylenediamine
TsOH	*p*-Toluenesulfonic acid
Triton B	Benzyltrimethylammonium hydroxide
Tf_2O	Trifluoromethanesulfonic anhydride
TTBP	2,4,6-Tri-*tert*-butylphenol
4 Å MS	Molecular sieves 4Å
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane

General Introduction

Carbohydrates are the main source of energy for all living organisms to sustain life activities. It is not only a nutrient, but some also have special physiological activities. Glycoconjugates are formed by a sugar part which often plays an important role in increasing vectorization, solubility and biodisponibility, and an aglycon part that mainly promote biological activity. Carbohydrates may thus combine with other chemicals, including lipids, proteins or (hetero)aromatic compounds to form one of the most versatile classes of biomolecules in nature. Among glycoconjugates, *O*-aryl and *C*-aryl glycosides occupy an important position since they have a wide range of applications in drugs, glycobiology, and chemical synthesis. Since the late 1890s,[1] synthetic chemists have been indeed attracted by glycoconjugates in which an aromatic planar sugar group is covalently bonded to a densely functionalized chiral sugar unit with, most commonly, a *O*-glycosidic linkage (**Figure 1**).[2;3]

In aryl *O*-glycosides, the aglycone parts are linked *via* a C-O bond. These glycoconjugates do exhibit a broad spectrum of biological activities. Natural product phlorizin is for example a precursor of the yellow dye POP and a competitive inhibitor of SGLT (Sodium-GLucose Transport protein).[4] The list includes also the antibiotic Vancomycin[5] which is a more complex *O*-glycosylated phenolic cyclic peptide, or the antidiabetic phthalocyanine.[6] The synthetic challenges associated with aryl glycosides depend on the complexity of their structures, ranging from arbutin,[7] a simple phenolic glycoside, which was used in the treatment of hyperpigmentation, to more complex condensed polycyclic systems (**Figure 1**). For example, the natural product serjanione A,[8] which was extracted from the leaves of *Serjania marginata* has antioxidant activities. Structural originality may also arise from unusual linkages between the aromatic aglycone moiety and the sugar moiety, such as in sucro-neolambertellin.[9] This compound, isolated from *Lambertella sp.* 1346, is the first described natural product in which sucrose is oxidized at the C-5' position, allowing it to bind to neolambertellin.



sucro-neolambertellin
(discovered from *Lambertella sp*. 1346)

Vancomycin
(glycopeptide antibiotic)

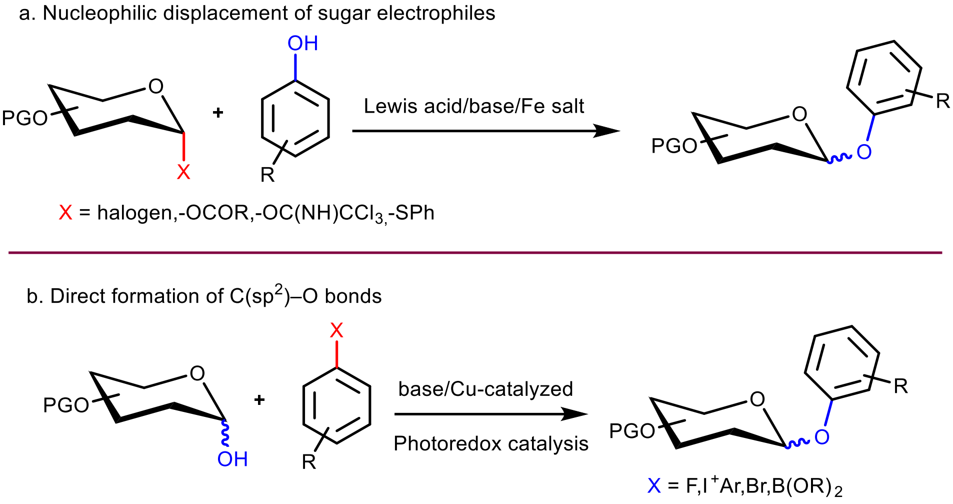
phlorizin
(inhibitor of SGLT)

serjanione A, R=b-D-Glc
(antioxidant activity)

arbutin
(tyrosinase inhibitor)

Figure 1. *Selected O-aryl glycoside products of biological and therapeutic interest.*

For the synthesis of *O*-glycosides,[2;3;10] in the early days of glycochemistry, Michael[11] and Knorr[12] groups reported the synthesis of *O*-aryl glycosides from glycosyl halides and phenols. It was the very first pioneering studies on the construction of glycosidic bonds. Displacement of the leaving group from the anomeric position with a phenol or *O*-phenoxy nucleophile by Jensen,[13] Ellervik's[14] and Molla[15] groups remains a common method for obtaining *O*-aryl glycosides, which have now been intensively explored (**Scheme 1a**). Taylor[2] describes the direct *O*-arylation of hydroxyl and hemiacetal *via* C(sp^2)-O bond formation in 2021 (**Scheme 1b**). Currently, *O*-aryl glycosides have been synthesized with higher efficiency, better stereoselectivity, and more functional group tolerance thanks to the continuous progress in phenolic glycosylation methods.[16-22] It is important to note that there are few precedents concerning the synthesis of *O*-aryl glycosides bearing a quaternary pseudo anomeric carbon.[23;24]



Scheme 1. *(a) Conventional routes to access O-aryl glycosides from activated carbohydrate electrophiles; (b) direct arylation of carbohydrate OH groups.*

Natural products, bioactive compounds or marketed drugs based on a *C*-glycoside motif have also attracted the attention of scientists (**Figure 2**). Structurally, the labile C-O acetal bond is replaced by a stable C-C bond. We can also view it as a mimetic of *O*-glycosides.

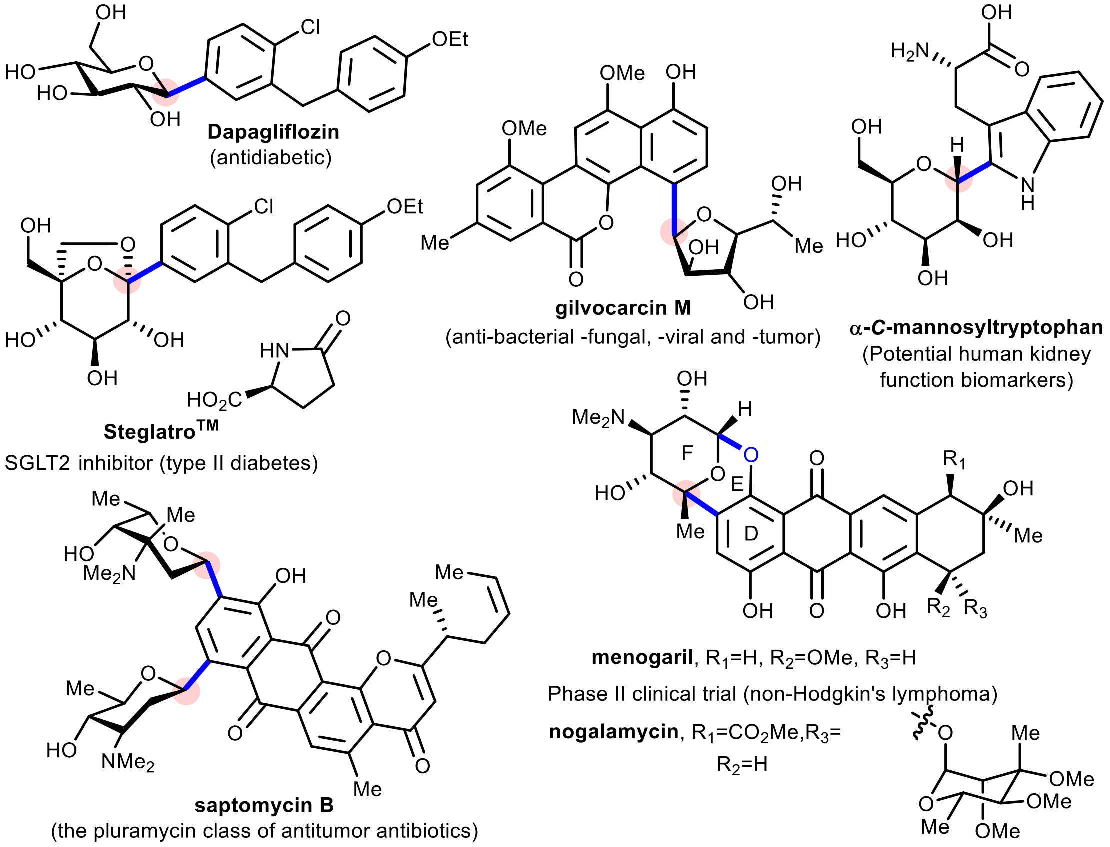
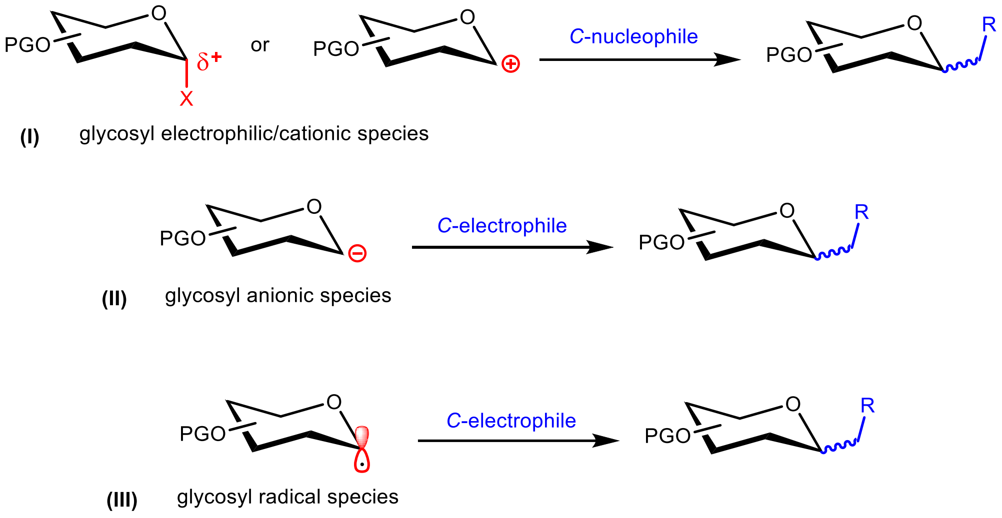


Figure 2. *Selected C-glycosyl compounds of biological and therapeutic interest.*

In aryl *C*-glycosides,[25-27] the aglycone moiety is linked by a *C*-glycosidic bond[28], improving significantly their stability to hydrolases *in vivo*, and their potential as therapeutic drugs and biological probes.[29;30] For example, in recent years, a series of SGLT2 inhibitors against type II diabetes have been developed.[31-33] Among them, Steglatro™[34] and Dapagliflozini[35] improve glycemic control in adults with type 2 diabetes. Furthermore, the total synthesis route of the antitumor, antidiabetic diamino sugar saptomycin B has been reported.[36] Five-membered ring sugar antibiotic gilvocarcin M[37] and α-C-mannosyltryptophan, a potential human kidney function biomarker, were also reported.[38] Various other natural *C*-glycosides have been studied. These studies have been presented in several recent authoritative reviews[25;27;39;40] and will consequently not be detailed in the present report.

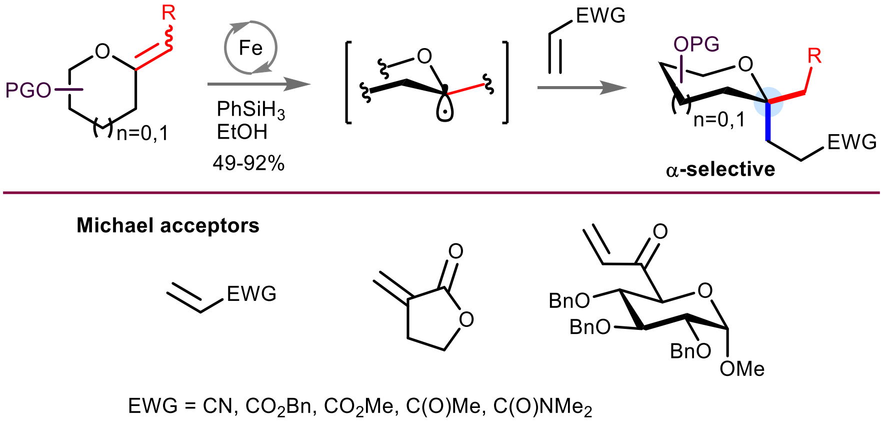
Concerning synthetic strategies towards *C*-glycosides, significant progress has been made over the past decades.[27;41-43] Most methods for building pseudo glycosidic C-C bonds make use of electrophilic/cationic species (route I),[44-46] anionic species (route II),[47-49] or free radicals species (route III) (**Scheme 2**).[42;43;50]



Scheme 2. *General strategies for C-glycosidic bond construction*

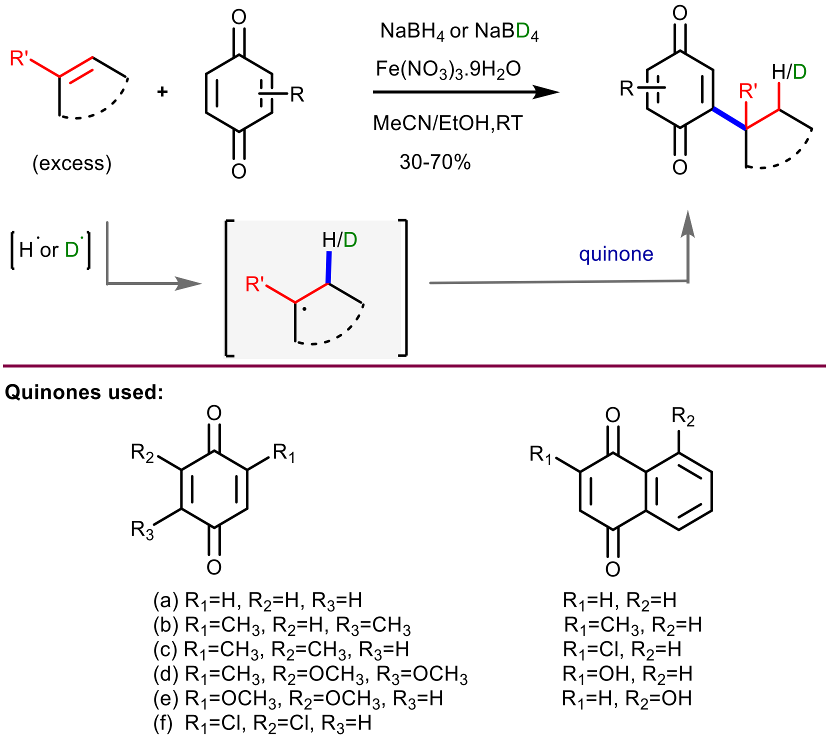
So far, there are a wide variety of methods for synthesizing *C*-glycosides. Among them, *C*-glycosylation with glycosyl radicals as intermediates is particularly attractive due to its following characteristics: (i) mild reaction conditions; (ii) good compatibility with various functions; (iii) no elimination and/or epimerization or other side reactions.[43;50;51] However, in sharp contrast to the numerous approaches targeting *C*-glycosides, only a few are described for the stereoselective construction of quaternary pseudoanomeric carbons to give *C,C*-glycosides, also referred to as *C*-ketosides.[52] Natural *C,C*-glycosides and related synthetic products have a high potential in drug discovery. As examples, we may mention nogalamycin[53] and its synthetic derivatives menogaril[54] or the SGLT2 inhibitor Steglatro™ (**Figure 2**).[34] Notably, there has been no report on the total synthesis of nogalamycin. Therefore, studies on the stereocontrolled construction of *C,C*-glycosides bond are still needed as well as challenging considering the relative complexity of such structures.

In 2019, our group reported a mild, highly stereoselective synthesis of *C*,*C*-glycosides from *exo*-glycals enabled by iron-mediated hydrogen atom transfer (HAT). The stereocontrolled *C*-quaternization of the anomeric center was achieved by trapping transient tertiary pseudoanomeric radicals with a series of Michael acceptors (**Scheme 3**).[55]



***Scheme 3.** Highly stereoselective synthesis of C,C-glycosides from exo-glycals enabled by iron-mediated HAT*

Additionally, Liu *et al*. reported a practical and step-economic Fe(III)-mediated C-H radical alkylation of 1,4-quinones using simple unactivated olefins. A range of biologically active molecules with quinone motifs were obtained by using $NaBH_4$ or $NaBD_4$ (**Scheme 4**).[56]

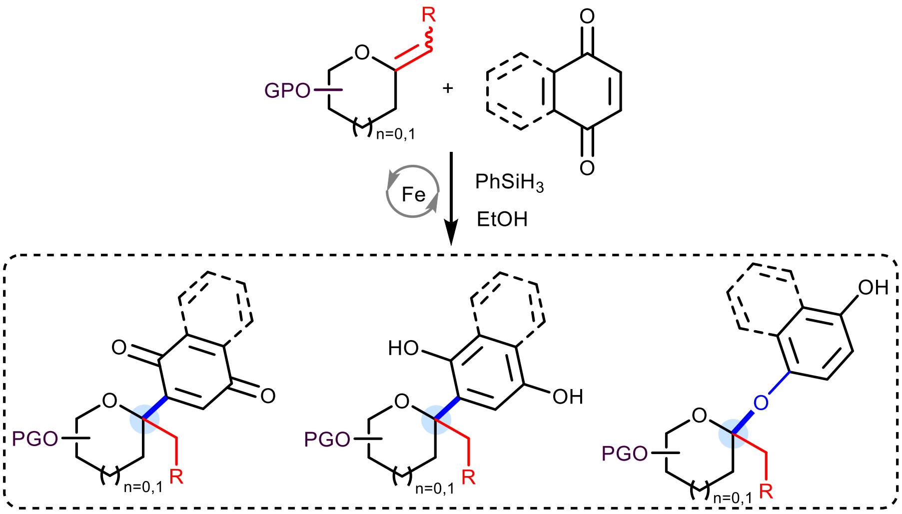


***Scheme 4.** Fe(III)-mediated C-H radical alkylation of 1,4-quinones using unactivated olefins*

The two methods mentioned above gave us the idea of a direct construction of the DEF ring systems of nogalamycin and related compounds from an *exo*-glycal precursor. We were also encouraged by recent advances in HAT-initiated reactions that use inexpensive Fe(III) and Mn(III) complexes to improve the efficiency of HAT from metal hydrides to unactivated alkenes.[57-62]

In order to develop a convergent, step-economical approach to access benzoxocin cores in *C*,*C*- or *C*,*O*-fused glycosyl arenes such as serjanione A or nogalamycin, we envisaged the addition of HAT-induced pseudoanomeric radicals to 1,4-quinones to directly introduce the phenol moiety. The study of efficient methods for the radical alkylation of 1,4-quinones is a very active field of research.[63] The broad biological activities of these compounds and their interest as dye molecules have motivated many research studies.[64] However, synthetic challenges associated with the unique electrochemical properties of 1,4-quinone scaffolds are numerous.

Despite recent progress, many of the methods reported so far suffer from limited substrate scope, regioselectivity issues, and/or harsh reaction conditions.[63] Additionally, there is little precedents concerning the selective coupling of glycosyl radicals with 1,4-quinones.[23;65] The control of the regioselectivity and diastereoselectivity of HAT-mediated coupling involving an *exo*-glycals and a quinone is expected to be very challenging. In a non-selective process, at least six different glycosylation products could be obtained with different stereochemistry, connectivity, or oxidation state (**Scheme 5**). Nevertheless, considering the differences in aromatic ring linkages and sugar moieties in serjanione A, nogalamycine and related compounds (**Figures 1** and **2**), both the C-O bond and C-C bond forming reaction processes are attractive.

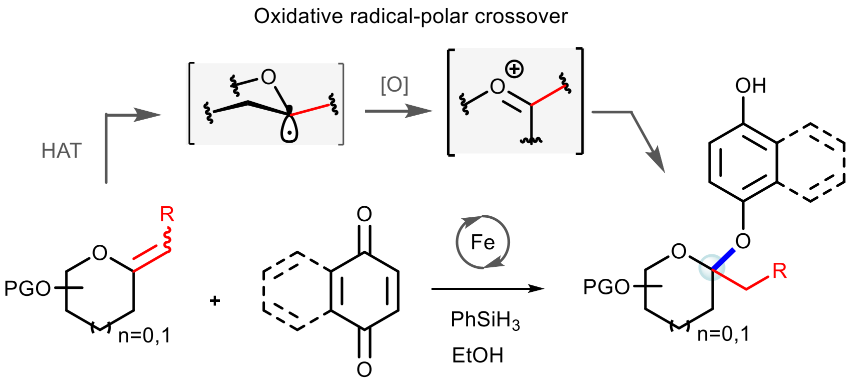


Scheme 5. *Our project for the synthesis of C,C- or C,O-aryl glycosides from exo-glycals and quinones*

My work will be presented in three chapters as follows:

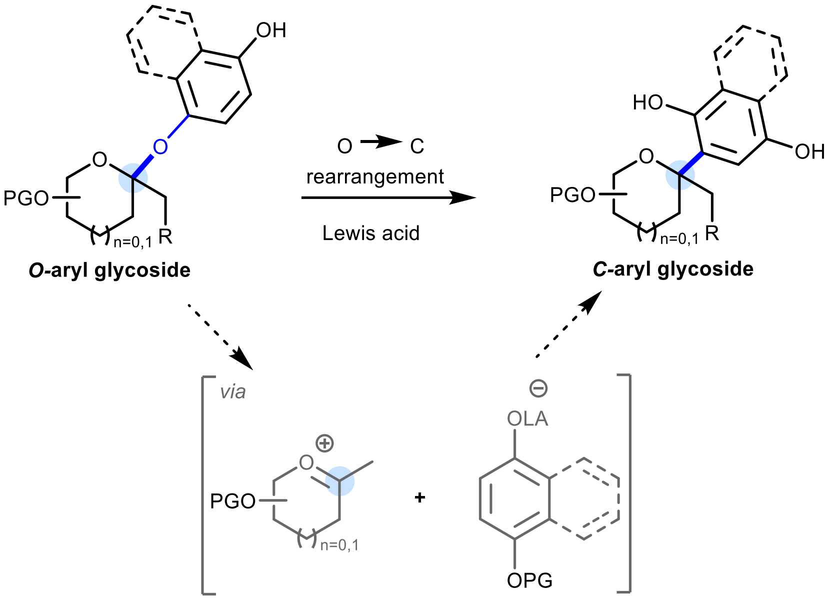
In the **first chapter**, we will present the structures, isolation, and interest of nogalamycin, serjanione A and related compounds. We will focus also on their biological activities and therapeutic interests. Studies towards the synthesis of these compounds will be also described.

In the **second chapter**, we will present HAT reactions and the current research progress on the application of HAT to *exo*-glycals. Then, we will focus on our study concerning the formal glycosylation of quinones by HAT (**Scheme 6**).



Scheme 6. *Formal glycosylation of quinones by HAT*

In the **third chapter**, the application of the Suzuki rearrangement to the phenolic ketosides obtained *via* HAT to give the corresponding *C*,*C*-aryl glycosides will be presented (**Scheme 7**).



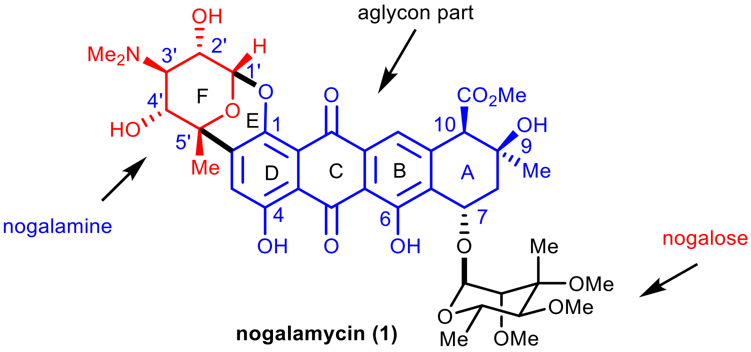
Scheme 7. *The proposed mechanism of Suzuki rearrangement*

Chapter 1: Nogalamycin/serjanione A and related compounds

1. Nogalamycin and related compounds

1.1. Overview of research on nogalamycin

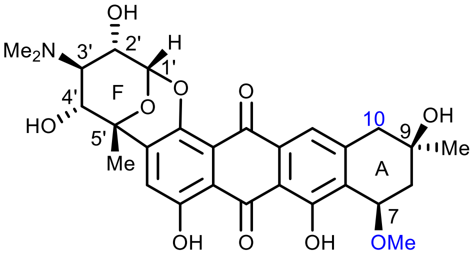
Nogalamycin (**Figure 3**), a unique member of the anthracycline natural product family, was found from the organism *Streptomyces nogalator* in 1965 by Bhuyan and Dietz for the Upjohn company.[66] This natural compound is a highly active antibiotic in the fight against gram-positive bacteria and KB cells, *in vitro*. Its structure has been confirmed through analysis of some spectral data as well as structural analysis of degradation products.[53;67] Studies have shown that nogalamycin has potent biological activity which requires two carbohydrate units: nogalose and nogalamine that located in the minor and major grooves of DNA, respectively.[68;69] Both nogalamycin and the DNA molecules undergo a change in conformation in order to maximize hydrogen bonding, electrostatic and van der Waals interactions. The interaction induces highly specific topoisomerase I-mediated DNA cleavage, which plays an antitumor role.[70]



nogalamycin (1)

Figure 3*. Structure of nogalamycin*

However, nogalamycin also shows a prominent cytotoxicity against L1210 and KB cell lines *in vitro* and have a weak activity against solid tumors *in vivo*. In addition, nogalamycin was not accepted by the National Cancer Institute because its unacceptable toxicity in large animals.[71] Its semi-synthetic derivative, 7-*con*-*O*-methylnogarol (menogaril) (**Figure 4**), has a stronger antitumor activity and lower cytotoxicity. So it was selected to be evaluated in clinical trials.[71] However, menogaril does not appear to have sufficient antitumor activity in this study. Consequently, phase II trials were stopped.[72]



7-*con*-*O*-methylnogarol (2)
(menogaril)

Figure 4. *Structure of menogaril*

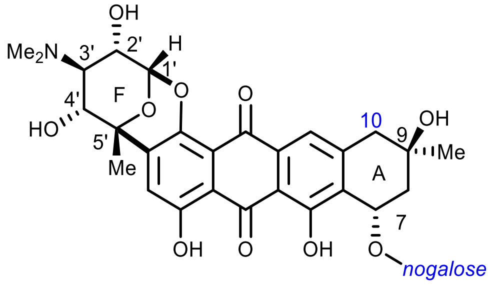
Interestingly, nogalamycin and its derivatives contain an original DEF-benzoxocin ring system. In this family of molecules, an original sugar −nogalamine −, and an aromatic polyketide aglycone part are connected through an *O*-glycosidic and an aryl *C*-glycosidic bonds leading to the formation of a DEF ring system. These interesting structures as well as their promising antimicrobial and antitumor activities have attracted the attention of many chemists. The total synthesis of nogalamycin has still not been reported. Interestingly, the successful report of total synthesis of menogaril encouraged chemists to continue research on the total synthesis of nogalamycin.[54;73] Until now, most research on the synthesis of nogalamycin has focused on the construction of the DEF-benzoxocine ring system by using different methods to increase the yield and improve the regioselectivity.[73-79] In addition, while some chemists are working on the total synthesis of nogalamycin, chemical biologists are studying on the biosynthesis of this natural product and its analogues.[80-83]

In this chapter, I will first introduce the biological activity of nogalamycin and its congeners. Then, I will describe the progress made in the total synthesis of these molecules. Finally, I will discuss on the biosynthesis of nogalamycin.

1.2. Exploration of biological activity relationship of nogalamycin and its related compounds

1.2.1. Structure of nogalamycin and selected related compounds

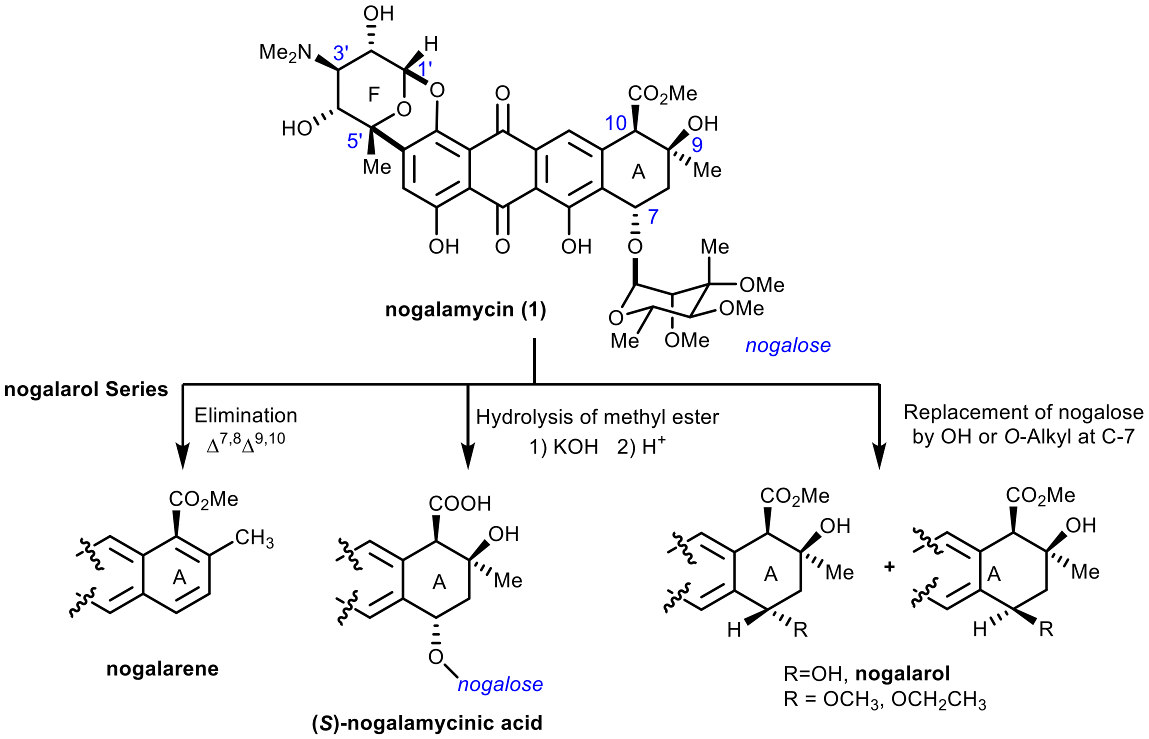
At first, as we have seen above, nogalamycin has been isolated from the fermentation broth of *Streptomyces nogalater* by Wiley in 1968.[53] In 1982, Wiley *et al.* reported a structure-activity relationship study based mainly on degradation products of nogalamycin.[71] About 60 derivatives were obtained during this work. Selected degradation products and analogs of nogalamycin will be presented and compared with nogalamycin (**1**), 7-*con*-*O*-methylnogarol (**2**) and disnogamycin (**3**) in order to further understand and analyze the biological activity of these compounds.[84]

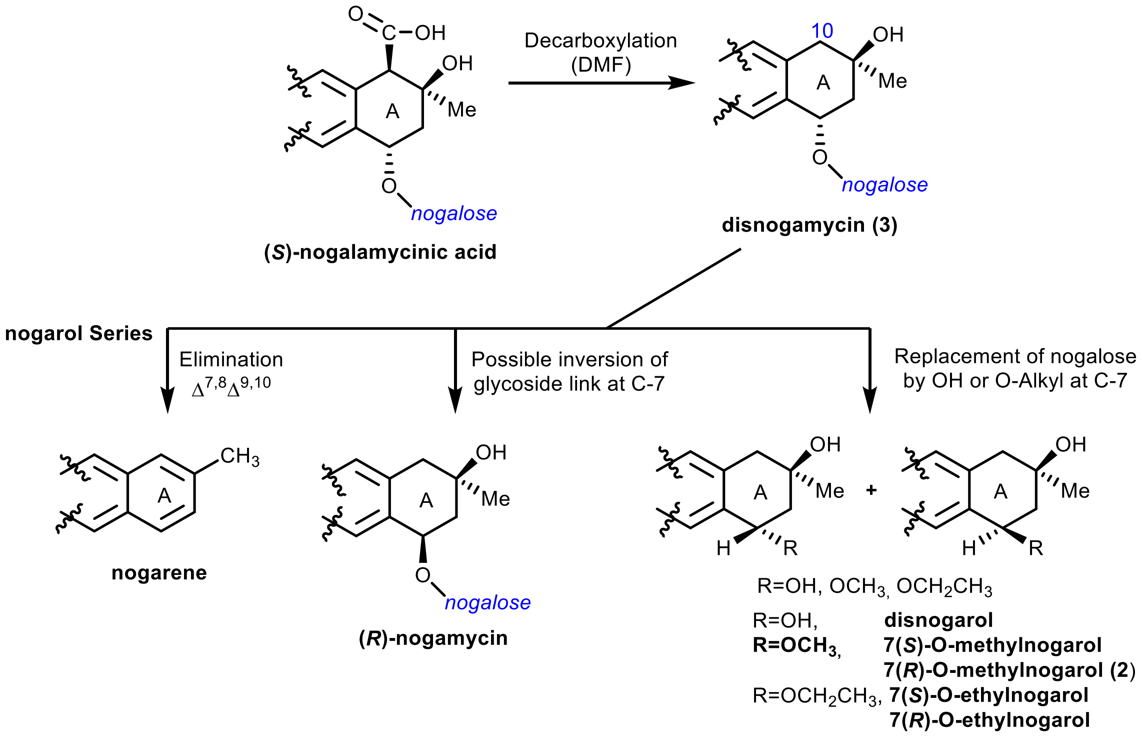


disnogamycin (3)

***Figure 5**. Structure of disnogamycin*

The partial chemical degradation pathway originating from nogalamycin and the structure of its derivatives are shown in **Scheme 8**.[85] Under heating conditions, the elimination reaction of nogalamycin at positions C7/C8 and C9/C10 gives nogalarene. Under various acidic conditions, the cleavage of the glycosidic bond in nogalose afforded nogalarol and *O*-alkyl derivatives (OCH_3, OCH_2CH_3). In addition, the saponification of nogalamycin, afford (*S*)-nogalamycinic acid. Decarboxylation of (*S*)-nogalamycinic acid gives disnogamycin, which is treated using the above-mentioned conditions to obtain the corresponding "noga" derivatives. It is important to emphasis here that derivatives that retain the carboxyl group at the C10 position are referred to as "nogala" while those without this function are referred to as "noga".[71;84]





Scheme 8. *Chemical degradation pathway, structure, and nomenclature of nogalamycin derivative*

Moreover, compound **6**, an acetylated analogue of nogalamycin, was also chosen to study the effect of the group at C-2' and C-4' on the biological activity (**Figure 6**). Also, compounds **4**, **5**, **6** and **7** play an important role in the study of the effect of different substituents at the C-3' position and different configurations at the C-9 position on the activity of nogalamycin and related compounds. Both cororubicin and viriplanin D contain oligosaccharide fractions. The effect of the size of the saccharide chain on the biological activity of the compound has also been studied.[86]

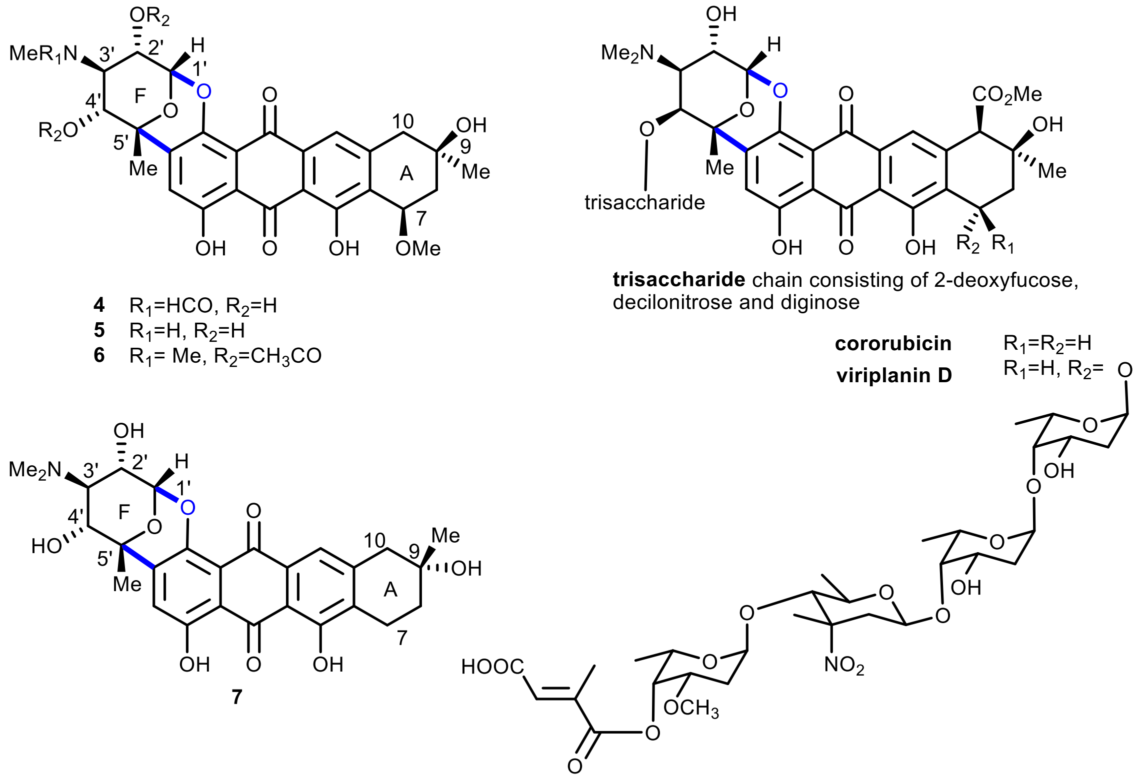


Figure 6. Structures of selected congeners of nogalamycin

In conclusion, the degradation and modification of nogalamycin occur mainly at the C-7, C-9, C-10 positions of the A ring and at C-3’ and C-2’/ C-4’ positions of the amino sugar moiety. The specific degradation process has been detailed in a series of publications from Wiley *et al.* between 1968 and 1982.[53;71;84]

1.2.2. Antitumor activity and cytotoxicity of nogalamycin and selected related compounds

Structure-activity relationship study of nogalamycin reported by Neil[87] and Wiley[71;84;88] revealed interesting insights. Compared to nogalamycin, nogalamycinic acid was much less potent and somewhat less effective against L1210 leukemia, whereas disnogamycin (**3**) was equally or more effective against L1210 leukemia. This study points the way for scientists to investigate the synthesis of related bioactive products. In addition, compared to disnogamycin (**3**), methylnogarol **2** and its derivative bearing a methoxy group at C-7 showed stronger biological activities. Compounds **4** and **5** have much lower *vitro* activities than their dimethylamino analogue **2**. No significant in *vivo* antitumor activity against P388 murine leukemia was observed for **7**. This phenomenon suggests that the methoxy group at the C-7 position plays an important role in enhancing the biological activity. The length of the sugar chain did not correlate with the potency of *in vivo* antitumor activity.

Strikingly, from experiments reported by Li,[89] we can clearly see that menogaril (**2**) has most significant cytotoxicity compared to other nogalamycin degradation products (**Table 1**). The IC_{50} of 7(*R*)-*O*-methylnogalarol was obviously higher than that of menogaril. This result suggests that the ester group at the C-10 position has an obvious toxicogenic effect in L1210 leukemia. The cytotoxicity of the derivatives was markedly diminished when the nogalose of disnogamycin (**3**) at the C-7 position was replaced by a hydrogen atom or functional groups such as NH_2, $CH_3OCH_2CH_2NH$, N_3 in L1210 cells. Relevant data have been also reported by Wiley in 1982.[71] The replacement of an OH group by an acetate at C-2' and C-4' in compound **6** had little effect on cytotoxicity against P388 Murine Leukemia Cells. In the case of the aureolic acid antibiotic chromomycin A3, its trisaccharide stabilizes the dimeric drug-metal complex which binds to DNA.[90] Seto and co-workers isolated cororubicin, a new anthracycline antibiotic, from *Micromonospora* sp. JY16[91] and viriplanin D, the photo-oxidation product of viriplanin A.[92]

Table 1. *Cytotoxicity of nogalamycin and its Derivatives*[71;85;89]

Cell growth assay[a] **L1210 leukemia**		
compound	IC_{50} (µg/ml)	IC_{90} (µg/ml)
nogalamycin	0.078	0.18
(*S*)-nogalamycinic acid	1.00	1.94
disnogamycin	0.18	0.27
7(*R*)-*O*-methylnogalarol	0.13	0.30
7(*R*)-*O*-methylnogarol	0.033-0.061	0.068-0.091
7(*S*)-*O*-methylnogarol	0.41	0.91

[a]Drug concentration required for 50% and 90% inhibition of cell growth in culture (at 37 °C for 3 days)

1.3. Progress in the total synthesis of nogalamycin and related compounds

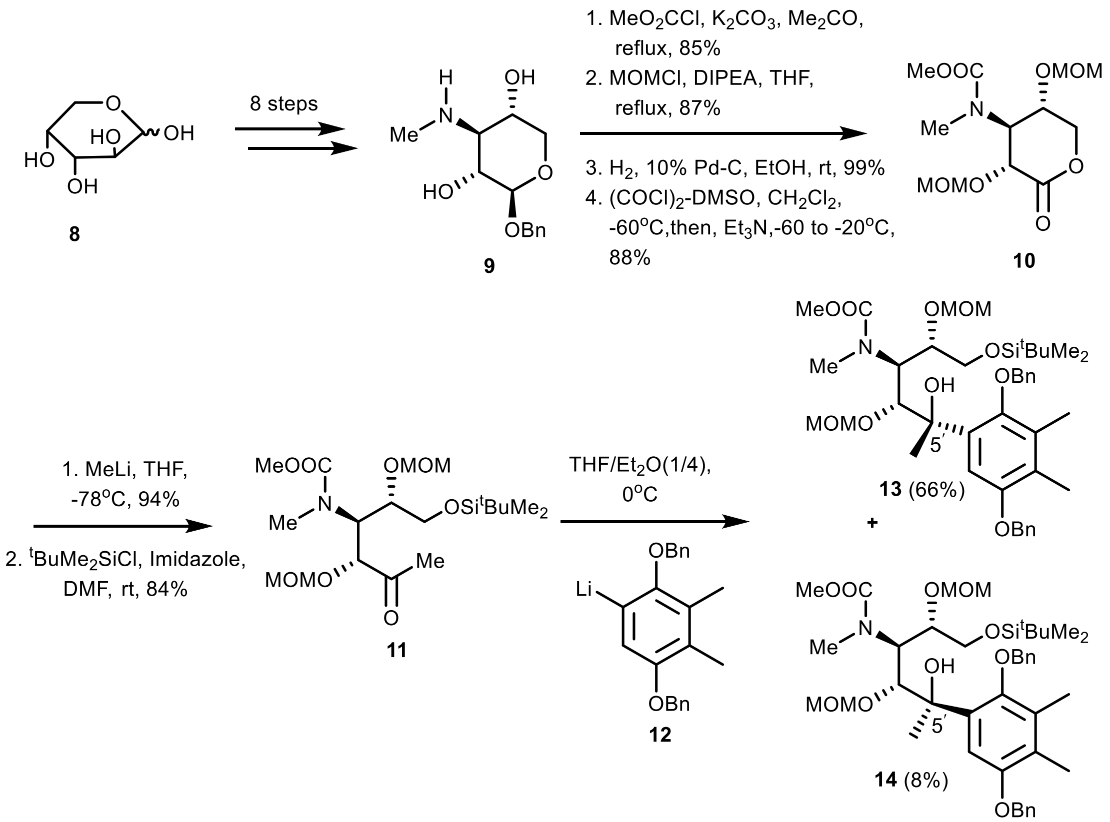
So far, the total synthesis of nogalamycin (**1**) has not been reported. It is likely to be due to the complexity of its structure which contains a complex, fused carbohydrate-based benzoxocin motif and several quaternary asymmetric centres that make the synthesis very challenging. However, the total synthesis for its semisynthetic derivative, menogaril (**2**), has been reported by Terashima[54] and Hauser.[73] Furthermore, other analogues of nogalamycin were also synthesized,[93] for example (+)-nogarene and (+)-7-deoxynogarol (see **Scheme 8**). Nogalamycin and its analogues contain the ABCDEF ring system which was constructed mainly through Diels-Alder reaction[93-97] and Hauser annulation.[98] The selective formation of the CDEF-benzoxocin ring in which the sugar residue is joined to the aromatic moiety *via* both glycosidic and C-C bonds to form a benzoxocin ring system represent certainly one of the major synthetic challenge associated to the synthesis of nogalamycin.

In the following part, methods to access the CDEF-benzoxocin ring systems will be introduced first. The formation of the ABCDEF ring and some precedents will then be presented.

1.3.1. Construction of the CDEF-ring system of nogalamycin

1.3.1.1. Works by Terashima

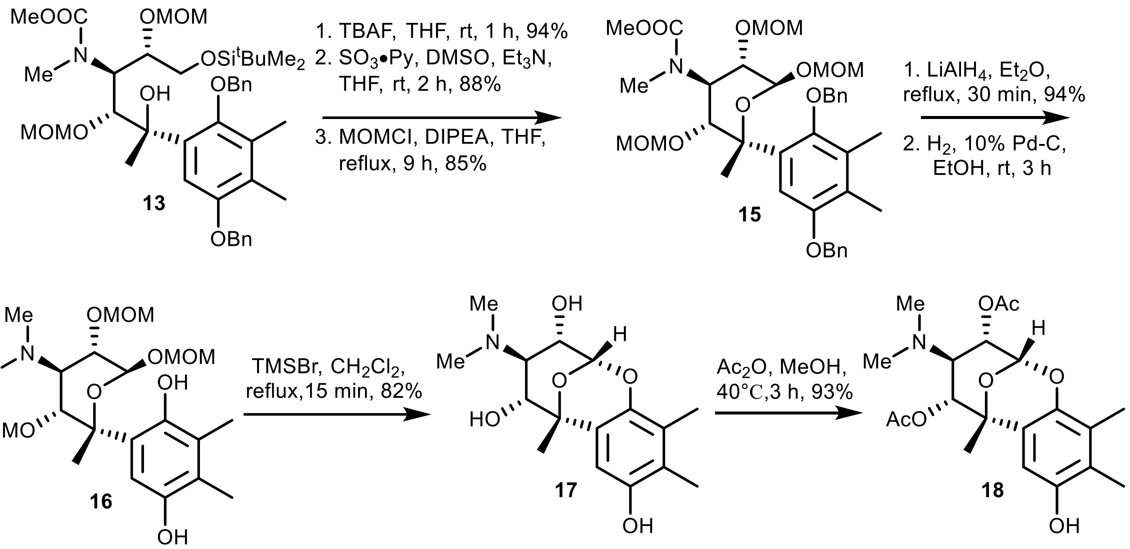
Terashima *et al.* were the first to achieve the synthesis of the nogalamycin DEF-ring system in the mid-1980s.[76;99] Their synthesis began with the 8-step preparation of methyl β-D-gentosaminide **9** from D-arabinose following the synthesis route reported by D. J. Copper (**Schemes 9** and **10**).[100] Then, lactone **10** was obtained through the protection of methylamine and two hydroxyl groups, followed by debenzylation and Swern oxidation. Addition of methyllithium to **10** followed by silylation, gave ketone **11**. In order to obtain the C5'-asymmetric center of nogalamycin, the nucleophilic addition reaction of **12** to ketone **11** was studied using different conditions. The optimized conditions shown below afforded the desired product **13** in 66% yield. The corresponding C5’ epimer **14** was obtained in 8% yield **(Scheme 9)**.



Scheme 9. *Synthesis of key intermediate* ***13***

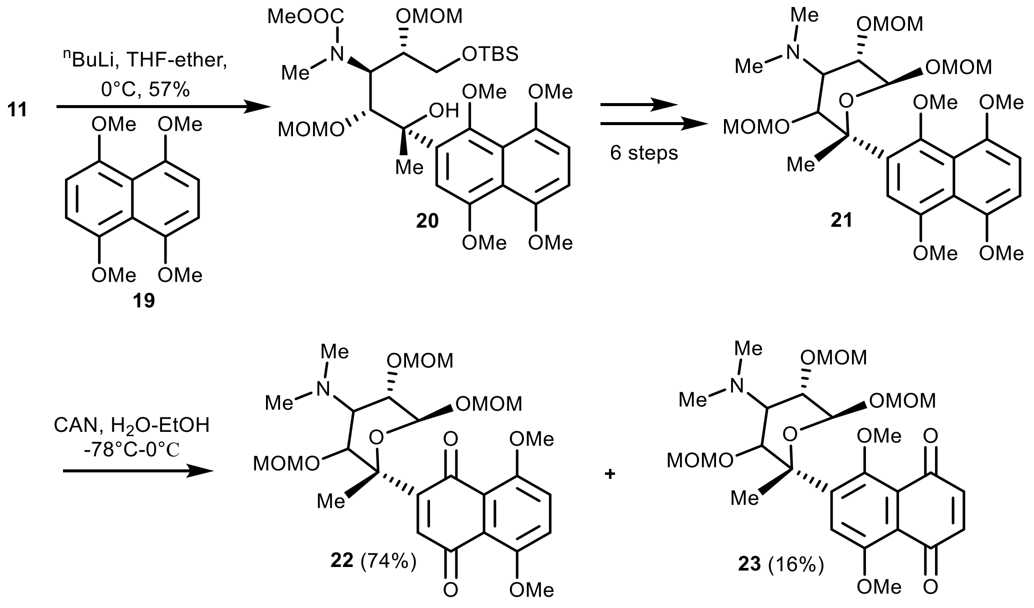
After desilylation of the desired product **13**, the resulting product was subjected to Parikh-Doering oxidation, followed by protection of the formed hemiacetal to give compound **15** (**Scheme 10**). The reduction of compound **15** with lithium aluminium hydride followed by debenzylation afforded the unstable *p*-hydroquinone **16**. Finally, DEF fragment (+)-bicyclic acetal **17** was obtained by exposing **16** to trimethylbromosilane, a process in which three methoxymethyl ethers were neatly cleaved and intramolecular acetal formed. In addition, selective acetylation of the two hydroxyl groups of compound

17 at C-2’ and C-4’ produced **18**.



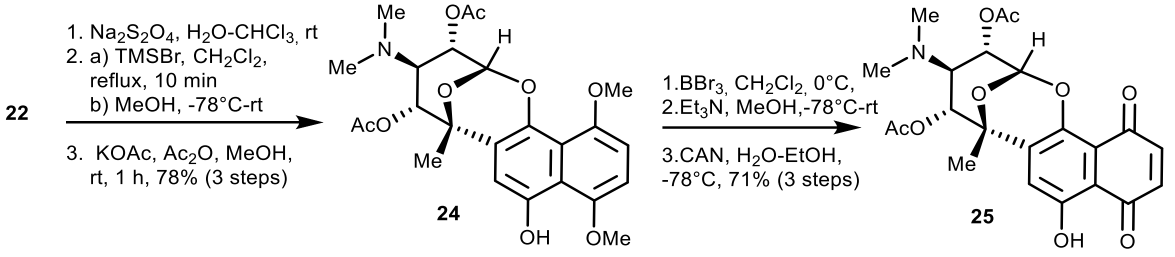
__Scheme 10.__ Formation of DEF ring system reported by Terashima et al.

A few years later, based on previous studies, this group improved the synthetic strategy for this fragment (DEF), allowing the CDEF-ring system of nogalamycin to be constructed (**Schemes 11** and **12**).[93] The ketone **11** was coupled with compound **19** in the presence of *n*-BuLi to produce the desired tertiary alcohol **20** and its minor $C_{5'}$-epimer (57:4) in a good yield. Intermediate **21** was obtained in 6 steps following a sequence similar to the one described above (**Schemes 9** and **10**). Compound **21** was oxidized by cerium ammonium nitrate (CAN) to give the desired naphthoquinone **22** as the major product along with the minor regioisomer **23** (**22**:**23**=74:16).



__Scheme 11.__ Synthesis of key intermediate __22__

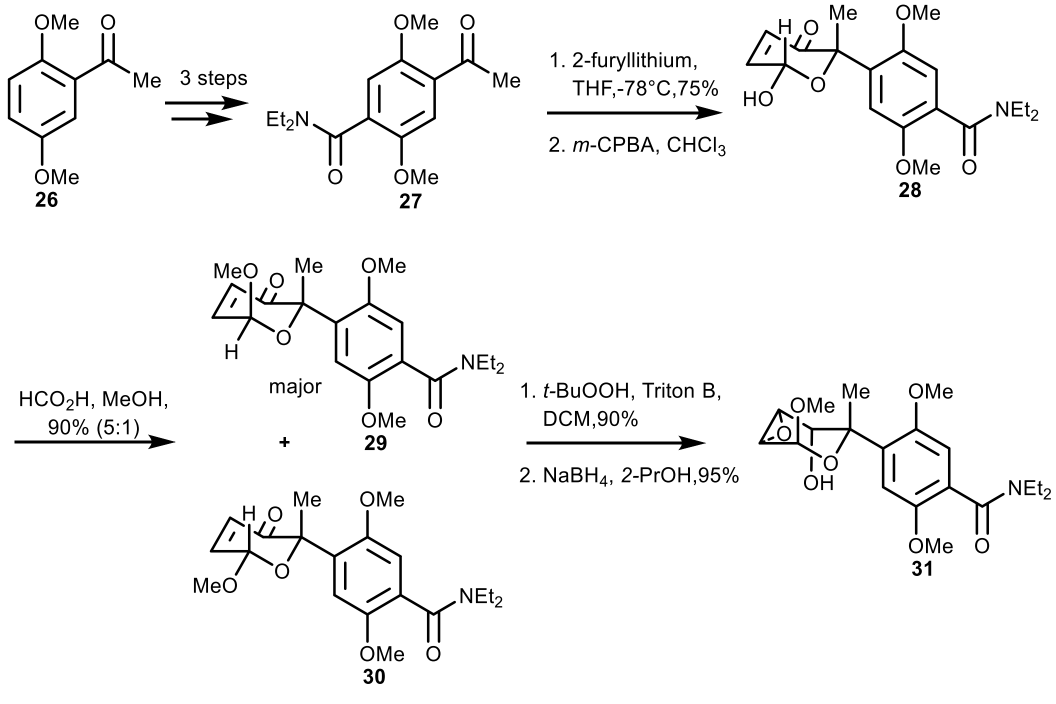
Then naphthoquinone **22** is reduced and undergoes essentially the same process as above (**Scheme 10**) to give acetal **24**. Then, the *p*-methoxy group was deprotected and further oxidized to give naphthoquinone **25**. Thus, the CDEF ring was created by the methodology described by Terashima *et al.* Naphthoquinone **25** is a promising intermediate for further functionalization leading to nogalamycin and its analogues (see below).



Scheme 12. *Synthesis of the CDEF-ring system reported by Terashima et al.*

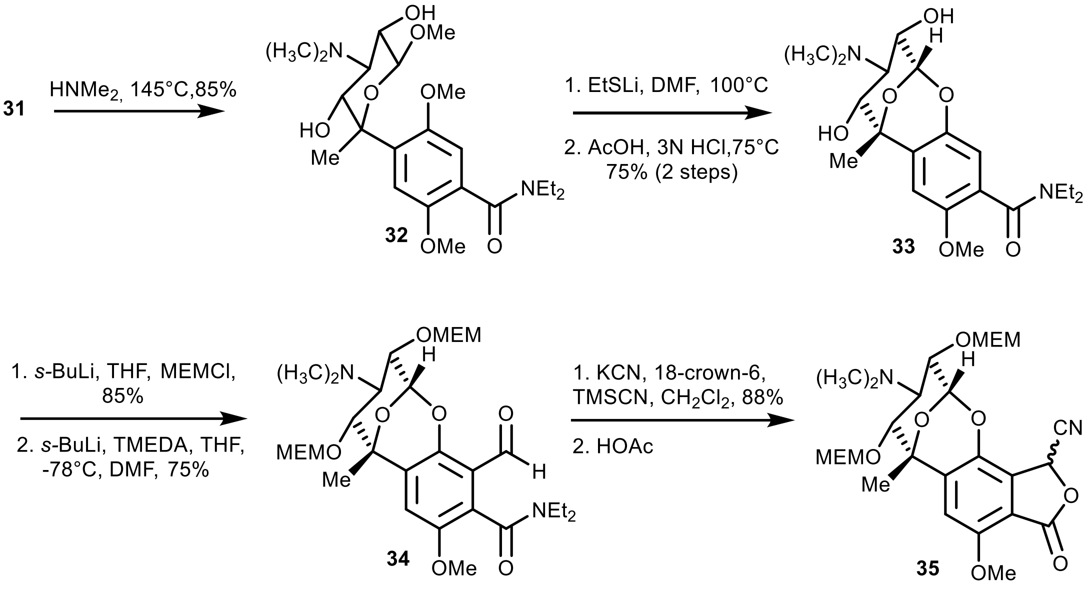
1.3.1.2. Works by Hauser

In 1991, Hauser[73] *et al.* reported a racemic synthesis of the DEF-ring system of nogalamycin from commercially available 2,5-dimethoxyacetophenone (**26**) (**Schemes 13** and **14**). The diethylamide **27** was obtained in 63% overall yield *via* sequential ketalization ($HOCH_2CH_2OH$, PhH, TsOH), metalation (*s*BuLi, TMEDA, THF) and then reaction with diethylcarbamoyl chloride. Furyllithium was added to **27**, at which point the intermediate obtained was further oxidized to obtain the hexenulose **28**. The methylated products **29** and **30** (5:1) of **28** were epoxidized and isolated at this step to obtain the major product, which was further reduced to give compound **31**.



Scheme 13. *Synthesis of key intermediates* ***31***

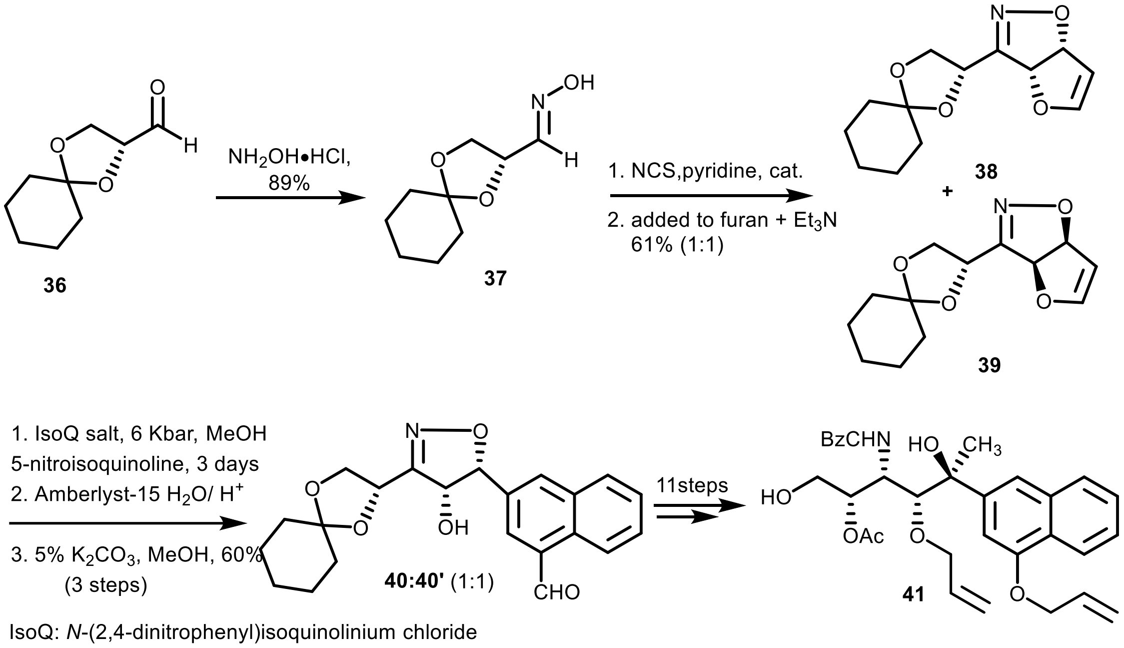
The ring opening of the oxirane **31** in the presence of dimethylamine is regio- and stereospecific and the amino diol **32** is obtained. The intramolecular cyclisation of the regioselective demethylation product of **32** gives **33**. After protection of the hydroxyl groups, compound **33** underwent metalation to give aldehyde **34**. And then, the CDEF-ring system in **35** is achieved directly *via* a method reported by Yoshii *et al.*[101]



Scheme 14. *Formation of CDEF-ring system reported by Hauser et al.*

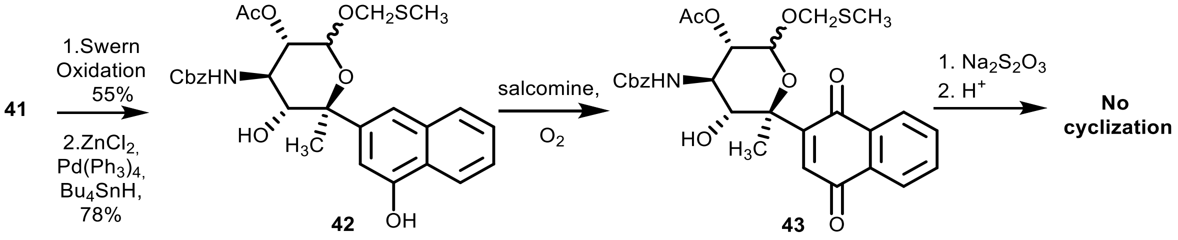
1.3.1.3. Works by Yin

In 1991, Yin *et al.*[77] studied the formation of the CDEF-benzoxocin ring systems of analogues of nogalamycin by using two key cycloadditions involving the regioselective addition of nitrile oxide with furan and the Bradsher cyclization reactions (**Schemes 15** and **16**). The furoisoxazoline **38** was easily prepared by the known furan-nitrile oxide cycloaddition method,[102-104] using cyclohexylidene glyceraldehyde[105] **36** as the chiral pool source for the nitrile oxide. In this process, **37** is first chlorinated to give the final precursor of the desired oxide nitrile. Following this, furoisoxazoline **38** and its epimer **39** (1:1) were obtained in the presence of furan and triethylamine. These two isomers were not separated. Then, the regioselective Bradsher cycloaddition occurred at 6 Kbar using 5-nitroisoquinoline as a soluble acid scavenger. The choice of a soluble base was critical because more basic amines catalyzed the addition of methanol to the isoquinolinium salt, forming an unreactive pseudobase. After a 3-day reaction period, workup *via* acid hydrolysis and base-catalyzed aromatization afforded the desired naphthaldehydes **40** and **40’** (1:1). Following this, the key intermediate alcohol **41** was obtained by careful purification during the 11-step reaction.



Scheme 15. *Formation of key intermediate **41***

Alcohol **41** is oxidized to give the corresponding (methylthio)methyl glycoside intermediate, followed by palladium-catalyzed tributyltin hydride reduction with cleavage of the bis-allyl ether to give the cyclized product alcohol **42**. Naphthol **42** was then easily oxidized to naphthoquinone, using salcomine and oxygen.[106] The final step in their synthesis required the reduction of naphthoquinone **43** to naphthohydroquinone with $Na_2S_2O_3$ as reductant and the construction of the E ring by acid-catalyzed cyclisation.[107] However, the naphthoquinone **43** obtained could not be converted to naphthohydroquinone.



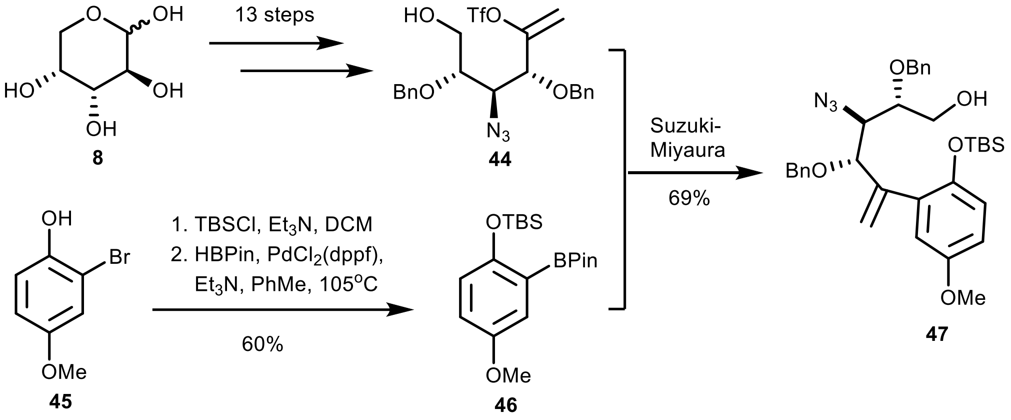
Scheme 16. *Formation of CD-ring and EF-ring precursor reported by Yin et al.*

1.3.1.4. Works by VanNieuwenhze

1.3.1.4.1. Suzuki-Miyaura cross-coupling reaction

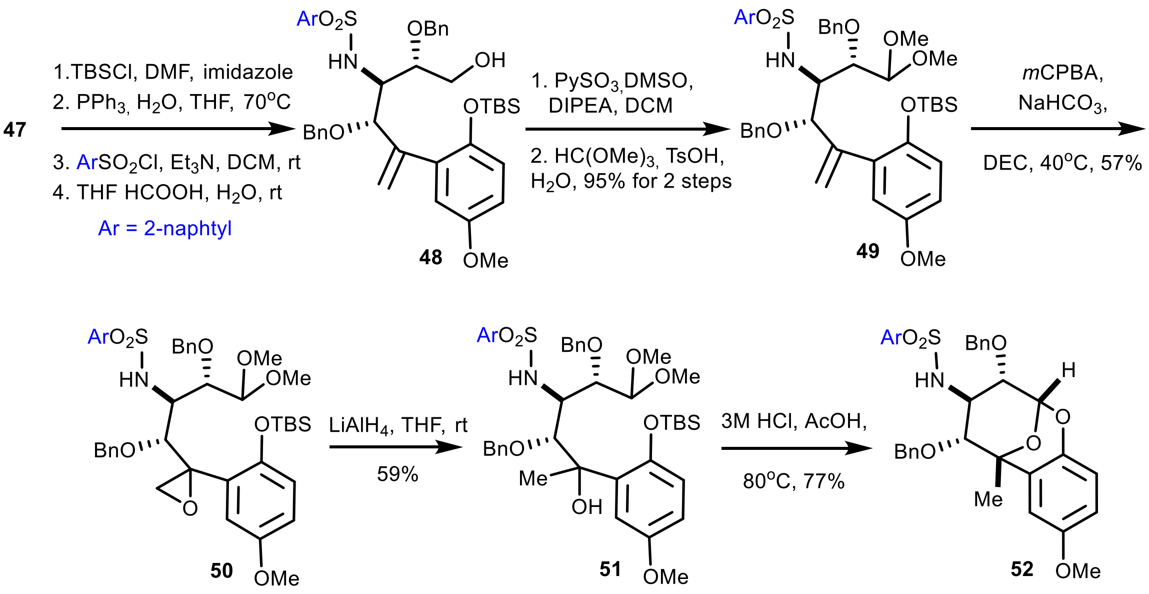
It is well known that the Suzuki-Miyaura cross-coupling reaction[108] is a very useful palladium-catalyzed reaction in the formation of C-C bonds. In 2017, the group of VanNiewenhze[78] developed a new route for the synthesis of DEF-ring system using Suzuki-Miyaura reaction.

First, enol triflate **44** was synthesized in 13 steps using readily available D-arabinose (**8**) (**Scheme 17**), whose chirality was harnessed to generate the carbohydrate moiety of the DEF-ring system. The D-ring precursor **46** is obtained in two steps by protection of phenol **45** with TBSCl, followed by formation of the BPin ester. Finally, the D-ring precursor **46** and the F-ring precursor **44** were linked together by way of a Suzuki-Miyaura reaction. This reaction condition was then further optimized, culminating in the desired product **47** being obtained in 69% yield using 0.1 eq $PdCl_2$(dppf) as the catalyst and 1 M KOH.



Scheme 17. *Formation of Suzuki-Miyaura cross-coupling product **47***

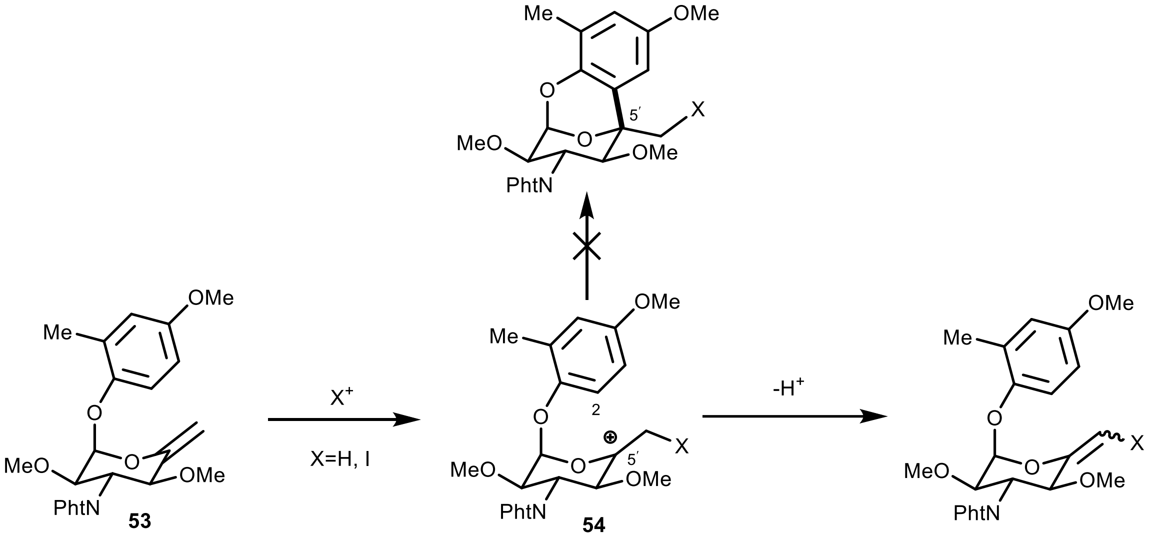
After that, the hydroxyl group in **47** was protected using TBSCl, the azide group of this resultant product was then reduced and the resulting amine was protected with 2-naphthalenesulfonyl, after which the TBS protecting group of the primary alcohol was selectively removed under weakly acidic conditions to give compound **48**. Compound **48** is then oxidized to an aldehyde which is protected to give the corresponding dimethyl acetal **49**. The epoxidation product **50** is obtained with *m*-CPBA as a single diastereomer, although the absolute configuration of this product was not determined. Reduction of the epoxide **50** afforded tertiary alcohol **51** in a modest yield by using excess of $LiAlH_4$. Finally, compound **52** was obtained by intramolecular cyclisation of alcohol **51** under acidic conditions.



Scheme 18. Formation of the DEF-ring via Suzuki-Miyaura reaction

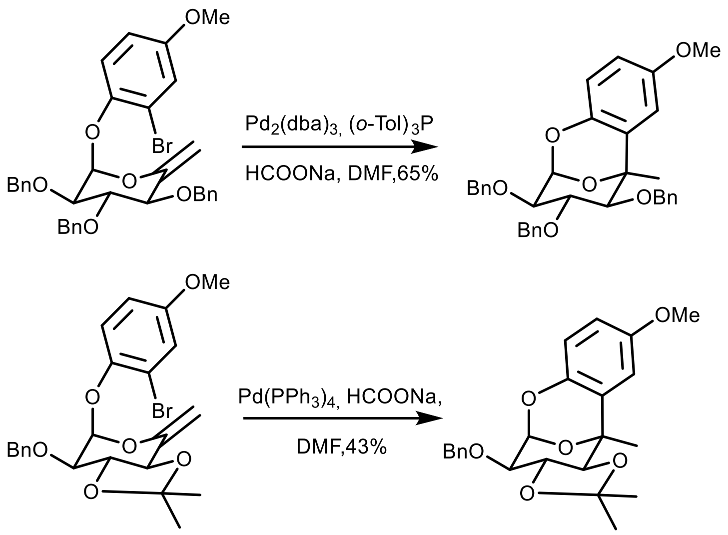
1.3.1.4.2. *Via exo*-glycals

In the 1980s, Smith's group[109] tried to construct nogalamycin DEF-ring system by using *O*-glycosyl compounds **53**. They obtained cation **54** by treating the olefin with a proton source (TFA) or a positive halogen donor such as NBS or iodonium dicollidine perchlorate. Their objective was the formation of the C-C bond between C-5' of the amino sugar residue and C-2 of aromatic ring. However, they did not get the desired product (**Scheme 19**).



Scheme 19. Previous attempts towards the DEF-ring system of nogalamycin

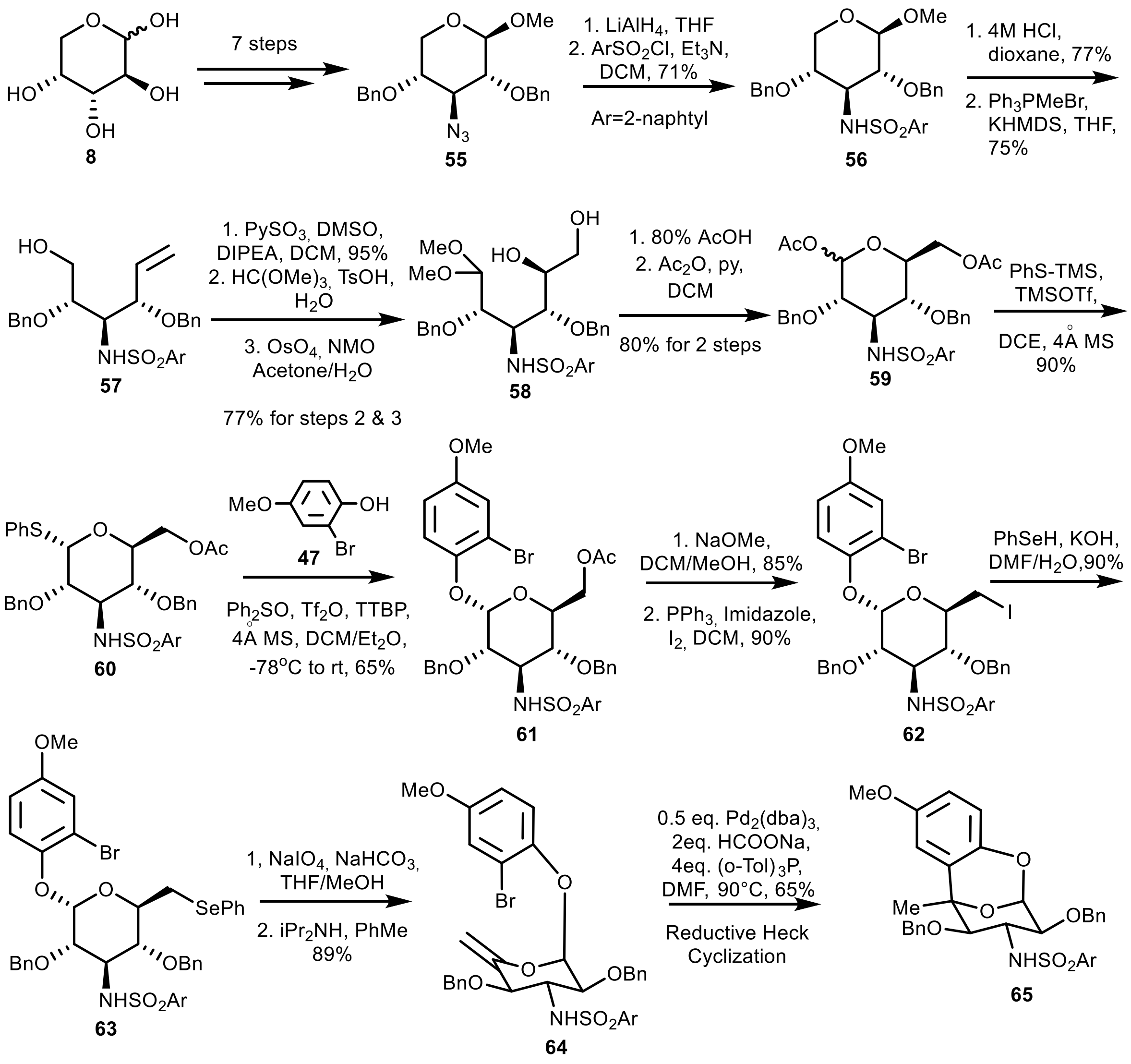
In 2012, a model DEF-benzoxocin ring system was successfully constructed by the VanNieuwenhze group[110] through a reductive Heck cyclization approach. The key intermediates were shown in **Scheme 20**.



Scheme 20. *A model study for the construction of the DEF-ring system of nogalamycin via reductive Heck cyclization*

In 2019, based on the success of their model study, VanNieuwenhze *et al.* turned their attention to the synthesis of the synthesis of the DEF-ring fragment of nogalamycin.[111] Details of the synthesis process can be found in **Scheme 21**. First, for the preparation of the F-ring, compound **55** was synthesized in 7 steps following previous precedents in the literature.[99] To avoid side reactions, azide **55** was reduced by LAH to the corresponding primary amine. The resulting intermediate was then protected by 2-naphthalenesulfonyl to give compound **56**. The alkenol **57** was obtained after hydrolysis and Wittig olefination. Hydroxyl group in **57** is oxidized into the corresponding aldehyde under Parikh-Doering conditions, followed by protection into dimethoxy acetal and dihydroxylation of the olefin affording compound **58** in high diastereoselectivity. Cyclisation under acidic conditions and diacetylation furnished compound **59**. Subsequently, thioglycoside **60** as a pure α-anomer was obtained after thioglycosylation of **59**. Under the glycosylation conditions reported by van der Marel, the desired α-glycoside **61** was obtained in 65% yield from thioglycoside **60** and phenol **47**. Iodide **62** was obtained by deacetylation of **61** and iodination of the corresponding alcohol. Since olefin **64** cannot be obtained directly from iodide in the presence of DBU or AgF, the phenylselenide intermediate **63** was prepared by way of selenide substitution using PhSeH and KOH. The selenide **63** undergoes a two-step reaction (oxidation and elimination) to give the olefin **64** in high yields. With the obtention of this key intermediate **64**, the desired tricyclic compound **65** was obtained through the reductive Heck cyclization reported in the model study presented above (**Scheme 20**).

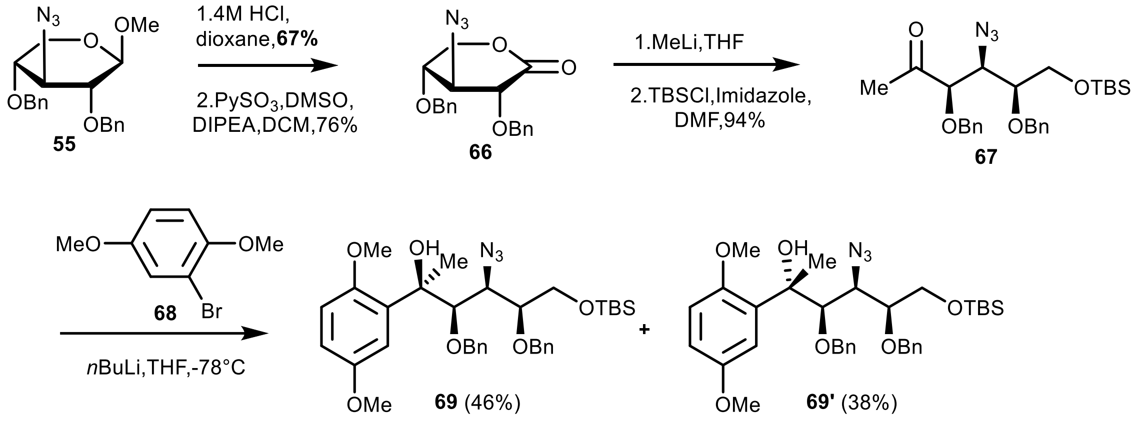
This study proved that the formation of the nogalamycin DEF-ring segment *via* Heck cyclization is feasible. Of note, the anomeric effect helps to facilitate the construction of the tricyclic system with the desired absolute configurations at the ring junctions.



Scheme 21. *Formation of the DEF-ring via Heck reaction*

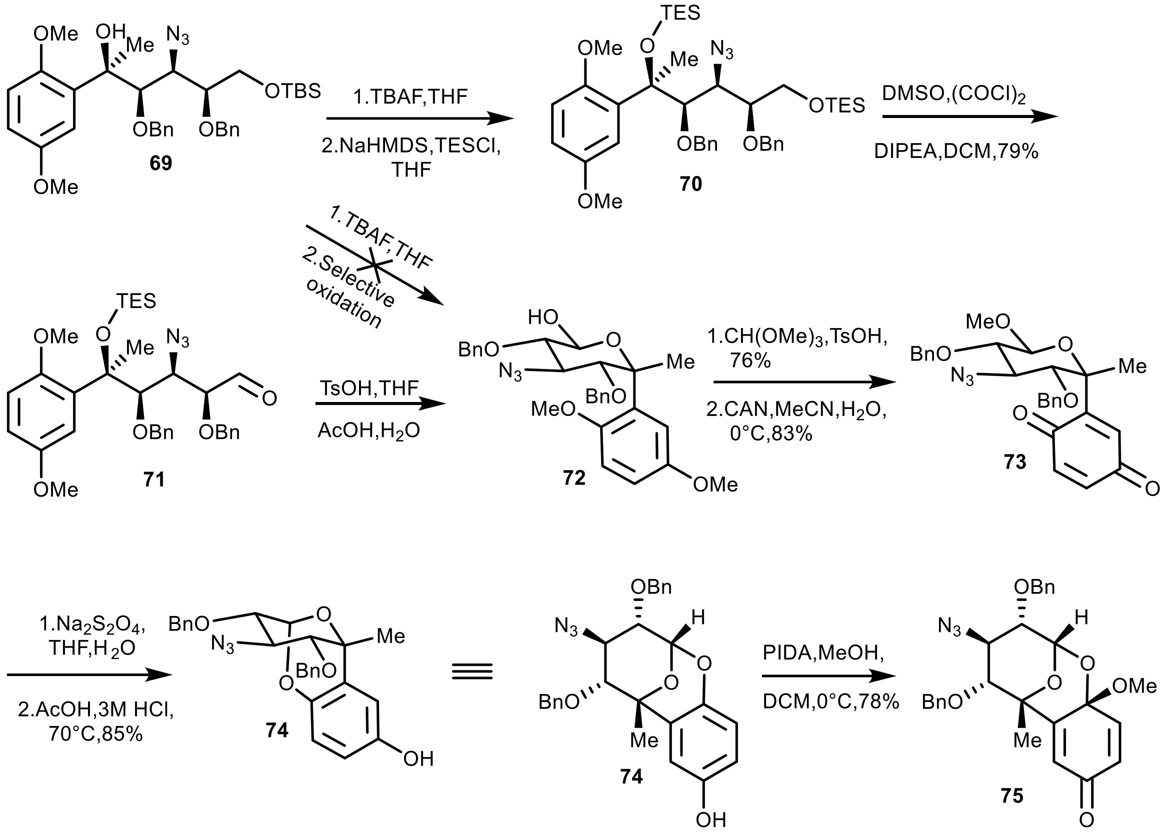
1.3.1.4.3. A modified route from Terashima's work[99]

In 2019, VanNieuwenhze 's team developed a more efficient access to the DEF-ring fragment [79] from azide **55** (**Schemes 22** and **23**). The lactone **66** is obtained by a 2-step sequence (hydrolysis of **55** and subsequent oxidation). Afterwards, the obtained lactone is reacted with MeLi to give a hemiketal intermediate that is selectively protected by TBSCl to give the ketone **67**. Addition of a lithium derivative of compound **68** to this ketone, gave the desired tertiary alcohol diastereomer **69** as the major product.



Scheme 22. *Formation of compound* ***69***

Initially, the authors tried to obtain lactol **72** by direct oxidation of the primary alcohol, after deprotection of **69**, but this sequence was not successful (**Scheme 23**). They next selected TESCl as a reagent for the protection of the two alcohol groups to obtain compound **70**. The primary TES ether **70** obtained was then oxidized under Swern conditions[112] to give the aldehyde **71** in a good yield. Then, the silyl group in **71** was deprotected by *p*-toluenesulfonic acid and the tertiary alcohol obtained was cyclized *in situ* to give the *C*-glycosyl compound **72**. The hydroxyl group in **72** was protected and subsequently oxidized to give quinone **73**. After reduction, the hydroquinone intermediate was cyclized under acidic conditions to give the DEF-ring fragment precursor **74**. Then, DEF-ring fragment **75** was synthesized by dearomatization using (diacetoxyiodo)benzene (PIDA) and MeOH. Compound **75** was used as a key intermediate in the synthesis of the ABCDEF-ring of nogalamycin and its analogues (see below).



__Scheme 23.__ Formation of the DEF-ring system in __75__

1.3.2. Construction of the ABCDEF-ring system of nogalamycin

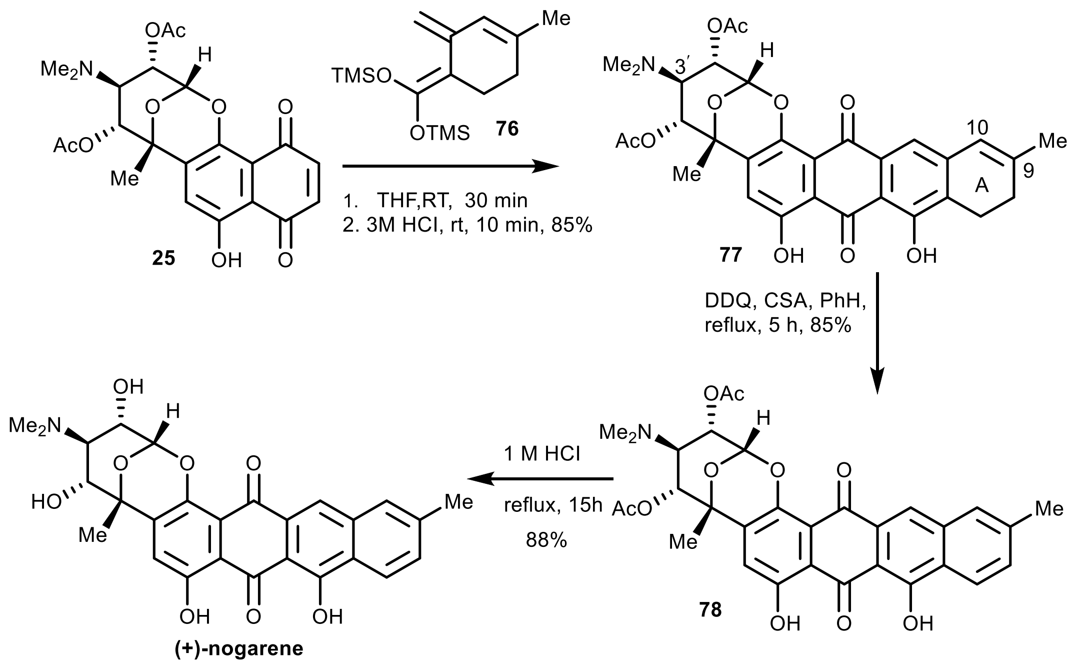
Another key challenge in the total synthesis of nogalamycin and its congeners is to design strategy for the connection of the DEF-ring and AB-ring moieties. Over decades, chemists have worked two main reactions to achieve this goal: the Diels-Alder reaction and the Hauser Annulation reaction.

1.3.2.1. By Diels-Alder reaction

The Diels-Alder reaction is a chemical reaction between a conjugated diene and a dienophile. In this reaction, two new carbon-carbon bonds can be constructed simultaneously, providing a reliable route to six-membered structures with usually good regio- and diastereocontrol. This method has been used by several chemists to connect the DEF-ring and AB-ring moieties in the total synthesis of nogalamycin analogues.[93] These studies are a good source of inspiration for future works on the total synthesis of these molecules.

1.3.2.1.1. Total Synthesis of (+)-nogarene

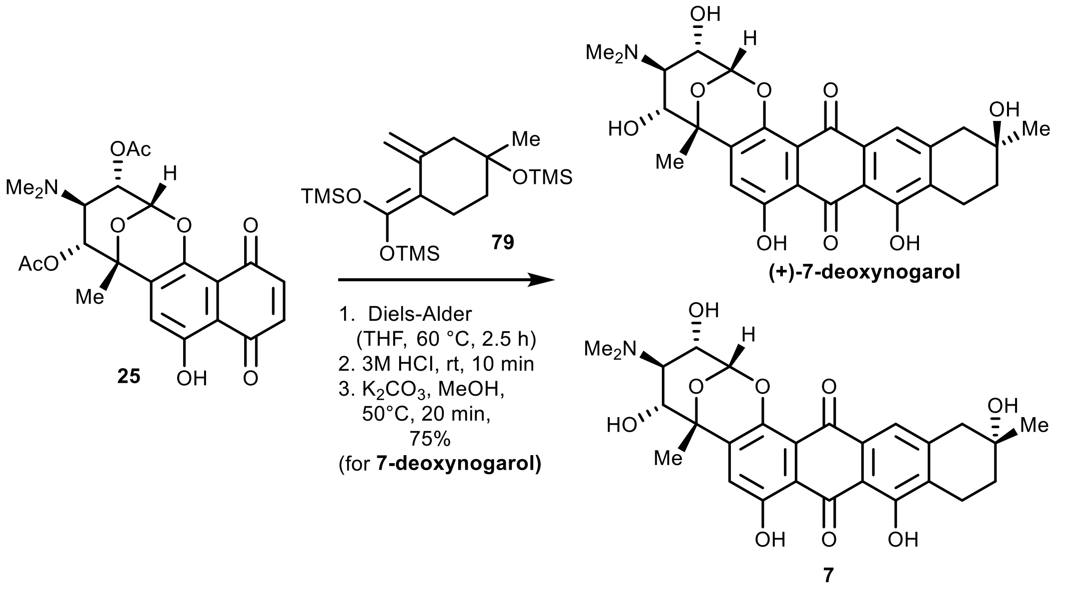
First, a route to the total synthesis of the simplest nogalamycin congener, (+)-nogarene, was developed by Terashima[54] (**Scheme 24**). The tetracyclic compound **25** (**Scheme 12**) was reacted with the optimized bis(trimethylsilyloxy)diene **76**, followed by treatment under acidic conditions to give (+)-2',4'-di-*O*-acetyl-7,8-dihydronogarene (**77**). Dehydration of **77** with 2,3-dichloro-5,6-dicyano-l,4-benzoquinone (DDQ) in the presence of CSA afforded compound **78** which was transformed to (+)-nogarene after deprotection.



Scheme 24. Total synthesis of (+)-nogarene

1.3.2.1.2. Total Synthesis of (+)-7-deoxynogarol

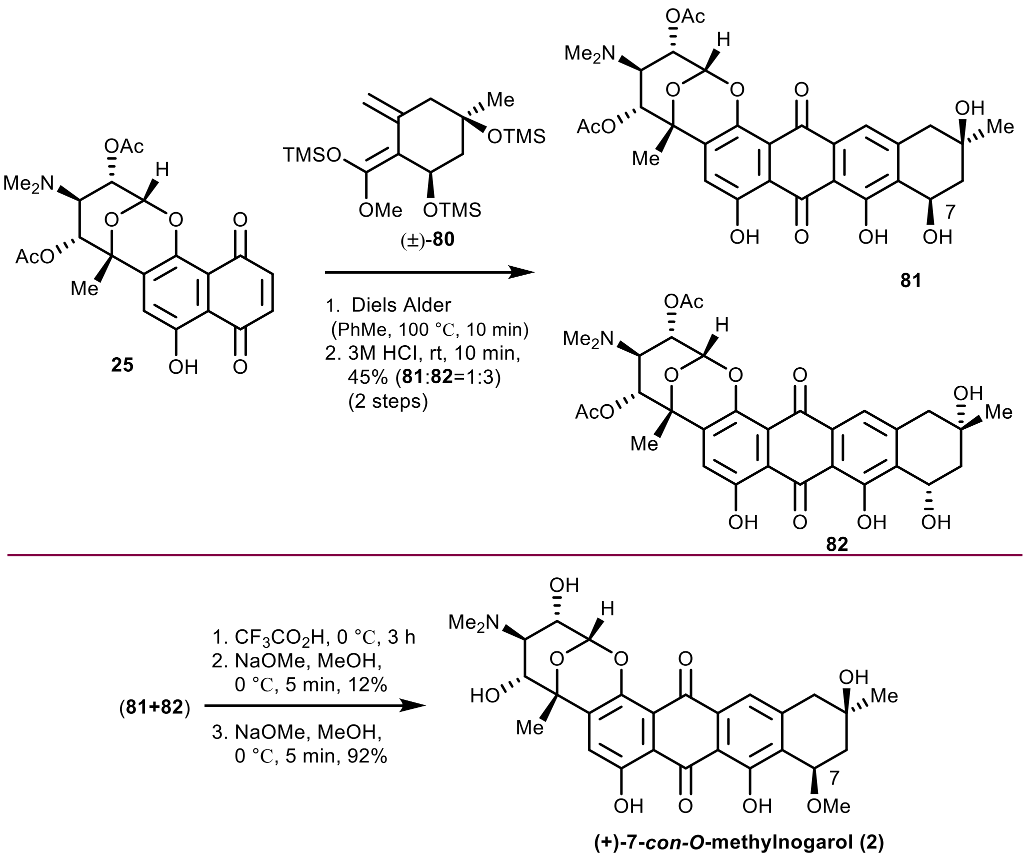
Next, the total synthesis of (+)-7-deoxynogarol, a more highly functionalized congener of nogalamycin was synthesized,[54] on the basis of the total synthesis of nogarene. Initially, it was expected that the A-ring of (+)-7-deoxynogarol could be readily constructed by functionalization of the A-ring of **77**. However, when oxidative reactions of the C_9-C_{10} double bond of **77** were carried out under a variety of conditions, complex mixtures were always found, mainly due to preferential oxidative removal of the C3’-dimethylamino group. The (+)-naphthoquinone **25** was thus reacted with the new functionalized diene **79**. The Diels-Alder product was then oxidized to give a pair of stereoisomers in lower yields. After separation, these two isomers were deacetylated to give the natural product (+)-7-deoxynogarol and the unnatural (+)-9-*epi*-7-deoxynogarol **7**, respectively (**Scheme 25**).



Scheme 25. *Total Synthesis of (+)-7-deoxynogarol*

1.3.2.1.3. Total Synthesis of (+)-7-*con*-*O*-methylnogarol

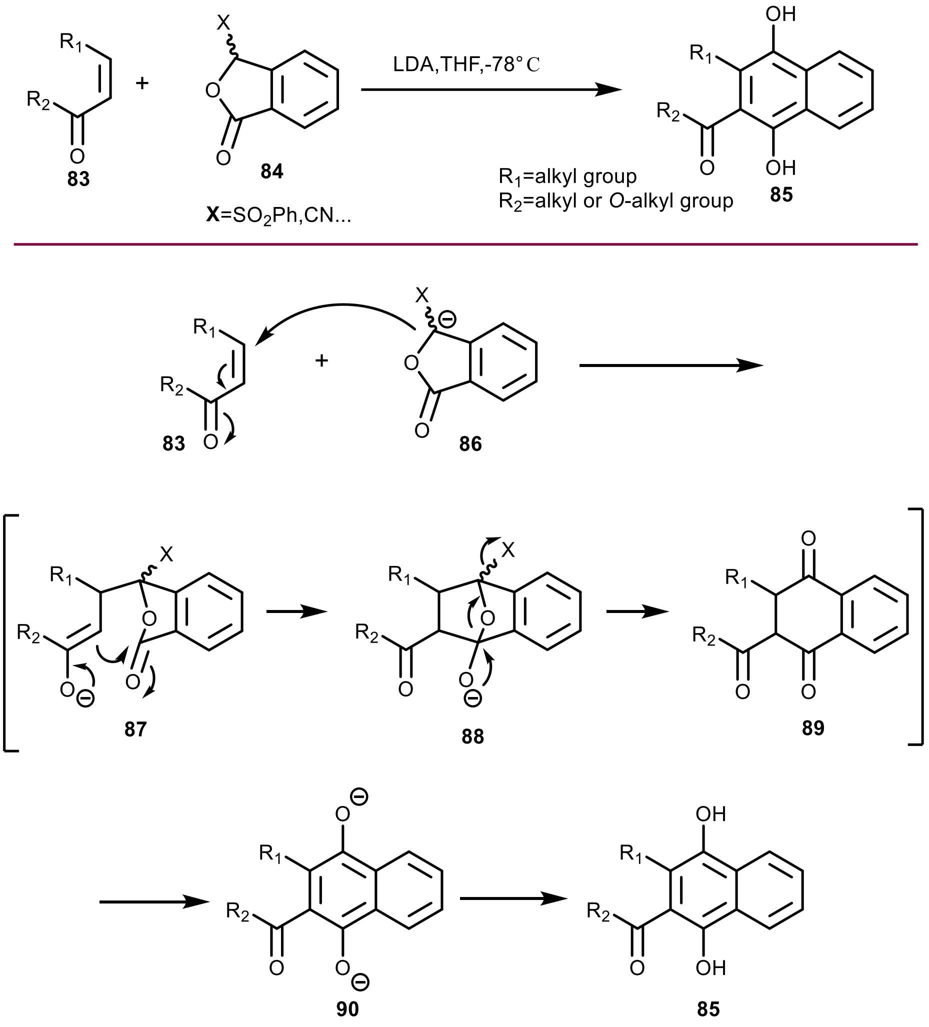
Experimentally, it was demonstrated that severe difficulties were encountered in the preparation of dienes such as **79** due to their increased tendency towards aromatization. After many attempts, functionalized diene **80** was nevertheless obtained. Subsequently, **80** underwent a Diels-Alder reaction with (+)-naphthoquinone **25** at 100 °C (**Scheme 26**). The resulting addition products were oxidized giving a mixture of 2',4'-di-*O*-acetyl-*con*-nogarol **81** and 2',4'-di-*O*-acetyl-7,9-di-*epi*-*con*-nogarol **82** (dr=1:3). Of note, if the reaction temperature is lowered to 60 °C, the reaction is slower and give a higher diastereoisomeric ratio (1:10) in favor of the undesired compound **82**. The mixture of **81** and **82** is engaged in the next synthetic sequence. The methoxy group at position C-7 is selectively introduced by a method reported by Wiley.[84] The obtained mixture is separated by TLC on silica gel in the second step. After deprotection, (+)-7-*con*-*O*-methylnogarol (**2**) was obtained (**Scheme 26**).



Scheme 26. *Total synthesis of (+)-7-con-O-methylnogarol*

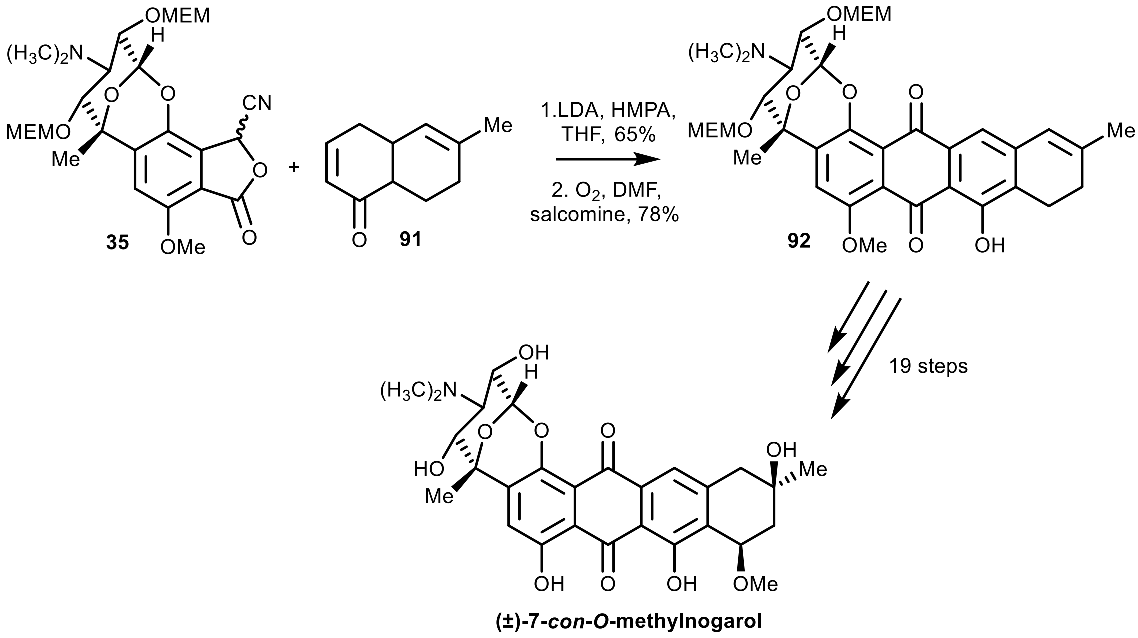
1.3.2.2. By Hauser Annulation reaction

Hauser Annulation is an anionic benzene cyclization reaction which has been well known since 1960.[98] It was named after the continuous efforts of Prof. F. M. Hauser and his group which led to the full development of this cyclisation reaction.[98] Hauser Annulation is a condensation that gives a 1,4-dioxygenated naphthalene derivative (e.g., **85**) in a one-pot operation with a 3-phenylsulfonylphthalide (e.g., **84**) and a Michael acceptor (e.g., **83**) in the presence of LDA. This method has now been successfully used for the synthesis of a large number of natural products bearing naphthoquinone or anthraquinone moieties.[113] In the late 1970s, Hauser's research on the famous anti-cancer drug anthracyclines triggered the development of this reaction. The mechanism originally proposed is described in **Scheme 27**.[114] The first step is the deprotonation of phthalide **84** at C-3. The resulting anion **86** undergoes Michael addition with the acceptor **83**. The resulting anion **87** then undergoes intramolecular Dieckmann cyclization to give **88**. Through charge transfer and the efflux of the leaving group X, intermediate **88** forms the cyclic product **89**. Base-promoted tautomerization of **89** ultimately gives naphthoquinol **85**. Later, several Hauser donors were also studied. These results are presented in a review reported by Pahari.[98]



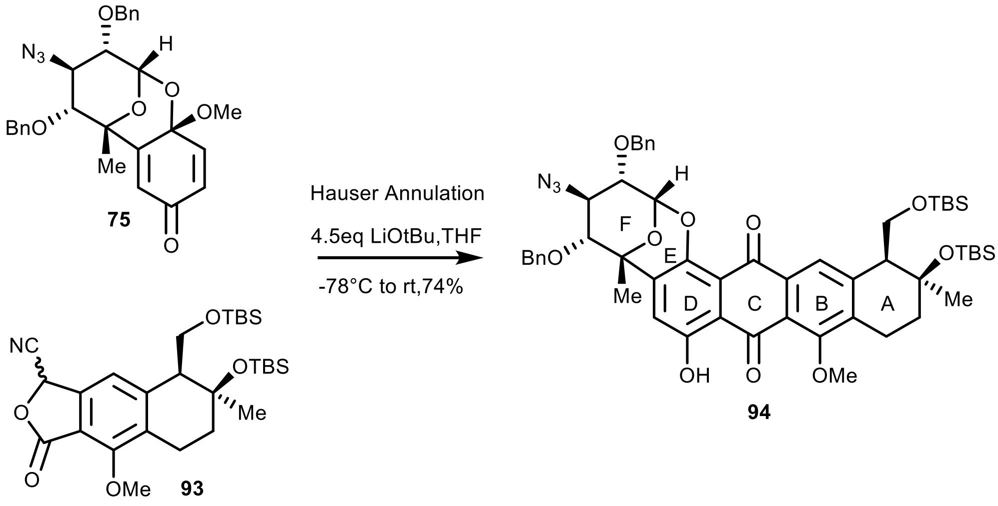
__Scheme 27.__ The originally proposed mechanism of Hauser Annulation

In 1991, Hauser[73] reported a short route to the total synthesis of (±)-7-*con*-*O*-methylnogarol *via* Hauser Annulation reaction. The key ring formation process is shown in **Scheme 28**. The tetracyclic compound **35** mentioned above (**Scheme 14**) reacts with the unsaturated ketone **91** *via* a Hauser annulation reaction, as the key step to form **92** with the desired ABCDEF-ring skeleton. This resulting polycycle was then modified to give the target product (±)-7-*con*-*O*-methylnogarol.



Scheme 28. *Total synthesis of (±)-7-con -O-methylnogarol via Hauser Annulation*

Recently, VanNieuwenhze[79] reported the synthesis of the ABCDEF-ring system **94** by Hauser annulation. Two highly functionalized segments: the cyanophthalide **93** (AB-ring segment) and the tricyclic quinone monoketal **75** (DEF-ring segment)[79] are connected in the presence of LiOtBu (**Scheme 29**).

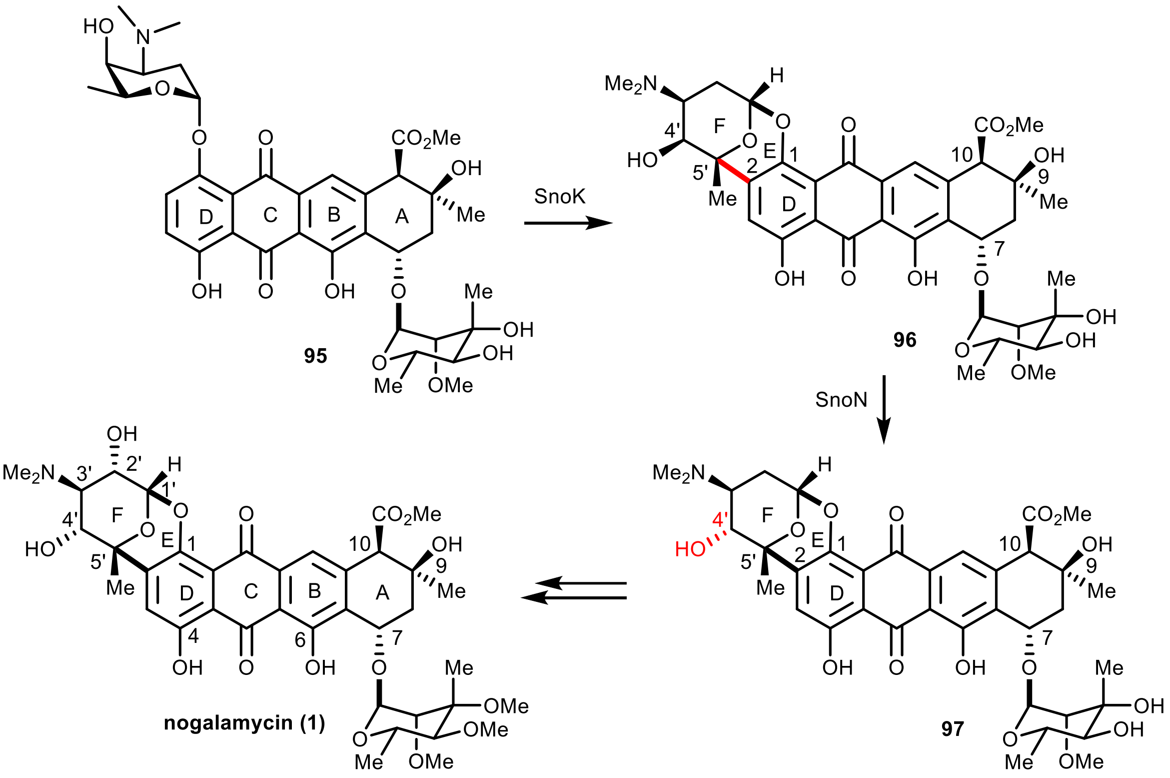


Scheme 29. *Construction of the ABCDEF-ring system* ***94*** *by Hauser annulation*

1.4. Biosynthesis of nogalamycin

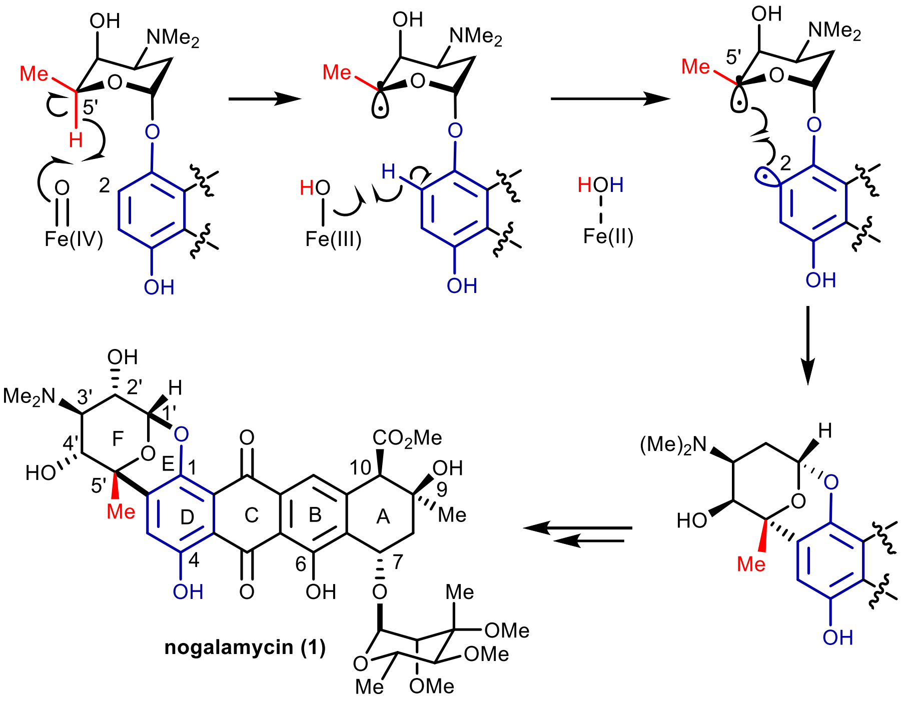
As seen above, progress in the chemical synthesis of nogalamycin have been made in recent decades, mainly in the construction of the DEF and ABCDEF rings. However, a successful route to its total synthesis has still not been developed so far.

Beyond scientific curiosity, a better understanding of nogalamycin biosynthesis may suggest inspiring synthetic strategies to chemists. Excitingly, interesting insights on the biosynthesis of nogalamycin has been reported recently.[115] It was found that α-ketoglutarate and nonheme iron-dependent enzyme SnoK catalyzed the key C5′–C2 carbocyclization.[115] Furthermore, the epimerization step at the adjacent C4′ carbon was catalyzed by the homologous enzyme SnoN in the biosynthesis of nogalamycin (**Scheme 30**).



Scheme 30. *The biosynthesis of nogalamycin catalyzed by SnoK and SnoN*

The proposed mechanism for the catalytic cycle of SnoK (**Scheme 31**) shows a consistency with the data obtained from the experiments. In the process, the Fe(IV)=O center abstracts the H5′ atom from the amino sugar of the substrate, leading to the generation of a glycosyl radical. Subsequently, iron-mediated generation of a radical at the aromatic C2 carbon led to intramolecular ring closure by radical recombination. In the same metabolic pathway, it was also shown that the homologous SnoN catalyzes an epimerization step at the adjacent C4′ carbon, most likely *via* a radical mechanism involving the Fe(IV)=O center. To date, the mechanism of SnoN catalysis is not fully clear. More work needs to be done to elucidate all the catalytic steps of SnoN. The formation of a glycosyl radical generated by iron complexes in the biosynthesis of the key *C*-aryl glycoside linkage is very encouraging, considering our proposed methodology (**Schemes 3** and **4**).



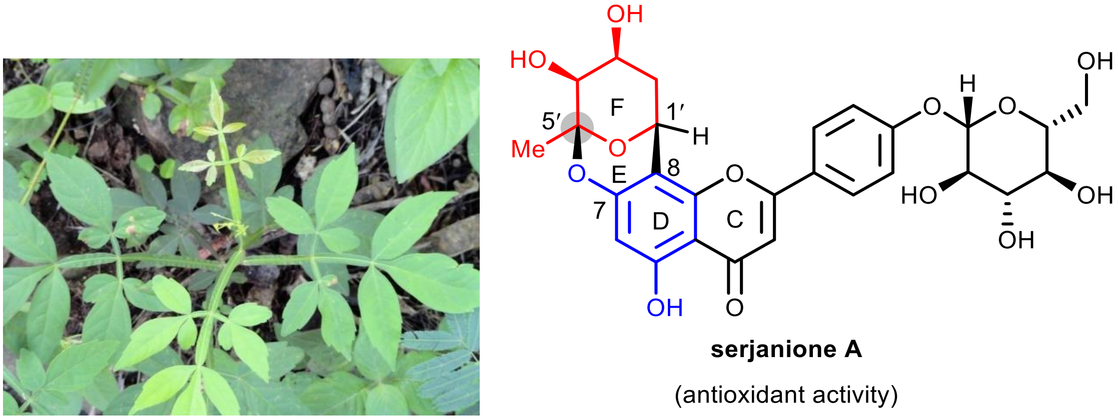
Scheme 31. *Mechanistic proposal for the catalytic cycle of SnoK*

In summary, for the chemical synthesis of nogalamycin, several methods have been developed to form the DEF-ring system which is common to the different members of this family. Using the strategies described above, only two total synthesis of menogaril have been developed. Terashima[54] prepared menogaril through a 28-step synthesis from D-arabinose in an overall yield of 4%. In comparison, the synthetic route to menogaril reported by Hauser[73] went through 30 steps in an overall yield of only 0.6%. In these studies, the two less bioactive nogalamycin congeners, (+)-7-deoxynogarol and (+)-nogarene, were also synthesized.

2. Serjanione A and related compounds

2.1. Serjanione A

Serjanione A was isolated from the ethanolic extract of the leaves of *Serjania marginata* in 2015 by Francisco A. Macías group.[8] *Serjania marginata,* a liana found in tropical and subtropical regions, is a member of the *Serjania* genus which belongs to the *Sapindaceae* family.[116] *Serjania* extracts showed diverse biological activities including anti-inflammatory,[117] antioxidant, antibacterial,[118] and antiulcer[119] in *Serjania erecta*; antiprotozoal,[120] larvicidal,[121] antibacterial,[122] and anti-inflammatory[123] in *S. lethalis*; molluscicidal and antifungal[124] in *S. triquetra*; antioxidant[125] in *S. glabrata*; trypanocidal[126] in *S. yucatanensis*; and antiulcer and antispasmodic[127] in *S. caracasana*. Herein, the focus will be made on an ethanolic extract with a specific chemical structure, serjanione A, which displays a high antioxidant activity. The structure of serjanione A shows that it contains two sugar units and a phenolic aglycone. The DEF-ring is connected by an *O*-aryl glycosidic bond and a *C*-aryl glycosidic bond. This natural product would be very interesting to study because of its significant pharmacological activities and a specific CDEF-ring system. However, to date, no total synthesis of serjanione A has been reported.



serjanione A

(antioxidant activity)

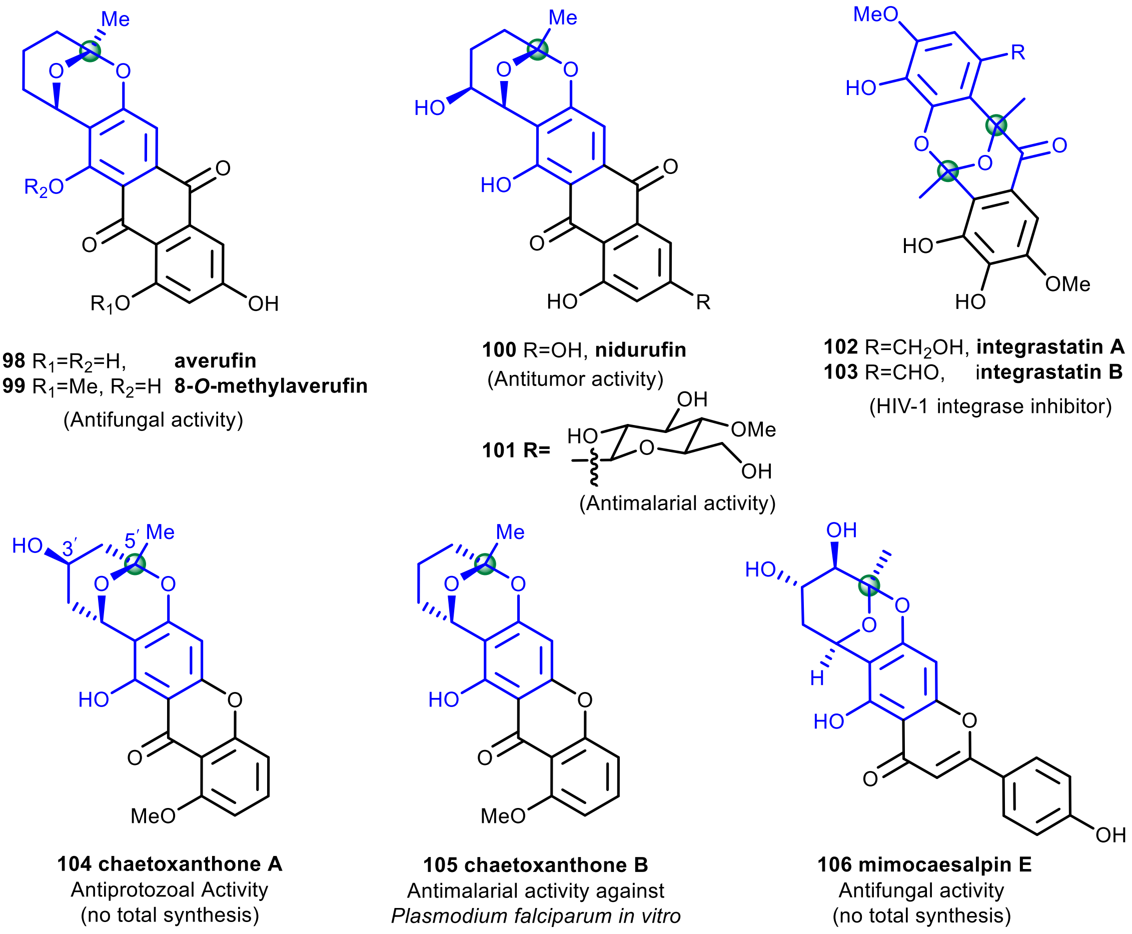
Scheme 32. *Structure of serjanione A and the plant Serjania marginata*

2.2. Related compounds of serjanione A

Only very few compounds related to serjanione A have been reported so far. If very few have a hydroxylated pyran moiety, all of them have a DEF ring skeleton, which contains a 1,3-benzodioxan system with a quaternary carbon center (**Scheme 33**). For example, in 1963, averufin[128] (**98**), a red pigment, was isolated from *Aspergillus versicolor* (Vuillemin) Tiraboschi. It was the first claim that a natural product contains a 1,3-benzodioxan system. Averufin (**98**) is stable to acid but unstable to prolonged treatment by alkali. In 2003, 8-*O*-methylaverufin (**99**) was isolated from the culture broth of *Penicillium chrysogenum* with moderate antifungal activity.[129] Averufin (**98**) lacks inhibitory activity against the tested bacteria and fungus (*cillus subtilis*, *staphylococcus aureus*, *Mucor miehei*) at the indicated concentration, whereas 8-*O*-methylaverufin (**99**) showed activity against the fungus *Mucor miehei*. In 2011, Liu's team reported the natural product nidurufin[130] (**100**), a new G2/M inhibitor in K562 cells, which was isolated from the marine-derived fungus *Penicillium flavidorsum* SHK1-27. In 2012, anthraquinone **101**[131] was isolated from the scale insect fungus *Aschersonia coffeae* Henn. BCC 28712. Compound **101** exhibited moderate antimalarial activity against *Plasmodium falciparum* and cytotoxic activity against NCI-H187 cells. In 2002, Singh's team[132] reported two rare aromatic natural products, integrastatin A (**102**) and integrastatin B (**103**), which derived from fungal fermentations and have two asymmetric centers with potent inhibitory activities for HIV-1 integrase. Integrastatin B was two-fold less active than integrastatin A but was about 5- to 10-fold selective for HIV-1 integrase when compared with deoxyribonuclease (DNase). In 2008, Konig[133] isolated natural products chaetoxanthone

A (**104**) and chaetoxanthone B (**105**) from the marine-derived fungus *Chaetomium* sp. Chaetoxanthone B showed selective antiprotozoal activity against *Plasmodium falciparum* with an IC_{50} value of 0.5 µg/mL without being cytotoxic toward cultured eukaryotic cells. However, chaetoxanthone A, with an additional hydroxyl group at C-3′ compared to chaetoxanthone B, had a much weaker activity toward *Plasmodium falciparum.* Furthermore, Macías'group reported the isolation of the closest analogue of serjanione A, mimocaesalpin E (**106**) which was extracted from *Mimosa caesalpiniifolia* leaves and has antifungal activity.

For the analogues of serjanione A mentioned above (**Scheme 33**), total synthetic routes have been successfully obtained for some of these compounds. Some of the synthesis will be discussed below as they provide inspiring routes to the formation the oxa-bridged benzoxocin skeleton.



98 $R_1=R_2=H$, **averufin**
99 $R_1=Me$, $R_2=H$ **8-*O*-methylaverufin**
(Antifungal activity)

100 R=OH, **nidurufin**
(Antitumor activity)

101 R=
(Antimalarial activity)

102 $R=CH_2OH$, **integrastatin A**
103 R=CHO, **integrastatin B**
(HIV-1 integrase inhibitor)

104 chaetoxanthone A
Antiprotozoal Activity
(no total synthesis)

105 chaetoxanthone B
Antimalarial activity against
Plasmodium falciparum in vitro

106 mimocaesalpin E
Antifungal activity
(no total synthesis)

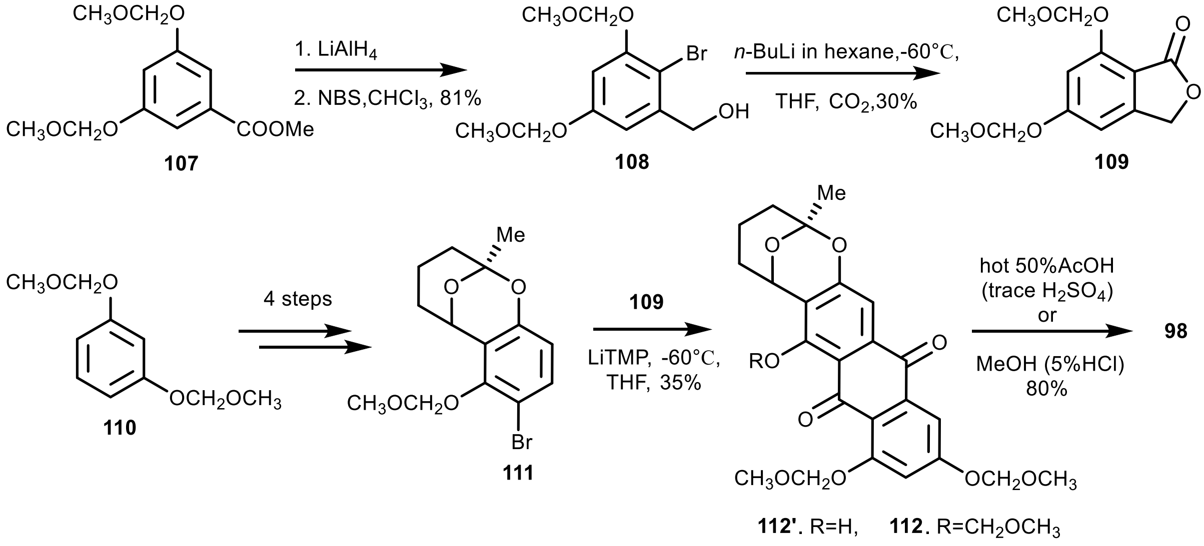
Scheme 33. *Compounds related to serjanione A*

2.2.1. Total synthesis of selected natural products related to serjanione A

2.2.1.1. Total synthesis of (±)-averufin and (±)-nidurufin

2.2.1.1.1. Works by Townsend

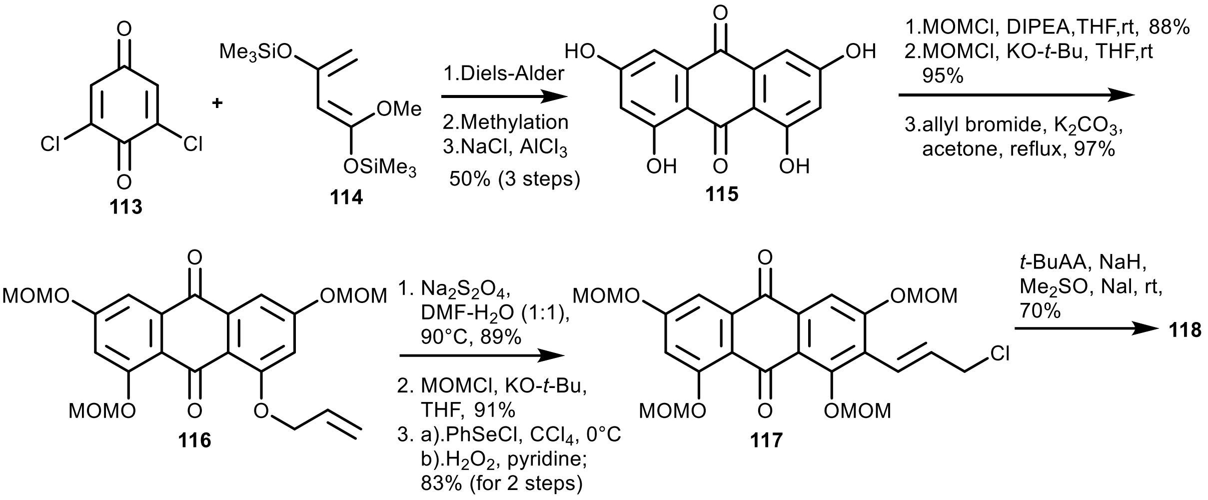
In 1981, Townsend's team reported the total synthesis of (±)-averufin (**98**) (**Scheme 34**).[134] Methyl 3,5-bis(methoxymethoxy)benzoate (**107**) was first reduced using lithium aluminum hydride, then, the resulting product was treated with *N*-bromosuccinimide in chloroform to afford bromide **108**, which was transmetalated at -60 °C in tetrahydrofuran and reacted with carbon dioxide to afford phthalide **109**. The key intermediate **111** was synthesized in 4 steps according to the method reported by Wittig and Zummack.[135;136] Finally, reaction of **109** with bromide **111** gave the triprotected anthraquinone **112**, which was readily hydrolyzed to give a mixture of tri- and diprotected anthraquinones **112** and **112'**. Deprotection in a 50% aqueous solution of hot acetic acid containing a trace of concentrated sulfuric acid or in methanol containing 5% of concentrated hydrochloric acid proceeded smoothly to give (±)-averufin (**98**) in 8% overall yield from starting ester **107**.



__Scheme 34.__ Total synthesis of (±)-averufin (__98__) by Townsend

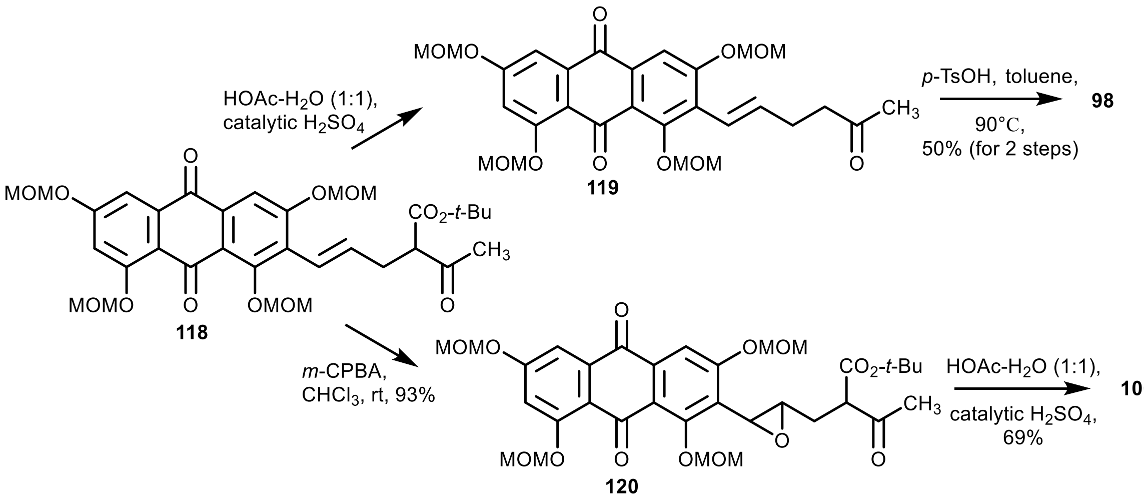
2.2.1.1.2. Works by Cava

In 1985, Cava's team reported a one-pot synthesis of 1,3,6,8-tetrahydroxyanthraquinone[137] (**115**) in a good yield without purification using an improved method inspired from Brassard synthesis (**Scheme 35**).[138] After selective protection of three of the hydroxyl groups of **115**, the corresponding triprotected anthraquinone was alkylated to give **116**. The allylic chloride **117** was obtained by a method that has been previously reported by Raucher.[139] This synthetic sequence is based on a rearrangement, followed by re-protection of the OH groups and a kinetic addition-elimination process using PhSeCl. Treatment of allylic chloride **117** with the anion of *tert*-butyl acetoacetate (*t*-BuAA) gave the pivotal intermediate **118**.



Scheme 35. *Synthesis of pivotal intermediate (**118**)*

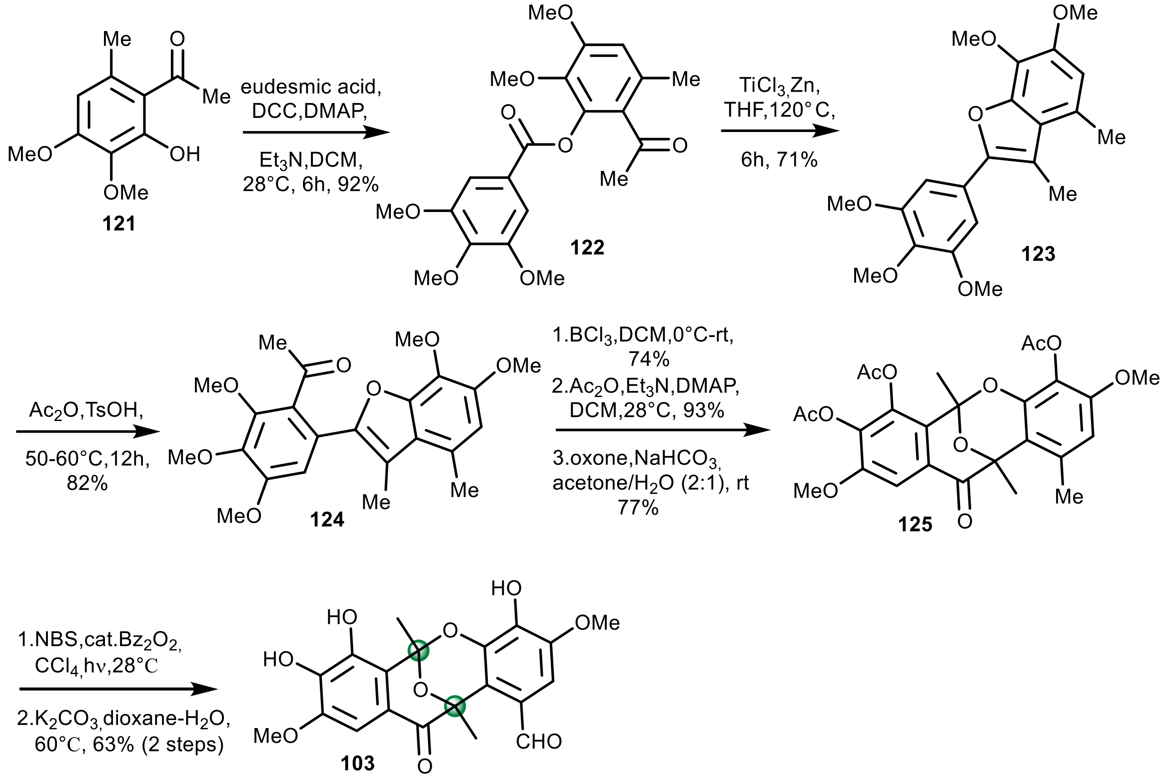
Compound **119** was obtained when **118** was heated in a 1:1 acetic acid-water solution containing a catalytic amount of sulfuric acid. Then, averufin (**98**) was obtained when product **119** was treated with a catalytic amount of *p*-toluenesulfonic acid in hot toluene in an overall yield of 20% from **115**. In addition, when the *trans*-alkene **118** was epoxidized and subjected to mild acidic cyclization conditions, (±)-nidurufin (**100**) was generated in an overall yield of 24% from **115** (**Scheme 36**).



Scheme 36. *Total synthesis of (±)-averufin (**98**) and (±)-nidurufin (**100**)*

2.2.1.2. Total synthesis of integrastatin B

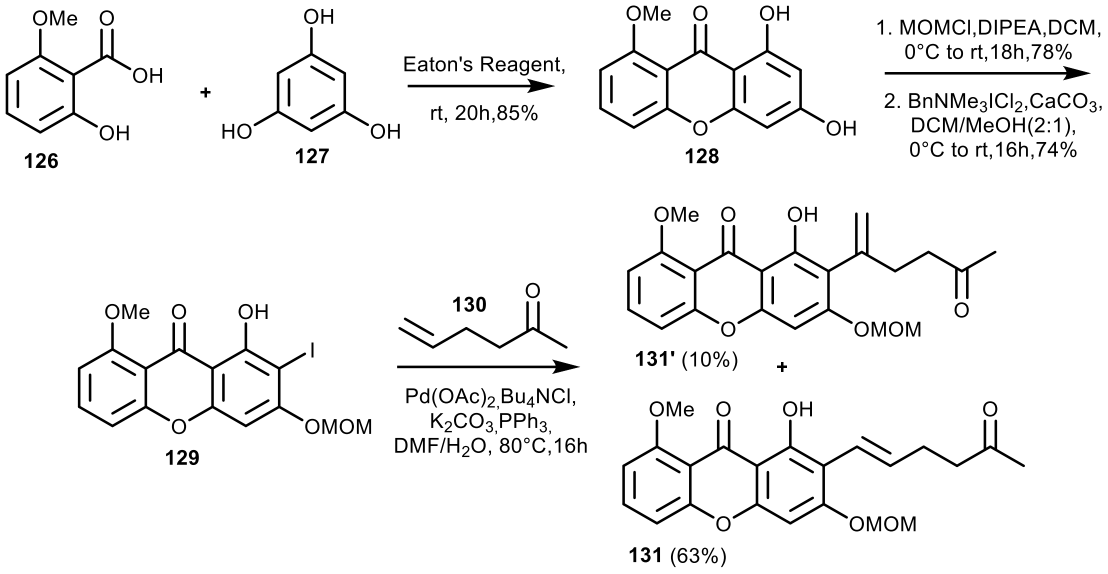
In 2016, Ramana's team[140] accomplished the first total synthesis of integrastatin B in seven steps in a 17.9% overall yield employing easily accessible starting compounds (**Scheme 37**). In this synthetic sequence, the intermediate benzofuran **123** was prepared by employing $TiCl_3$-mediated intramolecular Fürstner−McMurry coupling[141] of ester **122** that was prepared by coupling of **121** with the commercially available eudesmic acid. Compound **124** was obtained *via* the Friedel-Crafts acylation reaction of **123**. Then, the selective hydrolysis of three out of five methoxy groups was achieved using 5 equiv of boron trichloride (BCl_3) in CH_2Cl_2. Acetylation of the hydroxyl groups afforded the corresponding intermediates, which were treated with Oxone−$NaHCO_3$ to give cyclisation products **125**. Selective oxidation of the aryl-CH_3 group gave the corresponding aldehyde, which was deacetylated to yield the natural product integrastatin B (**103**).



Scheme 37. *Total synthesis of integrastatin B (**103**)*

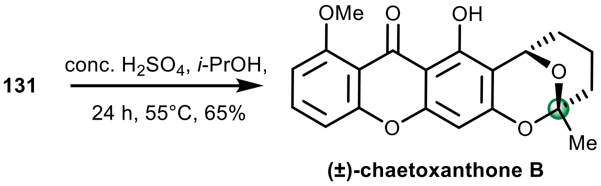
2.2.1.3. Total synthesis of (±)-chaetoxanthone B

In 2021, Gladen's team reported the first total synthesis of the antimalarial natural product (±)-chaetoxanthone B (**Scheme 38** and **Scheme 39**).[142] The synthesis was completed in 5 steps in an overall yield of 21%. Hydroxyxanthone **128** was obtained from commercially available 6-methoxysalicylic acid (**126**) and phloroglucinol (**127**). Compound **128** was treated with MOMCl to afford the corresponding monoprotected xanthone, followed by regioselective iodination to provide aryl iodide **129**. Subsequent palladium-catalyzed Heck reaction provided the desired aryl alkene **131** in 63% yield, along with the isomeric alkene **131’** (10%).



Scheme 38. *Synthesis of intermediate* ***131***

Finally, deprotection of the methoxymethyl ether of aryl olefin **131** and concomitant ketalization give (±)-chaetoxanthone B in 65% yield in the presence of concentrated H_2SO_4 at 55 °C.



Scheme 39. *Total synthesis of (±)-chaetoxanthone B* ***(105)***

In summary, nogalamycin, serjanione A and related analogues are biologically relevant *C*-aryl glycosides with C-O and C-C glycosidic bonds. Their original skeletons and therapeutic potential have attracted the interest of many scientists including chemists and biologists. In this context, our team has designed and developed new approaches for the construction of C-O and C-C aryl glycosidic bonds by metal-induced HAT. A complete overview of these studies will be presented in the two next chapters.

Chapter 2: Formal glycosylation of quinone by Hydrogen Atom Transfer (HAT)

Some of the work presented in this chapter has been published:
Liu, H., Laporte, A. G., Tardieu, D., Hazelard, D., & Compain, P. Formal Glycosylation of Quinones with *exo*-Glycals Enabled by Iron-Mediated Oxidative Radical–Polar Crossover. *J. Org. Chem.* **2022**, *87*, 13178-13194.

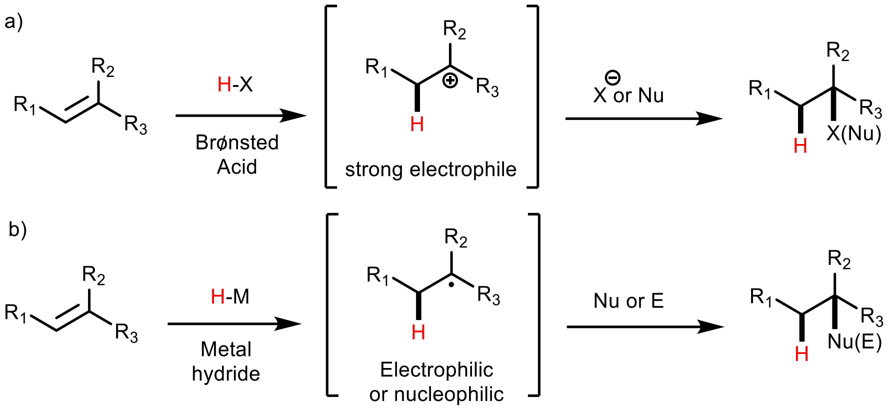
1. Introduction

In the previous chapter, we introduced nogalamycin and serjanione A and their congeners having *C*,*O*- and *C*,*C*-glycosidic bonds. Before proceeding to a specific description of our synthetic strategy, a short bibliographic study of hydroalkylation of olefins by HAT reactions initiated by metal hydrides (MHAT) will be carried out. Finally, our work on the formal glycosylation of quinone by HAT will be described in details.

1.1. Background research on HAT

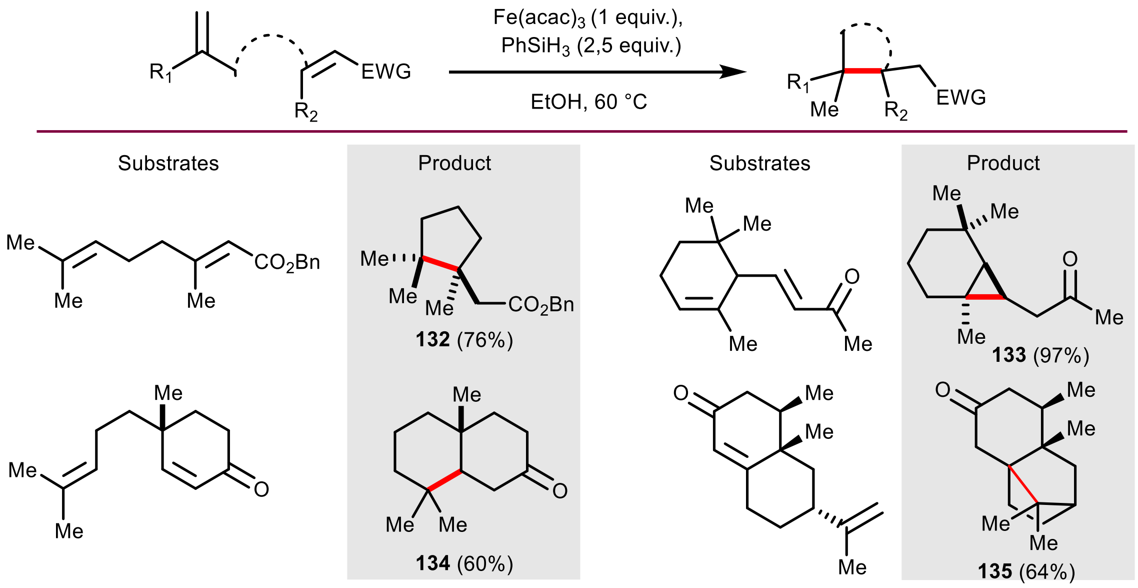
1.1.1. General presentation

The hydrofunctionalisation of alkenes is a common strategy in organic synthesis because of the wide availability of olefins as a raw material. The addition of Brønsted acid to a C-C double bond to produce a carbon cation with Markovnikov selectivity, which is then captured with a nucleophilic reagent, is one of the most important transformation of alkenes (**Scheme 40a**). However, this method is limited to simple olefins. In recent years, MHAT of alkenes has been successfully developed. This reaction is milder with a wider range of applicability and good chemoselectivity, making it a popular choice for synthetic chemists (**Scheme 40b**).[59]



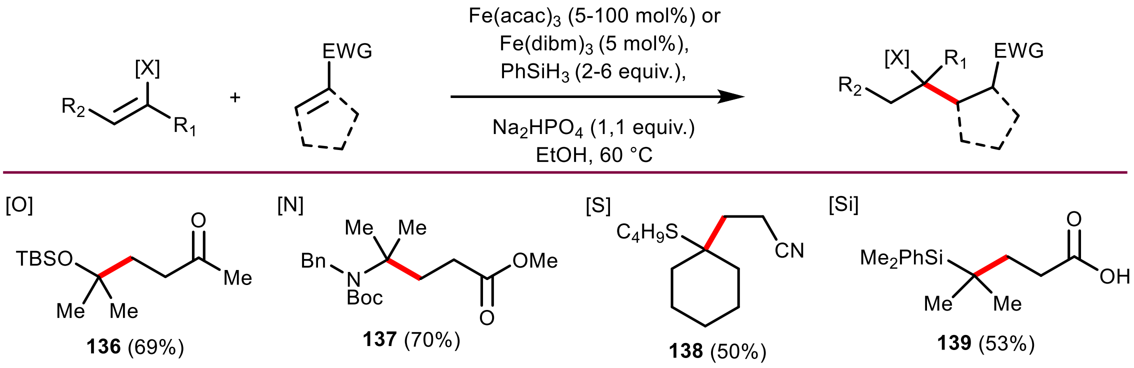
Scheme 40. *Hydrofunctionalisation of olefins via cationic or radical pathways*

For construction of carbon quaternary centers, as we know, tertiary carbon free radicals are important intermediates.[52] MHAT reactions play an important role in the formation of tertiary carbon radicals. Many MHAT processes have been developed over the last few years. Most notably, milder conditions were first developed by Baran[58] for hydroalkylation. For example, the reactions could be carried out in an air atmosphere, and the reaction times were shortened using a combination of $Fe(acac)_3$ and $PhSiH_3$ as the reductant in the presence of EtOH. These conditions allow the formation of radicals from unactivated alkenes that react with electron-deficient olefins to form new C-C bonds intra- or inter-molecularly. The authors reported many electron-deficient olefins (**Schemes 41** and **42**). The formation of three- to six-membered carbacycles **132-135** with quaternary carbon centers proceeds well under these reaction conditions (**Scheme 41**).[143]



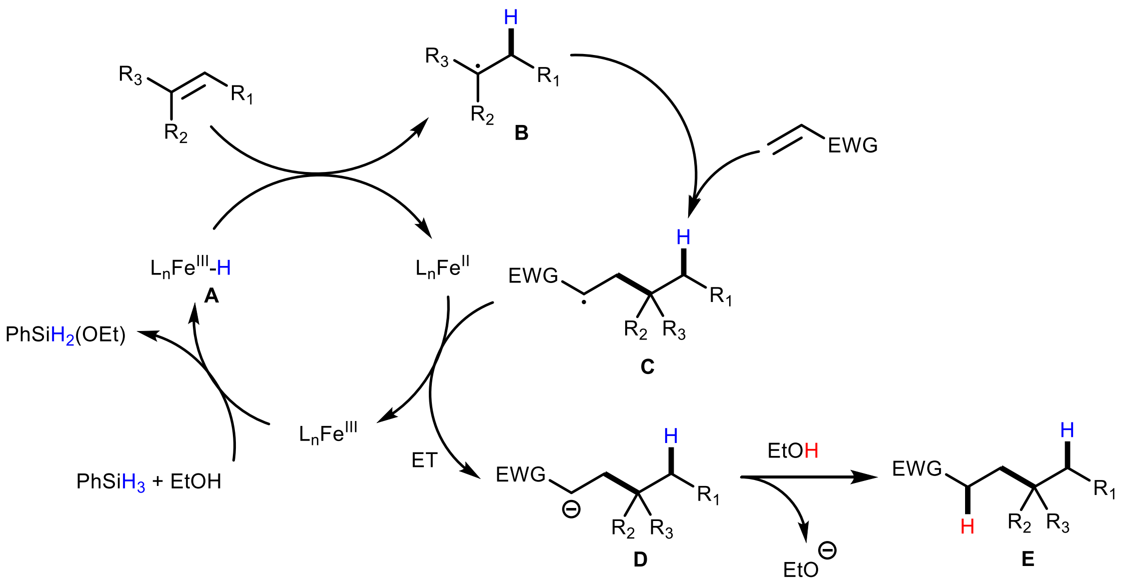
Scheme 41. *Selected examples of quaternary carbon centers synthetized via intramolecular radical addition*

In a detailed study published in 2017,[57] Baran's group extended this reactivity to a variety of heterogeneously substituted olefins (O, N, S, Si…) as well as new acceptors (**Scheme 42**).



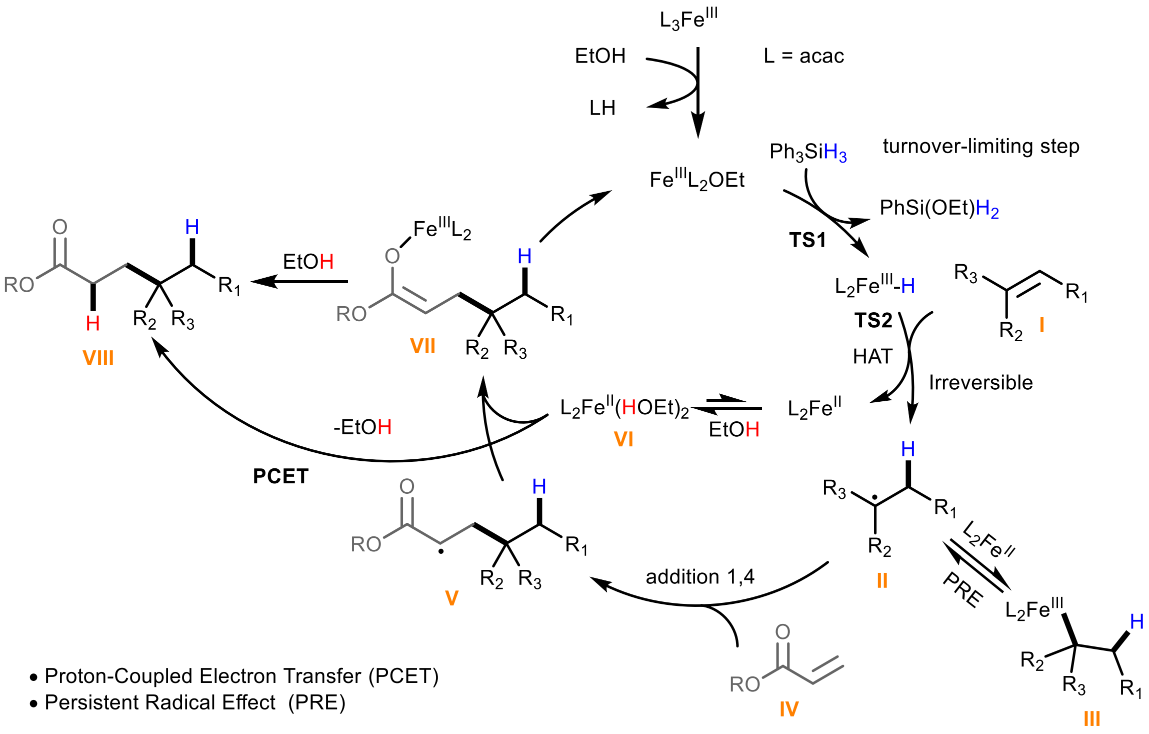
Scheme 42. *Selected examples of quaternary carbon centers synthetized via intermolecular radical addition with heterogeneously substituted olefins*

To explain their results and the chemoselectivity observed, Baran and his team proposed a first mechanism for the MHAT in 2014 (**Scheme 43**).[58] Firstly they suggested the formation of Fe(III) hydride species **A**. The hydrogen atom is then transferred to the olefin by a Markovnikov-type addition to form a carbon-centered radical **B**, which attacks the electron-deficient olefin giving alkyl radical **C**. Reduction of alkyl radical **C** to anion **D**, *via* an electron transfer process from Fe(II) to give Fe(III). Fe(III) is thus regenerated to restart the catalytic cycle, while the carbanion is protonated by the reaction solvent ethanol affording the adduct **E**.



Scheme 43. *The initial mechanism proposed by Baran*

A more detailed mechanism was proposed by the team of Patrick L. Holland in 2019 (**Scheme 44**).[144] Firstly, Fe(III) hydrides are produced by the interaction of phenylsilane, ethanol and Fe catalyst. Various experiments and calculations indicate that the transfer of hydride from the silane to iron (**TS1**) is a turnover-limiting step in this process. Subsequently, the transfer of a hydrogen atom from the transient metal hydride (**TS2**) to the donor olefin **I** gives the intermediate alkyl radical **II**. This was accompanied by the production of Fe(II) and the subsequent coordination of Fe(II) with ethanol to form the Fe-alcohol complex **VI**. Density functional theory (DFT) calculations for this step showed that the complex reduced the O-H bond dissociation free energy in ethanol, making the alcohol a good proton-coupled electron transfer (PCET) reductant. In addition, the HAT step is irreversible due to the very low bond dissociation enthalpies (BDE) of the Fe-H bond (17.3 kcal/mol). Of note, an equilibrium reaction between the radical **II** and the organoiron compound **III** may occur at any time in the presence of Fe(II). The electron-deficient olefin **IV** is coupled *via* a 1,4-addition reaction with radical **II** to give the radical addition product **V**. Finally, the target product **VIII** is formed *via* PCET or a two-step mechanism involving **VI** as the reductant and EtOH as the proton source, regenerating the catalyst.



***Scheme 44.** Detailed mechanism of iron-catalyzed HAT by Holland*

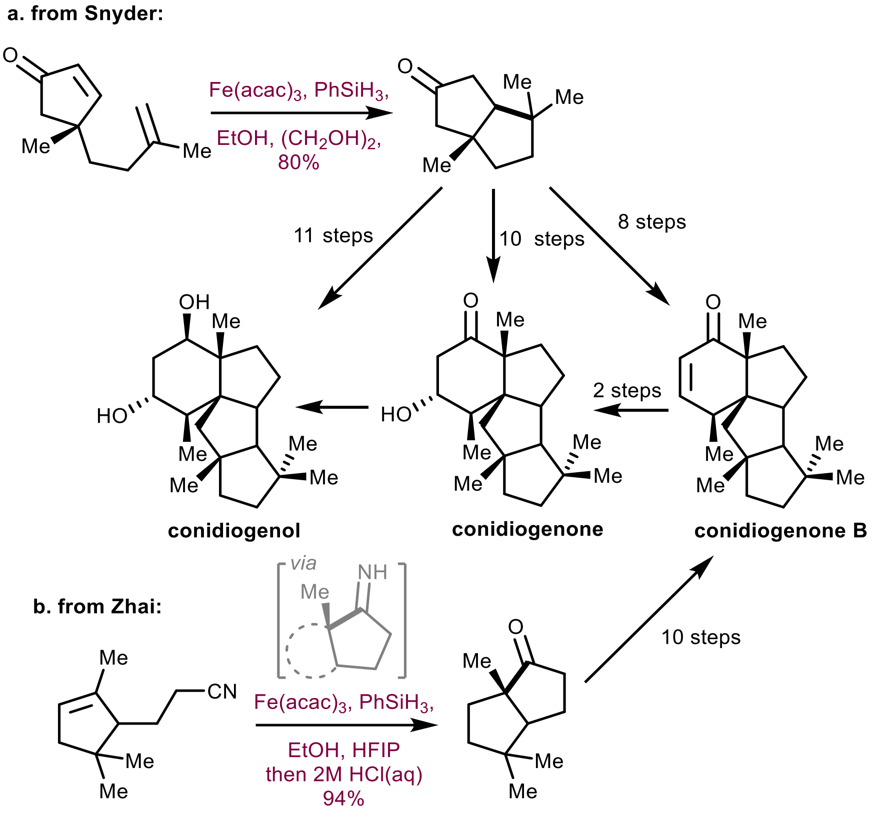
1.1.2. Some applications of HAT for the synthesis of natural products

The applications of MHAT reactions in total synthesis of natural products have been booming over the last decade. In 2021, a review for the synthesis of natural products *via* MHAT has been reported.[145] Several relevant iron-catalyzed HAT reactions are presented below.

1.1.2.1. Works by Snyder and Zhai

In 2019, Snyder[146] reported the asymmetric total synthesis of the bioactive natural products conidiogenone B, conidiogenone, and conidiogenol *via* a quaternary center-directed synthetic strategy using iron-catalyzed HAT-initiated radical conjugate addition (**Scheme 45a**). In 2020, Zhai group[147] reported the total synthesis of conidiogenone B in 14 steps and with 4.7% overall yield, featuring a

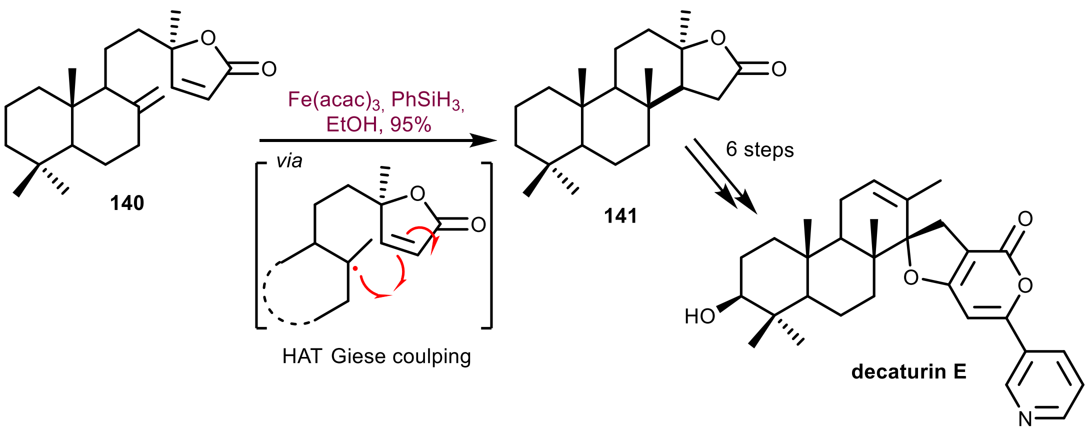
Danheiser annulation reaction for the rapid assembly of the challenging tetracyclic skeleton of these natural products. In this process, Zhai used iron-mediated HAT alkene–nitrile cyclization under Talbot's conditions,[148] providing this key intermediate bicyclic ketone in higher yields (**Scheme 45b**).



Scheme 45. *Synthesis of conidiogenol, conidiogenone, conidiogenone B by Snyder and Zhai*

1.1.2.2. Works by Reanta

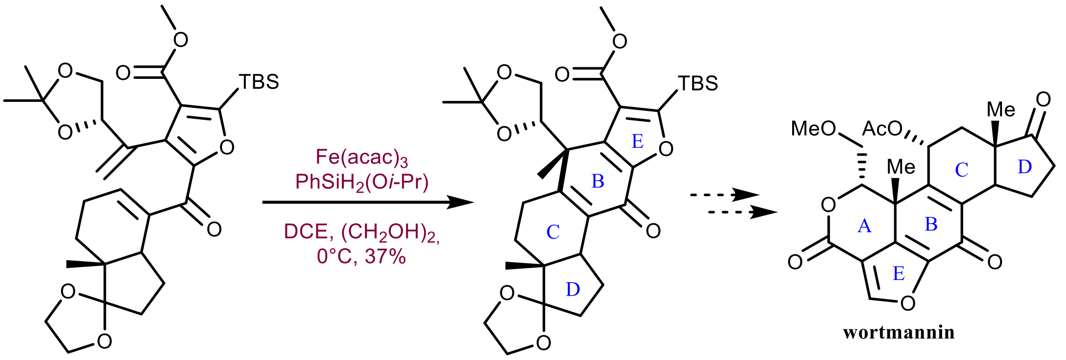
In 2020, Renata and co-workers[149] achieved the synthesis of the natural product decaturin E applying MHAT reaction as the key step. The critical intermediate **141** was obtained from **140** by HAT-based intramolecular Giese coupling with complete diastereoselectivity and excellent yields using Fe(acac)$_3$ and PhSiH$_3$ (**Scheme 46**).



Scheme 46. *Synthesis of decaturin E by Renata*

1.1.2.3. Works by Zhou

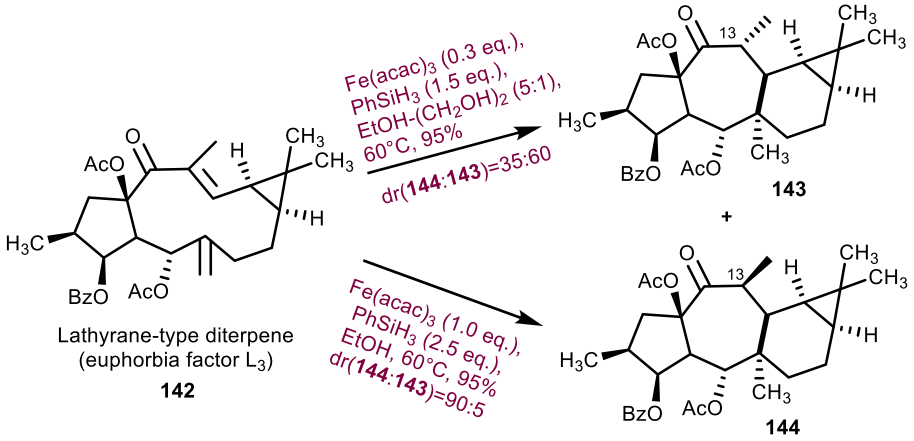
In 2020, Zhou group[150] reported a rapid construction of the BCDE tetracyclic framework of the natural product wortmannin by way of MHAT-mediated intramolecular reductive olefin coupling in seven steps from a commercially available reagent (**Scheme 47**).



Scheme 47. *Synthesis of the tetracyclic core of wortmannin by Zhou's*

1.1.2.4. Works by Gao

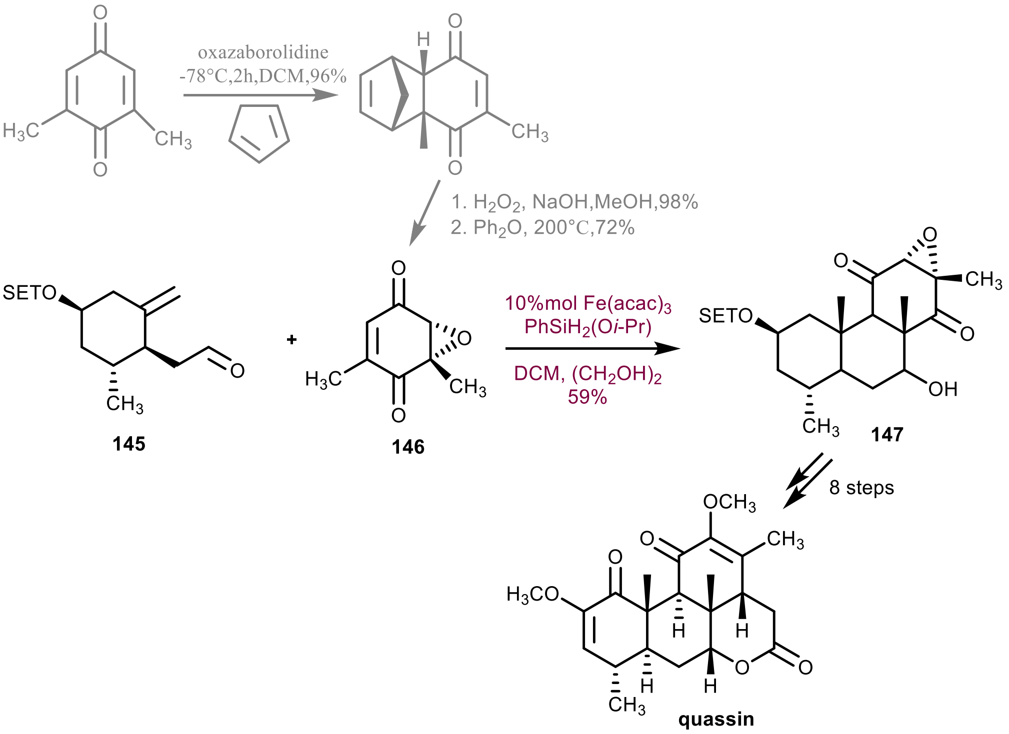
In 2021, Gao team[151] reported the synthesis of two new premyrsinane-type diterpenes **143** and **144** as diastereomers from lathyrane-type diterpene euphorbia factor L$_3$ **142**, which was isolated from the seeds of *Euphorbia lathyris* L. for the first time *via* an efficient Fe(acac)$_3$-catalyzed skeleton conversion process (**Scheme 48**). Interestingly, different ratios of catalyst and solvent give different absolute configurations at C-13 in the HAT products. The use of a catalytic amount of iron salt in a mixture of EtOH-(CH$_2$OH)$_2$ (5:1) gave a pair of premyrsinane-type isomers with low dr (1.7:1), whereas applying 1 equiv. of iron salt in a single solvent (EtOH) gave a premyrsinane-type diterpene with a β-methyl group at C-13 as a major product (90% yield). In addition, the study suggests that **143** and **144** exhibit cytotoxic activity against 4T1 breast cancer cell lines, while the parent compound euphorbia factor L3 **142** was inactive. Furthermore, the development of these conditions provides convenient pathways for the preparation of naturally rare premyrsinane diterpenes with high bioactivity from naturally abundant lathyrane diterpenes.



Scheme 48. *Synthesis of premyrsinane-type diterpenes* ***143*** *and* ***144*** *via iron-mediated HAT*

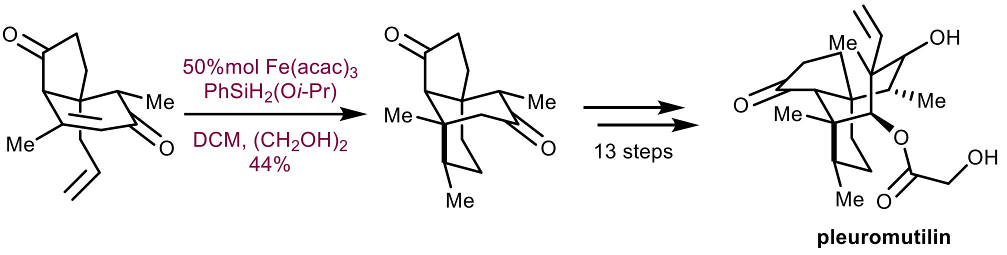
1.1.2.5. Works by Sergey V. Pronin

In 2022, the natural product quassin isolated from the quassia tree was synthesized from a key tetracyclic core **147** that relied on efficient and selective cyclization between two unsaturated carbonyl components **145** and **146** *via* iron-catalyzed HAT (**Scheme 49**).[152] Compound **146** was obtained by way of regio- and diastereoselective epoxidation of tricyclic diene generated from 2,6-dimethylbenzoquinone.[153] The application of this strategy reduced significantly functional group manipulations leading to a shorter strategy compared to previous efforts in the field.



Scheme 49. *Synthesis of the natural product quassin*

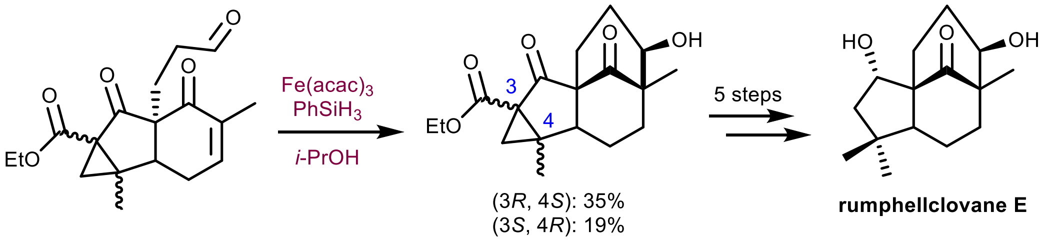
In the same year, another natural product, pleuromutilin, which was obtained from basidiomycetes (*Clitopilus genus*) with a potent activity against Gram-positive pathogens, was synthesized by the construction of a key tricyclic skeleton using the same Pronin's HAT conditions shown above (**Scheme 50**).[154]



Scheme 50. *Synthesis of the natural product pleuromutilin*

1.1.2.6. Works by Liu

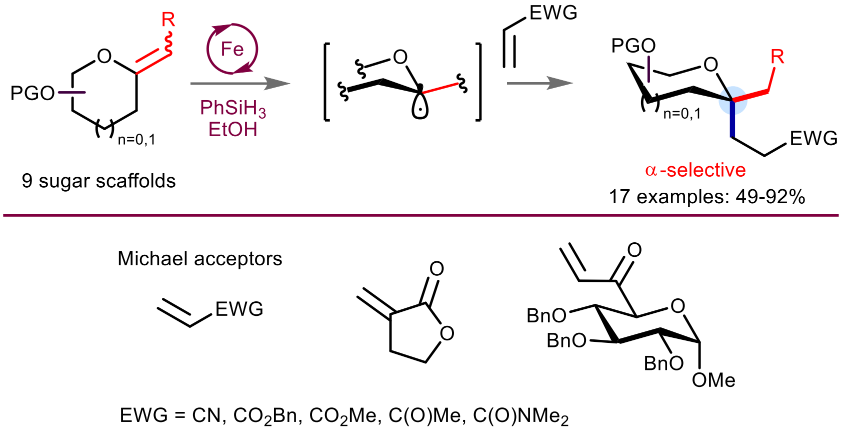
In 2021, Liu and co-workers[155] reported the first asymmetric total synthesis of rumphellclovane E in eight steps from commercially available (*R*)-carvone. One of the key steps in this process is the application of iron-catalyzed reductive aldol reaction (**Scheme 51**).



Scheme 51. *Synthesis of rumphellclovane E by Liu*

1.1.3. Other applications of HAT

Most notably, our group[156] reported a convenient strategy for the synthesis of *C*,*C*-glycosides from *exo*-glycals through a Baran-type iron-mediated HAT/Michael–Giese coupling sequence in 2019 (**Scheme 52**). The capture of the transient tertiary pseudoanomeric radicals by a range of Michael acceptors enables the stereocontrolled *C*-quaternization of the anomeric center. In this process, 17 *C*,*C*-glycosides, including the synthesis of a *C*-disaccharide, were obtained in acceptable to high yields ranging from 49% to 92%. This approach was inspired by the recent progress in Fe-catalyzed radical hydrofunctionalization of unactivated olefins.[57-60;62;157]



Scheme 52. *Iron-hydride HAT-enabled synthesis of C,C-glycosyl compounds from exo-glycals*

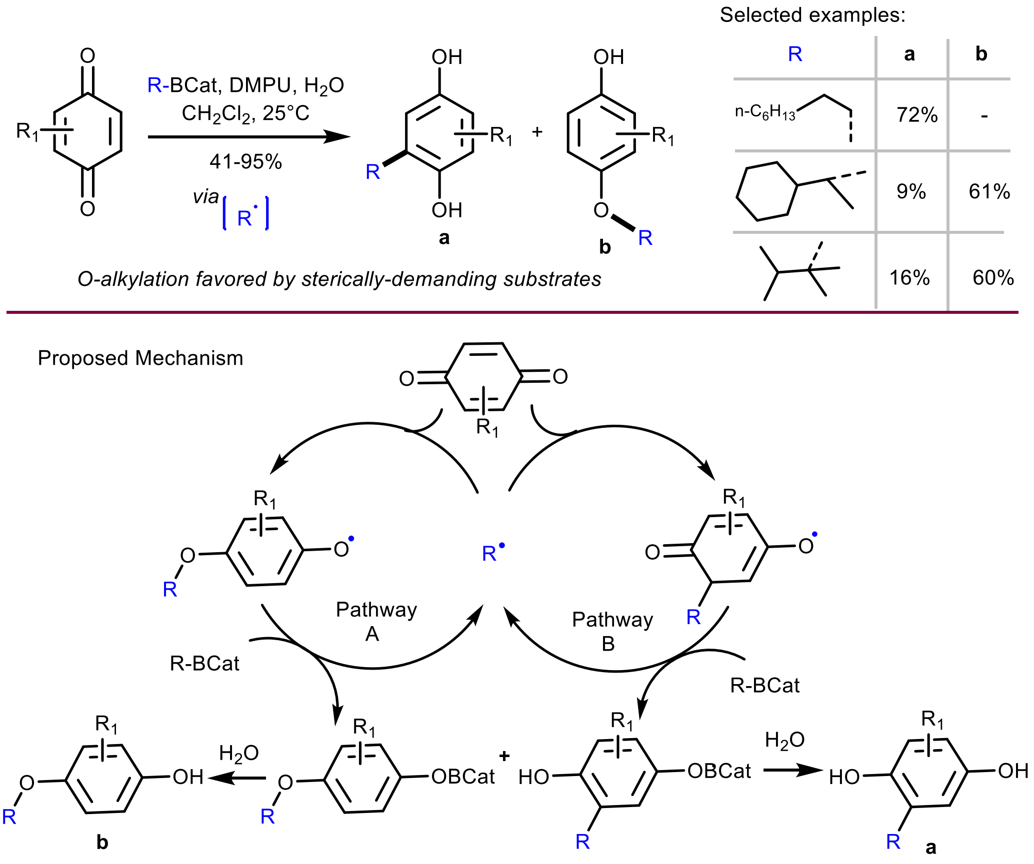
1.2. Direct C-H Radical Alkylation of 1,4- Quinones

1,4-Quinones are an important and widespread class of compounds found in nature, particularly in plants, bacteria or fungi. It has a variety of applications in a wide range of fields, including health, due to the unique redox and biological properties displayed.[158-160]

Furthermore, over the last decades, free radical chemistry has slowly become a major component of organic synthesis. In addition, the remarkable ability of quinones to act as effective free radical receptors has attracted many chemists. Radical alkylation of 1,4-quinones has evolved rapidly over the last number of years.[63] Herein, the focus will be made on the works of Renaud, Liu, Wang and Praly which are relevant regarding our synthetic objectives.

1.2.1. Works by Renaud

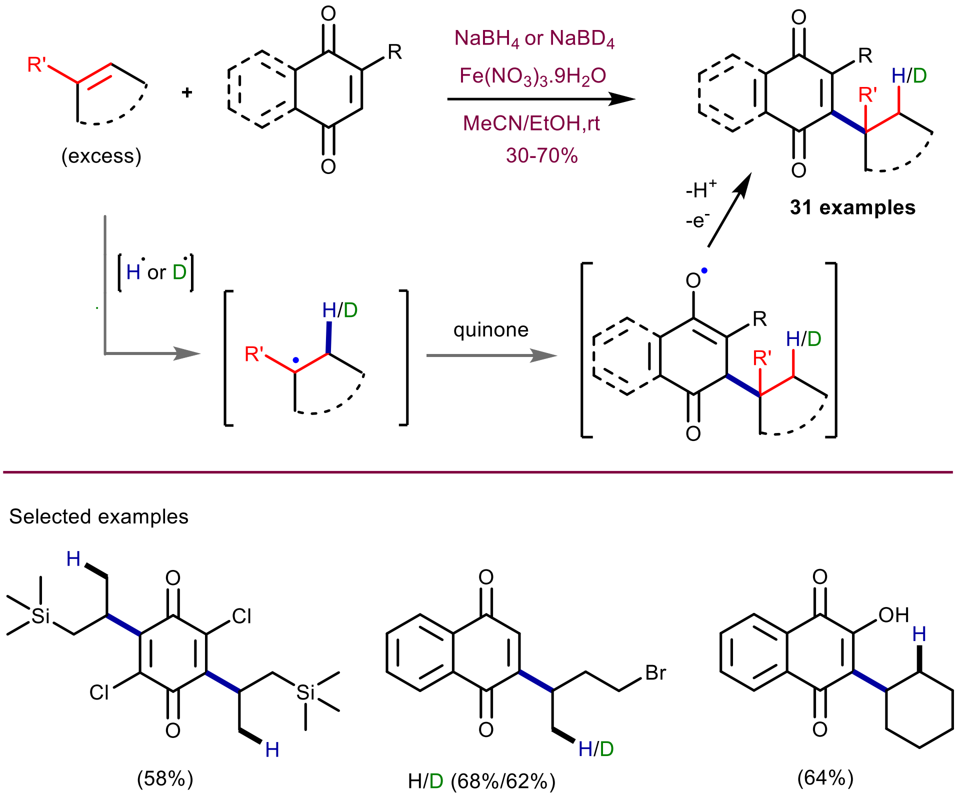
In 2006, Renaud and co-workers[161] reported a radical addition reaction to 1,4-benzoquinones using *B*-alkylcatecholboranes (R-BCat). Substituted hydroquinones were obtained in good overall yields. The results of Renaud's study show that this radical addition may lead to different regioselectivity. Addition of bulky secondary or tertiary alkyl radicals onto 1,4-benzoquinones afforded the formation of the corresponding phenol ethers **b**, whereas less hindered alkyl radicals provide the 1,4-addition products **a** (**Scheme 53**). The quinone is likely to react with an alkyl radical *via* either *O*-addition (pathway A, 1,6-addition) or *C*-addition (pathway B, 1,4-addition). The radical adduct reacts rapidly with R-BCat to produce a boron phenolate and the alkyl radical R• (**Scheme 53)**. Hydrolysis of the boron phenolates yields hydroquinone **a** and aryl ether **b**.



Scheme 53. Renaud's work with alkylborane-derived radical addition onto quinones

1.2.2. Works by Liu

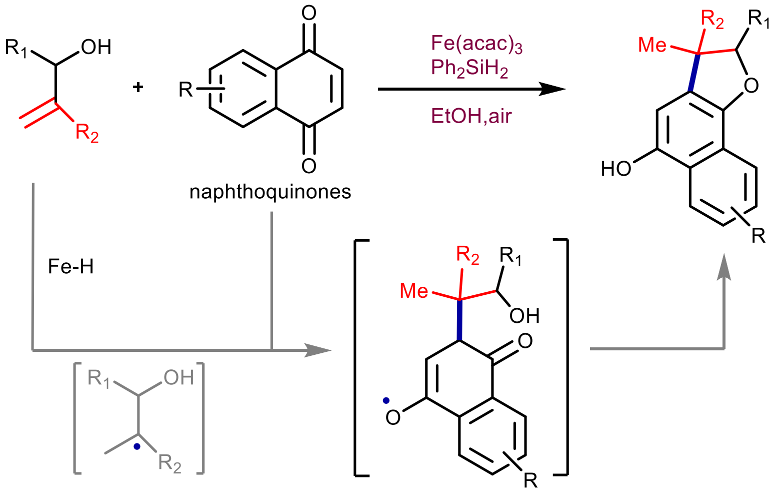
In 2019, Liu group[56] developed a mild, rapid, and step-economic Fe(III)-mediated radical alkylation of quinones with unactivated olefins using readily available and inexpensive $NaBH_4$ or $NaBD_4$ as a hydride source (**Scheme 54**). In this study a series of functionalized quinones were obtained in low to good yields (30−70%). In addition, deuterium atoms can be easily introduced at predictable positions in organic molecules using this method. The proposed mechanism, reaction conditions and some selected examples are shown in **Scheme 54**.



Scheme 54. *Liu's work using Fe(III)-mediated radical alkylation of quinones*

1.2.3. Works by Wang

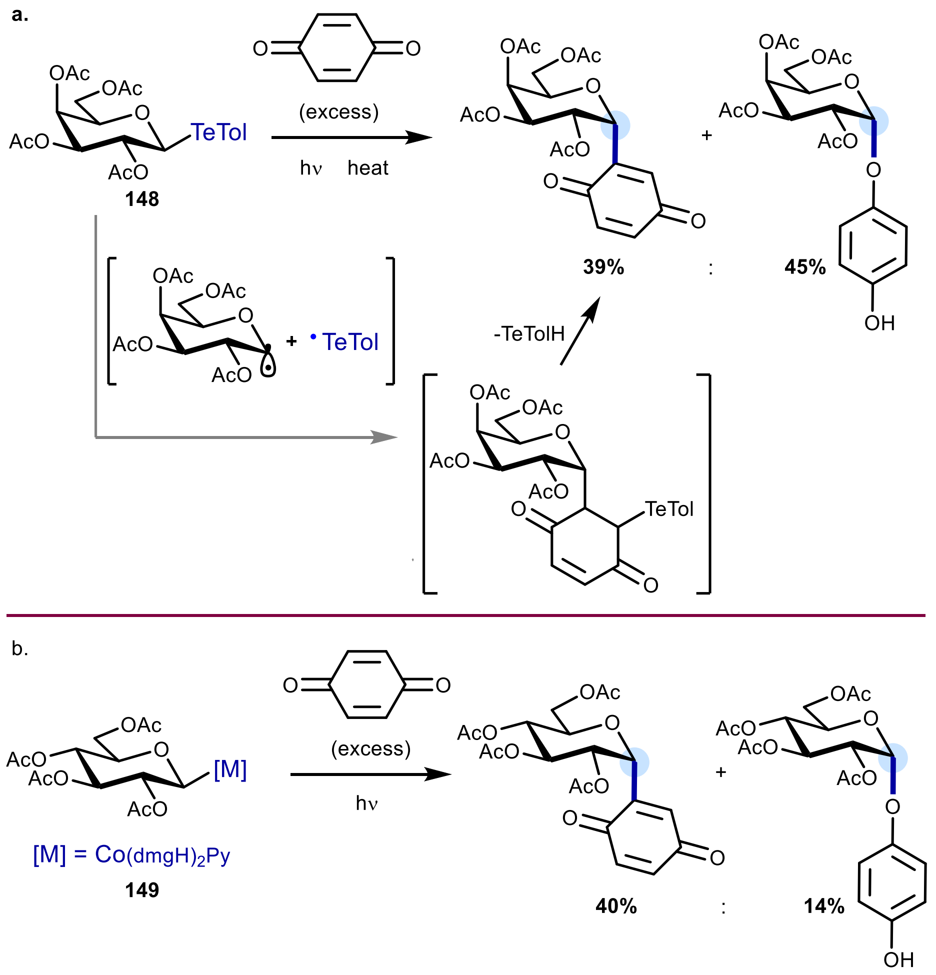
In 2021, Wang team[162] reported the synthesis of naphthodihydrofurans by way of iron-mediated radical cascade reaction (**Scheme 55**). In this process, alkyl radicals generated from the corresponding allyl alcohols were engaged in a Michael-type reaction with various naphthoquinones.



Scheme 55. *Wang's work with Fe(III)-mediated radical cascade reaction*

1.2.4. Works by Yamago and Praly

In 2002, Yamago *et al.*[23] reported the reaction of 1,4-benzoquinone with a galactos-1-yl radical generated from the corresponding organotellurium compound. Although proceeding in good yields and high *α*-stereoselectivity, the reaction was found to be poorly regioselective as shown by product distribution: the 4-hydroxyphenyl *α*-D-galactopyranosyl product and its corresponding 2-(galactosyl)-1,4-benzoquinone analogues were obtained in 45% and 39% yields, respectively (**Scheme 56a**). Few years later, attempts of the group of Praly[65] to perform related radical coupling failed using glucopyranosyl bromide as anomeric radical precursor in the presence of tri-*n*-butyltin hydride. Coupling products were eventually obtained with high *α*-stereoselectivity but in modest yields by irradiation of the glucosylcobaloxime derivative **149** to form the corresponding glucosyl radical by homolytic cleavage of the Co-C bond.[24] Product distribution pointed to a modest selectivity in favor of the *C*-glycosylated 1,4-benzoquinone derivative (**Scheme 56b**). One of the main drawbacks of these methods, in addition to low regioselectivity, is the preparation of glycosyl complexes **148** and **149**.

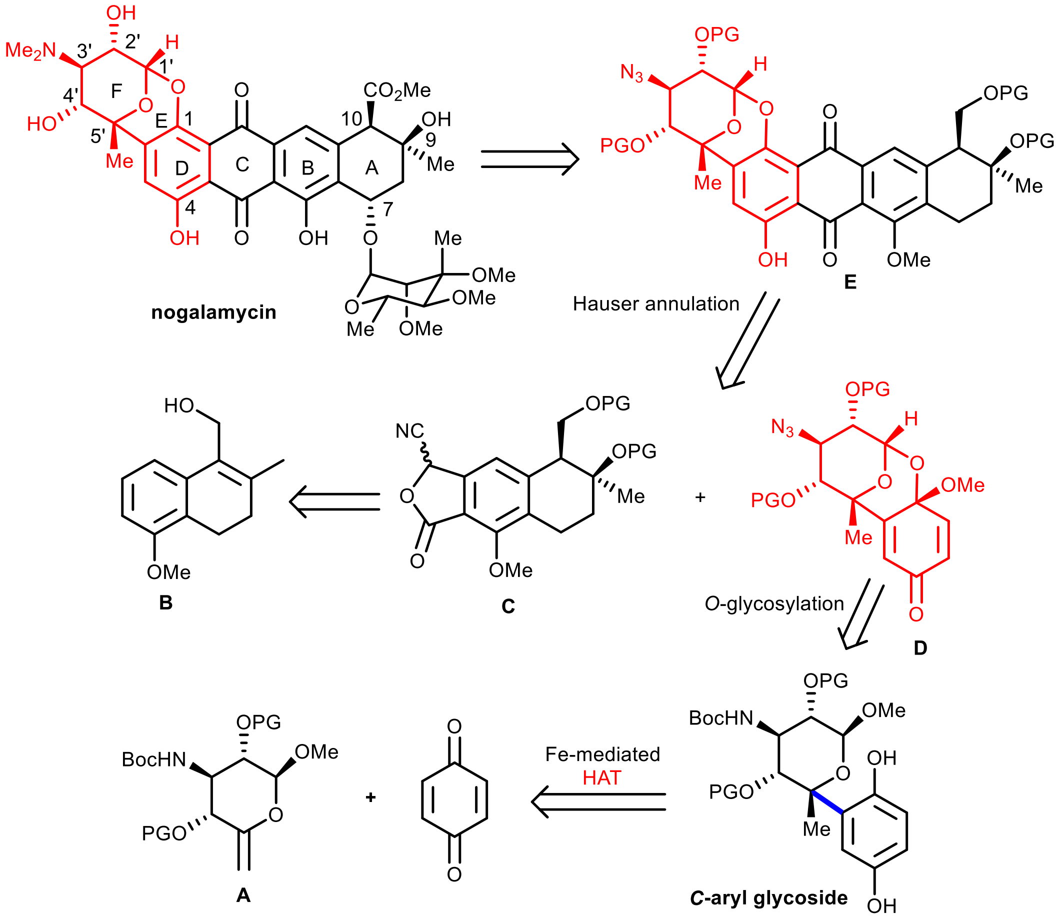


Scheme 56. *Praly's and Yamago's work on radical-mediated coupling of glycosyl metal complexes and quinone*

1.2.5. Our strategy towards the DEF-ring system of nogalamycin

With the development of free radical chemistry, the formation of free radicals *via* metal-induced HAT to olefins has attracted extensive attention in recent years. To date, however, there are very few examples of such strategies for the formation of glycosyl radicals despite its potential for the development of *C*-glycosylation methods.[163] In 2019, we prepared a diversity of *C*,*C*-glycosyl compounds from *exo*-glycals *via* the intermediacy of tertiary pseudoanomeric radicals.[156] In addition, considering that the quinone moieties are often found in bioactive natural products as well as drugs,[164;165] and that the natural product nogalamycin with its unique structure has not been synthesized yet, our initial objective was to develop a strategy towards its synthesis, with a focus on the glycobenzoxocin part. Based on the previous report of VanNieuwenhze's team[79] showing that the ABC-ring system could be successfully constructed through a convergent Hauser Annulation[98] (**Scheme 29**), we envisaged the retrosynthesis route shown on **Scheme 57**. The first intermediate **E** could be indeed synthesized *via* a convergent Hauser annulation between two highly functionalized segments: **C** (AB-ring segment) and **D** (DEF-ring segment). Fragment **C** could be synthesized from **B**.[79]

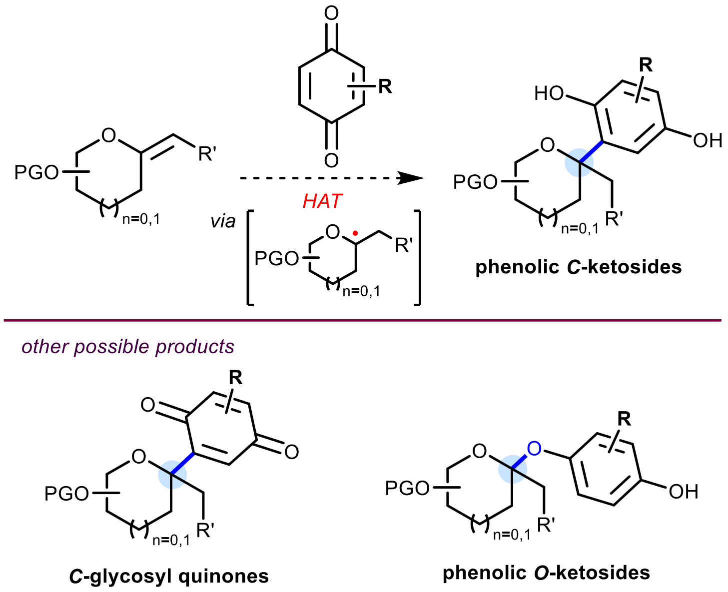
The key intermediate **D** with nogalamycin DEF-ring system may be formed *via* *O*-glycosylation under acidic conditions from a *C*,*C*-glycoside intermediate, which may be obtained from *exo*-glycal **A** and 1,4-benzoquinone *via* iron-mediated HAT reaction.



Scheme 57. *Retrosynthetic analysis for synthesis of nogalamycin*

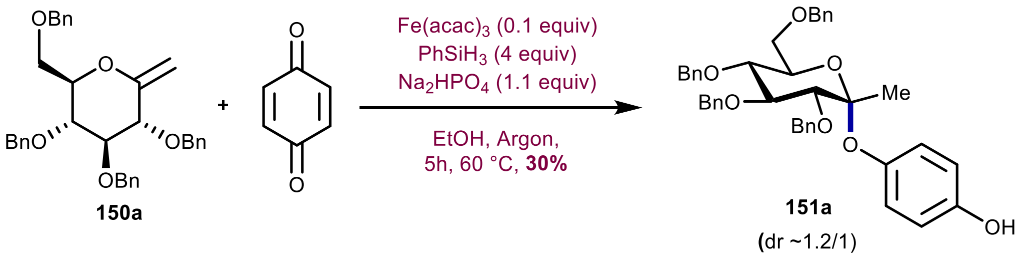
2. Research strategy and model study

Based on the above plans for the direct alkylation of olefins with quinones (see **Chapter 2**: **1.2**), our strategy was to first construct *C*-aryl glycosides *via* iron-mediated HAT with *exo*-glycals and 1,4-quinones, which is an important step for the synthesis of the DEF ring system of nogalamycin. However, the control of regio-, chemo-, and diastereoselectivity in the MHAT-mediated generation of quaternary (pseudo)- anomeric centers using quinone substrates is expected to be highly challenging. At least six different glycosylated products with different stereochemistries, connectivities, or oxidation states could be obtained in a non-selective process (**Scheme 58**).



Scheme 58. *Our strategy for the construction of C,C-glycosides*

In order to study the feasibility of direct MHAT-mediated *O*/*C*-glycosylation of quinones, *exo*-glucal **150a**, which is known and readily available in our group,[156] was chosen as a model for our study. In a first attempt using optimized conditions previously reported with classical Michael acceptors,[156] reaction of **150a** with 2 equiv of 1,4-benzoquinone (1,4-BQ) in the presence of $PhSiH_3$ (4 equiv), $Fe(acac)_3$ as a catalyst, and Na_2HPO_4 as buffer in degassed EtOH under argon led to the formation of phenolic *O*-glycosides **151a** in 30% yield with low *α*-stereoselectivity.



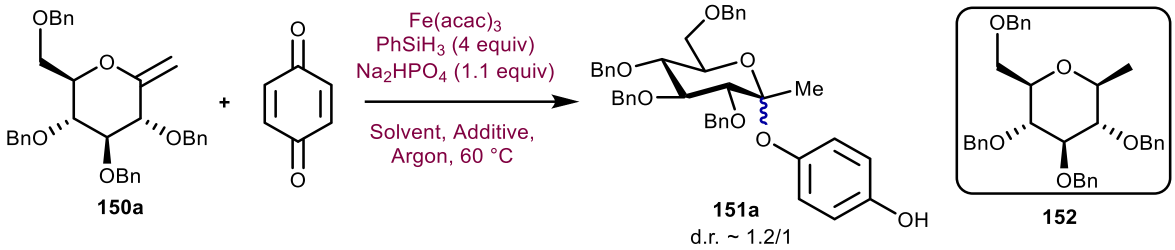
Scheme 59. *Model study for the HAT-mediated coupling*

However, we were pleased that the Fe-mediated HAT reaction worked and carried out with high regioselectivity. No *C*-glycoside corresponding to the 1,4-conjugate addition product was indeed detected in this process. Despite their interest as natural products and bioactive compounds, only few synthetic methods have been described to obtain phenolic *O*-ketosides.[166-171] After a survey of previous literature, we found that no free radical-based methods were reported so far to obtain this class of compounds. In addition, our preliminary results are meaningful considering that the natural product serjanione A and related compounds have a similar structural skeleton and display a wide range of biological activities.

3. Optimization of the reaction conditions

In order to optimize the reaction described above (**Scheme 59**), various experimental parameters have been studied (**Table 3**). First, increasing the amount of catalyst to 1.0 equiv., we found a noticeable improvement of the reaction efficiency, phenolic *O*-glycosides **151a** being obtained in 46% yield (**entry 2**). Subsequently, different reaction concentrations were tried. In contrast to our previous studies,[156] the results showed that the concentration of the reaction medium has almost no effect on the reaction yield. However, the reaction rate increased with higher reaction concentration (**entries 2-4**). The reaction was run at room temperature with noticeably lower yields (**entry 5**). At the same time, the formal alkene hydrogenation product **152** arising from *exo*-glucal **150a** was also isolated in yields up to 25% (**entries 2-5**). In addition, a careful thin-layer chromatography (TLC) analysis showed that 1,4-BQ was sufficiently consumed, but the starting material **150a** was still there, therefore the amount of quinone was increased to ensure completion of the reaction (**entry 6**). Using 4 equiv. of 1,4-BQ with ethanol (8 equiv) used as a simple additive to limit the solvolysis rate of $PhSiH_3$[57;172;173] and changing the solvent to tetrahydrofuran significantly improved the yield from 55% to 68% (**entries 6** and **7**). The yield of *O*-glycoside **151a** increased to 77% when 1,4-BQ was added in two portions. However, the direct addition of 6 eq 1,4-BQ at the beginning of the reaction gave less satisfactory results (**entries 8** and **9**). Of note, 80% of the product was obtained when the amount of the additive ethanol was reduced from 8 equiv. to 2 equiv., accompanied by an increase in reaction time from 1 h to 7.5 h (**entry 10**). Remarkably, the reaction efficiency could be further increased by reducing the catalyst loading in $Fe(acac)_3$ to 0.5 equiv. (**entry 11**) and 0.2 equiv. (**entry 12**), leading to yields up to 82% (**entry 11**). Naturally, in order to further demonstrate the importance of each reagent, five control experiments were carried out. First, the use of Ph(*i*-PrO)SiH_2 has been described by Shenvi *et al.* to improve metal-catalyzed radical hydrofunctionalization reactions that are non-optimal under standard conditions.[174] In our case, when $PhSiH_3$ was replaced by (*i*-PrO)-$PhSiH_2$, the reaction process was significantly less efficient (**entry 13**). The buffer Na_2HPO_4 was removed and the result obtained was slightly affected (**entry 14**). However, due to the fact that Na_2HPO_4 is commercially available and cheap, and that we were not sure whether other substrates would be affected when we removed Na_2HPO_4, we chose to keep it during the substrate scope study. The utilization of a combination of Fe(II) and Fe(III) salts as well as running the reaction in air also significantly reduced the process efficiency (**entries 15** and **16**).[175] The replacement of Fe(acac)$_3$ by Mn(acac)$_3$ was found to be detrimental to the formal *O*-glycosylation process (**entry 17**). Finally, the best conditions were obtained with THF as the solvent, EtOH (8 equiv.) as the additive and 0.5 equiv. Fe(acac)$_3$ as catalyst (**entry 11**). With the best conditions in hand, the scope of HAT-mediated formal glycosylation was studied with a diversity of quinones and *exo*-glycals, the synthesis of which will be presented in the next section.

Table 3. *Reaction optimization*



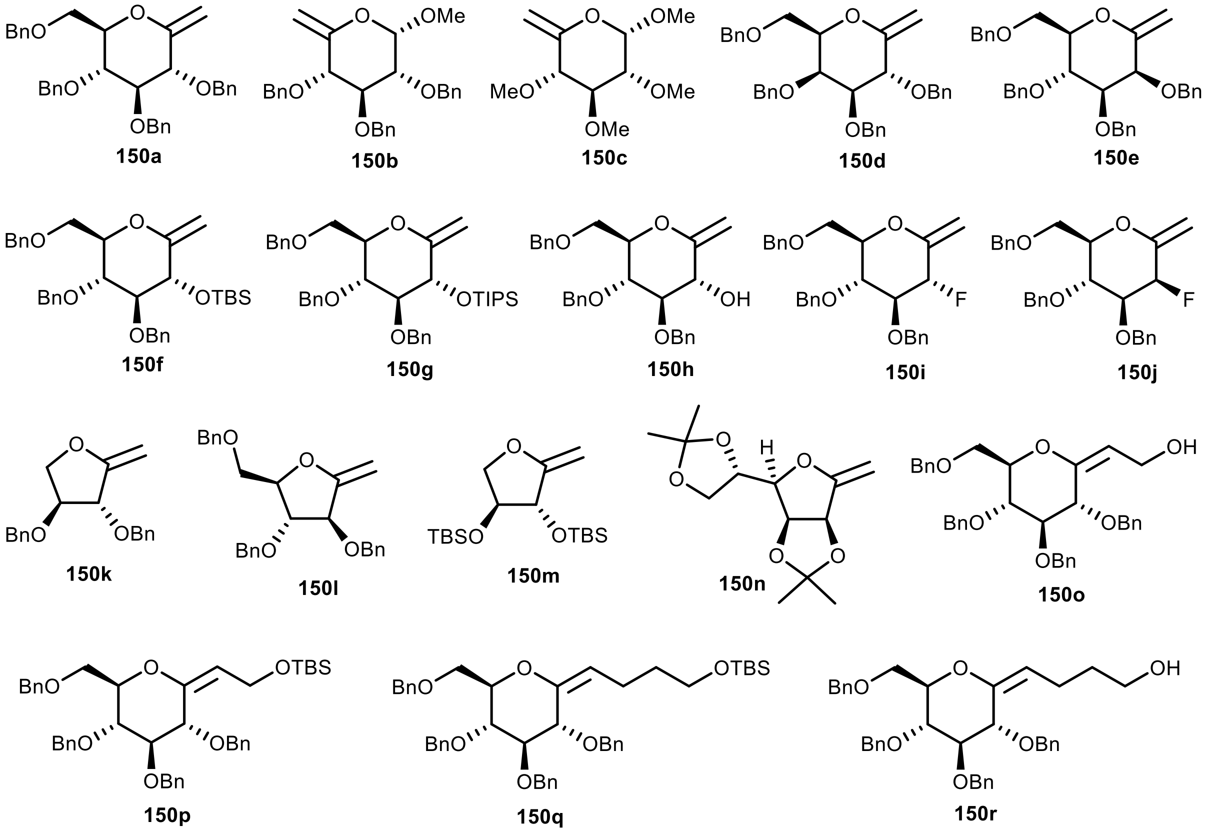
Entry	1,4-BQ	Solvent	Additive	[Fe](eq)	C(M)	Time	151a
1	2 eq	EtOH	-	0.1	0.03	5h	30%
2	2 eq	EtOH	-	1.0	0.03	7h	46%
3	2 eq	EtOH	-	1.0	0.05	5h	45%
4	2 eq	EtOH	-	1.0	0.10	2h	42%
5[a]	2 eq	EtOH	-	1.0	0.05	4h	28%
6	4 eq	EtOH	-	1.0	0.05	0.25h	55%
7	4 eq	THF	EtOH(8 eq)	1.0	0.05	1h	68%
8	4+2 eq	THF	EtOH(8 eq)	1.0	0.05	1h	77%
9	6 eq	THF	EtOH(8 eq)	1.0	0.05	1h	65%
10	4+2 eq	THF	EtOH(2 eq)	1.0	0.03	7.5h	80%
11	4+2 eq	THF	EtOH(8 eq)	0.5	0.05	1h	82%
12	4+3 eq	THF	EtOH(8 eq)	0.2	0.05	22h	77%
13[b]	4+2 eq	THF	EtOH(8 eq)	0.5	0.05	22h	59%
14[c]	4+2 eq	THF	EtOH(8 eq)	0.5	0.05	1h	79%
15[d]	4+3 eq	THF	EtOH(8 eq)	0.5	0.05	6.5h	52%
16	4+1 eq	THF	EtOH(8 eq)	1.0[e]	0.05	0.5h	66%
17	4+4 eq	THF	EtOH(8 eq)	0.5[f]	0.05	48h	NR[g]

a) Experimental temperature is 25 °C; b) (i-PrO)-PhSiH$_2$ was used instead of PhSiH$_3$. c) Without Na$_2$HPO$_4$; d) Experiment under air atmosphere; e) 0.5+0.5 eq [Fe(acac)$_3$/Fe(acac)$_2$] were used; f) Mn(acac)$_3$ was used instead of Fe(acac)$_3$; g) NR: no reaction.

4. Synthesis of quinones and *exo*-glycals (HAT substrates)

4.1. *Exo*-glycal library

In our work, a number of *exo*-glycals have been used to synthesize a small library of *O*-aryl ketosides. The structures of these compounds are shown in **Figure 7**. Following this, their synthetic routes will be presented. The *exo*-glycals **150e**, **150f**, **150g**, **150h**, were obtained from Mylène Lang (PhD student in our group).



150a 150b 150c 150d 150e

150f 150g 150h 150i 150j

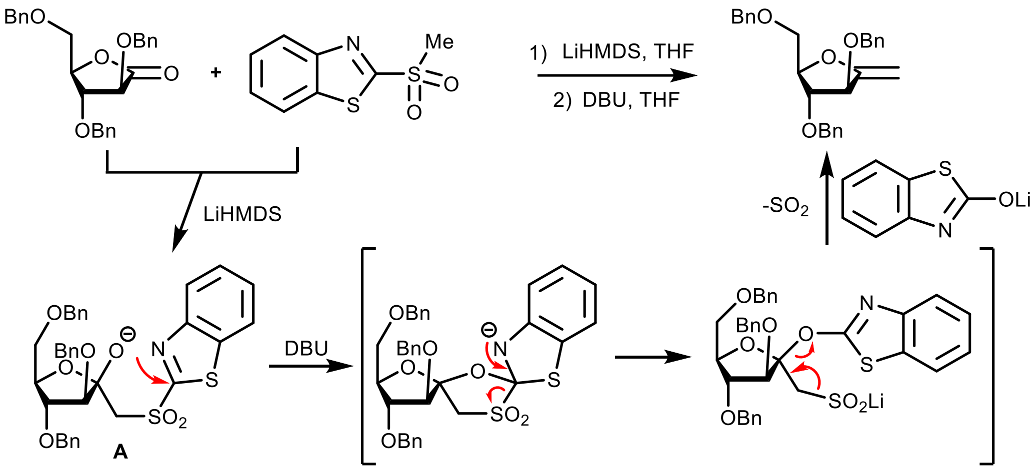
150k 150l 150m 150n 150o

150p 150q 150r

Figure 7. *Structures of the exo-glycals used for formal glycosylation study*

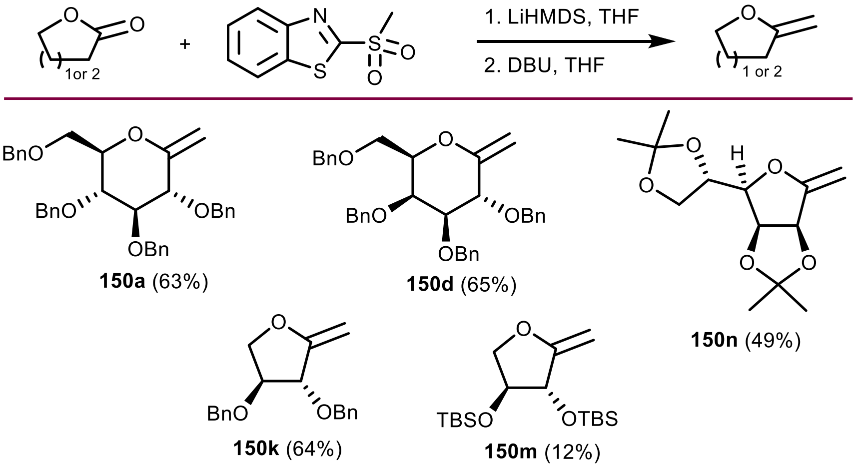
4.1.1. The synthesis of *exo*-glycals using the methodology of Gueyrard

Initially, a direct synthesis of olefins by reaction of carbonyl compounds with lithio derivatives of 2-[alkyl- or (2′-alkenyl)- or benzyl-sulfonyl]-benzothiazoles was reported in 1991.[176] More than a decade after, Gueyrard *et al.* described the synthesis of methylene *exo*-glycals using a modified Julia olefination.[177] In the optimization of the reaction conditions, the authors isolated adduct **A** in addition to the olefinic product. As expected from this result, addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) after the initial nucleophilic addition favored the reaction by inducing the key Smiles rearrangement step (**Scheme 60**).



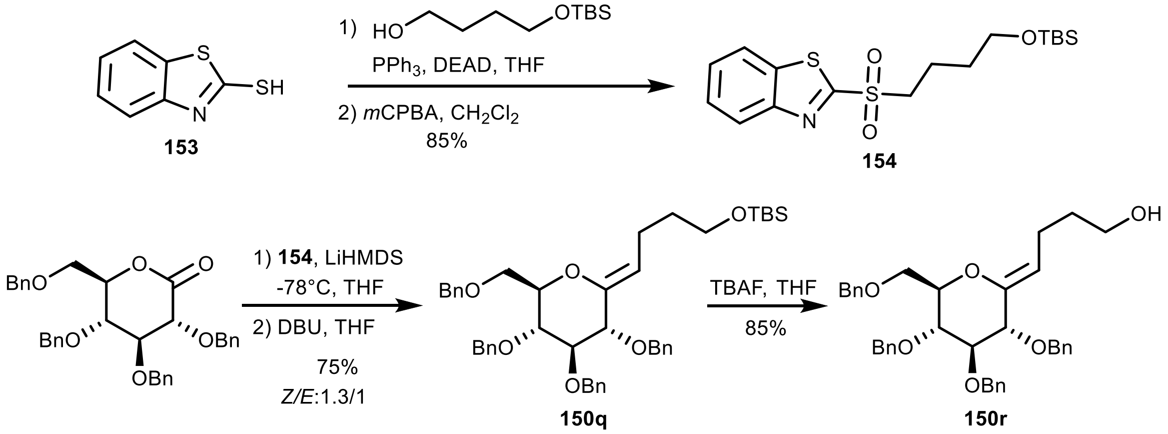
Scheme 60. Mechanism of Julia olefination from glycolactone

Exo-glycals **150a**, **150d**, **150n**, **150k** and **150m** were synthesized by the method described above (**Scheme 60**) from the corresponding glycolactones (**Scheme 61**).[156;177] For six-membered rings, *exo*-glycals **150a**, **150d**, we obtained moderate yields of 63% and 65%, respectively. For five-membered rings *exo*-glycals **150m**, **150n** and **150k**, the presence of large protecting groups seems to strongly impact the reaction yields (**150m**).



Scheme 61. Synthesis of exo-glycal **150a**, **150d**, **150n**, **150k**, **150m** *based on Gueyrard's methodology*

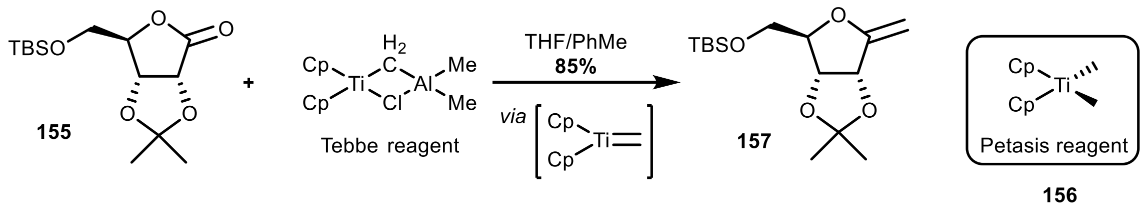
For the synthesis of *exo*-glycal **150q** and **150r** (**Scheme 62**), we first used benzo[d]thiazole-2-thiol (**153**) to synthesize benzo[d]thiazole **154** by Mitsunobu reaction[178] and oxidation of the sulfide group. Then *exo*-glycal **150q** was obtained by the method described above from the corresponding lactone. Deprotection reaction using TBAF afforded *exo*-glycal **150r**.



Scheme 62. *Synthesis of exo-glycal **150q** and **150r***

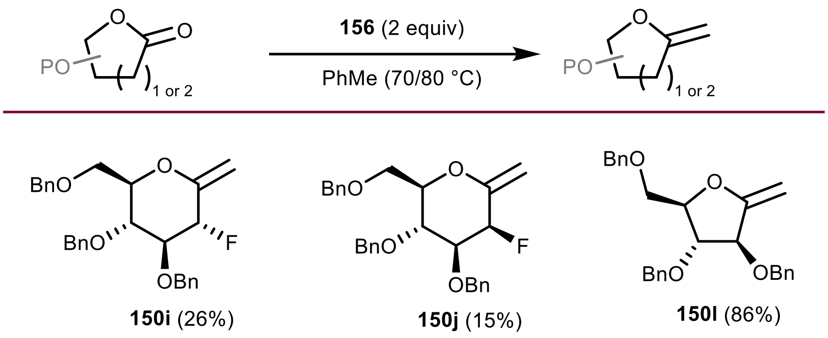
4.1.2. The synthetic method of *exo*-glycals by Wilcox

Another approach to *exo*-glycals, is the olefination of lactone **155** by Wilcox[179] using Tebbe reagent [180] (**Scheme 63**). Inspired by the work of Grubbs and Evans[181] on the olefination of various esters and lactones a few years ago, this approach allows for the methylenation of compound **155** by the *in situ* generation of Schrock carbene. In our synthesis, we use the Petasis reagent instead of Tebbe reagent. The Tebbe reagent and the Petasis reagent share a similar reaction mechanism. The active olefinating reagent, Cp_2TiCH_2, is generated *in-situ* upon heating.[182] Furthermore, Petasis reagent has a wide range of applications and is very stable in air.[183]



Scheme 63. *First synthesis of exo-glycal using Tebbe reagent[180]*

Exo-glycals **150i** and **150j** were synthesized from the corresponding lactones using the method already reported by Thiem *et al.*[184] in the presence of Petasis reagent. For *exo*-glycal **150l**, the corresponding lactone was prepared using Muzart conditions.[185] The *exo*-glycals **150e**, **150f**, **150g**, **150h** have been obtained by the same methodology.

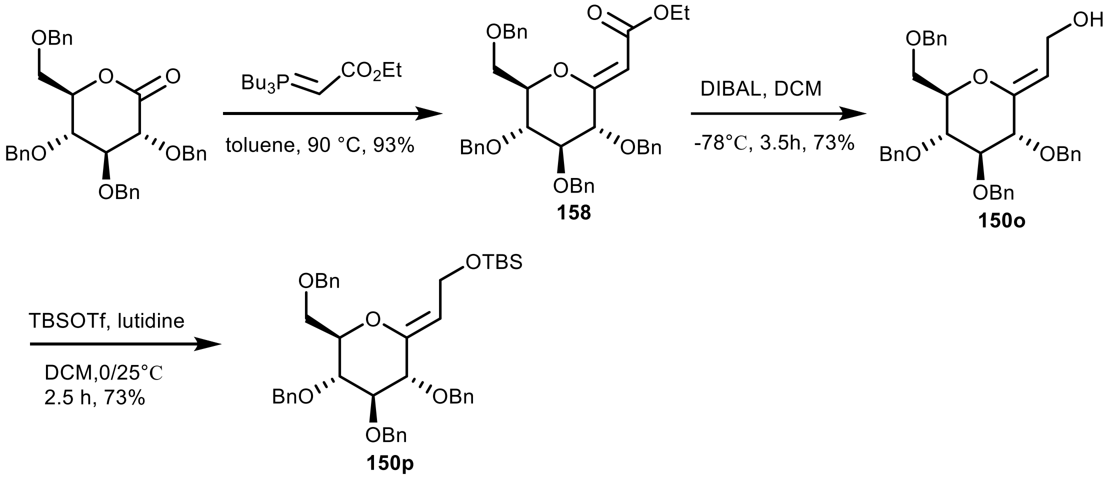


Scheme 64. Synthesis of exo-glycal **150i**, **150j**, **150l**

4.1.3. Synthesis of *exo*-glycals by other ways

4.1.3.1. Synthesis of *exo*-glycals 150o and150p

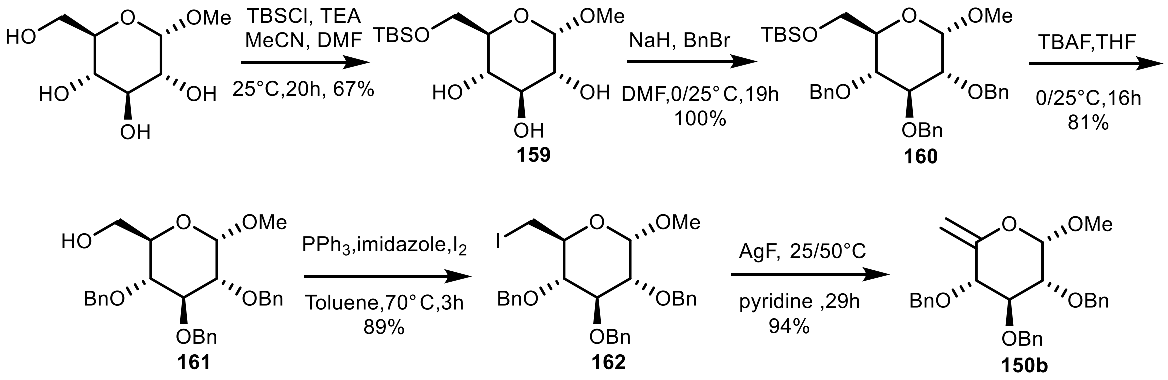
First, we synthesized the *C*-glycosylidene compound **158** *via* a Wittig olefination of lactones following a method reported by Chapleur.[186] Then, **158** is reduced by DIBAL to give compound **150o**, which was protected to afford *exo*-glycal **150p** in good yields (**Scheme 65**).



Scheme 65. *Synthesis of exo-glycals* ***150o,150p***

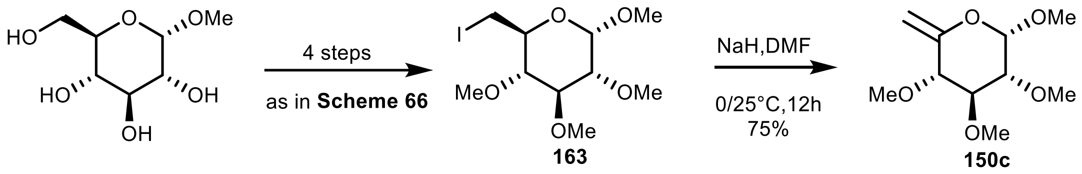
4.1.3.2. Synthesis of *exo*-glycals 150b and150c

For the synthesis of *exo*-glycal **150b**, the first step was the selective protection of commercially available methyl *α*-D-glucopyranoside in the presence of TBSCl and TEA affording compound **159** (**Scheme 66**). Then benzylation with NaH and BnBr in DMF gave **160** in quantitative yield. Removal of the TBS group to give **161** was obtained by treatment with TBAF (81% yield). The subsequent iodination reaction gave compound **162** in 89% yield. *Exo*-glycal **150b** was then obtained by treatment with AgF in 94% yield, which is better than the one reported in the literature.[156]



Scheme 66. Synthesis of exo-glycal ***150b***

The iodination product **163** was obtained in four steps using the same conditions than the ones described for the synthesis of **162** (**Scheme 66**). The elimination reaction took place in the presence of NaH and DMF at room temperature, giving *exo*-glycal **150c** in 75% yield (**Scheme 67)**.



Scheme 67. Synthesis of exo-glycal ***150c***

4.2. Quinone library

Ten quinones have been selected to evaluate the scope of the formal glycosylation. Their structures are shown below.

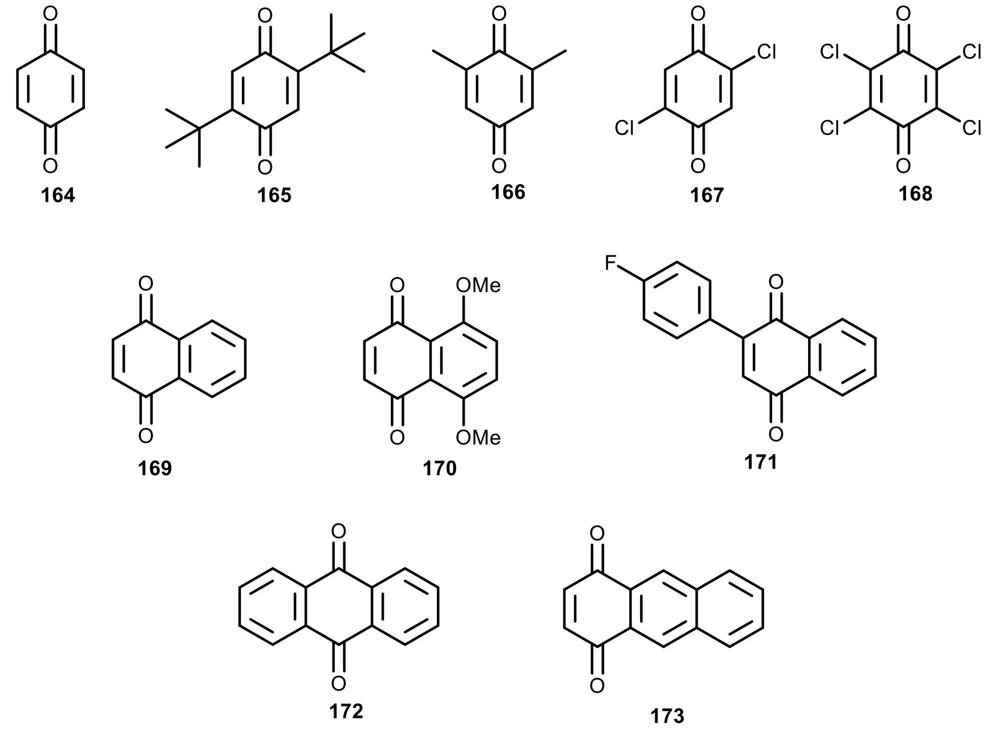
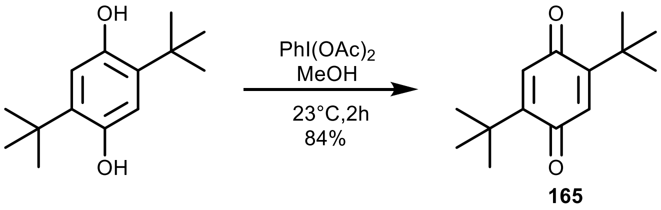


***Figure 8.** Structures of quinones*

4.2.1. Synthesis of quinones

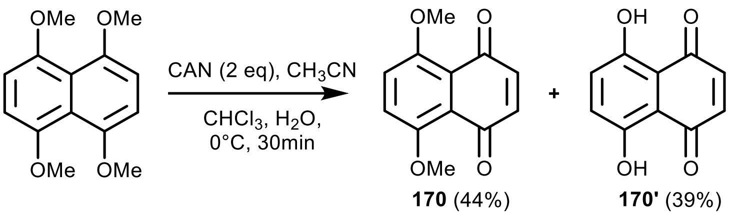
Quinones **164**, **166**, **167**, **168**, **169**, **172**, **173** are commercially available.

Compound **165** was synthesized in one step from commercially available 2,5-di-*tert*-butylbenzene-1,4-diol through oxidation in the presence of $PhI(OAc)_2$ (**Scheme 68**).[187]



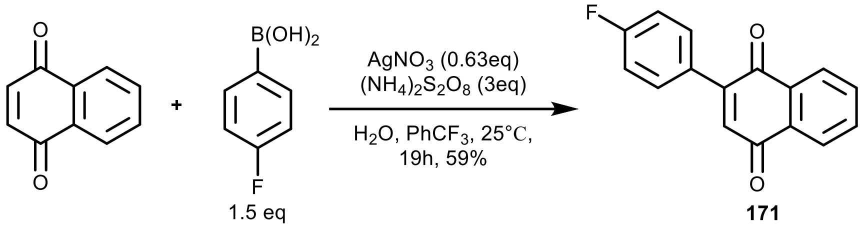
Scheme 68.** Synthesis of **165

Compound **170** was obtained in the presence of ceric ammonium nitrate (CAN) in a modest yield using the method reported by Macías.[188] Deprotected quinone **170’** was also isolated as a side-product in 39% yield (**Scheme 69**).



Scheme 69. *Synthesis of* ***170***

Quinone **171** was prepared by the reaction of 1,4-naphthoquinone (**169**) with (4-fluorophenyl)boronic acid in the present of catalytic amounts of silver nitrate and ammonium persulfate as oxidizing agents in a mixture of trifluorotoluene and water. The yield of the target product was 59%, which is almost identical to the one reported in the literature (**Scheme 70**).[189]

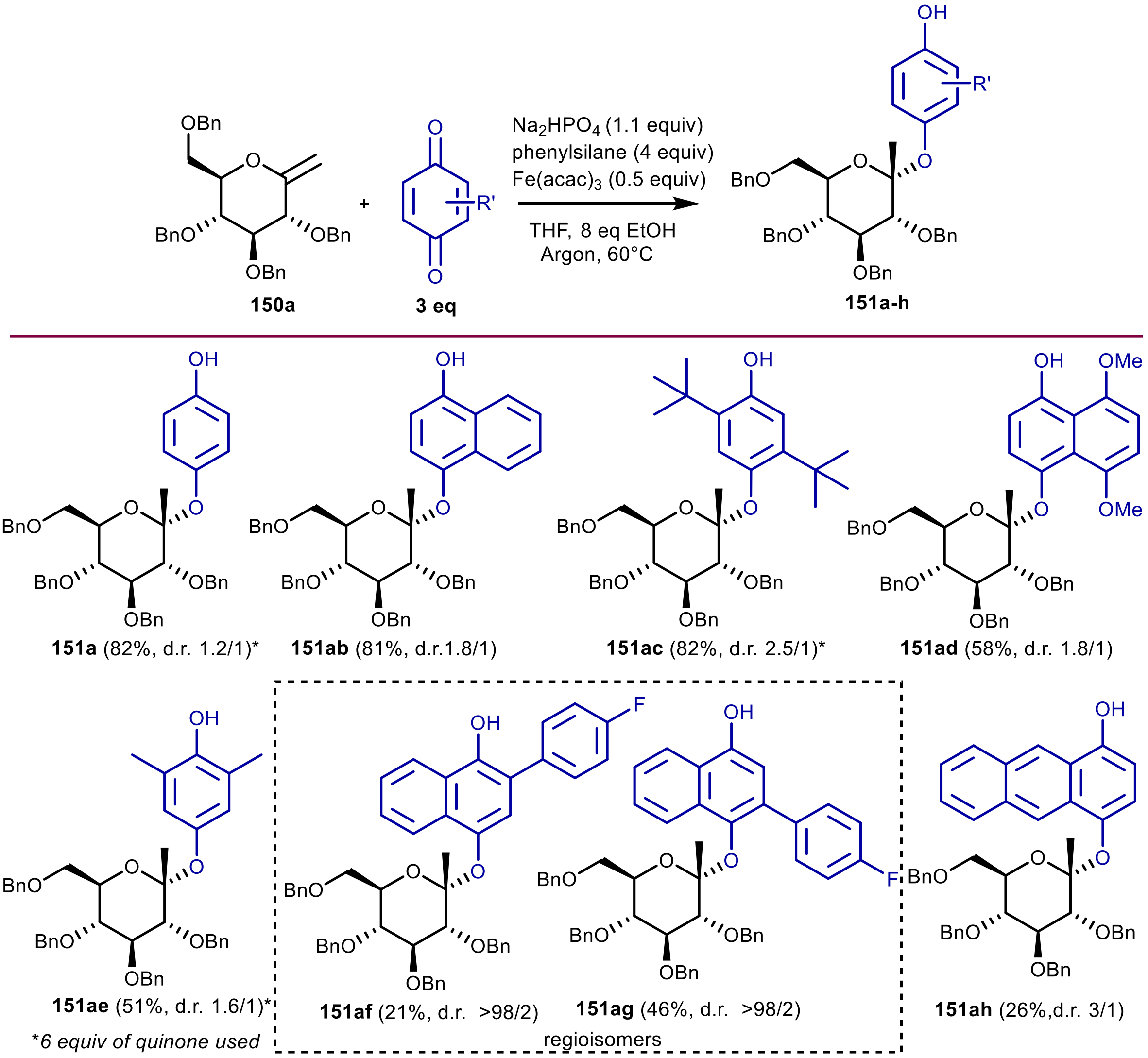


Scheme 70. *Synthesis of* ***171***

5. Substrate scope with different quinones and *exo*-glycals

5.1. Scope with different quinones

Using the optimal conditions found for formal *O*-glycosylation, we first evaluated the substrate scope with different quinones. The HAT-mediated coupling process worked well with sterically demanding 1,4-quinones, such as naphthoquinones **169** and **170** or 2,5-di-*tert*-butyl-1,4-benzoquinone (**165**) (products **151ab**, **151ac** and **151ad**). Of note, formal *O*-glycosylation of **169** to give **151ab** could be performed on a mmol scale with no reduction in efficiency. Subsequently, when **166** was selected for this *O*-glycosylation, a regioselective *O*-glycoside **151ae** was obtained in a good yield. When quinone **171** was applied to this *O*-glycosylation, the two regioisomers **151af** and **151ag** were obtained with high stereoselectivity. In this reaction **151ag** was isolated as the main product. When the formal glycosylation reaction was carried out with **173**, the *O*-glycoside **151ah** was obtained in only 26% yield. The results obtained show that formal glycosylation reaction is in general poorly stereoselective in the D-glucose series. The rationalization of the observed stereoselectivity will be carried out in the following part (**Scheme 71**).

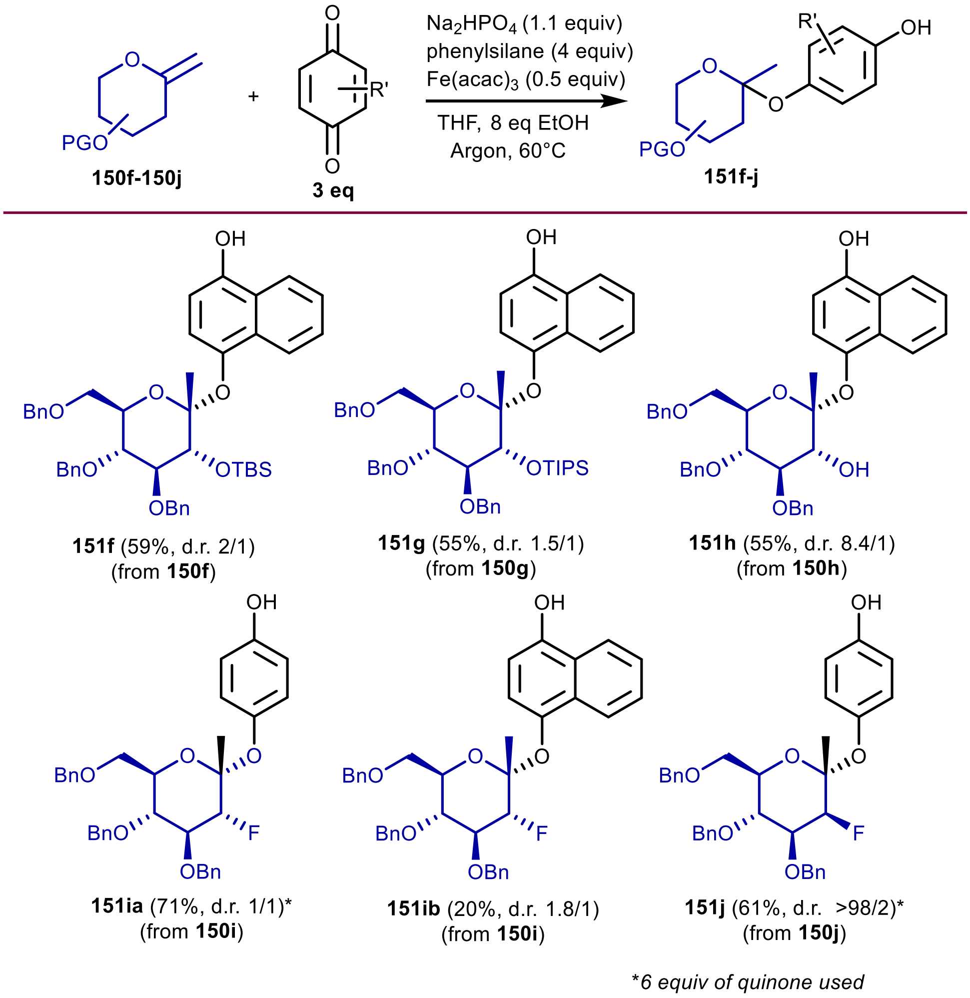


Scheme 71. *Substrate scope with different quinones*

5.2. Scope with different sugars

To demonstrate the generality of the radical-mediated *O*-glycosylation process, a range of *exo*-glycal with different configurations, ring size, and protecting group patterns were examined. In **Scheme 72**, we focused on the impact of the C-2 substituent on the reaction outcome. In **Scheme 73**, hexopyranose derivatives with various configurations were evaluated. Subsequently, 5-membered *exo*-glycals (**Scheme 74**), *exo*-glycals with a methoxy group at C-1 (**Scheme 75**), and finally *exo*-glycals with a tri-substituted double bond at C-1 (**Scheme 76**) were also assessed.

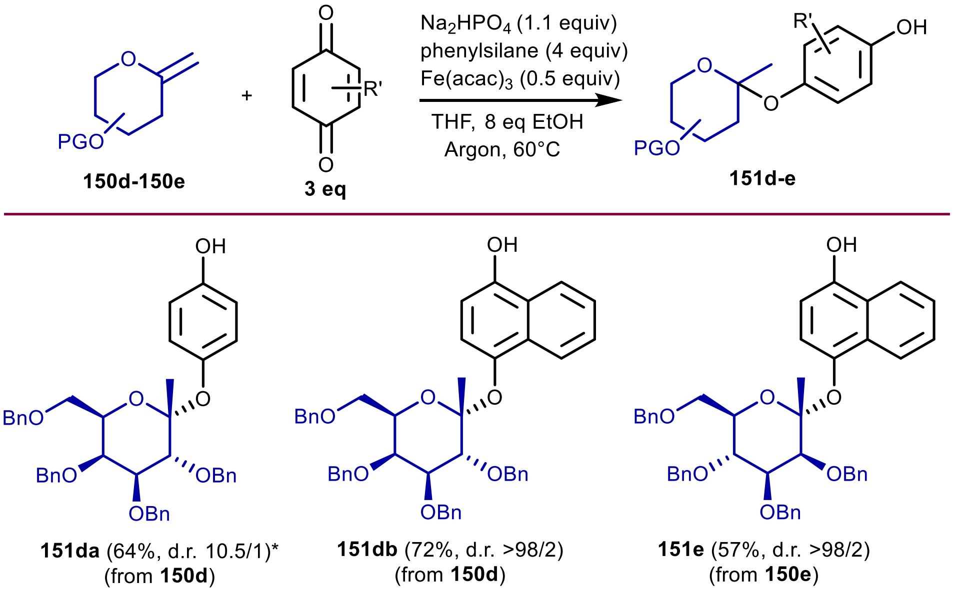
In the D-glucose series, the OBn protecting group at C2 was replaced by bulky protecting groups (TBS, TIPS) and the corresponding *O*-glycosides were obtained in moderate yields (**151f**, **151g**). Interestingly, *exo*-glycals with free hydroxyl group and electron-withdrawing fluorine group at C2 also work well under the MHAT conditions (**151h**, **151ia**). A dramatic influence of the sugar configuration was also observed for the transformation of 2-fluoro *exo*-glycal derivatives **150i** and **150j**. The α-ketoside **151j** in the D-manno series was obtained as a single diastereomer, whereas a complete loss of stereoselectivity was observed for its 2-fluoro D-gluco epimers **151ib** and **151ia** (**Scheme 72**).



***Scheme 72.** Substrate scope with exo-glycals having different substituents at C-2*

Fluorinated drugs have received increasing attention for decades due to the advantages of fluorinated glycomimetics in maintaining electrostatic interactions, reducing hydrophilicity and avoiding metabolic degradation. They have been also useful in the development of radiotracers and in enhancing the antigenicity of glycan-based vaccines.[190;191] However, fluorinated glycomimetics have been somewhat underutilized to date due to the challenges associated with their synthesis. Here, we obtained F-substituted *O*-glycosides (**151ia**, **151j**, **151ib**) that may contribute to the development of fluorinated drug candidates.

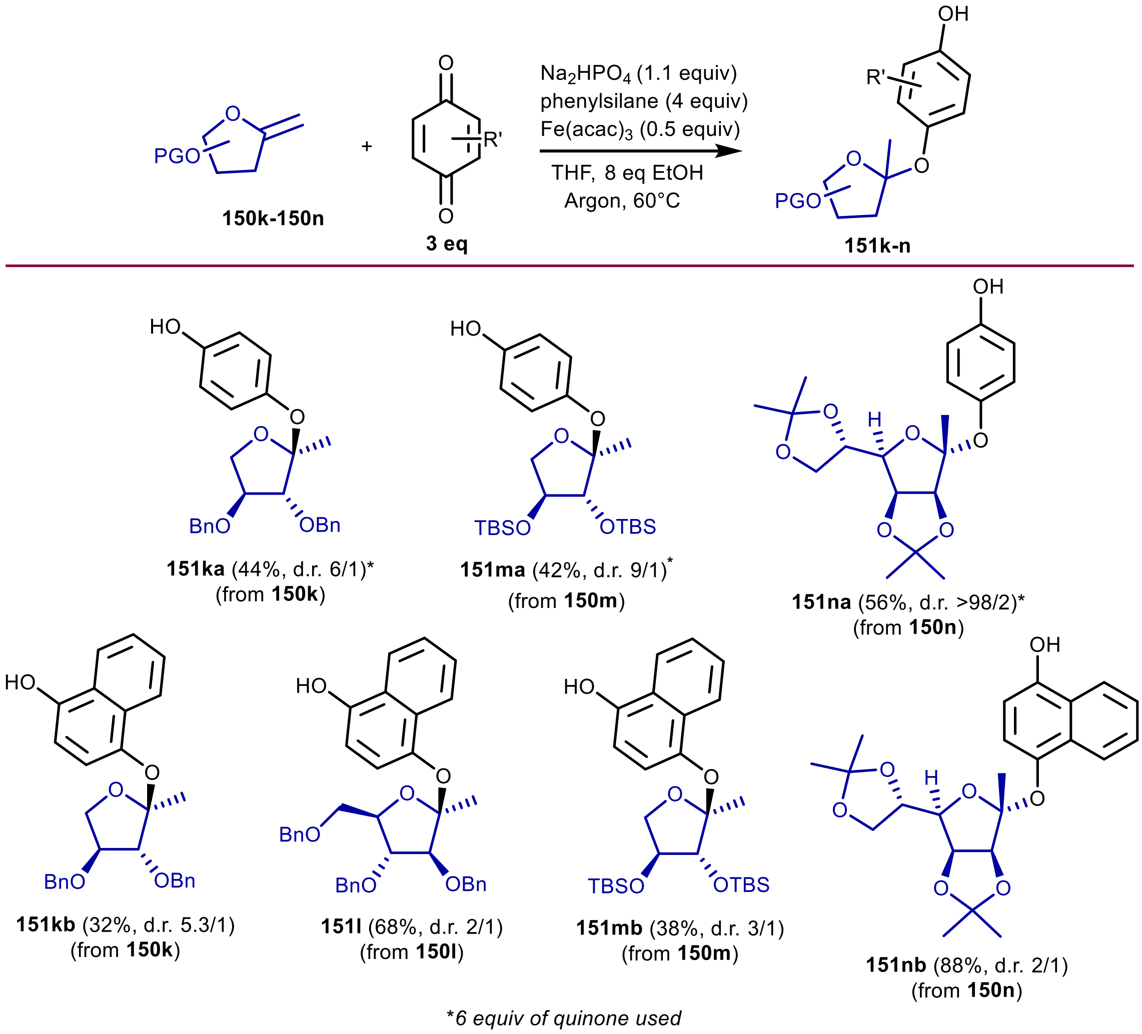
Other *exo*-glycals with different configurations were studied. In the D-hexopyranose series, switching from the D-glucose to the D-galactose or D-mannose configurations led to lower yields but much higher *α*-stereoselectivity (**151da**, **151db**, **151e**) (**Scheme 73**).



**6 equiv of quinone used*

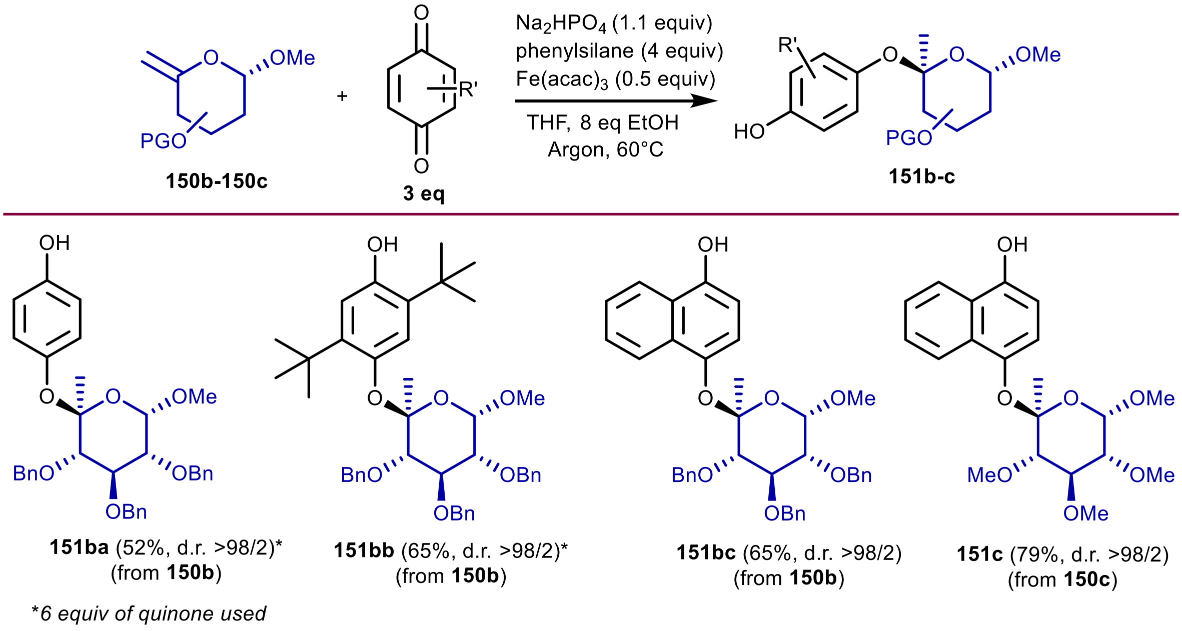
Scheme 73. *Substrate scope with exo-glycals having different configurations*

Next, five-membered *exo*-glycals were tested with the optimized conditions of the MHAT-mediated coupling reaction, giving the corresponding *O*-ketosides with low to high stereocontrol. Meanwhile, acid-sensitive protecting groups such as TBS or acetonide (**151ma**, **151na**, **151mb**, and **151nb**) were well tolerated (**Scheme 74**).



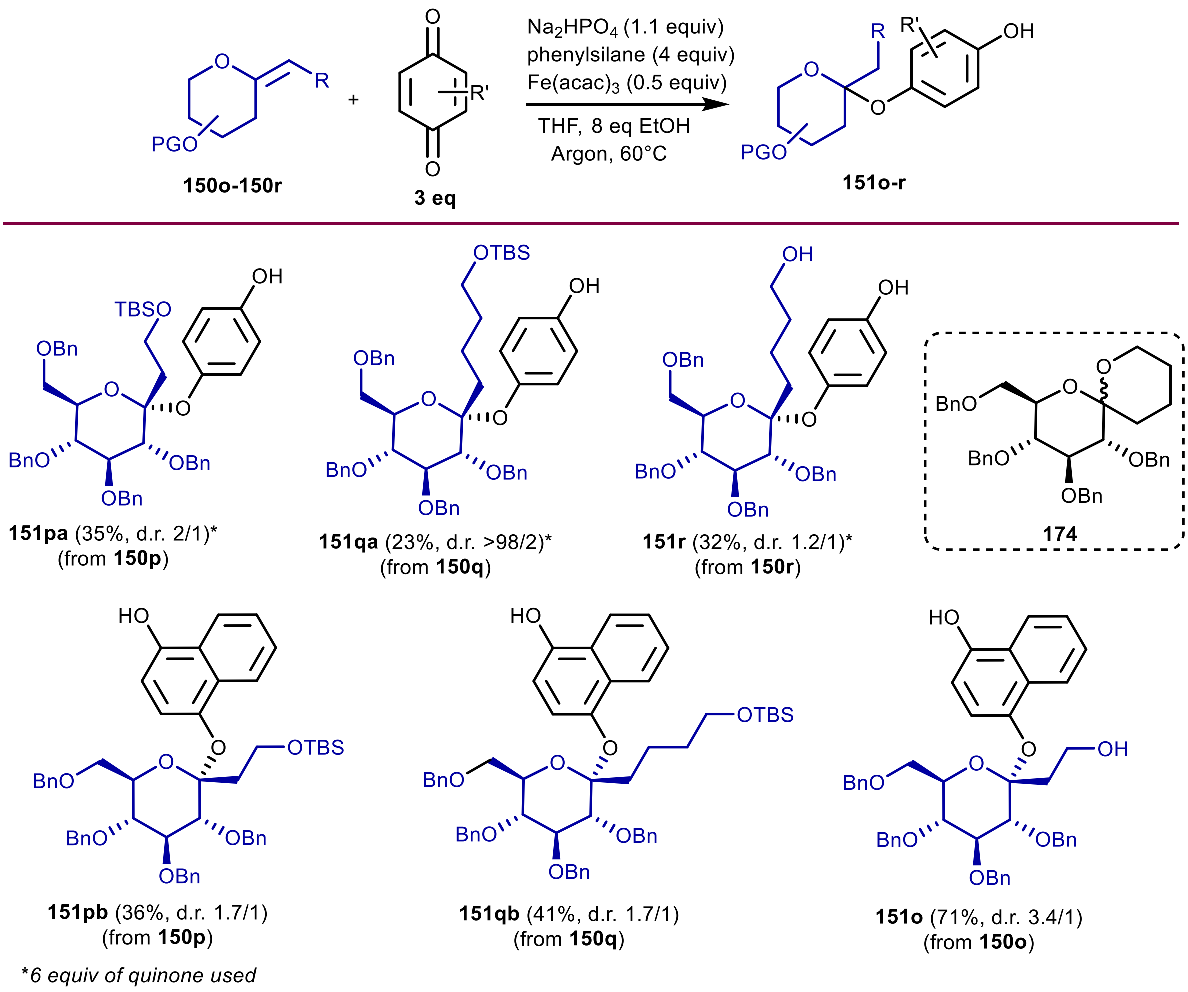
Scheme 74. *Substrate scope with five-membered exo-glycals*

The challenging bifunctional *exo*-glycal **150b** bearing an anomeric methoxy substituent at C-1 provided the corresponding 1,5-bis-glycosides in acceptable yields and high diastereoselectivity without cleavage of the glycosidic bonds (**151ba**, **151bb**, **151bc**). Bifunctional *exo*-glycal **150c** in which all OBn groups were replaced by OMe groups gave 1,5-bis-glycoside **151c** in better yields (**Scheme 75**).



Scheme 75. *Substrate scope with bifunctional exo-glycals **150b**, **150c***

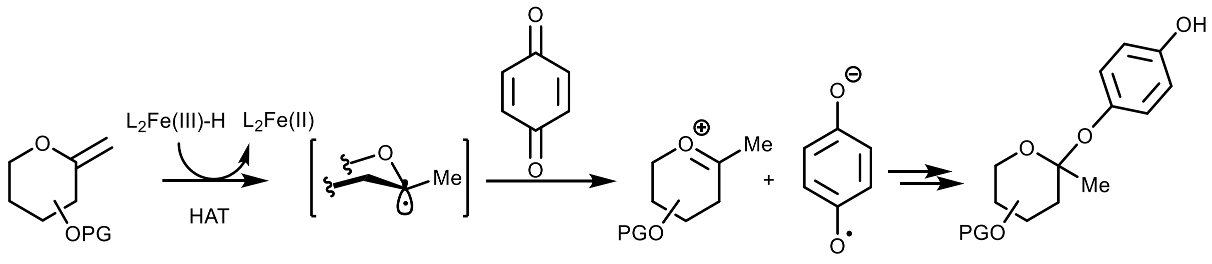
Finally, to further demonstrate the applicability of our methodology, more complex alkyl-substituted *exo*-glycals **150p-150r** were evaluated. The results obtained showed that the yields of the corresponding products **151p-151r** were low to moderate. We suppose that this is due to the influence of the steric hindrance of the two partners in the critical HAT-mediated coupling step. *Exo*-glycal **150r** was designed as a mechanistic probe to assess if the formal glycosylation proceeds through an oxocarbenium intermediate (see **section 6**; **mechanistic aspects**). The formation of the six-membered cyclization product **174** was not observed. Instead, the formal glycosylation product **151r** was obtained with a moderate yield.



Scheme 76. *Substrate scope with complex alkyl-substituted exo-glycals*

6. Mechanistic aspects

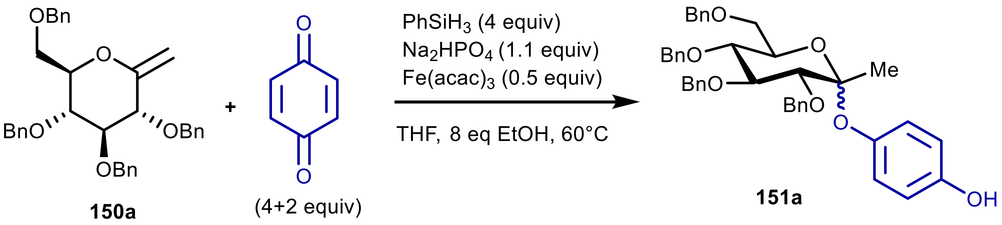
Based on the results observed for the formal *O*-glycosylation of quinones (see **sections 4** and **5**), in particular in terms of diastereoselectivity, we envisaged the formation of an oxocarbenium intermediate obtained by quinone-mediated oxidation of the HAT-generated glycosyl radical, following by subsequent reaction with the resulting hydroquinone (**Scheme 77**).



Scheme 77. *Hypothesis for an oxocarbenium intermediate*

To elucidate the mechanism, first, we performed some control experiments in the absence of Fe(acac)$_3$ or PhSiH$_3$ (**Scheme 78**, **entries 1** and **2**). In both cases, we find only the presence of starting materials. These results suggest that Fe(acac)$_3$ and PhSiH$_3$ are mandatory for the completion of the reaction. The mechanism of HAT with alkenes in the presence of Fe(acac)$_3$ and PhSiH$_3$ has been studied by Baran[57] and Poli[144] showing the formation of a radical (**Scheme 44**). To prove the formation of a glycosyl radical in our process, radical inhibitor TEMPO (2,2,6,6-tetramethylpiperidin-1-yl) was added to the reaction (**entry 3**). As expected, we found only the starting materials and no traces of the coupling product.

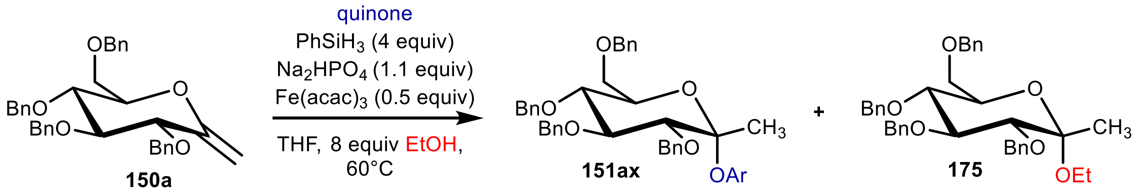
To prove the formation of an oxocarbenium intermediate, 5 equiv of 4-methoxyphenol was chosen as the competing nucleophile. The reaction resulted in no production of the corresponding methoxylated phenolic *O*-ketoside and only the product **151a** derived from benzoquinone was obtained in comparable yields than the one obtained under standard conditions. However, we cannot exclude at this stage the formation of an oxocarbenium intermediate (see below and proposed mechanism **Scheme 82**).



Entry	deviation	Result
1	no Fe(acac)$_3$	recovered **150a**
2	no PhSiH$_3$	recovered **150a**
3	TEMPO (4 equiv)	recovered **150a**
4	4-methoxyphenol (5 equiv)	**151a** (83% yield)

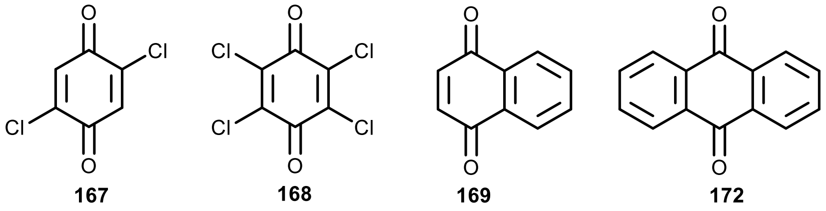
Scheme 78. *Control experiments*

When the MHAT reaction of **150a** was carried out with naphthoquinone in air rather than under an inert atmosphere, the corresponding ethyl *O*-ketoside by-product **175** was isolated in ~29%, along with the desired *O*-aryl glycoside product **151ab** (**Scheme 79**, **entry 2**). This result caught our attention. The cause of the production of compound **175** may be the formation of an oxocarbenium ion in the process, followed by an attack by ethanol. How does the oxocarbenium ion form? Based on the results obtained, we hypothesized that this oxocarbenium ion may have come from the quinone-mediated oxidation of the MHAT-generated glycosyl radical intermediate *via* a charge transfer complex. To prove our hypothesis, several quinones were selected according to their oxidative power (**Scheme 79**). First, **167** was selected, and only 37% of the target product *O*-glycoside **151ai** was obtained, accompanied by the production of the *O*-ethyl glycoside **175** in 24% yield. Another more oxidizing quinone **168** was also tried. According to our hypothesis, more amount of compound **175** was obtained (61% yield) and less *O*-aryl glycoside **151aj** was isolated (34% yield) (**entry 5**). The results obtained showed a nice correlation between the quinone's reduction potentials and the yields of the *O*-ethyl glycoside product **175** (**Scheme 79**). As expected, the presence of electron-withdrawing chlorine atoms favored the trapping of the oxocarbenium intermediate by ethanol by decreasing substantially the nucleophilic character of the semi-quinone anion generated upon reduction. Notably, the use of **172**, which showed the lowest reduction potential in the series, resulted in no production of *O*-ethyl glycoside.



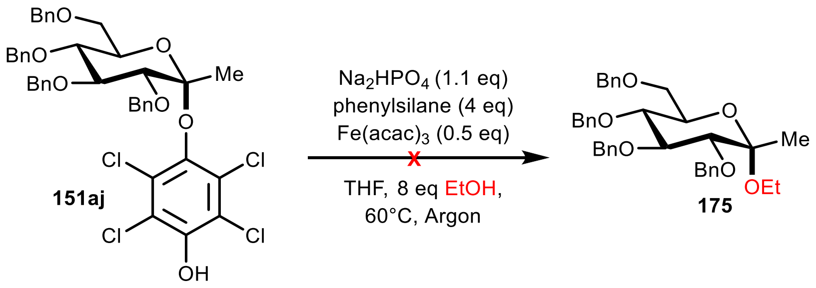
Entry	Atm.	quinone (n eq)	$E°(V)^a$	*O*-aryl ketoside	**175**
1	Ar	**172** (6)	-0.670	-	-
2[b]	Air	**169** (4)	-0.492	50% (**151ab**)	29%
3	Ar	**169** (4)	-0.492	81% (**151ab**)	-
4	Ar	**167** (5)	0.002	37% (**151ai**)	24%
5	Ar	**168** (4)	0.278	34% (**151aj**)	61%

[a] *E*°(V) : one-electron reduction potential in acetonitrile vs Normal Hydrogen Electrode (NHE); [b] 1 equiv of Fe(acac)$_3$ was used.



***Scheme 79.** Mechanistic studies for oxocarbenium intermediate trapping*

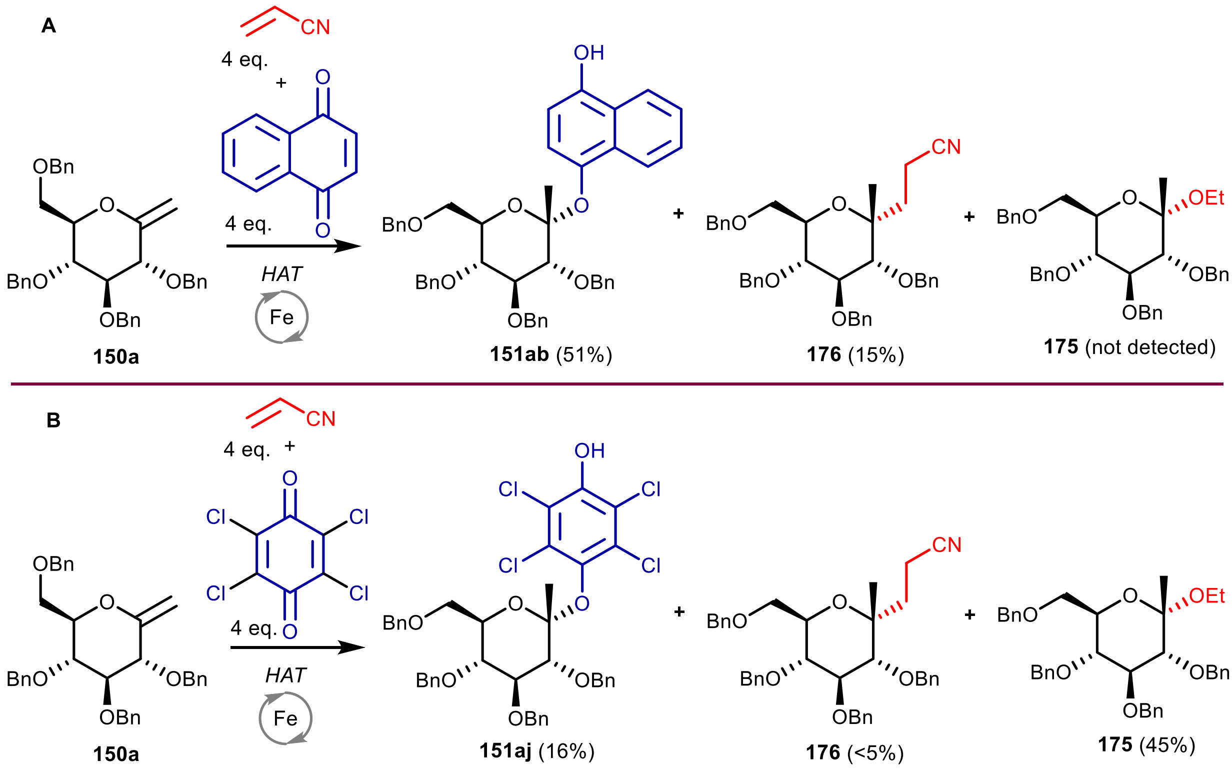
Additionally, a control experiment with **151aj** under typical HAT conditions showed that the formation of *O*-ethyl ketoside **175** was not the result of a transglycosylation reaction, which would proceed through a carbonyl cationic intermediate produced by the deglycosylation of the phenol glycoside (**Scheme 80**).



Scheme 80.** Control experiment with **151aj

Then, to further prove our hypothesis, a competition experiment was performed using an equimolar amount of naphthoquinone and acrylonitrile which was employed as a radical trapping agent (**Scheme**

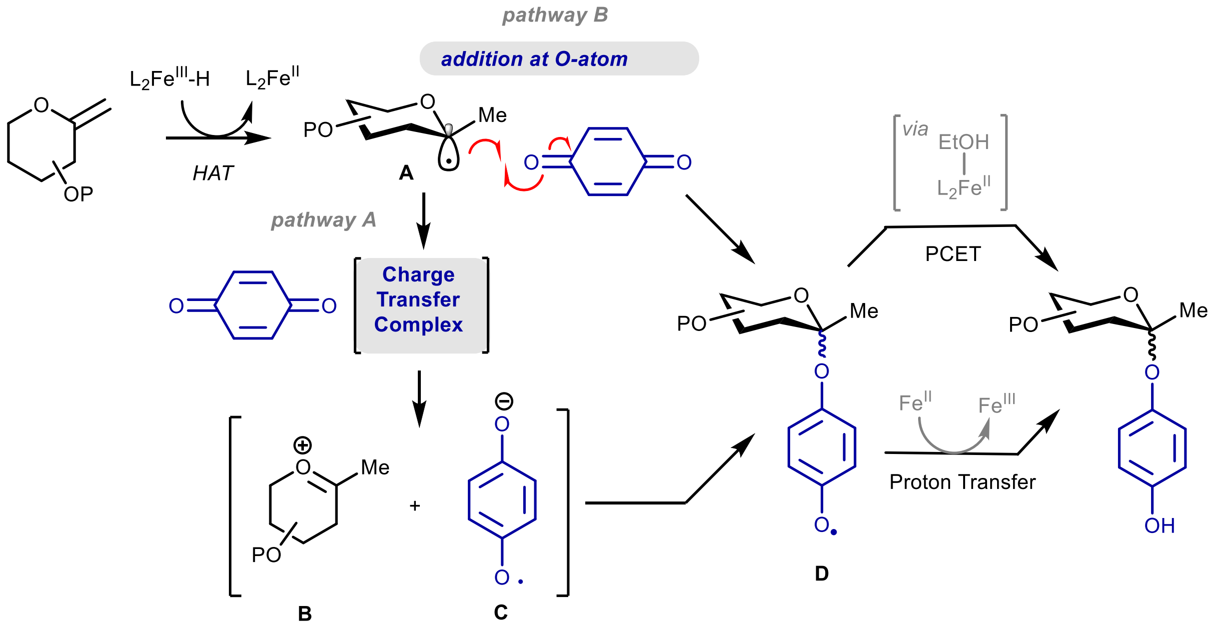
81A). The formation of the *α-C,C*-glycosyl product **176**[156] unambiguously confirmed that the reaction proceeded through the formation of a glycosyl radical intermediate. However, the fact that naphthol glycoside **151ab** was obtained as a major product under these conditions strongly advocates the ionic scenario described above. Indeed, acrylonitrile is expected to be a better radicophilic partner than naphthoquinone in coupling processes involving hindered electron-rich glycosyl groups. Adduct **176** would have been obtained as a major compound if a pure radical mechanism was involved. In order to obtain more evidence, another competitive experiment was carried out with the more oxidizing quinone chloranil (**Scheme 81B**). In agreement with the observation described above (**Scheme 79**), ethyl *O*-ketoside by-product **175** was isolated as the main product in 45% yield along with aryl ketoside **151aj** in 16% yield. In addition, the use of chloranil almost abolished the formation of *C,C*-glycosyl compound **176**, further corroborating the cationic pathway. Under these reaction conditions, large amount of the initially formed glycosyl radical intermediate is likely to be oxidized before being intercepted by acrylonitrile.



Scheme 81. *Competition experiments*

One other important observation is the fact that *O*-ketoside **175** was not obtained in our optimized condition although an excess of ethanol is present (see **sections 3-5**). This result and our mechanistic studies (**Schemes 78-81**) may suggest the formation of a charge-transfer (CT) complex between the glycosyl radical **A** and the electron acceptor quinone, followed by a single electron transfer process (**Scheme 82**). In addition, based on the previous mechanistic studies on MHAT reactions to alkenes[57-

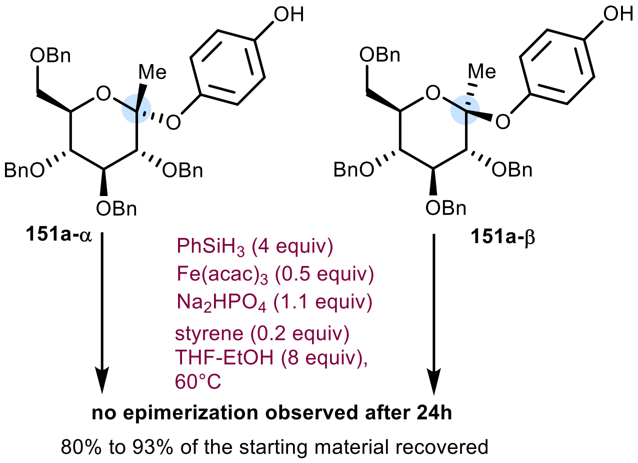
[62]and our own work,[156] a possible mechanism roadmap is presented in **Scheme 82**. We assumed that a fast, irreversible HAT from highly reactive transient Fe(III)−H species to the carbohydrate olefin afforded the tertiary pseudoanomeric radical intermediate **A**. Then, a charge transfer (CT) complex is formed between the glycosyl radical **A** and the electron acceptor quinone (pathway A) which results in the formation of two reaction intermediates, the glycosyl oxocarbenium ion **B** and the semi-quinone anion **C** in close proximity. These two intermediates are most likely located within the tetrahydrofuran solvent cage. This also explains the absence of ethanol or 4-methoxyphenol capture of the oxocarbenium ion in an argon atmosphere. However, another pathway cannot be totally excluded (pathway B). In this pathway the radical **A** is coupled directly to the oxygen atom of the quinone according to the mechanism reported by Renaud (**Scheme 53**).[161] Both pathways lead to the same intermediate product: the rather stable phenoxy radical **D**. The formation of phenolic *O*-ketoside products may be then obtained *via* proton-coupled electron transfer (PCET) from the ethanolic complex of Fe(II) or *via* a stepwise reduction/proton transfer pathway.



Scheme 82. *Putative mechanistic pathways*

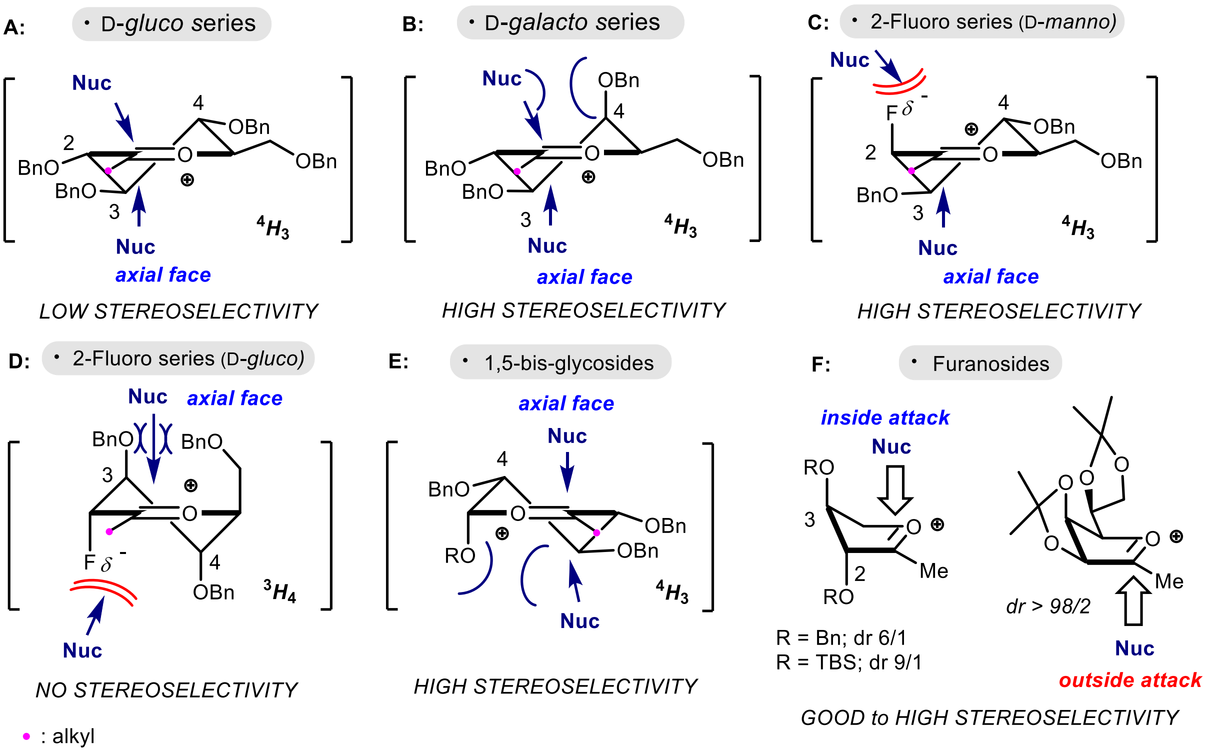
7. Explanation of observed stereoselectivity

From the results obtained above, we note that the low diastereoselectivity observed in the D-gluco series contrasts with related studies involving highly α-selective radical processes (**Schemes 71-76**).[23;65;156] To some extent, this difference in stereoselectivity also supports our mechanistic hypothesis involving a glycosyl oxocarbenium cation intermediate. To be more convincing, an equilibration experiment as a control was performed from pure **151a**-α to assess whether the formation of the β- anomer was due to the re-equilibration of the α- anomer resulting in a $^4C_1$ conformer with the bulky aromatic aglycon moiety in an equatorial orientation. In addition, the same experiments were performed from **151a**-β to explore the possibility of a thermodynamically driven equilibration from the *β*- to *α*- anomer, which can be attributed to the anomeric effect. Under typical MHAT reaction conditions, no epimerization of the anomeric center was observed after 24 h, regardless of whether the *O*-ketoside substrate was *α*- or *β*-configured (**Scheme 83**). To be close to the reaction conditions, 10 mol% of styrene was added to the equilibration reactions to generate all the iron species and other transient intermediates present during the HAT-mediated coupling reaction. Studies related to the role of styrene as an additive in the iron-catalyzed hydrogenation of olefins have been reported.[57]



Scheme 83. *Equilibration experiments*

Furthermore, in previous reports we could see that a stereoelectronic effect controls the origin of the ***α***-selectivity in the radical process. This stereoelectronic effect increases the stability and nucleophilicity of the axial σ-radical over its equatorial counterpart.[41;43;163;192] In addition, the stereoselectivity of glycosylation reactions processing through oxocarbenium intermediates have been frequently rationalized according to Woerpel's model.[193-197] This model assumes that the nucleophilic attack occurs preferentially along with an axial trajectory on the most favored/reactive half chair of the pyranosyl oxocarbenium ion intermediate to minimize torsional strain during the transition to the final chair conformation. In the D-gluco and D-galacto series, the $^4H_3$ conformers are strongly favored, owing to (a) the pseudoequatorial position of the hydroxymethyl side chain at C-5; (b) the pseudoaxial position of the electron-donating C2−H bond which provides stabilizing hyperconjugation interactions with the 2p orbital on the electrophilic carbon atom; and (c) the pseudoaxial position of the electronegative C-4 alkoxy in the D-galacto series allowing electron density donation to the positively charged ring oxygen.[198] For bulky phenol-type nucleophiles, steric effects may significantly compete with stereoelectronic factors mentioned above to control facial selectivity, equatorial attack on the $^4H_3$ conformer (i.e., attack at the face that would lead to the *β*-ketoside) being sterically favored over the axial attack. Steric effects may thus explain why the HAT-mediated glycosylation reaction proceeded with poor stereocontrol in the D-gluco series and why introduction of steric bulk on the equatorial face of the favored half-chair oxocarbenium ion resulted in higher stereoselectivity as observed in the D-galacto series and with bifunctional *exo*-glycals **150b**. Opposite stereoselectivity with 82:18 dr was observed for HAT-mediated radical addition of bifunctional glycoside **150b** to acrylonitrile, further confirming that the glycosylation reaction proceeds through a cationic mechanism.[156] Increasing steric hindrance on the $^4H_3$ conformer top face by formal inversion of the configuration at C-4 led to higher α-selectivity in the D-galacto series (**Scheme 84B**). A massive improvement of stereoselectivity in favor of the α-product was also observed by modifying the C-2 position of D-glucal **150a** to afford the corresponding D-manno-configured 2-fluoro-derivative **150j**. The orientation of the polarized C−F bond toward the electropositive center may play a crucial role by inducing a rigidification of the $^4H_3$ oxonium cation conformer.[199-203] In addition, equatorial attack from the upper β-face is expected to be disfavored by repulsive electrostatic interactions between the axial-F atom and the incoming anionic nucleophile (**Scheme 84C**). Inversion of configuration at C-2 had a dramatic effect on stereo-induction. This may be explained by the fact that the D-gluco-configured 2-fluoro oxocarbenium cation exists predominantly in a $^3H_4$ conformation in which all the substituents are axial for the reasons mentioned above. Attack from the stereoelectronically favored upper face which is opposite to the axial-F atom is strongly impeded by sugar substituents (**Scheme 84D**). In line with the complete loss of stereoselectivity observed, none of the other scenarios/alternatives involving both half-chair conformers are favored for stereoelectronic reasons (equatorial attack) and/or due to repulsive electrostatic interactions. Concerning *exo*-glycals **150k** and **150m**, the observed stereoselectivity is in agreement with the model proposed by Woerpel to explain stereoselectivity in nucleophilic additions to five-membered ring oxocarbenium cations (**Scheme 84F**).[204;205] According to this model, the formation of the 1,3-*cis* products **151ka** and **151ma** may be rationalized by a stereoelectronically controlled inside attack of the incoming nucleophile on the lowest energy conformer of the oxocarbenium cation intermediate (i.e., the ^3E conformation with the C-3 alkoxy group in a pseudoaxial position to maximize electrostatic effects). The use of bulky protecting groups in **150m** led to good stereoselectivity (dr 9/1) by favoring the ^3E envelope conformation with the 2,3-silyloxy groups oriented diaxially to avoid vicinal steric interactions.[206] The lower stereocontrol observed with benzyloxy groups (*exo*-glycal **150k**) may be due to the tendency of the C-2 alkoxy group to adopt preferentially a pseudoequatorial orientation, leading to partial destabilization of the ^3E conformer (**Scheme 84F**).[204;205] In the D-mannofuranose series, the inside face being strongly hindered, the nucleophilic attack from the opposite side to the all *cis* substituents provided the *O*-glycosylated product **151na** in high diastereoselectivity.



Scheme 84. *A possible stereoselectivity model*

8. Conclusion

In conclusion, we have developed a general strategy for the construction of *C*,*O*-aryl glycoside building blocks from *exo*-glycals and quinones under iron-mediated HAT conditions. This mild one-step reaction which provides regiospecific access to phenolic *O*-ketosides of biological interest *via* a tertiary pseudoanomeric radical may be viewed as a very rare example of formal glycosylation of quinones. This work has been published in *JOC* in 2022.[207] A series of *O*-aryl glycoside compounds was obtained in this work. With these *O*-aryl glycosides in hand, we were eager to develop a new method to access *C*-aryl ketosides through *O*- to *C*-glycosyl migration. The Suzuki rearrangement that is mechanistically related to the Fries rearrangement has demonstrated its synthetic utility for the transformation of *O*-aryl glycosides into the corresponding *C*-aryl glycosides as illustrated by the synthesis of a number of natural products, including gilvocarcin or ravidomycin.[41;208-211] In this context, the synthesis of the corresponding bis-*C*,*C*-glycosyl compounds has no precedent. Our results towards this objective are presented in **Chapter 3**.

Chapter 3: Conversion of *O*-Aryl to *C*-Aryl ketosides

1. Introduction

Aryl and heteroaryl *C*-glycosides are very important among the many glycoconjugates having biological and therapeutic significance.[25-27;31;40;212-214] Pseudoanomeric centers of *C*-aryl glycosides are covalently linked to the carbon atoms of aromatic or heterocyclic rings *via* *C*-glycosidic bonds.[215] They tend to have high oral bioavailability and do not require conversion to prodrug to achieve high plasma levels.[40] Stable linkages between sugars and aromatic or heterocyclic fractions *via* C-C bonds can resist enzymatic hydrolysis, allowing these compounds to interfere more effectively with DNA and RNA synthases.[32] Both natural and synthetic aryl *C*-glycosides have been shown to have significant medicinal properties. Representative examples include the SGLT2 inhibitor Dapagliflozin (see **Figure 2**) and derivatives of Dapagliflozin with stronger activity,[216] as well as the antidiabetic drug Steglatro™,[217-219] the immunomodulator bergenin[220] or the antibiotic kidamycin (**Figure 9**).[221]

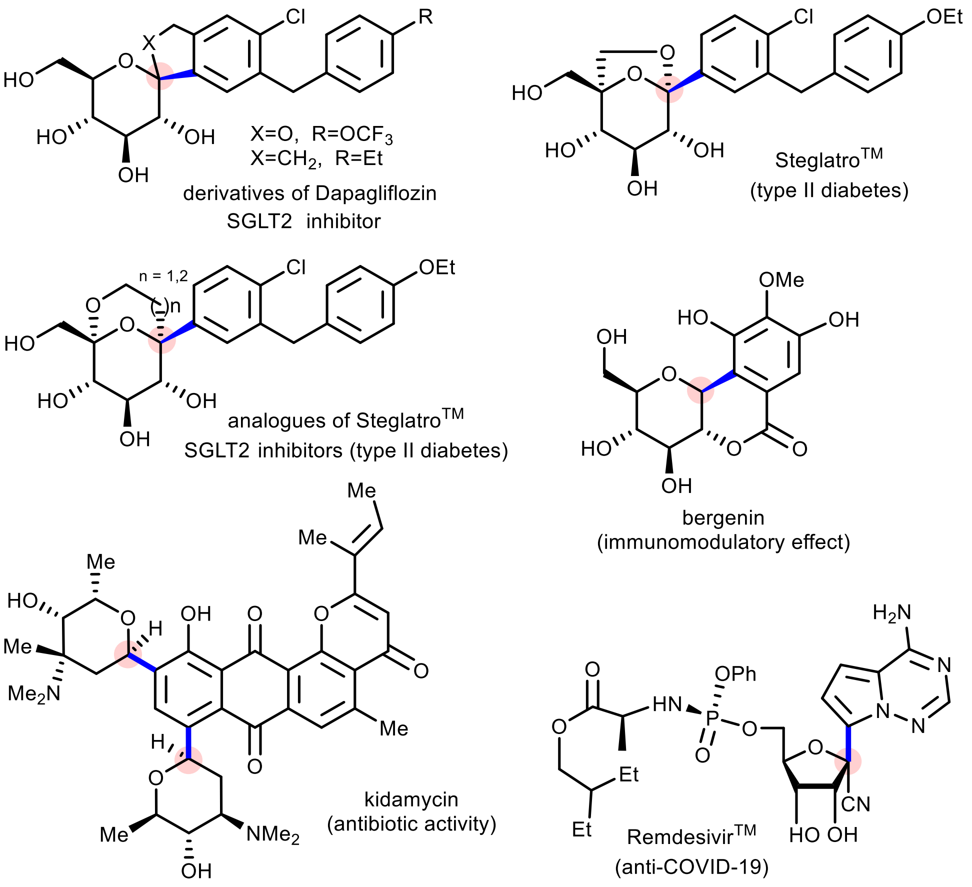


Figure 9. *Selected C-aryl and bis-C,C-aryl-glycosides of biological and therapeutic interest.*

In recent years, specific stereoselectivity and high yields in glycosylation processes have been the goal of scientists. The conventional *C*-glycosylation reactions usually involve nucleophilic reactions of metal reagents (e.g., organotin, organozinc, organolithium, organoaluminium and Grignard reagents) with the glycosyl donors. These reactions are effective, but not easy to handle due to the sensitivity of the metal reagents to air and moisture. Over the last decade, scientists have made considerable efforts to develop milder, more effective, and highly stereoselective methods. To date, the Fries-type,[211] Ferrier-type,[222;223] Pd-catalyzed Heck-type[224] and Tsuji–Trost-type *C*-glycosylations[225] have been established.

The synthesis of *C*-aryl glycosides that contain quaternary pseudoanomeric center bearing two exocyclic *C*-substituents remains a serious challenge. Among these compounds, as we have seen previoulsy, the anthracycline antibiotic nogalamycin[53;85] and its congeners[214] are synthetically attractive due to their unusual complex structures in which the aglycon aromatic moiety is joined to the sugar residue *via* both *O*- and *C*- glycosidic bonds to form a benzoxocin ring system (**Figure 10**). Nogalamycin is a typical example of this kind of anthracycline, which has potent antitumour activity. Its semi-synthetic derivative, menogaril, was selected for evaluation in clinical trials in different tumour types and showed lower cardiotoxicity and better antitumour activity compared to nogalamycin.[71;72] The *C*-aryl ketoside motif is also found in purely synthetic drugs or drug candidates. Some selected examples were shown in **Figure 9**, the recently released prodrug Remdesivir™ (anti-COVID-19),[226] and novel SGLT2 inhibitors related to Steglatro™, but with different linkages between the aromatic rings and carbohydrate/glucose moieties.[32;227]

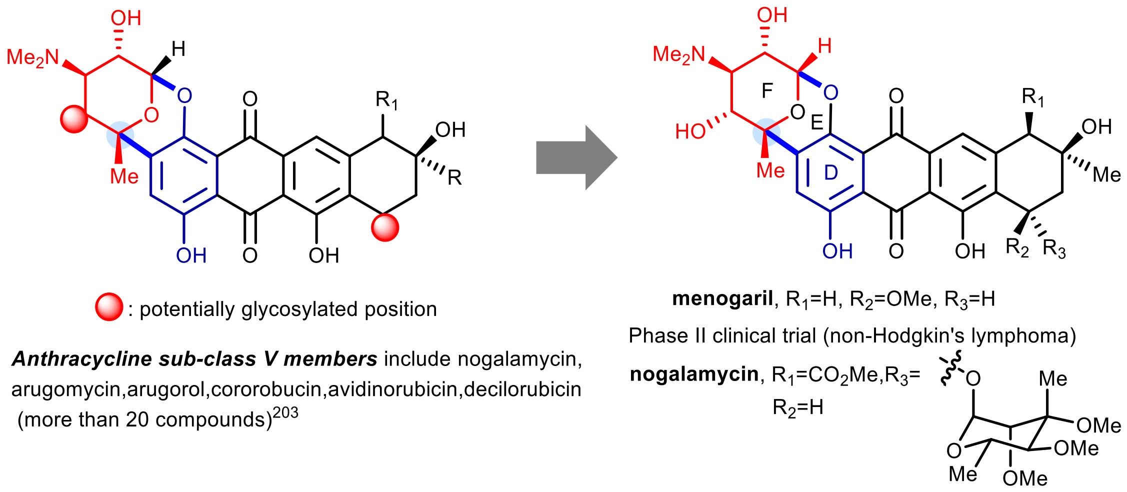
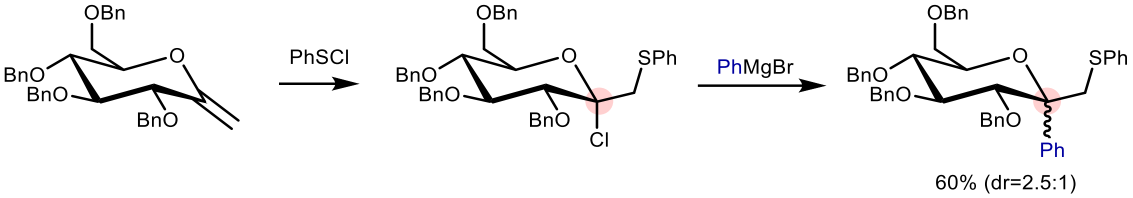


__Figure 10.__ The anthracycline sub-class V and structures of nogalamycin and menogaril

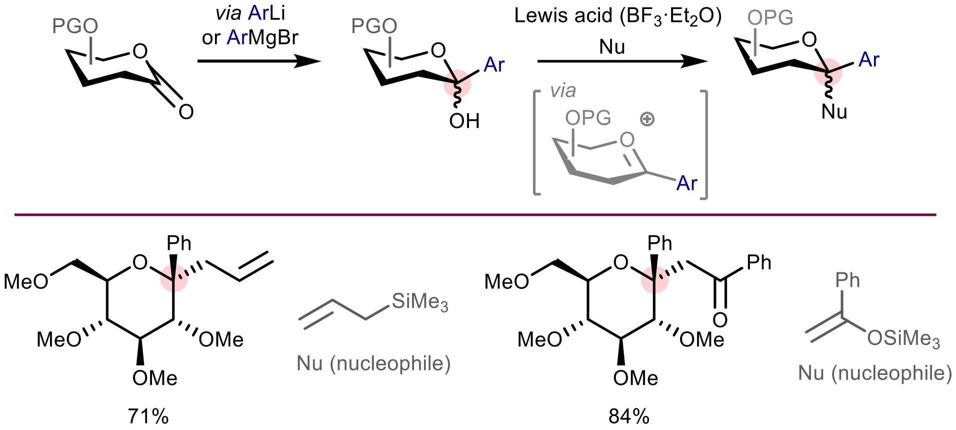
Although a number of *C*-aryl glycoside preparations have been reported so far, strategies for constructing the quaternary pseudoanomeric center embedded in bis-*C*,*C*-aryl-glycosides are scarce.[25-27;31;40;212;213] Most approaches involve the reaction of an electrophilic sugar donor generated from a lactone or a glycal with a nucleophile (**Schemes 85 - 87**).[228-230] For example, in 1995, Smoliakova's group[228] reported the synthesis of bis-*C*,*C*-aryl-glycoside *via* PhSCl-mediated coupling of *exo*-glycal with PhMgBr (**Scheme**

85).



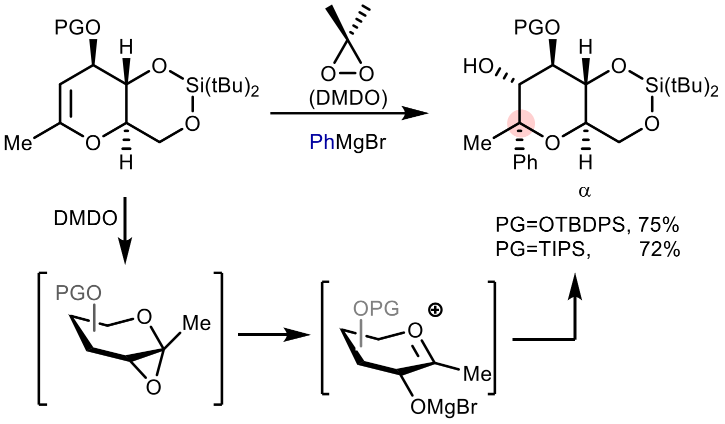
Scheme 85. *Example of the preparation of a bis-C,C-aryl-glycoside from exo-glycals*

In 2003, López's team[229] reported a concise strategy for the stereocontrolled preparation of *C*-aryl ketosides by Lewis acid-catalyzed *C*-glycosidation from lactones. Examples were presented in **Scheme 86**. This strategy was applied in the synthesis of derivatives of dapagliflozin (see **Figure 9**) in 2010.[216]



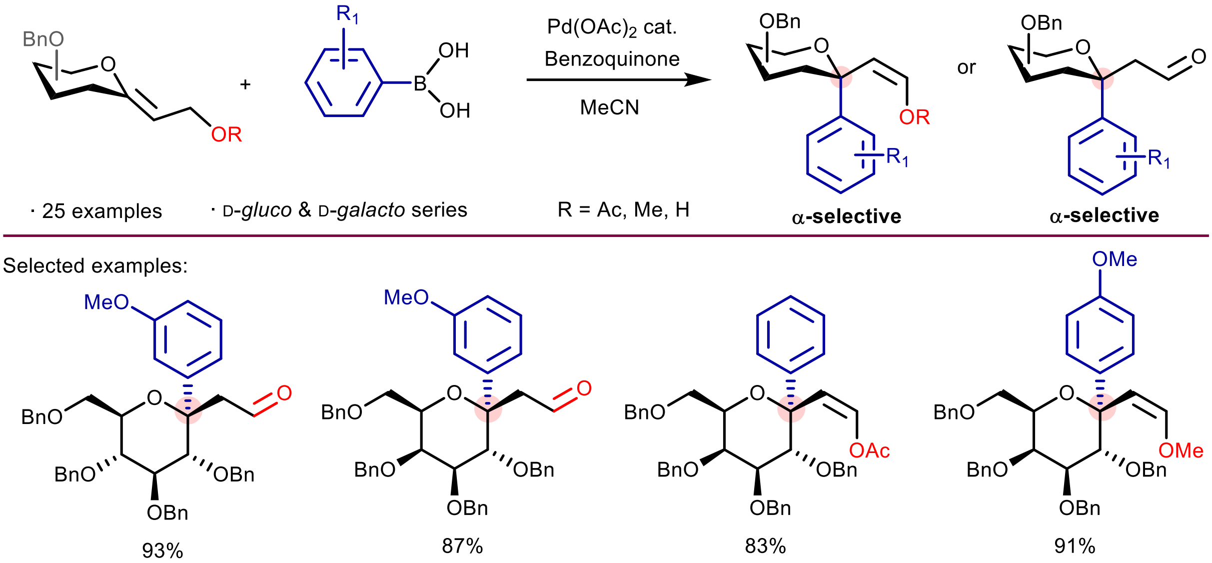
Scheme 86. *Synthesis of C-ketosides from lactones*

In 2005, Rainier's team[230] reported the high stereoselective synthesis of bis-*C*,*C*-aryl-glycosides from *endo*-glycals *via* the nucleophilic ring-opening of the corresponding epoxide intermediate using PhMgBr (**Scheme 87**).



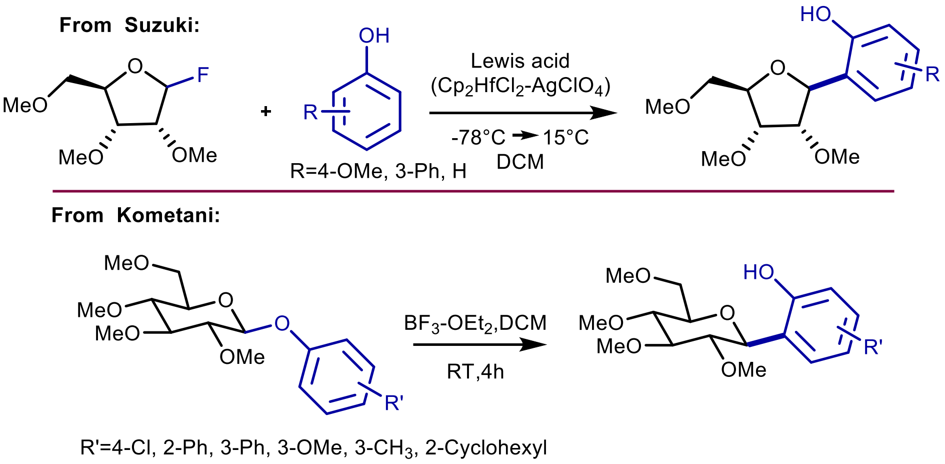
Scheme 87. *Preparation of C-ketosides from endo-glycals by way of nucleophilic ring-opening of epoxide intermediate*

Recently, Lin *et al*. reported a stereocontrolled synthesis of *C*-aryl ketosides by Heck type *C*-aryl addition of *exo*-glycals with arylboronic acids.[111;231;232] The reported reaction scope was however limited to the obtention of α-*C*-aryl ketosides bearing an alkoxyvinyl or ethanal moiety at the pseudoanomeric position. Some selected examples were presented in **Scheme 88**.



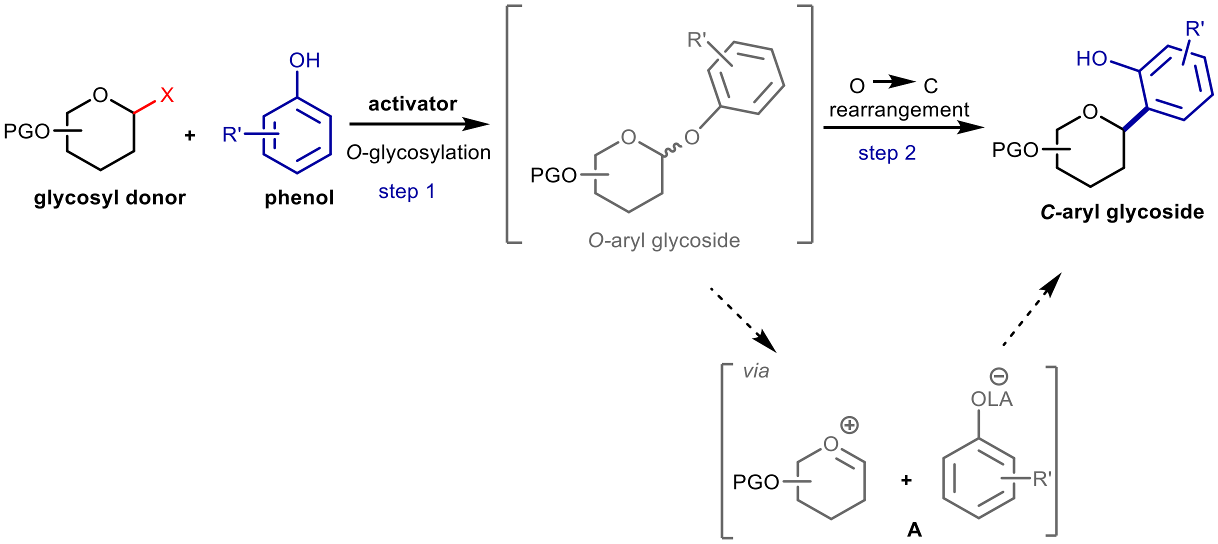
Scheme 88. *Synthesis of C-aryl ketosides by Heck type C-aryl addition of exo-glycals with arylboronic acids*

Considering the high potential of bis-*C*,*C*-aryl-glycosides, novel and stereocontrolled approaches to this understudied class of *C*-glycosyl compounds are needed to facilitate the exploration of new biological targets. Coupled with the fact that we have obtained *O*-glycoside compounds by way of HAT-mediated radical-polar crossover coupling[207] (see **Chapter 2**, **Schemes 71-76**), we were encouraged by the previously reported synthesis of *C*-glycosides *via* Fries-type rearrangement reaction.[211] The first application of Fries-type rearrangement in the synthesis of *C*- glycosides was discovered by Suzuki's group[208] and Kometani's group[209] in 1988 (**Scheme 89**). For Suzuki's reaction, the Fries-type reaction involves a glycosyl donor (glycosyl fluoride), acceptors (phenols) and activators (BF_3-OEt_2, $SnCl_4$, and Cp_2HfCl_2-$AgClO_4$). This process begins with the formation of a *O*-aryl glycoside at low temperature, followed by a slow warming to selectively obtain *ortho*-hydroxy *C*-glycosyl aromatic derivatives with good yields in a one-pot reaction. For Kometani's reaction, the *C*-glycosylation products were obtained directly from *O*-aryl glycosides *via* Fries-type rearrangement reaction. As Fries-type rearrangement reaction became widely used, the scope of substrates for the reaction was expanded and more Lewis acids were discovered as activators of the reaction.[211] The list includes trimethylsilyl trifluoromethanesulfonate (TMSOTf) and scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$).



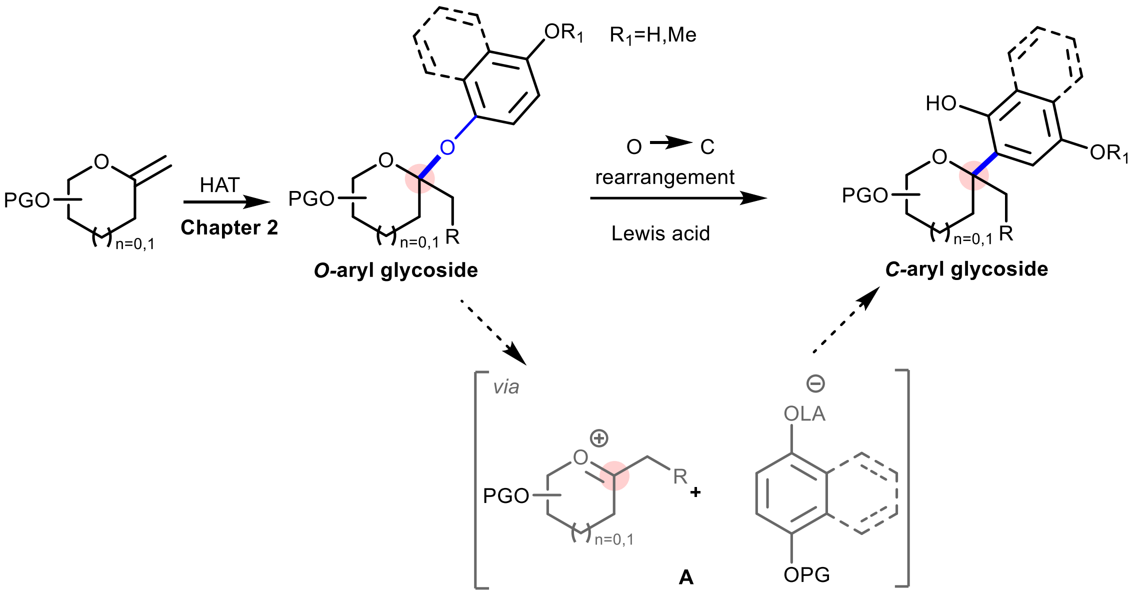
Scheme 89. *The first application of Fries-type rearrangement reported by Suzuki and Kometani*

In 2011, more details related to this reaction were reviewed.[211] The mechanism of Suzuki reaction is shown in **Scheme 90**. The reaction mechanism consists of two key steps. The first step is the activation of the glycosyl donor with Lewis acid, followed by coupling with a phenol derivative to produce the *O*-aryl glycoside. The following rearrangement of *O*-aryl glycoside gives the *C*-aryl glycoside *via* the ion pair **A**. The reaction undergoes irreversible Friedel-Crafts coupling leading to the formation of a C-C bond in the *ortho* position with respect to the phenolic hydroxyl group.



Scheme 90. *Mechanism proposed for phenol C-glycosylation by Fries-type rearrangement.*

To our knowledge, there was no precedent of the use of the so-called Suzuki rearrangement for the construction of quaternary pseudoanomeric anomeric center in *C*-aryl ketosides. Our aim was to apply this reaction to the conversion of *O*-ketosides obtained by HAT (see **Chapter 2**) in order to obtain the corresponding *C*-glycosides (**Scheme 91**).

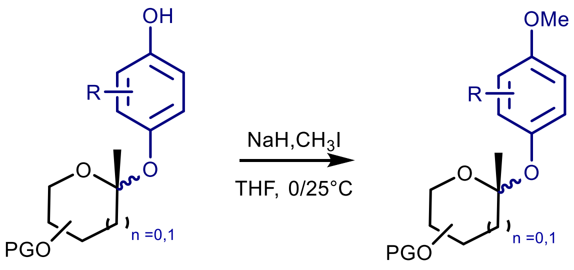


Scheme 91. Conversion of O-glycosides to C-glycosides via Fries-type rearrangement

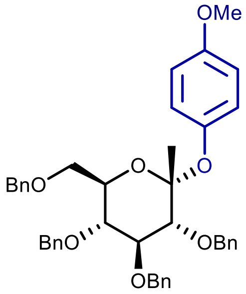
2. Methylation of *O*-aryl glycosides

First, we methylated the phenoxy group to see the influence of a protecting group on the Fries-type rearrangement. For the methylation of *O*-aryl glycosides **151** (see **Schemes 71-76**), we use two main methods. The phenoxy group was first deprotonated by the strong base NaH or by the milder base K_2CO_3 followed by reaction with iodomethane (CH_3I) as an electrophilic methyl source. The corresponding methylation products are shown in **Scheme 92** and **Scheme 93**.

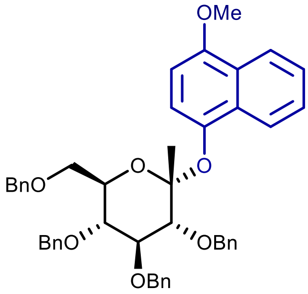
In the D-glucose series (**151a-151af**) and 1,5-bis-glycoside series (**151ba-151c**), these methylations worked well with NaH except for **177ad** and **177af**. The methylation proceeded with moderate yields in D-galactose series (**151db**), with *O*-glycosides with a fluor or a TBS-protecting group at C-2 (**151f**, **151ib**), 5-membered *C*-ketosides (**151kb-151nb**) and complex trisubstituted *O*-glycosides (**151pb**, **151qb**).



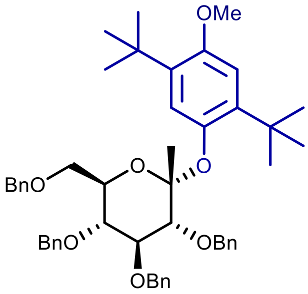
151a-151qb **177a-177qb**



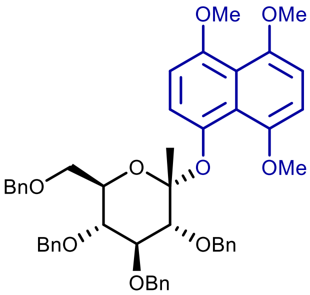
177a (80%, d.r. 1.2/1)
(from **151a**)



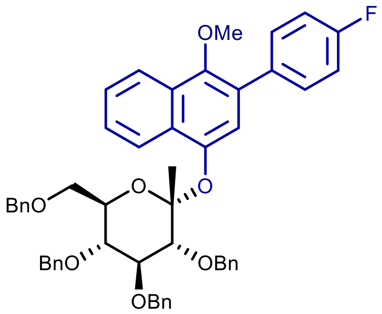
177ab (86%, d.r.1.8/1)
(from **151ab**)



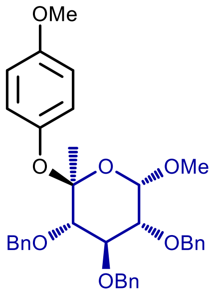
177ac (89%, d.r. 2.5/1)
(from **151ac**)



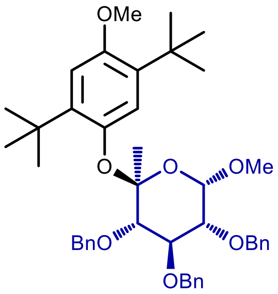
177ad (44%, d.r. 1.8/1)
(from **151ad**)



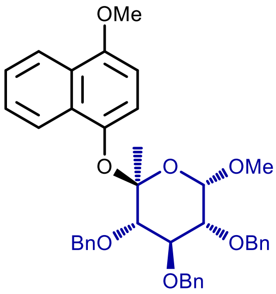
177af (55%, d.r. >98/2)
(from **151af**)



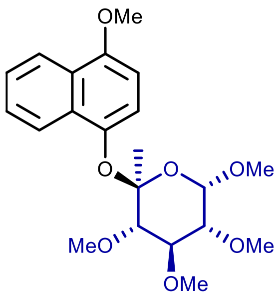
177ba (75%, d.r. >98/2)
(from **151ba**)



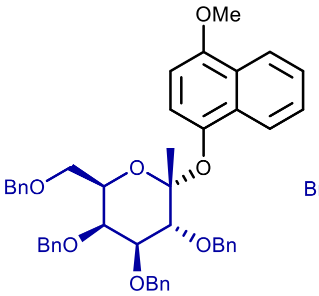
177bb (96%, d.r. >98/2)
(from **151bb**)



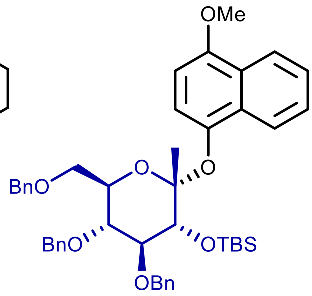
177bc (74%, d.r. >98/2)
(from **151bc**)



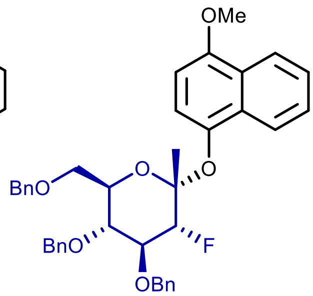
177c (75%, d.r. >98/2)
(from **151c**)



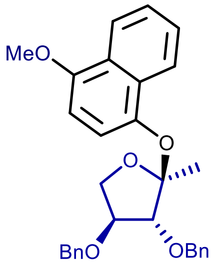
177db (61%, d.r. >98/2)
(from **151db**)



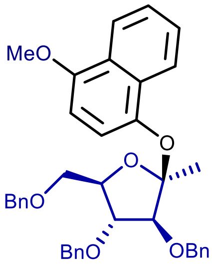
177f (59%, d.r. 2.7/1)
(from **151f**)



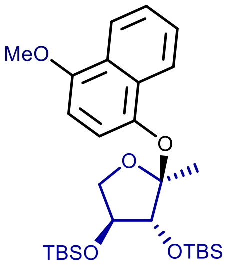
177ib (57%, d.r. 1.8/1)
(from **151ib**)



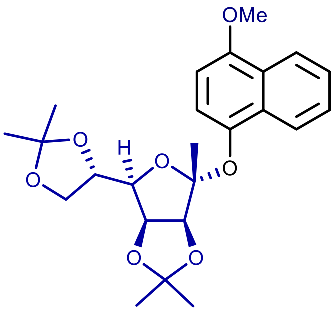
177kb (48%, d.r. 1.8/1)
(from **151kb**)



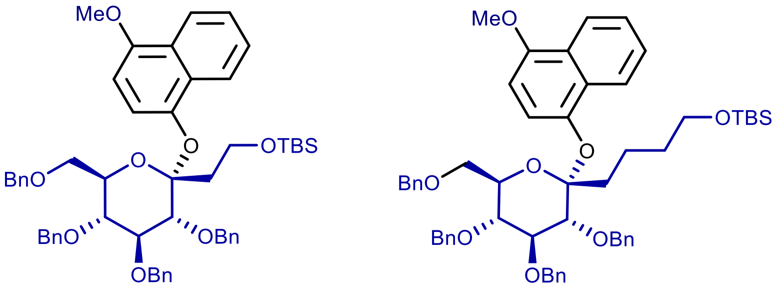
177l (68%, d.r. 8/1)
(from **151l**)



177mb (53%, d.r. 5.6/1)
(from **151mb**)



177nb (69%, d.r. 2/1)
(from **151nb**)

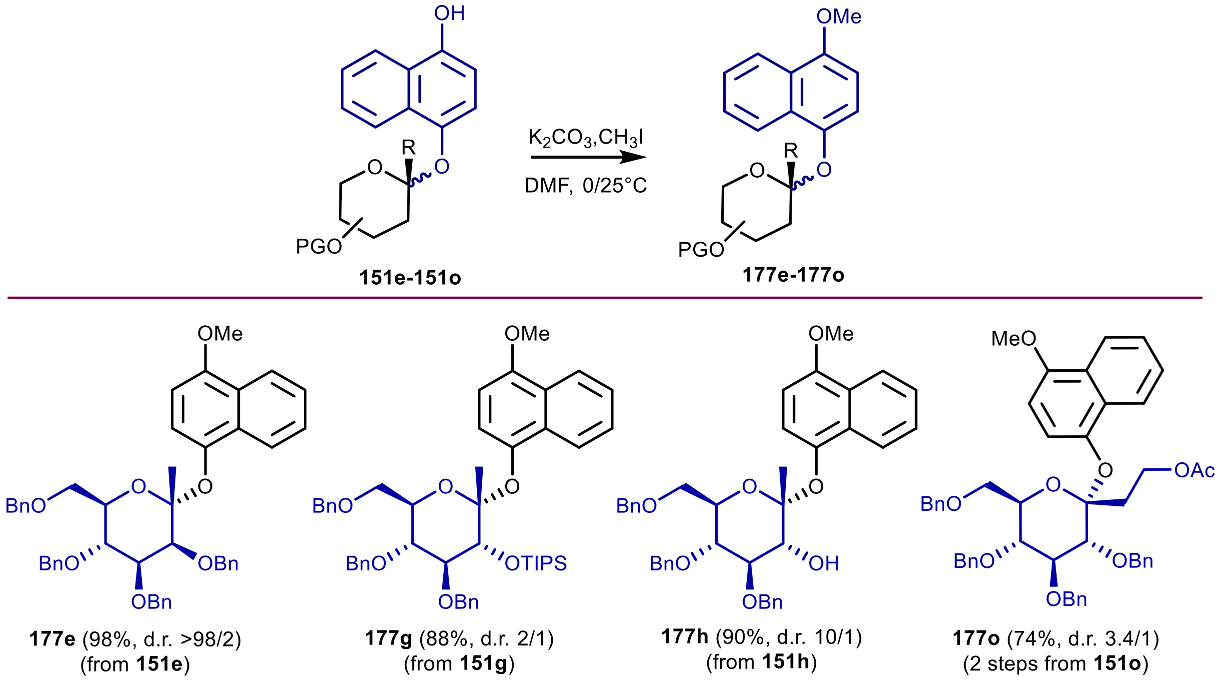


177pb (54%, d.r. 3/1)
(from **151pb**)

177qb (57%, d.r. 1.7/1)
(from **151qb**)

Scheme 92. *Methylation of O-glycosides using MeI and NaH*

For D-mannose **151e**, methylation was first performed using NaH, leading to a modest yield of only 27%. Subsequently, we chose a milder base, K_2CO_3, and the corresponding product was obtained in 98% yield. Then, the methylation reactions of **151g** and **151h** were run with K_2CO_3, and we obtained the corresponding products in 88% and 90% yields, respectively. Finally, **177o** is obtained in 74% yield by a two-step reaction through selective methylation with K_2CO_3, followed by an acylation reaction.



151e-151o

177e-177o

177e (98%, d.r. >98/2)
(from **151e**)

177g (88%, d.r. 2/1)
(from **151g**)

177h (90%, d.r. 10/1)
(from **151h**)

177o (74%, d.r. 3.4/1)
(2 steps from **151o**)

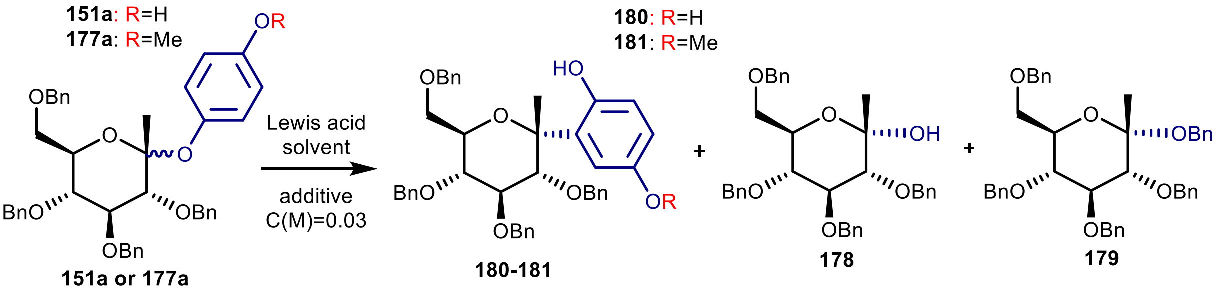
Scheme 93. *Methylation of O-glycosides using MeI and K_2CO_3*

3. Synthesis of *C*-aryl ketosides

3.1. Attempts to synthesize phenolic *C*-ketosides by way of Fries-type rearrangement

For the synthesis of phenolic *C*-ketosides, we initially attempted to convert *O*-ketoside **151a** into *C*-aryl glycosides utilizing the method reported by Kometani's group (**Scheme 89**) *via* Fries-type rearrangement.[208;209] In the first attempt with stoichiometric amount of $BF_3.OEt_2$, only the byproduct compound **178** was isolated (**entry 1**). The possible reason is that in the presence of Lewis acid, **151a** is converted into an oxonium (**A**) (**Scheme 91**), which is subsequently trapped by traces of water (**entry 1**). Compound **178** was still isolated when the reaction was held at -15 °C (**entry 2**). Furthermore compound **179** was also isolated. This product was probably obtained *via* the decomposition of *O*-aryl glycoside **151a** or **177a** in this process (**entries 2**, **6** and **7**).[233] Following this, $Sc(OTf)_3$ or a Brønsted acid (TfOH) in different solvent systems were used in this conversion and we did not obtain the desired product in all attempts even though the free hydroxyl group was protected by a methyl group (**entries 3-8**).

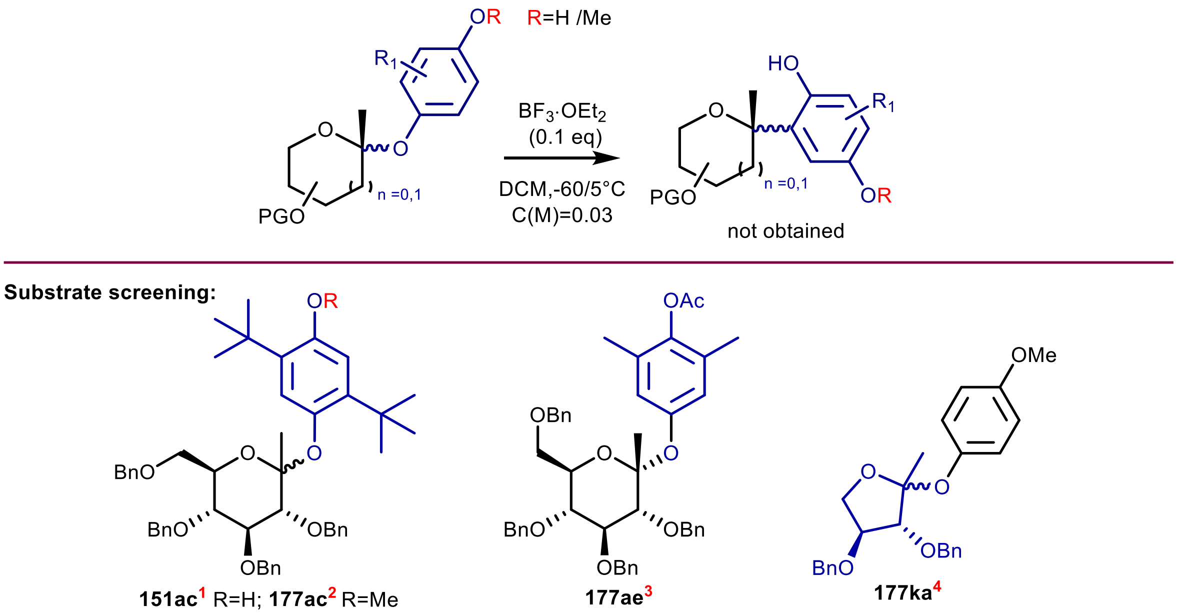
Table 3. *Attempts to convert O-aryl glycosides* ***151a*** *and* ***177a*** *into C-aryl glycosides by way of Fries-type rearrangement.*



Entry	R	Lewis Acid	additive	T/°C	solvent	Time	178	179
1[a]	H	$BF_3.OEt_2$ (2 eq)	4Å MS	-40 to 15°C	CH_2Cl_2	4h	56%	-
2	H	$BF_3.OEt_2$ (2 eq)	4Å MS	-15°C	CH_2Cl_2	4h	25%	12%
3[a]	H	$BF_3.OEt_2$ (2 eq)	4Å MS	0	CH_3CN	1h	32%	-
4[a]	H	$Sc(OTf)_3$ (0.2 eq)	-	70°C	toluene	15h	Degradation	
5	H	TfOH (1 eq)	Drierite®	-30 to 25°C	DCE	31h	Degradation	
6	Me	$BF_3.OEt_2$ (0.1 eq)	-	-60 to 25°C	DCM	6h	-	16%
7	Me	$Sc(OTf)_3$ (0.3 eq)	Drierite®	0 to 25°C	DCE	29h	-	15%
8	Me	TfOH (0.5 eq)	Drierite®	-30 to 25°C	DCE	29h	Degradation	

a) C(M)=0.02

The subsequent attempts with other substrates (**151ac**, **177ac**, **177ae**, **177ka**), unfortunately, did not succeed (**Scheme 94**). Only compounds **178** and **179** were isolated. The failure of the conversion of *O*-ketosides to phenolic *C*-ketosides may be due to the presence of the methyl group at C1 which reduces the reactivity of the oxocarbonium ion intermediate.



1. Compounds **178** and **179** were obtained in 40% and 11% yields, respectively.
2. Compounds **178** and **179** were obtained in 32% and 25% yields respectively, at -60/25 °C.
3. Compound **179** was obtained in 34% yield; 4. Degradation.

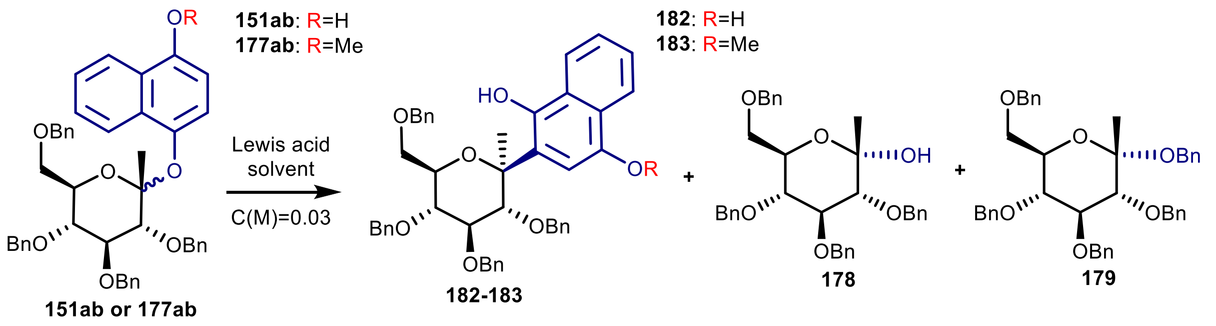
Scheme 94. *Substrate screening of O-aryl ketosides for the synthesis of C-aryl ketosides*

3.2. Synthesis of *C*-naphthol ketosides by way of Fries-type rearrangement

We then tried the Fries-type reaction using naphthol *O*-ketosides. In the first attempt with $BF_3.OEt_2$ as activator, 4Å MS as a drying agent, acetonitrile as solvent at 0 °C, we isolated the desired *C*-aryl glycoside in 4% yield (in **Table 4**, **entry 1**). Using Drierite® as a drying agent, this reaction was run in DCM at -60 to 22 °C, giving the *C*-aryl glycoside **182** in an appreciable yield (**entry 2**). The removal of the desiccant makes the reaction less efficient, with byproduct **178** being isolated in 26% yield (**entry 3**). Other acids (such as TfOH and $Sc(OTf)_3$) were subsequently tested, but led to unsatisfactory results (**entries 4** and **5**). However, when methylated compound **177ab** was reacted with different acids (TfOH, $Sc(OTf)_3$, $BF_3.OEt_2$) in the presence of Drierite® as a drying agent, good yields were obtained except for $Sc(OTf)_3$ (**entries 6-8**). We chose $BF_3.OEt_2$ as the activator to use milder reaction conditions. With this positive result in hand, optimization experiments were carried out. First, Drierite® was replaced by 4Å MS to give the desired product in only 6% yield (**entry 9**). The desiccant was removed, and the starting material was azeotropically boiled 3 times with toluene to remove any moisture. In these conditions *C*-aryl glycoside **183** was obtained in 68% yield at -60 to 25 °C (**entry 10**). The final reaction temperature was then limited to 5 °C, leading to a significant yield improvement (**entry 11**). When the amount of $BF_3.OEt_2$ was decreased to 0.1 equiv., *C*-aryl glycoside was obtained in excellent yields (**entry 12**).

Finally, we obtained the best conditions with 0.1 equiv. of $BF_3.OEt_2$ as the activator and DCM as the solvent at -60 °C to 5 °C. Warming up to room temperature and the increase in the amount of Lewis acid may lead to partial decomposition of the *O*-aryl glycoside starting materials.[233]

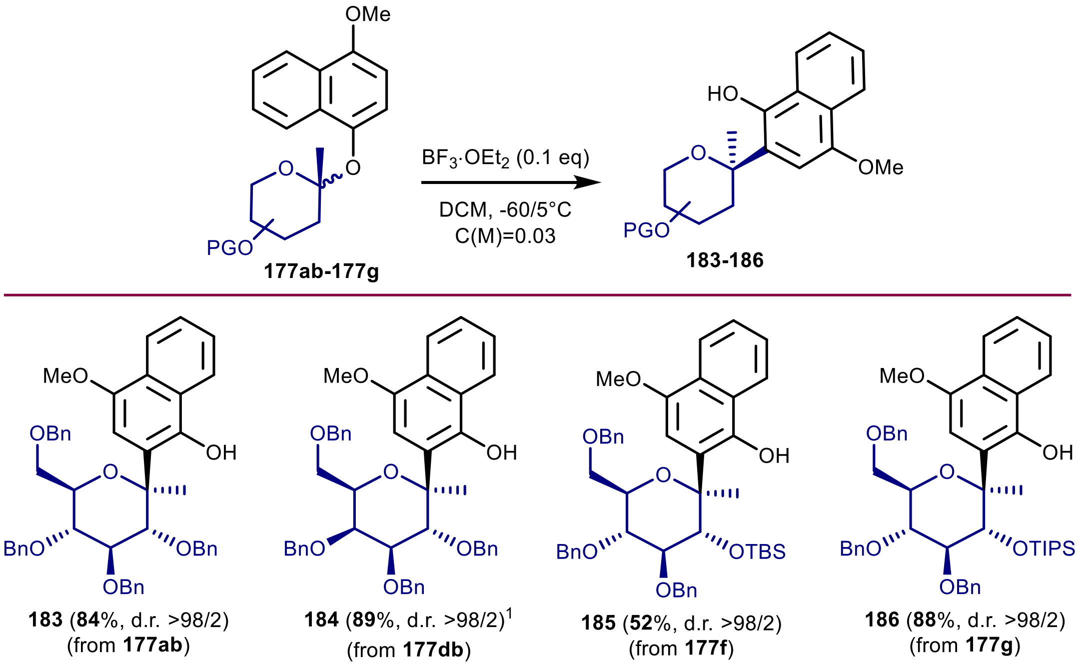
Table 4. *Optimization of the conversion of O-aryl glycoside* ***151ab*** *and* ***177ab*** *to C-aryl glycosides by way of Fries-type rearrangement*



Entry	R	Lewis Acid	additive	T/°C	solvent	Time	182/183	178
1	H	$BF_3.OEt_2$ (2 eq)	4Å MS	0°C	CH_3CN	3.5h	4%	-
2	H	$BF_3.OEt_2$ (0.3 eq)	Drierite®	-60 to 22°C	DCM	20h	46%	-
3	H	$BF_3.OEt_2$ (0.3 eq)	-	-60 to 5°C	DCM	2.5h	29%	26%
4	H	TfOH (0.5 eq)	Drierite®	-30°C	DCE	5h	-	28%
5[a]	H	$Sc(OTf)_3$ (0.3 eq)	Drierite®	0 to 25°C	DCE	30.5h	9%	-
6[b]	Me	$Sc(OTf)_3$ (0.3 eq)	Drierite®	-30 to 25°C	DCE	28h	4%	
7	Me	TfOH (0.5 eq)	Drierite®	-30 to 25°C	DCE	2h	60%	
8	Me	$BF_3.OEt_2$ (0.34 eq)	Drierite®	-78 to 25°C	DCM	7.5h	60%	
9	Me	$BF_3.OEt_2$ (0.34 eq)	4Å MS	-78 to 25°C	DCM	29h	6%	
10	Me	$BF_3.OEt_2$ (0.34 eq)	-	-60 to 25°C	DCM	23h	68%	
11	Me	$BF_3.OEt_2$ (0.34 eq)	-	-60 to 5°C	DCM	3.5h	77%	
12	Me	$BF_3.OEt_2$ (0.1 eq)	-	-60 to 5°C	DCM	4h	84%	

a) **179** was obtained in 17% yield; b) **179** was obtained in 54% yield.

With the best conditions in hand, the scope of the reaction was studied with various methylated *O*-naphthol ketosides **177** (**Schemes 95-98**). First, in the D-glucose and D-galactose series, Fries-type rearrangement reactions of **177** worked very well in high stereoselectivity affording compounds **183** and **184** in good yields. The influence of the substitution at C-2 was then evaluated. Thus, for **185** and **186** with acid-sensitive protecting groups, we obtained the corresponding *C*-aryl glycosides as single diastereoisomer in acceptable to high yields. The presence of large silyl ether protecting groups[234] were found to have no deleterious effect on the level of stereocontrol (**Scheme 95**).



1) $BF_3 \cdot OEt_2$ (0.35 eq) used

Scheme 95. *Reaction scope (six-membered C-naphthyl glucosides)*

The structure of **186** and absolute configuration of the newly created stereogenic center was unambiguously confirmed by X-ray crystallographic analysis (see **Figure 11A**). Furthermore, NOESY experiments were also performed, confirming the absolute configuration at the C1 position. For example, we observed the correlations between the methyl hydrogen at C1 and H-3/H-5 in compound **183** (**Scheme 95**); H-3' and H-2 in **190** (**Scheme 96**) (see **Figure 11B**).

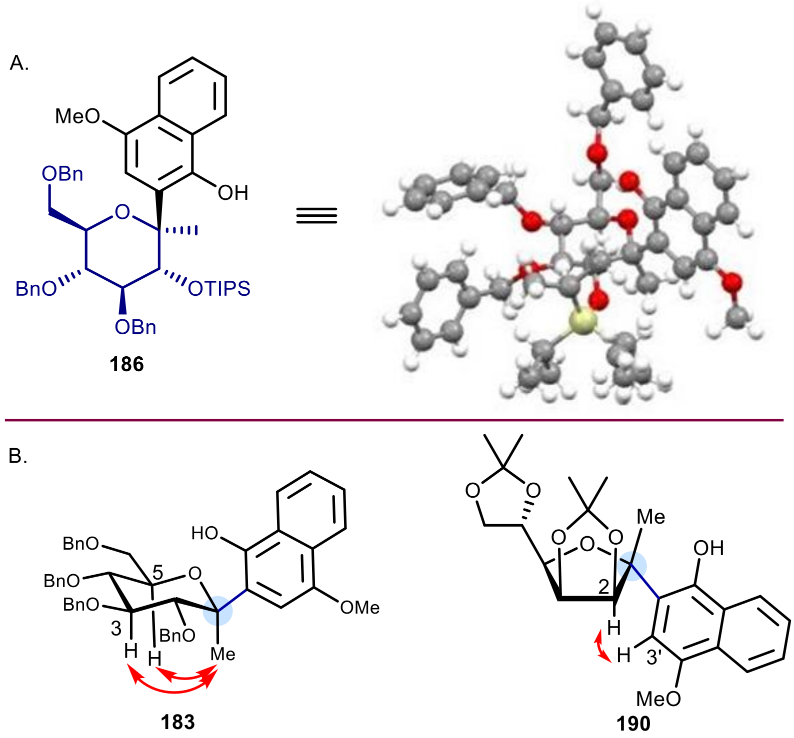
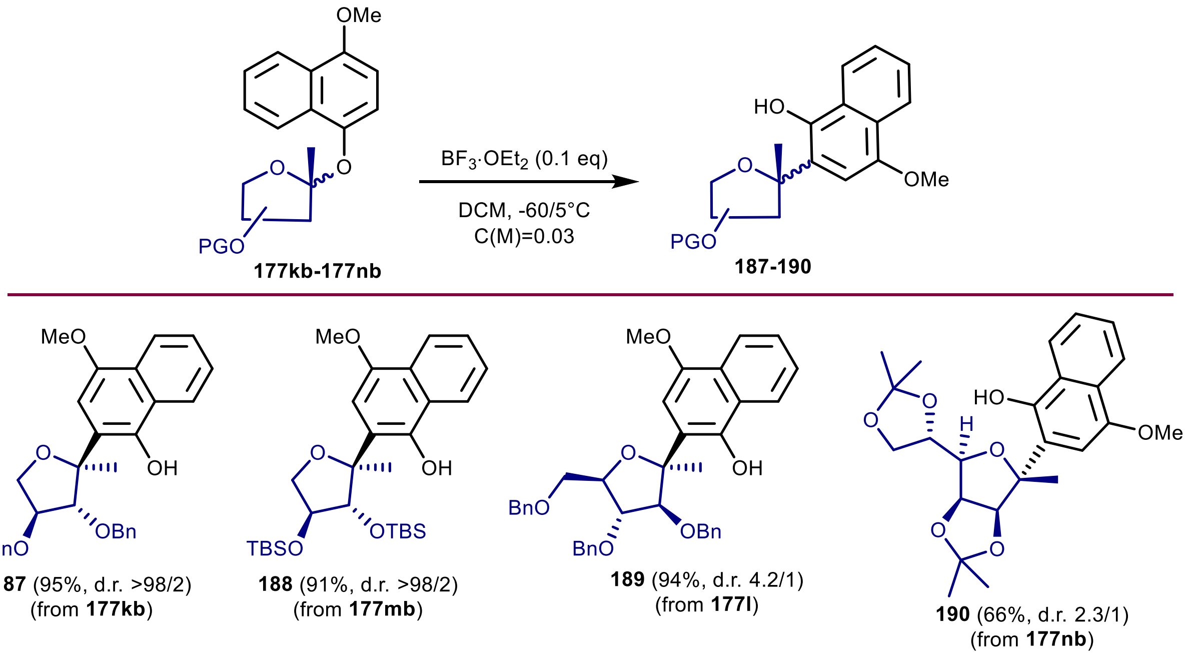


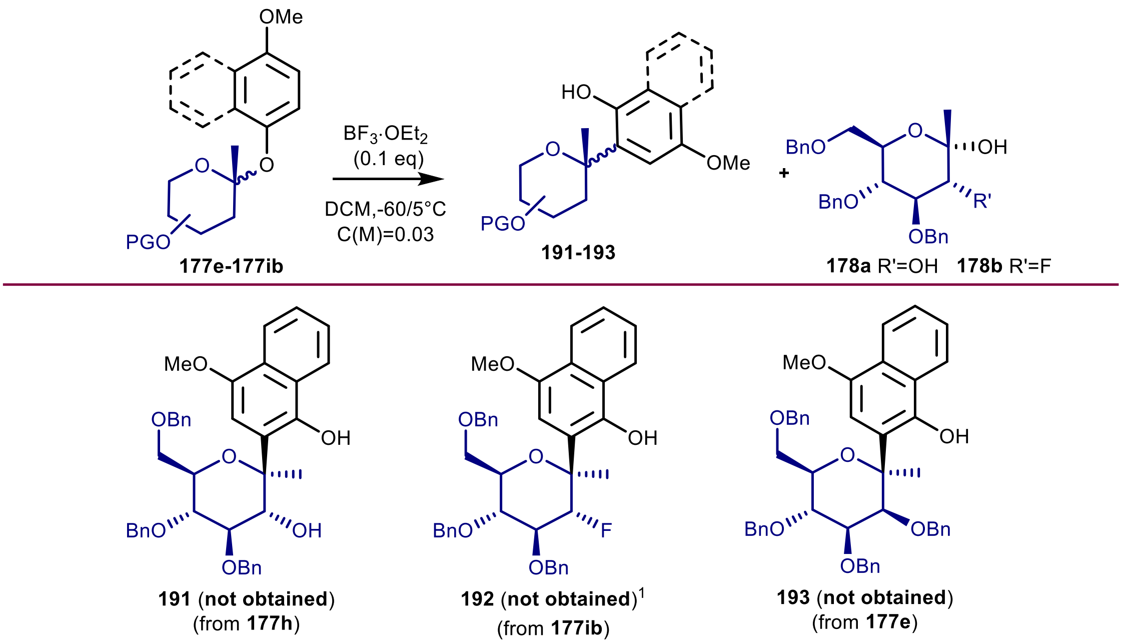
Figure 11. *A. Confirmation of the structure of **186** by X-ray crystallographic analysis; B. Confirmation of the absolute conformation of **183** and **190** by NOESY.*

Pleasingly, our optimized conditions were also effective for the synthesis of 5-membered *C*-ketosides **187**, **188**, **189** and **190** (**Scheme 96**). In the L-threo series, the 1,3-*cis* products **187** and **188** were obtained as single diasteroisomers in high yields. However, erosion of diastereoselectivity was observed for the conversion of bisacetonide *O*-ketoside **177nb** and *O*-arabinosyl naphtol **177l**.



Scheme 96. *Reaction scope of 5-membered substrates*

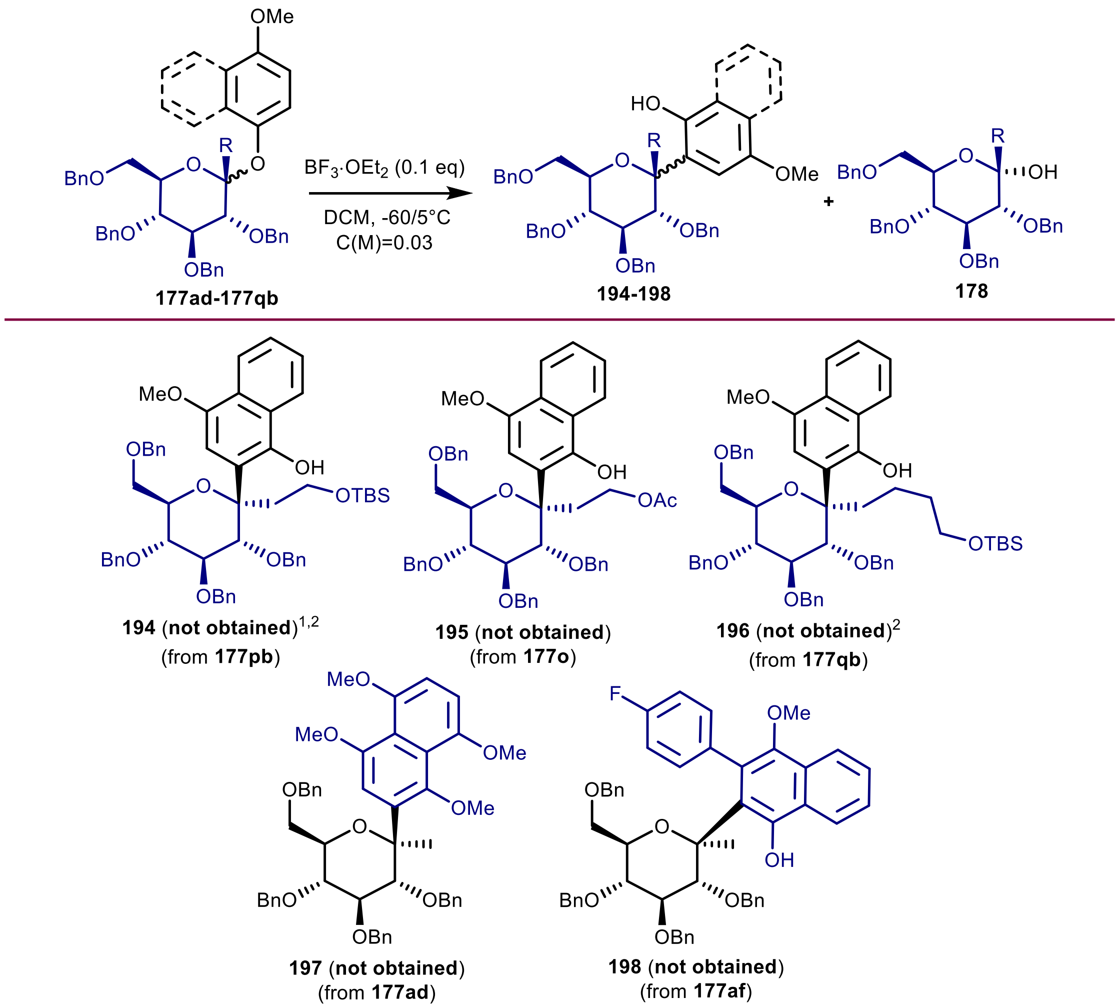
Reactions with *O*-ketosides **177h**, **177ib** did not afford any desired products. Only the corresponding byproducts resulting from the reaction of the oxocarbenium with water were obtained (**Scheme 97**). The strong electronegativity of the fluor atom in **177ib** may impede the Fries-type rearrangement by disfavoring the formation of the oxocarbenium intermediate. Quite surprisingly, switching from D-gluco (**177a**) to D-manno (**177e**) series led to the formation of numerous side-products and consequently to inseparable crude reaction mixtures.



1) $BF_3 \cdot OEt_2$ (0.35 eq) was used

***Scheme 97.** Reaction scope of six-membered substrates*

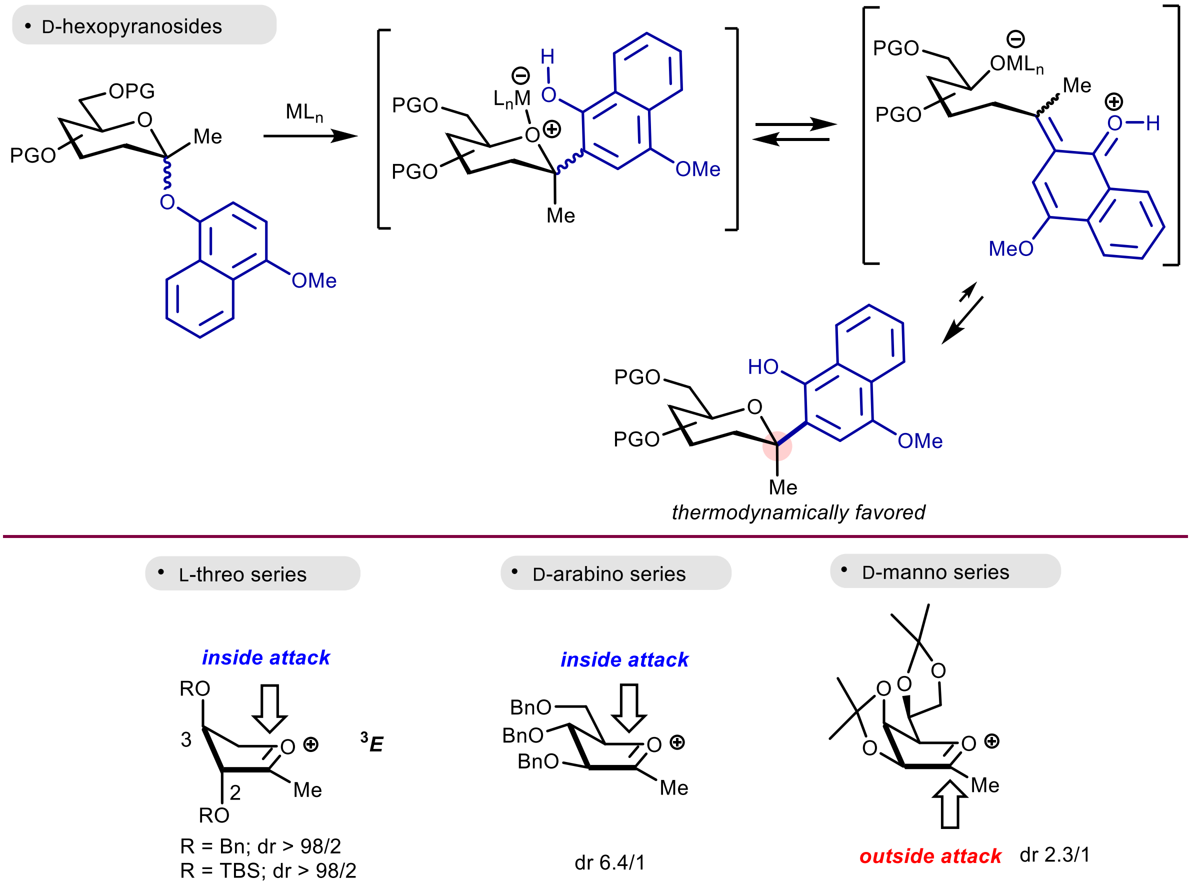
In addition, the conversion of more complex *O*-ketoside substrates **177pb**, **177o**, **177qb** was performed using the best condition descibed (**Scheme 98**). We did not obtain the desired bis-*C*,*C*-glycosides. Only degradation compounds without the OTBS moiety were isolated for **177pb** and **177qb**. One of the possible reasons is that the TBS protecting group of the primary alcohol is readily deprotected in the presence of Lewis acid. On the other hand, the increased steric hindrance and lower reactivity of tertiary oxocarbenium ion intermediates over secondary ones may be detrimental to the key coupling process. In almost all of these reactions, **178** was obtained. The scope of the Fries-type rearrangement reactions was also evaluated using *O*-glycosides with bulky aromatic moieties (**177ad**, **177af**). The key C-C coupling reaction failed with aromatic moieties that are sterically hindered and/or not sufficiently electron-rich for the pivotal Friedel-Crafts reaction to proceed.



1) $BF_3{\cdot}OEt_2$ (0.35 eq) was used; 2) TBS group is not stable under the reaction conditions

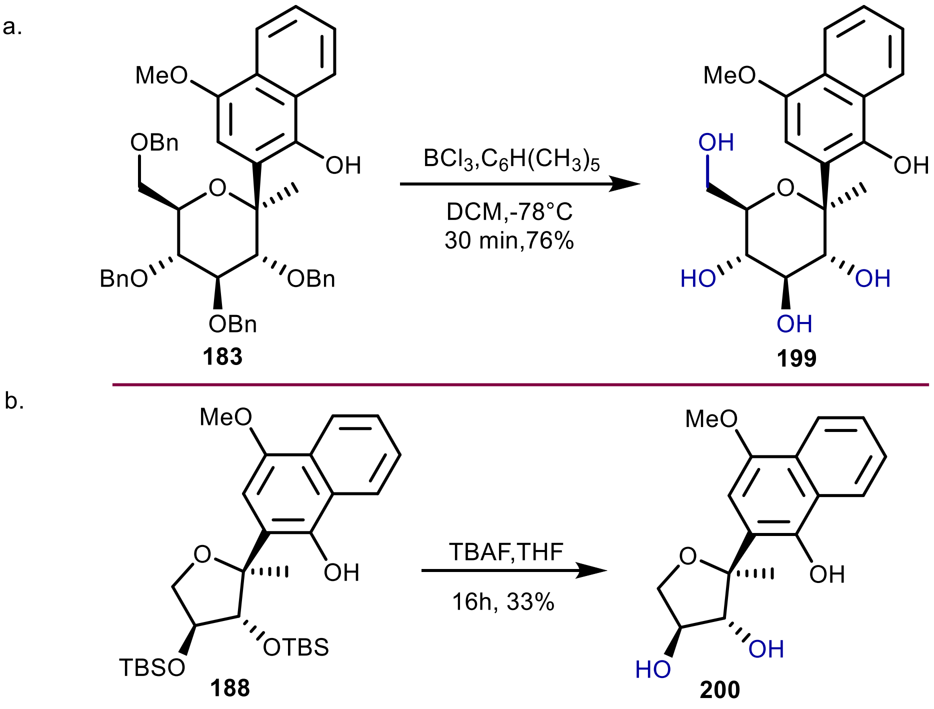
Scheme 98. *Reaction scope study using bulky substrates*

Trends in observed stereoselectivities may be explained as follow. In the D-hexopyranose series, the exclusive formation of the *C*-ketosyl naphthol β-anomers is likely to be rationalized by the formation of the thermodynamically favored $^4C_1$ conformer with the bulky aromatic aglycon moiety in an equatorial orientation.[211] This thermodynamically driven equilibration would proceed by way of Lewis acid-promoted ring opening-closure of the *C*-ketosyl naphtol product *via* the corresponding *ortho*-quinone methide intermediate (**Scheme 99**). For the ketofuranoside substrates, the stereochemical outcome of the reaction may be accounted for other factors than the formation of the thermodynamically-controlled products. The higher conformational flexibility of five-membered rings over six-membered rings is indeed expected to reduce the thermodynamic driving force towards the more stable products by better accommodating steric clashes of ring substituents. The stereoselectivity of the key C-C bond forming step is consistent with Woerpel's model [204;205] in which the lowest energy envelope conformer of the furanosyl oxocarbenium ion intermediate undergoes a stereoelectronically controlled inside attack of the incoming nucleophile (**Scheme 99**). As shown by Filippov, Codée *et al.*,[235;236] the presence of a pseudoanomeric methyl substituent leads to higher energy differences between the envelopes than in the case of secondary oxocarbenium ions generated from aldoses.[235] In *O*-ketosides **177kb** and **177mb** (L-threo series), the pseudo-axial position of the C-3 alkoxy group makes the ^3E conformer more favorable than the E_3-conformation by maximizing favorable electrostatic effects with the electron-depleted pseudoanomeric center.[204;205;235] According to Woerpel's model, the stereoselective formation of the 1,3-*cis* products **187**, **188** and **189** would thus result from the inside attack of the *in situ* generated *C*-nucleophile on the most stable ^3E oxocarbenium ion intermediate. The lower stereocontrol observed in the arabinofuranose series may be explained considering the fact that the conformational preference between the two envelope conformers is less pronounced.[235] The arabinofuranosyl oxocarbenium ion is believed to adopt preferentially an ^3E conformation in which all the substituents are equatorially oriented, leading to partial destabilization due to the tendency of the C-3 alkoxy group to adopt a pseudoaxial position. The alternative E_3 conformation is however less favorable due to syn-butanol interaction[205] between the pseudoaxial substituents at C-2 and C-4. In the D-mannofuranose series, a strong conformational preference for the ^3E conformation is expected with the C-3 alkoxy group in a pseudoaxial position and the substituent at C-2 in a pseudoequatorial position.[204;205;235] Steric hindrance of the stereoelectronically favored inside face accounts for the lower sterocontrol observed in the rearrangement of *O*-ketoside **177l** and the selective formation of the 1,2-*trans* product.



Scheme 99. *A possible stereoselectivity model for the formation of C-ketosides.*

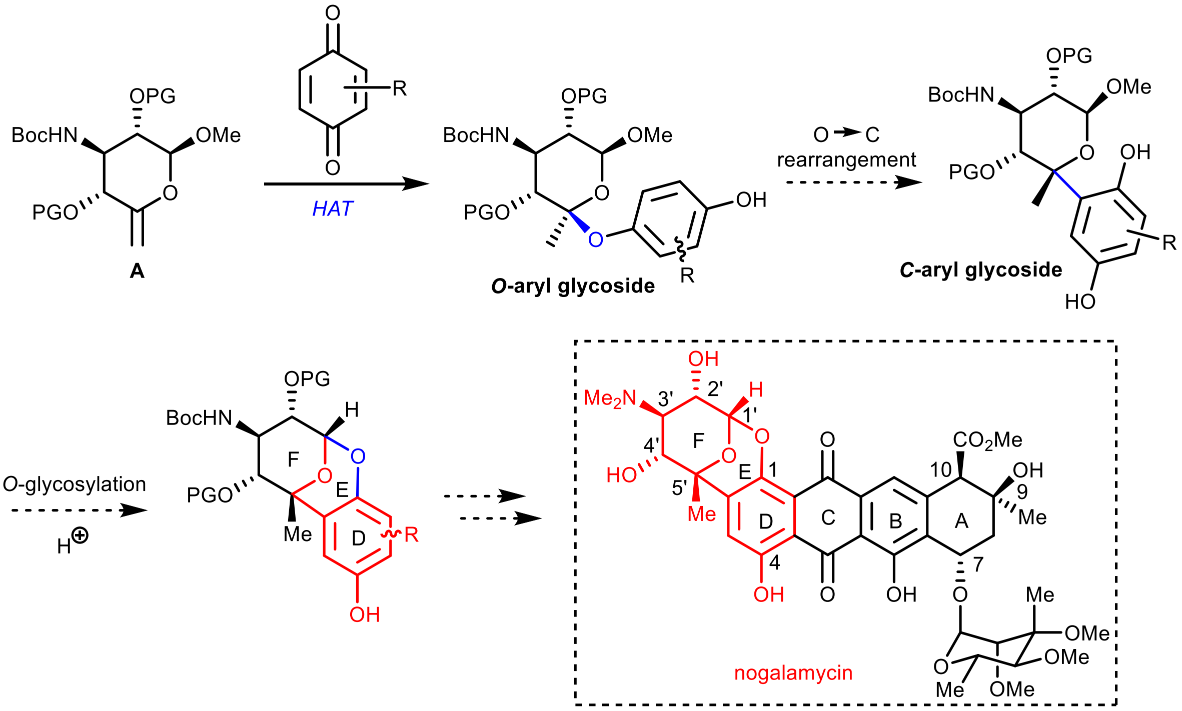
Subsequent deprotection of *O*-benzyl groups using a combination of pentamethylbenzene and boron trichloride afforded the expected deprotected *C*,*C*-glycosyl product **199** (**Scheme 100a**). In addition, the deprotection product of *C*,*C*-glycoside **188** was obtained in 33% yield with TBAF (**Scheme 100b**).



Scheme 100. *Deprotection of C-aryl ketosides* ***183*** *and* ***188***

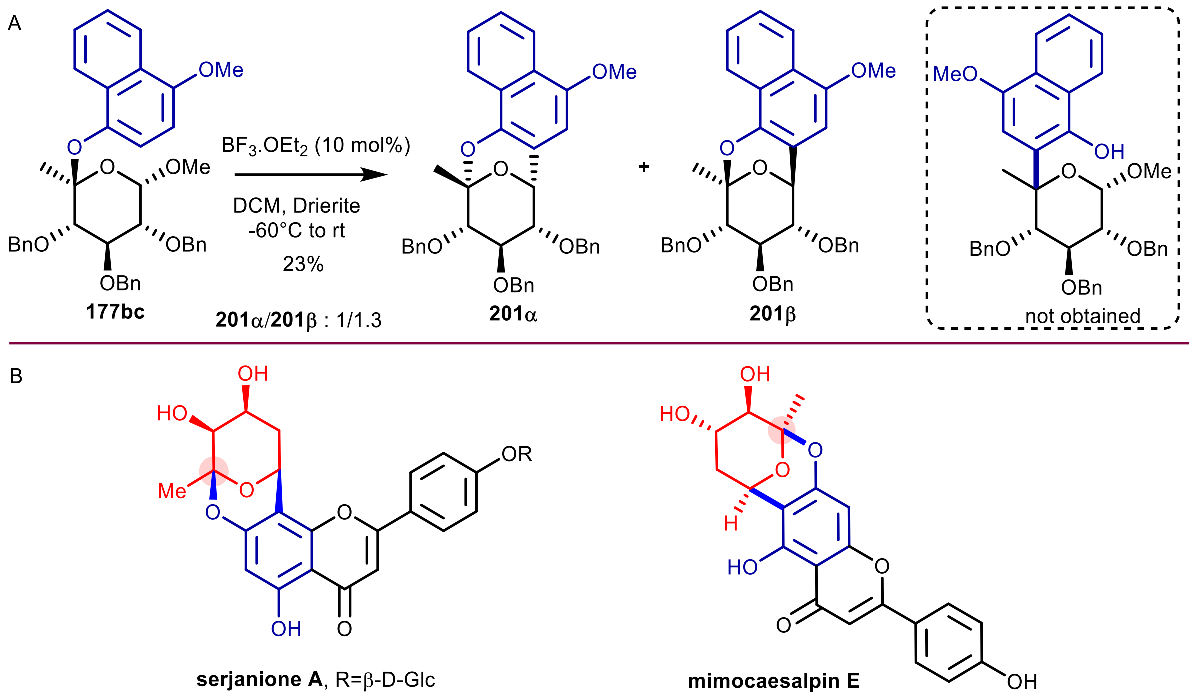
4. Fries-type rearrangement on 1,5-bis-glycoside derivatives

Based on the results obtained in part 3 we considered to use the *C*,*C*-glycosylation methodology for the synthesis of the benzoxocin ring (DEF core) found in nogalamycin (**Scheme 101)**. After HAT-mediated reaction on 1,5-bis-glycoside **A**, the Fries-type rearrangement was expected to give the desired tetrasubstituted pseudoanomeric center and a phenol aglycone that would then undergo an intramolecular glycosylation reaction. As a substrate model, we selected 1,5-bis-glycoside **177bc** (**Scheme 102**).



Scheme 101. *Application of our methodology to the synthesis of the benzoxocin core of nogalamycin*

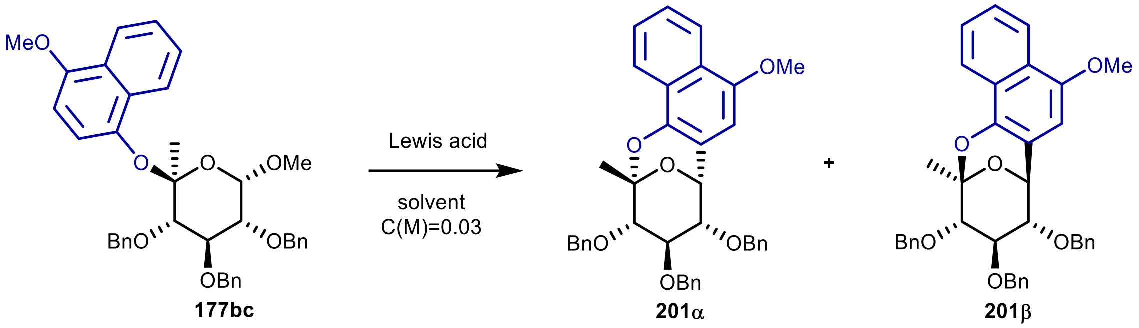
In first attempts using our previously described best conditions (0.1 eq. of $BF_3.OEt_2$/DCM), the starting material **177bc** was degraded. By adding Drierite® and increasing the reaction time and temperature, two new cyclized products were obtained in 23% yield (dr 1/1.3). No desired *C*-aryl glycoside was obtained in this process (**Scheme 102A**). Interestingly, serjanione A[8] and mimocaesalpin E,[237] which are biologically active products (see **general introduction**, **part 2**), share a common benzoxocin ring system with the compounds obtained in **Scheme 102A**. Notably, neither of these natural products has been chemically synthesized to date (**Scheme 102B**).



***Scheme 102.** A. Application of Fries-type rearrangement to **177bc**; B. Structure of the natural products serjanione A and mimocaesalpin E*

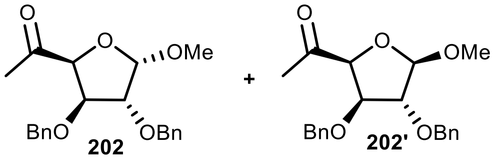
The reaction was then optimized by adjusting various parameters. Two other Lewis acids ($TiCl_4$, TMSOTf) and a Brønsted acid, TfOH, were selected to activate this reaction. Starting material was decomposed with TfOH and $TiCl_4$ (**Table 5**, **entries 3** and **4**). We found that the cyclization products were obtained in 31% yield (dr 1/2.4) when TMSOTf was used (**entry 5**). Based on **entry 5**, adding Drierite® had no significant impact on the reaction outcome (**entry 6**). The process was found to be highly regioselective by reducing the amount of TMSOTf, but with no improvement in the yield of the cyclization process (**entry 7**). The use of $SnCl_4$ led to a significant increase in the yields of the two cyclisation products (**entry 8**). The replacement of Drierite® by 4Å MS gave decomposition products (**entry 9**). Based on **entry 8**, the removal of Drierite® led to the formation of the two cyclisation products in good yields (**entry 10**). Reducing the amount of $SnCl_4$ to 0.05 equiv. or increasing it to 0.25 equiv. did not improve the efficiency of the reaction (**entries 11-12**). The change in concentration of the reaction had a clear impact on the formation of the products (**entries 13** and **14**). We subsequently attempted different solvent systems, including toluene and $CHCl_3/CH_3NO_2$, and achieved a 54% yield of cyclization products in toluene (**entry 15**). Only trace amounts of the desired products were detected in the mixture of $CHCl_3/CH_3NO_2$ (**entry 16**).

Table 5**. Optimization study with **177bc

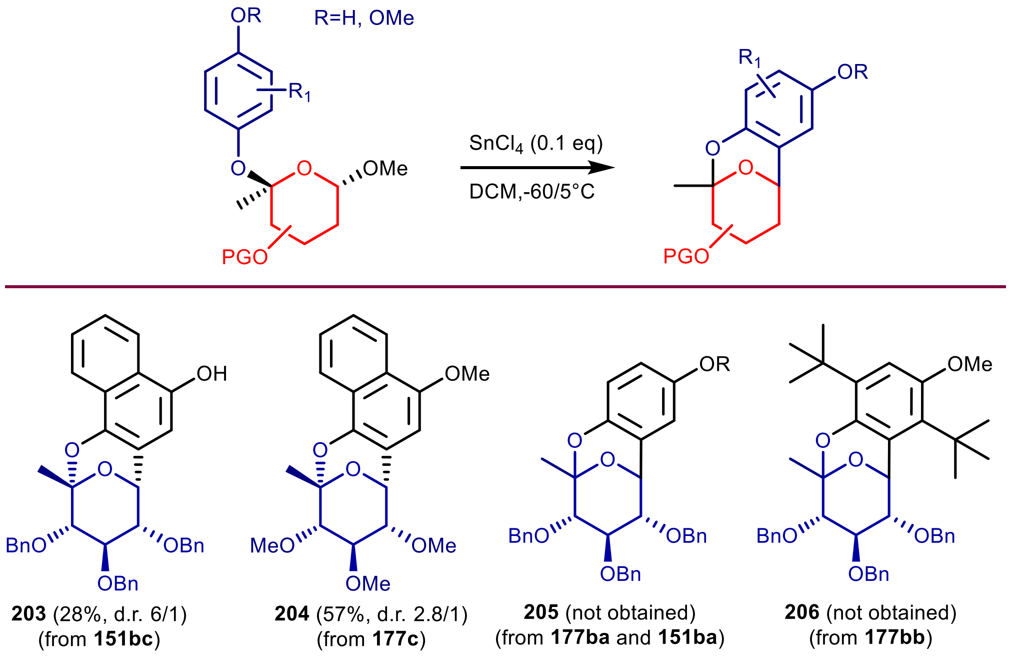


Entry	Lewis Acid	additive	solvent	T/°C	Time	201α	201β
1	$BF_3.OEt_2$ (0.1 eq)	-	DCM	-60°C to 0°C	2.5h	-	-
2	$BF_3.OEt_2$ (0.05 eq)	Drierite®	DCM	-60°C to 25°C	14h	10%	13%
3	TfOH (0.5 eq)	Drierite®	DCE	-30°C to 25°C	5h	Degradation	
4	$TiCl_4$ (0.25 eq)	-	DCM	-60°C to 25°C	3h	0%	
5	TMSOTf (0.05 eq)	-	DCM	-60°C to 5°C	2.5h	9%	22%
6	TMSOTf (0.05 eq)	Drierite®	DCM	-60°C to 5°C	2.5h	11%	24%
7	TMSOTf (0.01+0.02 eq)	-	DCM	-60°C to RT	23h	20%	-
8	$SnCl_4$ (0.1 eq)	Drierite®	DCM	-60°C to 10°C	3h	18%	27%
9[a]	$SnCl_4$ (0.1+0.4 eq)	4Å MS	DCM	-60°C to RT	20h	Degradation	
10	$SnCl_4$ (0.1 eq)	-	DCM	-60°C to 5°C	3h	45%	20%
11	$SnCl_4$ (0.05 eq)	-	DCM	-60°C to RT	3.5h	37%	17%
12	$SnCl_4$ (0.25 eq)	-	DCM	-60°C to 5°C	3h	45%	18%
13[b]	$SnCl_4$ (0.1 eq)	-	DCM	-60°C to 16°C	5.5h	38%	14%
14[c]	$SnCl_4$ (0.1 eq)	-	DCM	-60°C to 25°C	5h	Trace	Trace
15	$SnCl_4$ (0.1 eq)	-	Toluene	-60°C to 63°C	9h	43%	11%
16	$SnCl_4$(0.1eq)	-	$CHCl_3/CH_3NO_2$ (1:1)	-30°C to 5°C	3h	Trace	Trace

a) Byproducts **202** and **202'** were obtained. b) C(M)=0.01; c) C(M)=0.05.



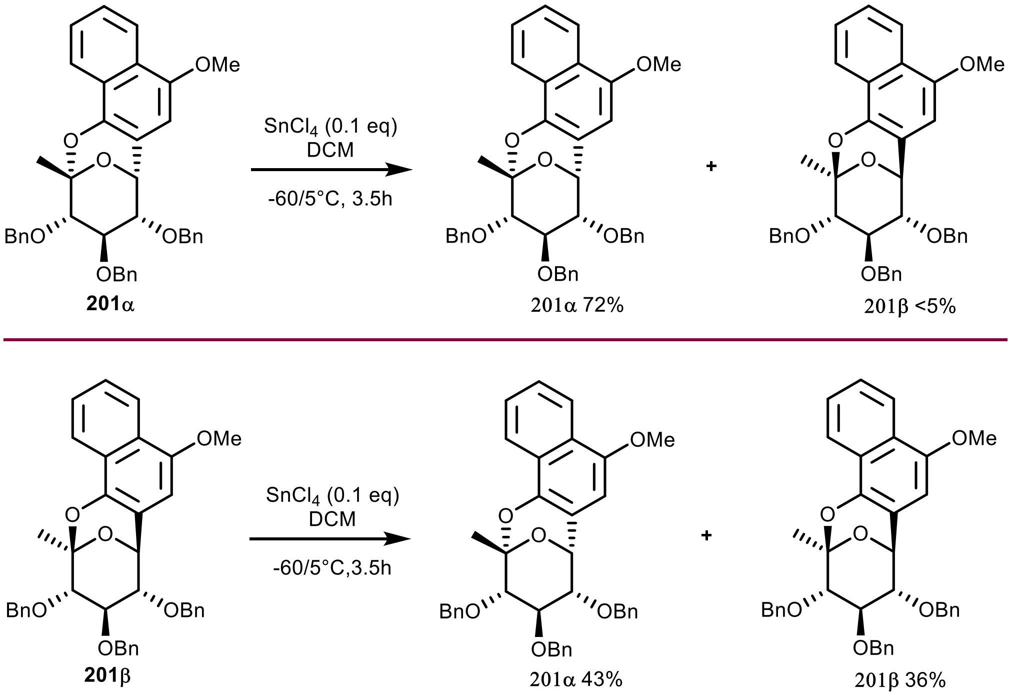
With the best conditions in hand (**entry 10**), a substrate scope study was carried out. First, 1,5-bis-glycosides **151bc** with a free phenolic hydroxyl group was studied giving the corresponding cyclized products **203** in 28% yield (dr 6/1). After that, another substrate **177c**, in which the OBn group is replaced by the OMe group, was tried giving the cyclized product **204** in 57% yield (dr 2.8/1). Unfortunately, substrates (**177ba**, **177bb**, **151ba)** underwent degradation during the cyclisation reaction (**205** and **206**) (**Scheme 103**).



203 (28%, d.r. 6/1) (from **151bc**)
204 (57%, d.r. 2.8/1) (from **177c**)
205 (not obtained) (from **177ba** and **151ba**)
206 (not obtained) (from **177bb**)

Scheme 103. *Substrate scope study*

In addition, we saw that the two cyclization products were obtained with different ratios of diastereoisomers in the optimization experiments (**Table 5**). Equilibration experiments were conducted under optimal conditions as listed in **Table 5**. The results indicate that the conversion of compound **201β** to **201α** is feasible, while the reverse process under identical conditions is not. This result suggests that **201α** is likely to be the thermodynamic product in the cyclization process.



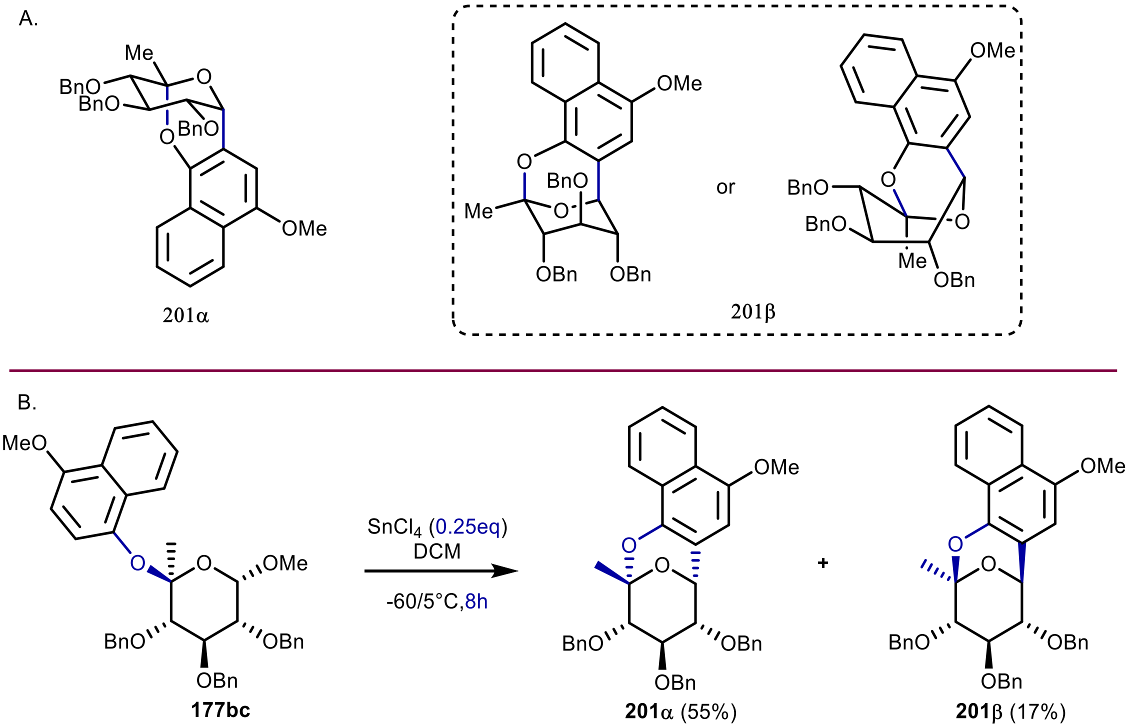
201α → 201α 72% + 201β <5%

201β → 201α 43% + 201β 36%

Scheme 104. *Equilibration experiments*

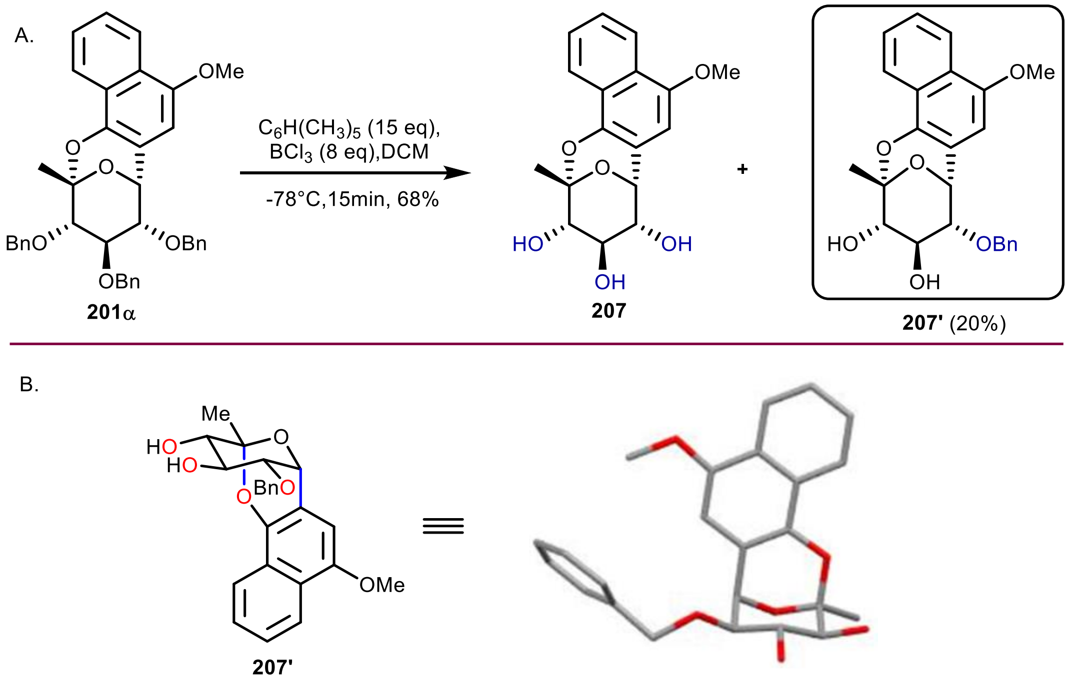
As seen in ^{1}H NMR, **201α** possesses a more stable chair conformation with the three OBn groups and the methyl substituent adopting an equatorial position (see **Scheme 105A**). This was also confirmed by the the X-ray crystallographic analysis of **207'**, which is a partially deprotected analogue of **201α** (see **Scheme 106B**). However, for compound **201β**, two possible conformations are shown (a chair conformation with OBn and methyl groups in axial positions or a twisted boat conformation) in **Scheme 105A**.

Then, the cyclization reaction was run for 8 h with more $SnCl_4$ (0.25 equiv.) to favor the formation of the thermodynamic product **(Scheme 105B)**. The results obtained indeed showed that the diastereoselectivity could be increased when the reaction was run for a longer time (dr 3.2/1).



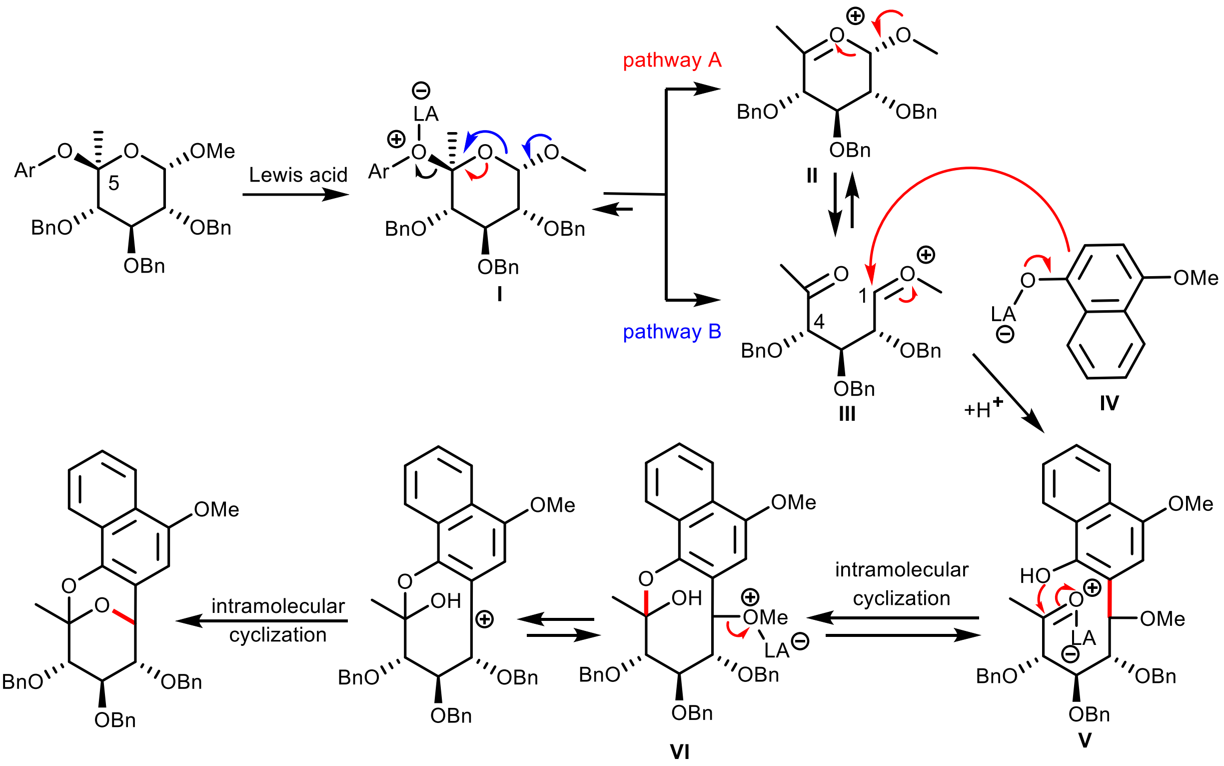
Scheme 105. *A. Stability analysis of **201α** and **201β**; B. Cyclization reaction with longer time*

Subsequent deprotection of *O*-benzyl groups using a combination of pentamethylbenzene and boron trichloride afforded the full deprotected cyclized product **207** in 68% yield along with a non-fully deprotected product **207'** in 20% yield (**Scheme 106A**). Further experiments are needed to optimize the deprotection process by increasing the reaction time or the amount of boron reagent.



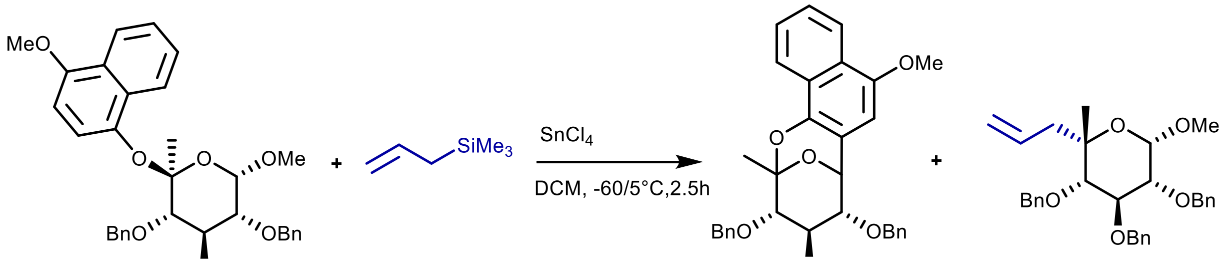
*Scheme 106. A. Deprotection of cyclization product **201α**; B. Confirmation of the structure of **207**' by X-ray crystallographic analysis.*

Based on these observations, we propose two possible mechanistic pathways for the cyclization reaction (**Scheme 107**). Activation of the aromatic leaving group in 1,5-bis-glycoside intermediate **I** is likely to provide oxocarbenium **II** (pathway A) that could be in equilibrium with the more reactive oxocarbenium intermediate **III**. In pathway B, the oxocarbenium ion **III** is obtained directly from **I**. This process would involve the lone pair of the anomeric methoxy group.[238] Finally, a Friedel-Craft reaction between complex **IV** and oxocarbenium **III** would generate **V** and the *C*-aryl glycosidic bond found in the final product. Intramolecular formation of hemi-acetal intermediate **VI** followed by a final cyclization involving the Lewis acid-mediated formation of a thermodynamically favoured benzylic cation would lead to the final product. This mechanism explains why the glycosidic bond at C-5 is epimerized during the process.



Scheme 107. *Possible mechanism for the cyclization reaction*

To elucidate the mechanism, several experiments were performed with allyltrimethylsilane as an oxocarbenium trapping agent (**Scheme 108**). The obtention of product **208** unambiguously demonstrated the presence of intermediate **II** in the reaction process. In addition, the observation of compound **202** (**Table 5**) give a very important mechanistic insight on the reaction mechanism. This compound is likely to result from the intramolecular attack of the benzyloxy group at C-4 onto the C-1 position of the oxocarbenium cation intermediate **III**.



208

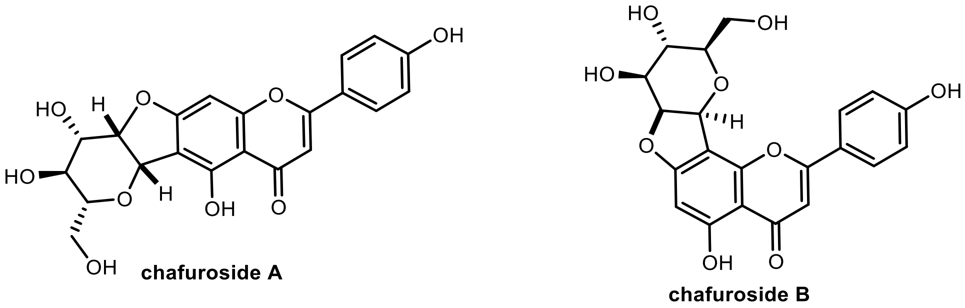
1eq	2eq	50%	trace by MS
1eq	15eq	trace	15%
1eq	6eq	0%	16%

Scheme 108. *Trapping experiments using allyltrimethylsilane*

5. Application of our methodology

5.1. Dihydrofuran cyclisation products

Chafuroside A and chafuroside B (**Figure 12**) are isolated from oolong tea leaves. They display several beneficial pharmacological activities related to anti-inflammation.[239-241] The formation of the dihydrofuran ring is a crucial step in their synthesis.



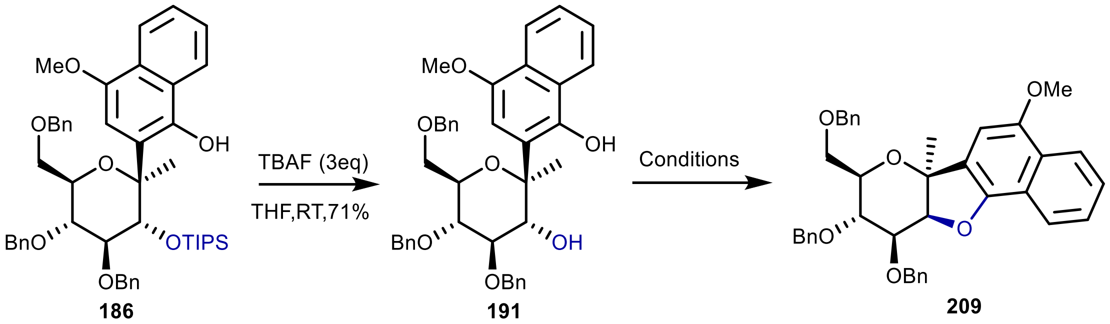
chafuroside A

chafuroside B

Figure 12. Structure of the natural products chafuroside A and chafuroside B

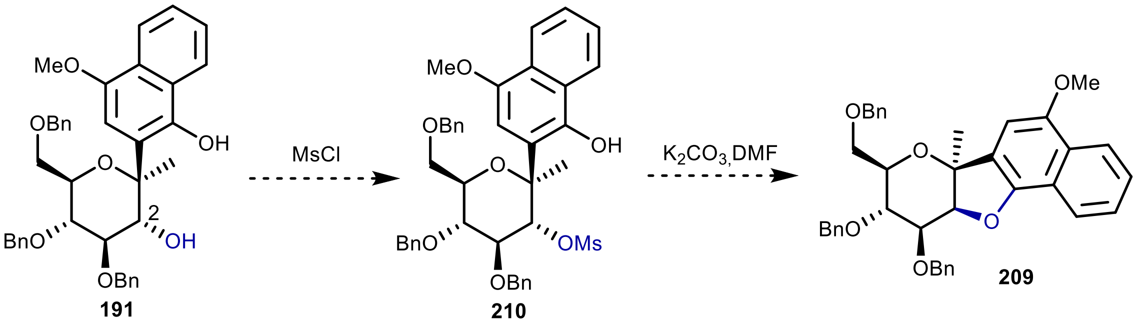
To further evaluate the interest of the *C*-aryl glycosides synthesized *via* Fries-type rearrangement, we tried to construct the dihydrofuran ring *via* an intramolecular Mitsunobu reaction (**Table 6**).[178;242;243] First **191** was obtained from the deprotection of the TIPS group of compound **186**. The experimental results showed that our compounds were not suitable for Mitsunobu reaction (**entries 1-4**), probably due to the influence of the quaternary carbon center at C-1. After that, we tried the cyclodehydration reaction with compound **191** in the presence of *p*-TsOH.[244] We only found the starting material in the NMR analysis of the crude reaction mixture (**entry 5**).

Table 6.** Exploration of the cyclization of compound **191



Entry	Active reagent		Solvent	Temp.	Time	Comments
1	DEAD	PPh_3	THF	0℃	2.5h	Decomposed
2	ADDP	Bu_3P	Toluene	0-25℃	24h	SM+byproducts
3	CMBP	-	Benzene	100℃	24h	SM+byproducts
4	DIAD	PPh_3	DMF	0-25℃	3days	Decomposed
5	*p*-TsOH	-	Toluene	25℃	18h	SM+byproducts

Subsequently, to obtain the cyclisation product **209**, another route was designed. First, the hydroxyl group at C-2 of **191** could be mesylated and the target product **209** may then be obtained *via* an intramolecular nucleophilic substitution in the presence of K_2CO_3.[245]



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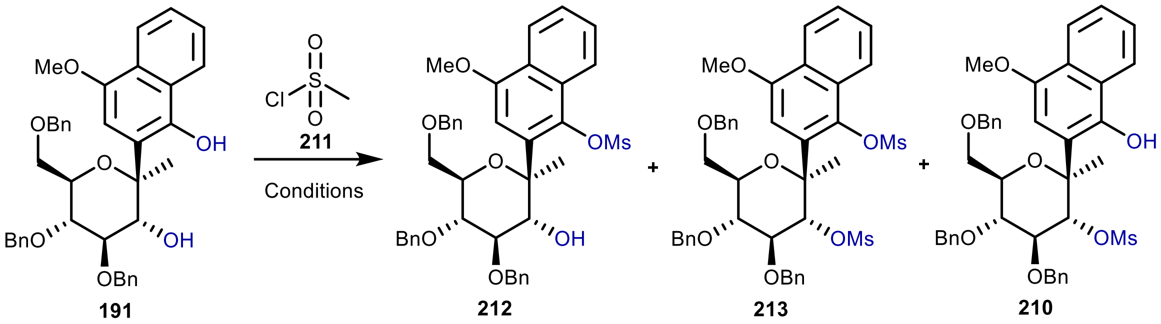
Scheme 109.** A possible route for the synthesis of the desired product **209

However, when mesylation[246] was first carried out with pyridine in DCM at 0 °C, we did not find any new products (**Table 7**, **entry 1**). The pyridine was replaced by triethylamine. In this case, the reaction proceeded at room temperature but we obtained a mixture of mesylate compounds **210**, **212** and **213** in 10%, 30%, and 35 yields, respectively (**entry 2**). Pyridine was then used again, but no significant change was observed when we tried to warm the reaction to room temperature overnight. At this point, an additional 1.5 equiv. of MsCl was added and the reaction was heated to 50 °C overnight. The desired product **210** was isolated in 18% yield along with dimesylate compound **213** (8% yield). Curiously, **212** was not observed, but another new unidentified compound was produced as the main product. We have been unable to identify the exact structure of this compound so far. Of note, the IR spectra of this compound demonstrates the absence of an OH peak.

Table 7. *Mesylation of compound* ***191***



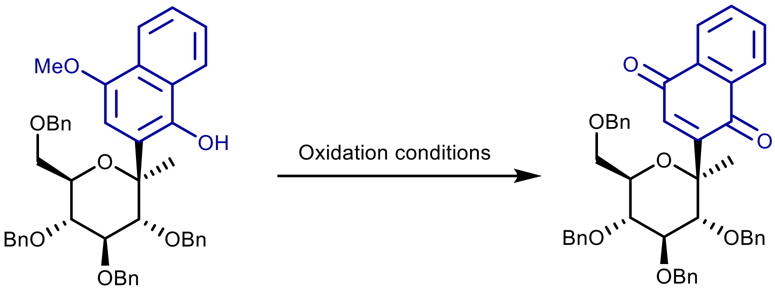
Entry	MsCl	Conditions	210 (desired)	212	213
1	1.5 eq	Pyridine, DCM, 0°C	No reaction (only SM)		
2	1.5 eq	Et_3N, DCM, RT	10%	30%	35%
3	1.5 +1.5 eq	Pyridine, DCM, 0-50°C, 49h	18%	-	8%

To improve this step, we could envisage to protect the phenol function before the mesylation of the secondary alcohol. Then compound **209** would be obtained by deprotection and cyclisation steps.

5.2. Synthesis of *C*-naphthoquinone glycosides

C-Naphthoquinone glycosides possess significant bioactivity and they are good intermediates in the synthesis of many natural products.[164;165;247] To obtained original analogues bearing a quaternary pseudoanomeric center, a mild oxidation of **183** with ceric ammonium nitrate (CAN) in aqueous acetonitrile first was carried out at 0 °C, giving a mixture of the desired product **214**, starting material and other byproducts (**Table 8**, **entry 1**). CAN was then replaced by TBAB and Oxone, accompanied by a gradual warming to room temperature for 24 h. Under these conditions, we just recovered a large amount of the starting material **183** (**entry 2**). Going back to CAN reagent but using DCM and rising the temperature to 60 °C for 3 days still led to complex mixtures of products (**entries 3** and **4**). We were however delighted to see that running directly the reaction at 50 °C for 4 h gave the desired product in 80% yield without purification (**entry 5**). NMR of the crude demonstrates that it is pure enough.

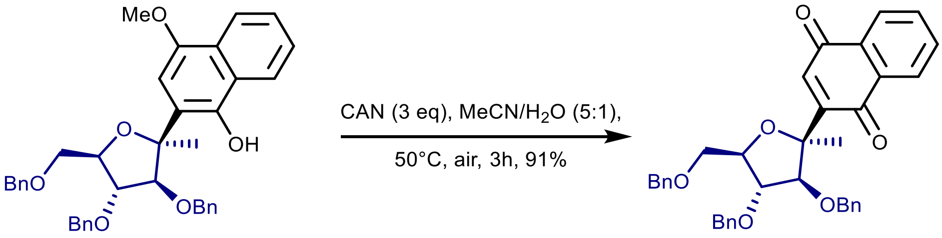
Table 8. *Synthesis of C-naphthoquinone glycoside* ***214*** *by oxidation of compound* ***183***



183 **214**

Entry	Oxidant	Solvent system	Temp.	Time	Comments
1	CAN	MeCN-H_2O	0°C	2h	(product+SM+byproducts)
2	TBAB, Oxone	MeCN-H_2O	0-RT	24h	SM 65%
3	CAN	DCM (silica gel with H_2O)	RT	3days	(product+ byproducts)
4	CAN	MeCN-H_2O	0-60°C	3days	(product+ byproducts)
5	CAN	MeCN-H_2O	50°C	4h	80%

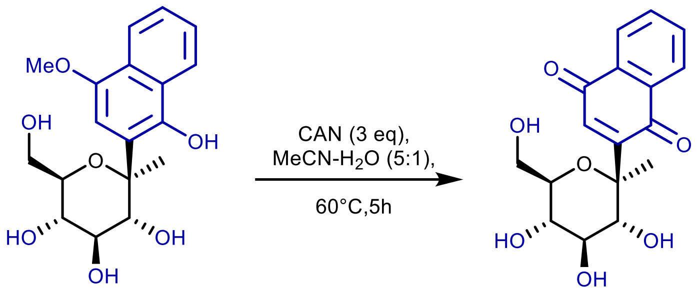
With the best conditions in hand, to further reveal the applicability of this method for the oxidation of our *C*-aryl glycosides with quaternary carbon centers, a five-membered cyclic *C*-glycoside **189** was selected. Desired quinone **215** was obtained in 91% yield (**Scheme 110**).



189 **215**

Scheme 110. *Oxidation reaction of* ***189*** *to quinone* ***215***

Finally, the deprotected product **199** was oxidized using the same conditions. It seems that we obtained the desired product **216**. This crude product was analyzed by ^{1}H NMR and mass spectrometry as well as IR spectroscopy showing a strong peak at 1663 cm^{-1}. Disappointingly, the product was degraded after column with silica gel using DCM and MeOH as eluting solvent. In second attempt, we used isopropanol instead of MeOH as the eluent and we still failed to obtain the desired pure product.



199

216 (<77%)

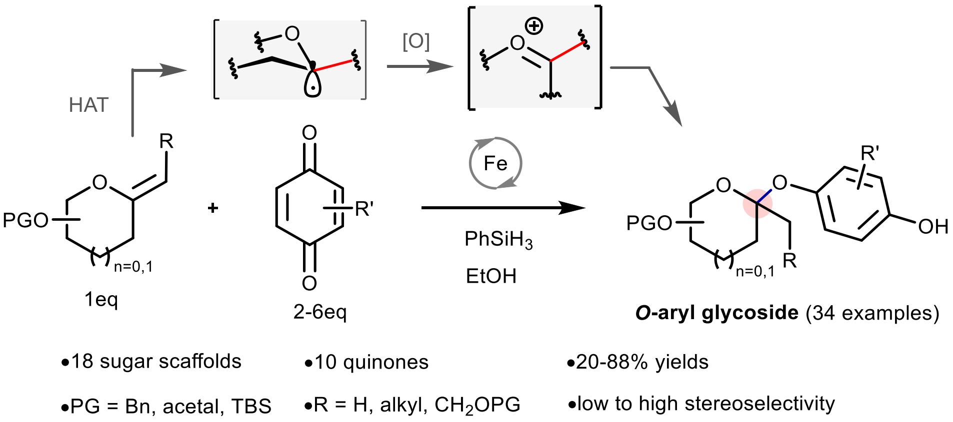
Scheme 111. *Oxidation of* ***199*** *to quinone* ***216***

6. Conclusion

Based on a general strategy for the construction of *C*,*O*-glycoside building blocks from *exo*-glycals and quinones under iron-mediated HAT conditions (**Chapter 2**), the synthesis of *C*-aryl ketosides *via* Lewis acid-catalyzed *O* → *C* glycoside rearrangement was demonstrated, opening the way to a unified strategy for the construction of *C*-glycoside motifs characterized by a stereodefined quaternary pseudoanomeric center bearing an exocyclic *O*- or *C*-aryl substituent. The one-step conversion of the *C*-naphthyl ketosides to the corresponding *C*-naphthoquinone glycosides opens also new perspectives in terms of future biological applications.

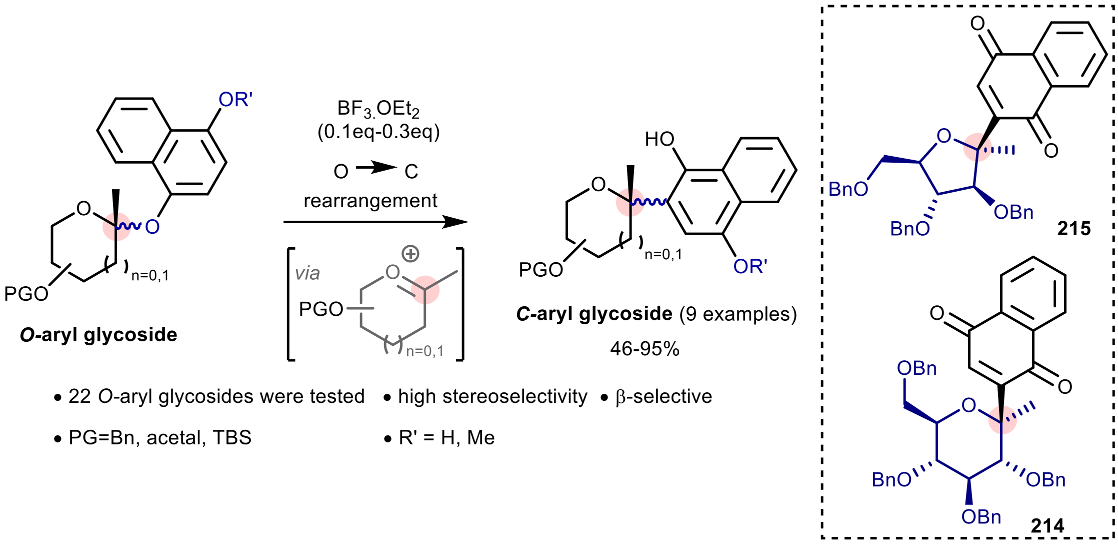
General conclusions and perspectives

In this thesis, we have successfully obtained a mild and economical strategy for the synthesis of *C*,*O*-glycosides with quaternary anomeric center in one step from *exo*-glycals and quinones under iron-mediated HAT conditions. With the development of this strategy, *O*-aryl glycosides were synthesized in yields up to 88% with low to high stereoselectivity. In this process, 18 sugar skeletons with different ring sizes, configurations were tested and 10 different quinones were used (**Scheme 112)**. This work was published in the *Journal of Organic Chemistry*.[207]



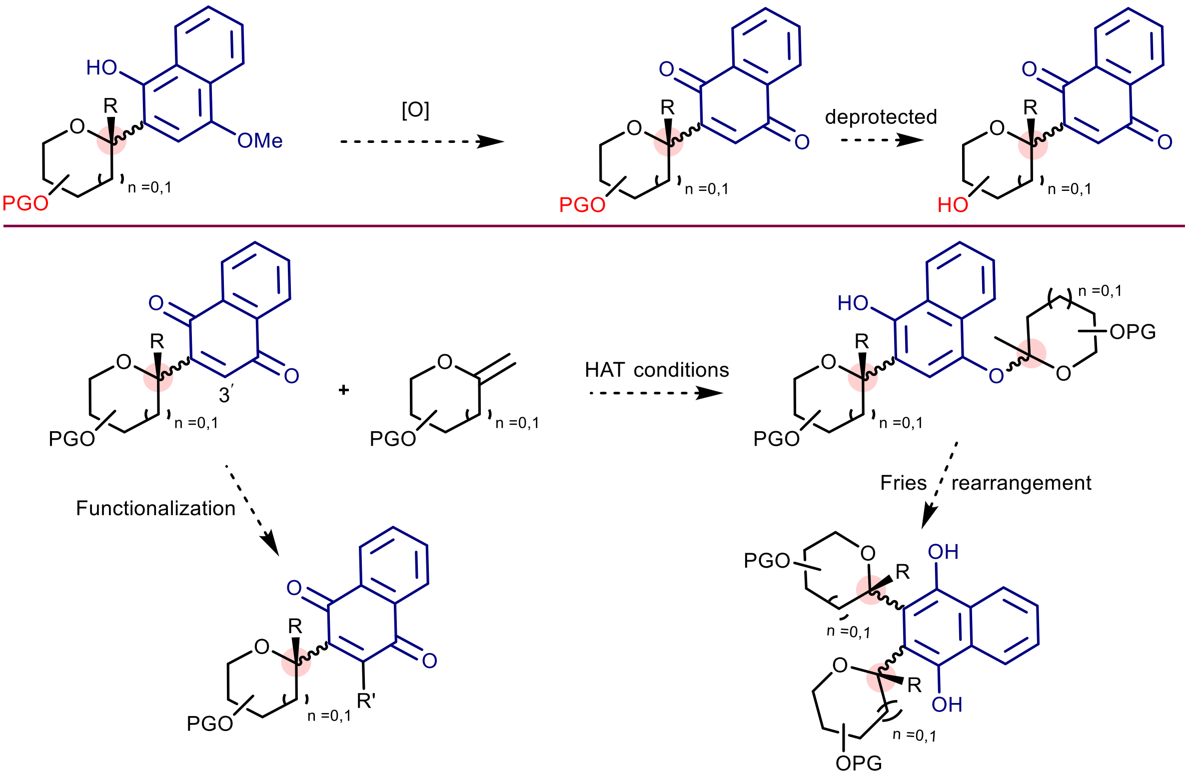
Scheme 112. *Formal O-glycosylation of quinones*

In addition, we obtained the first synthesis of *C*-aryl glycosides bearing a quaternary carbon center by way of Fries-type rearrangement (**Scheme 113)**. So far, we have tried 22 different *O*-aryl glycosides to run the *O* →*C* transformation. However, we only obtained 9 *C*-aryl glycosides with different sugar part in high yields and high stereoselectivity. So far, the scope of this method is limited to naphthyl glycosides. Excitingly, the corresponding oxidation products **214** and **215**, which could be important intermediates in the synthesis of bioactive compounds were synthesized in high yields.



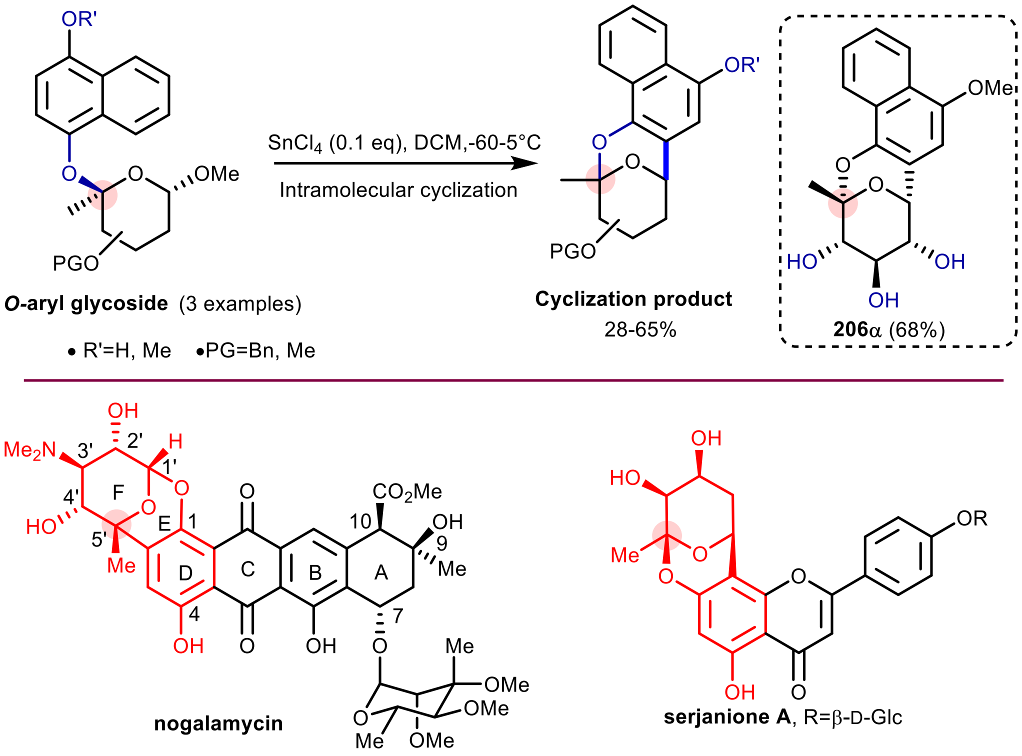
Scheme 113. *O → C glycoside rearrangement and application*

Furthermore, more *C*-naphthoquinone glycosides may be obtained. After that, the activity of the corresponding deprotected products will be tested. We could also combine the different methodologies described above to synthesized rather complex bis-*C*-aryl glycosides in a convergent manner (**Scheme 114)**.



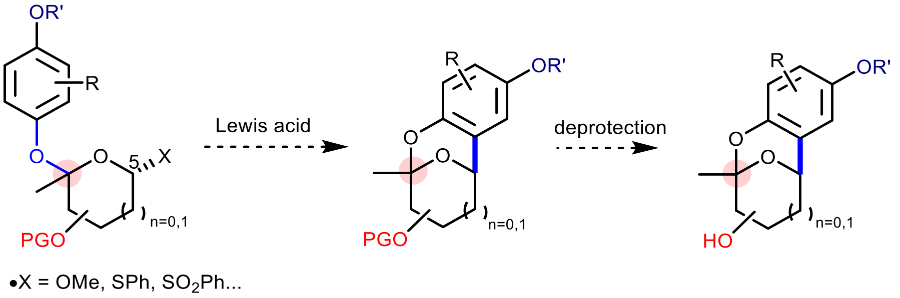
Scheme 114. *Convergent access to bis-C-aryl glycosides*

Finally, original cyclization products were obtained from bifunctional *O*-aryl glycosides. Although it is different from the DEF-ring system of nogalamycin, it is attractive due to the fact that the natural product serjanione A, which has not been synthesized so far, has an identical ring system. The cyclization reaction has been optimized with a variety of parameters. We obtained the best conditions with $SnCl_4$ as activator and DCM as solvent. In addition, the deprotected cyclized product **206α** was obtained with a good yield.



Scheme 115. Cyclization reaction

With the initial results in hand, we will continue to expand substrate studies with different protective groups, configurations and ring sizes. Different leaving groups at C-5 will also be tried. We are very interested in the activities of these cyclisation products as well as their deprotected products.



Scheme 116. Perspectives of cyclization reaction

Résumé en Français*

*_Les numérotations des références, des schémas et des figures sont identiques à celles du texte anglais_

Les _O_- et _C_-aryl glycosides représentent d'importantes classes de composés synthétiques et naturels d'intérêt thérapeutique.[2;3;10;29;30] Dans les _O_-aryl glycosides, l'aglycone est lié par une liaison C-O labile. Ces glycoconjugués présentent un large spectre d'activités biologiques. Le produit naturel phlorizine est par exemple un précurseur du colorant jaune POP et un inhibiteur compétitif de la SGLT (protéine de transport du sodium et du glucose).[4] La liste comprend également l'antibiotique vancomycine[5] ou la phtalocyanine (antidiabétique).[6] Les défis synthétiques associés à ces glycosides dépendent de la complexité de leurs structures, allant de l'arbutine,[7] un glycoside phénolique simple, utilisé dans le traitement de l'hyperpigmentation, à des systèmes polycycliques plus complexes comme la serjanione A,[8] extrait des feuilles de _Serjania marginata_, possède des activités antioxydantes (**Figure 1**). L'originalité structurelle peut également provenir de liaisons inhabituelles entre la partie aglycone aromatique et la partie sucre, comme dans la sucro-néolambertelline,[9] isolée _de Lambertella sp._ 1346. Ce produit naturel est le premier décrit dans lequel le saccharose est oxydé en position C-5', ce qui lui permet de se lier à la néolambertelline.

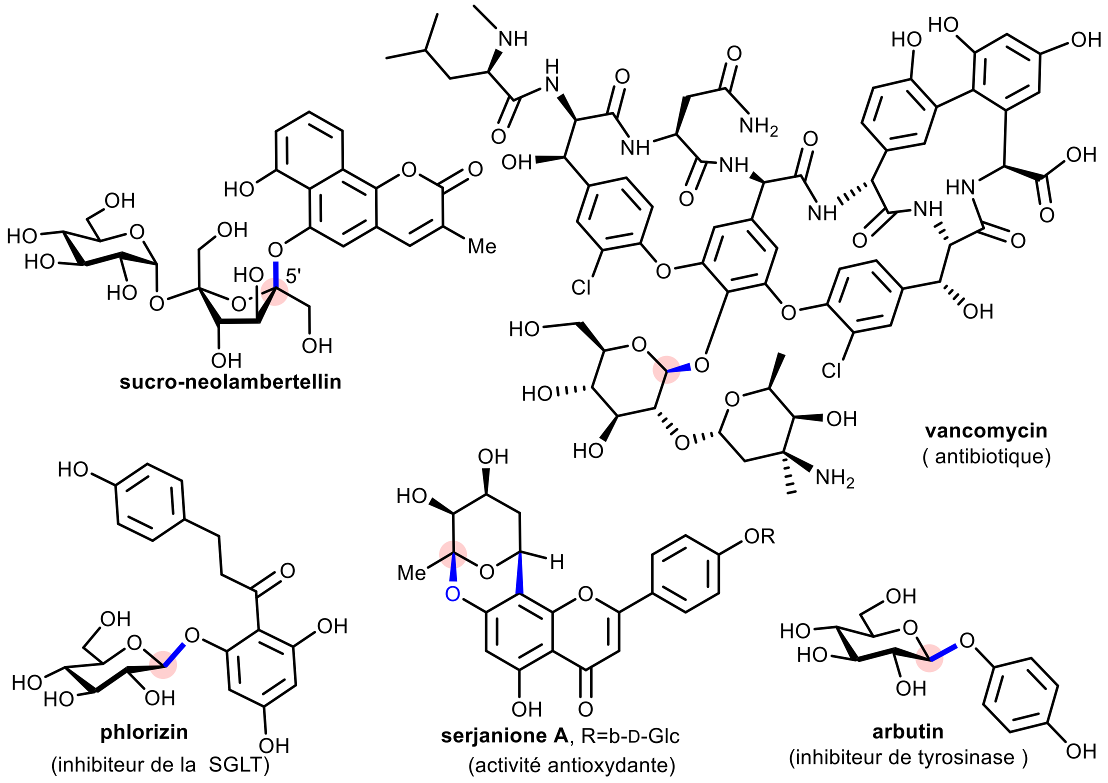


Figure 1. *Exemples de O-aryl glycosides ayant des propriétés biologiques et thérapeutiques.*

Les produits naturels, les composés bioactifs ou les médicaments commercialisés basés sur un motif _C_-glycoside ont également attiré l'attention des scientifiques (**Figure 2**). D'un point de vue structurel, la liaison C-O labile est remplacée par une liaison C-C stable. Nous pouvons considérer ces composés comme des mimes de *O*-glycosides. Dans les *C*-aryl glycosides,[25-27] les parties aglycones sont liées par des liaisons *C*-glycosidiques chimiquement plus fortes.[28] Cette modification améliore considérablement la stabilité des C-glycosides vis-à-vis des hydrolases *in vivo*, augmentant ainsi leur potentiel en tant que médicaments thérapeutiques et sondes biologiques.[29;30] Par exemple, ces dernières années, une série d'inhibiteurs du SGLT2 contre le diabète de type II a été développée,[31-33] parmi lesquels le Steglatro™[34] et le dapagliflozin.[35] Ces composés améliorent considérablement le contrôle de la glycémie chez les adultes atteints de diabète de type 2. De plus, la synthèse totale du diamino-sucre saptomycine B possédant des propriétés antidiabétiques et antitumorales a été décrite[36] ainsi que l'antibiotique gilvocarcine M.[37] D'autres *C*-aryl glycosides naturels ont été étudiés ou synthétisés. Ces études ont été présentées dans plusieurs revues récentes[25;27;39;40] et ne seront donc pas détaillées dans le présent rapport. Contrairement aux nombreuses approches ciblant les *C*-glycosides, seules quelques-unes ont été décrites pour la construction stéréosélective de carbones pseudo-anomères quaternaires pour donner des *C*,*C*-glycosides.[52]] Les C,C-glycosides naturels et les produits synthétiques associés ont un fort potentiel pour la découverte de médicaments. À titre d'exemple, nous pouvons citer la nogalamycine[53] et ses dérivés synthétiques tel le ménogaril,[54] ou l'inhibiteur du SGLT2, le Steglatro™ (**Figure 2**).[34] A ce jour aucune synthèse totale de la nogalamycine a été décrite. Par conséquent, la construction stéréocontrôlée de liaisons *C*,*C*-glycosidiques est d'intérêt et représente un défi compte tenu de la complexité de ces structures.

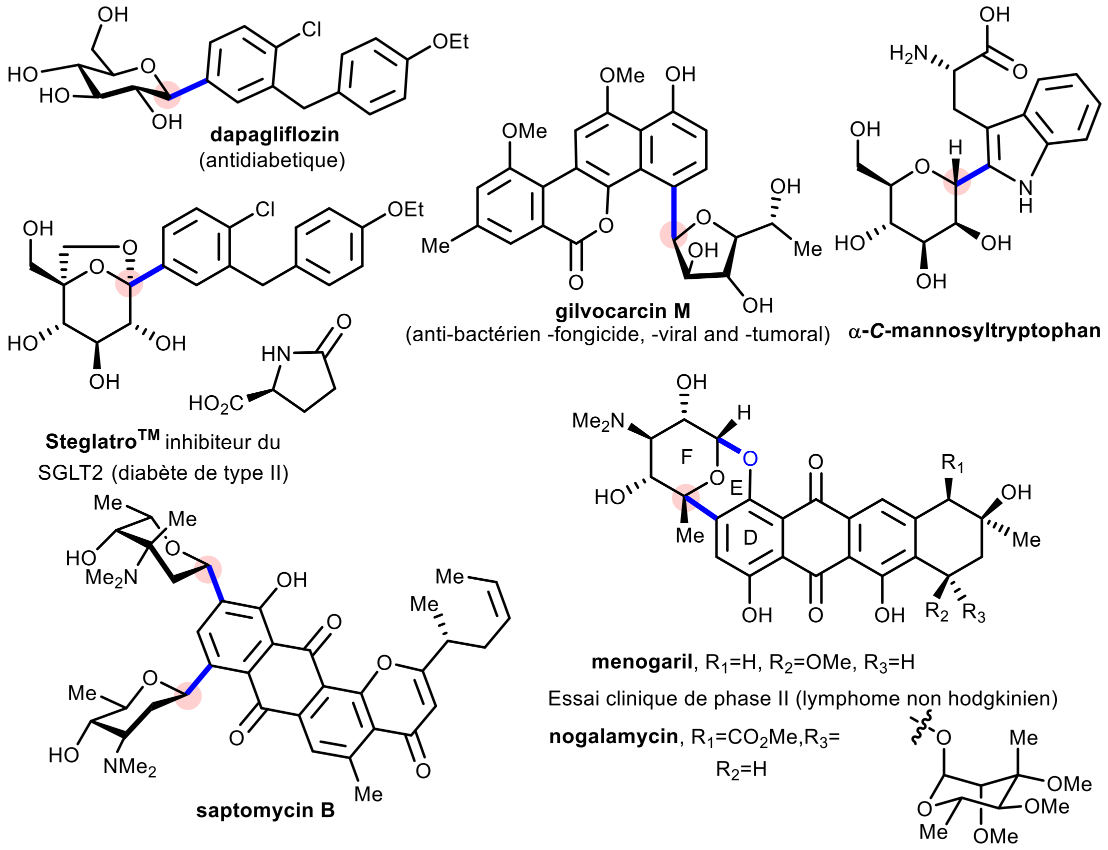


Figure 2. *Exemples de C,C-glycoside d'intérêt biologique et thérapeutique.*

En 2019, dans cadre d'études sur les glycomimétiques notre groupe a décrit une stratégie pour la synthèse de *C*,*C*-glycosides à partir d'*exo*-glycals *via* un transfert d'atome d'hydrogène (HAT) catalysé par un métal en présence d'accepteurs de Michael (**Schéma 3**).[55]

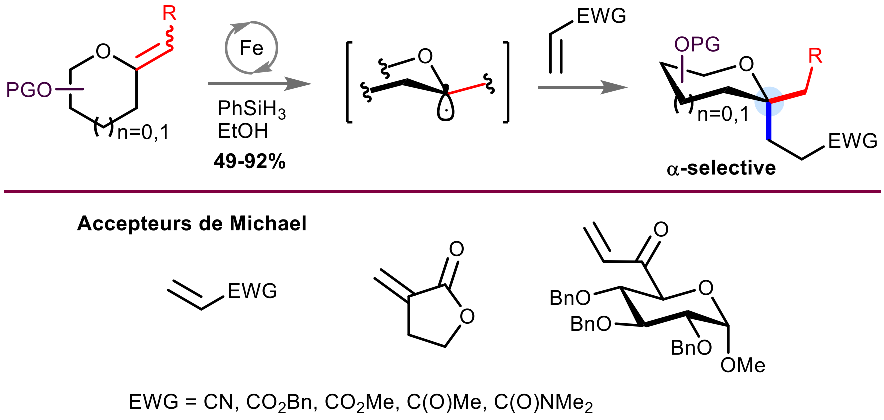


Schéma 3. *Synthèse hautement stéréosélective de C,C-glycosides à partir d'exo-glycals par HAT*

Afin de développer une approche convergente pour accéder aux noyaux benzoxocine dans les composés tels que la serjanione A ou la nogalamycine, nous avons envisagé le couplage direct de radicaux glycosyles générés par MHAT avec des 1,4-quinones. Cependant, le contrôle de la régio-, chimio- et diastéréosélectivité dans la génération de centres (pseudo)-anomères quaternaires par MHAT en utilisant des quinones constitue un vrai défi. Au moins six produits glycosylés avec des stéréochimies, des connectivités ou des états d'oxydation différents peuvent être en effet obtenus dans un processus non sélectif (**Schéma 5**).

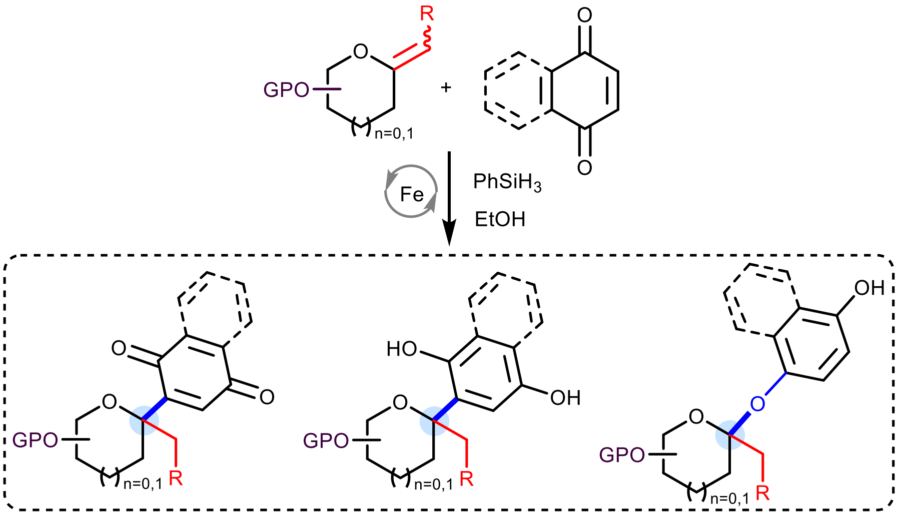


Schéma 5. *Synthèse envisagée de C,C- ou C,O-aryl glycosides à partir d'exo-glycals et de quinones*

Chapitre 1

Dans **un premier chapitre bibliographique**, les structures et l'intérêt de la nogalamycine, de la serjanione A et des composés naturels ou synthétiques apparentés sont décrites. Leurs activités biologiques et leurs intérêts thérapeutiques sont présentés. Les études de synthèse de la nogalamycine, de la serjanione A et de leurs analogues sont également décrites dans ce chapitre. Cette étude bibliographique apporte des informations importantes notamment pour la conception de stratégies de synthèses dirigées vers le motif *C*,*C*-aryl glycosides. Il est à noter qu’à ce jour aucune synthèse de la nogalamycine n’a été décrite.

Chapitre 2

Ces dernières années, l’hydrofonctionnalisation par transfert d’atome d’hydrogène d’alcènes[57-59] a pris un essor important permettant la synthèse de molécules fonctionnalisés en particulier des produits naturels. Cependant à ce jour, il existe peu d'exemples de telles stratégies pour la formation de radicaux glycosylés malgré son potentiel pour le développement de méthodes de *C*-glycosylation.[163]. En 2019, nous avons obtenu une diversité de composés *C*,*C*-glycosylés à partir d'*exo*-glycals par l'intermédiaire de radicaux pseudoanomères tertiaires.[156] Basés sur ces résultats, notre objectif initial était de développer une stratégie pour la synthèse totale de la nogalaycine, en se concentrant sur sa partie glycobenzoxocine. Nous avons ainsi envisagé la voie de rétrosynthèse présentée dans le schéma 57. Le premier intermédiaire **E** pourrait en effet être synthétisé par une annulation de Hauser convergente entre deux segments hautement fonctionnalisés **C** et **D**. Le fragment **C** pourrait être synthétisé à partir de B.[79]

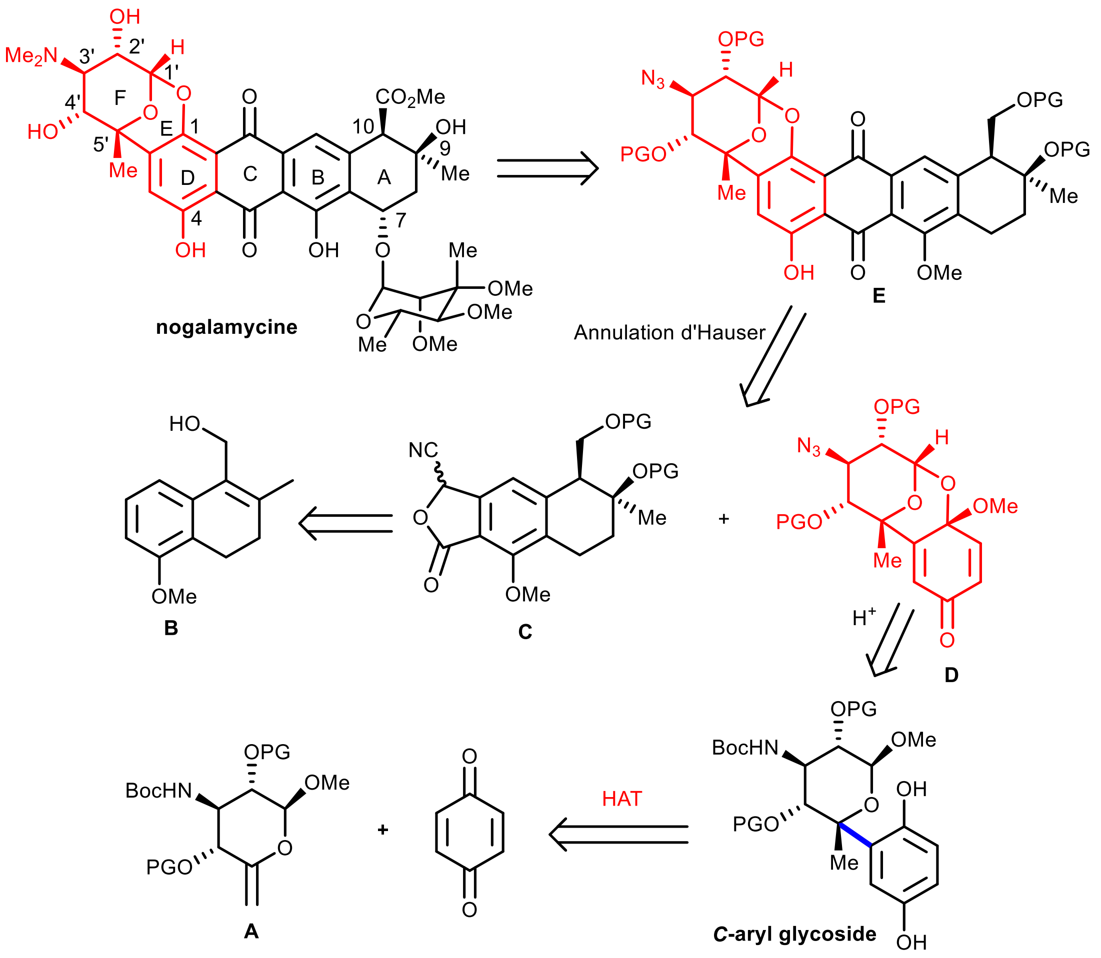
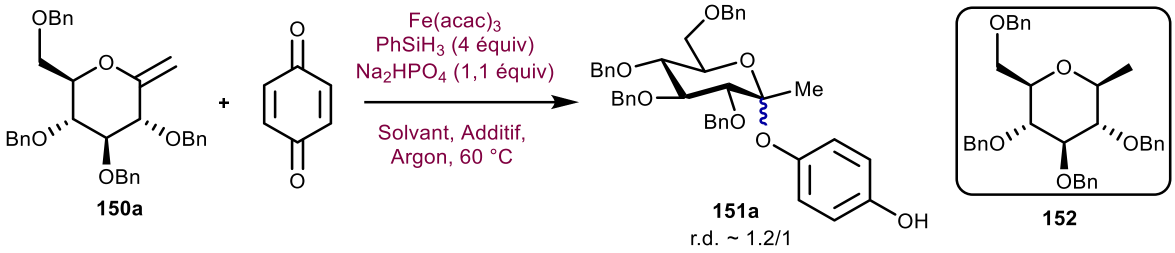


***Schéma 57.** Rétrosynthèse proposée de la nogalamycine*

L'intermédiaire clé **D** possédant le squelette DEF de la nogalamycine pourrait être formé par O-glycosylation dans des conditions acides à partir d'un *C*,*C*-glycoside, qui pourrait être obtenu à partir de l'*exo*-glycal **A** et de la 1,4-benzoquinone par une réaction d'HAT catalysée par le fer.

Premièrement nous avons réalisé une étude modèle à partir de l'*exo*-glucal **150a** (**Tableau 3**). Lors d'un premier essai utilisant les conditions optimisées obtenues précédemment avec des accepteurs de Michael classiques,[156] la réaction de **150a** avec 2 équiv. de 1,4-benzoquinone (1,4-BQ) en présence de $PhSiH_3$ (4 équiv.), $Fe(acac)_3$ comme catalyseur, et Na_2HPO_4 comme tampon dans de l'EtOH dégazé sous argon a conduit à la formation des *O*-aryl glycosides **151a** avec un rendement de 30% et une faible α-stéréosélectivité (**tableau 3, entrée 1**)

Tableau 3. *Réaction d'HAT entre l'exogycal* ***150a*** *et la benzoquinone*



Entrée	1,4-BQ	Solvant	Additif	[Fe](éq)	C(M)	Temps	151a
1	2 éq	EtOH	-	0,1	0,03	5h	30%
2	2 éq	EtOH	-	1,0	0,03	7h	46%
3	2 éq	EtOH	-	1,0	0,05	5h	45%
4	2 éq	EtOH	-	1,0	0,10	2h	42%
5[a]	2 éq	EtOH	-	1,0	0,05	4h	28%
6	4 éq	EtOH	-	1,0	0,05	0,25h	55%
7	4 éq	THF	EtOH(8 éq)	1,0	0,05	1h	68%
8	4+2 éq	THF	EtOH(8 éq)	1,0	0,05	1h	77%
9	6 éq	THF	EtOH(8 éq)	1,0	0,05	1h	65%
10	4+2 éq	THF	EtOH(2 éq)	1,0	0,03	7,5h	80%
11	4+2 éq	THF	EtOH(8 éq)	0,5	0,05	1h	82%
12	4+3 éq	THF	EtOH(8 éq)	0,2	0,05	22h	77%
13[b]	4+2 éq	THF	EtOH(8 éq)	0,5	0,05	22h	59%
14[c]	4+2 éq	THF	EtOH(8 éq)	0,5	0,05	1h	79%
15[d]	4+3 éq	THF	EtOH(8 éq)	0,5	0,05	6.5h	52%
16	4+1 éq	THF	EtOH(8 éq)	1,0[e]	0,05	0.5h	66%
17	4+4 éq	THF	EtOH(8 éq)	0,5[f]	0,05	48h	-

a) Réaction effectuée à température ambiante; b) (i-PrO)-PhSiH$_2$ à été utilisé au lieu de PhSiH$_3$. c) Sans Na$_2$HPO$_4$; d) Réaction effectuée à l'air; e) 0.5+0.5 éq [Fe(acac)$_3$/Fe(acac)$_2$]ont été utilisés; f) Mn(acac)$_3$ a été utilisé au lieu de Fe(acac)$_3$

Malgré leur intérêt en tant que produits naturels et composés bioactifs, seules quelques méthodes synthétiques ont été décrites pour obtenir des *O*-aryl glycosides.[166-171] Nous avons alors étudié cette réaction plus en détail. L'optimisation de la réaction a permis d'obtenir le composé **151a** avec un rendement de 82% (**entrée 11**). En utilisant les conditions optimales, nous avons d'abord évalué la réaction avec différentes quinones (**Schéma 71**).

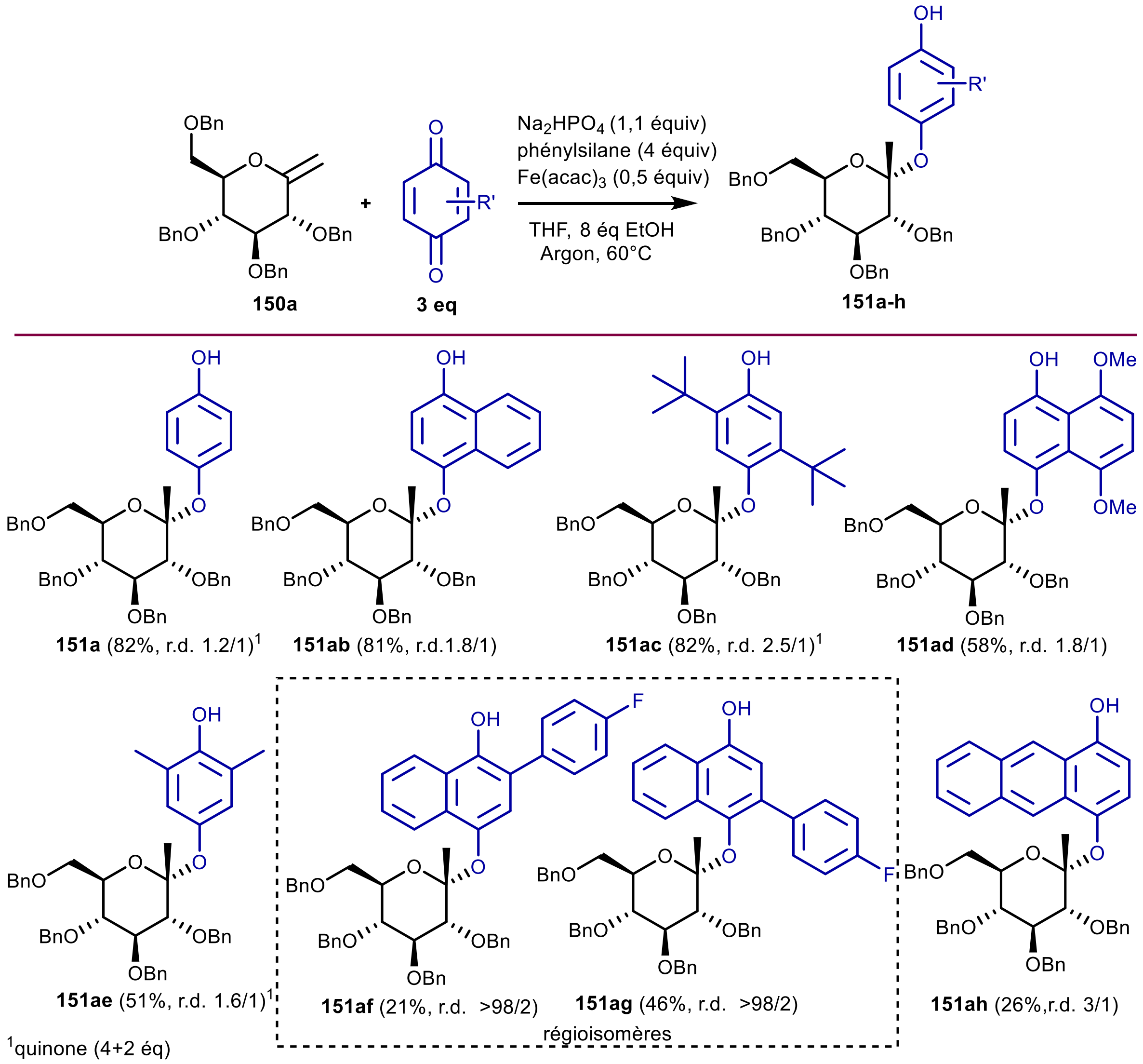


Schéma 71. *Etude de la réaction avec différentes quinones*

Le processus de couplage par HAT donne de bons résultats avec des 1,4-quinones encombrées stériquement qui conduisent aux composés **151ab**, **151ac,** et **151ad**. Il est à noter que la *O*-glycosylation formelle permettant la formation de **151ab** a pu être réalisée à l'échelle du mmol sans réduction de l'efficacité de la réaction. Nous avons pu obtenir régiosélectivement **157ae** avec un bon rendement. De même, deux régioisomères **151af** et **151ag** ont été obtenus avec une stéréosélectivité élevée. La réaction de glycosylation formelle avec la 1,4 anthraquinone a permis d'obtenir le *O*-glycoside **151ah** avec un rendement de 26% seulement. Une raison possible pour ce résultat est que le système conjugué encombrant de la 1,4 anthraquinone affecte l'efficacité du transfert d'électrons. Les résultats obtenus montrent que la réaction de glycosylation formelle est en général peu stéréosélective dans la série D-glucose. D'autres *exo*-glycals avec différentes configurations ont été étudiés. Dans la série des D-hexopyranoses, le passage de la configuration D-glucose à la configuration D-galactose ou D-mannose a conduit à des rendements plus faibles mais à des stéréosélectivités beaucoup plus élevées (composés

151da, **151db**, **151e**) (**Schéma73**).

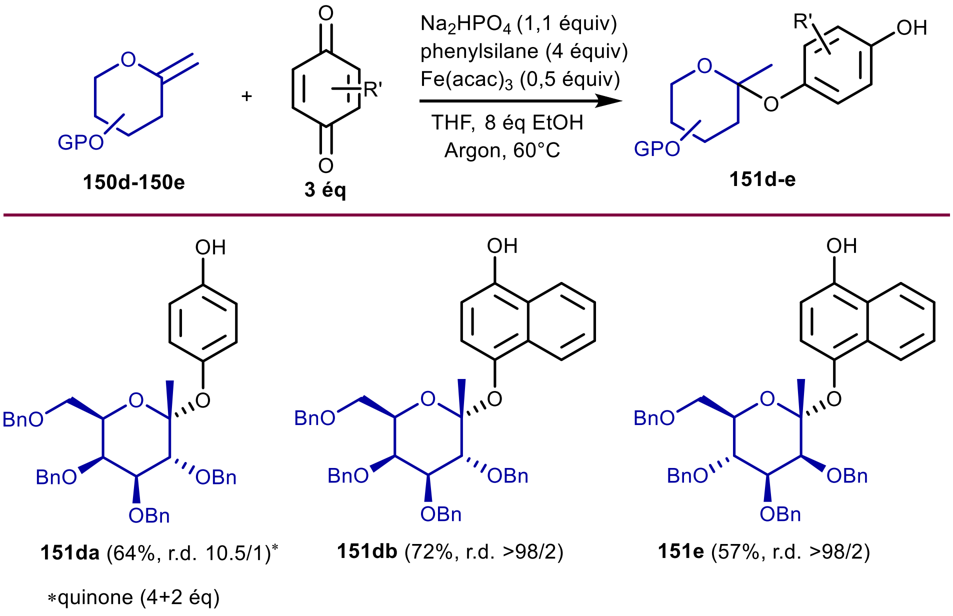
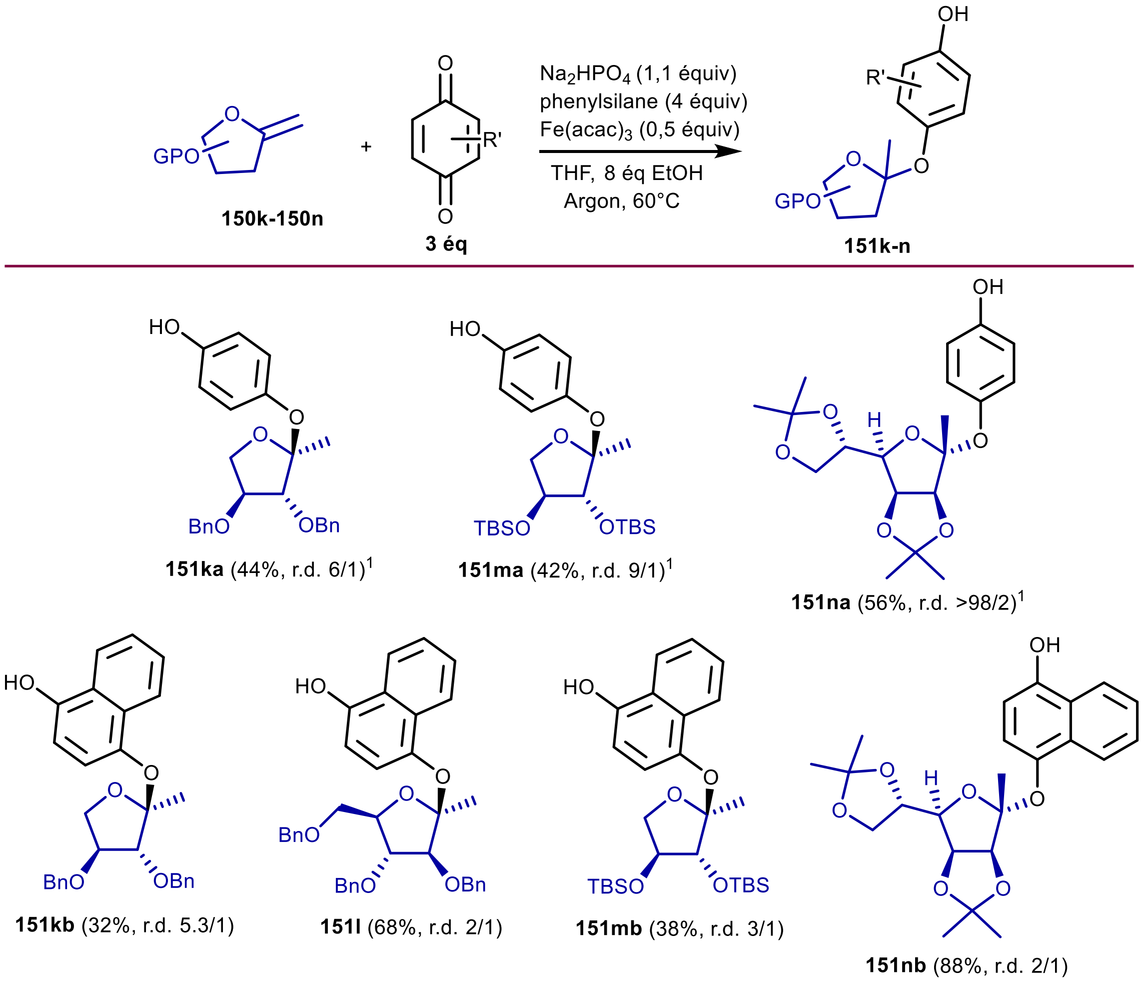


Schéma 73. *Etude de la réaction avec des exo-glycals de différentes configurations*

Ensuite, des *exo*-glycals à cinq membres ont été testés avec les conditions optimisées de la réaction de couplage donnant les *O*-cétosides correspondants avec une diastéréosélectivité faible à élevée. Il est à noter que les groupes protecteurs sensibles aux acides tels que les groupements TBS ou acétonide (**151ma**, **151na**, **151mb** et **151nb**) ont été bien tolérés (**Schéma74**).



[1]quinone (4+2 éq)

Schéma 74. Etude de la réaction avec des exo-glycals à 5 membres

L'*exo*-glycal bifonctionnel **150b** portant un substituant méthoxy anomérique en C-1 a fourni les 1,5-bis-glycosides correspondants avec des rendements acceptables et une diastéréosélectivité élevée sans clivage des liaisons glycosidiques (**151ba**, **151bb**, **151bc**). L'*exo*-glycal bifonctionnel **150c** dans lequel tous les groupes OBn ont été remplacés par des groupes OMe a donné le 1,5-bis-glycoside **151c** avec un meilleur rendement (**Schéma 75**).

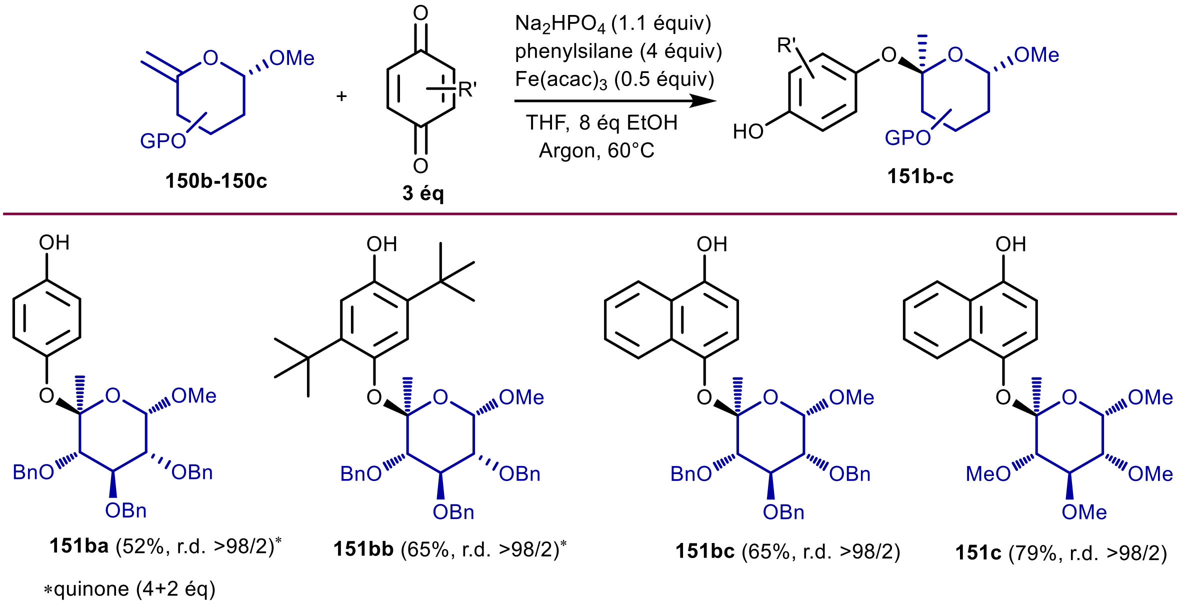


Schéma 75. *Etude de la réaction avec les exo-glycals bifonctionnels **150b** et **150c***

Finalement, pour démontrer davantage l'applicabilité de notre méthodologie, des *exo*-glycals **150o-150r** substitués par des alkyles plus complexes ont été évalués (**Schéma 76**). Les résultats obtenus ont montré que les rendements des produits correspondants **151o-151r** étaient faibles à modérés. Nous supposons que cela est dû à l'influence de l'encombrement stérique des deux partenaires dans l'étape critique de couplage par HAT. L'*exo*-glycal **150r** a été conçu comme une sonde mécanistique pour évaluer si la glycosylation formelle passait par un intermédiaire oxocarbénium (voir **aspects mécanistiques**, ci-dessous). La formation du produit de cyclisation à six chaînons **174** n'a pas été observée. Au lieu de cela, le produit de glycosylation formelle **151r** a été obtenu avec un rendement modéré.

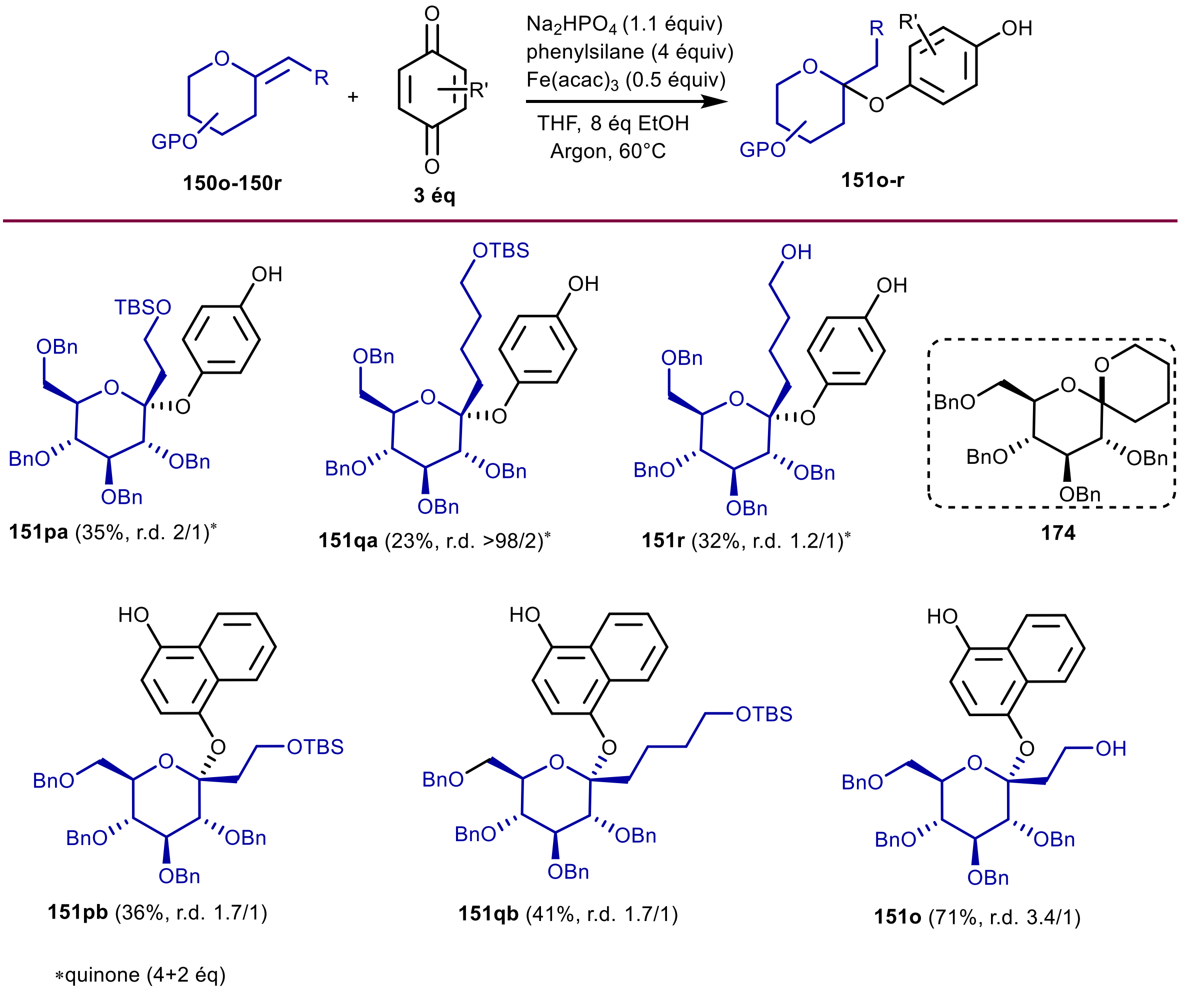


***Schéma 76.** Etude de la réaction avec des exo-glycals trisubstitués*

Nous avons effectué une étude mécanistique et émis l'hypothèse de la formation d'un complexe de transfert de charge (CT) entre le radical glycosylé **A** et la quinone, suivie d'un processus de transfert d'électrons (**Schéma 82**). Premièrement, nous avons supposé qu'une réaction d'HAT à partir de l'*exo*-glycal correspondant permettait d'obtenir l'intermédiaire radical tertiaire pseudoanomérique **A**. Ensuite, un complexe de transfert de charge (CT) serait formé entre le radical glycosyle **A** et la quinone (voie **A**), ce qui entraînerait la formation de deux intermédiaires réactionnels, l'oxocarbénium **B** et l'anion semi-quinone **C** à proximité immédiate. Ces deux intermédiaires sont très probablement situés dans la cage du solvant tétrahydrofurane. Ceci explique également l'absence de capture de l'ion oxocarbénium par l'éthanol ou le 4-méthoxyphénol sous atmosphère d'argon. Cependant, une autre voie ne peut être totalement exclue (voie **B**). Dans cette voie, le radical A est couplé directement à l'atome d'oxygène de la quinone selon un mécanisme décrit par P. Renaud (**Schéma 53**).[161] Les deux voies conduisent au même intermédiaire : le radical phénoxy **D**. La formation des produits phénoliques *O*-cétosides peut alors être obtenue par « proton-coupled electron transfer » (PCET) à partir du complexe éthanolique du Fe (II) ou par une voie de réduction/transfert de proton.

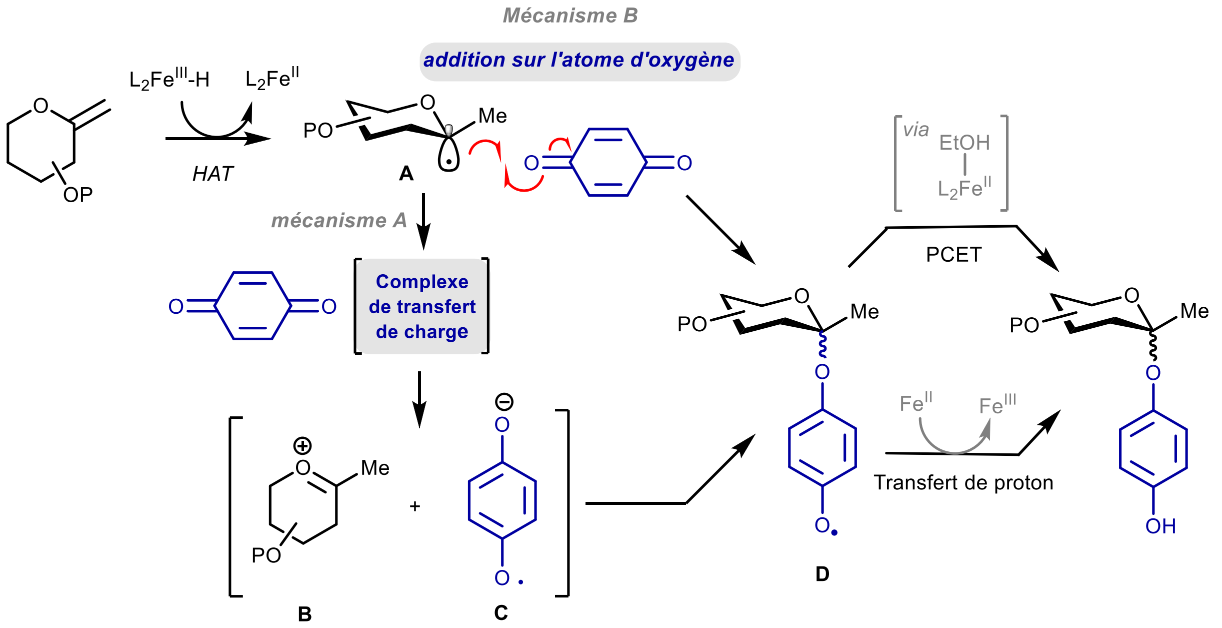
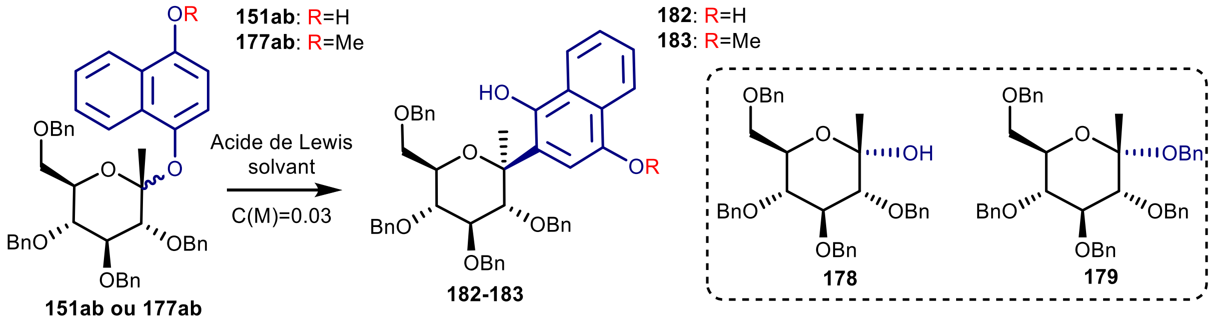


Schéma 82. *Mécanisme proposé pour la formation de O-aryl glycosides par HAT*

Chapitre 3

Nous avons ensuite évalué le potentiel de notre méthodologie de glycosylation par HAT en tant qu'étape clé dans la synthèse directe de *C*-aryl glycosides. En effet, les *O*-glycosides pourraient être transformés en *C*-glycosides par une réaction de type Fries (réaction de Suzuki).[208] Dans notre étude, seuls les dérivés *O*-naphtol ont pu conduire aux composés *C*-aryl correspondants. Ainsi les *O*-aryl glycosides **151ab**, ont conduit au β-*C*-aryl glycoside **182** avec 46% de rendement et une excellente diastéréosélectivité en utilisant des quantités substoichiométriques de $BF_3.OEt_2$ (30 mol%) (**Tableau 4, entrée 2**). La protection de la fonction hydroxyle phénolique a conduit à une augmentation significative de l'efficacité du réarrangement de Suzuki, conduisant au β-*C*-aryl glycoside **183** avec un rendement de 84% après optimisation

Tableau 4. *Optimisation de la conversion des O-aryl glycosides* ***151ab*** *et* ***177ab*** *en C-aryl glycosides par réarrangement de type Fries.*



Entrée	R	Acide de Lewis	additif	T/°C	solvant	Temps	182/183	178
1	H	$BF_3.OEt_2$ (2 éq)	4Å MS	0°C	CH_3CN	3.5h	4%	-
2	H	$BF_3.OEt_2$ (0,3 éq)	Drierite®	-60-22°C	DCM	20h	46%	-
3	H	$BF_3.OEt_2$ (0,3 éq)	-	-60 -5°C	DCM	2.5h	29%	26%
4	H	TfOH (0,5 éq)	Drierite®	-30°C	DCE	5h	-	28%
5[a]	H	$Sc(OTf)_3$ (0,3 éq)	Drierite®	0-25°C	DCE	30,5h	9%	-
6[b]	Me	$Sc(OTf)_3$ (0,3 eéq)	Drierite®	-30-25°C	DCE	28h	4%	
7	Me	TfOH (0,5 éq)	Drierite®	-30-25°C	DCE	2h	60%	
8	Me	$BF_3.OEt_2$ (0,34 éq)	Drierite®	-78-25°C	DCM	7.5h	60%	
9	Me	$BF_3.OEt_2$ (0,34 éq)	4Å MS	-78-25°C	DCM	29h	6%	
10	Me	$BF_3.OEt_2$ (0,34 éq)	-	-60-25°C	DCM	23h	68%	
11	Me	$BF_3.OEt_2$ (0,34 éq)	-	-60-5°C	DCM	3,5h	77%	
12	Me	$BF_3.OEt_2$ (0,1 éq)	-	-60-5°C	DCM	4h	84%	

a) **179** a été obtenu avec un rendement de 17%; b) **179** a été obtenu avec un rendement de 54%.

Avec les meilleures conditions, le réarrangement de type Fries a été étudié avec divers substrats (**Schéma 95-98**). Tout d'abord, dans les séries D-glucose et D-galactose, les réactions de réarrangement de type Fries de **177** ont très bien fonctionné avec une stéréosélectivité élevée permettant d'obtenir les composés **183** et **184** avec de bons rendements. L'influence de la substitution en C-2 a ensuite été évaluée. Ainsi, pour **185** et **186** avec des groupements protecteurs sensibles à l'acide, nous avons obtenu les glycosides *C*-aryle correspondants avec des rendements acceptables à élevés sous la forme d'un seul diastéréoisomère. La présence de protecteurs silylés encombrés[234] n'a pas eu d'effet délétère sur la réaction (**Schéma 95**).

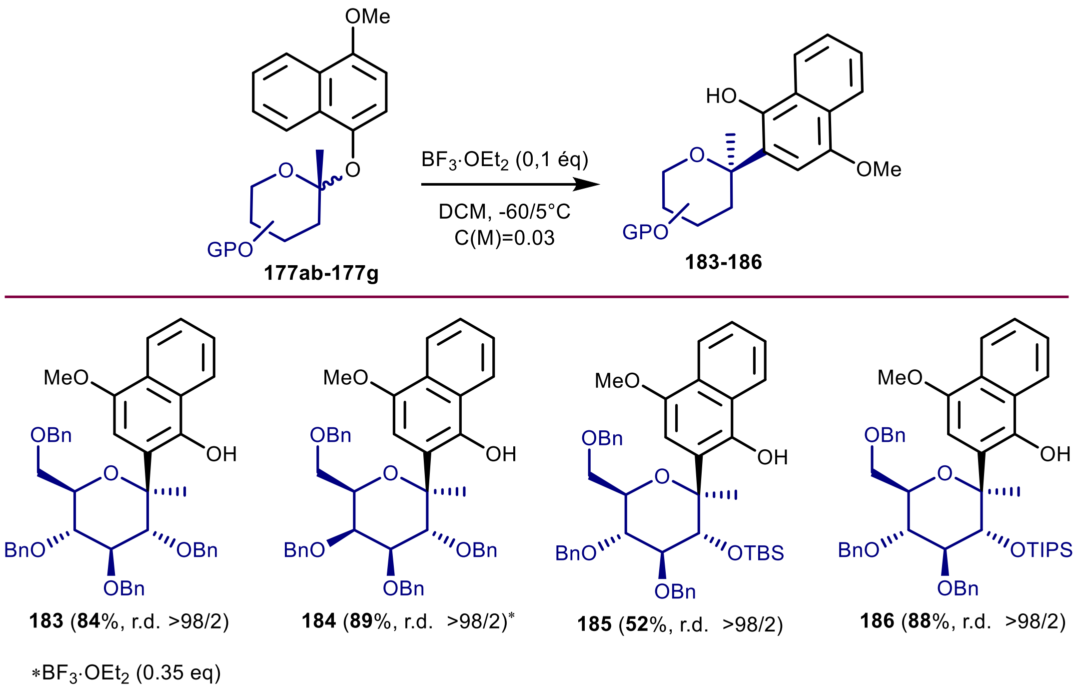


__Schéma 95.__ Etude du réarrangement de Fries en série glucose et galactose

Nos conditions optimisées ont également été efficaces pour la synthèse des *C*-aryl glycosides à 5 chaînons **187**, **188**, **189** et **190 (Schéma 96)**. Dans la série L-thréo, les produits 1,3-*cis* **187** et **188** ont été obtenus sous forme d'un seul diastéréoisomère avec des rendements élevés. Cependant, une érosion de la diastéréosélectivité a été observée pour la conversion des *O*-aryl glycoside **177nb** et **177l** en composés **189** et 1**90.**

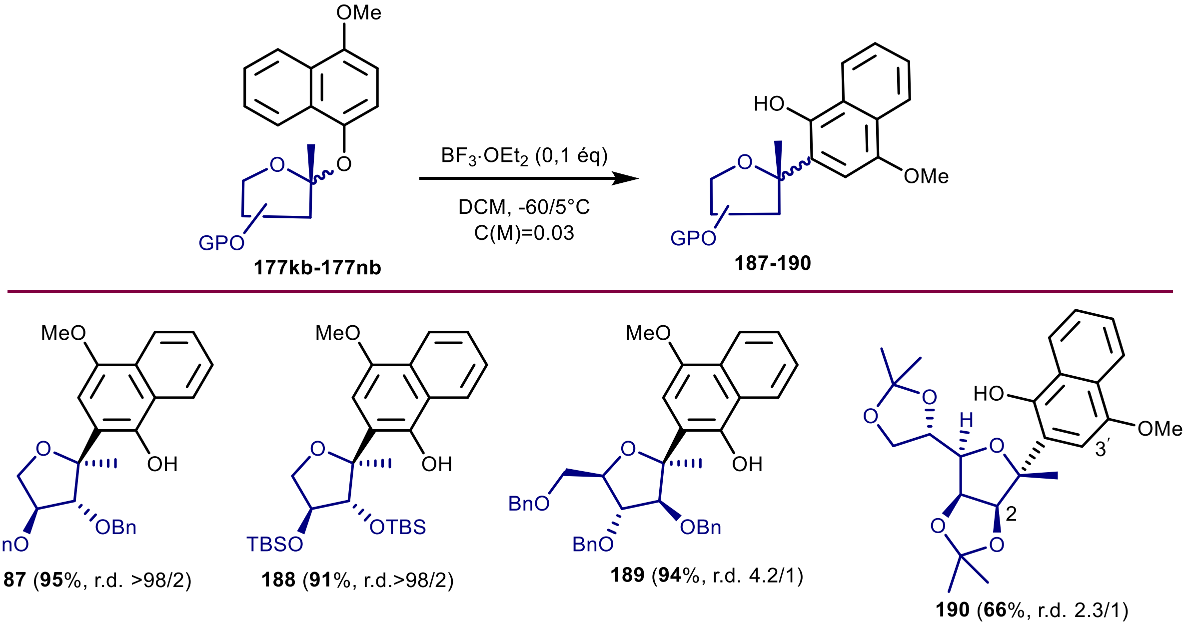


__Schéma 96.__ Etude du réarrangement de Fries pour la synthèse de C-aryl glycosides à 5 membres

La conversion de *O*-aryl glycosides bifonctionnels a aussi été étudiée. En utilisant les meilleures conditions décrites précédemment (0,1 eq. de BF$_3$.OEt$_2$/DCM), le produit de départ **177bc** a été dégradé. En ajoutant de la Drierite® et en augmentant le temps de réaction et la température, deux nouveaux produits cyclisés **201α** et **201β** ont été obtenus avec un rendement de 23% (r.d. 1/1.3). Aucun des *C*-aryl glycosides souhaités n'a été obtenu au cours de ce processus (**Schéma 102A**). Il est intéressant de noter que la serjanione A[8] et la mimocaesalpine E,[237] qui sont des produits biologiquement actifs partagent un système benzoxocine commun avec les composés **201α** et **201β** obtenus (**Schéma 102B**).

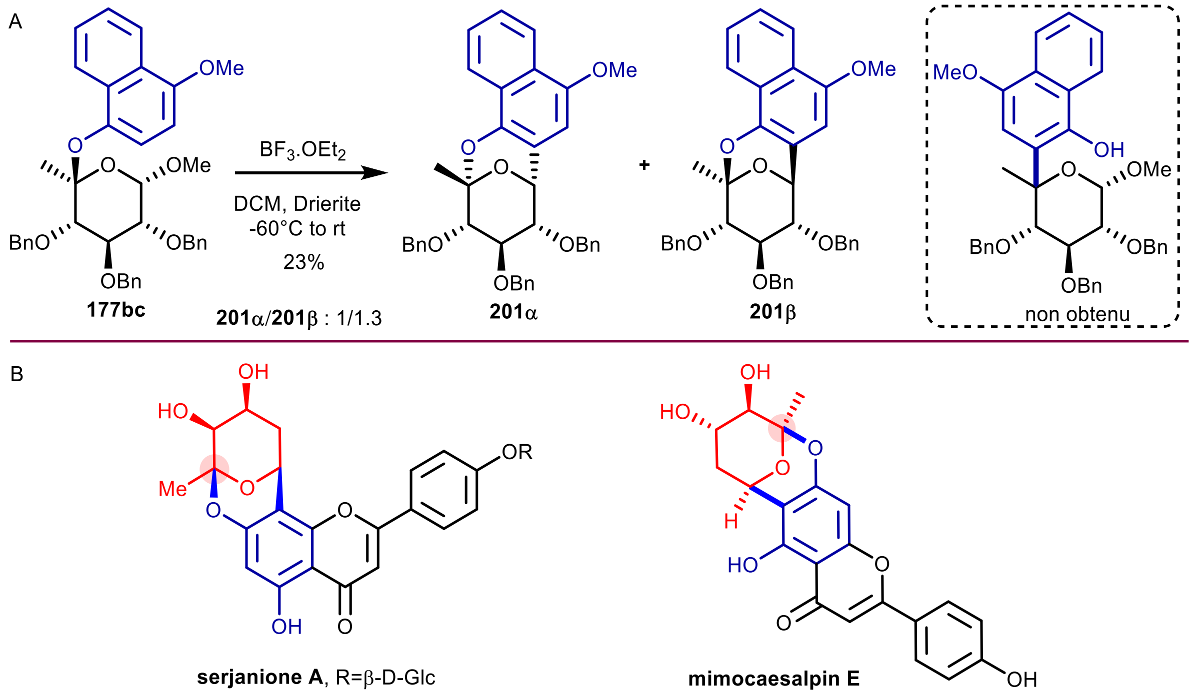
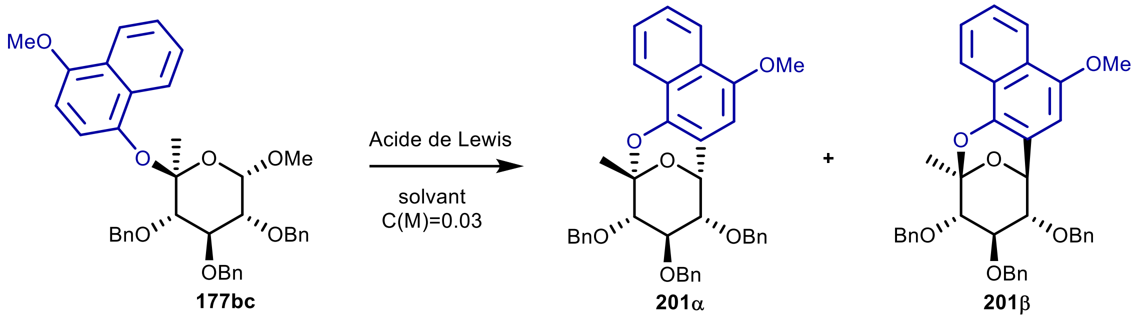


***Schéma 102.** Réarrangement de type Fries du composé **177bc** catalysé par BF$_3$.OEt$_2$; B. Structure des produits naturels serjanione et mimocaesalpin E*

La réaction a ensuite été optimisée en ajustant différents paramètres. Deux autres acides de Lewis (TiCl$_4$, TMSOTf) et un acide de Brønsted, TfOH, ont été utilisées comme activateur de cette réaction. Le produit de départ a été décomposé avec TfOH et TiCl$_4$ (**Tableau 5, entrées 3** et **4**). Nous avons constaté que les produits de cyclisation étaient obtenus avec un rendement de 31 % (dr 1/2,4) lorsque TMSOTf était utilisé (**entrée 5**). D'après l'entrée 5, l'ajout de Drierite® n'a pas eu d'impact significatif sur le résultat de la réaction (**entrée 6**). Le processus s'est avéré hautement régiosélectif en réduisant la quantité de TMSOTf, mais sans amélioration du rendement du processus de cyclisation (**entrée 7**). L'utilisation de SnCl$_4$ a conduit à une augmentation significative des rendements des deux produits de cyclisation (**entrée 8**). Le remplacement de la Drierite® par du tamis moléculaire 4Å a donné des produits de décomposition (**entrée 9**). Sur la base des résultats de l'entrée 8, la réaction a été effectuée sans additifs et a conduit à la formation des deux produits de cyclisation avec de bons rendements (**entrée 10**). La réduction de la quantité de SnCl$_4$ à 0,05 équiv. ou son augmentation à 0,25 équiv. n'a pas amélioré l'efficacité de la réaction (**entrées**

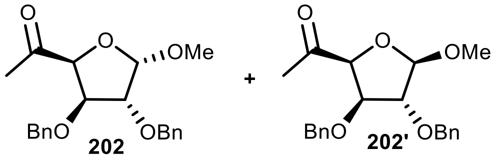
11-12).

Tableau** 5. Optimisation de la réaction à partir de **177bc



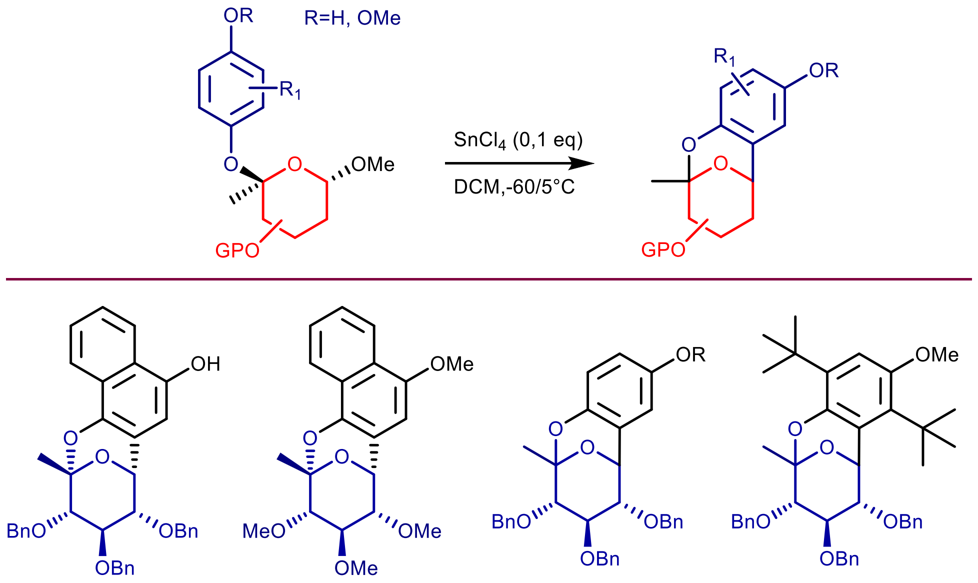
Entrée	Acide de Lewis	additif	solvant	T/°C	Temps	201α	201β
1	$BF_3.OEt_2$ (0,1 éq)	-	DCM	-60°C to 0°C	2.5h	-	-
2	$BF_3.OEt_2$ (0,05 éq)	Drierite®	DCM	-60°C to 25°C	14h	10%	13%
3	TfOH (0,5 éq)	Drierite®	DCE	-30°C to 25°C	5h	Dégradation	
4	$TiCl_4$ (0,25 éq)	-	DCM	-60°C to 25°C	3h	0%	
5	TMSOTf (0,05 éq)	-	DCM	-60°C to 5°C	2.5h	9%	22%
6	TMSOTf (0,05 éq)	Drierite®	DCM	-60°C to 5°C	2.5h	11%	24%
7	TMSOTf (0,01+0,02 éq)	-	DCM	-60°C to RT	23h	20%	-
8	$SnCl_4$ (0,1 eq)	Drierite®	DCM	-60°C to 10°C	3h	18%	27%
9[a]	$SnCl_4$ (0,1+0,4 éq)	4Å MS	DCM	-60°C to RT	20h	Dégradation	
10	$SnCl_4$ (0,1 éq)	-	DCM	-60°C to 5°C	3h	45%	20%
11	$SnCl_4$ (0,05 éq)	-	DCM	-60°C to RT	3.5h	37%	17%
12	$SnCl_4$ (0,25 éq)	-	DCM	-60°C to 5°C	3h	45%	18%
13[b]	$SnCl_4$ (0,1 éq)	-	DCM	-60°C to 16°C	5.5h	38%	14%
14[c]	$SnCl_4$ (0,1 éq)	-	DCM	-60°C to 25°C	5h	Trace	Trace
15	$SnCl_4$ (0,1 éq)	-	Toluene	-60°C to 63°C	9h	43%	11%
16	$SnCl_4$ (0,1éq)	-	$CHCl_3/CH_3NO_2$ (1:1)	-30°C to 5°C	3h	Trace	Trace

b) **202** et **202’** ont été obtenus dans ces conditions. b) C(M)=0,01; c) C(M)=0,05.



Le changement de concentration de la réaction a eu un impact négatif sur la formation des produits (**entrées 13** et **14**). Nous avons ensuite essayé différents systèmes de solvants, tel que le toluène et $CHCl_3/CH_3NO_2$. Nous avons obtenu un rendement de 54% de produits de cyclisation dans le toluène (**entrée 15**). Seules des traces des produits désirés ont été détectées dans le mélange $CHCl_3/CH_3NO_2$ (**entrée 16**).

Avec les meilleures conditions en main (**tableau 5, entrée 10**), la réaction a été effectuée sur différents substrats. Tout d'abord, les 1,5-*bis*-glycosides **151bc** avec un groupe hydroxyle phénolique libre ont été étudiés et ont donné les produits cycliques correspondants **203** avec un rendement de 28% (r.d. 6/1). Ensuite, un autre substrat **177c**, dans lequel le groupe OBn est remplacé par un groupe OMe, a été étudié et a donné le produit cyclisé **204** avec un rendement de 57% (r.d. 2.8/1). Malheureusement, les substrats (**177ba, 177bb**, **151ba**) ont subi une dégradation au cours de la réaction de cyclisation (**205** et **206**) (**Schéma 103**).



203 (28%,r.d. 6/1) (à partir de **151bc**)

204 (57%, r.d. 2.8/1) (à partir de**177c**)

205 (non obtenu) (à partir de **177ba** and **151ba**)

206 (non obtenu) (à partir de **177bb**)

Schéma 103. *Etude de la réaction avec différents exo-glycals*

Sur la base de ces observations, nous proposons deux voies mécanistiques possibles pour la réaction de cyclisation (**Schéma 107**). L'activation du groupe partant aromatique du 1,5-*bis*-glycoside intermédiaire **I** est susceptible de fournir l'oxocarbénium **II** (voie **A**) qui pourrait être en équilibre avec l'oxocarbénium intermédiaire **III** plus réactif. Dans la voie B, l'ion oxocarbénium **III** est obtenu directement à partir de **I**. Ce processus impliquerait le doublet libre de l'atome d'oxygène du groupe méthoxy anomérique.[238] Enfin, une réaction de Friedel-Craft entre le complexe **IV** et l'oxocarbénium **III** générerait **V** et la liaison glycosidique *C*-aryle présente dans le produit final. La formation intramoléculaire de l'intermédiaire hémi-acétal **VI**, suivie d'une cyclisation finale impliquant la formation d'un cation benzylique thermodynamiquement favorisé conduirait au produit final. Ce mécanisme explique pourquoi la liaison glycosidique en C-5 est épimérisée au cours du processus.

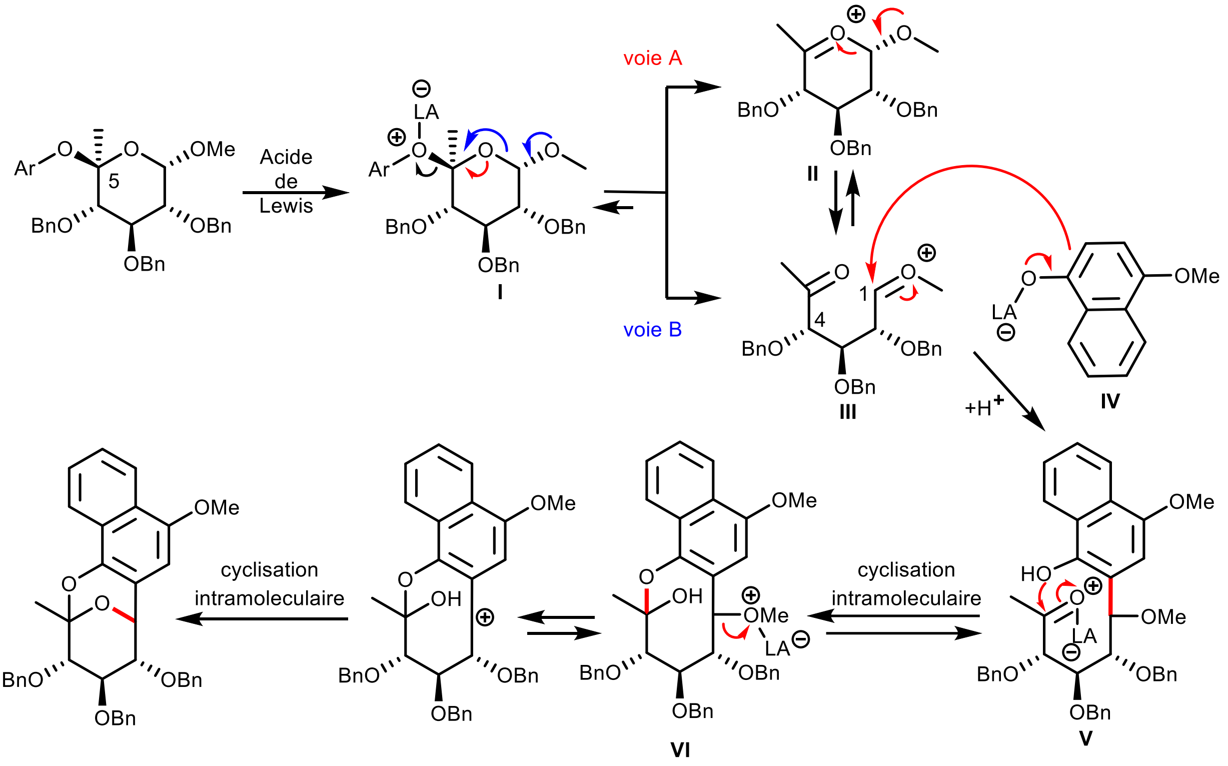
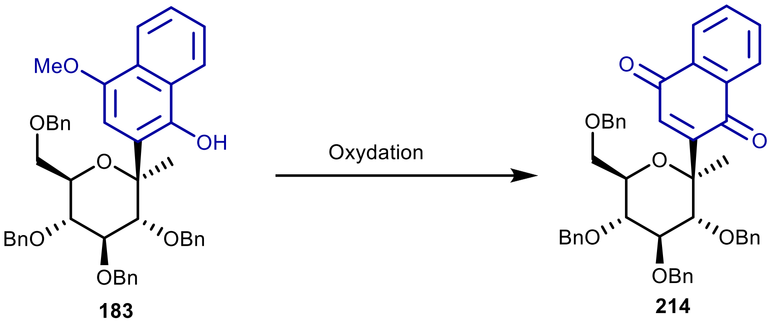


Schéma 107. *Mécanisme proposé*

Afin d’évaluer l’intérêt de notre méthodologie, une oxydation douce de **183** avec du nitrate d'ammonium cérique (CAN) a été réalisée afin d’obtenir des dérivés *C*-Naphthoquinone glycosides qui sont connus pour avoir des propriétés biologiques intéressantes et qui sont de bons intermédiaires dans la synthèse de nombreux produits naturels.[247] Après optimisation de la réaction, la quinone **214** a été obtenue avec un rendement de 80% (**Tableau 8**).

Table 8. *Synthèse du C-naphthoquinone glycoside* ***214*** *par oxidation de* ***183***



Entry	Oxydant	Solvant	Temp.	Temps	Commentaires
1	CAN	MeCN-H_2O	0°C	2 h	mélange de produits
2	TBAB, Oxone	MeCN-H_2O	0-25°C	24 h	**183** (65%)
3	CAN	DCM/H_2O (CAN supporté sur gel de silice)	RT	3 jours	mélange de produits
4	CAN	MeCN-H_2O	0-60°C	3 jours	mélange de produits
5	CAN	MeCN-H_2O	50°C	4 h	**214** (80%)

En conclusion, nous avons développé une stratégie pour la synthèse de *C*,*O*-aryl glycosides à partir d'*exo*-glycals et de quinones *via* un radical pseudo-anomérique tertiaire généré par transfert d’atome d’hydrogène catalysé par le fer. Cette réaction peut être considérée comme un rare exemple de glycosylation formelle de quinones. En outre, la synthèse de *C*-aryl glycosides *via* un réarrangement catalysé par un acide de Lewis a également été étudiée, ouvrant la voie à une stratégie unifiée pour la construction stéreocontrôlée de motifs *O*- ou *C*-aryl glycosides caractérisés par un centre pseudoanomérique quaternaire. Les applications des résultats présentés dans cette étude à la synthèse du noyau benzoxocine de diverses molécules naturelles telles que la serjanione A et la nogalamycine sont en cours d’étude dans notre laboratoire.

Experimental section

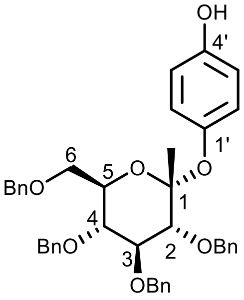
General Methods and Remarks

Commercially available starting materials were purchased from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled over sodium/benzophenone under argon. Triethylamine and pyridine were distilled over KOH and were stored over KOH under argon. Fe(acac)$_3$ was purchased from Merck (99% purity). All the reactions were carried out in standard glassware under argon unless otherwise noted. Heating mantles were used for reactions requiring heating unless otherwise specified. Most of the crude mixtures were purified by flash chromatography on silica gel 60 (230−400 mesh, 0.040−0.063 mm). Automated flash chromatography was performed using a system equipped with UV−vis and ELSD detectors. TLC was performed on aluminum sheets coated with silica gel 60 F254 purchased from E. Merck. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer, and wavelengths are quoted in wavenumbers (cm^{-1}). NMR spectra were recorded on 400 MHz and 500 MHz spectrometers. The chemical shifts are reported as δ values in parts per million (ppm) relative to residual solvent signals used as the internal reference. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and b = broad), integration, and coupling constants (J/Hz). Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. ^{1}H and ^{13}C signals were assigned by 2D experiments (COSY, HSQC, and HMBC). High-resolution mass spectra (HRMS) data were recorded on a microTOF spectrometer equipped with the orthogonal electrospray interface (ESI). Specific rotations were determined on a polarimeter with sodium lamp (λ = 589 nm).

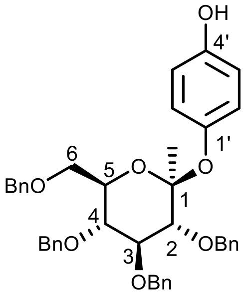
General Procedure for the Synthesis of Phenolic-*O*-ketosides by HAT

A 25 mL round-bottom flask equipped with a stirrer was charged with *exo*-glycal (0.1 mmol, 1.0 equiv, limiting reactant), Fe(acac)$_3$ (0.5 equiv), Na_2HPO_4 (1.1 equiv), and quinone (2−4 equiv). The reaction flask was evacuated under vacuum and then filled with argon; the cycle was repeated three times. Freshly distilled THF (2 mL) was added at room temperature under Ar by a syringe (molarity = 0.05 M). Subsequently, phenylsilane (4 equiv) was added dropwise, and then degassed EtOH (8 equiv) was added. The mixture was heated at 60 °C under constant stirring. For the formal glycosylation of benzoquinones, 2 more equiv of the appropriate quinone dissolved in THF (0.4 mL) was added dropwise. The reaction was continuously monitored using TLC until the starting material was completely consumed. Then, the reaction solution was concentrated. The resulting crude product was purified by flash column chromatography using an appropriate eluent system.

4-(((3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151a)**



major



minor

According to the general procedure, *exo*-glucal **150a** (1 equiv., 53.7 mg, 0.1 mmol), *p*-benzoquinone (4 equiv., 43.2 mg, 0.4 mmol), Na_2HPO_4 (1.1 equiv., 15.6 mg, 0.11 mmol), $Fe(acac)_3$ (0.5 equiv., 17.7 mg, 0.05 mmol), phenylsilane (4 equiv., 0.05 mL, 0.4 mmol), EtOH (8 equiv., 0.047 mL, 0.8 mmol) in THF (2 mL) were heated at 60 °C. After 5 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (400 μL) was added dropwise during 1 h. The reaction was completed after 65 mins. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 15/1-11/1), yielding **151a** (53.1 mg, 0.082 mmol, 82%, dr=1.2:1) as a colourless oil liquid. Isomers α and β can be separated after a careful purification.

α-isomer (major compound):

R_f 0.5 (Cyclohexane/EtOAc: 2.5/1).;

$[\alpha]_D^{20}$=+71 (*c*=0.9, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 18H, H_{Ar}), 7.18 (dd, *J* = 7.4, 2.1 Hz, 2H, H_{Ar}), 7.06 – 7.00 (m, 2H, H-2'), 6.68 – 6.62 (m, 2H, H-3'), 4.99 (d, *J* = 11.7 Hz, 1H, OC$\underline{H_2}$Ph), 4.96 (d, *J* = 11.6 Hz, 1H, OC$\underline{H_2}$Ph), 4.89 (d, *J* = 10.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.88 (d, *J* = 10.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.74 (d, *J* = 11.4 Hz, 1H, OC$\underline{H_2}$Ph), 4.63 (d, *J* = 12.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.57 (d, *J* = 10.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.55 (d, *J* = 12.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.22 (t, *J* = 9.3 Hz, 1H, H-3), 4.16 (ddd, *J* = 10.1, 4.9, 2.2 Hz, 1H, H-5), 3.81 – 3.71 (m, 2H, H-6), 3.67 (t, *J* = 9.6 Hz, 1H, H-4), 3.44 (d, *J* = 9.6 Hz, 1H, H-2), 1.26 (s, 3H, C$\underline{H_3}$);

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7 (C-4´), 147.9 (C-1´), 138.8 (CqAr), 138.4 (CqAr), 138.3 (CqAr), 138.2 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 122.9 (2 C-2´), 115.8 (2 C-3´), 103.4 (C-1), 84.2 (C-2), 83.3 (C-3), 78.8 (C-4), 75.7 (2 O$\underline{C}H_2$Ph), 75.0 (O$\underline{C}H_2$Ph), 73.6 (O$\underline{C}H_2$Ph), 72.0 (C-5), 69.2 (C-6), 21.3 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{41}H_{42}NaO_7$ $[M+Na]^+$: 669.2823; found 669.2796;

IR (film): 3373, 2923, 2866, 1507, 1453, 1361, 1203, 1123, 1066, 1027, 889, 749, 735, 696 cm^{-1}.

β-isomer (minor compound):

R_f 0.49 (Cyclohexane/EtOAc: 2.5/1).;

[α]$_D$^{20}=+7.8 (*c*=1.5, $CHCl_3$).;

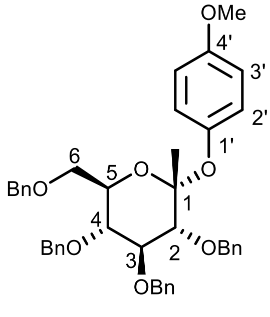
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.40 – 7.27 (m, 18H, H_{Ar}), 7.21 (dd, *J* = 7.5, 2.1 Hz, 2H, H_{Ar}), 7.12 – 7.07 (m, 2H, H-2' or H-3'), 6.69 – 6.61 (m, 2H, H-2' or H-3'), 4.96 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.91 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.86 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.80 (d, *J* = 10.7 Hz, 1H, $OC\underline{H_2}Ph$), 4.78 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.64 (d, *J* = 11.9 Hz, 2H, $OC\underline{H_2}Ph$), 4.62 – 4.56 (m, 2H, $OC\underline{H_2}Ph$ and O$\underline{H}$), 3.80 – 3.70 (m, 5H, H-2, H-3, H-4, H-6), 3.65 – 3.57 (m, 1H, H-5), 1.46 (s, 3H, $C\underline{H_3}$);

^{13}C NMR (125 MHz, $CDCl_3$) *δ* 151.9 (C-4´ or C-1´), 147.5 (C-4´ or C-1´), 138.8 (CqAr), 138.7 (CqAr), 138.3 (CqAr), 138.2 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 123.5 (2 C-2´ or C-3´), 115.7 (2 C-2´ or C-3´), 105.1 (C-1), 84.2 (C-2), 83.7 (C-3), 78.2 (C-4), 75.8 ($O\underline{C}H_2Ph$), 75.2 ($O\underline{C}H_2Ph$), 74.9 ($O\underline{C}H_2Ph$), 73.5 ($O\underline{C}H_2Ph$), 73.45 (C-5), 69.5 (C-6), 16.9 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{41}H_{42}NaO_7$ $[M+Na]^+$: 669.2823; found 669.2817;

IR (film): 3379, 2914, 2869, 1506, 1453, 1209, 1087, 1071, 1028, 736, 697 cm^{-1}.

(2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-methoxyphenoxy)-2-methyltetrahydro-2H-pyran **(177a)**



NaH (60% in oil, 3 equiv., 21.8 mg, 0.54 mmol) was added portionwisely to solution of **151a** (1 equiv., 117.4 mg, 0.18 mmol) in freshly distilled THF (2.50 mL) at 0 °C under argon. And then, CH_3I (4 equiv., 0.045 mL, 0.73 mmol) was added and the mixture was stirred at RT until the starting material was completely consumed. After 8 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 25/1-13/1), yielding the product **177a** (95.7 mg, 0.14 mmol, 80%, dr=1.2/1) as a blue oil liquid.

α-isomer (major compound):

R*f* 0.67 (Cyclohexane/EtOAc: 3/1).;

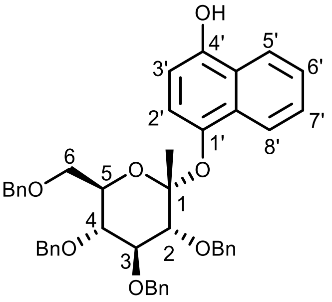
^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.44 – 7.27 (m, 18H, H_{Ar}), 7.22 (dd, *J* = 7.7, 1.9 Hz, 2H, H_{Ar}), 7.15 – 7.10 (m, 2H, H-2'), 6.78 – 6.73 (m, 2H, H-3'), 5.02 (d, *J* = 11.4 Hz, 1H, $OC\underline{H_2}Ph$), 4.99 (d, *J* = 10.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.93 (d, *J* = 10.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.91 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.78 (d, *J* = 11.4 Hz, 1H, OC$\underline{H}_2$Ph), 4.66 (d, *J* = 12.1 Hz, 1H, OC$\underline{H}_2$Ph), 4.63 – 4.56 (m, 2H, OC$\underline{H}_2$Ph), 4.26 (t, *J* = 9.3 Hz, 1H, H-3), 4.23 – 4.18 (m, 1H, H-5), 3.85 – 3.78 (m, 2H, H-6), 3.77 (s, 3H, OC$\underline{H}_3$), 3.70 (dd, *J* = 10.2, 9.0 Hz, 1H, H-4), 3.47 (d, *J* = 9.6 Hz, 1H, H-2), 1.30 (s, 3H, C$\underline{H}_3$).

^{13}C NMR (125 MHz, CDCl$_3$) δ 155.7 (C-4´), 148.0 (C-1´), 138.9 (CqAr), 138.5 (CqAr), 138.38 (CqAr), 138.36 (CqAr), 128.54 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.46 (C$_{Ar}$), 128.1 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.88 (C$_{Ar}$), 127.86 (C$_{Ar}$), 127.83 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 122.8 (2 C-2´), 114.2 (2 C-3´), 103.4 (C-1), 84.3 (C-2), 83.3 (C-3), 78.9 (C-4), 75.7 (2 O$\underline{C}$H$_2$Ph), 75.0 (O$\underline{C}$H$_2$Ph), 73.6 (O$\underline{C}$H$_2$Ph), 72.0 (C-5), 69.4 (C-6), 55.6 (O$\underline{C}$H$_3$), 21.4 ($\underline{C}$H$_3$)

HRMS (ESI) m/z: calcd for $C_{42}H_{44}NaO_7$ $[M+Na]^+$: 683.2979; found 683.2982.

IR (film): 2924, 2860, 1506, 1454, 1362, 1216, 1088, 1071, 1028, 736, 697 cm^{-1}.

4-(((3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151ab)**



According to the general procedure, *exo*-glucal **150a** (1 equiv., 53.6 mg, 0.1 mmol), 1,4-naphthoquinone (4 equiv., 63.2 mg, 0.4 mmol), Na$_2$HPO$_4$ (1.1 equiv., 15.6 mg, 0.11 mmol), Fe(acac)$_3$ (0.5 equiv., 17.6 mg, 0.05 mmol), phenylsilane (4 equiv., 0.05 mL, 0.4 mmol), EtOH (8 equiv., 0.047 mL, 0.8 mmol) in THF (2 mL) were heated at 60 °C. The reaction was completed after 1.5 h. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 10/1-6/1), yielding **151ab** (56.5 mg, 0.081 mmol, 81%, dr=1.8:1) as a brown oil liquid. Analytical samples of α-isomer (major compound) can be obtained after a careful purification.

α-isomer (major compound):

R$_f$ 0.25 (Cyclohexane/EtOAc: 5/1);

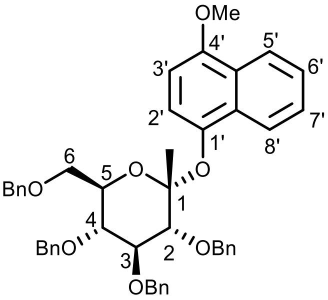
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.48 (dt, *J* = 8.4, 1.0 Hz, 1H, H-8´), 8.10 (d, *J* = 8.3 Hz, 1H, H-5´), 7.48 – 7.26 (m, 20H, H$_{Ar}$ and H-6´ and H-7´), 7.22 (dd, *J* = 7.5, 2.0 Hz, 2H, H$_{Ar}$), 7.13 (d, *J* = 8.1 Hz, 1H, H-3´), 6.57 (d, *J* = 8.1 Hz, 1H, H-2´), 5.06 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 5.05 (d, *J* = 10.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.95 (d, *J* = 10.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.93 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.77 (d, *J* = 10.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.69 (d, *J* = 12.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.61 (m, 2H, OC$\underline{H_2}$Ph), 4.39 (t, *J* = 9.2 Hz, 1H, H-3), 4.39 – 4.34 (m, 1H, H-5), 3.87 (dd, *J* = 10.0, 2.0 Hz, 1H, H-6a), 3.85 – 3.79 (dd, *J* = 10.4, 5.0 Hz, 1H, H-6b), 3.74 (dd, *J* = 10.1, 9.0 Hz, 1H, H-4), 3.56 (d, *J* = 9.5 Hz, 1H, H-2), 1.27 (s, 3H, C$\underline{H_3}$);

^{13}C NMR (125 MHz, CDCl$_3$) *δ* 147.6 (C-4´), 143.8 (C-1´), 138.9 (CqAr), 138.7 (CqAr), 138.4 (CqAr), 138.3 (CqAr), 130.1 (CqAr), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.6 (C$_{Ar}$), 126.2 (C-7´), 125.5 (C-6´), 125.1 (CqAr), 123.6 (C-8´), 121.4 (C-5´), 116.5 (C-3´), 108.3 (C-2´), 104.1 (C-1), 85.1 (C-2), 83.5 (C-3), 78.8 (C-4), 76.1 (O$\underline{C}$H$_2$Ph), 75.9 (O$\underline{C}$H$_2$Ph), 75.0 (O$\underline{C}$H$_2$Ph), 73.6 (O$\underline{C}$H$_2$Ph), 72.1 (C-5), 69.4 (C-6), 20.6 ($\underline{C}$H$_3$);

HRMS (ESI) m/z: calcd for $C_{45}H_{44}NaO_7$ [M+Na]$^+$: 719.2979; found 719.2942;

IR (film): 3360, 2923, 2861, 1592, 1454, 1379, 1353, 1270, 1087, 1063, 1028, 735, 697 cm^{-1}.

(2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran (**177ab**)



NaH (60% in oil, 3 equiv., 58.1 mg, 1.45 mmol) was added portionwisely to solution of **151ab** (1 equiv., 337.6 mg, 0.48 mmol) in freshly distilled THF (6 mL) at 0 °C under argon. And then, CH$_3$I (4 equiv., 0.12 mL, 1.94 mmol) was added and the mixture was stirred at RT until the starting material was completely consumed. After 21 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc=3%-5%), yielding the product **177ab** (297 mg, 0.42 mmol, 86%, dr=1.8/1) as a brown oil liquid.

α-isomer (major compound):

R$_f$ 0.60 (Cyclohexane/EtOAc: 5/1);

[α]$_D$^{20}=+112 (*c*=0.3, DCM).

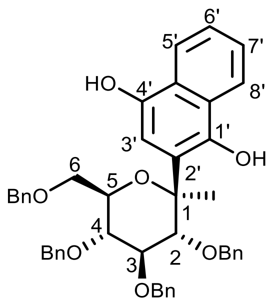
^{1}H NMR (400 MHz, CDCl$_3$) *δ* 8.49 (d, *J* = 8.3 Hz, 1H, H-8´), 8.20 (d, *J* = 8.3 Hz, 1H, H-5´), 7.61 – 7.07 (m, 23H, H$_{Ar}$ and H-3´, H-6´ and H-7´), 6.56 (d, *J* = 8.3 Hz, 1H, H-2´), 5.07 (dd, *J* = 12.5, 11.0 Hz, 2H, OC$\underline{H_2}$Ph), 5.00 – 4.89 (m, 2H, OC$\underline{H_2}$Ph), 4.79 (d, *J* = 11.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.70 (d, *J* = 12.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.67 – 4.59 (m, 2H, OC$\underline{H}_2$Ph), 4.45 – 4.34 (m, 2H, H-3 and H-5), 3.95 (s, 3H, OC$\underline{H}_3$), 3.90 (dd, J = 10.6, 2.0 Hz, 1H, H-6a), 3.82 (dd, J = 10.6, 5.5 Hz, 1H, H-6b), 3.78 – 3.69 (m, 1H, H-4), 3.57 (d, J = 9.5 Hz, 1H, H-2), 1.33 (s, 3H, C$\underline{H}_3$).

^{13}C NMR (125 MHz, CDCl$_3$) δ 151.6 (C-4´), 143.6 (C-1´), 138.9 (CqAr), 138.7 (CqAr), 138.5 (CqAr), 138.4 (CqAr), 130.0 (CqAr), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 126.2 (C-7´ and CqAr), 125.6 (C-6´), 123.4 (C-8´), 121.7 (C-5´), 116.3 (C-3´), 104.0 (C-1), 103.4 (C-2´), 85.1 (C-2), 83.5 (C-3), 78.9 (C-4), 76.0 (O$\underline{C}$H$_2$Ph), 75.9 (O$\underline{C}$H$_2$Ph), 75.0 (O$\underline{C}$H$_2$Ph), 73.6 (O$\underline{C}$H$_2$Ph), 72.2 (C-5), 69.5 (C-6), 55.7 (O$\underline{C}$H$_3$), 20.7 ($\underline{C}$H$_3$)

HRMS (ESI) m/z: calcd for $C_{46}H_{46}NaO_7$ [M+Na]$^+$: 733.3136; found 733.3130.

IR (film): 3030, 2863, 1592, 1462, 1454, 1389, 1269, 1236, 1205, 1126, 1087, 1067, 1022, 980, 863, 847, 771, 734, 697 cm^{-1}.

2-((2S,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)naphthalene-1,4-diol (**182**)



To a solution of compound **151ab** (mixture of α and β-isomers, 1 equiv., 56.7 mg, 0.081 mmol) and drierite (1 g) in dry DCM (2.7 mL) was added dropwise a solution of BF$_3$ OEt$_2$ (0.3 equiv., 0.003 mL, 0.024 mmol) in dry DCM for 1 min at -60 °C. The temperature was gradually increased to 25 °C for 20 h. The reaction mixture was quenched using water (1 mL) and the aqueous mixture was extracted with DCM (3 x10 mL). The organic phase was washed with water (10 mL) and brine (10 mL), dried with Na$_2$SO$_4$, filtered and concentrated. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 15/1-8/1), yielding **182** (25.8 mg, 0.037 mmol, 46%) as a brown oil.

R$_f$ 0.49 (Cyclohexane/EtOAc: 3/1);

[α]$_D$^{20}=-56.0 (c=0.38, DCM).

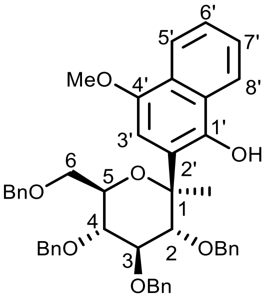
^{1}H NMR (400 MHz, CDCl$_3$) δ 9.32 (s, 1H, O<u>H</u>), 8.38 (dd, *J* = 6.6, 3.2 Hz, 1H, H-5´), 8.07 (dd, *J* = 6.3, 3.3 Hz, 1H, H-8´), 7.53 (d, *J* = 3.3 Hz, 1H, H-6´ or H-7´), 7.51 (d, *J* = 3.3 Hz, 1H, H-6´ or H-7´), 7.49 – 6.99 (m, 20H, H$_{Ar}$), 6.72 (s, 1H, H-3´), 4.98 (d, *J* = 11.1 Hz, 1H, OC<u>H$_2$</u>Ph), 4.92 – 4.86 (m, 2H, OC<u>H$_2$</u>Ph), 4.83 (s, 1H, O<u>H</u>), 4.70 (d, *J* = 12.0 Hz, 1H, OC<u>H$_2$</u>Ph), 4.55 – 4.45 (m, 3H, OC<u>H$_2$</u>Ph), 4.10 (t, *J* = 9.5 Hz, 1H, H-4), 3.95 (d, *J* = 9.7 Hz, 1H, H-2), 3.92 – 3.81 (m, 3H, H-6$_a$, H-3 and H-5), 3.73 (d, *J* = 10.4 Hz, 1H, OC<u>H$_2$</u>Ph), 3.68 (dd, *J* = 10.0, 2.4 Hz, 1H, H-6$_b$), 1.72 (s, 3H, C<u>H$_3$</u>);

^{13}C NMR (125 MHz, CDCl$_3$) δ 145.5 (C-4´), 143.6 (C-1´), 138.8 (CqAr), 138.1 (2 CqAr), 137.8 (CqAr), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.3 (C$_{Ar}$), 128.2 (C$_{Ar}$) , 128.0 (C$_{Ar}$), 127.7 (C$_{Ar}$), 127.6 (C$_{Ar}$), 126.9 (CqAr), 126.0 (C-6´ or C-7´), 125.6 (C-6´ or C-7´), 125.0 (CqAr), 123.3 (C-5´), 121.0 (C-8´), 120.5 (C-2´), 108.7 (C-3´), 83.5 (C-5), 83.4 (C-2), 82.2 (C-1), 77.6 (C-4), 76.0 (O<u>C</u>H$_2$Ph), 75.5 (2 O<u>C</u>H$_2$Ph), 73.7 (O<u>C</u>H$_2$Ph), 72.6 (C-3), 67.7 (C-6), 16.2 (<u>C</u>H$_3$);

HRMS (ESI) m/z: calcd for $C_{45}H_{42}NaO_7$ [M+Na]$^+$: 717.2823; found 719.2986;

IR (film): 3327, 2920, 2865, 1601, 1497, 1454, 1362, 1325, 1085, 1068, 1028, 750, 732, 697 cm^{-1}.

4-Methoxy-2-((2S,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)naphthalen-1-ol (**183**)



To a solution of compound **177ab** (mixture of α and β-isomers, 1 equiv., 34 mg, 0.048 mmol) in dry DCM (1.6 mL) was dropwise added the solution of BF_3 OEt_2 (0.1 equiv., 0.0006 mL, 0.0048 mmol) in dry DCM at -60 °C. The temperature was gradually increased to 5 °C for 4 h. The reaction was quenched using Et_3N (5 drops). The solution was evaporated under reduced pressure and the obtained residue was purified by flash chromatography (SiO_2, Cyclohexane/DCM: 1/1-1/3), yielding **183** (28.6 mg, 0.040 mmol, 84%) as a blue oil.

R$_f$ 0.45 (Cyclohexane/EtOAc: 5/1);

$[\alpha]_D^{20}$=+58 (*c*=0.26, DCM).

^{1}H NMR (400 MHz, CDCl$_3$) δ 9.32 (s, 1H, O<u>H</u>), 8.41 – 8.36 (m, 1H, H-6´ or H-7´), 8.20 – 8.14 (m, 1H, H-6´ or H-7´), 7.57 – 7.47 (m, 4H, H-5´, H-8´ and H$_{Ar}$), 7.45 – 7.38 (m, 2H, H$_{Ar}$), 7.37 – 7.27 (m, 9H,

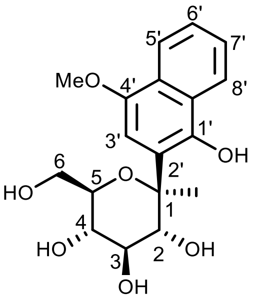
H_{Ar}), 7.24 – 7.16 (m, 5H, H_{Ar}), 7.05 – 6.98 (m, 2H, H_{Ar}), 6.67 (s, 1H, H-3´), 4.98 (d, *J* = 11.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.91 (d, *J* = 11.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.90 (d, *J* = 10.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.72 (d, *J* = 12.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.56 (d, *J* = 11.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.53 (d, *J* = 12.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.52 (d, *J* = 10.6 Hz, 1H, OC$\underline{H_2}$Ph), 4.16 – 4.09 (m, 1H, H-4), 4.00 (d, *J* = 9.8 Hz, 1H, H-2), 3.97 – 3.90 (m, 2H, H-3 and H-5), 3.89 – 3.84 (m, 1H, H-6_a), 3.77 (s, 3H, OC$\underline{H_3}$), 3.75 – 3.67 (m, 2H, H-6_b and OC$\underline{H_2}$Ph), 1.82 (s, 3H, C$\underline{H_3}$);

^{13}C NMR (125MHz, $CDCl_3$) *δ* 148.1 (C-4´), 145.3 (C-1´), 138.8 (CqAr), 138.2 (2 CqAr), 137.8 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 126.9 (CqAr), 126.1 (CqAr), 125.9 (C-6´ or C-7´), 125.7 (C-6´ or C-7´), 123.0 (C-8´), 121.4 (C-5´), 120.1 (CqAr), 103.9 (C-3´), 83.5 (C-5), 83.4 (C-2), 82.5 (C-1), 77.6 (C-4), 75.8 (O$\underline{C}H_2$Ph), 75.6 (O$\underline{C}H_2$Ph), 75.5 (O$\underline{C}H_2$Ph), 73.7 (O$\underline{C}H_2$Ph), 72.6 (C-3), 67.8 (C-6), 55.7 (O$\underline{C}H_3$), 16.3 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{46}H_{46}NaO_7$ $[M+Na]^+$: 733.3136; found 733.3152;

IR (film): 3320, 2866, 1454, 1361, 1321, 1215, 1084, 1059, 1027, 750, 730, 695 cm^{-1}.

(2S,3R,4S,5S,6R)-2-(1-Hydroxy-4-methoxynaphthalen-2-yl)-6-(hydroxymethyl)-2-methyltetrahydro-2H-pyran-3,4,5-triol (**199**)



To a cold (-78 °C) solution of compound **183** (1 equiv., 53.6 mg, 0.075 mmol) and pentamethylbenzene (562 mg, 3.72 mmol) in anhydrous CH_2Cl_2 (2.5 mL) were added BCl_3 (1M in DCM, 8 equiv., 0.60 mL, 0.603 mmol) for 10 mins. The reaction mixture was stirred at -78 °C for 55 mins and then quenched by adding MeOH (1 mL) at -78 °C before warming up to room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel (SiO_2, DCM/MeOH: 30/1-10/1) to yield **199** (20 mg, 0.057 mmol, 76%) as a white solid.

R_f 0.51 (DCM/MeOH: 6/1);

$[\alpha]_D^{20}$=+8.4 (*c*=0.4, MeOH).

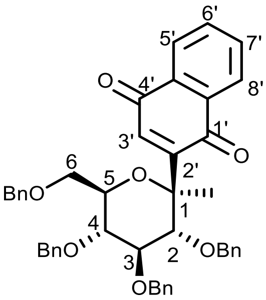
^{1}H NMR (400 MHz, Methanol-d_4) *δ* 8.25 – 8.17 (m, 1H, H-8´), 8.10 – 8.04 (m, 1H, H-5´), 7.45 – 7.38 (m, 2H, H-6´ and H-7´), 7.00 (s, 1H, H-3´), 3.95 (s, 3H, OC$\underline{H_3}$), 3.90 – 3.87 (m, 2H, H-6), 3.81 – 3.76 (m, 1H, H-5), 3.75 (d, J = 9.1 Hz, 1H, H-2), 3.66 (t, J = 9.0 Hz, 1H, H-3), 3.60 (t, J = 9.3 Hz, 1H, H-4), 1.75 (s, 3H, C$\underline{H}_3$);

^{13}C NMR (100 MHz, Methanol-d$_4$) δ 149.1 (C-4´), 145.4 (C-1´), 127.9 (CqAr), 126.9 (CqAr), 126.4 (C-6´ or C-7´), 126.2 (C-6´ or C-7´), 123.5 (C-8´), 123.4 (C-1), 122.1 (C-5´), 105.1 (C-3´), 83.6 (C-2´), 76.9 (C-2), 76.1 (C-3), 75.6 (C-5), 71.3 (C-4), 61.8 (C-6), 56.2 (O$\underline{C}$H$_3$), 16.6 ($\underline{C}$H$_3$).

HRMS (ESI) m/z: calcd for $C_{18}H_{22}NaO_7$ [M+Na]$^+$: 373.1258; found 373.1250;

IR (film): 3311, 2935, 1702, 1599, 1457, 1364, 1327, 1230, 1158, 1106, 1071, 1046, 1016, 769, 727, 712 cm^{-1}.

2-((2S,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)naphthalene-1,4-dione **(214)**



183 (1 equiv., 38.9 mg, 0.055 mmol) was dissolved in MeCN (1 mL). To this, a solution of CAN (3 equiv., 90 mg, 0.16 mmol) in H_2O (0.2 mL) was added at once at RT. The reaction mixture was then stirred at 50 °C for 4 h. It was then quenched with ethyl acetate and water. The organic phase was washed several times with water. It was then dried over Na_2SO_4, concentrated in vacuo to afford the desired quinone **214** (30 mg, 0.043 mmol, 80%) as a yellow oil.

R$_f$ 0.50 (Cyclohexane/EtOAc: 4/1).

$[\alpha]_D^{20}$=-0.7 (c=1.6, DCM).

^{1}H NMR (400 MHz, C_6D_6) δ 7.96 (s, 1H, H-3'), 7.95 – 7.91 (m, 1H, H-5' or H-8'), 7.88 – 7.84 (m, 1H, H-5' or H-8'), 7.47 – 7.41 (m, 2H, H$_{Ar}$), 7.34 – 7.24 (m, 4H, H$_{Ar}$), 7.20 – 6.93 (m, 16H, H-6' and H-7' and H$_{Ar}$), 4.80 (d, J = 3.9 Hz, 1H, H-2), 4.64 – 4.51 (m, 4H, OC$\underline{H}_2$Ph), 4.46 (d, J = 11.6 Hz, 1H, OC$\underline{H}_2$Ph), 4.42 – 4.35 (m, 2H, OC$\underline{H}_2$Ph), 4.34 – 4.30 (m, 1H, H-5), 4.27 (d, J = 11.4 Hz, 1H, OC$\underline{H}_2$Ph), 4.16 (dd, J = 10.7, 5.6 Hz, 1H, H-4), 3.88 (dd, J = 5.6, 3.9 Hz, 1H, H-3), 3.81 – 3.73 (m, 2H, H-6), 1.75 (s, 3H, C$\underline{H}_3$).

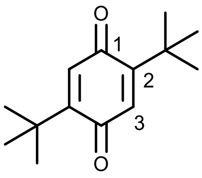
^{13}C NMR (125 MHz, C_6D_6) δ 185.3 (C-1´ or C-4´), 185.0 (C-1´ or C-4´), 154.2 (C-2´), 139.3 (CqAr), 139.0 (CqAr), 138.5 (CqAr), 138.4 (CqAr), 136.5 (C-3´), 133.7 (CqAr), 133.1 (2 C-6´ or C-7´), 132.4 (CqAr), 128.7 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.4 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 127.6 (C$_{Ar}$), 127.59

(C_{Ar}), 126.7 (C-5´ or C-8´), 125.7 (C-5´ or C-8´), 83.2 (C-3), 79.3 (C-2), 77.8 (C-1), 77.76 (C-4), 74.1 ($O\underline{C}H_2Ph$), 73.6 ($O\underline{C}H_2Ph$), 73.5 ($O\underline{C}H_2Ph$), 72.9 (C-5), 72.4 ($O\underline{C}H_2Ph$), 69.8 (C-6), 22.5 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{45}H_{42}NaO_7$ $[M+Na]^+$: 717.2823; found 717.2832.

IR (film): 2923, 2861, 1662, 1595, 1497, 1454, 1363, 1329, 1306, 1254, 1229, 1210, 1088, 1027, 735, 697 cm^{-1}.

2,5-Di-tert-butylcyclohexa-2,5-diene-1,4-dione **(165)**

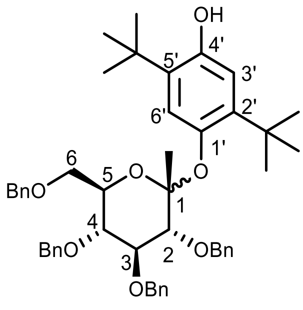


2,5-Di-tert-butylhydroquinone (1 equiv., 804 mg, 3.62 mmol) was added to (diacetoxyiodo)benzene (1.3 equiv., 1.5 g, 4.70 mmol) in methanol (12 mL). The mixture was stirred for 2 h at room temperature under an argon atmosphere. Then, the reaction mixture was filtered. Solids were washed with methanol several times and dried under vacuum to obtain the product **165** (671 mg, 3.046 mmol, 84%)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.48 (s, 2H, H-3), 1.27 (s, 18H, $C\underline{H}_3$).

This data is consistent with the reported literature.[187]

2,5-Di-tert-butyl-4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151ac)**



According to the general procedure, *exo*-glucal **150a** (1 equiv., 53.2 mg, 0.1 mmol), 2,5-di-tert-butyl-1,4-benzoquinone (4 equiv., 87.4 mg, 0.40 mmol), Na_2HPO_4 (1.1 equiv., 15.5 mg, 0.11 mmol), $Fe(acac)_3$ (0.5 equiv., 17.6 mg, 0.05 mmol), phenylsilane (4 equiv., 0.05 mL, 0.4 mmol), EtOH (8 equiv., 0.05 mL, 0.8 mmol) in THF (2 mL) were heated at 60 °C. After 5 mins, 2,5-di-tert-butyl-1,4-benzoquinone (2 equiv.) dissolved in THF (400 μL) was added dropwise during 4.5 h. The reaction was completed after 4.5 h. The crude was purified by flash chromatography (SiO_2, Pentane/Et_2O: 50/1-15/1), yielding **151ac** (61.9 mg, 0.082 mmol, 82.3%, dr=2.5:1) as a colorless oil liquid.

Rf 0.49 (Cyclohexane/EtOAc: 14/1);

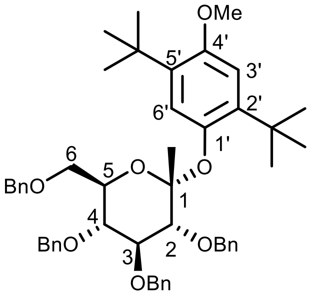
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 0.41H, H-3', β-isomer), 7.44 (s, 1H, H-3', α-isomer), 7.41 – 7.15 (m, 28H, H_{Ar}, α and β-isomer), 6.59 (s, 1H, H-6', α-isomer), 6.58 (s, 0.4H, H-6', β-isomer), 5.02 (d, J = 11.3 Hz, 1H, OC$\underline{H}_2$Ph), 4.97 (d, J = 10.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.95 – 4.85 (m, 3H, OC$\underline{H}_2$Ph, α and β-isomer), 4.82 (d, J = 10.9 Hz, 0.4H, β-isomer), 4.78 (d, J = 11.3 Hz, 1H, OC$\underline{H}_2$Ph, α-isomer), 4.70 – 4.56 (m, 5H, α and β-isomer), 4.34 – 4.24 (m, 1H, H-3), 4.00 – 3.94 (m, 1H, H-5), 3.93 (d, J = 8.2 Hz, 1H, H-4), 3.85 (dd, J = 10.9, 2.8 Hz, 1H, H-6a), 3.75 (dd, J = 10.8, 1.5 Hz, 1H, H-6b), 3.50 (d, J = 9.7 Hz, 1H, H-2, α-isomer), 1.53 (s, 3H, C$\underline{H}_3$), 1.39 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.37 (s, 9H, C(C$\underline{H}_3$)$_3$);

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.4 (C-4´, β-isomer), 148.3 (C-4´, α-isomer), 146.9 (C-1´, α-isomer), 146.8 (C-1´, β-isomer), 139.1 (C-2´, α-isomer), 138.7 (CqAr), 138.6 (CqAr), 138.5 (CqAr), 138.4 (CqAr, β-isomer), 138.2 (CqAr), 138.1 (CqAr, β-isomer), 133.5 (C-5´, α-isomer), 133.4 (C-5´, β-isomer), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.5 (C_{Ar}), 127.1 (C_{Ar}, β-isomer), 126.7 (C_{Ar}), 120.1 (C-3´, β-isomer), 118.3 (C-3´, α-isomer), 115.4 (C-6´, α-isomer), 115.3 (C-6´, β-isomer), 104.8 (C-1, β-isomer), 103.8 (C-1, α-isomer), 85.4 (C-2), 85.3 (C-2, β-isomer), 83.5 (C-3, α-isomer), 83.1 (C-3, β-isomer), 78.5 (C-4, β-isomer), 78.4 (C-4, α-isomer), 76.1 (O$\underline{C}H_2$Ph), 75.7 (O$\underline{C}H_2$Ph), 75.6 (O$\underline{C}H_2$Ph, β-isomer), 75.1 (O$\underline{C}H_2$Ph, β-isomer), 74.9 (O$\underline{C}H_2$Ph), 74.5 (O$\underline{C}H_2$Ph, β-isomer), 73.6 (O$\underline{C}H_2$Ph, α-isomer and β-isomer), 71.9 (C-5), 69.4 (C-6, β-isomer), 68.7 (C-6), 34.5 ($\underline{C}$(CH$_{\underline{3}}$)$_3$), 34.4 ($\underline{C}$(CH$_{\underline{3}}$)$_3$, α-isomer and β-isomer), 34.3 ($\underline{C}$(CH$_{\underline{3}}$)$_3$, β-isomer), 20.1 ($\underline{C}H_3$, α-isomer), 16.4 ($\underline{C}H_3$, β-isomer);

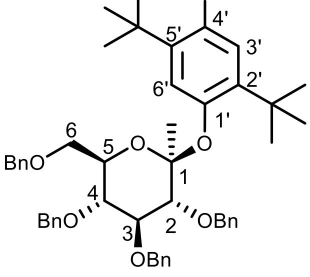
HRMS (ESI) m/z: calcd for $C_{41}H_{42}NaO_7$ $[M+Na]^+$: 781.4075; found 781.4125.;

IR (film): 3415, 2954, 2867, 1507, 1454, 1400, 1382, 1360, 1121, 1069, 908, 886, 730, 696 cm^{-1}.

(3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-(2,5-di-tert-butyl-4-methoxyphenoxy)-2-methyltetrahydro-2H-pyran (**177ac**)



major



minor

NaH (60% in oil, 3 equiv., 19.4 mg, 0.48 mmol) was added portionwisely to solution of **151ac** (1 equiv., 122.5 mg, 0.16 mmol) in freshly distilled THF (2 mL) at 0 °C. And then, CH_3I (4 equiv., 0.040 mL, 0.65 mmol) was added and the mixture was stirred at RT until the starting material was completely consumed. After 8 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/DCM=2/1-1/2), yielding the product **177ac** (111.6 mg, 0.14 mmol, 89%, dr=3:1) as a colorless oil liquid.

α-isomer (major compound):

R_f 0.36 (Cyclohexane/DCM: 1/2);

^{1}H NMR (400 MHz, Chloroform-d) *δ* 7.42 (s, 1H, H-3'), 7.37 – 7.22 (m, 18H, H_{Ar}), 7.19 – 7.14 (m, 2H, H_{Ar}), 6.80 (s, 1H, H-6'), 4.98 (d, *J* = 11.4 Hz, 1H, $OC\underline{H_2}Ph$), 4.92 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.90 – 4.83 (m, 2H, $OC\underline{H_2}Ph$), 4.75 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.65 – 4.57 (m, 2H, $OC\underline{H_2}Ph$), 4.55 (d, *J* = 12.4 Hz, 1H, $OC\underline{H_2}Ph$), 4.25 (dd, *J* = 9.6, 8.2 Hz, 1H, H-3), 3.91 (ddd, *J* = 10.7, 3.6, 2.2 Hz, 1H, H-5), 3.89 – 3.84 (m, 1H, H-4), 3.83 – 3.76 (m, 4H, H-6 and $OC\underline{H_3}$), 3.70 (dd, *J* = 10.8, 1.7 Hz, 1H, H-6), 3.45 (d, *J* = 9.6 Hz, 1H, H-2), 1.50 (s, 3H, $C\underline{H_3}$), 1.39 (s, 9H, $C(C\underline{H_3})_3$), 1.29 (s, 9H, $C(C\underline{H_3})_3$).

^{13}C NMR (100 MHz, Chloroform-*d*) *δ* 152.8 (C-4´), 146.9 (C-1´), 138.8 (CqAr), 138.7 (CqAr), 138.5 (CqAr and C-2´), 138.3 (CqAr), 136.0 (C-5´), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 118.1 (C-3´), 111.2 (C-6´), 103.7 (C-1), 85.5 (C-2), 83.5 (C-3), 78.5 (C-4), 76.1 ($O\underline{C}H_2Ph$), 75.7 ($O\underline{C}H_2Ph$), 74.9 ($O\underline{C}H_2Ph$), 73.6 ($O\underline{C}H_2Ph$), 71.9 (C-5), 68.7 (C-6), 55.6 ($O\underline{C}H_3$), 35.0 ($\underline{C}(CH_3)_3$), 34.6 ($\underline{C}(CH_3)_3$), 30.0 ($C(\underline{C}H_3)_3$), 30.1 ($C(\underline{C}H_3)_3$), 20.2 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{50}H_{60}KO_7$ $[M+K]^+$: 811.3971; found 811.3958.

IR (film): 2952, 2912, 2866, 1505, 1454, 1396, 1375, 1201, 1126, 1087, 1075, 1028, 985, 881, 734, 697 cm^{-1}.

β-isomer (major compound):

R_f 0.42 (Cyclohexane/DCM: 1/2);

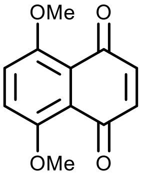
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.75 (s, 1H, H-3'), 7.38 – 7.11 (m, 20H, H_{Ar}), 6.79 (s, 1H, H-6'), 4.97 (d, *J* = 11.6 Hz, 1H, $OC\underline{H_2}Ph$), 4.90 (d, *J* = 11.6 Hz, 1H, $OC\underline{H_2}Ph$), 4.88 – 4.80 (m, 2H, $OC\underline{H_2}Ph$), 4.79 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.65 – 4.53 (m, 3H, $OC\underline{H_2}Ph$), 3.97 – 3.91 (m, 1H, H-3), 3.88 – 3.80 (m, 2H, H-4 and H-2), 3.80 (s, 3H, $OC\underline{H_3}$), 3.81 – 3.74 (m, 2H, H-6), 3.77 – 3.69 (m, 1H, H-5), 1.62 (s, 3H, $C\underline{H_3}$), 1.32 (s, 9H, $C(C\underline{H_3})_3$), 1.32 (s, 9H, $C(C\underline{H_3})_3$).

^{13}C NMR (100 MHz, Chloroform-*d*) *δ* 153.0 (C-4´), 146.8 (C-1´), 138.9 (CqAr), 138.4 (CqAr), 138.2 (2 CqAr), 138.1 (C-2´), 135.9 (C-5´), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 127.7 (C_{Ar}), 127.2 (C_{Ar}), 126.8 (C_{Ar}), 119.9 (C-3´), 111.0 (C-6´), 104.8 (C-1), 85.3 (C-2), 83.3 (C-3), 78.5 (C-4), 75.6 ($O\underline{C}H_2Ph$), 75.1 ($O\underline{C}H_2Ph$), 74.5 ($O\underline{C}H_2Ph$), 73.6 ($O\underline{C}H_2Ph$ and C-5), 69.4 (C-6), 55.6 ($O\underline{C}H_3$), 34.8 ($\underline{C}(CH_3)_3$), 34.6 ($\underline{C}(CH_3)_3$), 30.1 ($C(\underline{C}H_3)_3$), 30.0 ($C(\underline{C}H_3)_3$), 16.4 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{50}H_{60}KO_7$ [M+K]+ : 811.3971; found 811.3985.

IR (film): 2952, 2912, 2866, 1504, 1454, 1396, 1373, 1202, 1123, 1089, 1075, 1028, 984, 734, 697 cm^{-1}.

5,8-Dimethoxynaphthalene-1,4-dione **(170)**

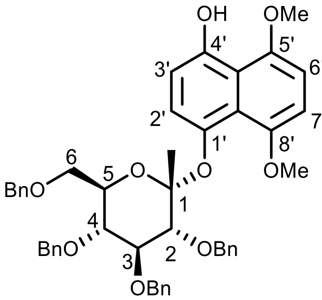


An aqueous solution (5 mL) of CAN (2 equiv., 1104.0 mg, 2.014 mmol) was added to a solution of 1,4,5,8-tetramethoxynaphthalene (1 equiv., 250 mg, 1.007 mmol) in acetonitrile (5 mL) and $CHCl_3$ (2 mL) in an ice bath. After stirring for 30 mins in ice bath, the mixture was extracted with AcOEt. The combined extracted were washed with brine and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the product was chromatographed over silica gel yielding **170** (96.5 mg, 0.44 mmol, 44%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 (s, 2H), 6.78 (s, 2H), 3.96 (s, 6H).

This data is consistent with the reported literature.[188]

5,8-Dimethoxy-4-(((3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151ad)**



According to the general procedure, *exo*-glucal **150a** (1 equiv., 53.6 mg, 0.1 mmol), 1,8-dimethoxy-1,4-dihydronaphthalene-1,4-dione (2 equiv., 43.6 mg, 0.2 mmol), Na_2HPO_4 (1.1 equiv., 15.6 mg, 0.11 mmol), $Fe(acac)_3$ (0.5 equiv., 17.6 mg, 0.05 mmol), phenylsilane (4 equiv., 0.05 mL, 0.4 mmol), EtOH (8 equiv., 0.047 mL, 0.8 mmol) in THF (2 mL) were heated at 60 °C. The reaction was completed after 50 min. The crude was purified by (SiO_2, Cyclohexane /EtOAc:5/1-1/1), yielding **151ad** (44 mg, 0.058 mmol, 58%, dr=1.8:1) as an orange red oil liquid. Analytical samples of α-isomer (major compound) can be obtained after a careful purification.

α-isomer (major compound):

R_f 0.56 (Cyclohexane/EtOAc: 2/1);

$[\alpha]_D^{20}$=+100 (*c*=0.7, $CHCl_3$);

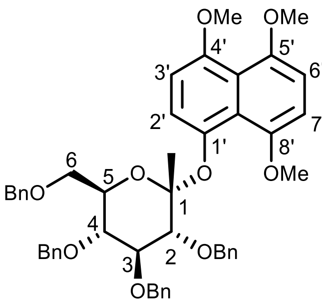
^{1}H NMR (500 MHz, $CDCl_3$) *δ* 9.52 (s, 1H, $O\underline{H}$), 7.41 (d, *J* = 8.7 Hz, 1H, H-2'), 7.40 – 7.23 (m, 18H, H_{Ar}), 7.20 – 7.15 (m, 2H, H_{Ar}), 6.70 (d, *J* = 8.6 Hz, 2H, H-3' and H-6'), 6.60 (d, *J* = 8.6 Hz, 1H, H-7'), 5.02 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.98 (d, *J* = 11.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.92 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.89 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.75 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.67 (d, *J* = 12.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.57 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.54 (d, *J* = 11.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.43 (dd, *J* = 9.7, 8.9 Hz, 1H, H-3), 4.15 (ddd, *J* = 10.1, 4.0, 2.8 Hz, 1H, H-5), 4.00 (s, 3H, $OC\underline{H_3}$), 3.80 – 3.73 (m, 3H, H-6, H-4), 3.58 (s, 3H, $OC\underline{H_3}$), 3.48 (d, *J* = 9.7 Hz, 1H, H-2), 1.47 (s, 3H, $C\underline{H_3}$);

^{13}C NMR (125 MHz, $CDCl_3$) *δ* 152.6 (C-8´), 149.8 (C-5´), 149.7 (C-4´), 143.8 (C-1´), 139.0 (CqAr), 138.9 (CqAr), 138.6 (CqAr), 138.4 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.0 (C_{Ar}),127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 122.0 (CqAr), 118.5 (C-2´), 117.3 (CqAr), 111.0 (C-3´ or C-6´), 105.3 (C-7´), 104.7 (C-3´ or C-6´), 104.4 (C-1), 85.7 (C-2), 83.2 (C-3), 79.0 (C-4), 76.2 ($O\underline{C}H_2Ph$), 75.8 ($O\underline{C}H_2Ph$), 74.9 ($O\underline{C}H_2Ph$), 73.5 ($O\underline{C}H_2Ph$), 72.1 (C-5), 69.4 (C-6), 56.7 ($O\underline{C}H_3$), 56.3 ($O\underline{C}H_3$), 20.4 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{47}H_{48}NaO_9$ $[M+Na]^+$: 779.3191; found 779.3147;

IR (film): 3393, 2923, 2861, 1615, 1453, 1404, 1386, 1255, 1086, 1068, 1053, 1022, 734, 697 cm^{-1}.

(2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyl-2-((4,5,8-trimethoxynaphthalen-1-yl)oxy)tetrahydro-2H-pyran (**177ad**)



NaH (60% in oil, 3 equiv., 8.0 mg, 0.20 mmol) was added portionwisely to solution of **151ad** (1 equiv., 50.3 mg, 0.066 mmol) in freshly distilled THF (1.50 mL) at 0 °C. And then, CH_3I (4 equiv., 0.017 mL, 0.27 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 7.5 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/DCM =1:50), yielding the product **177ad** (22.7 mg, 0.029 mmol, 44% dr=1.8/1) as an orange oil liquid.

R_f 0.56 (Cyclohexane/EtOAc: 3/1);

$[\alpha]_D^{20}$=+93(*c*=0.5, DCM);

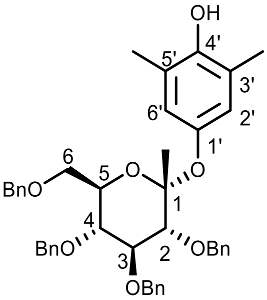
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.8 Hz, 1H, H-6´), 7.42 – 7.24 (m, 18H, H_{Ar}), 7.23 – 7.13 (m, 2H, H_{Ar}), 6.82 (d, *J* = 8.5 Hz, 1H, H-2´), 6.72 (d, *J* = 8.5 Hz, 1H, H-3´), 6.64 (d, *J* = 8.8 Hz, 1H, H-7´), 5.07 – 4.97 (m, 2H, $OC\underline{H_2}Ph$), 4.96 – 4.88 (m, 2H, $OC\underline{H_2}Ph$), 4.77 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.66 (d, *J* = 12.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.63 – 4.51 (m, 2H, $OC\underline{H_2}Ph$), 4.45 (t, *J* = 9.3 Hz, 1H, H-3), 4.16 (ddd, *J* = 10.1, 5.0, 2.3 Hz, 1H, H-5), 3.90 (s, 3H, $OC\underline{H_3}$), 3.88 (s, 3H, $OC\underline{H_3}$), 3.84 – 3.77 (m, 2H, H-6), 3.77 – 3.70 (m, 1H, H-4), 3.62 (s, 3H, $OC\underline{H_3}$), 3.49 (d, *J* = 9.7 Hz, 1H, H-2), 1.51 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1 (C-1´ or C-5´), 152.0 (C-5´ or C-1´), 150.7 (C-4´), 145.4 (C-8´), 139.0 (CqAr), 138.8 (CqAr), 138.6 (CqAr), 138.5 (CqAr), 129.0 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 122.6 (CqAr), 120.9 (CqAr), 116.4 (C-6´), 108.9 (C-2´), 108.0 (C-7´), 107.0 (C-3´), 104.4 (C-1), 85.7 (C-2), 83.2 (C-3), 79.1 (C-4), 76.2 ($O\underline{C}H_2Ph$), 75.8 ($O\underline{C}H_2Ph$), 74.9 ($O\underline{C}H_2Ph$), 73.4 ($O\underline{C}H_2Ph$), 72.0 (C-5), 69.6 (C-6), 58.1 ($O\underline{C}H_3$), 57.4 ($O\underline{C}H_3$), 56.6 ($O\underline{C}H_3$), 20.3 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{48}H_{50}KO_9$ $[M+K]^+$: 809.3086; found 809.3095.

IR (film): 3030, 2927, 2861, 1595, 1497, 1454, 1383, 1271, 1206, 1137, 1069, 1038, 1029, 1003, 863, 735, 698 cm^{-1}.

2,6-Dimethyl-4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151ae)**



According to the general procedure, *exo*-glucal **150a** (1 equiv., 80.5 mg, 0.15 mmol), 2,6-dimethylbenzoquinone (4 equiv., 81.7 mg, 0.6 mmol), Na_2HPO_4 (1.1 equiv., 23.4 mg, 0.17 mmol), $Fe(acac)_3$ (0.5 equiv., 26.5 mg, 0.075 mmol), phenylsilane (4 equiv., 0.075 mL, 0.6 mmol), EtOH (8 equiv., 0.07 mL, 1.2 mmol) in THF (3 mL) were heated at 60 °C. After 5 mins, the quinone (2 equiv.) dissolved in THF (140 µL) was added dropwise during 1 h. The reaction was completed after 1 h. The crude was purified by flash chromatography (SiO_2, Pentane/EtOAc:15/1-9/1), yielding **151ae** (51.6 mg, 0.076 mmol, 51%, dr=1.6:1) as a colorless oil liquid. Analytical samples of β-isomer (major compound) can be obtained after a careful purification

β-isomer (major compound):

R_f 0.5 (Cyclohexane/EtOAc: 4/1);

$[\alpha]_D^{20}$=+42 (*c*=0.65, $CHCl_3$);

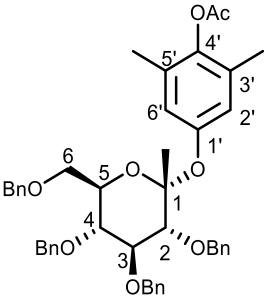
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.42 – 7.27 (m, 18H, H_{Ar}), 7.22 (dd, *J* = 7.5, 2.0 Hz, 2H, H_{Ar}), 6.85 (s, 2H, H-2´), 4.96 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.91 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.87 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.81 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.80 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.65 (d, *J* = 12.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.63 – 4.58 (m, 2H, $OC\underline{H_2}Ph$), 4.35 (s, 1H, $O\underline{H}$), 3.81 – 3.69 (m, 5H, H-2, H-3, H-4, H-6), 3.61 m, 1H, H-5), 2.12 (s, 6H, $ArC\underline{H_3}$), 1.46 (s, 3H, $C\underline{H_3}$);

^{13}C NMR (125 MHz, $CDCl_3$) *δ* 148.4 (C-4´), 146.8 (C-1´), 139.0 (CqAr), 138.7 (CqAr), 138.8 (CqAr), 138.2 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 127.8 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 123.4 (2 C-3´), 122.4 (2 C-2´), 105.0 (C-1), 84.2 (C-2), 83.7 (C-3), 78.3 (C-4), 75.9 ($O\underline{C}H_2Ph$), 75.3 ($O\underline{C}H_2Ph$), 74.9 ($O\underline{C}H_2Ph$), 73.6 ($O\underline{C}H_2Ph$ and C-5), 69.5 (C-6), 17.0 ($\underline{C}H_{3)}$ (16.2 (2 $Ar\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{43}H_{46}NaO_7$ $[M+Na]^+$: 697.3136; found 697.3155;

IR (film): 3347, 2919, 1484, 1454, 1361, 1126, 1086, 1071, 1027, 735, 697 cm^{-1}.

2,6-Dimethyl-4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenyl acetate **(177ae)**



151ae (1 equiv., 37.1 mg, 0.055 mmol) was dissolved in pyridine (1.5 mL) at 0 °C. Ac_2O (154.94 equiv., 0.8 mL, 8.52 mmol) was added slowly. The reaction was moved to room temperature overnight. After 17.5 h, the reaction was quenched by addition of water (9 mL) and a HCl 1M solution (1 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with a saturated solution of $NaHCO_3$ (3 x 20 mL), dried and evaporated yielding the product **177ae** (30.6 mg, 0.043 mmol, 78%) as a brown oil liquid.

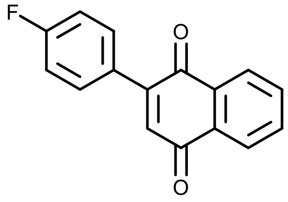
R_f 0.51 (Cyclohexane/EtOAc: 4/1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 18H, H_{Ar}), 7.17 (dd, *J* = 7.4, 2.2 Hz, 2H, H_{Ar}), 6.91 (s, 2H, H-2´), 4.99 (d, *J* = 11.4 Hz, 1H, $OC\underline{H_2}Ph$), 4.96 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.89 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.87 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.75 (d, *J* = 11.4 Hz, 1H, $OC\underline{H_2}Ph$), 4.62 (d, *J* = 12.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.56 (d, *J* = 11.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.54 (d, *J* = 12.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.20 (t, *J* = 9.3 Hz, 1H, H-3), 4.09 (ddd, *J* = 10.1, 5.0, 2.3 Hz, 1H, H-5), 3.81 – 3.69 (m, 2H, H-6), 3.65 (dd, *J* = 10.1, 8.9 Hz, 1H, H-4), 3.42 (d, *J* = 9.5 Hz, 1H, H-2), 2.31 (s, 3H, $C{=}OC\underline{H_3}$), 2.03 (s, 6H, 2 $C\underline{H_3}$), 1.35 (s, 3H, $C\underline{H_3}$)

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1 ($\underline{C}{=}OCH_3$), 151.7 (C-1´), 143.9 (2 C-3´), 138.9 (CqAr), 138.4 (2 CqAr), 138.3 (CqAr), 130.8 (C-4´), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 121.0 (2 C-2´), 103.4 (C-1), 84.3 (C-2), 83.3 (C-3), 78.9 (C-4), 75.8 ($O\underline{C}H_2Ph$), 75.7 ($O\underline{C}H_2Ph$), 74.9 ($O\underline{C}H_2Ph$), 73.5 ($O\underline{C}H_2Ph$), 72.0 (C-5), 69.3 (C-6), 21.2 ($\underline{C}H_3$), 20.6 ($C{=}O\underline{C}H_3$), 16.5 (2 $\underline{C}H_3$)

HRMS (ESI) m/z: calcd for $C_{45}H_{48}NaO_8$ $[M+Na]^+$: 739.3241; found 739.3240.

2-(4-Fluorophenyl)naphthalene-1,4-dione **(171)**



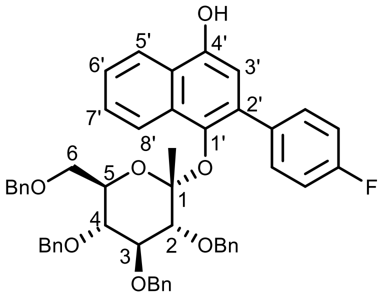
To a solution of 1,4-naphthoquinone (1 equiv., 500.1 mg, 3.16 mmol) in $PhCF_3$ (8 mL) was added the (4-fluorophenyl)boronic acid (1.5 equiv., 664.6 mg, 4.75 mmol), water (8 mL), silver(I) nitrate (0.1 M solution in water, 0.63 mmol, 20 mol %, 6 mL) and ammonium persulfate (2.15 g, 9.5 mmol, 3.0 equiv). The solution was stirred vigorously at room temperature for 19 h. After 19 h, the reaction was diluted with dichloromethane (20 mL) and washed with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL), dried over sodium sulfate and evaporated in vacuo. Purification was performed by silica gel chromatography (Cyclohexane /DCM 50:50) to yield **171** (470.9 mg, 1.87 mmol, 59%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.16 (m, 1H), 8.14 – 8.11 (m, 1H), 7.82 – 7.76 (m, 2H), 7.62 – 7.56 (m, 2H), 7.21 – 7.14 (m, 2H), 7.06 (s, 1H).

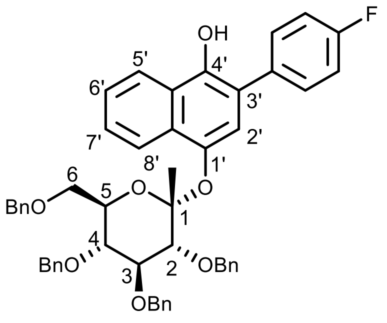
The data are consistent with those reported in the literature.[189]

3-(4-Fluorophenyl)-4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151ag)**

2-(4-Fluorophenyl)-4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151af)**



major (**151ag**)



minor (**151af**)

According to the general procedure, *exo*-glucal **150a** (1 equiv., 54.1 mg, 0.1008 mmol), 2-(4-fluorophenyl)-1,4-dihydronaphthalene-1,4-dione (4 equiv., 101.7 mg, 0.403 mmol), Na_2HPO_4 (1.1 equiv., 15.7 mg, 0.11 mmol), Fe(acac)$_3$ (0.5 equiv., 17.8 mg, 0.0504 mmol) were dissolved in freshly distilled THF (2 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.0502 mL, 0.403 mmol) was added dropwise and following EtOH (8 equiv., 0.047 mL, 0.806 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring. After 50 mins, the quinone (2 equiv.) dissolved in THF (400 µL) was added dropwise. After 3 h, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 30/1-22/1), yielding the product **151ag** (36.7 mg, 0.046 mmol, 46.0%) and **151af** (16.8 mg, 0.021 mmol, 21.1%).

major compound (151ag):

R_f 0.48 (Cyclohexane/EtOAc: 5/1).

$[\alpha]_D^{20}$=+112 (*c*=0.3, DCM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 8.4 Hz, 1H, H-8´), 8.22 (d, *J* = 8.4 Hz, 1H, H-5´), 7.56 – 7.06 (m, 27H, H_{Ar} and H-6´ and H-7´, H-3´), 5.49 (s, 1H, O$\underline{H}$), 5.08 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 5.05 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.95 (d, *J* = 10.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.90 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.79 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.56 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.53 – 4.46 (m, 2H, OC$\underline{H}_2$Ph), 4.39 (t, *J* = 9.4 Hz, 1H, H-3), 4.36 – 4.31 (m, 1H, H-5), 3.76 (dd, *J* = 10.5, 1.9 Hz, 1H, H-6), 3.72 – 3.69 (m, 1H, H-6), 3.69 – 3.66 (m, 1H, H-4), 3.56 (d, *J* = 9.5 Hz, 1H, H-2), 1.37 (s, 3H, C$\underline{H}_3$).

^{13}C NMR (125 MHz, CDCl$_3$) *δ* 163.4 (C$_{Ar}$), 161.5 (C$_{Ar}$), 143.9 (C-4´), 143.7 (C-1´), 138.9 (CqAr), 138.7 (CqAr), 138.3 (CqAr), 138.2 (CqAr), 133.5 (C-2´), 131.3 (C$_{Ar}$), 131.2 (C$_{Ar}$), 129.8 (CqAr), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 126.3 (C-6´), 126.1 (C-7´), 125.1 (CqAr), 123.5 (C-8´), 122.0 (C-5´), 119.9 (CqAr), 118.2 (C-3´), 116.6 (C$_{Ar}$), 116.4 (C$_{Ar}$), 104.1 (C-1), 85.1 (C-2), 83.5 (C-3), 78.9 (C-4), 76.1 (O$\underline{\mathrm{C}}$H$_2$Ph), 75.9 (O$\underline{\mathrm{C}}$H$_2$Ph), 75.0 (O$\underline{\mathrm{C}}$H$_2$Ph), 73.3 (O$\underline{\mathrm{C}}$H$_2$Ph), 72.3 (C-5), 69.1 (C-6), 20.8 ($\underline{\mathrm{C}}$H$_3$)

HRMS (ESI) m/z: calcd for $C_{51}H_{47}FKO_7$ [M+K]$^+$: 829.2937; found 829.2930.

IR (film): 3340, 3031, 2922, 2865, 1601, 1511, 1497, 1455, 1401, 1381, 1364, 1299, 1225, 1207, 1159, 1126, 1090, 1065, 1028, 867, 839, 750, 735, 698 cm^{-1}.

minor compound (151af):

R_f 0.47 (Cyclohexane/EtOAc: 5/1).

[α]$_D^{20}$=+86 (*c*=0.51, DCM).

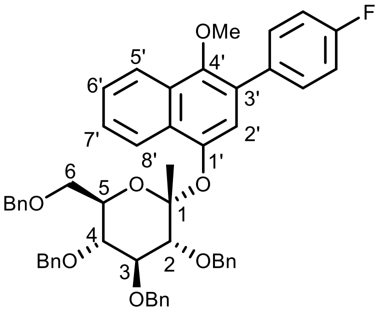
^{1}H NMR (400 MHz, CDCl$_3$) *δ* 8.90 (d, *J* = 8.6 Hz, 1H, H-8´), 8.07 (dd, *J* = 8.4, 1.2 Hz, 1H, H-5´), 7.42 – 7.38 (m, 1H, H-6´), 7.37 – 7.15 (m, 22H, H$_{Ar}$), 7.03 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H, H-7´), 6.97 – 6.86 (m, 2H, H$_{Ar}$), 6.51 (s, 1H, H-2´), 5.38 (s, 1H, OH), 5.02 (d, *J* = 11.0 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.95 (d, *J* = 11.1 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.85 (d, *J* = 10.5 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.83 (d, *J* = 10.8 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph),4.58 – 4.45 (m, 3H, OC$\underline{\mathrm{H}_2}$Ph), 4.38 (d, *J* = 12.1 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.29 (t, *J* = 9.5 Hz, 1H, H-3), 3.78 (t, *J* = 9.6 Hz, 1H, H-4), 3.71 – 3.62 (m, 1H, H-5), 3.40 (dd, *J* = 10.9, 2.9 Hz, 1H, H-6), 3.34 (d, *J* = 10.0 Hz, 1H, H-2), 2.65 (d, *J* = 10.8 Hz, 1H, H-6), 1.01 (s, 3H, C$\underline{\mathrm{H}_3}$).

^{13}C NMR (125 MHz, CDCl$_3$) *δ* 163.0 (C$_{Ar}$), 161.1 (C$_{Ar}$), 147.7 (C-4´), 141.6 (C-1´), 139.0 (CqAr), 138.6 (CqAr), 138.3 (CqAr), 138.2 (CqAr), 137.1 (C-3´), 131.9 (CqAr), 131.7 (2 C$_{Ar}$), 128.8 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.4 (C$_{Ar}$), 128.1 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 126.6 (C-7´), 125.5 (C-6´ and C-8´), 124.4 (CqAr), 121.1 (C-5´), 115.0 (C$_{Ar}$), 114.8 (C$_{Ar}$), 111.7 (C-2´), 106.0 (C-1), 85.4 (C-2), 82.7 (C-3), 78.3 (C-4), 76.4 (O$\underline{\mathrm{C}}$H$_2$Ph), 75.7 (O$\underline{\mathrm{C}}$H$_2$Ph), 75.1 (O$\underline{\mathrm{C}}$H$_2$Ph), 73.5 (O$\underline{\mathrm{C}}$H$_2$Ph), 72.3 (C-5), 68.0 (C-6), 22.2 ($\underline{\mathrm{C}}$H$_3$)

HRMS (ESI) m/z: calcd for $C_{51}H_{47}FKO_7$ [M+K]$^+$: 829.2937; found 829.2956.

IR (film): 3330, 3031, 2927, 2867, 1599, 1509, 1497, 1454, 1394, 1363, 1218, 1157, 1090, 1068, 1027, 909, 869, 858, 834, 776, 752, 733, 697 cm^{-1}.

(2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-((3-(4-fluorophenyl)-4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran **(177af)**



NaH (60% in oil, 3 equiv., 10.6 mg, 0.27 mmol) was added portionwisely to solution of **151af** (1 equiv., 70 mg, 0.089 mmol) in freshly distilled THF (1.50 mL) at 0 °C. And then, CH_3I (4 equiv., 0.022 mL, 0.27 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 7.5 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc=20:1), yielding the product **177af** (39.3 mg, 0.049 mmol, 55%) as a brown oil liquid.

R

$\boldsymbol{R_f}$ 0.70 (Cyclohexane/EtOAc: 5/1).

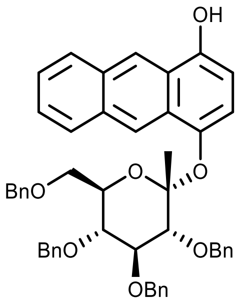
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.5 Hz, 1H, H-8´), 8.18 (d, *J* = 8.0 Hz, 1H, H-5´), 7.53 (dd, *J* = 8.7, 5.5 Hz, 2H, H-6´ and H-7´), 7.44 – 7.20 (m, 18H, H_{Ar}), 7.16 – 7.08 (m, 4H, H_{Ar}), 6.91-6.83 (m, 2H, H_{Ar}), 6.70 (s, 1H, H-2´), 5.04 (d, *J* = 11.5 Hz, 1H, $OC\underline{H_2}Ph$), 4.96 (d, *J* = 11.5 Hz, 1H, $OC\underline{H_2}Ph$), 4.86 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.80 (d, *J* = 10.7 Hz, 1H, $OC\underline{H_2}Ph$), 4.76 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.52 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.13 (d, *J* = 12.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.06 (d, *J* = 12.3 Hz, 1H, $OC\underline{H_2}Ph$), 3.98 (s, 3H, $OC\underline{H_3}$), 3.86 – 3.79 (m, 1H, H-3), 3.66 – 3.59 (m, 2H, H-4 and H-5), 3.36 – 3.30 (m, 2H, H-6), 3.25 (d, *J* = 5.8 Hz, 1H, H-2), 1.01 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (C_{Ar}), 161.1 (C_{Ar}), 151.7 (C-4´), 141.4 (C-1´), 139.0 (CqAr), 138.7 (CqAr), 138.4 (CqAr), 138.2 (CqAr), 137.6 (C-3´), 131.8 (C_{Ar}), 131.75 (C_{Ar}), 131.7 (CqAr), 131.68 (CqAr), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.75 (C_{Ar}), 127.7 (C_{Ar}), 126.6 (C-7´), 125.5 (C-6´ and C-8´), 121.3 (C-5´), 115.0 (C_{Ar}), 114.8 (C_{Ar}), 107.1 (C-2´), 106.0 (C-1), 85.4 (C-2), 82.8 (C-3), 78.4 (C-4), 76.4 ($O\underline{C}H_2Ph$), 75.7 ($O\underline{C}H_2Ph$), 75.1 ($O\underline{C}H_2Ph$), 73.5 ($O\underline{C}H_2Ph$), 72.4 (C-5), 68.1 (C-6), 55.7 ($O\underline{C}H_3$), 22.2 ($\underline{C}H_3$)

HRMS (ESI) m/z: calcd for $C_{52}H_{49}FKO_7$ $[M+K]^+$: 843.3094; found 843.3139.

IR (film): 2926, 2860, 1595, 1511, 1496, 1455, 1364, 1229, 1159, 1094, 1070, 1028, 835, 770, 735, 698 cm^{-1}.

4-(((2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)anthracen-1-ol **(151ah)**



Compound **150a** (1 equiv., 60 mg, 0.11 mmol), 1,4-dihydroanthracene-1,4-dione (3 equiv., 69.8 mg, 0.34 mmol), Na_2HPO_4 (1.1 equiv., 17.5 mg, 0.12 mmol), $Fe(acac)_3$ (0.5 equiv., 19.7 mg, 0.056 mmol) were dissolved in dry THF (2.2 mL) under Ar at RT. Subsequently, phenylsilane (4 equiv., 0.056 mL, 0.45 mmol) was added dropwise and EtOH (8 equiv., 0.052 mL, 0.89 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring. After 4 h, the mixture was evaporated. The crude was purified by flash chromatography (SiO_2, EtOAc: Cyclohexane =5%-8%), yielding the product **151ah** (21.9 mg, 0.029 mmol, 26%).

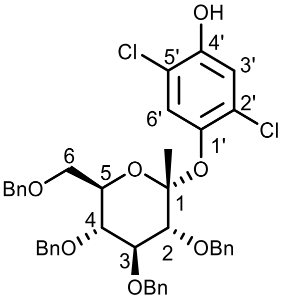
Major compound:

^{1}H NMR (400 MHz, Acetone-*d*$_6$) *δ* 9.02 (s, 1H, H-10'), 8.79 (s, 1H, H-5'), 8.06 (d, *J* = 8.3 Hz, 1H, H-9'), 7.58 (dd, *J* = 6.6, 2.9 Hz, 2H, H-7' and H-8'), 7.50 – 7.20 (m, 22H, H-2' or H-3' and H-6' and H_{Ar}), 6.71 (d, *J* = 7.9 Hz, 1H, H-2' or H-3'), 5.18 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 5.15 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 5.04 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.97 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.88 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.74 (d, *J* = 11.4 Hz, 1H, $OC\underline{H_2}Ph$), 4.70 – 4.64 (m, 2H, $OC\underline{H_2}Ph$), 4.45 – 4.36 (m, 2H, H-5 and H-3), 4.02 – 3.97 (m, 1H, H-6), 3.89 – 3.83 (m, 1H, H-6), 3.77 – 3.71 (m, 1H, H-4), 3.68 (d, *J* = 9.6 Hz, 1H, H-2), 1.35 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (125 MHz, Acetone-*d*$_6$) *δ* 150.2 (C-4´), 143.5 (C-1´), 140.1 (CqAr), 140.0 (CqAr), 139.8 (CqAr), 139.7 (CqAr), 132.5 (CqAr), 132.0 (CqAr), 130.0 (CqAr), 129.5 (C_{Ar}), 129.4 (C_{Ar}), 129.2 (C_{Ar}), 129.15 (C_{Ar}), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.54 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.36 (C-9´), 128.2 (C-8´), 126.2 (C-6´ or C-7'), 126.1(C-6´ or C-7'), 126.0 (CqAr), 122.8 (C-10´), 121.8 (C-5´), 116.9 (C-2´ or C-3´), 105.8 (C-2´ or C-3´), 104.8 (C-1), 85.8 (C-2), 84.4 (C-3), 79.9 (C-4), 76.7 ($O\underline{C}H_2Ph$), 76.1 ($O\underline{C}H_2Ph$), 75.4 ($O\underline{C}H_2Ph$), 73.9 ($O\underline{C}H_2Ph$), 73.3 (C-5), 70.7 (C-6), 20.7 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{49}H_{46}KO_7$ $[M+K]^+$: 785.2875; found 785.2844.

2,5-Dichloro-4-(((3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151ai)**



According to the general procedure, *exo*-glucal **150a** (1 equiv., 53.7 mg, 0.1 mmol), 2,5-dichlorocyclohexa-2,5-diene-1,4-dione (4 equiv., 70.8 mg, 0.4 mmol), Na_2HPO_4 (1.1 equiv., 15.6 mg, 0.11 mmol), Fe(acac)$_3$ (0.5 equiv., 17.6 mg, 0.05 mmol), phenylsilane (4 equiv., 0.05 mL, 0.4 mmol), EtOH (8 equiv., 0.047 mL, 0.8 mmol) in THF (2 mL) were heated at 60 °C. After 5 mins, quinone (0.8 equiv.) dissolved in THF (170 µL) was added dropwise during 4 h. The reaction was completed after 4 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 20/1-11/1), yielding **151ai** (26.3 mg, 0.037 mmol, 37%, dr=1.4:1) as a colorless oil liquid.

R$_f$ 0.25 (Pentane/Et$_2$O: 5/1);

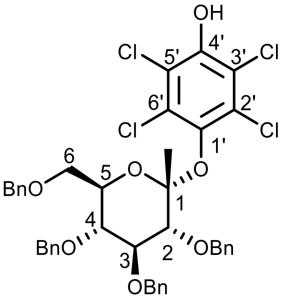
^{1}H NMR (400 MHz, CDCl$_3$) *δ* 7.74 (s, 1H, H-6’, β-isomer), 7.51 (s, 1H, H-6', α-isomer), 7.44 – 7.26 (m, 29H, H$_{Ar}$), 7.24-7.15 (m, 3H, H$_{Ar}$), 7.05 (s, 1H, H-3', α-isomer), 7.04 (s, 0.66H, H-3', β -isomer), 5.40 (s, 0.66H, OH, β-isomer), 5.39 (s, 1H, OH, α-isomer), 5.19 (d, *J* = 11.4 Hz, 1H, OC$\underline{H}_2$Ph, β-isomer), 5.00 (d, *J* = 11.4 Hz, 1H, OC$\underline{H}_2$Ph, α-isomer), 4.97-4.52 (m, 12H, OC$\underline{H}_2$Ph, α and β-isomers), 4.24 (t, *J* = 9.3 Hz, 1H, H-3, α-isomer), 4.16 (ddd, *J* = 10.2, 6.0, 1.9 Hz, 1H, H-5, α-isomer), 3.84 – 3.54 (m, 7.8H, H-4, H-6, α and β-isomers; H-2, H-3, H-5, β-isomer), 3.46 (d, *J* = 9.6 Hz, 1H, H-2, α-isomer), 1.52 (s, 3H, C$\underline{H}_3$, β-isomer), 1.35 (s, 3H, C$\underline{H}_3$, α-isomer);

^{13}C NMR (125 MHz, CDCl$_3$) *δ* 147.6 (C-4´), 144.0 (C-1´, α-isomer), 143.7 (C-1´, β -isomer)138.7 (CqAr), 138.6 (CqAr), 138.2 (CqAr), 138.1 (CqAr), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.4 (C$_{Ar}$), 128.2 (C$_{Ar}$), 128.1 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 127.4 (C-2´ or C-5´, α-isomer), 126.1 (C-2´ or C-5´, β -isomer), 124.3 (C-6´, β -isomer), 123.4 (C-6´, α-isomer), 118.1 (C-2´ or C-5´, α-isomer), 118.0 (C-2´ or C-5´, β -isomer), 117.1 (C-3´, α-isomer), 117.0 (C-3´, β -isomer), 106.7 (C-1, β -isomer), 104.9 (C-1, α-isomer), 84.4 (C-2, α-isomer), 84.0 (CH-O, β-isomer), 83.8 (CH-O, β-isomer), 83.0 (C-3, α-isomer), 78.6 (C-4, α-isomer), 78.0 (CH-O, β-isomer), 75.8 (O$\underline{C}H_2$Ph), 75.7 (O$\underline{C}H_2$Ph), 75.2 (O$\underline{C}H_2$Ph), 75.0 (O$\underline{C}H_2$Ph), 73.7 (O$\underline{C}H_2$Ph), 73.6 (CH-O, β-isomer) 73.55 (O$\underline{C}H_2$Ph), 72.1 (C-5, α-isomer), 69.4 (C-6, β-isomer), 69.2 (C-6, α-isomer), 21.1 ($\underline{C}H_3$, α-isomer), 16.4 ($\underline{C}H_3$, β -isomer);

HRMS (ESI) m/z: calcd for $C_{41}H_{40}NaCl_2O_7$ [M+Na]$^+$: 737.2043; found 737.2048;

IR (film): 3320, 2922, 1496, 1479, 1454, 1380, 1362, 1196, 1072, 1028, 870, 734, 696 cm^{-1}.

2,3,5,6-Tetrachloro-4-(((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151aj)**



According to the general procedure, *exo*-glucal **150a** (1 equiv., 40.2 mg, 0.075 mmol), 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione (4 equiv., 73.7 mg, 0.3 mmol), Na_2HPO_4 (1.1 equiv., 11.7 mg, 0.082 mmol), $Fe(acac)_3$ (0.5 equiv., 13.2 mg, 0.037 mmol), phenylsilane (4 equiv., 0.037 mL, 0.3 mmol), EtOH (8 equiv., 0.035 mL, 0.6 mmol) in THF (2 mL) were heated at 60 °C. The reaction was completed after 4 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 30/1-20/1), yielding **151aj** (20 mg, 0.025 mmol, 34%, dr>98:2) as a colorless oil liquid.

R$_f$ 0.33 (Cyclohexane/EtOAc: 5/1);

$[\alpha]_D^{20}$ =+60 (*c*=0.89, DCM).

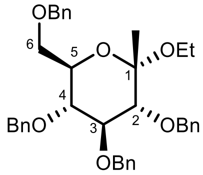
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 – 7.24 (m, 18H, H_{Ar}), 7.19 (dd, *J* = 7.5, 2.1 Hz, 2H, H_{Ar}), 5.01 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.96 (d, *J* = 11.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.93 (d, *J* = 11.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.92 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.75 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.67 (d, *J* = 12.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.59 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.55 (m, 1H, H-5), 4.50 (d, *J* = 12.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.32 (t, *J* = 9.5 Hz, 1H, H-3), 3.94 – 3.84 (m, 2H, H-4 and H-6), 3.71 (dd, *J* = 10.8, 2.0 Hz, 1H, H-6), 3.47 (d, *J* = 9.9 Hz, 1H, H-2), 1.31 (s, 3H, $C\underline{H_3}$);

^{13}C NMR (125 MHz, CDCl$_3$) δ 146.5 (CqAr), 143.5 (CqAr), 138.8 (CqAr), 138.5 (CqAr), 138.3 (2 CqAr), 128.9 (CqAr or C_{Ar}), 128.5 (CqAr or C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 119.3 (CqAr), 108.5 (C-1), 85.0 (C-2), 82.5 (C-3), 78.2 (C-4), 76.2 ($O\underline{C}H_2Ph$), 75.7 ($O\underline{C}H_2Ph$), 75.1 ($O\underline{C}H_2Ph$), 73.7 ($O\underline{C}H_2Ph$), 72.8 (C-5), 68.8 (C-6), 21.7 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{41}H_{38}Cl_4KO_7$ $[M+K]^+$: 823.0981; found 823.0994;

IR (film): 3342, 2927, 2868, 1497, 1453, 1431, 1383, 1364, 1269, 1197, 1126, 1088, 1064, 1028, 904, 735, 697 cm^{-1}.

(2S,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-ethoxy-2-methyltetrahydro-2H-pyran **(175)**



Compound **175** was obtained as a byproduct in several HAT reactions (see **Scheme 79**).

R_f 0.49 (Cyclohexane/EtOAc: 6/1);

$[\alpha]_D^{20}$=+37 (*c*=0.3, CH$_2$Cl$_2$);

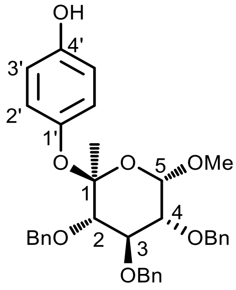
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.24 (m, 18H, $\mathrm{H_{Ar}}$), 7.16 (dd, *J* = 7.2, 2.4 Hz, 2H, $\mathrm{H_{Ar}}$), 4.97 – 4.92 (m, 2H, $\mathrm{OC\underline{H_2}Ph}$), 4.89 (d, *J* = 11.0 Hz, 1H, $\mathrm{OC\underline{H_2}Ph}$), 4.84 (d, *J* = 10.7 Hz, 1H, $\mathrm{OC\underline{H_2}Ph}$), 4.71 (d, *J* = 11.5 Hz, 1H, $\mathrm{OC\underline{H_2}Ph}$), 4.63 (d, *J* = 12.3 Hz, 1H, $\mathrm{OC\underline{H_2}Ph}$), 4.54 (d, *J* = 10.7 Hz, 1H, $\mathrm{OC\underline{H_2}Ph}$), 4.53 (d, *J* = 12.2 Hz, 1H, $\mathrm{OC\underline{H_2}Ph}$), 4.11 (dd, *J* = 9.6, 8.4 Hz, 1H, H-3), 3.75 – 3.69 (m, 1H, H-6), 3.69 – 3.65 (m, 2H, H-5 and H-6), 3.65 – 3.60 (m, 1H, H-4), 3.52 (q, *J* = 7.1 Hz, 2H, $\mathrm{C\underline{H_2}CH_3}$), 3.33 (d, *J* = 9.6 Hz, 1H, H-2), 1.28 (s, 3H, $\mathrm{C\underline{H_3}}$), 1.22 (t, *J* = 7.0 Hz, 3H, $\mathrm{CH_2C\underline{H_3}}$);

^{13}C NMR (125 MHz, CDCl$_3$) δ 139.0 (CqAr), 138.4 (2 CqAr), 138.3 (CqAr), 128.9 ($\mathrm{C_{Ar}}$), 128.6 ($\mathrm{C_{Ar}}$), 128.5 ($\mathrm{C_{Ar}}$), 128.1 ($\mathrm{C_{Ar}}$), 127.9 ($\mathrm{C_{Ar}}$), 127.7 ($\mathrm{C_{Ar}}$), 100.5 (C-1), 84.1 (C-2), 83.4 (C-3), 79.0 (C-4), 75.7 (2 $\mathrm{O\underline{C}H_2Ph}$), 75.2 ($\mathrm{O\underline{C}H_2Ph}$), 73.5 ($\mathrm{O\underline{C}H_2Ph}$), 71.6 (C-5), 69.0 (C-6), 56.1 ($\mathrm{\underline{C}H_2CH_3}$), 21.1 ($\mathrm{\underline{C}H_3}$), 15.5 ($\mathrm{CH_2\underline{C}H_3}$);

HRMS (ESI) m/z: calcd for $\mathrm{C_{37}H_{42}NaO_6}$ $[\mathrm{M+Na}]^+$: 605.2874; found 605.2878;

IR (film): 3064, 3030, 2980, 2928, 2892, 2861, 1497, 1454, 1363, 1211, 1148, 1126, 1087, 1070, 1028, 954, 736, 697 cm^{-1}.

4-(((2S,3S,4R,5R,6S)-3,4,5-Tris(benzyloxy)-6-methoxy-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151ba)**



According to the general procedure, *exo*-glucal **150b** (1 equiv., 42.2 mg, 0.095 mmol), *p*-benzoquinone (4 equiv., 40.9 mg, 0.38 mmol), Na_2HPO_4 (1.1 equiv., 14.8 mg, 0.104 mmol), $Fe(acac)_3$ (0.5 equiv., 16.7 mg, 0.047 mmol, phenylsilane (4 equiv., 0.047 mL, 0.38 mmol), EtOH (8 equiv., 0.044 mL, 0.76 mmol) in THF (2 mL) were heated at 60 °C. After 5 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (400 μL) was added dropwise during 6 h. The reaction was completed after 6 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 12/1-6/1), yielding **151ba** (27 mg, 0.049 mmol, 52%, dr>98:2) as a colorless oil liquid.

R_f 0.25 (Cyclohexane/EtOAc: 4/1);

$[\alpha]_D^{20}$ =+6.7 (*c*=1.4, $CHCl_3$);

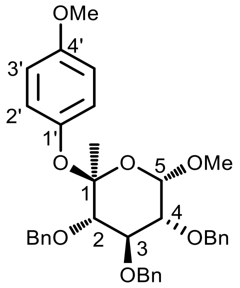
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 15H, H_{Ar}), 7.04 – 6.96 (m, 2H, 2'), 6.73 – 6.63 (m, 2H, 3'), 4.94 (d, *J* = 11.2 Hz, 1H, O$\underline{CH_2}$Ph), 4.90 (d, *J* = 10.6 Hz, 1H, O$\underline{CH_2}$Ph), 4.84 (d, *J* = 10.6 Hz, 2H, O$\underline{CH_2}$Ph), 4.83 (d, *J* = 11.2 Hz, 1H, O$\underline{CH_2}$Ph), 4.71 (d, *J* = 3.3 Hz, 1H, H-5), 4.69 (d, *J* = 11.0 Hz, 1H, O$\underline{CH_2}$Ph), 3.95 (t, *J* = 9.6 Hz, 1H, H-3), 3.73 (d, *J* = 9.6 Hz, 1H, H-2), 3.69 (dd, *J* = 9.7, 4.0 Hz, 1H, H-4), 3.42 (s, 3H, OC$\underline{H_3}$), 1.53 (s, 3H, C$\underline{H_3}$);

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0 (C-4´), 147.6 (C-1´), 138.9 (CqAr), 138.7 (CqAr), 138.2 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.1(C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 123.6 (2 C-2´), 115.7 2 (C-3´), 106.1 (C-1), 98.6 (C-5), 84.3 (C-2), 79.5 (C-4), 79.2 (C-3), 76.1 (O$\underline{C}H_2$Ph), 75.3 (O$\underline{C}H_2$Ph), 73.8 (O$\underline{C}H_2$Ph), 56.3 (O$\underline{C}H_3$), 21.0 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{34}H_{36}NaO_7$ $[M+Na]^+$: 579.2353; found 579.2374;

IR (film): 3392, 2924, 1506, 1454, 1209, 1068, 1028, 909, 737, 697 cm^{-1}.

(2S,3S,4R,5R,6S)-3,4,5-Tris(benzyloxy)-6-methoxy-2-(4-methoxyphenoxy)-2-methyltetrahydro-2H-pyran **(177ba)**



NaH (60% in oil, 3 equiv., 27.7 mg, 0.69 mmol) was added portionwisely to solution of **151ba** (1 equiv., 128.5 mg, 0.23 mmol) in freshly distilled THF (2.8 mL) at 0 °C. And then, CH_3I (4 equiv., 0.057 mL, 0.92 mmol) was added and the mixture was stirred at RT until the starting material was completely consumed. After 6 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc:15/1-14/1), yielding the product **177ba** (99.2 mg, 0.17 mmol, 75%) as a colorless oil liquid.

Rf 0.49 (Cyclohexane/EtOAc: 4/1).

$[\alpha]_D^{20}$=+38.95 (*c*=0.8, DCM).

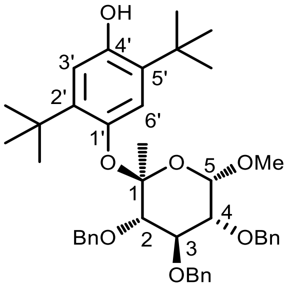
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 15H, H_{Ar}), 7.10 – 7.00 (m, 2H, H-3'), 6.85 – 6.73 (m, 2H, H-2'), 4.95 (d, *J* = 11.2 Hz, 1H, $O\underline{CH_2}Ph$), 4.90 (d, *J* = 10.6 Hz, 1H, $O\underline{CH_2}Ph$), 4.87 – 4.80 (m, 3H, $O\underline{CH_2}Ph$), 4.72 (d, *J* = 4.1 Hz, 1H, H-5), 4.69 (d, *J* = 12.1 Hz, 1H, $O\underline{CH_2}Ph$), 3.94 (t, *J* = 9.7 Hz, 1H, H-3), 3.78 (s, 3H, $OC\underline{H_3}$), 3.72 (d, *J* = 9.6 Hz, 1H, H-2), 3.68 (dd, *J* = 9.6, 4.0 Hz, 1H, H-4), 3.44 (s, 3H, $OC\underline{H_3}$), 1.54 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0 (C-4´), 147.6 (C-1´), 138.9 (CqAr), 138.8 (CqAr), 138.3 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 123.4 (2 C-3´), 114.2 (2 C-2´), 106.1 (C-1), 98.7 (C-5), 84.3 (C-2), 79.6 (C-4), 79.2 (C-3), 76.1 ($O\underline{C}H_2Ph$), 75.3 ($O\underline{C}H_2Ph$), 73.8 ($O\underline{C}H_2Ph$), 56.4 ($O\underline{C}H_3$), 55.6 ($O\underline{C}H_3$), 21.0 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{35}H_{38}NaO_7$ $[M+Na]^+$: 593.2510; found 593.2539.

IR (film): 3063, 3031, 3007, 2931, 2909, 2836, 1505, 1454, 1373, 1360, 1244, 1215, 1172, 1144, 1072, 1029, 957, 909, 844, 830, 737, 697 cm^{-1}.

2,5-Di-tert-butyl-4-(((2S,3S,4R,5R,6S)-3,4,5-tris(benzyloxy)-6-methoxy-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151bb)**



According to the general procedure, *exo*-glucal **150b** (1 equiv., 69.5 mg, 0.16 mmol), 2,5-di-tert-butyl-1,4-benzoquinone (3 equiv., 102.9 mg, 0.47 mmol), Na_2HPO_4 (1.1 equiv., 24.3 mg, 0.17 mmol), $Fe(acac)_3$ (0.5 equiv., 27.5 mg, 0.078 mmol) were dissolved in freshly distilled THF (3 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.077 mL, 0.62 mmol) was added dropwise and EtOH (8 equiv., 0.073 mL, 1.25 mmol) was added. Then, the mixture was transferred to 60 °C and heated with constant stirring. After about 5 mins, 2,5-di-tert-butyl-1,4-benzoquinone (1.5 equiv.) dissolved in THF

(400 μL) was added dropwise. After 3 h, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/DCM: 3/1-2/1), yielding the product **151bb** (67.5 mg, 0.1 mmol, 65%, dr>98:2) as a colorless oil liquid.

R_f 0.50 (Cyclohexane/EtOAc: 7/1).

$[\alpha]_D^{20}$=+44.78 (*c*=0.50, DCM).

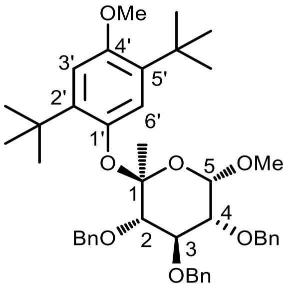
^{1}H NMR (400 MHz, Chloroform-d) δ 7.56 (s, 1H, H-3´), 7.44 – 7.17 (m, 15H, H_{Ar}), 6.55 (s, 1H, H-6´), 5.05 (d, *J* = 11.5 Hz, 1H, $O\underline{CH_2}Ph$), 4.94 (d, *J* = 10.6 Hz, 1H, $O\underline{CH_2}Ph$), 4.89 – 4.81 (m, 2H, $O\underline{CH_2}Ph$), 4.78 (d, *J* = 3.9 Hz, 1H, H-5), 4.76 – 4.66 (m, 2H, $O\underline{CH_2}Ph$), 4.08 (t, *J* = 9.4 Hz, 1H, H-3), 3.90 (d, *J* = 9.3 Hz, 1H, H-2), 3.80 (dd, *J* = 9.5, 3.9 Hz, 1H, H-4), 3.55 (s, 3H, $OC\underline{H_3}$), 1.75 (s, 3H, $C\underline{H_3}$), 1.37 (s, 9H, $C(C\underline{H_3})_3$), 1.27 (s, 9H, $C(C\underline{H_3})_3$).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 148.4 (C-4´), 146.5 (C-1´), 138.8 (CqAr), 138.6 (C-2´), 138.4 (CqAr), 138.1 (CqAr), 133.3 (C-5´), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 127.1 (C_{Ar}), 126.7 (C_{Ar}), 118.7 (C-3´), 115.6 (C-6´), 106.0 (C-1), 98.9 (C-5), 83.5 (C-2), 80.0 (C-3), 79.3 (C-4), 75.9 ($O\underline{C}H_2Ph$), 74.7 ($O\underline{C}H_2Ph$), 73.7 ($O\underline{C}H_2Ph$), 56.7 ($O\underline{C}H_3$), 34.4 ($\underline{C}(CH_3)_3$), 34.3 ($\underline{C}(CH_3)_3$), 29.9 ($C(\underline{C}H_3)_3$), 29.8 ($C(\underline{C}H_3)_3$), 20.1 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{42}H_{52}NaO_7$ $[M+Na]^+$: 691.3605; found 691.3598.

IR (film): 3431, 2955, 2909, 2868, 1507, 1497, 1454, 1400, 1382, 1359, 1196, 1168, 1143, 1116, 1068, 1047, 1028, 1001, 956, 909, 892, 857, 730, 696 cm^{-1}.

(2S,3S,4R,5R,6S)-3,4,5-Tris(benzyloxy)-2-(2,5-di-tert-butyl-4-methoxyphenoxy)-6-methoxy-2-methyltetrahydro-2H-pyran **(177bb)**



NaH (60% in oil, 3 equiv., 10.7 mg, 0.27 mmol) was added portionwisely to solution of **151bb** (1 equiv., 59.5 mg, 0.089 mmol) in freshly distilled THF (2 mL) at 0 °C. And then, CH_3I (4 equiv., 0.022 mL, 0.36 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 4.5 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane:DCM=1/1-1/2), yielding the product **177bb** (58.3 mg, 0.085 mmol, 96%) as a colorless oil liquid.

R$_f$ 0.38 (Cyclohexane/DCM: 1/4).

$[\alpha]_D^{20}$=+33.2 (*c*=0.3, DCM).

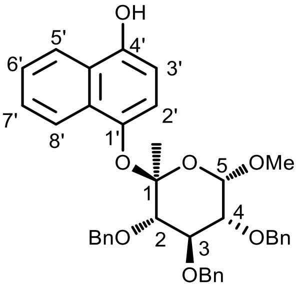
^{1}H NMR (400 MHz, Chloroform-d) δ 7.59 (s, 1H, H-3´), 7.44 – 7.18 (m, 15H, H$_{\mathrm{Ar}}$), 6.80 (s, 1H, H-6´), 5.06 (d, *J* = 11.4 Hz, 1H, O$\underline{\mathrm{CH_2}}$Ph), 4.94 (d, *J* = 10.5 Hz, 1H, O$\underline{\mathrm{CH_2}}$Ph), 4.91 – 4.82 (m, 2H, O$\underline{\mathrm{CH_2}}$Ph), 4.79 (d, *J* = 3.4 Hz, 1H, H-5), 4.73 (m, 2H, O$\underline{\mathrm{CH_2}}$Ph), 4.07 (t, *J* = 9.4 Hz, 1H, H-3), 3.90 (d, *J* = 9.2 Hz, 1H, H-2), 3.84 – 3.76 (m, 4H, H-4 and OC$\underline{\mathrm{H_3}}$), 3.56 (s, 3H, OC$\underline{\mathrm{H_3}}$), 1.76 (s, 3H, C$\underline{\mathrm{H_3}}$), 1.34 (s, 9H, C(C$\underline{\mathrm{H_3}}$)$_3$), 1.32 (s, 9H, C(C$\underline{\mathrm{H_3}}$)$_3$).

^{13}C NMR (100 MHz, Chloroform-d) δ 152.9 (C-4´), 146.4 (C-1´), 138.9 (CqAr), 138.5 (CqAr), 138.1 (CqAr and C-2´), 135.7 (C-5´), 128.6 (C$_{\mathrm{Ar}}$), 128.4 (C$_{\mathrm{Ar}}$), 128.2 (C$_{\mathrm{Ar}}$), 128.1 (C$_{\mathrm{Ar}}$), 127.8 (C$_{\mathrm{Ar}}$), 127.1 (C$_{\mathrm{Ar}}$), 126.7 (C$_{\mathrm{Ar}}$), 118.6 (C-3´), 111.3 (C-6´), 106.0 (C-1), 98.9 (C-5), 83.6 (C-2), 80.0 (C-3), 79.3 (C-4), 75.9 (O$\underline{\mathrm{C}}$H$_2$Ph), 74.7 (O$\underline{\mathrm{C}}$H$_2$Ph), 73.7 (O$\underline{\mathrm{C}}$H$_2$Ph), 56.8 (O$\underline{\mathrm{C}}$H$_3$), 55.5 (O$\underline{\mathrm{C}}$H$_3$), 34.8 ($\underline{\mathrm{C}}$(CH$_3$)$_3$), 34.6 ($\underline{\mathrm{C}}$(CH$_3$)$_3$), 30.0 (2 C($\underline{\mathrm{C}}$H$_3$)$_3$), 20.1 ($\underline{\mathrm{C}}$H$_3$).

HRMS (ESI) m/z: calcd for $C_{43}H_{54}KO_7$ $[M+K]^+$: 721.3501; found 721.3492.

IR (film): 2953, 2909, 2867, 1504, 1454, 1396,1373, 1359, 1225, 1201, 1169, 1143, 1118, 1070, 1051, 1028, 985, 910, 890, 855, 796, 732, 696 cm^{-1}.

4-(((2S,3S,4R,5R,6S)-3,4,5-Tris(benzyloxy)-6-methoxy-2-methyltetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151bc)**



According to the general procedure, *exo*-glucal **150b** (1 equiv., 192 mg, 0.43 mmol), 1,4-naphthoquinone (4 equiv., 272.0 mg, 1.72 mmol), Na$_2$HPO$_4$ (1.1 equiv., 67.1 mg, 0.47 mmol), Fe(acac)$_3$ (0.5 equiv., 75.9 mg, 0.21 mmol), phenylsilane (4 equiv., 0.21 mL, 1.72 mmol), EtOH (8 equiv., 0.2 mL, 0.85 mmol) in THF (8 mL) were heated at 60 °C. The reaction was completed after 8 h. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc=20/1-10/1), yielding **151bc** (170 mg, 0.28 mmol, 65%, dr>98:2) as a brown oil liquid.

R_f 0.27 (Cyclohexane/EtOAc: 4/1);

$[\alpha]_D^{20}$=+37 (*c*=1.2, DCM);

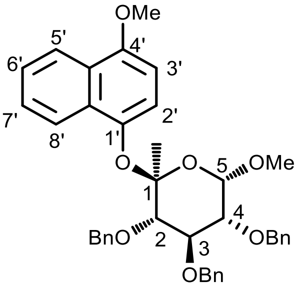
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.20 – 8.01 (m, 2H, H-8´ and H-5´), 7.53 – 7.10 (m, 18H, H_{Ar} and H-3´, H-6´, H-7´), 6.66 (d, *J* = 8.2 Hz, 1H, H-2´), 5.37 (s, 1H, OH), 5.02 (d, *J* = 11.2 Hz, 1H, O$\underline{CH_2}$Ph), 4.98 (d, *J* = 10.7 Hz, 1H, O$\underline{CH_2}$Ph), 4.92 (d, *J* = 11.2 Hz, 1H, O$\underline{CH_2}$Ph), 4.87 (m, 2H, O$\underline{CH_2}$Ph), 4.80 (d, *J* = 4.1 Hz, 1H, H-5), 4.73 (d, *J* = 12.0 Hz, 1H, O$\underline{CH_2}$Ph), 4.06 (t, *J* = 9.6 Hz, 1H, H-3), 3.94 (d, *J* = 9.6 Hz, 1H, H-2), 3.81 (dd, *J* = 9.5, 4.1 Hz, 1H, H-4), 3.44 (s, 3H, OC$\underline{H_3}$), 1.60 (s, 3H, C$\underline{H_3}$);

^{13}C NMR (125 MHz, $CDCl_3$) *δ* 147.7 (C-4´), 143.56 (C-1´), 138.8 (CqAr), 138.7 (CqAr), 138.2 (CqAr), 129.8 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 127.6 C_{Ar}), 126.2 (C-7´), 125.6 (C-6´), 125.1 (CqAr), 123.1 (C-8´), 121.6 (C-5´), 117.0 (C-3´), 108.0 (C-2´), 106.7 (C-1), 98.7 (C-5), 84.1 (C-2), 79.8 (C-4), 79.7 (C-3), 76.1 (O$\underline{C}H_2$Ph), 75.7 (O$\underline{C}H_2$Ph), 73.8 (O$\underline{C}H_2$Ph), 56.3 (O$\underline{C}H_3$), 20.2 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{38}H_{38}NaO_7$ $[M+Na]^+$: 629.2510; found 629.2547;

IR (film): 3395, 2923, 1593, 1454, 1375, 1355, 1143, 1071, 1028, 735, 697 cm^{-1}.

(2S,3S,4R,5R,6S)-3,4,5-Tris(benzyloxy)-6-methoxy-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran **(177bc)**



NaH (60% in oil, 3 equiv., 65.9 mg, 1.65 mmol) was added portionwisely to solution of **151bc** (1 equiv., 333.3 mg, 0.55 mmol) in freshly distilled THF (7 mL) at 0 °C. And then, CH_3I (4 equiv., 0.14 mL, 2.20 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 7 h, the mixture was quenched with MeOH (2 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc=30/1-18/1), yielding the product **177bc** (253.2 mg, 0.41 mmol, 74%) as a colorless oil liquid.

R_f 0.49 (Cyclohexane/EtOAc: 5/1);

$[\alpha]_D^{20}$=+35.3 (*c*=0.8, DCM);

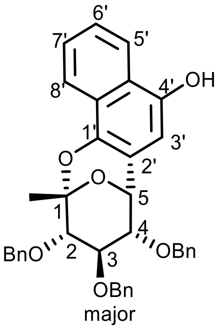
^{1}H NMR (400 MHz, Acetone-d$_6$) δ 8.21 – 8.14 (m, 2H, H-8´ and H-5´), 7.48 (d, *J* = 8.4 Hz, 1H, H-3´), 7.46 – 7.21 (m, 17H, H$_{Ar}$, H-6´, H-7´), 6.84 (d, *J* = 8.5 Hz, 1H, H-2´), 5.06 (d, *J* = 3.9 Hz, 1H, H-5), 5.01 (d, *J* = 11.3 Hz, 1H, O$\underline{CH_2}$Ph), 4.97 (d, *J* = 11.2 Hz, 1H, O$\underline{CH_2}$Ph), 4.86 (d, *J* = 11.3 Hz, 1H, O$\underline{CH_2}$Ph), 4.85 (d, *J* = 11.2 Hz, 1H, O$\underline{CH_2}$Ph), 4.77 (s, 2H, O$\underline{CH_2}$Ph), 4.01 (d, *J* = 9.3 Hz, 1H, H-3), 3.98 (s, 3H, OC$\underline{H_3}$), 3.93 (d, *J* = 9.2 Hz, 1H, H-2), 3.87 (dd, *J* = 9.1, 3.9 Hz, 1H, H-4), 3.44 (s, 3H, OC$\underline{H_3}$), 1.58 (s, 3H, C$\underline{H_3}$).

^{13}C NMR (125 MHz, Acetone-d$_6$) δ 152.3 (C-4´), 144.2 (C-1´), 140.0 (CqAr), 139.8 (CqAr), 130.4 (CqAr), 129.1 (CqAr), 129.0 (CqAr), 128.6 (C$_{Ar}$), 128.3 (C$_{Ar}$), 128.2 (C$_{Ar}$), 128.1 (C$_{Ar}$), 126.9 (C$_{Ar}$), 126.8 (C$_{Ar}$), 126.1 (C-7´ or C-6´), 123.6 (C-8´ and C-5´), 122.5 (C-7´ or C-6´), 117.8 (C-3´), 107.1 (C-1), 104.2 (C-2´), 99.2 (C-5), 84.6 (C-2), 81.0 (C-4), 80.1 (C-3), 76.0 (O$\underline{C}$H$_2$Ph), 75.8 (O$\underline{C}$H$_2$Ph), 73.2 (O$\underline{C}$H$_2$Ph), 56.4 (O$\underline{C}$H$_3$), 56.0 (O$\underline{C}$H$_3$), 20.9 ($\underline{C}$H$_3$).

HRMS (ESI) m/z: calcd for $C_{39}H_{40}NaO_7$ [M+Na]$^+$: 643.2666; found 643.2705.

IR (film): 2925, 2855, 1593, 1462, 1454, 1388, 1267, 1171, 1143, 1091, 1070, 1046, 1027, 1016, 981, 886, 768, 732, 696 cm^{-1}.

(2S,3S,4R,5S,6R)-3,4,5-Tris(benzyloxy)-2-methyl-3,4,5,6-tetrahydro-2H-2,6-epoxynaphtho[1,2-b]oxocin-8-ol **(203)**



Compound **151bc** (1 equiv., 50.3 mg, 0.083 mmol) was dissolved in the dry DCM (2.8 mL) at -60 °C under Ar. Then, $SnCl_4$ (0.1 equiv., 0.001 mL, 0.008 mmol) was added. The reaction was warmed gradually to 5 °C. After 3 h, the reaction was quenched with 7 drops saturated solution of $NaHCO_3$. The solution was dried with anhydrous Na_2SO_4, filtred. The filtrate was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/ EtOAc: 20/1-13/1), yielding the product **203** (13.5 mg, 0.024 mmol, 28%, dr=6/1) as a light-yellow oil liquid.

R$_f$ 0.38 (Cyclohexane/EtOAc: 4/1).

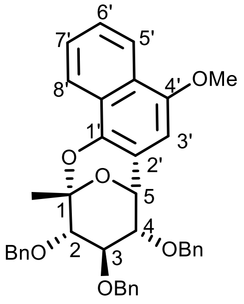
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.22 (d, *J* = 7.9 Hz, 1H, H-8´), 8.08 – 7.99 (m, 1H, H-5´), 7.58 – 7.45 (m, 2H, H-6´ and H-7´), 7.45 – 7.19 (m, 15H, H$_{Ar}$), 6.40 (s, 1H, H-3´), 4.96 (d, *J* = 11.5 Hz, 1H, O$\underline{CH_2}$Ph), 4.90 (d, *J* = 11.9 Hz, 1H, O$\underline{\mathrm{CH}_2}$Ph), 4.86 (d, *J* = 11.9 Hz, 1H, O$\underline{\mathrm{CH}_2}$Ph), 4.83 (d, *J* = 5.6 Hz, 1H, H-5), 4.77 (d, *J* = 11.5 Hz, 1H, O$\underline{\mathrm{CH}_2}$Ph), 4.73 (d, *J* = 10.8 Hz, 1H, O$\underline{\mathrm{CH}_2}$Ph), 4.62 (d, *J* = 10.8 Hz, 1H, O$\underline{\mathrm{CH}_2}$Ph), 3.99 (dd, *J* = 9.1, 4.8 Hz, 1H, H-4), 3.75 (t, *J* = 9.2 Hz, 1H, H-3), 3.65 (d, *J* = 9.2 Hz, 1H, H-2), 1.66 (s, 3H, CH3).

^{13}C NMR (100 MHz, CDCl$_3$) *δ* 144.3 (C-4´), 141.1 (C-1´), 138.7 (CqAr), 138.5 (CqAr), 138.1 (CqAr), 128.8 (C$_{\mathrm{Ar}}$), 128.5 (C$_{\mathrm{Ar}}$), 128.2 (C$_{\mathrm{Ar}}$), 128.1 (C$_{\mathrm{Ar}}$), 128.0 (C$_{\mathrm{Ar}}$), 127.9 (C$_{\mathrm{Ar}}$), 127.8 (C$_{\mathrm{Ar}}$), 127.7 (C$_{\mathrm{Ar}}$), 126.0 (C-6´ or C-7´), 125.9 (C-6´ or C-7´), 125.2 (C-2´), 124.7 (CqAr), 121.9 (C-8´), 121.6 (C-5´), 112.2 (CqAr), 107.4 (C-3´), 100.7 (C-1), 85.7 (C-2), 81.8 (C-4), 81.5 (C-3), 75.7 (O$\underline{\mathrm{C}}$H$_2$Ph), 75.3 (O$\underline{\mathrm{C}}$H$_2$Ph), 73.8 (O$\underline{\mathrm{C}}$H$_2$Ph), 70.6 (C-5), 25.2 ($\underline{\mathrm{C}}$H$_3$).

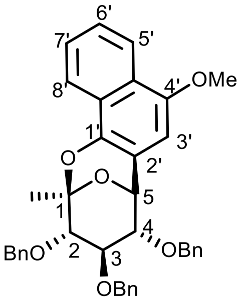
HRMS (ESI) m/z: calcd for $C_{37}H_{34}KO_6$ [M+K]$^+$: 613.1987; found 613.1957.

IR (film): 3391, 3064, 3031, 2925, 2874, 1640, 1601, 1497, 1454, 1437, 1410, 1380, 1302, 1270, 1225, 1204, 1150, 1113, 1071, 1053, 1028, 946, 910, 888, 857, 768, 736, 696 cm^{-1}.

(3S,4R,5S)-3,4,5-Tris(benzyloxy)-8-methoxy-2-methyl-3,4,5,6-tetrahydro-2H-2,6-epoxynaphtho[1,2-b]oxocine **(201)**



α



β

Compound **177bc** (1 equiv., 49.9 mg, 0.080 mmol) was dissolved in the dry DCM (2.60 mL) at -60 °C under Ar. Then, SnCl$_4$ (0.1 equiv., 0.00090 mL, 0.0080 mmol) was added. The reaction was warmed gradually to 5 °C. After 3 h, the reaction was quenched with 5 drops saturated NaHCO$_3$ solution. The solution was dried with anhydrous Na$_2$SO$_4$, filtred. The filtrate was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/DCM: 1/1-1/2), yielding the product **201** (30.9 mg, 0.052 mmol, 65%, dr=2.2:1) as a blue oil liquid.

α-isomer (major compound):

R$_f$ 0.50 (Cyclohexane/EtOAc: 5/1);

$[\alpha]_D^{20}$=+107.5 (*c*=0.7, DCM);

^{1}H NMR (400 MHz, CDCl$_3$) *δ* 8.26 – 8.15 (m, 2H, H-8´ and H-5´), 7.55 – 7.46 (m, 2H, H-6´ and H-7´), 7.46 – 7.17 (m, 15H, H$_{Ar}$), 6.41 (s, 1H, H-3´), 5.00 – 4.90 (m, 3H, OC$\underline{H_2}$Ph and H-5), 4.87 (d, *J* = 11.7 Hz, 1H, OC$\underline{H_2}$Ph), 4.77 (d, *J* = 11.5 Hz, 1H, OC$\underline{H_2}$Ph), 4.71 (d, *J* = 10.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.59 (d, *J* = 10.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.02 (dd, *J* = 8.9, 4.9 Hz, 1H, H-4), 3.84 (s, 3H, OC$\underline{H_3}$), 3.74 (t, *J* = 9.1 Hz, 1H, H-3), 3.66 (d, *J* = 9.3 Hz, 1H, H-2), 1.67 (s, 3H, C$\underline{H_3}$).

^{13}C NMR (101 MHz, CDCl$_3$) *δ* 148.5 (C-4´), 140.7 (C-1´), 138.8 (CqAr), 138.6 (CqAr), 138.4 (CqAr), 128.7 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 126.1 (CqAr and C-7´ or C-6´), 125.9 (C-7´ or C-6´), 124.7 (CqAr), 121.8 (C-5´), 121.7 (C-8´), 112.1 (C-2´), 103.1 (C-3´), 100.7 (C-1), 85.5 (C-2), 82.2 (C-4), 81.5 (C-3), 75.7 (O$\underline{C}H_2$Ph), 75.2 (O$\underline{C}H_2$Ph), 73.5 (O$\underline{C}H_2$Ph), 70.8 (C-5), 55.7 (O$\underline{C}H_3$), 25.3 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{38}H_{36}KO_6$ $[M+K]^+$: 627.2143; found 627.2151.

IR (film): 3064, 3030, 2998, 2937, 2865, 1638, 1601, 1497, 1459, 1428, 1390, 1304, 1275, 1228, 1205, 1150, 1126, 1101, 1072, 1059, 1028, 887, 855, 768, 737, 697 cm^{-1}.

β-isomer (minor compound):

R$_f$ 0.51 (Cyclohexane/EtOAc: 5/1);

$[\alpha]_D^{20}$=-139.9 (*c*=0.4, DCM);

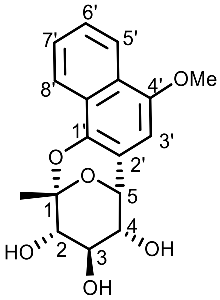
^{1}H NMR (400 MHz, CDCl$_3$) *δ* 8.20 – 8.12 (m, 1H, H-5´), 8.09 – 8.02 (m, 1H, H-8´), 7.55 – 7.45 (m, 4H, H-6´ and H-7´ and H$_{Ar}$), 7.43 – 7.18 (m, 13H, H$_{Ar}$), 6.05 (s, 1H, H-3´), 5.05 (s, 1H, H-5), 4.89 (d, *J* = 11.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.85 (s, 2H, OC$\underline{H_2}$Ph), 4.74 (d, *J* = 11.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.71 (d, *J* = 11.6 Hz, 1H, OC$\underline{H_2}$Ph), 4.56 (d, *J* = 11.5 Hz, 1H, OC$\underline{H_2}$Ph), 3.90 – 3.86 (m, 2H, H-2 and H-4), 3.83 (s, 3H, OC$\underline{H_3}$), 3.80 (dd, *J* = 10.7, 5.6 Hz, 1H, H-3), 1.84 (s, 3H, C$\underline{H_3}$).

^{13}C NMR (101 MHz, CDCl$_3$) *δ* 150.1 (C-4´), 139.3 (C-1´), 138.7 (CqAr), 138.1 (CqAr), 137.9 (CqAr), 128.7 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.4 (C$_{Ar}$), 128.3 (C$_{Ar}$), 128.1 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.6 (C$_{Ar}$), 126.6 (C-7´ or C-6´), 126.2 (C-7´ or C-6´), 125.9 (2 CqAr), 122.1 (C-5´), 121.1 (C-8´), 114.8 (C-2´), 103.3 (C-1), 100.1 (C-3´), 85.0 (C-4), 81.6 (C-2), 80.4 (C-3), 75.1 (O$\underline{C}H_2$Ph), 74.9 (C-5), 74.8 (O$\underline{C}H_2$Ph), 72.2 (O$\underline{C}H_2$Ph), 56.0 (O$\underline{C}H_3$), 22.1 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{38}H_{36}KO_6$ $[M+K]^+$: 627.2143; found 627.2151.

IR (film): 3086, 3064, 3030, 3002, 2935, 2865, 1637, 1599, 1497, 1455, 1387, 1360, 1279, 1237, 1207, 1130, 1098, 1070, 1055, 1028, 1002, 882, 821, 768, 735, 697 cm^{-1}.

(2S,3S,4R,5R,6R)-8-Methoxy-2-methyl-3,4,5,6-tetrahydro-2H-2,6-epoxynaphtho[1,2-b]oxocine-3,4,5-triol **(207)**



Under a nitrogen atmosphere, to a cold (-78 °C) solution of **201*α*** (1 equiv., 55.3 mg, 0.094 mmol) and pentamethylbenzene (15 equiv., 208.9 mg, 1.409 mmol) in anhydrous DCM (3 mL) were added BCl_3 (1M in DCM, 8 equiv., 0.75 mL, 0.75 mmol) for 10 mins and the mixture was stirred at -78 °C for 55 mins. TLC analysis indicated the starting material had been consumed at 30 mins. The reaction mixture was quenched by adding MeOH (1 mL) at -78 °C then was warmed up to room temperature. The mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography on silica gel to yield compound **207** (20.2 mg, 0.063 mmol, 68%) as a white solid.

R_f 0.48 (Cyclohexane/MeOH: 10/1);

$[\alpha]_D^{20}$=+91.8 (*c*=0.5, MeOH).

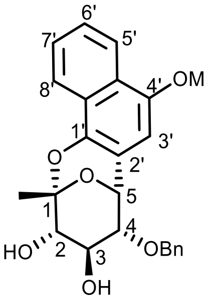
^{1}H NMR (400 MHz, Methanol-*d_4*) *δ* 8.18 – 8.09 (m, 2H, H-5′ and H-8′), 7.51 – 7.40 (m, 2H, H-6′ and H-7′), 6.62 (s, 1H, H-3′), 4.84 (d, *J* = 5.2 Hz, 1H, H-5), 3.95 (s, 3H, $OC\underline{H_3}$), 3.92 (dd, *J* = 9.3, 5.0 Hz, 1H, H-4), 3.53 (d, *J* = 9.3 Hz, 1H, H-2), 3.35 (d, *J* = 9.3 Hz, 1H, H-3), 1.70 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (100 MHz, Methanol-*d_4*) *δ* 149.5 (C-4′), 141.8 (C-1′), 127.1, 126.7 (C-6′ or C-7′), 126.5 (C-6′ or C-7′), 125.7, 122.7 (C-5′ or C-8′), 122.4 (C-5′ or C-8′), 114.0 (C-2′), 104.4 (C-3′), 102.3 (C-1), 79.9 (C-2), 74.9 (C-4), 74.5 (C-5), 74.2 (C-3), 56.1 ($O\underline{C}H_3$), 25.1 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{17}H_{18}NaO_6$ $[M+Na]^+$: 341.0996; found 341.1006.

IR (film): 3455, 2931, 1461, 1428, 1408, 1393, 1278, 1238, 1200, 1108, 1051, 1028, 884, 847, 765, 744, 699 cm^{-1}.

(2S,3S,4S,5R,6R)-5-(Benzyloxy)-8-methoxy-2-methyl-3,4,5,6-tetrahydro-2H-2,6-epoxynaphtho[1,2-b]oxocine-3,4-diol **(207’)**



Compound **207'** was obtained from the deprotection reaction of **201*α*** (see **Scheme 106**).

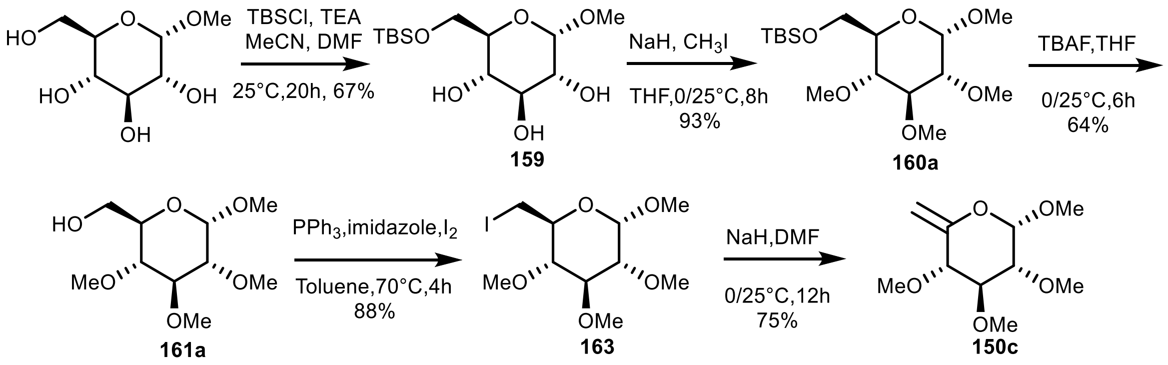
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.14 (m, 1H, H-5´), 8.15 – 8.06 (m, 1H, H-8´), 7.55 – 7.28 (m, 7H, H-6´ and H-7´, H$_{Ar}$), 6.37 (s, 1H, H-3´), 4.96 (d, J = 4.7 Hz, 1H, H-2), 4.90 (d, J = 11.7 Hz, 1H, OC$\underline{H}_2$Ph), 4.86 (d, J = 11.7 Hz, 1H, OC$\underline{H}_2$Ph), 3.86 (dd, J = 9.1, 4.7 Hz, 1H, H-3), 3.83 (s, 3H, OC$\underline{H}_3$), 3.65 (d, J = 9.1 Hz, 1H, H-5), 3.55 (t, J = 9.1 Hz, 1H, H-4), 1.77 (s, 3H, C$\underline{H}_3$).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 148.9 (C-4´), 140.1 (C-1´), 138.1 (CqAr), 128.8 (C$_{Ar}$), 128.2 (C$_{Ar}$), 127.9 (C$_{Ar}$), 126.4 (C-7´ or C-6´), 126.1 (C-7´ or C-6´ and CqAr), 124.4 (CqAr), 122.1 (C-5´), 120.9 (C-8´), 112.5 (CqAr), 102.6 (C-3´), 100.5 (C-1), 81.0 (C-3), 78.9 (C-5), 73.8 (C-4), 73.6 (O$\underline{C}$H$_2$Ph), 70.4 (C-2), 55.7 (O$\underline{C}$H$_3$), 24.6 ($\underline{C}$H$_3$).

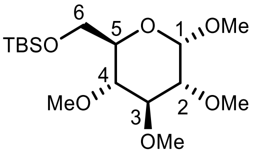
HRMS (ESI) m/z: calcd for $C_{24}H_{24}O_6$: 408.1567; found 408.1552.

IR (film): 3412, 2932, 2861, 1600, 1459, 1428, 1389, 1275, 1229, 1205, 1139, 1101, 1064, 1028, 889, 846, 768, 742, 698 cm^{-1}.

Compound **150c** was synthesized following the same synthetic sequence that the one used for its benzyl-protected analogue, compound **150b**.



Tert-butyldimethyl(((2R,3R,4S,5R,6S)-3,4,5,6-tetramethoxytetrahydro-2H-pyran-2-yl)methoxy)silane (**160a**)[248]

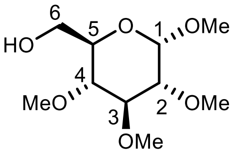


NaH (60% in oil, 6 equiv., 1.56 g, 38.98 mmol) was added portionwisely to solution of **159** (1 equiv., 2 g, 6.5 mmol) in freshly distilled THF (68 mL) at 0 °C. And then, CH_3I (7.5 equiv., 3.03 mL, 48.73 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 8 h, the mixture was diluted with EtOAc, a saturated solution of NH_4Cl was added, extracted with EtOAc, the organic phase was washed with brine, dried over anhydrous Na_2SO_4. The NMR of the crude product was good yielding the product **160a** (2.1 g, 6.04 mmol, 93%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.79 (d, J = 3.6 Hz, 1H), 3.82 – 3.77 (m, 2H), 3.63 (s, 3H), 3.55 (s, 3H), 3.51 (s, 3H), 3.49 – 3.40 (m, 2H), 3.39 (s, 3H), 3.20 – 3.13 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H).

This data is consistent with that reported in the literature.[248]

((2R,3R,4S,5R,6S)-3,4,5,6-Tetramethoxytetrahydro-2H-pyran-2-yl)methanol **(161a)**[248]

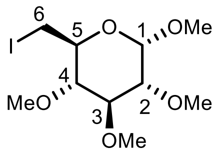


To a solution of **160a** (1 equiv., 2.1 g, 6.039 mmol) in dry THF (36 mL) was added TBAF (1M in THF, 2 equiv., 12.08 mL, 12.079 mmol). The mixture was then stirred at RT for 6 h. the reaction was diluted with ethyl acetate and washed with saturated aqueous solution of NH_4Cl and brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash column chromatography (SiO_2, DCM/MeOH=20/1) afforded **161a** (908 mg, 3.84 mmol, 64%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.80 (d, J = 3.5 Hz, 1H), 3.86 – 3.79 (m, 1H), 3.77 – 3.70 (m, 1H), 3.63 (s, 3H), 3.56 (s, 3H), 3.52 – 3.52 (m, 4H), 3.41 (s, 3H), 3.20 – 3.12 (m, 2H), 1.83 (dd, J = 7.8, 5.0 Hz, 1H).

This data is consistent with that reported in the literature.[248]

(2S,3S,4S,5R,6S)-2-(Iodomethyl)-3,4,5,6-tetramethoxytetrahydro-2H-pyran **(163)**[249]

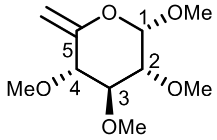


Compound **161a** (1 equiv., 908 mg, 3.84 mmol) was dissolved in toluene (30 mL) under an atmosphere of argon, PPh_3 (2.5 equiv., 2.5 g, 9.61 mmol), imidazole (4.24 equiv., 1.1 g, 16.29 mmol) and I_2 (2 equiv., 1.95 g, 7.69 mmol) were added. The reaction mixture was stirred at 70 °C for 3 h. The reaction mixture was cooled down at RT before it was quench with 10% aq $Na_2S_2O_3$ (30 mL) and subsequently stirred for 10 min, the aqueous phase was extracted with EtOAc (x3). The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column (SiO_2, Cyclohexane/ EtOAc =8:1) affording **163** (1.17 g, 3.38 mmol, 88%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.82 (d, *J* = 3.6 Hz, 1H), 3.61 (s, 3H), 3.61 (s, 3H), 3.56 – 3.48 (m, 5H), 3.45 (s, 3H), 3.39 – 3.28 (m, 2H), 3.20 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.96 (t, *J* = 8.9 Hz, 1H).

This data is consistent with that reported in the literature.[249]

(2S,3R,4S,5S)-2,3,4,5-Tetramethoxy-6-methylenetetrahydro-2H-pyran **(150c)**[250]

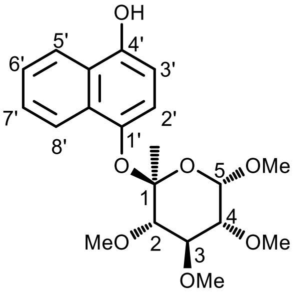


To a solution of **163** in dry DMF (18 mL) was added NaH (60% in oil, 2 equiv., 244.5 mg, 6.11 mmol) at 0 °C. The mixture was then warmed to RT for overnight. After 12 h, the reaction solution was quenched with 2 mL of MeOH, which was then washed with water, extracted with EtOAc, brine and dried over anhydrous sodium sulphate. The crude product was purified by flash column (SiO_2, Cyclohexane/ EtOAc =15:1-8:1) affording **150c** (502 mg, 2.3 mmol, 75%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.85 (d, *J* = 3.4 Hz, 1H, H-1), 4.77 (d, *J* = 1.9 Hz, 1H, $C\underline{H}_2$=C), 4.71 (dd, *J* = 2.1, 1.0 Hz, 1H, $C\underline{H}_2$=C), 3.63 (s, 3H, $OC\underline{H}_3$), 3.59 (s, 3H, $OC\underline{H}_3$), 3.56 (t, *J* = 2.1 Hz, 1H, H-4 or H-3), 3.54 (s, 3H, $OC\underline{H}_3$), 3.50 (t, *J* = 9.1 Hz, 1H, H-4 or H-3), 3.45 (s, 3H, $OC\underline{H}_3$), 3.30 (dd, *J* = 9.2, 3.4 Hz, 1H, H-2).

This data is consistent with that reported in the literature.[250]

4-(((2S,3S,4R,5R,6S)-3,4,5,6-Tetramethoxy-2-methyltetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151c)**



According to the general procedure, *exo*-glucal **150c** (1 equiv., 47.9 mg, 0.22 mmol), 1,4-naphthoquinone (3 equiv., 104.1 mg, 0.66 mmol), Na_2HPO_4 (1.1 equiv., 34.3 mg, 0.24 mmol), $Fe(acac)_3$ (0.5 equiv., 38.8 mg, 0.11 mmol) were dissolved in freshly distilled THF (4.4 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.11 mL, 0.88 mmol) was added dropwise and following EtOH (8 equiv., 0.10 mL, 1.76 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring until the reaction was basically completed for 3 h. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/ EtOAc= 16:1-2:1), yielding the product **151c** (65.7 mg, 0.17 mmol, 79%) as a light brown oil.

R_f 0.36 (Cyclohexane/ EtOAc: 1/1);

$[\alpha]_D^{20}$=+81.9 (*c*=0.4, DCM);

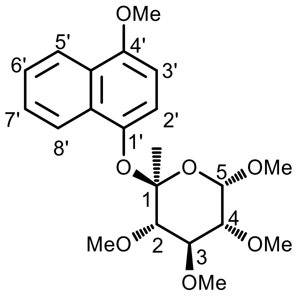
^{1}H NMR (400 MHz, MeOD) δ 8.19 – 8.10 (m, 2H, H-5´ and H-8´), 7.49 – 7.37 (m, 2H, H-6´ and H-7´), 7.29 (d, *J* = 8.2 Hz, 1H, H-2´ or H-3´), 6.73 (d, *J* = 8.3 Hz, 1H, H-2´ or H-3´), 4.99 (d, *J* = 3.4 Hz, 1H, H-5), 3.59 (s, 3H, $OC\underline{H}_3$), 3.58 (s, 3H, $OC\underline{H}_3$), 3.49 – 3.42 (m, 5H, $OC\underline{H}_3$ and H-2, H-3), 3.45 – 3.36 (m, 4H, $OC\underline{H}_3$ and H-4), 1.43 (s, 3H, $C\underline{H}_3$).

^{13}C NMR (125 MHz, MeOD) δ 150.8 (C-4´), 143.5 (C-1´), 131.1 (CqAr), 126.9 (CqAr), 126.8 (C-7´ or C-6´), 125.8 (C-7´ or C-6´), 123.6 (C-5´ or C-8´), 123.2 (C-5´ or C-8´), 118.9 (C-3´), 108.0 (C-2´), 107.3 (C-1), 98.9 (C-5), 86.5 (C-2), 82.5 (C-3 or C-4), 82.4 (C-3 or C-4), 61.7 ($O\underline{C}H_3$), 60.9 ($O\underline{C}H_3$), 59.0 ($O\underline{C}H_3$), 56.4 ($O\underline{C}H_3$), 20.8 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{20}H_{26}NaO_7$ $[M+Na]^+$: 401.1571; found 401.1555.

IR (film): 3356, 2935, 2835, 1593, 1376, 1268, 1163, 1145, 1106, 1076, 1043, 1024, 1002, 879, 769, 736 cm^{-1}.

(2S,3S,4R,5R,6S)-3,4,5,6-Tetramethoxy-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran **(177c)**



NaH (60% in oil, 3 equiv., 202.7 mg, 5.07 mmol) was added portionwisely to solution of **151c** (1 equiv., 639.3 mg, 1.69 mmol) in freshly distilled THF (21 mL) at 0 °C. And then, CH_3I (4 equiv., 0.42 mL, 6.76 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 14 h, the mixture was quenched with MeOH (2 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 8/1-4/1), yielding the product **177c** (494.5 mg, 1.26 mmol, 75%) as a light brown oil.

R_f 0.32 (Cyclohexane/ EtOAc: 2/1);

$[\alpha]_D^{20}$=+79.2 (*c*=0.7, DCM);

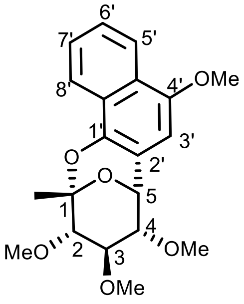
^{1}H NMR (400 MHz, MeOD) δ 8.21 – 8.12 (m, 2H, H-8´ and H-5´), 7.47 (m, 2H, H-6´ and H-7´), 7.39 (d, *J* = 8.4 Hz, 1H, H-3´), 6.79 (d, *J* = 8.4 Hz, 1H, H-2´), 5.01 (d, *J* = 3.5 Hz, 1H, H-5), 3.97 (s, 3H, $OC\underline{H_3}$), 3.59 (s, 3H, $OC\underline{H_3}$), 3.59 (s, 3H, $OC\underline{H_3}$), 3.49 (s, 3H, $OC\underline{H_3}$), 3.48-3.46 (m, 2H, H-2 and H-3), 3.45 – 3.43 (m, 1H, H-4), 3.42 (s, 3H, $OC\underline{H_3}$), 1.45 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (125 MHz, MeOD) δ 153.1 (C-4´), 144.4 (C-1´), 130.9 (CqAr), 127.4 (CqAr), 127.1 (C-7´ or C-6´), 126.4 (C-7´ or C-6´), 123.6 (C-5´ or C-8´), 122.8 (C-5´ or C-8´), 118.3 (C-3´), 107.4 (C-1), 104.2 (C-2´), 99.0 (C-5), 86.4 (C-2), 82.6 (C-3 or C-4), 82.4 (C-3 or C-4), 61.7 ($O\underline{C}H_3$), 60.9 ($O\underline{C}H_3$), 59.0 ($O\underline{C}H_3$), 56.5 ($O\underline{C}H_3$), 56.1 ($O\underline{C}H_3$), 20.8 ($\underline{C}H_3$).

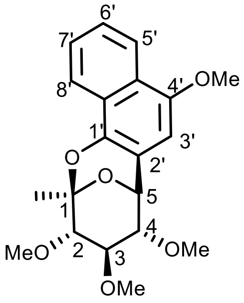
HRMS (ESI) m/z: calcd for $C_{21}H_{28}NaO_7$ $[M+Na]^+$: 415.1727; found 415.1714.

IR (film): 2935, 2836, 1594, 1463, 1388, 1267, 1236, 1166, 1155, 1108, 1093, 1079, 1044, 1018, 1007, 982, 879, 769 cm^{-1}.

(3S,4R,5S)-3,4,5,8-Tetramethoxy-2-methyl-3,4,5,6-tetrahydro-2H-2,6-epoxynaphtho[1,2-b]oxocine **(204)**



α



β

Compound **177c** (1 equiv., 42.9 mg, 0.11 mmol) was dissolved in the dry DCM (3.63 mL) at -60 °C under Ar. Then, $SnCl_4$ (1M in DCM, 0.1 equiv., 0.011 mL, 0.011 mmol) was added. The reaction was warmed gradually to 5 °C. After 5 h, the reaction was quenched with 8 drops saturated solution of $NaHCO_3$. The solution was dried with anhydrous Na_2SO_4, filtred. The filtrate was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 15/1-8/1), yielding the product **204** (22.6 mg, 0.063 mmol, 57%, dr=2.8:1) as a light brown oil liquid.

α-isomer (major compound):

R_f 0.28 (Cyclohexane/ EtOAc: 3/1);

$[\alpha]_D^{20}$=+138.5 (*c*=0.1, DCM);

^{1}H NMR (400 MHz, MeOD) *δ* 8.17 – 8.10 (m, 1H, H-5´), 8.13 – 8.05 (m, 1H, H-8´), 7.51 – 7.43 (m, 2H, H-6´ and H-7´), 6.51 (s, 1H, H-3´), 5.04 (d, *J* = 4.9 Hz, 1H, H-5), 3.94 (s, 3H, $OC\underline{H}_3$), 3.66 (s, 3H, $OC\underline{H}_3$), 3.63 (s, 3H, $OC\underline{H}_3$), 3.62 – 3.58 (m, 1H, H-4), 3.41 (s, 3H, $OC\underline{H}_3$), 3.32 (d, *J* = 2.7 Hz, 1H, H-2), 3.10 (t, *J* = 9.2 Hz, 1H, H-3), 1.69 (s, 3H, $C\underline{H}_3$).

^{13}C NMR (125 MHz, MeOD) δ 149.7 (C-4´), 141.5 (C-1´), 127.2 (CqAr), 126.9 (C-7´ or C-6´), 126.7 (C-7´ or C-6´), 125.6 (CqAr), 122.8 (C-5´), 122.2 (C-8´), 113.8 (CqAr), 103.9 (C-3´), 101.8 (C-1), 88.8 (C-2), 85.0 (C-4), 83.9 (C-3), 71.1 (C-5), 61.7 ($O\underline{C}H_3$), 61.0 ($O\underline{C}H_3$), 59.3 ($O\underline{C}H_3$), 56.1 ($O\underline{C}H_3$), 25.2 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{20}H_{24}NaO_6$ $[M+Na]^+$: 383.1465; found 383.1496.

IR (film): 2938, 2830, 1600, 1460, 1428, 1390, 1275, 1231, 1207, 1152, 1129, 1102, 1057, 1021, 887, 850, 768, 741, 697 cm^{-1}.

β-isomer (minor compound):

R_f 0.29 (Cyclohexane/ EtOAc: 3/1);

$[\alpha]_D^{20}$=-144 (*c*=0.2, DCM);

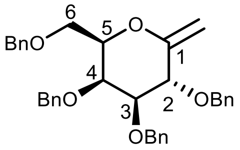
^{1}H NMR (400 MHz, MeOD) δ 8.20 – 8.13 (m, 1H, H-5´), 8.08 – 8.01 (m, 1H, H-8´), 7.56 – 7.44 (m, 2H, H-6´ and H-7´), 6.53 (s, 1H, H-3´), 5.01 (s, 1H, H-5), 3.98 (s, 3H, OC$\underline{H}_3$), 3.61 (s, 3H, OC$\underline{H}_3$), 3.50 (dd, J = 5.7, 0.6 Hz, 1H, H-4), 3.47 (s, 3H, OC$\underline{H}_3$), 3.47 – 3.39 (m, 4H, OC$\underline{H}_3$ and H-2), 3.27 (dd, J = 10.2, 5.7 Hz, 1H, H-3), 1.68 (s, 3H, C$\underline{H}_3$).

^{13}C NMR (125 MHz, MeOD) δ 151.5 (C-4´), 140.4 (C-1´), 127.6 (C-7´ or C-6´), 127.2 (CqAr), 127.1 (C-7´ or C-6´), 127.0 (CqAr), 123.1 (C-5´), 121.7 (C-8´), 116.1 (C-2´), 104.1 (C-1), 101.2 (C-3´), 88.4 (C-4), 84.6 (C-2), 82.0 (C-3), 75.0 (C-5), 60.8 (O$\underline{C}$H$_3$), 60.2 (O$\underline{C}$H$_3$), 57.5 (O$\underline{C}$H$_3$), 56.3 (O$\underline{C}$H$_3$), 21.8 ($\underline{C}$H$_3$).

HRMS (ESI) m/z: calcd for $C_{20}H_{24}NaO_6$ $[M+Na]^+$: 383.1465; found 383.1470.

IR (film): 2934, 2831, 1599, 1461, 1388, 1279, 1237, 1130, 1097, 1052, 1006, 879, 823, 805, 768 cm^{-1}.

(2R,3S,4S,5R)-3,4,5-Tris(benzyloxy)-2-((benzyloxy)methyl)-6-methylenetetrahydro-2H-pyran **(150d)**

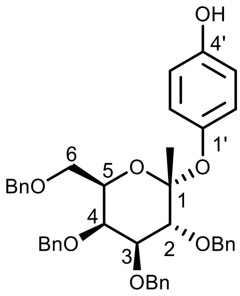


In a 50 mL round flask, (3*R*,4*S*,5*S*,6*R*)-3,4,5-tris(benzyloxy)-6-[(benzyloxy)methyl]oxan-2-one (1 equiv., 818.4 mg, 1.52 mmol) and 2-methanesulfonyl-1,3-benzothiazole (1.2 equiv., 388.9 mg, 1.82 mmol) were dissolved in freshly distilled THF (8 mL) under argon. The solution was cooled at -78 °C. Then, LiHMDS (1M in THF, 2.37 equiv., 3.6 mL, 3.6 mmol) was added dropwise over 8 min. The mixture was stirred for 3.5 h, and was quenched by addition of AcOH (3.67 equiv., 0.32 mL, 5.58 mmol). The mixture was extracted with EtOAc, the organic layers were washed with brine, dried over Na_2SO_4 and evaporated and then dried under vacuum pump. The yellow oil obtained was dissolved in dry THF (24 mL) under Ar, and DBU (1.95 equiv., 0.44 mL, 2.96 mmol) was added slowly at RT. After about 15.5 h, the mixture was concentrated by rotary evaporation and purified by flash chromatography (SiO_2, Cyclohexane/EtOAc =40:1) to afford **150d** as a light-yellow solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.26 (m, 20H, H$_{Ar}$), 4.92 (d, J = 11.5 Hz, 1H, OC$\underline{H}_2$Ph), 4.81 – 4.69 (m, 6H, OC$\underline{H}_2$Ph and C$\underline{H}_2$=CH), 4.60 (d, J = 11.5 Hz, 1H, OC$\underline{H}_2$Ph), 4.52 (d, J = 11.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.45 (d, J = 11.8 Hz, 1H, OC$\underline{H}_2$Ph), 4.37 (dt, J = 9.0, 1.7 Hz, 1H, H-2), 4.06 (t, J = 2.4 Hz, 1H, H-4), 3.82 (td, J = 6.3, 1.9 Hz, 1H, H-5), 3.74 – 3.58 (m, 3H, H-6 and H-3).

This data is consistent with the reported literature.[251]

4-(((3R,4S,5S,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151da)**



According to the general procedure, *exo*-glucal **150d** (1 equiv., 55.3 mg, 0.103 mmol), *p*-benzoquinone (4 equiv., 44.6 mg, 0.41 mmol), Na_2HPO_4 (1.1 equiv., 16.1 mg, 0.11 mmol), $Fe(acac)_3$ (0.5 equiv., 18.2 mg, 0.052 mmol), phenylsilane (4 equiv., 0.051 mL, 0.41 mmol), EtOH (8 equiv., 0, 0.048 mL, 0.82 mmol) in THF (2 ml) were heated at 60 °C. After 4 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (200 µL) was added dropwise during 1.5 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 20/1-9/1), yielding **151da** (42.6 mg, 0.066 mmol, 64%, dr=10.5:1) as a colourless oil liquid. Analytical samples of α-isomer (major compound) can be obtained after a careful purification.

α-isomer (major compound):

R$_f$ 0.29 (Cyclohexane/EtOAc: 4/1);

[α]$_D^{20}$=+75 (*c*=0.6, CH_2Cl_2);

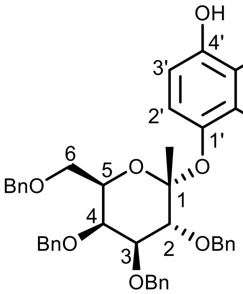
^{1}**H NMR (500 MHz, CDCl$_3$)** *δ* 7.45 – 7.27 (m, 20H, H_{Ar}), 7.01 (d, *J* = 8.7 Hz, 2H, H-2'), 6.62 (d, *J* = 8.8 Hz, 2H, H-3'), 5.05 (d, *J* = 11.6 Hz, 1H, $OC\underline{H_2}Ph$), 5.01 (d, *J* = 11.7 Hz, 1H, $OC\underline{H_2}Ph$), 4.94 (s, 1H, $O\underline{H}$), 4.84 – 4.73 (m, 3H, $OC\underline{H_2}Ph$), 4.66 (d, *J* = 11.5 Hz, 1H, $OC\underline{H_2}Ph$), 4.57 (d, *J* = 11.7 Hz, 1H, $OC\underline{H_2}Ph$), 4.48 (d, *J* = 11.7 Hz, 1H, $OC\underline{H_2}Ph$), 4.30 (t, *J* = 6.2 Hz, 1H, H-5), 4.19 (dd, *J* = 10.0, 2.8 Hz, 1H, H-3), 4.10 – 4.04 (m, 1H, H-4), 3.97 (d, *J* = 10.0 Hz, 1H, H-2), 3.71 (dd, *J* = 9.6, 6.5 Hz, 1H, H-6a), 3.61 (dd, *J* = 9.7, 5.9 Hz, 1H, H-6b), 1.25 (s, 3H, $C\underline{H_3}$);

^{13}**C NMR (125 MHz, CDCl$_3$)** *δ* 151.7 (C-4´or C-1´), 148.0 (C-4´or C-1´), 138.9 (CqAr), 138.8 (CqAr), 138.7 (CqAr), 138.2 (CqAr), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 123.4 (2 C-2´), 115.7 (2 C-3´), 103.9 (C-1), 80.7 (C-3), 80.5 (C-2), 75.7 ($O\underline{C}H_2Ph$), 75.1 ($O\underline{C}H_2Ph$), 74.7 ($O\underline{C}H_2Ph$), 73.6 ($O\underline{C}H_2Ph$), 72.9 ($O\underline{C}H_2Ph$), 71.0 (C-5), 69.8 (C-6), 21.6 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{41}H_{42}NaO_7$ $[M+Na]^+$: 669.2823; found 669.2809;

IR (film): 3371, 2920, 1507, 1454, 1208, 1088, 1061, 909, 730, 695 cm^{-1}.

4-(((3R,4S,5S,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151db)**



According to the general procedure, *exo*-glucal **150d** (1 equiv., 52.8 mg, 0.098 mmol), 1,4-naphthoquinone (4 equiv., 62.2 mg, 0.39 mmol), Na_2HPO_4 (1.1 equiv., 15.4 mg, 0.108 mmol), $Fe(acac)_3$ (0.5 equiv., 17.4 mg, 0.049 mmol), phenylsilane (4 equiv., 0.049 mL, 0.39 mmol), EtOH (8 equiv., 0.046 mL, 0.79 mmol) in THF (2 mL) were heated at 60 °C. The reaction was completed after 2.5 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 20/1-15/1), yielding **151db** (38 mg, 0.055 mmol, 55%, dr>98:2) as a colourless oil liquid.

R$_f$ 0.45 (Cyclohexane/EtOAc: 4/1).

$[\alpha]_D^{20}$ =+94 (*c*=0.4, CH_2Cl_2);

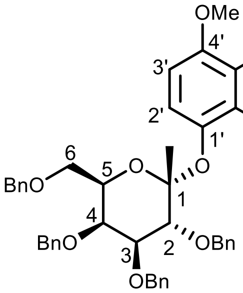
^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (dt, *J* = 8.5, 0.9 Hz, 1H, H-8´), 8.12 (dt, *J* = 8.4, 0.9 Hz, 1H, H-5´), 7.45 – 7.25 (m, 21H, H_{Ar} and H-6´), 7.25 – 7.21 (m, 2H, H-7´and H-3'), 6.59 (d, *J* = 8.1 Hz, 1H, H-2´), 5.03 (d, *J* = 10.7 Hz, 1H, $OC\underline{H_2}Ph$), 4.86 – 4.80 (m, 3H, $OC\underline{H_2}Ph$), 4.72 (d, *J* = 10.7 Hz, 1H, $OC\underline{H_2}Ph$), 4.58 – 4.51 (m, 2H, $OC\underline{H_2}Ph$), 4.46 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.40 (ddd, *J* = 7.6, 4.3, 1.3 Hz, 1H, H-5), 4.30 (dd, *J* = 10.0, 2.9 Hz, 1H, H-3), 3.98 (dd, *J* = 2.9, 1.2 Hz, 1H, H-4), 3.94 (d, *J* = 10.1 Hz, 1H, H-2), 3.69 (dd, *J* = 9.8, 7.7 Hz, 1H, H-6a), 3.45 (dd, *J* = 9.9, 4.3 Hz, 1H, H-6b), 1.21 (s, 3H, $C\underline{H_3}$);

^{13}C NMR (125 MHz, CD_3OD) δ 150.7 (C-4´), 143.8 (C-1´), 140.1 (2 CqAr), 140.0 (CqAr), 139.8 (CqAr), 131.7 (CqAr), 129.4 (C_{Ar}), 129.3 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 126.8 (CqAr), 126.7 (C-7´), 125.8 (C-6´), 124.5 (C-8´), 123.0 (C-5´), 119.1 (C-3´), 108.3 (C-2´), 105.5 (C-1), 82.6 (C-2), 81.8 (C-3), 77.3 ($O\underline{C}H_2Ph$), 77.2 (C-4), 76.1 ($O\underline{C}H_2Ph$), 74.5 ($O\underline{C}H_2Ph$), 73.9 ($O\underline{C}H_2Ph$), 72.5 (C-5), 71.6 (C-6), 21.1 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd $C_{45}H_{44}NaO_7$ $[M+Na]^+$: 719.2979; found 719.2949;

IR (film): 3368, 2918, 2866, 1593, 1454, 1379, 1216, 1094, 1060, 1027, 1010, 734, 696 cm^{-1}.

(2R,3R,4S,5S,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran **(177db)**



NaH (60% in oil, 3 equiv., 72.1 mg, 1.80 mmol) was added portionwisely to a solution of **151db** (1 equiv., 418.9 mg, 0.60 mmol) in freshly distilled THF (7.40 mL) at 0 °C. And then, CH_3I (4 equiv., 0.15 mL, 2.41 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 6 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 30/1-25/1), yielding the product **177db** (259.1 mg, 0.36 mmol, 61%) as an oil liquid.

R$_f$ 0.52 (Cyclohexane/EtOAc: 5/1);

$[\alpha]_D^{20}$=+141 (*c*=0.3, DCM);

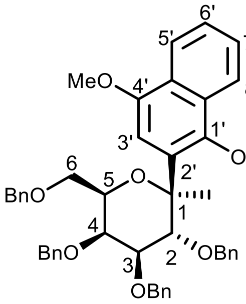
^{1}H NMR (400 MHz, Acetone-*d$_6$*) δ 8.54 (ddd, *J* = 8.4, 1.3, 0.7 Hz, 1H, H-8'), 8.16 (dt, *J* = 8.4, 0.9 Hz, 1H, H-5'), 7.53 – 7.26 (m, 23H, H_{Ar}, H-3', H-6' and H-7'), 6.58 (d, *J* = 8.4 Hz, 1H, H-2'), 5.14 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 5.05 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.95 (d, *J* = 11.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.87 (d, *J* = 11.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.81 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.70 – 4.63 (m, 2H, $OC\underline{H_2}Ph$), 4.61 (d, *J* = 11.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.48 (ddd, *J* = 7.4, 4.7, 1.3 Hz, 1H, H-5), 4.38 (dd, *J* = 10.0, 2.9 Hz, 1H, H-3), 4.25 (dd, *J* = 3.0, 1.3 Hz, 1H, H-4), 4.05 (d, *J* = 10.0 Hz, 1H, H-2), 3.92 (s, 3H, $OC\underline{H_3}$), 3.90 – 3.81 (m, 1H, H-6), 3.75 (dd, *J* = 9.8, 4.6 Hz, 1H, H-6), 1.26 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (100 MHz, Acetone-*d$_6$*) δ 152.3 (C-4´), 144.4 (C-1´), 140.2 (CqAr), 140.1 (CqAr), 140.0 (CqAr), 139.8 (CqAr), 131.1 (CqAr), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 126.8 (CqAr), 126.7 (C-7´), 126.2 (C-6´), 124.3 (C-8´), 122.3 (C-5´), 117.9 (C-3´), 105.1 (C-1), 104.3 (C-2´), 82.2 (C-2), 81.5 (C-3), 76.7 (C-4), 76.6 ($O\underline{C}H_2Ph$), 75.4 ($O\underline{C}H_2Ph$), 73.9 ($O\underline{C}H_2Ph$), 73.1 ($O\underline{C}H_2Ph$), 72.3 (C-5), 71.2 (C-6), 55.9 ($O\underline{C}H_3$), 21.1 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{46}H_{46}KO_7$ $[M+K]^+$: 749.2875; found 749.2835.

IR (film): 3064, 3030, 3004, 2916, 2862, 1592, 1462, 1454, 1389, 1362, 1269, 1238, 1217, 1189, 1144, 1090, 1051, 1021, 981, 965, 933, 846, 824, 771, 733, 695 cm^{-1}.

4-Methoxy-2-((2S,3R,4S,5S,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)naphthalen-1-ol **(184)**



To a solution of **177db** (1 equiv., 49.3 mg, 0.069 mmol) in dry DCM (2.3 mL) was dropwise added the solution of $BF_3 OEt_2$ (0.35 equiv., 0.0030 mL, 0.024 mmol) in the dry DCM at -60 °C under Ar atmosphere. The temperature gradually rised to 5 °C for 3 h. The reaction was quenched using water (5 drops). The solution was dried with Na_2SO_4, filtred and concentrated. The solvent was removed under reduced pressure, yielding the product **184** (44.1 mg, 0.062 mmol, 89%) as a brown oil.

R_f 0.35 (Cyclohexane/ EtOAc: 5/1);

$[\alpha]_D^{20}$=-59.7 (*c*=0.3, DCM);

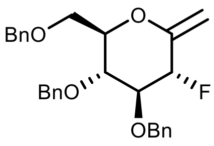
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H, O$\underline{H}$), 8.34 – 8.27 (m, 1H, H-8'), 8.17 – 8.10 (m, 1H, H-5'), 7.51 – 7.46 (m, 2H, H-6' and H-7'), 7.46 – 7.24 (m, 16H, H_{Ar} and H-2'), 7.18 – 7.11 (m, 3H, H_{Ar}), 7.05 – 6.96 (m, 2H, H_{Ar}), 6.72 (s, 1H, H-3'), 5.16 (d, J = 11.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.81 – 4.73 (m, 3H, OC$\underline{H_2}$Ph), 4.55 (d, J = 9.9 Hz, 1H, H-2), 4.53 (d, J = 10.7 Hz, 1H, OC$\underline{H_2}$Ph), 4.46 (d, J = 11.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.41 (d, J = 11.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.16 (d, J = 2.5 Hz, 1H, H-4), 4.07 (dd, J = 7.6, 5.3 Hz, 1H, H-5), 3.88 (d, J = 10.7 Hz, 1H, OC$\underline{H_2}$Ph), 3.84 (s, 3H, OC$\underline{H_3}$), 3.78 (dd, J = 9.9, 2.4 Hz, 1H, H-3), 3.71 (dd, J = 9.1, 7.6 Hz, 1H, H-6), 3.59 (dd, J = 9.1, 5.2 Hz, 1H, H-6), 1.79 (s, 3H, C$\underline{H_3}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0 (C-4´), 145.6 (C-1´), 138.61 (CqAr), 138.6 (CqAr), 138.4 (CqAr), 137.9 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 127.7 (C_{Ar}), 127.5 (C_{Ar}), 127.4 (C_{Ar}), 126.6 (CqAr), 126.1 (CqAr), 125.9 (C-6´ or C-7´), 125.6 (C-6´ or C-7´), 123.0 (C-8´), 121.4 (C-5´), 120.3 (C-2´), 103.9 (C-3´), 82.5 (C-1), 81.2 (C-3), 80.1 (C-2), 76.0 (O$\underline{C}H_2$Ph), 74.7 (O$\underline{C}H_2$Ph), 74.5 (C-4), 73.8 (O$\underline{C}H_2$Ph), 72.8 (O$\underline{C}H_2$Ph), 71.7 (C-5), 68.8 (C-6), 55.9 (O$\underline{C}H_3$), 15.9 ($\underline{C}H_3$).

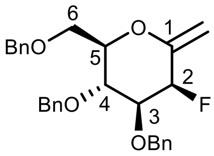
HRMS (ESI) m/z: calcd for $C_{46}H_{46}KO_7$ $[M+K]^+$: 749.2875; found 749.2888.

IR (film): 3381, 2921, 2867, 1454, 1395, 1360, 1344, 1207, 1160, 1093, 1060, 1027, 987, 768, 734, 696 cm^{-1}.

(2R,3R,4S,5R)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-fluoro-6-methylenetetrahydro-2H-pyran **(150i)** *and (2R,3R,4S,5S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-fluoro-6-methylenetetrahydro-2H-pyran* **(150j)**



150i



150j

To a solution of (4*S*,5*R*,6*R*)-4,5-bis(benzyloxy)-6-[(benzyloxy)methyl]-3-fluorooxan-2-one (1 equiv., 229 mg, 0.508 mmol) in dry toluene (6 mL) was added Petasis Reagent (1.3M in toluene, 4 equiv., 1.56 mL, 2.033 mmol) at RT under Ar. The mixture was stirred at 70 °C in the dark overnight. After completion, the solvent was removed in vacuo, and the residue was purified by column chromatography (SiO_2, Cyclohexane/EtOAc =30:1-21:1) to obtain **150i** (58.7 mg, 0.13 mmol, 26%) and **150j** (34.2 mg, 0.076 mmol, 15%).[184]

Compound **150i**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.25 (m, 13H), 7.20 – 7.11 (m, 2H), 4.94 (ddt, *J* = 50.2, 8.1, 1.9 Hz, 1H), 4.92 (dd, *J* = 11.3, 1.0 Hz, 1H), 4.85 – 4.79 (m, 2H), 4.76 (d, *J* = 11.2 Hz, 1H), 4.72 (dt, *J* = 3.2, 1.6 Hz, 1H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.56 – 4.50 (m, 2H), 3.84 – 3.71 (m, 4H), 3.58 (ddd, *J* = 9.6, 3.3, 2.3 Hz, 1H).

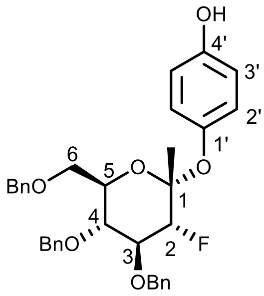
This data is consistent with the reported literature.[184]

Compound **150j**

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.25 (m, 13H), 7.22 – 7.15 (m, 2H), 5.05 (dd, *J* = 50.6, 2.6 Hz, 1H), 4.87 – 4.82 (m, 2H), 4.79 (d, *J* = 11.8 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 4.60 (dd, *J* = 4.6, 1.2 Hz, 1H), 4.57 – 4.52 (m, 2H), 4.07 (td, *J* = 9.0, 1.5 Hz, 1H), 3.80 – 3.67 (m, 3H), 3.67 – 3.62 (m, 1H).

This data is consistent with the reported literature.[184]

4-(((2R,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-3-fluoro-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151ia)**



According to the general procedure, *exo*-glucal **150i** (1 equiv., 45.5 mg, 0.101 mmol), *p*-benzoquinone (4 equiv., 43.9 mg, 0.406 mmol), Na_2HPO_4 (1.1 equiv., 15.8 mg, 0.11 mmol), Fe(acac)$_3$ (0.5 equiv., 17.9 mg, 0.0507 mmol), phenylsilane (4 equiv., 0.0505 mL, 0.406 mmol), EtOH (8 equiv., 0.047 mL, 0.81 mmol) in THF (2 mL) were heated at 60 °C. After 5 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (400 μL) was added dropwise during 2 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 15/1-9/1), yielding **151ia** (40.2 mg, 0.072 mmol, 71%, dr=1:1) as a colorless oil liquid.

R_f 0.40 (Cyclohexane/EtOAc: 3/1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 26H, H_{Ar}), 7.20 (m, 4H, H_{Ar}), 7.11-7.05 (m, 2H, H-2’, β-isomer), 7.04 – 6.98 (m, 2H, H-2’ α-isomer), 6.66 – 6.62 (m, 4H, H-3', α and β-isomers), 5.04 (s, 2H, O$\underline{\mathrm{H}}$, α and β-isomers), 4.97 (d, J = 11 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.94 – 4.87 (m, 2H, OC$\underline{\mathrm{H}_2}$Ph), 4.84 (d, J = 11 Hz, OC$\underline{\mathrm{H}_2}$Ph), 4.81 (d, J = 11 Hz, OC$\underline{\mathrm{H}_2}$Ph), 4.76 (d, J = 11 Hz, OC$\underline{\mathrm{H}_2}$Ph), 4.65 – 4.52 (m, 6H, OC$\underline{\mathrm{H}_2}$Ph), 4.53 (dd, J = 50.0, 9.2 Hz, 1H, H-2), 4.34 (dd, J = 50.0, 9.2 Hz, 1H, H-2), 4.33 – 4.25 (m, 1H, H-3), 4.18 (ddd, J = 10.1, 5.0, 2.1 Hz, 1H, H-5, α-isomer), 3.92-3.82 (m, 1H, H-3), 3.80 – 3.72 (m, 4H, H-6, α and β-isomers), 3.71 – 3.60 (m, 3H, H-4, β-H-5), 1.51 (d, 3H, J = 2.7 Hz, C$\underline{\mathrm{H}_3}$, β-isomer), 1.39 (s, 3H, J = 1.3 Hz, C$\underline{\mathrm{H}_3}$);

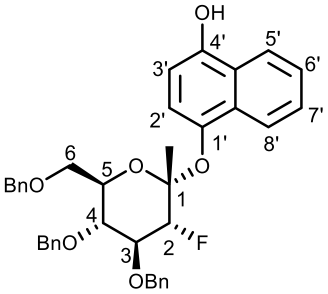
^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4 (C-4´or C-1´), 151.9 (C-4´or C-1´), 147.5 (C-4´or C-1´), 146.3 (C-4´or C-1´), 138.6 (CqAr), 138.3 (CqAr), 138.2 (CqAr), 138.15 (CqAr), 138.1 (CqAr), 138.0 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 124.6 (2 C-2´, α-isomer), 122.6 (2 C-2´, α-isomer), 115.9 (2 C-3´), 115.7 (2 C-3´), 102.4 ($J_{C,F}$ = 21.2 Hz, C-1), 101.3 ($J_{C,F}$ = 18.8 Hz, C-1), 95.1 ($J_{C,F}$ = 196.0 Hz, C-2), 92.7 ($J_{C,F}$ = 191.3 Hz, C-2), 82.6 ($J_{C,F}$ = 16.4 Hz, C-3), 81.2 ($J_{C,F}$ = 16.3 Hz, C-3), 77.6 ($J_{C,F}$ = 8.3 Hz, C-4), 77.2 ($J_{C,F}$ = 8.0 Hz, C-4), 75.4 (O$\underline{\mathrm{C}}$H$_2$Ph), 75.3 (O$\underline{\mathrm{C}}$H$_2$Ph), 75.1 (O$\underline{\mathrm{C}}$H$_2$Ph), 73.7 (C-5, β-isomer), 73.6 (O$\underline{\mathrm{C}}$H$_2$Ph), 73.5 (O$\underline{\mathrm{C}}$H$_2$Ph), 71.9 (C-5, α-isomer), 69.2 (C-6), 69.1 (C-6), 20.6 ($\underline{\mathrm{C}}$H$_3$), 17.4 ($\underline{\mathrm{C}}$H$_3$);

^{19}F NMR (376 MHz, $CDCl_3$) δ -194.8; -196.6;

HRMS (ESI) m/z: calcd for $C_{34}H_{35}KFO_6$ $[M+K]^+$: 597.2049; found 597.2036;

IR (film): 3382, 2923, 2865, 1506, 1454, 1366, 1207, 1122, 1066, 1027, 735, 697 cm^{-1}.

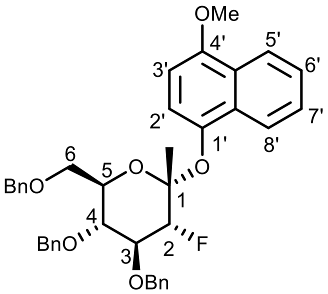
4-(((2R,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-3-fluoro-2-methyltetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151ib)**



Compound **150i** (1 equiv., 142.0 mg, 0.32 mmol), 1,4-naphthoquinone (2.5 equiv., 125.2 mg, 0.79 mmol), Na_2HPO_4 (1.1 equiv., 49.4 mg, 0.36 mmol), $Fe(acac)_3$ (0.50 equiv., 55.9 mg, 0.16 mmol) were dissolved in freshly distilled THF (6.40 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.16 mL, 1.27 mmol) was added dropwise and following EtOH (8 equiv., 0.15 mL, 2.53 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring until the reaction was basically completed for 2 h. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 15/1-8/1), yielding the product **150ib** (38.4 mg, 0.063 mmol, 20%, dr=2.5/1) as a solid.

^{1}H NMR (500 MHz, Acetone-*d*$_6$) δ 8.85 (s, 1H), 8.28 – 8.25 (m, 1H), 8.23 – 8.20 (m, 1H), 7.56 – 7.24 (m, 29H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.02 (d, *J* = 11.2 Hz, 1H), 4.94 (d, *J* = 11.5 Hz, 2H), 4.72 – 4.57 (m, 6H), 4.38 (dt, *J* = 12.5, 9.0 Hz, 1H), 4.32 (ddd, *J* = 10.2, 6.1, 1.7 Hz, 1H), 3.97 – 3.93 (m, 1H), 3.85 – 3.79 (m, 2H), 3.75 – 3.68 (m, 2H), 1.35 (d, *J* = 1.2 Hz, 3H).

(2R,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-3-fluoro-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran **(177ib)**

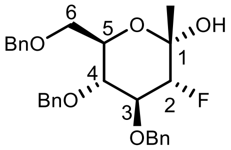


NaH (60% in oil, 3 equiv., 8.7 mg, 0.22 mmol) was added portionwisely to a solution of **151ib** (1 equiv., 44.0 mg, 0.072 mmol) in freshly distilled THF (1.00 mL) at 0 °C. And then, CH_3I (4 equiv., 0.018 mL, 0.29 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 7 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/DCM: 1/1-1/4), yielding the product **177ib** (25.5 mg, 0.041 mmol, 57%, dr=1.7/1) as a colorless oil.

Major compound:

^{1}H NMR (500 MHz, Acetone-*d*$_6$) δ 8.29 – 8.26 (m, 1H), 8.21 – 8.18 (m, 1H), 7.62 – 7.21 (m, 18H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.02 (d, *J* = 11.2 Hz, 1H), 4.94 (d, *J* = 11.4 Hz, 1H), 4.89 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 10.8 Hz, 1H), 4.67 – 4.63 (m, 2H), 4.62 – 4.56 (m, 1H), 4.50 (d, *J* = 9.2 Hz, 1H), 4.42 – 4.34 (m, 1H), 4.31 (ddd, *J* = 10.2, 6.3, 1.8 Hz, 1H), 3.98 – 3.96 (m, 2H), 3.96 (s, 3H), 3.85 – 3.79 (m, 2H), 3.77 – 3.68 (m, 2H), 1.37 (d, *J* = 1.2 Hz, 3H).

(2S,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-3-fluoro-2-methyltetrahydro-2H-pyran-2-ol **(178c)**

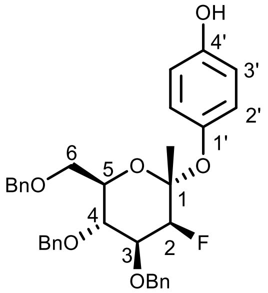


Compound **178c** were obtained as a byproduct in Fries rearrangement (see **Scheme 97**).

R$_f$ 0.15 (Cyclohexane/EtOAc: 5/1);

^{1}H NMR (400 MHz, Acetone-*d*$_6$) δ 7.32 – 7.12 (m, 15H), 4.77 (d, *J* = 11.0 Hz, 2H, $OC\underline{H_2}Ph$), 4.68 (d, *J* = 11.4 Hz, 1H, $OC\underline{H_2}Ph$), 4.52 (d, *J* = 11.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.48 (d, *J* = 12.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.42 (d, *J* = 12.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.11 (ddd, *J* = 50.2, 9.1, 1.2 Hz, 1H, H-2), 3.98 – 3.87 (m, 2H, H-5 and H-3), 3.65 (dd, *J* = 10.8, 4.4 Hz, 1H, H-6), 3.57 (dd, *J* = 10.9, 1.9 Hz, 1H, H-6), 3.50 (dd, *J* = 9.9, 9.0 Hz, 1H, H-4), 1.39 (d, *J* = 1.2 Hz, 3H, $C\underline{H_3}$).

4-(((2R,3S,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-3-fluoro-2-methyltetrahydro-2H-pyran-2-yl)oxy)phenol **(151j)**



According to the general procedure, *exo*-glucal **150j** (1 equiv., 32 mg, 0.071 mmol), *p*-benzoquinone (4 equiv., 30.9 mg, 0.29 mmol), Na_2HPO_4 (1.1 equiv., 11.1 mg, 0.078 mmol), Fe(acac)$_3$ (0.5 equiv., 12.6 mg, 0.036 mmol), phenylsilane (4 equiv., 0.035 mL, 0.29 mmol), EtOH (8 equiv., 0.033 mL, 0.57 mmol) in THF (2 mL) were heated at 60 °C. After 5 mins, *p*-benzoquinone (1.6 equiv.) dissolved in THF (180 μL) was added dropwise. The reaction was completed after 1 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 10/1-8/1), yielding **151j** (24.3 mg, 0.043 mmol, 61%, dr>98:2) as a colourless oil liquid.

R$_f$ 0.43 (Cyclohexane/EtOAc: 3/1);

[α]$_D^{20}$=+96 (*c*=1.0, $CHCl_3$).

^{1}**H NMR (400 MHz, CDCl$_3$)** δ 7.47 – 7.27 (m, 13H, H$_{Ar}$), 7.22 (dd, *J* = 7.4, 2.1 Hz, 2H, H$_{Ar}$), 7.00 – 6.92 (m, 2H, H-2'), 6.68 – 6.60 (m, 2H, H-3'), 5.08 (d, *J* = 10.5 Hz, 1H, OH), 4.92 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.82 (d, *J* = 11.6 Hz, 1H, $OC\underline{H_2}Ph$), 4.77 (d, *J* = 11.6 Hz, 1H, $OC\underline{H_2}Ph$) 4.69 (dd, *J* = 50.5, 2.4 Hz, 1H, H-2), 4.65 (d, *J* = 12.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.57 (d, *J* = 12.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.57 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.19 (ddd, *J* = 29.6, 9.4, 2.4, 1H, H-3), 4.13 (ddd, *J* = 10.1, 5.5, 2.1 Hz, 1H, H-5), 3.89 (t, *J* = 9.7 Hz, 1H, H-4), 3.83 (dd, *J* = 10.8, 2.1 Hz, 1H, H-6a), 3.77 (dd, *J* = 10.8, 5.8 Hz, 1H, H-6b), 1.38 (d, *J* = 2.5 Hz, 1H, $C\underline{H_3}$);

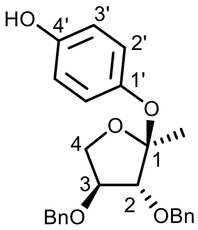
^{13}**C NMR (125 MHz, CDCl$_3$)** δ 151.9(C-4´), 147.0 (C-1´), 138.4 (CqAr), 138.3 (CqAr), 138.1 (CqAr), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.1 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.7 (C$_{Ar}$), 122.4 (2 C-2´), 116.1 (2 C-3´), 102.2 ($J_{C,F}$ = 23.3 Hz, C-1), 89.7 ($J_{C,F}$ = 180.6 Hz, C-2), 79.1 ($J_{C,F}$ = 17.1 Hz C-3), 75.3 ($O\underline{C}H_2Ph$), 74.4 (C-4), 73.5 ($O\underline{C}H_2Ph$), 72.9 (C-5), 72.5 ($O\underline{C}H_2Ph$), 69.5 (C-6), 20.3 ($J_{C,F}$ = 3.3 Hz, $\underline{C}H_3$),

^{19}**F NMR (376 MHz, CDCl$_3$)** δ -203.0;

HRMS (ESI) m/z: calcd for $C_{34}H_{35}NaFO_6$ $[M+Na]^+$: 581.2310; found 581.2282;

IR (film): 3381, 2923, 2870, 1508, 1454, 1368, 1206, 1083, 902, 840, 735, 698 cm^{-1}.

4-(((2S,3R,4S)-3,4-Bis(benzyloxy)-2-methyltetrahydrofuran-2-yl)oxy)phenol **(151ka)**



According to the general procedure, *exo*-glycal **150k** (1 equiv., 57 mg, 0.19 mmol), *p*-benzoquinone (4 equiv., 83.2 mg, 0.77 mmol), Na_2HPO_4 (1.1 equiv., 30.0 mg, 0.21 mmol), $Fe(acac)_3$ (0.5 equiv., 34 mg, 0.096 mmol), phenylsilane (4 equiv., 0.096 mL, 0.77 mmol), EtOH (8 equiv., 0.09 mL, 1.54 mmol) in THF (4 mL) were heated at 60 °C. After 5 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (400 μL) was added dropwise during 2 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 15/1-8/1), yielding **151ka** (34.4 mg, 0.085 mmol, 44%, dr=6:1) as a white solid.

Major isomer:

R_f 0.24 (Cyclohexane/EtOAc: 4/1);

$[\alpha]_D^{20}$=-88 (*c*=1.0, $CHCl_3$);

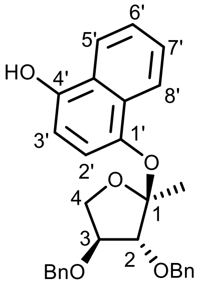
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 10H, H_{Ar}), 7.00 – 6.94 (m, 2H, H-2'), 6.74 – 6.66 (m, 2H, H-3'), 4.79 (s, 1H, O$\underline{H}$), 4.67 (d, J = 11.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.64 (d, J = 11.8 Hz, 1H, OC$\underline{H}_2$Ph), 4.60 (d, J = 12.1 Hz, 1H, OC$\underline{H}_2$Ph), 4.53 (d, J = 12.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.21 (m, 3H, H-2, H-3 H-4a), 3.96 (dd, J = 8.3, 6.0 Hz 1H, H-4b), 1.44 (s, 3H, C$\underline{H}_3$);

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8 (C-4´), 147.6 (C-1´), 138.0 (CqAr), 137.9 (CqAr), 128.6 (C_{Ar}), 128.0 (C_{Ar}), 127.92 (C_{Ar}), 127.9 (C_{Ar}), 123.7 (2 C-2´), 115.7 (2 C-3´), 111.3 (C-1), 89.1 (C-2), 83.0 (C-3), 72.42 (O$\underline{C}$H$_2$Ph), 72.4 (O$\underline{C}$H$_2$Ph), 69.7 (C-4), 19.4 ($\underline{C}$H$_3$);

HRMS (ESI) m/z: calcd for $C_{25}H_{26}NaO_5$ $[M+Na]^+$: 429.1672; found 429.1651.

IR (film): 3382, 2927, 2872, 1506, 1454, 1379, 1204, 1092, 1042, 1029, 890, 829, 738, 698 cm^{-1}.

4-(((2S,3R,4S)-3,4-Bis(benzyloxy)-2-methyltetrahydrofuran-2-yl)oxy)naphthalen-1-ol **(151kb)**



Compound **150k** (1 equiv., 184.1 mg, 0.62 mmol), 1,4-naphthoquinone (4 equiv., 196.5 mg, 1.24 mmol), Na_2HPO_4 (1.1 equiv., 97.0 mg, 0.68 mmol), $Fe(acac)_3$ (0.5 equiv., 109.7 mg, 0.31 mmol) were dissolved in freshly distilled THF (12.5 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.31 mL, 2.48 mmol) was added dropwise and EtOH (8 equiv., 0.29 mL, 4.97 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring until the reaction was basically completed for 70 mins. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 15/1-11/1), yielding the product **151kb** (114.7 mg, 0.25 mmol, 40% dr=2.4:1) as a colorless oil liquid.

R_f 0.29 (Cyclohexane/EtOAc: 4/1);

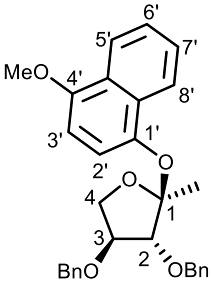
^{1}H NMR (400 MHz, Acetone-*d_6*) *δ* 8.75 (s, 1H, O$\underline{H}$), 8.36 – 8.29 (m, 0.17H, H-8´, α-isomer), 8.25 – 8.16 (m, 1H, H-5´, β-isomer), 8.15 – 8.06 (m, 1H, H-8´, β-isomer), 7.50 – 7.26 (m, 12H, H_{Ar}, H-6´ and H-7´, β-isomer), 7.21 (d, *J* = 8.2 Hz, 1H, H-2´or H-3´, β-isomer), 7.16 (d, *J* = 8.1 Hz, 0.2H, H-2´or H-3´, α-isomer), 6.81 (d, *J* = 8.2 Hz, 1H, H-2´or H-3´, β-isomer), 4.96 (d, *J* = 11.8 Hz, 0.17H, OC$\underline{H}_2$Ph, α-isomer), 4.92 (d, *J* = 11.9 Hz, 0.18H, OC$\underline{H}_2$Ph, α-isomer), 4.83 (d, *J* = 11.8 Hz, 1H, OC$\underline{H}_2$Ph, β-isomer), 4.78 (d, *J* = 11.9 Hz, 1H, OC$\underline{H}_2$Ph, β-isomer), 4.69 (d, *J* = 11.9 Hz, 1H, OC$\underline{H}_2$Ph, β-isomer), 4.62 (d, *J* = 11.9 Hz, 1H, OC$\underline{H}_2$Ph, β-isomer), 4.43 (d, *J* = 2.6 Hz, 1H, H-2, β-isomer), 4.41 (d, *J* = 2.5 Hz, 0.11H, H-4, α-isomer), 4.34 – 4.26 (m, 2H, H-3 and H-4, β-isomer), 4.08 (d, *J* = 5.8 Hz, 0.17H, H-2, α-isomer), 4.02 – 3.92 (m, 1H, H-4, β-isomer), 3.91 (dd, *J* = 9.5, 4.1 Hz, 0.18H, H-4, α-isomer), 1.42 (s, 3H, C$\underline{H}_3$, β-isomer), 1.37 (s, 0.49H, C$\underline{H}_3$, α-isomer).

^{13}C NMR (125 MHz, Acetone-d$_6$) *δ* 149.6 (C-4´, β-isomer), 149.5 (C-4´, α-isomer), 143.8 (C-1´, α-isomer), 143.5 (C-1´, β-isomer), 139.8 (CqAr, β-isomer), 139.5 (CqAr, β-isomer), 139.3 (CqAr, β-isomer), 130.8 (CqAr, α-isomer), 130.5 (CqAr, β-isomer), 129.2 (C_{Ar}, β-isomer), 129.15 (C_{Ar}, β-isomer), 129.1 (C_{Ar}, β-isomer), 128.8 (C_{Ar}, α-isomer), 128.7 (C_{Ar}, β-isomer), 128.6 (C_{Ar}, β-isomer), 128.5 (C_{Ar}, β-isomer), 128.4 (C_{Ar}, β-isomer), 126.5 (C-6´ or C-7´, β-isomer), 126.4 (C-6´ or C-7´, α-isomer), 125.7 (C-6´ or C-7´, α-isomer), 125.6 (C-6´ or C-7´, β-isomer), 123.6 (C-8´, α-isomer), 123.4 (C-8´, β-isomer), 123.0 (C-5´, β-isomer), 122.9 (C-5´, α-isomer), 117.5 (C-2´or C-3´, α-isomer), 117.2 (C-2´or C-3´, β-isomer), 112.6 (C-1, β-isomer), 108.2 (C-2´or C-3´, β-isomer), 108.1 (C-2´or C-3´, α-isomer), 90.6 (C-2, α-isomer), 90.0 (C-2, β-isomer), 84.2 (C-3, β-isomer), 83.5 (C-3, α-isomer), 73.4 (O$\underline{C}H_2$Ph, α-isomer), 72.74 (O$\underline{C}H_2$Ph, β-isomer), 72.7 (O$\underline{C}H_2$Ph, β-isomer), 72.6 (O$\underline{C}H_2$Ph, β-isomer), 70.3 (C-4, β-isomer), 70.2 (C-4, α-isomer), 20.6 ($\underline{C}H_3$, α-isomer), 19.2 ($\underline{C}H_3$, β-isomer).

HRMS (ESI) m/z: calcd for $C_{29}H_{28}KO_5$ $[M+K]^+$: 495.1568; found 495.1570.

IR (film): 3377, 2925, 2870, 1595, 1454, 1380, 1269, 1101, 1167, 1043, 1029, 1010, 876, 768, 739, 698 cm^{-1}.

(2S,3R,4S)-3,4-Bis(benzyloxy)-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydrofuran **(177kb)**



NaH (60% in oil, 3 equiv., 30.2 mg, 0.75 mmol) was added portionwisely to solution of **151kb** (1 equiv., 114.7 mg, 0.25 mmol) in freshly distilled THF (6 mL) at 0 °C. And then, CH_3I (4 equiv., 0.063 mL, 1.00 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 6 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc=30:1), yielding the product **177kb** (57.2 mg, 0.12 mmol, 48% dr=1.8:1) as a colorless oil liquid.

R_f 0.67 (Cyclohexane/EtOAc: 4/1);

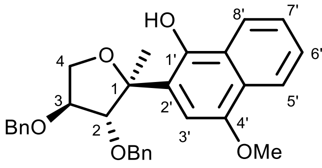
^{1}H NMR (400 MHz, Acetone-*d_6*) *δ* 8.38 – 8.31 (m, 0.17H, H-8´, α-isomer), 8.23 – 8.14 (m, 1H, H-5´, β-isomer), 8.17 – 8.08 (m, 1H, H-8´, β-isomer), 7.59 – 7.23 (m, 15H, H_{Ar} and H-3´, H-6´ and H-7´, β-isomer and α-isomer), 6.83 (d, *J* = 8.4 Hz, 1H, H-2´, β-isomer), 4.96 (d, *J* = 11.7 Hz, 0.2H, $OC\underline{H}_2Ph$, α-isomer), 4.92 (d, *J* = 11.8 Hz, 0.2H, $OC\underline{H}_2Ph$, α-isomer), 4.84 (d, *J* = 11.9 Hz, 1H, $OC\underline{H}_2Ph$, β-isomer), 4.78 (d, *J* = 11.8 Hz, 1H, $OC\underline{H}_2Ph$, β-isomer), 4.69 (d, *J* = 11.9 Hz, 1H, $OC\underline{H}_2Ph$, β-isomer), 4.62 (d, *J* = 11.8 Hz, 1H, $OC\underline{H}_2Ph$, β-isomer), 4.44 (d, *J* = 2.6 Hz, 1H, H-2, β-isomer), 4.37 – 4.26 (m, 2H, H-3 and H-4, β-isomer), 4.09 (d, *J* = 5.8 Hz, 0.2H, H-2, α-isomer), 4.02 – 3.90 (m, 4H, $OC\underline{H}_3$ and H-4, β-isomer), 1.46 (s, 3H, $C\underline{H}_3$, β-isomer), 1.39 (s, 0.55H, $C\underline{H}_3$, α-isomer).

^{13}C NMR (125 MHz, Acetone-d_6) *δ* 152.1 (C-4´, α-isomer), 151.9 (C-4´, β-isomer), 144.6 (C-1´, α-isomer), 144.3 (C-1´, β-isomer), 139.8 (CqAr, α-isomer), 139.4 (CqAr, β-isomer), 139.3 (CqAr, β-isomer), 130.6 (CqAr, α-isomer), 130.2 (CqAr, β-isomer), 129.2 (C_{Ar}, β-isomer), 129.16 (C_{Ar}, α-isomer), 129.15 (C_{Ar}, α-isomer), 129.1 (C_{Ar}, β-isomer), 128.8 (C_{Ar}, α-isomer), 128.7 (C_{Ar}, β-isomer), 128.6 (C_{Ar}, α-isomer), 128.57 (C_{Ar}, β-isomer), 128.5 (C_{Ar}, β-isomer), 128.44 (C_{Ar}, α-isomer), 128.4 (C_{Ar}, α-isomer), 128.38 (C_{Ar}, β-isomer), 127.0 (CqAr, β-isomer), 126.9 (CqAr, α-isomer), 126.8 (C-6´ or C-7´, β-isomer), 126.75 (C-6´ or C-7´, α-isomer), 126.2 (C-6´ or C-7´, α-isomer), 126.1 (C-6´ or C-7´, β-isomer), 123.7 (C-8´, α-isomer), 123.4 (C-8´, β-isomer), 122.5 (C-5´, β-isomer), 122.46 (C-5´, α-isomer), 116.9 (C-3´, α-isomer), 116.4 (C-3´, β-isomer), 112.7 (C-1, β-isomer), 108.6 (C-2´, α-isomer), 104.3 (C-2´, β-isomer), 90.6 (C-2, α-isomer), 90.0 (C-2, β-isomer), 84.2 (C-3, β-isomer), 83.4 (C-3, α-isomer), 73.4 ($O\underline{C}H_2Ph$, α-isomer), 72.74 ($O\underline{C}H_2Ph$, β-isomer), 72.7 ($O\underline{C}H_2Ph$, α-isomer), 72.6 ($O\underline{C}H_2Ph$, β-isomer), 70.5 (C-4, β-isomer), 70.3 (C-4, α-isomer), 56.0 ($O\underline{C}H_3$, β-isomer), 20.5 ($\underline{C}H_3$, α-isomer), 19.2 ($\underline{C}H_3$, β-isomer).

HRMS (ESI) m/z: calcd for $C_{30}H_{30}NaO_5$ $[M+Na]^+$: 493.1985; found 493.1990.

IR (film): 2939, 2878, 1594, 1462, 1387, 1268, 1235, 1091, 1039, 1022, 980, 872, 819, 768, 735, 697 cm^{-1}.

2-((2S,3R,4S)-3,4-Bis(benzyloxy)-2-methyltetrahydrofuran-2-yl)-4-methoxynaphthalen-1-ol **(187)**



To a solution of **177kb** (1 equiv., 54.8 mg, 0.12 mmol) in dry DCM (4 mL) was dropwise added the solution of $BF_3 OEt_2$ (0.1 equiv., 0.0014 mL, 0.012 mmol) in the dry DCM at -60 °C under Ar atmosphere. The temperature gradually rised to 5 °C for 3 h. The reaction was quenched using H_2O (1 mL). The solution was extracted with DCM (3 x10 mL). Organic phase was washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtred and concentrated. The solvent was removed under reduced pressure, yielding the product **187** (52.7 mg, 0.11 mmol, 96%) as a light-yellow oil.

R$_f$ 0.58 (Cyclohexane/EtOAc: 5/1);

$[\alpha]_D^{20}$=-94.7 (*c*=0.3, DCM);

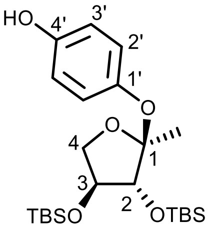
^{1}H NMR (400 MHz, Acetone-d$_6$) δ 9.52 (s, 1H, $O\underline{H}$), 8.26 – 8.15 (m, 1H, H-8´), 8.13 – 8.03 (m, 1H, H-5´), 7.53 – 7.42 (m, 4H, H-6´ and H-7´ and H_{Ar}), 7.45 – 7.37 (m, 2H, H_{Ar}), 7.38 – 7.30 (m, 1H, H_{Ar}), 7.20 – 7.05 (m, 5H, H_{Ar}), 6.58 (s, 1H, H-3´), 4.90 (d, *J* = 12.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.78 (d, *J* = 11.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.58 – 4.49 (m, 2H, H-2 and $OC\underline{H_2}Ph$), 4.48 (d, *J* = 11.7 Hz, 1H, $OC\underline{H_2}Ph$), 4.41 (dt, *J* = 5.5, 2.8 Hz, 1H, H-3), 4.34 (dd, *J* = 9.9, 5.2 Hz, 1H, H-4), 4.11 (dd, *J* = 9.9, 2.9 Hz, 1H, H-4), 3.77 (s, 3H, $OC\underline{H_3}$), 1.65 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (100 MHz, Acetone-d$_6$) δ 149.0 (C-4´), 144.4 (C-1´), 139.2 (CqAr), 139.0 (CqAr), 129.3 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 127.3 (CqAr), 126.3 (C-6´ or C-7´ and CqAr), 126.2 (C-6´ or C-7´), 123.1 (C-8´), 122.1 (C-5´), 121.6 (CqAr), 103.5 (C-3´), 90.1 (C-1), 89.0 (C-2), 83.9 (C-3), 72.9 ($O\underline{C}H_2Ph$), 72.0 ($O\underline{C}H_2Ph$), 71.0 (C-4), 56.0 ($O\underline{C}H_3$), 23.6 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{30}H_{30}NaO_5$ $[M+Na]^+$: 493.1985; found 493.1986.

IR (film): 3280, 2933, 1635, 1600, 1497, 1454, 1394, 1362, 1331, 1289, 1256, 1230, 1207, 1179, 1157, 1106, 1095, 1068, 1027, 986, 768, 736, 698 cm^{-1}.

4-(((2S,3R,4S)-3,4-Bis((tert-butyldimethylsilyl)oxy)-2-methyltetrahydrofuran-2-yl)oxy)phenol **(151ma)**



According to the general procedure, *exo*-glucal **150m** (1 equiv., 57.5 mg, 0.17 mmol), *p*-benzoquinone (6 equiv., 72.14 mg, 0.67 mmol), Na_2HPO_4 (1.1 equiv., 26.1 mg, 0.18 mmol), $Fe(acac)_3$ (0.5 equiv., 29.5 mg, 0.083 mmol), phenylsilane (4 equiv., 0.083 mL, 0.67 mmol), EtOH (8 equiv., 00.078 mL, 1.33 mmol) in THF (3.4 mL) were heated at 60 °C. After 5 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (400 μL) was added dropwise during 1.5 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 15/1-10/1), yielding **151ma** (34.4 mg, 0.073 mmol, 43%, dr=9:1) as a colourless oil liquid.

R_f 0.32 (Cyclohexane/EtOAc: 8/1);

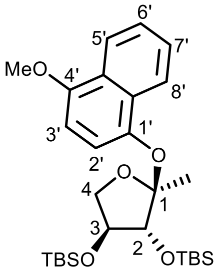
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.91 (m, 2.4H, H-2'), 6.74 – 6.67 (m, 2.4H, H-3'), 4.73 (s, 1H, OH, major isomer), 4.53-4.45 (m, 0.2H, H-3, minor isomer), 4.27 (dd, *J* = 9.0, 7.2 Hz, 0.2H, H-4a, minor isomer), 4.20 (d, *J* = 4.8 Hz, 1H, H-2, major isomer), 4.11 (ddd, *J* = 8.1, 6.7, 4.8 Hz ,1H, H-3, major isomer), 4.01 (dd, *J* = 8.5, 6.6 Hz, 1H, H-4a, major isomer), 3.92 (d, *J* = 6.3 Hz, 1H, H-2, minor isomer), 3.77 (t, *J* = 8.3 Hz, 1H, H-4b), 3.66 (dd, *J* = 8.9, 5.2 Hz, 0.2H, H-4b, minor isomer) 1.30 (s, 3H, $C\underline{H}_3$, minor isomer), 1.27 (s, 3H, $C\underline{H}_3$, major isomer), 0.98 (s, 1.8H, Si-$C(C\underline{H}_3)_3$, minor isomer), 0.94 (s, 9H, Si-$C(C\underline{H}_3)_3$, major isomer), 0.90 (s, 1.8H, Si-$C(C\underline{H}_3)_3$, minor isomer), 0.89 (s, 9H, Si-$C(C\underline{H}_3)_3$, major isomer), 0.18-0.14 (m, 7.2H, Si-$(C\underline{H}_3)_2$), 0.10-0.08 (m, 3.6H, Si-$(C\underline{H}_3)_2$), 0.05 (s, 3H, Si-$(C\underline{H}_3)_2$, major isomer), 0.04 (s, 0.6H, Si-$(C\underline{H}_3)_2$, minor isomer);

^{13}C NMR (125 MHz, Acetone-d_6) δ 154.3 (C-4´), 154.2 (C-4’), 147.7 (C-1´), 124.4 (2 C-2´, major isomer), 124.3 (2 C-2´, minor isomer), 116.1 (2 C-3´, major isomer), 116.0 (2 C-3´, minor isomer), 111.6 (C-1, major isomer), 107.5 (C-1, minor isomer), 86.9 (C-2, major isomer), 85.0 (C-2, minor isomer), 79.5 (C-3, major isomer), 77.6 (C-3, minor isomer), 71.7 (C-4, minor isomer), 70.6 (C-4, major isomer), 26.3 (2 Si-$C(\underline{C}H_3)_3$, minor isomer), 26.2 (2 Si-$C(\underline{C}H_3)_3$, major isomer), 21.4 ($\underline{C}H_3$, minor isomer), 20.8 ($\underline{C}H_3$, major isomer), 18.6 (Si-$\underline{C}(CH_3)_3$), 18.4 (Si-$\underline{C}(CH_3)_3$), -3.6 (Si-$(\underline{C}H_3)_2$), -4.2 (Si-$(\underline{C}H_3)_2$), 4.5 (Si-$(\underline{C}H_3)_2$);

HRMS (ESI) m/z: calcd for calcd for $C_{23}H_{42}NaO_5Si_2$ $[M+Na]^+$: 477.2463; found 477.2451;

IR (film): 3402, 2930, 2858, 1506, 1472, 1252, 1203, 1108, 1079, 1041, 900, 835, 775 cm^{-1}.

(((2S,3R,4S)-2-((4-Methoxynaphthalen-1-yl)oxy)-2-methyltetrahydrofuran-3,4-diyl)bis(oxy))bis(tert-butyldimethylsilane **(177mb)**



Compound **150m** (1 equiv., 350 mg, 1.02 mmol), 1,4-naphthoquinone (2.5 equiv., 401.5 mg, 2.54 mmol), Na_2HPO_4 (1.1 equiv., 158.6 mg, 1.12 mmol), $Fe(acac)_3$ (0.5 equiv., 179.3 mg, 0.51 mmol) were dissolved in freshly distilled THF (20.3 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.51 mL, 4.06 mmol) was added dropwise and EtOH (8 equiv., 0.47 mL, 8.12 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring until the reaction was basically completed for 4 h. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/Et_2O: 10/1), yielding a mixture of product **151mb** (192.7 mg, 0.38 mmol, 38%) as a brown oil liquid and 1,4-naphthoquinone.

Next, NaH (60% in oil, 3 equiv., 45.80 mg, 1.15 mmol) was added portionwisely to a solution of **151mb** (1 equiv., 192.7 mg, 0.38 mmol) in freshly distilled THF (5.50 mL) at 0 °C. And then, CH_3I (4 equiv., 0.095 mL, 1.53 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 8 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane:DCM =3/1-2/1), yielding the product **177mb** (105.8 mg, 0.25 mmol, 53% dr=5.6:1) as an oil liquid.

R_f 0.49 (Cyclohexane/DCM: 1.5/1);

$[\alpha]_D^{20}$=-65.8 (*c*=0.4, DCM);

^{1}H NMR (400 MHz, Acetone-d$_6$) δ 8.23 – 8.14 (m, 2H, H-8´ and H-5´), 7.54 – 7.44 (m, 2H, H-7´ and H-6´), 7.32 (d, *J* = 8.4 Hz, 1H, H-2´ or H-3´), 6.82 (d, *J* = 8.4 Hz, 1H, H-2´ or H-3´), 4.50 (d, *J* = 3.7 Hz, 1H, H-2), 4.29 (td, *J* = 7.0, 3.7 Hz, 1H, H-3), 4.20 (dd, *J* = 8.5, 6.7 Hz, 1H, H-4), 3.98 (s, 3H, O$C\underline{H_3}$), 3.84 (dd, *J* = 8.6, 7.2 Hz, 1H, H-4), 1.36 (s, 3H, $C\underline{H_3}$), 0.99 (s, 9H, Si-C(C$\underline{H}_3$)$_3$), 0.91 (s, 9H, Si-C(C$\underline{H}_3$)$_3$), 0.28 (s, 6H, 2 Si-(C$\underline{H}_3$)$_2$), 0.17 (s, 3H, Si-(C$\underline{H}_3$)$_2$), 0.11 (s, 3H, Si-(C$\underline{H}_3$)$_2$).

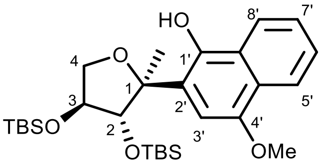
^{13}C NMR (125 MHz, Acetone-d$_6$) δ 151.8 (C-4´), 144.5 (C-1´), 130.2 (CqAr), 127.0 (CqAr), 126.6 (C-6´ or C-7´), 126.1 (C-6´ or C-7´), 123.4 (C-5´ or C-8´), 122.6 (C-5´ or C-8´), 116.4 (C-2´ or C-3´), 113.0 (CqAr), 104.3 (C-2´ or C-3´), 87.3 (C-2), 80.3 (C-3), 71.5 (C-4), 56.0 (O$\underline{C}H_3$), 26.2 (2 Si-C($\underline{C}H_3$)$_3$), 19.8 ($\underline{C}H_3$), 18.6 (Si-$\underline{C}$(CH$_3$)$_3$), 18.4 (Si-$\underline{C}$(CH$_3$)$_3$), -3.9 (Si-($\underline{C}H_3$)$_2$), -4.1 (Si-($\underline{C}H_3$)$_2$), -4.3 (Si-($\underline{C}H_3$)$_2$), -4.5 (Si-

$(\underline{C}H_3)_2$).

HRMS (ESI) m/z: calcd for $C_{28}H_{46}NaO_5Si_2$ $[M+Na]^+$: 541.2776; found 541.2762.

IR (film): 2954, 2930, 2858, 1596, 1463, 1387, 1268, 1235, 1153, 1112, 1095, 1038, 1022, 874, 864, 838, 777, 767 cm^{-1}.

2-((2S,3R,4S)-3,4-Bis((tert-butyldimethylsilyl)oxy)-2-methyltetrahydrofuran-2-yl)-4-methoxynaphthalen-1-ol **(188)**



To a solution of **177mb** (1 equiv., 20.4 mg, 0.039 mmol) in dry DCM (1.3 mL) was dropwise added the solution of BF_3 OEt_2 (0.1 equiv., 0.00050 mL, 0.0039 mmol) in the dry DCM at -60 ℃ under Ar atmosphere. The temperature gradually rised to -5 °C for 2.5 h. The reaction was quenched using a saturated solution of $NaHCO_3$ (5 drops). The solution was extracted with DCM (3 x10 mL). Organic phase was washed with brine (10 mL), dried with Na_2SO_4, filtred and concentrated. The solvent was removed under reduced pressure, yielding the product **188** (18.6 mg, 0.036 mmol, 91%) as a light-yellow oil.

R_f 0.48 (Cyclohexane/DCM: 1.5/1);

$[\alpha]_D^{20}$=-66.5 (*c*=0.4, DCM);

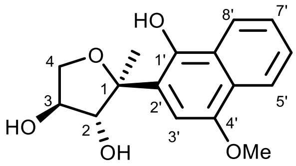
^{1}H NMR (400 MHz, Acetone-*d*$_6$) δ 9.90 (s, 1H, O$\underline{H}$), 8.18 – 8.13 (m, 1H, H-8´), 8.09 – 8.03 (m, 1H, H-5´), 7.47 – 7.39 (m, 2H, H-7´ and H-6´), 6.53 (s, 1H, H-3´), 4.60 (d, *J* = 1.4 Hz, 1H, H-2), 4.29 – 4.27 (m, 1H, H-3), 4.25 (dd, *J* = 9.0, 3.5 Hz, 1H, H-4), 3.96 (dd, *J* = 9.2, 1.1 Hz, 2H, H-4), 3.94 (s, 3H, $OC\underline{H_3}$), 1.61 (s, 3H, $C\underline{H_3}$), 1.00 (s, 9H, Si-$C(C\underline{H}_3)_3$), 0.47 (s, 9H, Si-$C(C\underline{H}_3)_3$), 0.27 (s, 3H, Si-$(C\underline{H}_3)_2$), 0.25 (s, 3H, Si-$(C\underline{H}_3)_2$), -0.02 (s, 3H, Si-$(C\underline{H}_3)_2$), -0.15 (s, 3H, Si-$(C\underline{H}_3)_2$).

^{13}C NMR (125 MHz, Acetone-d$_6$) δ 148.7 (C-4´), 144.8 (C-1´), 127.6 (CqAr), 126.11 (CqAr), 126.06 (C-6´ or C-7´), 125.9 (C-6´ or C-7´), 122.9 (C-8´), 122.0 (C-5´), 121.5 (CqAr), 104.4 (C-3´), 92.5 (CqAr), 84.8 (C-2), 80.0 (C-3), 74.3 (C-4), 56.0 ($O\underline{C}H_3$), 26.2 (Si-$C(\underline{C}H_3)_3$), 25.6 (Si-$C(\underline{C}H_3)_3$), 24.9 ($\underline{C}H_3$), 18.7 (Si-$\underline{C}(CH_3)_3$), 18.0 (Si-$\underline{C}(CH_3)_3$), -4.2 (Si-$(\underline{C}H_3)_2$), -4.6 (Si-$(\underline{C}H_3)_2$), -4.76 (Si-$(\underline{C}H_3)_2$), -4.78 (Si-$(\underline{C}H_3)_2$).

HRMS (ESI) m/z: calcd for $C_{28}H_{46}KO_5Si_2$ $[M+K]^+$: 557.2515; found 557.2537.

IR (film): 3271, 2952, 2930, 2858, 1473, 1462, 1361, 1331, 1255, 1145, 1112, 1066, 1010, 866, 836, 809, 775 cm^{-1}.

(2S,3R,4S)-2-(1-Hydroxy-4-methoxynaphthalen-2-yl)-2-methyltetrahydrofuran-3,4-diol **(200)**



To a solution of **188** (1 equiv., 70.4 mg, 0.14 mmol) in freshly distilled THF (2 mL) was added TBAF (1M in THF, 2 equiv., 0.27 mL, 0.27 mmol). The mixture was then stirred at room temperature overnight. After completion of the reaction, the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc:1/1-1/2), yielding the product **200** (13.3 mg, 0.046 mmol, 33%) as a white solid.

R_f 0.25 (Cyclohexane/EtOAc: 1/2);

$[\alpha]_D^{20}$=-21.6 (*c*=0.7, MeOH);

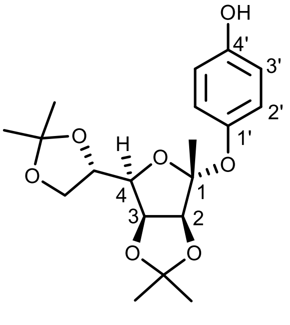
^{1}H NMR (400 MHz, Methanol-*d*$_4$) *δ* 8.18 – 8.13 (m, 1H, H-8´), 8.11 – 8.02 (m, 1H, H-5´), 7.47 – 7.36 (m, 2H, H-7´ and H-6´), 6.83 (s, 1H, H-3´), 4.38 (d, *J* = 4.8 Hz, 1H, H-2), 4.36 – 4.27 (m, 1H, H-3), 4.24 (dd, *J* = 9.1, 6.2 Hz, 1H, H-4), 3.94 (s, 3H, $OC\underline{H_3}$), 3.76 (dd, *J* = 9.1, 5.4 Hz, 1H, H-4), 1.55 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (100 MHz, Methanol-*d*$_4$) *δ* 149.7 (C-4´), 144.0 (C-1´), 127.7 (CqAr), 126.7 (CqAr), 126.5 (C-6´ or C-7´), 126.2 (C-6´ or C-7´), 123.7 (C-2´), 123.1 (C-8´), 122.4 (C-5´), 103.4 (C-3´), 89.2 (C-1), 85.1 (C-2), 78.1 (C-3), 71.5 (C-4), 56.2 ($O\underline{C}H_3$), 23.5 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{16}H_{17}O_5$ $[M-H]^-$: 289.1081; found 289.1088.

IR (film): 3326, 2933, 1635, 1599, 1456, 1378, 1360, 1329, 1230, 1157, 1106, 1039, 985, 767, 734, 688 cm^{-1}.

4-(((3aS,4S,6R,6aS)-6-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2,4-trimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)oxy)phenol **(151na)**



According to the general procedure, *exo*-glycal **150n** (1 equiv., 37.4 mg, 0.15 mmol), *p*-benzoquinone (6 equiv., 63.1 mg, 0.58 mmol), Na_2HPO_4 (1.1 equiv., 22.8 mg, 0.16 mmol), $Fe(acac)_3$ (0.5 equiv., 25.8 mg, 0.073 mmol), phenylsilane (4 equiv., 0.073 mL, 0.58 mmol), EtOH (8 equiv., 0.068 mL, 1.17 mmol) in THF (3 mL) were heated at 60 °C. After 5 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (300 µL) was added dropwise during 3.5 h. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 15/1-8/1), yielding **151na** (30 mg, 0.082 mmol, 55%, dr>98:2) as a white solid.

$\boldsymbol{R_f}$ 0.40 (Cyclohexane/EtOAc: 3/1);

$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$=+122 (*c*=1.1, CHCl$_3$).

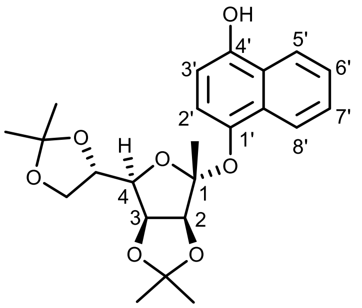
^{1}H NMR (400 MHz, CDCl$_3$) δ 6.96 (d, *J* = 8.9 Hz, 2H, H-2'), 6.71 (d, *J* = 9.0 Hz, 2H, H-3'), 4.80 (dd, *J* = 5.9, 4.0 Hz, 1H, H-3), 4.65 (d, *J* = 5.9 Hz, 1H, H-2), 4.44 (dt, *J* = 8.7, 6.6 Hz, 1H, H-5), 4.25 (dd, *J* = 8.6, 6.7 Hz, 1H, H-6a), 4.19 (dd, *J* = 8.6, 4.0 Hz, 1H, H-4), 3.81 (dd, *J* = 8.6, 6.4 Hz, 1H, H-6b), 1.47 (s, 6H, $2C\underline{H}_3$), 1.41 (s, 3H, $C\underline{H}_3$), 1.40 (s, 3H, $C\underline{H}_3$), 1.32 (s, 3H, $C\underline{H}_3$);

^{13}C NMR (125 MHz, CDCl$_3$) δ 152.1 (C-4´ or C-1´), 147.3 (C-4´ or C-1´), 123.1 (2 C-2´), 115.9 (2 C-3´), 113.2 (Cq), 111.3 (Cq), 110.1 (Cq), 86.8 (C-2), 81.9 (C-4), 80.6 (C-3), 75.6 (C-5), 66.3 (C-6), 27.0 ($\underline{C}H_3$), 26.2 ($\underline{C}H_3$), 25.5 ($\underline{C}H_3$), 25.1 ($\underline{C}H_3$), 17.7 ($\underline{C}H_3$);

HRMS (ESI) m/z: calcd for $C_{19}H_{26}NaO_7$ [M+Na]$^+$: 389.1571; found 389.1589 ;

IR (film): 3397, 2988, 2940, 1507, 1374, 1206, 1160, 1078, 1012, 896, 844, 732 cm^{-1}.

4-(((3aS,4R,6R,6aS)-6-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2,4-trimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)oxy)naphthalen-1-ol **(151nb)**



Compound **150n** (1 equiv., 57 mg, 0.22 mmol), 1,4-naphthoquinone (3 equiv., 105.5 mg, 0.67 mmol), Na$_2$HPO$_4$ (1.1 equiv., 34.7 mg, 0.24 mmol), Fe(acac)$_3$ (0.5 equiv., 39.3 mg, 0.11 mmol) were dissolved in freshly distilled THF (4.40 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.11 mL, 0.89 mmol) was added dropwise and EtOH (8 equiv., 0.10 mL, 1.78 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring until the reaction was basically completed for 1.5 h. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 15/1-8/1), yielding the product **151nb** (81.1 mg, 0.19 mmol, 88%, dr=1.2/1) as an oil.

R_f 0.33 (Cyclohexane/ EtOAc: 4/1);

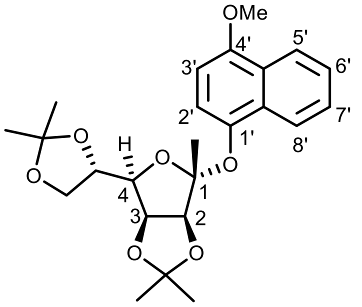
^{1}H NMR (400 MHz, Acetone-*d_6*) *δ* 8.77 (s, 1H), 8.25 – 8.18 (m, 1H), 8.12 – 8.09 (m, 1H), 7.55 – 7.40 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.08 (d, *J* = 6.1 Hz, 0.15H), 5.02 (dd, *J* = 5.8, 3.9 Hz, 1H), 4.93 (d, *J* = 5.9 Hz, 1H), 4.70 (dd, *J* = 6.1, 3.8 Hz, 0.15H), 4.39 (dt, *J* = 8.3, 6.7 Hz, 1H), 4.26 (dd, *J* = 8.4, 3.9 Hz, 1H), 4.19 (dd, *J* = 8.5, 6.6 Hz, 1H), 4.12 (dd, *J* = 8.5, 6.6 Hz, 0.16H), 3.87 (dd, *J* = 8.5, 6.9 Hz, 1H), 3.84 – 3.81 (m, 0.13H), 3.72 (dd, *J* = 8.5, 6.9 Hz, 0.15H), 1.59 (s, 0.44H), 1.51 (s, 0.52H), 1.46 (s, 3H), 1.40 (s, 3H), 1.36 (s, 9H), 1.30 (s, 0.53H).

^{13}C NMR (100 MHz, Acetone-*d_6*) *δ* 149.8 (C-4´), 149.7 (C-4´, α -isomer), 143.4 (C-1´), 130.4 (CqAr), 127.1 (C-6´ or C-7´, α -isomer), 126.7 (C-6´ or C-7´), 126.4 (CqAr), 125.7 (C-6´ or C-7´), 123.1 (C-8´), 123.0 (C-5´), 117.2 (C-3´), 113.4 (CqAr), 112.4 (C-1), 110.0 (CqAr), 109.9 (CqAr, α -isomer), 108.2 (C-2´), 108.1 (C-2´, α -isomer), 87.5 (C-2), 85.3 (C-2, α -isomer), 82.7 (C-4), 82.1 (C-3, α -isomer), 81.8 (C-4, α -isomer), 81.5 (C-3), 76.9 (C-5, α -isomer), 76.5 (C-5), 66.6 (C-6), 66.5 (C-6, α -isomer), 27.2, 26.4 ($C\underline{C}H_3$), 26.2 ($C\underline{C}H_3$, α -isomer), 25.9 ($C\underline{C}H_3$), 25.8 ($C\underline{C}H_3$, α -isomer), 25.1 ($C\underline{C}H_3$), 24.9 ($C\underline{C}H_3$, α -isomer), 23.4 ($C\underline{C}H_3$, α -isomer), 17.5 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{23}H_{28}NaO_7$ $[M+Na]^+$: 439.1727; found 439.1718.

IR (film): 3382, 2988, 2918, 2850, 1597, 1379, 1350, 1267, 1211, 1164, 1085, 1044, 1007, 894, 865, 849, 768 cm^{-1}.

(3aS,4R,6R,6aS)-6-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4-((4-methoxynaphthalen-1-yl)oxy)-2,2,4-trimethyltetrahydrofuro[3,4-d][1,3]dioxole **(177nb)**



NaH (60% in oil, 3 equiv., 68.3 mg, 1.71 mmol) was added portionwisely to a solution of **151nb** (1 equiv., 237.1 mg, 0.57 mmol) in freshly distilled THF (8.30 mL) at 0 °C. And then, CH_3I (4 equiv., 0.14 mL, 2.28 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 9.5 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 25/1-20/1), yielding the product **177nb** (168.2 mg, 0.39 mmol, 69%) as white solid.

R_f 0.52 (Cyclohexane/ EtOAc: 4/1);

[α]$_D$^{20}=+153.6 (*c*=0.4, DCM);

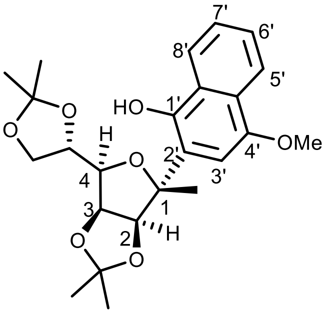
^{1}H NMR (400 MHz, Acetone-*d*$_6$) *δ* 8.22 – 8.17 (m, 1H, H-5'), 8.16 – 8.10 (m, 1H, H-8'), 7.56 – 7.46 (m, 2H, H-6' and H-7'), 7.41 (d, *J* = 8.4 Hz, 1H, H-3'), 6.84 (d, *J* = 8.4 Hz, 1H, H-2'), 5.02 (dd, *J* = 5.8, 3.9 Hz, 1H, H-3), 4.94 (d, *J* = 5.9 Hz, 1H, H-2), 4.44 – 4.36 (m, 1H, H-5), 4.26 (dd, *J* = 8.4, 3.8 Hz, 1H, H-4), 4.19 (dd, *J* = 8.5, 6.6 Hz, 1H, H-6), 3.99 (s, 3H, $OC\underline{H_3}$), 3.87 (dd, *J* = 8.5, 6.9 Hz, 1H, H-6), 1.47 (s, 3H, $CC\underline{H_3}$), 1.42 (s, 3H, $CC\underline{H_3}$), 1.37 (s, 3H, $C\underline{H_3}$), 1.36 (s, 6H, $CC\underline{H_3}$).

^{13}C NMR (100 MHz, Acetone-*d*$_6$) *δ* 152.2 (C-4´), 144.2 (C-1´), 130.3 (CqAr), 127.0 (C-6´ or C-7´), 126.9 (CqAr), 126.2 (C-6´ or C-7´), 123.1 (C-8´), 122.6 (C-5´), 116.7 (C-3´), 113.4 (CqAr), 112.5 (C-1), 110.0 (CqAr), 104.4 (C-2´), 87.5 (C-2), 82.8 (C-4), 81.4 (C-3), 76.5 (C-5), 66.6 (C-6), 56.0 ($O\underline{C}H_3$), 27.3 ($C\underline{C}H_3$), 26.4 ($C\underline{C}H_3$), 25.9 ($C\underline{C}H_3$), 25.1 ($C\underline{C}H_3$), 17.5 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{24}H_{30}NaO_7$ $[M+Na]^+$: 453.1884; found 453.1879.

IR (film): 2988, 2940, 1594, 1463, 1381, 1267, 1239, 1211, 1163, 1093, 1043, 1014, 977, 897, 883, 864, 850, 768 cm^{-1}.

2-((3aS,4R,6R,6aS)-6-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2,4-trimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-methoxynaphthalen-1-ol **(190)**



To a solution of **177nb** (1 equiv., 83.0 mg, 0.19 mmol) in dry DCM (6.50 mL) was dropwise added the solution of $BF_3\,OEt_2$ (0.1 equiv., 0.0024 mL, 0.019 mmol) in the dry DCM at -60 °C under Ar atmosphere. The temperature gradually rised to 22 °C for 5 h. The reaction was quenched using water (5 drops). The solution was dried with Na_2SO_4, filtred and concentrated. The solvent was removed under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane:DCM=1/1-1/3), yielding the product **190** (54.7 mg, 0.13 mmol, 66%, dr=2.3/1) as a white solid.

R$_f$ 0.32 (Cyclohexane/ EtOAc: 5/1);

[α]$_D$^{20}=-8.6 (*c*=0.3, DCM);

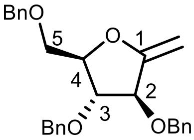
^{1}H NMR (400 MHz, Acetone-*d*$_6$) *δ* 9.38 (s, 1H, $O\underline{H}$), 8.24 – 8.19 (m, 1H, H-8'), 8.15 – 8.07 (m, 1H, H-5'), 7.54 – 7.45 (m, 2H, H-6' and H-7'), 6.80 (s, 1H, H-3'), 5.41 (d, *J* = 6.1 Hz, 1H, H-2), 4.81 (dd, *J* = 6.1, 3.9 Hz, 1H, H-3), 4.44 (dt, *J* = 8.5, 6.4 Hz, 1H, H-5), 4.13 (dd, *J* = 8.6, 6.7 Hz, 1H, H-6), 3.98 (s, 3H, $\mathrm{OC\underline{H}_3}$), 3.84 – 3.74 (m, 2H, H-6 and H-4), 1.64 (s, 3H, $\mathrm{C\underline{H}_3}$), 1.54 (s, 3H, $\mathrm{C\underline{H}_3}$), 1.41 (s, 3H, $\mathrm{C\underline{H}_3}$), 1.36 (s, 3H, $\mathrm{C\underline{H}_3}$), 1.35 (s, 3H, $\mathrm{C\underline{H}_3}$).

^{13}C NMR (100 MHz, Acetone-*d*$_6$) *δ* 149.3 (C-4´), 145.1 (C-1´), 127.4 (CqAr), 126.61 (CqAr), 126.57 (C-6´ or C-7´), 126.56 (C-6´ or C-7´), 122.9 (C-8´), 122.2 (C-5´), 118.5 (CqAr), 113.2 (CqAr), 110.2 (CqAr), 103.8 (C-3´), 90.4 (C-1), 86.4 (C-2), 83.1 (C-4), 81.6 (C-3), 76.2 (C-5), 66.4 (C-6), 56.2 ($\mathrm{O\underline{C}H_3}$), 27.1 ($\mathrm{C\underline{C}H_3}$), 26.4 ($\mathrm{C\underline{C}H_3}$), 25.8 ($\mathrm{C\underline{C}H_3}$), 25.1 ($\mathrm{C\underline{C}H_3}$), 24.0 ($\mathrm{\underline{C}H_3}$).

HRMS (ESI) m/z: calcd for $C_{24}H_{30}NaO_7$ $[M+Na]^+$: 453.1884; found 453.1880.

IR (film): 3303, 2987, 2936, 1702, 1600, 1455, 1372, 1246, 1210, 1158, 1101, 1056, 1026, 976, 896, 841, 804, 768, 730, 690, 513 cm^{-1}.

(2R,3R,4S)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-methylenetetrahydrofuran **(150l)**[252]

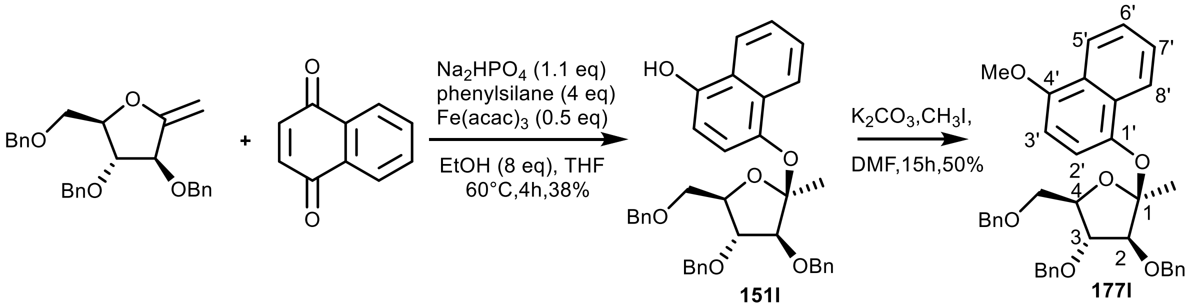


(3*S*,4*R*,5*R*)-3,4-bis(benzyloxy)-5-[(benzyloxy)methyl]oxolan-2-one (1 equiv., 512 mg, 1.22 mmol) was dissolved in dry toluene (10 mL) and Petasis Reagent (1.01M in toluene, 2 equiv., 2.42 mL, 2.45 mmol) was added slowly at room temperature, then the reaction mixture was stirred in the dark at 80 °C under argon for 16 h. The brown reaction mixture was concentrated, and subjected to silica-gel column chromatography, using Cyclohexane/ethyl acetate (containing 1% triethylamine) to give the corresponding product **150l** (437.5 mg, 1.05 mmol, 86%) as a colourless liquid.

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.43 – 7.17 (m, 15H, H_{Ar}), 4.66 (d, *J* = 11.7 Hz, 1H, $\mathrm{OC\underline{H}_2Ph}$), 4.60 – 4.49 (m, 6H, $\mathrm{OC\underline{H}_2Ph}$ and $\mathrm{C\underline{H}_2{=}CH}$), 4.41 (td, *J* = 6.0, 3.3 Hz, 1H, H-4), 4.38 (dt, *J* = 3.0, 1.1 Hz, 1H, H-2), 4.17 (dd, *J* = 1.9, 1.1 Hz, 1H, $\mathrm{C\underline{H}_2{=}CH}$), 4.05 (t, *J* = 3.1 Hz, 1H, H-3), 3.67 – 3.57 (m, 2H, H-5).

This data is consistent with the literature reported.[251]

(2S,3S,4R,5R)-3,4-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydrofuran **(177l)**



According to the general procedure, *exo*-glycal **150l** (1 equiv, 437 mg, 1.05 mmol), 1,4-naphthoquinone (3 equiv., 196.5 mg, 1.24 mmol), Na_2HPO_4 (1.1 equiv., 163.8 mg, 1.15 mmol), Fe(acac)$_3$ (0.50 equiv., 185.3 mg, 0.52 mmol), phenylsilane (4 equiv., 0.52 mL, 4.20 mmol), EtOH (8 equiv, 0.49 mL, 8.39 mmol) in THF (21 mL) were heated at 60 °C. The reaction was completed after 2 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 25/1-20/1), yielding compound **151l** (68%, dr=1.7/1) contaminated with 1,4-naphthoquinone.

K_2CO_3 (1.5 equiv., 122.9 mg, 0.89 mmol) and CH_3I (3 equiv., 0.11 mL, 1.78 mmol) were added to a solution of **151l** (1 equiv., 342 mg, 0.59 mmol) in DMF (12.0 mL) at 0 °C. Then, the mixture was stirred at room temperature for 15 hours. The reaction was quenched using water（50 mL) and extracted with ethyl acetate (3 x 50 mL). Organic phase was washed with water (30 mL) and brine (30 mL), dried with Na_2SO_4, filtred and concentrated under reduced pressure. Product **177l** (173.5 mg, 0.29 mmol, 50%, dr=7.7/1) was obtained as a brown oil.

Major isomer (177l):

R$_f$ 0.56 (Cyclohexane/EtOAc: 5/1);

$[\alpha]_D^{20}$ = +98 (*c*=0.5, DCM);

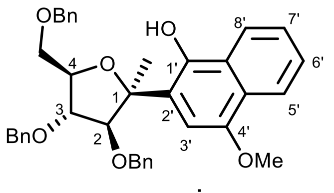
^{1}H NMR (400 MHz, Acetone-d$_6$) δ 8.23 – 8.13 (m, 2H, H-5’ and H-8’), 7.57 – 7.19 (m, 18H, H-6’ and H-7’ and H$_{Ar}$ and H-3’), 6.81 (d, *J* = 8.5 Hz, 1H, H-2’), 4.83 – 4.75 (m, 2H, OC$\underline{H}_2$Ph), 4.73 (d, *J* = 12.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.66 (d, *J* = 11.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.64 – 4.56 (m, 2H, OC$\underline{H}_2$Ph), 4.49 (d, *J* = 3.2 Hz, 1H, H-2), 4.43 (ddd, *J* = 6.5, 5.4, 4.0 Hz, 1H, H-4), 4.16 – 4.11 (m, 1H, H-3), 3.97 (s, 3H, OC$\underline{H}_3$), 3.82 – 3.69 (m, 2H, H-5), 1.49 (s, 3H, C$\underline{H}_3$).

^{13}C NMR (125 MHz, Acetone-d$_6$) δ 152.0 (C-4´), 144.3 (C-1´), 139.6 (CqAr), 139.5 (CqAr), 139.2 (CqAr), 130.3 (CqAr), 129.2 (C$_{Ar}$), 129.1 (C$_{Ar}$), 129.07 (C$_{Ar}$), 128.7 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.53 (C$_{Ar}$), 128.45 (C$_{Ar}$), 128.3 (C$_{Ar}$), 128.2 (C$_{Ar}$), 127.0 (CqAr), 126.8 (C-6´ or C-7´), 126.1 (C-6´ or C-7´), 123.4 (C-5´), 122.6 (C-8´), 116.6 (C-3´), 112.6 (CqAr), 104.4 (C-2´), 90.6 (C-2), 85.4 (C-3), 81.6 (C-4), 73.7 (O$\underline{C}$H$_2$Ph), 72.9 (O$\underline{C}$H$_2$Ph), 72.7 (O$\underline{C}$H$_2$Ph), 71.1 (C-5), 56.0 (O$\underline{C}$H$_3$), 19.5 ($\underline{C}$H$_3$).

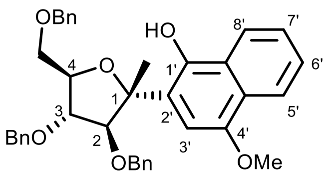
HRMS (ESI) m/z: calcd for $C_{38}H_{38}KO_6$ $[M+K]^+$: 629.2300; found 629.2303.

IR (film): 3030, 2863, 1594, 1462, 1454, 1387, 1268, 1236, 1091, 1070, 1022, 865, 768, 735, 697 cm^{-1}.

2-((3R,4S)-3,4-Bis(benzyloxy)-2-methyltetrahydrofuran-2-yl)-4-methoxynaphthalen-1-ol **(189)**



major



minor

To a solution of **177l** (1 equiv., 54.2 mg, 0.092 mmol) in dry DCM (3.0 mL) was dropwise added the solution of BF_3 OEt_2 (0.1 equiv., 0.0011 mL, 0.0092 mmol) in the dry DCM at -60 ℃ under an Ar atmosphere. The temperature gradually rised to 5 °C for 3 h. The reaction was quenched with $NaHCO_3$ (20 drops). The solution was extracted with DCM (3 x10 mL). Organic phase was washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtred and concentrated. The solvent was removed under reduced pressure, yielding the product **189** (50.9 mg, 0.086 mmol, 94%, dr=4.2/1) as a light-yellow oil.

Minor isomer:

R R_f 0.40 (Cyclohexane/EtOAc: 6/1).

$[\alpha]_D^{20}$=+68.8 (*c*=0.3, DCM).

^{1}H NMR (400 MHz, Acetone-d_6) δ 9.50 (s, 1H, OH), 8.25 – 8.16 (m, 1H, H-8’), 8.13 – 8.06 (m, 1H, H-5’), 7.54 – 7.26 (m, 12H, H-6’ and H-7’ and H_{Ar}), 7.21 – 7.08 (m, 3H, H_{Ar}), 7.08 – 7.01 (m, 2H, H_{Ar}), 6.64 (s, 1H, H-3’), 4.90 (d, *J* = 11.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.80 (d, *J* = 11.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.69 (d, *J* = 2.8 Hz, 1H, H-2), 4.66 – 4.54 (m, 4H, $OC\underline{H_2}Ph$), 4.33 – 4.24 (m, 2H, H-3 and H-4), 3.85 – 3.74 (m, 5H, H-5 and $OC\underline{H_3}$), 1.69 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (125 MHz, Acetone-d_6) δ 149.2 (C-4´), 144.4 (C-1´), 144.3 (CqAr), 139.5 (CqAr), 139.4 (CqAr), 139.1 (CqAr), 129.3 (C_{Ar}), 129.2 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 127.4 (CqAr), 126.4 (C-6´ or C-7´), 126.2 (C-6´ or C-7´), 123.0 (C-8´), 122.2 (C-5´), 121.7 (CqAr), 103.6 (C-3´), 90.4 (C-1), 88.4 (C-2), 85.4 (C-3), 82.3 (C-4), 73.8 ($O\underline{C}H_2Ph$), 72.8 ($O\underline{C}H_2Ph$), 72.3 ($O\underline{C}H_2Ph$), 71.6 (C-5), 56.0 ($O\underline{C}H_3$), 25.2 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{38}H_{38}KO_6$ $[M+K]^+$: 629.2300; found 629.2304.

IR (film): 3285, 2931, 2864, 1560, 1454, 1393, 1361, 1329, 1157, 1095, 1068, 1028, 987, 768, 736, 697 cm^{-1}.

Major isomer:

R_f 0.37 (Cyclohexane/EtOAc: 6/1).

$[\alpha]_D^{20}$=-8.2 (*c*=0.3, DCM).

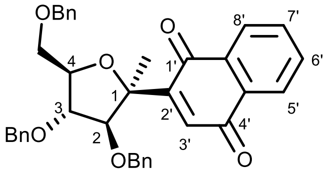
^{1}H NMR (400 MHz, Acetone-d_6) *δ* 9.52 (s, 1H, OH), 8.26 – 8.17 (m, 1H, H-8'), 8.14 – 8.05 (m, 1H, H-5'), 7.52 – 7.23 (m, 12H, H-6' and H-7' and H_{Ar}), 7.19 – 7.04 (m, 3H, H_{Ar}), 7.01 – 6.91 (m, 2H, H_{Ar}), 6.75 (s, 1H, H-3'), 4.73 (d, *J* = 11.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.67 (d, *J* = 11.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.64 (d, *J* = 12.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.60 (d, *J* = 12.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.55 (ddd, *J* = 6.6, 5.1, 3.2 Hz, 1H, H-4), 4.49 (d, *J* = 11.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.42 (d, *J* = 0.8 Hz, 1H, H-2), 4.40 (d, *J* = 11.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.18 (dd, *J* = 3.2, 0.8 Hz, 1H, H-3), 3.90 (s, 3H, OC$\underline{H_3}$), 3.80 (dd, *J* = 10.0, 6.6 Hz, 1H, H-5), 3.72 (dd, *J* = 10.0, 5.0 Hz, 1H, H-5), 1.84 (s, 3H, C$\underline{H_3}$).

^{13}C NMR (125 MHz, Acetone-d_6) *δ* 148.6 (C-4´), 145.8 (C-1´), 139.4 (CqAr), 139.2 (CqAr), 139.0 (CqAr), 129.2 (C_{Ar}), 129.1 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.56 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 127.5 (CqAr), 126.3 (CqAr), 126.1 (C-6´ or C-7´), 126.0 (C-6´ or C-7´), 123.2 (C-8´), 122.0 (C-5´), 119.0 (C-2´), 105.1 (C-3´), 93.1 (C-1), 88.9 (C-2), 85.3 (C-3), 83.8 (C-4), 73.8 (O$\underline{C}H_2$Ph), 72.5 (O$\underline{C}H_2$Ph), 72.4 (O$\underline{C}H_2$Ph), 71.4 (C-5), 56.1 (O$\underline{C}H_3$), 25.7 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{38}H_{38}KO_6$ $[M+K]^+$: 629.2300; found 629.2299.

IR (film): 3324, 2927, 2863, 1600, 1454, 1397, 1359, 1332, 1239, 1161, 1097, 1077, 1027, 987, 768, 737, 697 cm^{-1}.

2-((2S,3S,4R,5R)-3,4-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-methyltetrahydrofuran-2-yl)naphthalene-1,4-dione **(215)**



Compound **189** (major compound) (1 equiv., 25.7 mg, 0.044 mmol) was dissolved in MeCN (1 mL). To this, a solution of CAN (3 equiv., 71.6 mg, 0.13 mmol) in H_2O (0.20 mL) was added at once at RT. The reaction mixture was then stirred at 50 °C for 3 h. It was then quenched with ethyl acetate and water. The organic phase was washed several times with water. It was then dried over Na_2SO_4, concentrated in vacuo. After purification by column chromatography (SiO_2, cyclohexane/EtOAc: 20/1), compound **215** (22.8 mg, 0.04 mmol, 91%) was obtained as a light brown oil.

R_f 0.38 (Cyclohexane/EtOAc: 6/1).

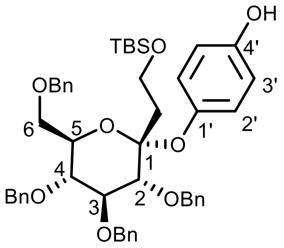
^{1}H NMR (400 MHz, C_6D_6) *δ* 8.01 – 7.98 (m, 1H, H-5' or H-8'), 7.96 – 7.93 (m, 1H, H-5' or H-8'), 7.56 (s, 1H, H-3'), 7.31 – 6.85 (m, 17H, H-6' and H-7' and H_{Ar}), 4.61 – 4.52 (m, 2H, H-2 and H-4), 4.40 (s, 2H, OC$\underline{H_2}$Ph), 4.32 (d, *J* = 12.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.28 – 4.20 (m, 3H, OC$\underline{H_2}$Ph), 4.08 (d, *J* = 2.2 Hz, 1H, H-3), 3.59 (dd, J = 9.5, 5.6 Hz, 1H, H-5), 3.45 (dd, J = 9.5, 7.8 Hz, 1H, H-5), 1.83 (s, 3H, C$\underline{H_3}$).

^{13}C NMR (125 MHz, C_6D_6) δ 185.0 (C-1´ or C-4´), 184.7 (C-1´ or C-4´), 153.9 (C-2´), 138.9 (CqAr), 138.5 (CqAr), 138.0 (CqAr), 134.1 (C-3´), 133.4 (C-6´ or C-7´), 133.12 (C-6´ or C-7´), 133.1 (CqAr), 132.6 (CqAr), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.7 (C_{Ar}), 127.72 (C_{Ar}), 126.4 (C_{Ar}), 126.10 (C-5´ or C-8´), 126.08 (C-5´ or C-8´), 89.0 (C-2), 86.9 (C-1), 85.3 (C-3), 82.7 (C-4), 73.4 (O$\underline{C}H_2$Ph), 72.4 (O$\underline{C}H_2$Ph), 71.7 (O$\underline{C}H_2$Ph), 71.2 (C-5), 24.7 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{37}H_{34}NaO_6$ $[M+Na]^+$: 597.2248; found 597.2244.

IR (film): 2931, 2864, 1663, 1595, 1454, 1303, 1253, 1097, 1073, 1028, 737, 720, 698 cm^{-1}.

4-(((3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-(2-((tert butyldimethylsilyl)oxy)ethyl)tetrahydro-2H-pyran-2-yl)oxy)phenol **(151pa)**



According to the general procedure, *exo*-glycal **150p** (1 equiv., 68.6 mg, 0.1007 mmol), *p*-benzoquinone (4 equiv., 43.6 mg, 0.403 mmol), Na_2HPO_4 (1.1 equiv., 15.7 mg, 0.11 mmol), $Fe(acac)_3$ (0.5 equiv., 17.8 mg, 0.0504 mmol), phenylsilane (4 equiv., 0.0501 mL, 0.4 mmol), EtOH (8 equiv., 0.047 mL, 0.8 mmol) in THF (2 mL) were heated at 60 °C. After 5 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (160 μL) was added dropwise during 4 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 100/3-50/3), yielding **151pa** (27.9 mg, 0.035 mmol, 35%, dr=2.3:1) as a colourless oil liquid. Analytical samples of α-isomer (major compound) can be obtained after a careful purification.

α-isomer (major compound):

***R**$_f$* 0.20 (Cyclohexane/EtOAc: 10/1);

$[\alpha]_D^{20}$=+67.5 (c=0.3, $CHCl_3$).

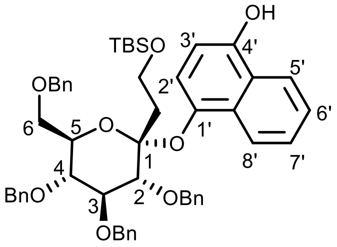
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 18H, H_{Ar}), 7.21 (dd, J = 7.4, 2.1 Hz, 2H, H_{Ar}), 7.05 – 6.98 (m, 2H, H-2'), 6.67 – 6.60 (m, 2H, H-3'), 4.97 (d, J = 11.3 Hz, 1H, OC$\underline{H_2}$Ph), 4.95 (d, J = 11.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.91 – 4.86 (m, 3H, OC$\underline{H_2}$Ph), 4.62 (d, J = 12.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.61 (d, J = 11.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.57 (s, 1H, O$\underline{H}$), 4.55 (d, J = 12.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.24 (t, J = 9.3 Hz, 1H, H-3), 4.17 (ddd, J = 10.2, 5.2, 2.0 Hz, 1H, H-5), 3.82 – 3.74 (m, 3H, H-6 and $CH_2C\underline{H_2}$OTBS), 3.73 (d, J = 9.5 Hz, 1H, H-2), 3.69 – 3.64 (m, 1H, $CH_2C\underline{H_2}$OTBS), 3.62 (dd, J = 10.2, 9.1 Hz, 1H, H-4), 2.11 (dt, J = 14.2, 7.7 Hz, 1H, $C\underline{H}_2CH_2OTBS$), 1.90 (ddd, J = 14.3, 7.1, 4.8 Hz, 1H, $C\underline{H}_2CH_2OTBS$), 0.84 (s, 9H, Si-C($C\underline{H}_3$)$_3$), -0.02 (s, 3H, Si-($C\underline{H}_3$)$_2$), -0.04 (s, 3H, Si-($C\underline{H}_3$)$_2$);

^{13}C NMR (125 MHz, CDCl$_3$) δ 151.5 (C-4´or C-1´), 147.8 (C-4´or C-1´), 139.0 (CqAr), 138.9 (CqAr), 138.6 (CqAr), 138.4 (CqAr), 128.5 (C_{Ar}), 128.0 (C_{Ar}), 127.8 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 122.9 (2 C-2´), 115.8 (2 C-3´), 103.7 (C-1), 83.4 (C-3), 81.9 (C-2), 78.8 (C-4), 75.6 ($O\underline{C}H_2Ph$), 75.1 ($O\underline{C}H_2Ph$), 75.0 ($O\underline{C}H_2Ph$), 73.5 ($O\underline{C}H_2Ph$), 72.2 (C-5), 69.6 (C-6), 59.3 ($CH_2\underline{C}H_2OTBS$), 35.4 ($\underline{C}H_2CH_2OTBS$), 26.2 (Si-C($\underline{C}H_3$)$_3$), 18.5 (Si-$\underline{C}$(CH_3)$_3$), -5.2 (Si-($\underline{C}H_3$)$_2$);

HRMS (ESI) m/z: calcd for $C_{48}H_{58}NaO_8Si$ $[M+Na]^+$: 813.3793; found 813.3793;

IR (film): 3375, 2928, 2856, 1506, 1454, 1210, 1084, 1069, 1027, 834, 734, 696 cm^{-1}.

4-(((3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-(2-((tert-butyldimethylsilyl)oxy)ethyl)tetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151pb)**



According to the general procedure, *exo*-glycal **150p** (1 equiv., 51.7 mg, 0.076 mmol), 1,4-naphthoquinone (4 equiv., 48.0 mg, 0.304 mmol), Na_2HPO_4 (1.1 equiv., 11.9 mg, 0.084 mmol), Fe(acac)$_3$ (1 equiv., 26.8 mg, 0.076 mmol), phenylsilane (4 equiv., 0.038 mL, 0.304 mmol), EtOH (8 equiv., 0.035 mL, 0.607 mmol) in THF (1.5 mL) were heated at 60 °C. After 6 h, phenylsilane (4 equiv.) was added dropwise. The reaction was stirred 23 h. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 20/1-14/1), yielding **151pb** (27.2 mg, 0.03 mmol, 39%, dr=1.7:1) as a brown oil liquid.

α-isomer (major isomer):

R$_f$ 0.38 (Cyclohexane/EtOAc: 6/1).

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.47 (dd, J = 8.4, 1.1 Hz, 1H, H-8´), 8.07 (d, J = 8.2 Hz, 1H, H-5´), 7.49 – 7.20 (m, 22H, H_{Ar} and H-6´ and H-7´), 7.13 (d, J = 8.1 Hz, 1H, H-3´), 6.56 (d, J = 8.1 Hz, 1H, H-2´), 5.04 (d, J = 10.8 Hz, 1H, $OC\underline{H}_2Ph$), 5.03 (d, J = 11.3 Hz, 1H, $OC\underline{H}_2Ph$), 4.98 – 4.89 (m, 3H, $OC\underline{H}_2Ph$), 4.69 – 4.62 (m, 2H, $OC\underline{H}_2Ph$), 4.60 (d, J = 12.1 Hz, 1H, $OC\underline{H}_2Ph$), 4.40 (t, J = 9.2 Hz, 1H, H-3), 4.40 – 4.32 (m, 1H, H-5), 3.90 (d, J = 9.6 Hz, 1H, H-2), 3.83 – 3.75 (m, 3H, H-6 and $CH_2C\underline{H}_2OTBS$), 3.65 (dd, J = 10.1, 9.1 Hz, 1H, H-4), 3.59 (ddd, J = 10.2, 7.0, 4.8 Hz, 1H, $CH_2C\underline{H}_2OTBS$), 2.14 (dt, J = 14.9, 7.6

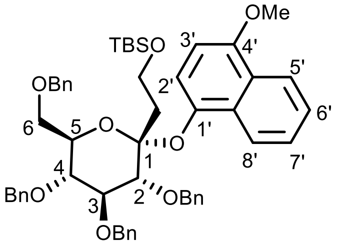
Hz, 1H, C$\underline{H_2}$CH$_2$OTBS), 1.86 (ddd, *J* = 14.4, 6.3, 4.7 Hz, 1H, C$\underline{H_2}$CH$_2$OTBS), 0.81 (s, 9H, Si-C(C$\underline{H_3}$)$_3$), -0.06 (s, 3H, Si-(C$\underline{H_3}$)$_2$), -0.08 (s, 3H, Si-(C$\underline{H_3}$)$_2$);

^{13}C NMR (125 MHz, CDCl$_3$) *δ* 147.4 (C-4´), 143.6 (C-1´), 139.2 (CqAr), 139.0 (CqAr), 138.6 (CqAr), 138.4 (CqAr), 130.3 (CqAr), 128.5 (C$_{Ar}$), 128.4 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 127.6 (C$_{Ar}$), 126.2 (C-7´), 125.7 (C-6´), 125.0 (CqAr), 123.8 (C-8´), 121.3 (C-5´), 116.3 (C-3´), 108.2 (C-2´), 104.5 (C-1), 83.7 (C-3), 82.4 (C-2), 78.8 (C-4), 75.7 (O$\underline{C}$H$_2$Ph), 75.3 (O$\underline{C}$H$_2$Ph), 75.0 (O$\underline{C}$H$_2$Ph), 73.5 (O$\underline{C}$H$_2$Ph), 72.3 (C-5), 69.8 (C-6), 59.4 (CH$_2\underline{C}$H$_2$OTBS), 34.5 ($\underline{C}$H$_2$CH$_2$OTBS), 26.2 (Si-C($\underline{C}$H$_3$)$_3$), 18.5 (Si-$\underline{C}$(CH$_3$)$_3$), -5.3 (Si-($\underline{C}$H$_3$)$_2$);

HRMS (ESI) m/z: calcd for $C_{52}H_{60}NaO_8Si$ [M+Na]$^+$: 863.3950; found 863.3935;

IR (film): 3350, 2927, 2856, 1593, 1454, 1361, 1271, 1257, 1086, 1066, 1028, 835, 772, 735, 697 cm^{-1}.

Tert-butyldimethyl(2-((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)tetrahydro-2H-pyran-2-yl)ethoxy)silane **(177pb)**



NaH (60% in oil, 3 equiv., 20.0 mg, 0.50 mmol) was added portionwisely to a solution of **151pb** (1 equiv., 140.0 mg, 0.17 mmol) in freshly distilled THF (2.40 mL) at 0 °C. And then, CH$_3$I (4 equiv., 0.041 mL, 0.67 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 7.5 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 40/1-30/1), yielding the product **177pb** (76.8 mg, 0.09 mmol, 54%, dr=3/1) as a brown oil.

R$_f$ 0.55 (Cyclohexane/ EtOAc: 8/1);

[α]$_D$^{20}=+102.3 (*c*=0.3, DCM);

^{1}H NMR (400 MHz, Acetone-*d*$_6$) *δ* 8.56 – 8.49 (m, 1H, H-8´), 8.19 – 8.12 (m, 1H, H-5´), 7.54 – 7.22 (m, 23H, H$_{Ar}$ and H-6´ and H-7´ and H-2´), 6.64 (d, *J* = 8.4 Hz, 1H, H-3´), 5.11 (d, *J* = 10.9 Hz, 1H, OC$\underline{H_2}$Ph), 5.05 (d, *J* = 11.4 Hz, 1H, OC$\underline{H_2}$Ph), 5.00 (d, *J* = 10.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.99 (d, *J* = 11.3 Hz, 1H, OC$\underline{H_2}$Ph), 4.95 (d, *J* = 11.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.74 (d, *J* = 11.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.72 (d, *J* = 12.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.66 (d, *J* = 12.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.41 – 4.33 (m, 1H, H-5), 4.33 (d, *J* = 9.3 Hz, 1H, H-

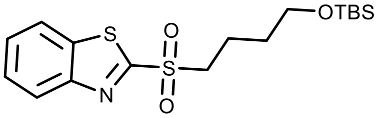
3), 4.03 (d, J = 9.6 Hz, 1H, H-2), 4.01 – 3.96 (m, 1H, H-6), 3.94 (s, 3H, $OC\underline{H_3}$), 3.91 (dt, J = 8.2, 1.7 Hz, 1H, $CH_2C\underline{H_2}OTBS$), 3.89 – 3.83 (m, 1H, H-6), 3.72 (dd, J = 10.2, 9.1 Hz, 1H, H-4), 3.69 – 3.63 (m, 1H, $CH_2C\underline{H_2}OTBS$), 2.23 – 2.12 (m, 1H, $C\underline{H_2}CH_2OTBS$), 1.82 (ddd, J = 14.2, 6.5, 4.7 Hz, 1H, $C\underline{H_2}CH_2OTBS$), 0.84 (s, 9H, Si-$C(C\underline{H_3})_3$), -0.02 (s, 3H, Si-$(C\underline{H_3})_2$), -0.04 (s, 3H, Si-$(C\underline{H_3})_2$).

^{13}C NMR (125 MHz, Acetone-*d*$_6$) δ 152.4 (C-4´), 143.9 (C-1´), 140.1 (CqAr), 140.0 (CqAr), 139.8 (CqAr), 139.6 (CqAr), 131.0 (CqAr), 129.2 (C_{Ar}), 129.1 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 126.9 (CqAr), 126.8 (C-6´ and C-7´), 126.3 (C-6´ and C-7´), 124.2 (C-8´), 122.4 (C-5´), 117.5 (C-2´), 105.2 (C-1), 104.3 (C-3´), 84.6 (C-3), 83.1 (C-2), 79.5 (C-4), 75.9 (2 $O\underline{C}H_2Ph$), 75.4 ($O\underline{C}H_2Ph$), 73.9 ($O\underline{C}H_2Ph$), 73.4 (C-5), 70.5 (C-6), 60.0 ($CH_2\underline{C}H_2OTBS$), 56.0 ($O\underline{C}H_3$), 35.3 ($\underline{C}H_2CH_2OTBS$), 26.4 (Si-$C(\underline{C}H_3)_3$), 18.9(Si-$\underline{C}(CH_3)_3$), -5.15 (Si-$(\underline{C}H_3)_2$), -5.20 (Si-$(\underline{C}H_3)_2$).

HRMS (ESI) m/z: calcd for $C_{53}H_{62}KO_8$ $[M+K]^+$: 893.3846; found 893.3862.

IR (film): 3031, 2928, 2856, 1462, 1454, 1389, 1361, 1269, 1238, 1128, 1089, 1028, 982, 835, 772, 733, 697 cm^{-1}.

2-((4-((Tert-butyldimethylsilyl)oxy)butyl)sulfonyl)benzo[d]thiazole **(154)**



To a solution of 4-[(tert-butyldimethylsilyl)oxy]butan-1-ol (1 equiv., 1.64 g, 8 mmol), **153** (1.5 equiv, 2.0 g, 12 mmol) and PPh_3 (1.5 equiv, 3.15 g, 12 mmol) in THF (24 mL) at 0 °C was added DEAD (1.5 equiv, 1.88 mL, 12 mmol). The reaction mixture was then stirred at room temperature until full conversion of the starting material. The reaction mixture was quenched by the addition of a saturated sodium bicarbonate solution (30 mL). The reaction mixture was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, and concentrated. The crude was purified by column chromatography yielding 2-((4-((tert-butyldimethylsilyl)oxy)butyl)thio)benzo[d]thiazole (2.7 g, 7.54 mmol, 95%). To a stirred solution of 2-((4-((tert-butyldimethylsilyl)oxy)butyl)thio)benzo[d]thiazole (1 equiv, 2.70 g, 7.64 mmol) in DCM (20 mL) at 0 °C under an argon atmosphere, was added portionwise MCPBA (3 equiv, 3.95 g, 7.059 mL, 22.907 mmol). The reaction was stirred at room temperature. After completion of the reaction, 10% aqueous solution of $Na_2S_2O_3$ (25 mL) was added. The layers were separated and the organic layer was washed with saturated solution of $NaHCO_3$ (25 mL), saturated aqueous solution of NaCl (25 mL), then dried (Na_2SO_4) and evaporated under reduced pressure. The crude was purified by column chromatography (SiO_2, Cyclohexane/EtOAc: 95/05) to give the product **154** (2.63 g, 6.82 mmol, 85%) as a white solid.

Rf 0.50 (Cyclohexane/EtOAc: 4/1);

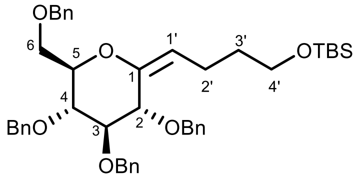
^{1}HNMR ($CDCl_3$, 400 MHz) *δ* 8.22 (ddd, *J* = 8.2, 1.5, 0.7 Hz, 1H, H_{Ar}), 8.02 (ddd, *J* = 7.8, 1.5, 0.7 Hz, 1H, H_{Ar}), 7.72 – 7.50 (m, 2H, H_{Ar}), 3.62 (t, *J* = 5.9 Hz, 2H, $ArSO_2CH_2CH_2CH_2C\underline{H_2}OTBS$), 3.59 – 3.53 (m, 2H, $ArSO_2C\underline{H_2}CH_2CH_2CH_2OTBS$), 2.07 – 1.88 (m, 2H, $ArSO_2CH_2C\underline{H_2}CH_2CH_2OTBS$), 1.74 – 1.58 (m, 2H, $ArSO_2CH_2CH_2C\underline{H_2}CH_2OTBS$), 0.81 (s, 9H, $Si\text{-}C(C\underline{H_3})_3$), -0.00 (s, 6H, $Si\text{-}(C\underline{H_3})_2$);

^{13}CNMR ($CDCl_3$, 125 MHz) *δ* 165.9 (CqAr), 152.9 (CqAr), 136.9 (Cq), 128.1 (C_{Ar}), 127.7 (C_{Ar}), 125.6 (C_{Ar}), 122.4 (C_{Ar}), 62.1 ($ArSO_2CH_2CH_2CH_2\underline{C}H_2OTBS$), 54.8 ($ArSO_2\underline{C}H_2CH_2CH_2CH_2OTBS$), 31.1 ($ArSO_2CH_2CH_2\underline{C}H_2CH_2OTBS$), 25.9 ($Si\text{-}C(\underline{C}H_3)_3$), 19.6 ($ArSO_2CH_2\underline{C}H_2CH_2CH_2OTBS$), 18.3 ($Si\text{-}\underline{C}(CH_3)_3$), -5.3 ($Si(\underline{C}H_3)_2$);

HRMS (ESI) m/z: calcd for $C_{41}H_{42}NaO_7$ $[M+Na]^+$: 408.1094; Found: 408.1066.;

IR (film): 2952, 2927, 2854, 1470, 1322, 1249, 1221, 1145, 1092, 1027, 1004, 830, 780, 761, 728, 689, 662, 610, 592, 555, 522, 489, 463 cm^{-1}.

Tert-Butyldimethyl-4-((3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-ylidene)butoxy)silane **(150q)**



2,3,4,6-Tetra-*O*-benzyl-D-gluconolactone (1 equiv, 303.2 mg, 0.56 mmol) and compound **154** (1.2 equiv, 260.5 mg, 0.68 mmol) were dissolved in freshly distilled THF (4 mL) and cooled at -78 °C under an argon atmosphere. LiHMDS (1M in THF, 1.5 equiv, 0.87 mL, 0.84 mmol) was added dropwise for 5 min and the reaction mixture was stirred for 3 h and then quenched by addition of AcOH (3 equiv, 97 µL, 1.69 mmol). Water (10 mL) was added and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, evaporated under reduced pressure and dried under vacuum pump. The residue was dissolved in freshly distilled THF (6 mL) and DBU (3 equiv, 0.25 mL, 1.69 mmol) was added dropwise at room temperature. Stirring was maintained at room temperature overnight. The mixture was concentrated under reduced pressure and purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 50:1-20:1) to afford compound **150q** (299.8 mg, 0.42 mmol, 75%) as a colourless oil liquid (*Z*/*E* 1.3/1). Pure *Z* isomer was obtained after careful purification.

Isomer *Z*:

Rf 0.52 (Cyclohexane/EtOAc: 4/1).

[α]$_D$^{20}=+52 (*c*=1, $CHCl_3$).

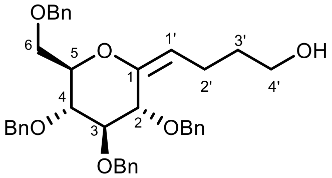
^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.42 – 7.28 (m, 18H, H_{Ar}), 7.21 (dd, *J* = 7.3, 2.2 Hz, 2H, H_{Ar}), 5.05 (td, *J* = 7.4, 1.3 Hz, 1H, H-1'), 4.90 (d, *J* = 11.2 Hz, 1H, $O\underline{CH_2}Ph$), 4.84 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.78 (d, *J* = 11.5 Hz, 1H, $OC\underline{H_2}Ph$), 4.76 (d, *J* = 11.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.71 (d, *J* = 12.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.61 (d, *J* = 11.6 Hz, 1H, $OC\underline{H_2}Ph$), 4.59 (d, *J* = 12.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.58 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 3.97 (dd, *J* = 7.2, 1.3 Hz, 1H, H-2), 3.88 – 3.78 (m, 3H, H-4 or H-5 and H-6), 3.76 – 3.70 (m, 2H, H-3 and H-4 or H-5), 3.67 (t, *J* = 6.6 Hz, 2H, H-4'), 2.37-2.16 (m, 2H, H-2'), 1.71-1.56 (m, 2H, H-3'), 0.95 (s, 9H, $Si\text{-}C(C\underline{H_3})_3$), 0.10 (s, 6H, $Si\text{-}(C\underline{H_3})_2$);

^{13}C NMR (125 MHz, $CDCl_3$) *δ* 148.3 (C-1), 138.6 (CqAr), 138.4(CqAr), 138.3 (CqAr), 138.2 (CqAr), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 110.3 (C-1'), 85.4 (C-3), 79.4 (C-2), 78.4 (C-4 or C-5), 77.9 (C-4 or C-5), 74.6 ($O\underline{C}H_2Ph$), 74.5 ($O\underline{C}H_2Ph$), 73.6 ($O\underline{C}H_2Ph$), 72.6 ($O\underline{C}H_2Ph$), 69.0 (C-6), 63.0 (C-4'), 33.1 (C-3'), 26.1 ($Si\text{-}C(\underline{C}H_3)_3$), 20.8 (C-2'), 18.5 ($Si\text{-}\underline{C}(CH_3)_3$), -5.1 ($Si\text{-}(\underline{C}H_3)_2$);

HRMS (ESI) m/z: calcd for $C_{34}H_{36}NaO_7$ $[M+Na]^+$: 747.3478; found 747.3452;

IR (film): 2928, 2857, 1497, 1454, 1360, 1254, 1080, 1028, 835, 776, 734, 696 cm^{-1}.

(Z)-4-((3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2H-pyran-2-ylidene)butan-1-ol **(150r)**



Compound **150q** (1 equiv, 205 mg, 0.29 mmol) was dissolved in freshly distilled THF (3 mL) and stirred at 0 °C. TBAF (1M in THF, 1.038 equiv, 0.3 mL, 0.3 mmol) was added dropwise and the mixture was stirred at 0 °C for 2 h, then at room temperature overnight. The reaction mixture was quenched with water and diluted with EtOAc. The organic layers were separated and the aqueous phase was extracted with EtOAc three times. The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 5/1 to 4/1) to afford compound **150r** (146.7 mg, 0.25 mmol, 85%) as a colourless oil.

R_f 0.22 (Cyclohexane/EtOAc: 3/1;

[α]$_D$^{20}=+49 (*c*=0.9, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.42 – 7.27 (m, 18H, H_{Ar}), 7.20 – 7.16 (m, 2H, H_{Ar}), 4.96 (td, *J* = 7.9, 1.1 Hz, 1H, H-1'), 4.84 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.79 (d, *J* = 11.4 Hz, 1H, $OC\underline{H_2}Ph$), 4.76 (d, *J* = 12.4

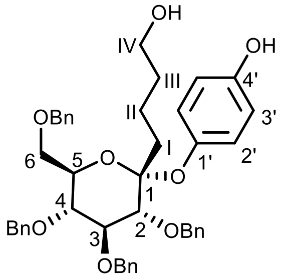
Hz, 1H, OC<u>H</u>$_2$Ph), 4.71 (d, *J* = 11.3 Hz, 1H, OC<u>H</u>$_2$Ph), 4.66 (d, *J* = 12.2 Hz, 1H, OC<u>H</u>$_2$Ph), 4.63 (d, *J* = 11.6 Hz, 1H, OC<u>H</u>$_2$Ph), 4.59 (d, *J* = 12.3 Hz, 1H, OC<u>H</u>$_2$Ph), 4.53 (d, *J* = 11.1 Hz, 1H, OC<u>H</u>$_2$Ph), 3.97 (d, *J* = 6.5 Hz, 1H, H-2), 3.88-3.82 (m, 1H, H-5), 3.79 (dd, *J* = 10.7, 2.0 Hz, 1H, H-6a), 3.76 – 3.67 (m, 3H, H-3, H-4 and H-6b), 3.63 (t, *J* = 6.0 Hz, 2H, H-4'), 2.40 – 2.19 (m, 2H, H-2'), 1.75 – 1.53 (m, 2H, H-3');

^{13}C NMR (125 MHz, CDCl$_3$) δ 148.7 (C-1), 138.4 (CqAr), 138.1 (CqAr), 138.0 (CqAr), 137.9 (CqAr), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.4 (C$_{Ar}$), 128.0 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 109.5 (C-1'), 84.9 (C-3), 78.9 (C-2), 78.0 (C-4), 77.5 (C-5), 74.3 (O<u>C</u>H$_2$Ph), 74.1 (O<u>C</u>H$_2$Ph), 73.5 (O<u>C</u>H$_2$Ph), 72.3 (O<u>C</u>H$_2$Ph), 68.9 (C-6), 61.2 (C-4'), 32.0 (C-3'), 20.0 (C-2');

HRMS (ESI) m/z: calcd for $C_{38}H_{42}NaO_6$ [M+Na]$^+$: 617.2874; found 617.2880;

IR (film): 3340, 2921, 2865, 1496, 1454, 1084, 1071, 1027, 734, 695 cm^{-1}.

4-(((2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-hydroxybutyl)tetrahydro-2H-pyran-2-yl)oxy)phenol **(151r)**



According to the general procedure, *exo*-glycal **150r** (1 equiv., 83.2 mg, 0.14 mmol), *p*-benzoquinone (6 equiv., 60.5 mg, 0.56 mmol), Na_2HPO_4 (1.1 equiv., 21.8 mg, 0.15 mmol), Fe(acac)$_3$ (0.5 equiv., 24.7 mg, 0.07 mmol), phenylsilane (4 equiv., 0.07 mL, 0.56 mmol), EtOH (8 equiv., 0.065 mL, 1.12 mmol) in THF (3 mL) were heated at 60 °C. After 5 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (750 µL) was added dropwise by syringe pump (210 µL/h) during 3.5 h. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 10/1-3/1), yielding **151r** (31.2 mg, 0.044 mmol, 32%, dr=1.2:1) as a colorless oil liquid.

α-isomer (major compound):

R$_f$ 0.21 (Cyclohexane/EtOAc: 2.5/1);

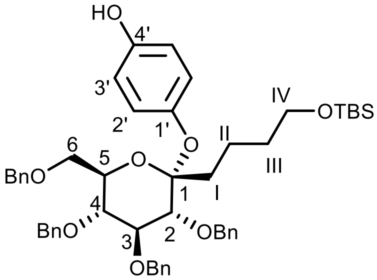
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.23 (m, 18H, H$_{Ar}$), 7.22 – 7.16 (m, 2H, H$_{Ar}$), 7.04 – 6.96 (m, 2H, H-2' or H-3'), 6.67 – 6.61 (m, 2H, H-2' or H-3'), 5.17 (s, 1H, O<u>H</u>), 5.02 (d, *J* = 11.6 Hz, 1H, OCH$_2$Ph), 4.96 (d, *J* = 11.0 Hz, 1H, OC<u>H</u>$_2$Ph), 4.93 (d, *J* = 11.0 Hz, 1H, OC<u>H</u>$_2$Ph), 4.84 (d, *J* = 12.8 Hz, 1H, OC<u>H</u>$_2$Ph), 4.75 (d, *J* = 11.6 Hz, 1H, OC<u>H</u>$_2$Ph), 4.62 (d, *J* = 12.1 Hz, 1H, OC<u>H</u>$_2$Ph), 4.59 (d, *J* = 11.0 Hz, 1H, OC<u>H</u>$_2$Ph), 4.53 (d, *J* = 12.0 Hz, 1H, OC<u>H</u>$_2$Ph), 4.28 (t, *J* = 9.3 Hz, 1H, H-3), 4.16 (dt, *J* = 9.9, 3.4 Hz, 1H, H-5), 3.76 (d, *J* = 3.5 Hz, 2H, H-6), 3.67 – 3.63 (m, 1H, H-4), 3.60 (d, *J* = 9.6 Hz, 1H, H-2), 3.43 (td, *J* = 6.4, 3.7 Hz, 2H, H-IV), 1.75 – 1.48 (m, 2H, H-I), 1.37 – 1.18 (m, 3H, H-II and H-III), 1.15 – 1.00 (m, 1H, H-II);

^{13}C NMR (125 MHz, CDCl$_3$) δ 151.7 (C-4´or C-1´), 147.5 (C-4´or C-1´), 138.8 (CqAr), 138.6 (CqAr), 138.3 (2 CqAr), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.1 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 122.9 (2 C-2´ or C-3´), 115.8 (2 C-2´ or C-3´), 104.9 (C-1), 83.6 (C-3), 79.9 (C-2), 78.8 (C-4), 75.7 (O$\underline{C}$H$_2$Ph), 75.1 (2 O$\underline{C}$H$_2$Ph), 73.4 (O$\underline{C}$H$_2$Ph), 72.1 (C-5), 69.3 (C-6), 62.4 (C-IV), 32.6 (C-III), 32.3 (C-I), 19.9 (C-II);

HRMS (ESI) m/z: calcd for $C_{44}H_{48}NaO_8$ [M+Na]$^+$: 727.3241; found 727.3262;

IR (film): 3371, 2926, 2870, 1508, 1454, 1361, 1211, 1089, 1028, 736, 697 cm^{-1}.

4-(((2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-((tert-butyldimethylsilyl)oxy)butyl)tetrahydro-2H-pyran-2-yl)oxy)phenol (**151qa**)



Compound **150q** (1 equiv., 86 mg, 0.12 mmol), *p*-benzoquinone (4 equiv., 52.5 mg, 0.49 mmol), Na_2HPO_4 (1.1 equiv., 18.9 mg, 0.13 mmol), Fe(acac)$_3$ (0.5 equiv., 21.4 mg, 0.0606 mmol) were dissolved in freshly distilled THF (2.4 mL) at room temperature under Ar, Subsequently, phenylsilane (4 equiv., 0.0603 mL, 0.49 mmol) was added dropwise and following EtOH (8 equiv., 0.057 mL, 0.97 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring. About 5 mins, *p*-benzoquinone (2 equiv.) dissolved in THF (400 µL) was added dropwise during 4 h. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 20/1-11/1), yielding the product **151qa** (23 mg, 0.028 mmol, 23%) as a colorless oil liquid.

R$_f$ 0.48 (Cyclohexane/EtOAc: 4/1).

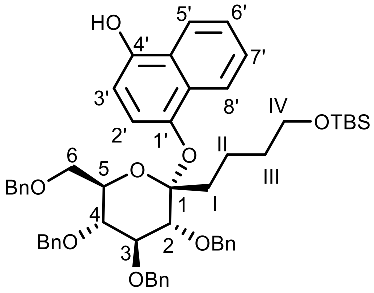
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.25 (m, 18H, H$_{Ar}$), 7.22 (dd, J = 7.5, 2.0 Hz, 2H, H$_{Ar}$), 7.05 – 6.98 (m, 2H, 2' or 3'), 6.67 – 6.61 (m, 2H, 2' or 3'), 5.00 (d, J = 11.4 Hz, 1H, OC$\underline{H}_2$Ph), 4.95 (d, J = 10.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.91 (d, J = 10.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.89 (d, J = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.77 – 4.71 (m, 2H, OC$\underline{H}_2$Ph and O$\underline{H}$), 4.66 – 4.59 (m, 2H, OC$\underline{H}_2$Ph), 4.55 (d, J = 12.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.27 (t, J = 9.2 Hz, 1H, H-3), 4.16 (ddd, J = 10.2, 4.5, 2.6 Hz, 1H, H-5), 3.79 – 3.74 (m, 2H, H-6), 3.66 – 3.58 (m, 2H, H-4 and H-2), 3.44 (t, J = 6.3 Hz, 2H, H-IV), 1.75 – 1.54 (m, 2H, H-II), 1.46 – 1.19 (m, 4H, H-III and H-I), 0.84 (s, 9H, Si-C(C$\underline{H_3}$)$_3$), -0.02 (s, 3H, Si-(C$\underline{H_3}$)$_2$), -0.03 (s, 3H, Si-(C$\underline{H_3}$)$_2$).

^{13}C NMR (125 MHz, CDCl$_3$) δ 151.4 (C-4´or C-1´), 147.8 (C-4´or C-1´), 138.8 (CqAr), 138.7 (CqAr), 138.6 (CqAr), 138.4 (CqAr), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.0 (C$_{Ar}$), 127.9 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.7 (C$_{Ar}$), 122.9 (2 C-2´ or C-3´), 115.7 (2 C-2´ or C-3´), 105.0 (C-1), 83.6 (C-3), 80.2 (C-2), 79.0 (C-4), 75.7 (O$\underline{C}$H$_2$Ph), 75.2 (O$\underline{C}$H$_2$Ph), 75.1 (O$\underline{C}$H$_2$Ph), 73.5 (O$\underline{C}$H$_2$Ph), 72.3 (C-5), 69.5 (C-6), 63.0 (C-IV), 33.1 (C-III), 32.8 (C-I), 26.1 (Si-C($\underline{C}$H$_3$)$_3$), 20.4 (C-II), 18.4 (Si-$\underline{C}$(CH$_3$)$_3$), -5.1 (Si-($\underline{C}$H$_3$)$_2$)

HRMS (ESI) m/z: calcd for $C_{50}H_{62}KO_8$ [M+K]$^+$: 857.3846; found 857.3836.

IR (film) Q: 3373, 2928, 2857, 1507, 1454, 1361, 1211, 1088, 1028, 835, 776, 735, 697 cm^{-1}.

4-(((2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-(4-((tert-butyldimethylsilyl)oxy)butyl)tetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151qb)**



According to the general procedure, *exo*-glycal **150q** (1 equiv., 237.6 mg, 0.34 mmol), 1,4-naphthoquinone (2.5 equiv., 132.5 mg, 0.84 mmol), Na$_2$HPO$_4$ (1.1 equiv., 52.3 mg, 0.37 mmol), Fe(acac)$_3$ (0.7 equiv., 82.9 mg, 0.23 mmol), phenylsilane (5 equiv., 0.21 mL, 1.68 mmol), EtOH (20 equiv., 0.39 mL, 6.70 mmol) in THF (6.80 mL) were heated at 60 °C. After 4 h, the mixture was evaporated. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 16:1-14:1), yielding the product **151qb** (119.8 mg, 0.14 mmol, 41% dr=1.7:1) as a brown oil.

Major compound:

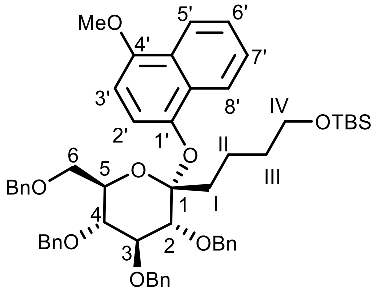
^{1}H NMR (400 MHz, Acetone-*d*$_6$) *δ* 8.75 (s, 1H, O$\underline{H}$), 8.56 – 8.51 (m, 1H, H-8'), 8.21 – 8.16 (m, 1H, H-5'), 7.54 – 7.22 (m, 23H, H$_{Ar}$, H-3' and H-7' and H-6'), 6.75 (d, *J* = 8.2 Hz, 1H, H-2'), 5.11 (d, *J* = 11.0 Hz, 1H, OC$\underline{H_2}$Ph), 5.04 (d, *J* = 11.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.99 (d, *J* = 11.4 Hz, 1H, OC$\underline{H_2}$Ph), 4.96 (d, *J* = 11.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.85 (d, *J* = 10.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.74 (d, *J* = 11.3 Hz, 1H, OC$\underline{H_2}$Ph), 4.70 (d, *J* = 12.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.64 (d, *J* = 12.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.40 – 4.32 (m, 2H, H-3 and H-5), 3.97 (dd, *J* = 10.8, 1.8 Hz, 1H, H-6), 3.86 (dd, *J* = 10.7, 5.9 Hz, 1H, H-6), 3.80 (d, *J* = 9.5 Hz, 1H, H-2), 3.71 (dd, *J* = 10.1, 9.0 Hz, 1H, H-4), 3.49 – 3.44 (m, 2H, H-IV), 1.86 – 1.76 (m, 1H H-I), 1.70 – 1.59 (m, 2H, H-I and H-II), 1.58 – 1.49 (m, 1H, H-II), 1.33 – 1.18 (m, 2H, H-III), 0.81 (s, 9H, Si-C(C$\underline{H}_3$)$_3$), -0.05 (s, 3H, Si-(C$\underline{H}_3$)$_2$), -0.07 (s, 3H, Si-(C$\underline{H}_3$)$_2$).

^{13}C NMR (125 MHz, Acetone-*d*$_6$) δ 149.9 (C-4´), 143.2 (C-1´), 140.1 (CqAr), 139.9 (CqAr), 139.85 (CqAr), 139.7 (CqAr), 131.3 (CqAr), 129.2 (C$_{Ar}$), 129.11 (C$_{Ar}$), 129.10 (C$_{Ar}$), 129.06 (C$_{Ar}$), 128.7 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.4 (C$_{Ar}$), 128.3 (C$_{Ar}$), 128.22 (C$_{Ar}$), 128.2 (C$_{Ar}$), 128.16 (C$_{Ar}$), 126.5 (C-6' or C-7'), 126.3 (CqAr), 125.7 (C-6' or C-7'), 124.3 (C-8´), 122.7 (C-5´), 117.9 (C-3'), 108.3 (C-2'), 106.4 (C-1), 84.7 (C-3), 81.6 (C-2), 79.7 (C-4), 76.1 (O$\underline{C}$H$_2$Ph), 76.0 (O$\underline{C}$H$_2$Ph), 75.4 (O$\underline{C}$H$_2$Ph), 73.9 (O$\underline{C}$H$_2$Ph), 73.5 (C-5), 70.6 (C-6), 63.2 (C-IV), 33.7 (C-III), 32.4 (C-I), 26.3 (Si-C($\underline{C}$H$_3$)$_3$), 21.1 (C-II), 18.8 (Si-$\underline{C}$(CH$_3$)$_3$), -5.14 (Si-($\underline{C}$H$_3$)$_2$), -5.16 (Si-($\underline{C}$H$_3$)$_2$).

HRMS (ESI) m/z: calcd for $C_{54}H_{64}KO_8Si$ [M+K]$^+$: 907.4002; found 907.3994.

IR (film): 3347, 2928, 2857, 1668, 1593, 1471, 1454, 1383, 1360, 1270, 1254, 1129, 1090, 1067, 1028, 1008, 835, 772, 737, 698 cm^{-1}.

Tert-butyldimethyl(4-((2R,3R,4S,5R,6R)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)tetrahydro-2H-pyran-2-yl)butoxy)silane **(177qb)**



NaH (60% in oil, 3 equiv., 13.3 mg, 0.33 mmol) was added portionwisely to solution of **151qb** (1 equiv., 96.5 mg, 0.11 mmol) in freshly distilled THF (1.6 mL) at 0 °C. And then, CH_3I (4 equiv., 0.028 mL, 0.44 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 6 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 40/1-35/1), yielding the product **177qb** (56 mg, 0.063 mmol, 57%, dr=3.4:1) as a brown oil liquid.

R$_f$ 0.73 (Cyclohexane/EtOAc: 8/1);

^{1}H NMR (500 MHz, Acetone-*d*$_6$) δ 8.56 – 8.50 (m, 1H, H-8'), 8.18 – 8.13 (m, 1H, H-5'), 7.52 – 7.24 (m, 23H, H$_{Ar}$, H-3' and H-7' and H-6'), 6.64 (d, *J* = 8.4 Hz, 1H, H-2'), 6.55 (d, *J* = 8.5 Hz, 0.1H, β-isomer), 5.11 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 5.04 (d, *J* = 11.2 Hz, 1H, OC$\underline{H}_2$Ph), 4.99 (d, *J* = 11.2 Hz, 1H, OC$\underline{H}_2$Ph), 4.95 (d, *J* = 11.2 Hz, 1H, OC$\underline{H}_2$Ph), 4.85 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.74 (d, *J* = 11.3 Hz, 1H, OC$\underline{H}_2$Ph), 4.71 (d, *J* = 12.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.66 (d, *J* = 12.1 Hz, 1H, OC$\underline{H}_2$Ph), 4.37 (d, *J* = 9.3

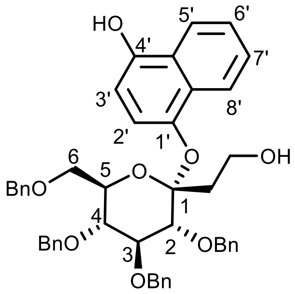
Hz, 1H, H-3), 4.36 – 4.31 (m, 1H, H-5), 3.98 (dd, *J* = 10.7, 1.8 Hz, 1H, H-6), 3.95 (s, 3H, OC$\underline{H_3}$), 3.90 – 3.82 (m, 1H, H-6), 3.80 (d, *J* = 9.4 Hz, 1H, H-2), 3.71 (dd, *J* = 10.2, 9.0 Hz, 1H, H-4), 3.46 (td, *J* = 6.2, 1.2 Hz, 2H, H-IV), 1.86 – 1.76 (m, 1H, H-I), 1.70 – 1.60 (m, 1H, H-I), 1.60 – 1.50 (m, 1H, H-II), 1.49 – 1.39 (m, 1H, H-II), 1.35 – 1.19 (m, 2H, H-III), 0.89 (s, 1H, Si-C(C$\underline{H_3}$)$_3$, β-isomer), 0.81 (s, 9H, Si-C(C$\underline{H_3}$)$_3$), 0.05 (s, 0.35H, β-isomer), 0.05 (s, 0.36H, β-isomer), -0.05 (s, 3H, Si-(C$\underline{H_3}$)$_2$), -0.07 (s, 3H, Si-(C$\underline{H_3}$)$_2$).

^{13}C NMR (125 MHz, Acetone-*d*$_6$) *δ* 152.2 (C-4´), 144.0 (C-1´), 140.1 (CqAr), 139.9 (CqAr), 139.7 (CqAr), 131.0 (CqAr), 129.2 (C$_{Ar}$), 129.1 (C$_{Ar}$), 128.7 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.4 (C$_{Ar}$), 128.3 (C$_{Ar}$), 128.2 (C$_{Ar}$), 126.9 (CqAr), 126.8 (6' or 7'), 126.2 (6' or 7'), 124.2 (C-8´), 122.4 (C-5´), 117.4 (2' or 3'), 106.5 (C-1), 104.3 (2' or 3'), 84.7 (C-3), 81.6 (C-2), 79.7 (C-4), 76.07 (O$\underline{C}$H$_2$Ph), 76.05 (O$\underline{C}$H$_2$Ph), 75.4 (O$\underline{C}$H$_2$Ph), 73.9 (C-5), 73.5 (O$\underline{C}$H$_2$Ph), 70.6 (C-6), 63.2 (C-IV), 55.9 (O$\underline{C}$H$_3$), 33.7 (C-III), 32.4 (C-I), 26.4 (Si-C($\underline{C}$H$_3$)$_3$, β-isomer), 26.3 (Si-C($\underline{C}$H$_3$)$_3$), 21.1 (C-II), 18.8 (Si-$\underline{C}$(CH$_3$)$_3$), -5.15 (Si-($\underline{C}$H$_3$)$_2$), -5.16 (Si-($\underline{C}$H$_3$)$_2$).

HRMS (ESI) m/z: calcd for C$_{55}$H$_{66}$KO$_8$Si [M+K]$^+$: 921.4159; found 921.4122.

IR (film): 3064, 3031, 2928, 2856, 1593, 1462, 1389, 1361, 1269, 1238, 1093, 1028, 984, 835, 772, 735, 697 cm^{-1}.

4-(((2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-(2-hydroxyethyl)tetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151o)**



According to the general procedure, *exo*-glycal **150o** (1 equiv., 180.0 mg, 0.32 mmol), 1,4-naphthoquinone (2.5 equiv., 125.6 mg, 0.79 mmol), Na$_2$HPO$_4$ (1.1 equiv., 49.6 mg, 0.36 mmol), Fe(acac)$_3$ (0.50 equiv., 56.1 mg, 0.16 mmol), phenylsilane (4 equiv., 0.16 mL, 1.27 mmol), EtOH (8 equiv., 0.15 mL, 2.54 mmol) in freshly distilled THF (6.40 mL) were heated at 60 °C. After 2 h, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 16/1-14/1), yielding the product **151o** (164.9 mg, 0.23 mmol, 71%, dr=3.4/1) as a brown solid.

Major compound:

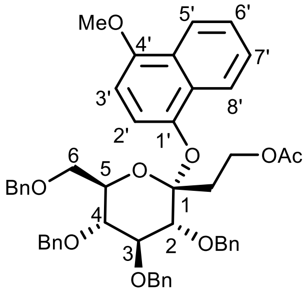
^{1}H NMR (400 MHz, Methanol-*d*$_4$) *δ* 8.46 (d, *J* = 8.4 Hz, 1H, H-8´), 8.14 (d, *J* = 8.4 Hz, 1H, H-5´), 7.46 – 7.10 (m, 23H, H$_{Ar,}$, H-7´, H-6´ and H-3´), 6.66 (d, *J* = 8.2 Hz, 1H, H-2´), 5.01 (d, *J* = 10.8 Hz, 1H, OC$\underline{H_2}$Ph), 4.90 (d, *J* = 11.2 Hz, 1H, OC$\underline{H_2}$Ph), 4.84 – 4.70 (m, 3H, OC$\underline{H_2}$Ph), 4.59 (d, *J* = 10.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.58 – 4.49 (m, 2H, OC$\underline{H_2}$Ph), 4.34 – 4.26 (m, 2H, H-3 and H-5), 3.80 (dd, *J* = 10.7, 1.6 Hz, 1H, H-6), 3.75 (d, *J* = 9.5 Hz, 1H, H-2), 3.69 (dd, *J* = 10.6, 5.7 Hz, 1H, H-6), 3.63 – 3.52 (m, 3H, H-4 and CH_2CH_2OH), 2.10 – 2.01 (m, 1H, CH_2CH_2OH), 1.87 – 1.77 (m, 1H, CH_2CH_2OH).

^{13}C NMR (125 MHz, Methanol-*d*$_4$) *δ* 150.8 (C-4´), 143.3 (C-1´), 140.1 (CqAr), 140.0 (CqAr), 139.6 (2 CqAr), 131.7 (CqAr), 129.42 (C$_{Ar}$), 129.4 (C$_{Ar}$), 129.36 (C$_{Ar}$), 129.3 (C$_{Ar}$), 129.27 (C$_{Ar}$), 129.04 (C$_{Ar}$), 129.0 (C$_{Ar}$), 128.98 (C$_{Ar}$), 128.9 (C$_{Ar}$), 128.8 (C$_{Ar}$), 128.74 (C$_{Ar}$), 128.71 (C$_{Ar}$), 128.64 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.3 (C$_{Ar}$), 126.9 (CqAr), 126.8 (C-6´ or C-7´), 126.0 (C-6´ or C-7´), 124.4 (C-8´), 123.0 (C-5´), 118.6 (C-3´), 108.2 (C-2´), 105.8 (C-1), 84.8 (C-3), 82.7 (C-2), 79.8 (C-4), 76.7 (O$\underline{C}H_2$Ph), 76.4 (O$\underline{C}H_2$Ph), 76.0 (O$\underline{C}H_2$Ph), 74.4 (O$\underline{C}H_2$Ph), 73.6 (C-5), 70.5 (C-6), 58.8 (CH_2CH_2OH), 35.7 (CH_2CH_2OH).

HRMS (ESI) m/z: calcd for $C_{46}H_{46}NaO_8$ $[M+Na]^+$: 749.3085; found 749.3064.

IR (film): 3251, 2920, 2866, 1592, 1497, 1454, 1382, 1357, 1271, 1240, 1211, 1063, 1028, 1010, 859, 830, 772, 735, 697 cm^{-1}.

2-((2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)tetrahydro-2H-pyran-2-yl)ethyl acetate **(177o)**



Add K_2CO_3 (1.5 equiv., 45.5 mg, 0.33 mmol) and CH_3I (3 equiv., 0.041 mL, 0.66 mmol) to a solution of **151o** (1 equiv., 159.4 mg, 0.22 mmol) in DMF (5.00 mL) at 0 °C. Then, stir the mixture at room temperature for 24 hours. The reaction was quenched using water（30 mL) and extracted with EtOAc (3 x 20 mL). Organic phase was washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, filtred and concentrated. the obtained residue was used in next step.

The obtained residue (1 equiv., 141.2 mg, 0.19 mmol) was dissolved in the pyridine (2 mL) at 0 °C. Following Ac_2O (48 equiv., 1088.7 mg, 1.00 mL, 10.66 mmol) was added slowly. The reaction is gradually warmed to room temperature for overnight. The reaction was quenched by a saturated aqueous solution of $NaHCO_3$ (30 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with a brine (3 x 20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 15/1-10/1), yielding the product **177o** (111.5 mg, 0.14 mmol, 74%, dr=3.9/1).

R_f 0.53 (Cyclohexane/EtOAc: 3/1);

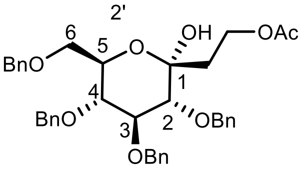
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 – 8.47 (m, 1H, H-8´), 8.26 – 8.20 (m, 1.5H, H-5´ and isomer), 7.54 – 7.22 (m, 23H, $H_{Ar,}$, H-7´, H-6´ and H-3´), 6.57 (d, *J* = 8.3 Hz, 1H, H-2´), 6.39 (d, *J* = 8.6 Hz, 0.26H, H-2´isomer), 5.17 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 5.07 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 5.01 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.97 (d, *J* = 11.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.93 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.75 – 4.66 (m, 2.74H, $OC\underline{H_2}Ph$ and isomer), 4.65 (d, *J* = 12.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.59 (d, *J* = 11.9 Hz, 0.74H, $OC\underline{H_2}Ph$ isomer), 4.49 (t, *J* = 9.3 Hz, 1H, H-3), 4.47 – 4.35 (m, 1H, H-5), 4.17 – 4.05 (m, 2H, CH_2CH_2OAc and isomer), 3.97 (s, 3H, $OC\underline{H_3}$), 3.97 – 3.87 (m, 2.3H, H-6 and isomer), 3.82 (dd, *J* = 10.7, 6.0 Hz, 1.64H, H-6 and isomer), 3.76 (d, *J* = 9.5 Hz, 1H, H-2), 3.70 (t, *J* = 9.6 Hz, 1H, H-4), 2.24 – 2.12 (m, 1H, CH_2CH_2OAc), 2.12 – 1.99 (m, 2H, CH_2CH_2OAc), 1.94 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (125 MHz, Chloroform-*d*) δ 171.2 (C-4´ isomer), 170.8 (C-4´), 151.7 (C-1´), 150.9 (C-1´ isomer), 143.1 (CqAr isomer), 142.9 (CqAr), 138.8 (CqAr), 138.72 (CqAr), 138.7 (CqAr isomer), 138.6 (CqAr), 138.3 (CqAr), 130.1 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.48 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.96 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.77 (C_{Ar}), 127.7 (C_{Ar}), 127.68 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 127.48 (C_{Ar}), 126.3 (C-6´), 126.2 (C-6´ isomer), 125.7 (C-8´), 125.6 (C-8´ isomer), 123.3 (C-5´), 122.4 (C-5´ isomer), 121.8 (C-7´ isomer), 121.7 (C-7´), 116.3 (C-3´), 114.5 (C-3´ isomer), 105.7 (C-1 isomer), 104.0 (C-1), 103.4 (C-2´), 103.35 (C-2´ isomer), 84.7 (C-3 isomer), 83.7 (C-3), 81.6 (C-2), 78.8 (C-4), 78.2 (C-4 isomer), 75.9 ($O\underline{C}H_2Ph$), 75.8 ($O\underline{C}H_2Ph$ isomer), 75.3 ($O\underline{C}H_2Ph$), 75.1 ($O\underline{C}H_2Ph$), 74.2 ($O\underline{C}H_2Ph$ isomer), 73.9 (C-5 isomer), 73.5 ($O\underline{C}H_2Ph$), 73.4 ($O\underline{C}H_2Ph$ isomer), 72.5 (C-5), 69.6 (C-6), 68.8 (C-6 isomer), 60.6 (, CH_2CH_2OAc), 60.0 (CH_2CH_2OAc isomer), 55.7 ($O\underline{C}H_3$), 30.8 (CH_2CH_2OAc), 30.5 (CH_2CH_2OAc isomer), 21.2 ($\underline{C}H_3$ isomer), 21.1 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{49}H_{50}NaO_9$ $[M+Na]^+$: 805.3347; found 805.3344.

IR (film): 2907, 2864, 1737, 1593, 1497, 1462, 1454, 1389, 1365, 1268, 1235, 1155, 1126, 1088, 1067, 1027, 981, 853, 822, 771, 733, 696, 604 cm^{-1}.

2-((2S,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-hydroxytetrahydro-2H-pyran-2-yl)ethyl acetate **(178c)**

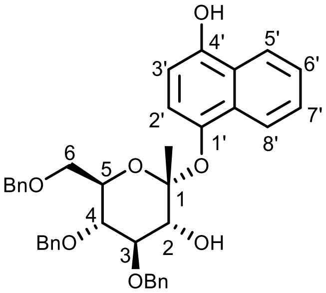


Compound **178** was obtained in Fries rearrangement reaction (see **Scheme 98**)

R_f 0.29 (Cyclohexane/EtOAc: 3/1);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.24 (m, 18H, H_{Ar}), 7.22 – 7.17 (m, 2H, H_{Ar}), 4.98 – 4.91 (m, 2H, $OC\underline{H_2}Ph$), 4.89 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.84 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.71 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.63 – 4.56 (m, 2H, $OC\underline{H_2}Ph$), 4.52 (d, *J* = 12.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.33 (dt, *J* = 11.9, 6.0 Hz, 1H, CH_2CH_2OAc), 4.24 (ddd, *J* = 11.4, 7.4, 5.5 Hz, 1H, CH_2CH_2OAc), 4.04 (t, *J* = 9.2 Hz, 1H, H-3), 3.98 (ddd, *J* = 10.1, 3.8, 1.9 Hz, 1H, H-5), 3.75 (dd, *J* = 10.9, 3.8 Hz, 1H, H-6), 3.71 – 3.65 (m, 1H, H-4), 3.63 (dd, *J* = 10.9, 1.9 Hz, 1H, H-6), 3.50 (s, 1H, $O\underline{H}$), 3.38 (d, *J* = 9.3 Hz, 1H, H-2), 2.11 (ddd, *J* = 14.5, 7.4, 5.7 Hz, 1H, CH_2CH_2OAc), 2.01 (s, 3H, $C\underline{H_3}$), 1.84 (dt, *J* = 14.5, 5.9 Hz, 1H, CH_2CH_2OAc).

(2R,3R,4R,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-((4-hydroxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran-3-ol (**151h**)



According to the general procedure, *exo*-glycal **150h** (1 equiv., 73.5 mg, 0.16 mmol), 1,4-naphthoquinone (2.5 equiv., 65.1 mg, 0.41 mmol), Na_2HPO_4 (1.1 equiv., 25.7 mg, 0.18 mmol), $Fe(acac)_3$ (0.50 equiv., 29.1 mg, 0.082 mmol) were dissolved in freshly distilled THF (2 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.082 mL, 0.66 mmol) was added dropwise and EtOH (8 equiv., 0.077 mL, 1.32 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring until the reaction was basically completed for 1.5 h. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc: 16/1-6/1), yielding the product **151h** (55.3 mg, 0.091 mmol, 55%, dr=8.4/1) as an oil.

R_f 0.49 (Cyclohexane/ EtOAc: 2/1);

$[\alpha]_D^{20}$=+88.5 (*c*=0.3, DCM);

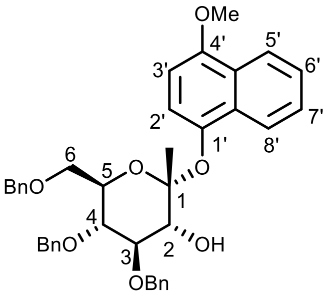
^{1}H NMR (400 MHz, Methanol-*d*$_4$) *δ* 8.58 – 8.41 (m, 1H, H-8´), 8.24 – 8.12 (m, 1H, H-5´), 7.48 – 7.14 (m, 18H, H$_{Ar,}$, H-7´, H-6´ and H-3´), 6.65 (d, *J* = 8.2 Hz, 1H, H-2´), 5.09 (d, *J* = 11.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.86 (d, *J* = 10.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.80 (d, *J* = 11.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.62 – 4.49 (m, 3H, OC$\underline{H_2}$Ph), 4.26 (ddd, *J* = 10.2, 5.9, 1.8 Hz, 1H, H-5), 4.11 (t, *J* = 9.2 Hz, 1H, H-3), 3.82 (dd, *J* = 10.6, 1.9 Hz, 1H, H-6), 3.70 (dd, *J* = 10.6, 5.9 Hz, 1H, H-6), 3.59 (d, *J* = 9.6 Hz, 1H, H-2), 3.55 (dd, *J* = 10.2, 9.0 Hz, 1H, H-4), 1.28 (s, 3H, C$\underline{H_3}$).

^{13}C NMR (125 MHz, Methanol-*d*$_4$) *δ* 150.5 (C-4´), 143.8 (C-1´), 140.4 (CqAr), 139.62 (CqAr), 139.55 (CqAr), 131.4 (CqAr), 129.4 (C$_{Ar}$), 129.3 (C$_{Ar}$), 129.02 (C$_{Ar}$), 128.98 (C$_{Ar}$), 128.9 (C$_{Ar}$), 128.70 (C$_{Ar}$), 128.68 (C$_{Ar}$), 128.5 (C$_{Ar}$), 126.9 (CqAr), 126.7 (C-6´ or C-7´), 125.8 (C-6´ or C-7´), 124.1 (C-5´), 123.0 (C-8´), 118.3 (C-3´), 108.2 (C-2´), 105.5 (C-1), 84.4 (C-3), 79.8 (C-4), 78.6 (C-2), 76.4 (O$\underline{C}$H$_2$Ph), 75.9 (O$\underline{C}$H$_2$Ph), 74.5 (O$\underline{C}$H$_2$Ph), 73.2 (C-5), 70.8 (C-6), 20.8 ($\underline{C}$H$_3$).

HRMS (ESI) m/z: calcd for $C_{38}H_{38}KO_7$ $[M+K]^+$: 645.2249; found 645.2239.

IR (film): 3391, 3031, 2920, 2870, 1593, 1454, 1379, 1356, 1269, 1237, 1118, 1064, 1028, 1011, 771, 737, 698 cm^{-1}.

(2R,3R,4R,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran-3-ol **(177h)**



Add K_2CO_3 (1.5 equiv., 19.3 mg, 0.14 mmol) and CH_3I (3 equiv., 0.017 mL, 0.28 mmol) to a solution of **151h** (1 equiv., 56.6 mg, 0.093 mmol) in DMF (2.00 mL) at 0 °C. Then, stir the mixture at room temperature for 16 hours. The reaction was quenched using water（30 mL) and extracted with EtOAc (3 x 20 mL). Organic phase was washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, filtred and concentrated under reduced pressure. NMR of the obtained residue is good. Yielding the product **177h** (52.2 mg, 0.084 mmol, 90%, dr=10/1) as an oil.

R$_f$ 0.49 (Cyclohexane/ EtOAc: 3/1);

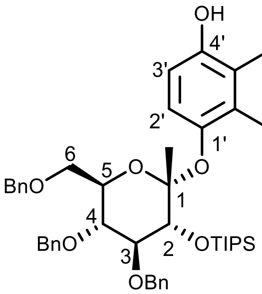
^{1}H NMR (400 MHz, Methanol-*d*$_4$) *δ* 8.52 – 8.41 (m, 1H, H-8´), 8.20 – 8.11 (m, 1H, H-5´), 7.52 – 7.15 (m, 18H, H$_{Ar,}$, H-7´, H-6´ and H-3´), 6.52 (d, *J* = 8.4 Hz, 1H, H-2´), 5.09 (d, *J* = 11.0 Hz, 1H, OC$\underline{H_2}$Ph), 4.86 (d, *J* = 10.3 Hz, 1H, OC$\underline{H_2}$Ph), 4.81 (d, *J* = 11.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.63 – 4.51 (m, 3H, OC$\underline{H_2}$Ph), 4.25 (ddd, J = 10.3, 6.2, 1.8 Hz, 1H, H-5), 4.10 (t, J = 9.2 Hz, 1H, H-3), 3.89 (s, 3H, OC$\underline{H_3}$), 3.85 (dd, J = 10.6, 1.8 Hz, 1H, H-6), 3.71 (dd, J = 10.7, 6.1 Hz, 1H, H-6), 3.60 (d, J = 9.6 Hz, 1H, H-2), 3.55 (dd, J = 10.2, 8.9 Hz, 1H, H-4), 1.28 (s, 3H, C$\underline{H_3}$).

^{13}C NMR (125 MHz, Methanol-*d_4*) δ 152.8 (C-4´), 144.6 (C-1´), 140.4 (CqAr), 139.7 (CqAr), 139.6 (CqAr), 131.1 (CqAr), 129.4 (C_{Ar}), 129.33 (C_{Ar}), 129.27 (C_{Ar}), 129.03 (C_{Ar}), 128.98 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 127.4 (CqAr), 127.0 (C-6´ or C-7´), 126.3 (C-6´ or C-7´), 124.0 (C-8´), 122.6 (C-5´), 117.7 (C-3´), 105.6 (CqAr), 104.3 (C-1), 84.5 (C-3), 79.8 (C-4), 78.6 (C-2), 76.4 (O$\underline{C}H_2$Ph), 75.9 (O$\underline{C}H_2$Ph), 74.4 (O$\underline{C}H_2$Ph), 73.3 (C-5), 70.9 (C-6), 56.1 (O$\underline{C}H_3$), 20.8 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{39}H_{40}NaO_7$ $[M+Na]^+$: 643.2666; found 643.2666.

IR (film): 3478, 3029, 2924, 2863, 1594, 1463, 1457, 1389, 1268, 1237, 1119, 1093, 1067, 1027, 737, 698 cm^{-1}.

4-(((2R,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-methyl-3-((triisopropylsilyl)oxy)tetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol (**151g**)



According to the general procedure, *exo*-glycal **150g** (1 equiv., 37.9 mg, 0.063 mmol), 1,4-naphthoquinone (2.5 equiv., 24.9 mg, 0.16 mmol), Na_2HPO_4 (1.1 equiv., 9.8 mg, 0.069 mmol), Fe(acac)$_3$ (0.50 equiv., 11.1 mg, 0.031 mmol) were dissolved in freshly distilled THF (1.3 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.031 mL, 0.25 mmol) was added dropwise and EtOH (8 equiv., 0.029 mL, 0.50 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring for 5 h. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/DCM: 1/1-1/10), yielding the product **151g** (26.6 mg, 0.035 mmol, 55%, dr=1.5/1) as a colorless oil.

R_f 0.55 (Cyclohexane/ DCM: 1/3);

$[\alpha]_D^{20}$=+38.2 (*c*=0.5, DCM);

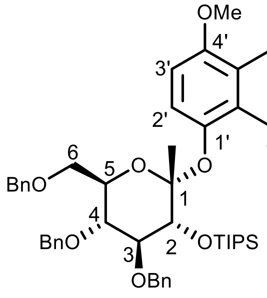
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.46 (m, 1H, H-8´), 8.14 – 8.07 (m, 1H, H-5´), 7.53 – 7.17 (m, 16H, $H_{Ar,}$ H-6´, H-7´ and H-3´), 7.07 – 7.00 (m, 2H, H_{Ar}), 6.60 (d, J = 8.2 Hz, 1H, H-2´), 5.22 (s, 1H, OH), 5.16 (d, J = 11.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.83 (d, J = 12.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.71 (d, J = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.69 (d, J = 11.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.60 (d, J = 12.1 Hz, 1H, $OC\underline{H_2}Ph$), 4.53 (d, J = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.27 – 4.16 (m, 2H, H-3 and H-5), 3.84 (d, J = 9.4 Hz, 1H, H-2), 3.83 – 3.80 (m, 2H, H-6), 3.75 (dd, J = 10.1, 8.9 Hz, 1H, H-4), 1.48 (s, 3H, $C\underline{H_3}$), 1.16 – 1.13 (m, 11H, $C\underline{H}(CH_3)_2$ and $CH(C\underline{H_3})_2$), 1.10 – 0.99 (m, 10H, $C\underline{H}(CH_3)_2$ and $CH(C\underline{H_3})_2$).

^{13}C NMR (125 MHz, Chloroform-*d*) δ 146.8 (C-4´), 144.0 (C-1´), 139.5 (CqAr), 138.3 (CqAr), 138.1 (CqAr), 129.2 (CqAr), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.1 (C_{Ar}), 126.6 (C_{Ar}), 125.9 (C-6´ or C-7´), 125.7 (C-6´ or C-7´), 125.2 (CqAr), 123.6 (C-8´), 121.3 (C-5´), 114.0 (C-3´), 108.2 (C-2´), 104.4 (C-1), 82.6 (C-3), 80.4 (C-4), 78.2 (C-2), 74.7 ($2O\underline{C}H_2Ph$), 73.7 ($O\underline{C}H_2Ph$), 72.0 (C-5), 69.4 (C-6), 20.4 ($\underline{C}H_3$), 18.7 ($CH(\underline{C}H_3)_2$), 18.5 ($CH(\underline{C}H_3)_2$), 13.9 ($C\underline{H}(CH_3)_2$).

HRMS (ESI) m/z: calcd for $C_{47}H_{58}KO_7Si_2$ $[M+K]^+$: 801.3583; found 801.3614.

IR (film): 3365, 2943, 2866, 1593, 1465, 1454, 1382, 1358, 1271, 1239, 1204, 1130, 1085, 1065, 1028, 1013, 884, 847, 820, 770, 735, 697, 681 cm^{-1}.

(((2R,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran-3-yl)oxy)triisopropylsilane **(177g)**



Add K_2CO_3 (1.5 equiv., 7.1 mg, 0. 051 mmol) and CH_3I (3 equiv., 0.0 064 mL, 0.10 mmol) to a solution of **151g** (1 equiv., 26.1 mg, 0.034 mmol) in DMF (1.00 mL) at 0 °C. Then, stir the mixture at room temperature for 20 hours. The reaction was quenched using water（30 mL) and extracted with EtOAc (3 x 20 mL). Organic phase was washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, filtred and concentrated under reduced pressure. NMR of the obtained residue is good. Yielding the product **177g** (23.2 mg, 0.03 mmol, 88%, dr=1.9/1) as a colorless oil.

R$_f$ 0.71 (Cyclohexane/ DCM: 1/3);

$[\alpha]_D^{20}$=+69.5 (*c*=1.2, DCM);

^{1}H NMR (400 MHz, Acetone-*d*$_6$) δ 8.62 – 8.53 (m, 1H, H-8´), 8.23 – 8.15 (m, 1H, H-5´), 7.54 – 7.14 (m, 18H, $H_{Ar,}$ H-6´, H-7´ and H-3´), 6.67 (d, J = 8.4 Hz, 1H, H-2´), 5.25 (d, J = 12.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.80

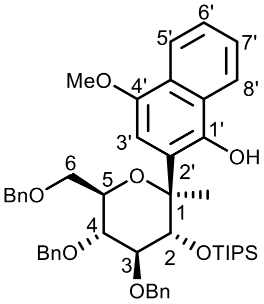
(d, *J* = 11.1 Hz, 1H, OC<u>H</u>$_2$Ph), 4.82 (d, *J* = 11.9 Hz, 1H, OC<u>H</u>$_2$Ph), 4.70 (d, *J* = 12.1 Hz, 1H, OC<u>H</u>$_2$Ph), 4.70 (d, *J* = 11.1 Hz, 1H, OC<u>H</u>$_2$Ph), 4.64 (d, *J* = 12.0 Hz, 1H, OC<u>H</u>$_2$Ph), 4.28 – 4.23 (m, 1H, H-5), 4.20 (t, *J* = 9.1 Hz, 1H, H-3), 3.98 – 3.93 (m, 4H, H-6 and OC<u>H</u>$_3$), 3.92 – 3.84 (m, 2H, H-2 and H-6), 3.81 (dd, *J* = 10.2, 8.8 Hz, 1H, H-4), 1.46 (s, 3H, C<u>H</u>$_3$), 1.27 – 1.14 (m, 12H, C<u>H</u>(CH$_3$)$_2$ and CH(C<u>H</u>$_3$)$_2$), 1.08 (d, *J* = 6.7 Hz, 9H, CH(C<u>H</u>$_3$)$_2$).

^{13}C NMR (100 MHz, Acetone-*d*$_6$) δ 151.9 (C-4´), 144.2 (C-1´), 140.2 (CqAr), 139.7 (CqAr), 139.3 (CqAr), 130.0 (CqAr), 129.2 (C$_{Ar}$), 129.0 (C$_{Ar}$), 128.9 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.4 (C$_{Ar}$), 128.3 (C$_{Ar}$), 127.8 (C$_{Ar}$), 127.3 (C$_{Ar}$), 127.0 (CqAr), 126.6 (C-6´ or C-7´), 126.3 (C-6´ or C-7´), 124.0 (C-8´), 122.4 (C-5´), 115.6 (C-3´), 105.0 (C-1), 104.3 (C-2´), 83.2 (C-3), 81.4 (C-4), 79.0 (C-2), 75.24 (O<u>C</u>H$_2$Ph), 75.2 (O<u>C</u>H$_2$Ph), 73.9 (O<u>C</u>H$_2$Ph), 73.3 (C-5), 70.4 (C-6), 56.0 (O<u>C</u>H$_3$), 20.9 (<u>C</u>H$_3$), 19.1 (CH(<u>C</u>H$_3$)$_2$), 18.8 (CH(<u>C</u>H$_3$)$_2$), 14.4 (C<u>H</u>(CH$_3$)$_2$).

HRMS (ESI) m/z: calcd for $C_{48}H_{60}KO_7Si$ [M+K]$^+$: 815.3740; found 815.3711.

IR (film): 2943, 2865, 1593, 1463, 1389, 1270, 1238, 1133, 1095, 1084, 1067, 1022, 982, 883, 839, 816, 770, 734, 697, 682 cm^{-1}.

2-((2S,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-methyl-3-((triisopropylsilyl)oxy)tetrahydro-2H-pyran-2-yl)-4-methoxynaphthalen-1-ol **(186)**



To a solution of **177g** (1 equiv., 108 mg, 0.14 mmol) in dry DCM (4.7 mL) was dropwise added the solution of BF_3 OEt_2 (0.10 equiv., 0.0017 mL, 0.014 mmol) in the dry DCM at -60 °C under an Ar atmosphere. The temperature gradually rised to 5 °C for 3 h. The reaction was quenched using saturated aqueous solution of $NaHCO_3$ (20 drops). The solution was extracted with DCM, organic phase was washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtred and concentrated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc:15/1), yielding the product **186** (96.2 mg, 0.13 mmol, 88%) as a white solid.

R$_f$ 0.60 (Cyclohexane/ EtOAc: 6/1);

[α]$_D$^{20}=-36.6(*c*=0.5, DCM);

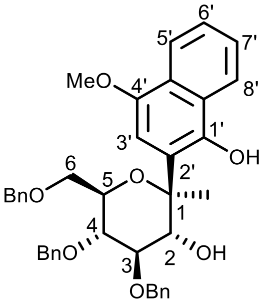
^{1}H NMR (400 MHz, Acetone-*d*$_6$) *δ* 9.14 (s, 1H, O<u>H</u>), 8.36 – 8.27 (m, 1H, H-8´), 8.17 – 8.07 (m, 1H, H-5´), 7.59 – 7.12 (m, 17H, H$_{Ar}$, H-6´, H-7´), 6.80 (s, 1H, H-3´), 5.26 (d, *J* = 11.9 Hz, 1H, OC<u>H$_2$</u>Ph), 4.79 (d, *J* = 10.8 Hz, 1H, OC<u>H$_2$</u>Ph), 4.73 – 4.61 (m, 4H, OC<u>H$_2$</u>Ph), 4.37 (d, *J* = 9.3 Hz, 1H, H-2), 4.16 – 4.01 (m, 2H, H-4 and H-5), 4.00 – 3.92 (m, 4H, H-6 and OC<u>H$_3$</u>), 3.82 (t, *J* = 8.9 Hz, 1H, H-3), 3.73 (dd, *J* = 10.4, 1.6 Hz, 1H, H-6), 1.90 (s, 3H, C<u>H$_3$</u>), 0.81 (d, *J* = 6.8 Hz, 9H, CH(C<u>H$_3$</u>)$_2$), 0.73 (d, *J* = 6.1 Hz, 9H, CH(C<u>H$_3$</u>)$_2$), 0.72 – 0.64 (m, 3H, C<u>H</u>(CH$_3$)$_2$).

^{13}C NMR (100 MHz, Acetone-*d*$_6$) *δ* 148.6 (C-4´), 146.3 (C-1´), 140.1 (CqAr), 139.2 (CqAr), 138.9 (CqAr), 129.2 (C$_{Ar}$), 129.17 (C$_{Ar}$), 129.1 (C$_{Ar}$), 128.9 (C$_{Ar}$), 128.7 (C$_{Ar}$), 128.6 (C$_{Ar}$), 128.5 (C$_{Ar}$), 127.8 (CqAr), 127.79 (C$_{Ar}$), 127.1 (C$_{Ar}$), 126.6 (CqAr), 126.4 (C-6´ or C-7´), 126.2 (C-6´ or C-7´), 123.4 (C-8´), 122.2 (C-2´), 122.0 (C-5´), 105.2 (C-3´), 84.3 (C-1), 83.5 (C-3), 80.3 (C-4), 76.3 (C-2), 75.4 (O<u>C</u>H$_2$Ph), 74.9 (O<u>C</u>H$_2$Ph), 74.1 (O<u>C</u>H$_2$Ph), 73.2 (C-5), 68.7 (C-6), 55.9 (O<u>C</u>H$_3$), 18.6 (CH(<u>C</u>H$_3$)$_2$), 18.3 (CH(<u>C</u>H$_3$)$_2$), 16.2 (<u>C</u>H$_3$), 14.2 (<u>C</u>H(CH$_3$)$_2$).

HRMS (ESI) m/z: calcd for $C_{48}H_{60}KO_7Si$ $[M+K]^+$: 815.3740; found 815.3733.

IR (film): 3333, 2943, 2864, 1455, 1391, 1364, 1321, 1157, 1086, 1061, 1027, 884, 803, 767, 734, 697, 682, 655 cm^{-1}.

(2S,3R,4R,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-(1-hydroxy-4-methoxynaphthalen-2-yl)-2-methyltetrahydro-2H-pyran-3-ol **(191)**



To a solution of **186** (1 equiv., 40.5 mg, 0.052 mmol) in freshly distilled THF (0.90 mL) was added TBAF (1M in THF, 2 equiv., 0.10 mL, 0.10 mmol). The mixture was then stirred at room temperature overnight. The reaction solution was diluted by EA, after that, 10 mL of NH_4Cl (10 mL) saturated aqueous solution was added and extracted with EtOAc. The organic phase was washed with brine, dried with Na_2SO_4, filtred and concentrated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc:30/1-12/1), yielding the product **191** (22.3 mg, 0.036 mmol, 69%) as a colourless oil.

R$_f$ 0.31 (Cyclohexane/EtOAc: 5/1);

$[\alpha]_D^{20}$=-8.5 (*c*=1.1, DCM);

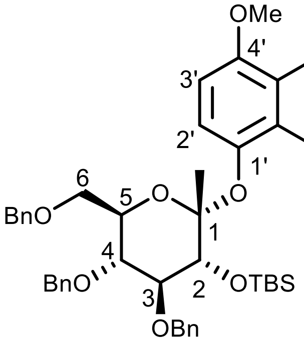
^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ 8.27 – 8.20 (m, 1H, H-8´), 8.12 – 8.05 (m, 1H, H-5´), 7.47 – 7.38 (m, 4H, H$_{Ar}$, H-6´, H-7´), 7.38 – 7.29 (m, 4H, H$_{Ar}$), 7.30 – 7.20 (m, 7H, H$_{Ar}$), 7.15 (dd, *J* = 7.4, 2.0 Hz, 2H, H$_{Ar}$), 6.91 (s, 1H, H-3´), 4.97 (d, *J* = 11.1 Hz, 1H, OC$\underline{H}_2$Ph), 4.81 (d, *J* = 11.2 Hz, 1H, OC$\underline{H}_2$Ph), 4.76 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.62 (d, *J* = 11.9 Hz, 1H, OC$\underline{H}_2$Ph), 4.48 (d, *J* = 11.0 Hz, 1H, OC$\underline{H}_2$Ph), 4.46 (d, *J* = 12.0 Hz, 1H, OC$\underline{H}_2$Ph), 3.93 (s, 3H, OC$\underline{H}_3$), 3.94 – 3.88 (m, 2H, H-2 and H-5), 3.81 (t, *J* = 9.5 Hz, 1H, H-4), 3.79 – 3.71 (m, 2H, H-3 and H-6), 3.65 (dd, *J* = 10.2, 2.4 Hz, 1H, H-4), 1.76 (s, 3H, C$\underline{H}_3$).

^{13}C NMR (125 MHz, Methanol-*d*$_4$) δ 149.1 (C-4´), 145.5 (C-1´), 140.2 (CqAr), 139.6 (CqAr), 139.2 (CqAr), 129.4 (C$_{Ar}$), 129.3 (C$_{Ar}$), 129.2 (C$_{Ar}$), 129.1 (C$_{Ar}$), 128.95 (C$_{Ar}$), 128.8 (C$_{Ar}$), 128.7 (C$_{Ar}$), 128.5 (C$_{Ar}$), 128.0 (CqAr), 127.0 (CqAr), 126.5 (C-6´ or C-7´), 126.3 (C-6´ or C-7´), 123.6 (C-8´), 122.8 (CqAr), 122.2 (C-5´), 105.3 (C-3´), 84.7 (C-3), 84.1 (C-1), 78.8 (C-4), 77.1 (C-2), 76.5 (O$\underline{C}$H$_2$Ph), 76.0 (O$\underline{C}$H$_2$Ph), 74.4 (O$\underline{C}$H$_2$Ph), 73.6 (C-5), 69.2 (C-6), 56.2 (O$\underline{C}$H$_3$), 16.4 ($\underline{C}$H$_3$).

HRMS (ESI) m/z: calcd for $C_{39}H_{40}NaO_7$ $[M+Na]^+$: 643.2666; found 643.2653.

IR (film): 3319, 2923, 1599, 1454, 1395, 1362, 1323, 1287, 1208, 1157, 1143, 1073, 1027, 987, 768, 729, 698 cm^{-1}.

(((2R,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran-3-yl)oxy)(tert-butyl)dimethylsilane **(177f)**



According to the general procedure, *exo*-glycal **150f** (1 equiv., 70.8 mg, 0.13 mmol), 1,4-naphthoquinone (2.5 equiv., 49.9 mg, 0.32 mmol), Na_2HPO_4 (1.1 equiv., 19.7 mg, 0.14 mmol), Fe(acac)$_3$ (0.50 equiv., 22.3 mg, 0.063 mmol) were dissolved in freshly distilled THF (2.6 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.063 mL, 0.51 mmol) was added dropwise and EtOH (8 equiv., 0.059 mL, 1.01 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring until the reaction was basically completed for 6 h. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO$_2$, Cyclohexane/EtOAc: 25/1-13/1), yielding the mixture of product **151f** (53.9 mg, 0.075 mmol, 59%, dr=2/1) and 1,4-naphthoquinone as an oil.

NaH (60% in oil, 3 equiv., 9.0 mg, 0.22 mmol) was added portionwisely to a solution of **151f** (1 equiv., 53.9 mg, 0.075 mmol) in freshly distilled THF (1.40 mL) at 0 °C. And then, CH_3I (4 equiv., 0.019 mL, 0.30 mmol) was added and the mixture was stirred at room temperature until the starting material was completely consumed. After 7.5 h, the mixture was quenched with MeOH (1 mL) and evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/DCM: 1/1-1/1.5), yielding the product **177f** (32.3 mg, 0.044 mmol, 59%, dr=2.7/1) as a light green oil.

R_f 0.60 (Cyclohexane/ DCM: 1/2);

$[\alpha]_D^{20}$=+68.5 (*c*=0.6, DCM);

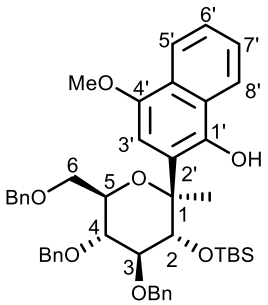
^{1}H NMR (500 MHz, Acetone-*d*$_6$) *δ* 8.59 – 8.55 (m, 1H, H-8´), 8.20 – 8.16 (m, 1H, H-5´), 7.53 – 7.13 (m, 18H, $H_{Ar,}$, H-7´, H-6´ and H-3´), 6.67 (d, *J* = 8.4 Hz, 1H, H-2´), 5.11 (d, *J* = 12.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.98 (d, *J* = 12.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.81 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.73 – 4.62 (m, 3H, $OC\underline{H_2}Ph$), 4.27 (ddd, *J* = 10.2, 5.9, 1.7 Hz, 1H, H-5), 4.18 (t, *J* = 9.2 Hz, 1H, H-3), 3.98 – 3.92 (m, 4H, $OC\underline{H_3}$ and H-6), 3.85 (dd, *J* = 10.6, 6.0 Hz, 1H, H-6), 3.79 – 3.73 (m, 2H, H-2 and H-4), 1.33 (s, 3H, $C\underline{H_3}$), 1.02 (s, 9H, $SiC(C\underline{H}_3)_3$), 0.15 (s, 3H, $Si(C\underline{H}_3)_2$), 0.12 (s, 3H, $Si(C\underline{H}_3)_2$).

^{13}C NMR (125 MHz, Acetone-*d*$_6$) *δ* 152.1 (C-4´), 144.2 (C-1´), 140.3 (CqAr), 139.7 (CqAr), 139.4 (CqAr), 130.4 (CqAr), 129.2 (C_{Ar}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 127.7 (C_{Ar}), 127.3 (C_{Ar}), 126.9 (CqAr), 126.7 (C-6´ or C-7´), 126.3 (C-6´ or C-7´), 124.0 (C-8´), 122.4 (C-5´), 116.5 (C-3´), 105.0 (C-1) , 104.3 (C-2´), 83.3 (C-5), 80.7 (C-4), 78.6 (C-2), 75.6 ($O\underline{C}H_2Ph$), 75.4 ($O\underline{C}H_2Ph$), 73.9 ($O\underline{C}H_2Ph$), 73.4 (C-3), 70.5 (C-6), 56.0 ($O\underline{C}H_3$), 26.7, 21.4 ($\underline{C}H_3$), 18.9 ($Si\underline{C}(CH_3)_3$), -3.3 ($Si(\underline{C}H_3)_2$), -3.9 ($Si(\underline{C}H_3)_2$).

HRMS (ESI) m/z: calcd for $C_{45}H_{54}KO_7Si$ $[M+K]^+$: 773.3270; found 773.3297.

IR (film): 3032, 2929, 2856, 1593, 1463, 1389, 1270, 1238, 1203, 1153, 1127, 1093, 1086, 1069, 1028, 981, 856, 842, 774, 734, 697 cm^{-1}.

2-((2S,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-3-((tert-butyldimethylsilyl)oxy)-2-methyltetrahydro-2H-pyran-2-yl)-4-methoxynaphthalen-1-ol **(185)**



To a solution of **177f** (1 equiv., 21.0 mg, 0.029 mmol) in dry DCM (0.98 mL) was dropwise added the solution of BF_3 OEt_2 (0.10 equiv., 0.0004 mL, 0.0029 mmol) in the dry DCM at -60 °C under an Ar atmosphere. The temperature gradually rised to 10 °C for 5 h. The reaction was quenched using saturated aqueous solution of $NaHCO_3$ (5 drops). The solution was dried with Na_2SO_4, filtred and concentrated. The solvent was removed under reduced pressure. The crude was purified by flash chromatography (SiO_2, Cyclohexane/EtOAc:30/1), yielding the product **185** (11 mg, 0.015 mmol, 52%).

R_f 0.50 (Cyclohexane/ EtOAc: 9/1);

$[\alpha]_D^{20}$=-9.6 (*c*=0.2, DCM);

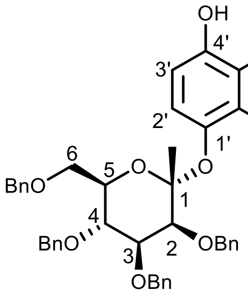
^{1}H NMR (400 MHz, Acetone-*d_6*) *δ* 9.01 (s, 1H, O$\underline{H}$), 8.35 – 8.28 (m, 1H, H-8´), 8.16 – 8.09 (m, 1H, H-5´), 7.55 – 7.09 (m, 17H, H_{Ar}, H-6´, H-7´), 6.80 (s, 1H, H-3´), 5.04 (d, *J* = 12.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.88 (d, *J* = 12.1 Hz, 1H, OC$\underline{H_2}$Ph), 4.82 (d, *J* = 10.7 Hz, 1H, OC$\underline{H_2}$Ph), 4.67 (d, *J* = 11.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.62 (d, *J* = 10.7 Hz, 1H, OC$\underline{H_2}$Ph), 4.59 (d, *J* = 11.9 Hz, 1H, OC$\underline{H_2}$Ph), 4.22 (d, *J* = 9.3 Hz, 1H, H-2), 4.09 (dd, *J* = 10.1, 9.0 Hz, 1H, H-4), 4.06 – 4.00 (m, 1H, H-5), 3.98 (s, 3H, OC$\underline{H_3}$), 3.95 – 3.87 (m, 1H, H-6), 3.82 (t, *J* = 9.2 Hz, 1H, H-3), 3.70 (dd, *J* = 10.2, 2.2 Hz, 1H, H-6), 1.87 (s, 3H, C$\underline{H_3}$), 0.79 (s, 9H, C(C$\underline{H_3}$)$_3$), -0.21 (s, 3H, Si(C$\underline{H_3}$)$_2$), -1.08 (s, 3H, Si(C$\underline{H_3}$)$_2$).

^{13}C NMR (100 MHz, Acetone-*d_6*) *δ* 148.8 (C-4´), 146.5 (C-1´), 140.1 (CqAr), 139.3 (CqAr), 139.0 (CqAr), 129.2 (C_{Ar}), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 127.9 (CqAr), 127.8 (C_{Ar}), 127.3 (C_{Ar}), 126.7 (CqAr), 126.4 (C-6´ or C-7´), 126.3 (C-6´ or C-7´), 123.4 (C-8´), 122.1 (C-1), 122.09 (C-5´), 105.5 (C-3´), 84.1 (C-2´), 84.0 (C-3), 79.2 (C-4), 75.74 (O$\underline{C}H_2$Ph), 75.7 (O$\underline{C}H_2$Ph), 75.4 (C-2), 74.0 (O$\underline{C}H_2$Ph), 73.4 (C-5), 68.8 (C-6), 55.9 (O$\underline{C}H_3$), 26.5 (C($\underline{C}H_3$)$_3$), 18.4 ($\underline{C}$(CH_3)$_3$), 16.0 ($\underline{C}H_3$), -3.3 (Si($\underline{C}H_3$)$_2$), -6.1 (Si($\underline{C}H_3$)$_2$).

HRMS (ESI) m/z: calcd for $C_{45}H_{54}KO_7Si$ $[M+K]^+$: 773.3270; found 773.3308.

IR (film): 3336, 2927, 2855, 1455, 1322, 1159, 1087, 1061, 1027, 859, 837, 779, 767, 734, 697 cm^{-1}.

4-(((2R,3S,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-yl)oxy)naphthalen-1-ol **(151e)**



According to the general procedure, *exo*-glycal **150e** (1 equiv., 110.0 mg, 0.21 mmol), 1,4-naphthoquinone (2.5 equiv., 81.0 mg, 0.51 mmol), Na_2HPO_4 (1.1 equiv., 32.0 mg, 0.23 mmol), $Fe(acac)_3$ (0.50 equiv., 36.2 mg, 0.10 mmol) were dissolved in freshly distilled THF (4.1 mL) at room temperature under Ar. Subsequently, phenylsilane (4 equiv., 0.10 mL, 0.82 mmol) was added dropwise and EtOH (8 equiv., 0.096 mL, 1.64 mmol) was added. And then, the mixture was transferred to 60 °C and heated with constant stirring until the reaction was basically completed for 2 h. After that, the mixture was evaporated under reduced pressure. The crude was purified by flash chromatography (SiO_2, DCM/MeOH: 150:1-130:1), yielding the product **151e** (81.4 mg, 0.12 mmol, 57%) as a light brown oil.

R_f 0.27 (Cyclohexane/ EtOAc: 5/1);

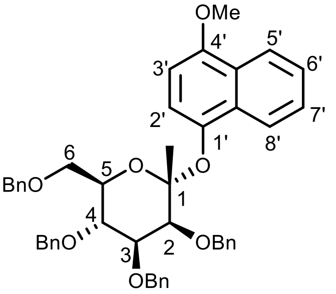
^{1}H NMR (400 MHz, Acetone-*d*$_6$) δ 8.25 – 8.18 (m, 1H, H-5´), 8.11 – 8.02 (m, 1H, H-8´), 7.57 – 7.23 (m, 23H, $H_{Ar,}$ H-6´, H-7´ and H-3´), 6.75 (d, *J* = 8.2 Hz, 1H, H-2´), 5.13 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 5.03 – 4.94 (m, 2H, $OC\underline{H_2}Ph$), 4.93 (d, *J* = 11.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.82 (d, *J* = 11.3 Hz, 1H, $OC\underline{H_2}Ph$), 4.72 – 4.64 (m, 2H, $OC\underline{H_2}Ph$), 4.59 (d, *J* = 11.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.44 (dd, *J* = 9.3, 2.8 Hz, 1H, H-3), 4.32 (d, *J* = 2.9 Hz, 1H, H-2), 4.17 (ddd, *J* = 10.0, 6.4, 1.7 Hz, 1H, H-5), 4.03 (t, *J* = 9.6 Hz, 1H, H-4), 3.93 (dd, *J* = 10.7, 1.7 Hz, 1H, H-6), 3.79 (dd, *J* = 10.7, 6.5 Hz, 1H, H-6), 1.35 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (125 MHz, Acetone-*d*$_6$) δ 149.6 (C-4´), 143.3 (C-1´), 140.0 (CqAr), 139.9 (2 CqAr), 139.87 (CqAr), 130.1 (CqAr), 129.2 (C_{Ar}), 129.04 (C_{Ar}), 129.0 (C_{Ar}), 128.99 (C_{Ar}), 128.9 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.59 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 128.17 (C_{Ar}), 128.1 (C_{Ar}), 126.7 (C-6´ or C-7´), 126.4 (CqAr), 125.7 (C-6´ or C-7´), 123.1 (C-8´), 123.0 (C-5´), 116.8 (C-3´), 108.3 (C-2´), 105.6 (C-1), 82.0 (C-3), 80.5 (C-2), 75.9 ($O\underline{C}H_2Ph$), 75.7 (C-4), 75.4 ($O\underline{C}H_2Ph$), 74.4 (C-5), 73.7 ($O\underline{C}H_2Ph$), 73.1 ($O\underline{C}H_2Ph$), 71.0 (C-6), 20.3 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{45}H_{44}KO_7$ $[M+K]^+$: 735.2719; found 735.2750.

IR (film): 3320, 3030, 2918, 2866, 1694, 1665, 1592, 1454, 1376, 1353, 1300, 1273, 1090, 1063, 1027, 872, 828, 767, 734, 696 cm^{-1}.

(2R,3S,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-((4-methoxynaphthalen-1-yl)oxy)-2-methyltetrahydro-2H-pyran **(177e)**



Add K_2CO_3 (1.5 equiv., 9.5 mg, 0. 069 mmol) and CH_3I (3 equiv., 0.0 086 mL, 0.14 mmol) to a solution of **151e** (1 equiv., 32 mg, 0.046 mmol) in DMF (1.50 mL) at 0 °C. Then, stir the mixture at room temperature for 6 hours. The reaction was quenched using water（30 mL) and extracted with EtOAc (3 x 20 mL). Organic phase was washed with water (20 mL) and brine (20 mL), dried with Na_2SO_4, filtred and concentrated under reduced pressure. The obtained residue showed a good NMR. Yielding the product **177e** (32.2 mg, 0.045 mmol, 98%) as an oil.

$\boldsymbol{R_f}$ 0.57 (Cyclohexane/ EtOAc: 5/1);

$[\alpha]_D^{20}$=+80.1 (*c*=0.5, DCM);

^{1}H NMR (400 MHz, Acetone-*d*$_6$) δ 8.22 – 8.15 (m, 1H, H-5´), 8.10 – 8.04 (m, 1H, H-8´), 7.57 – 7.23 (m, 23H, $H_{Ar,}$ H-6´, H-7´ and H-3´), 6.62 (d, *J* = 8.4 Hz, 1H, H-2´), 5.13 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.99 (d, *J* = 11.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.98 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.93 (d, *J* = 11.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.82 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.69 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.68 (d, *J* = 11.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.60 (d, *J* = 11.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.42 (dd, *J* = 9.2, 2.8 Hz, 1H, H-3), 4.33 (d, *J* = 2.9 Hz, 1H, H-2), 4.14 (ddd, *J* = 10.0, 6.6, 1.7 Hz, 1H, H-5), 4.02 (t, *J* = 9.6 Hz, 1H, H-4), 3.96 – 3.90 (m, 4H, H-6 and $OC\underline{H}_3$), 3.84 – 3.75 (m, 1H, H-6), 1.36 (s, 3H, $C\underline{H}_3$).

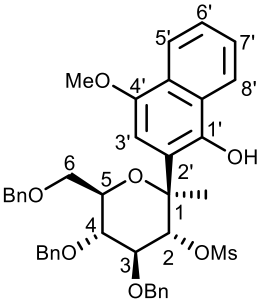
^{13}C NMR (100 MHz, Acetone-*d*$_6$) δ 151.9 (C-4´), 144.0 (C-1´), 140.0 (CqAr), 139.97 (CqAr), 139.9 (CqAr), 139.89 (CqAr), 129.9 (CqAr), 129.3 (C_{Ar}), 129.1 (C_{Ar}), 129.05 (C_{Ar}), 129.0 (C_{Ar}), 128.95 (C_{Ar}), 128.7 (C_{Ar}), 128.69 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.15 (C_{Ar}), 127.0 (C-6´ or C-7´), 126.95 (CqAr), 126.2 (C-6´ or C-7´), 123.1 (C-5´), 122.6 (C-8´), 116.2 (C-3´), 105.7 (C-1), 104.4 (C-2´), 82.0 (C-3), 80.5 (C-2), 76.0 ($O\underline{C}H_2Ph$), 75.7 (C-4), 75.4 ($O\underline{C}H_2Ph$), 74.5 (C-5), 73.7 ($O\underline{C}H_2Ph$), 73.2 ($O\underline{C}H_2Ph$), 71.0 (C-6), 56.0 ($O\underline{C}H_3$), 20.3 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{46}H_{46}KO_7$ $[M+K]^+$: 749.2875; found 749.2861.

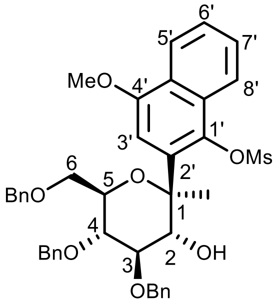
IR (film): 3030, 2913, 2865, 1595, 1462, 1454, 1388, 1270, 1095, 1077, 1057, 1027, 980, 865, 767, 735, 697 cm^{-1}.

(2S,3R,4S,5R,6R)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-(1-hydroxy-4-methoxynaphthalen-2-yl)-2-methyltetrahydro-2H-pyran-3-yl methanesulfonate **(210)** *2-((2S,3R,4R,5R,6R)-4,5-bis(benzyloxy)-6-*

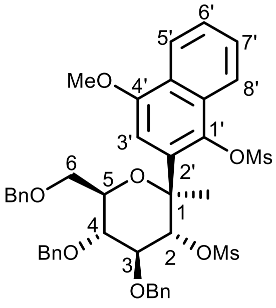
((benzyloxy)methyl)-3-hydroxy-2-methyltetrahydro-2H-pyran-2-yl)-4-methoxynaphthalen-1-yl methanesulfonate **(212)** *(2S,3R,4S,5R,6R)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-2-(4-methoxy-1-((methylsulfonyl)oxy)naphthalen-2-yl)-2-methyltetrahydro-2H-pyran-3-yl methanesulfonate* **(213)**



210



212



213

To a solution of **191** (1 equiv., 21 mg, 0.034 mmol) in DCM (1 mL) cooled to 0 °C was added Et_3N (4.9 equiv., 0.023 mL, 0.17 mmol), followed by MsCl (1.5 equiv., 5.8 mg, 0.0507 mmol). The reaction mixture was stirred overnight at room temperature. Water was added to quench the reaction, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried with Na_2SO_4 and concentrated. Purification by flash column chromatography (SiO_2, Cyclohexane/EtOAc:10/1), yielded the product **210** (2.4 mg, 0.0034 mmol, 10%) and **213** (9.2 mg, 0.012 mmol, 35%) and **212** (7 mg, 0.01 mmol, 29%).

Compound 210:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.80 (s, 1H, O$\underline{\mathrm{H}}$), 8.36 – 8.30 (m, 1H, H-8´ or H-5’), 8.17 – 8.08 (m, 1H, H-8´ or H-5’), 7.54 – 7.11 (m, 17H, H-6´ and H-7’ and H$_{\mathrm{Ar}}$), 6.65 (s, 1H, H-3’), 5.07 (d, *J* = 9.9 Hz, 1H, H-2), 4.95 (d, *J* = 10.5 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.87 (d, *J* = 10.5 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.83 (d, *J* = 10.9 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.66 (d, *J* = 11.9 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.47 (d, *J* = 10.9 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.45 (d, *J* = 11.9 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.19 (t, *J* = 9.6 Hz, 1H, H-4), 4.01 – 3.83 (m, 5H, OCH_3 and H-3, H-5), 3.79 (d, *J* = 9.7 Hz, 1H, H-6), 3.66 (dd, *J* = 10.1, 2.4 Hz, 1H, H-6), 2.20 (s, 3H, C$\underline{\mathrm{H}_3}$), 1.86 (s, 3H, C$\underline{\mathrm{H}_3}$).

HRMS (ESI) m/z: calcd for $C_{40}H_{42}O_9SK$ $[M+K]^+$: 737.22; found 737.22.

Compound 212:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 (dt, *J* = 8.6, 1.0 Hz, 1H, H-8´), 8.19 – 8.16 (m, 1H, H-5´), 7.60 – 7.54 (m, 1H, H-7’), 7.53 – 7.48 (m, 1H, H-6’), 7.39 – 7.24 (m, 15H, H$_{\mathrm{Ar}}$), 7.21 (s, 1H, H-3’), 4.95 (d, *J* = 11.2 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.90 (d, *J* = 11.0 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.86 (d, *J* = 11.2 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.66 (d, *J* = 10.8 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.56 (d, *J* = 11.9 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.51 (d, *J* = 11.8 Hz, 1H, OC$\underline{\mathrm{H}_2}$Ph), 4.13 (dd, *J* = 9.2, 2.5 Hz, 1H, H-2), 3.97 – 3.79 (m, 8H, H-3, H-4, H-5, H-6, OC$\underline{\mathrm{H}_3}$), 3.22 (s, 3H, C$\underline{\mathrm{H}_3}$), 1.85 (s, 3H, C$\underline{\mathrm{H}_3}$).

^{13}C NMR (125 MHz, Chloroform-*d*) δ 153.8 (C-4´), 138.6 (C-1´), 138.3 (CqAr), 138.2 (CqAr), 138.0

(CqAr), 134.4 (CqAr), 129.4 (CqAr), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.13 (C_{Ar}), 128.07 (C_{Ar}), 128.04 (C_{Ar}), 128.0 (C_{Ar}), 127.8 (C_{Ar}), 127.5 (C-7´), 126.5 (C-6´), 126.2 (CqAr), 123.8 (C-8´), 121.8 (C-5´), 103.7 (C-3´), 83.3 (C-3 or C-4), 80.0 (C-1), 78.5 (C-3 or C-4), 76.6 (C-2), 75.7 ($O\underline{C}H_2Ph$), 75.2 ($O\underline{C}H_2Ph$), 73.5 ($O\underline{C}H_2Ph$), 72.9 (C-5), 69.2 (C-6), 55.6 ($O\underline{C}H_3$), 38.4 ($\underline{C}H_3$), 16.4 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{40}H_{42}O_9SK$ [M+K]$^+$: 737.22; found 737.22.

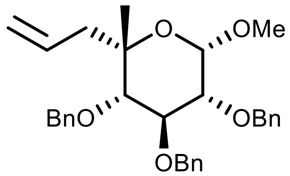
Compound 213:

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 8.29 (d, *J* = 8.4 Hz, 1H, H-8´ or H-5'), 8.24 – 8.18 (m, 1H, H-8´ or H-5'), 7.59 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H, H-6´ or H-7'), 7.53 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H, H-6´ or H-7'), 7.36 – 7.24 (m, 13H, H_{Ar}), 7.15 (dd, *J* = 6.6, 3.0 Hz, 2H, H_{Ar}), 7.07 (s, 1H, H-3'), 5.54 (d, *J* = 8.3 Hz, 1H, H-2), 4.90 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.86 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.78 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.57 (d, *J* = 10.9 Hz, 1H, $OC\underline{H_2}Ph$), 4.54 (s, 2H, $OC\underline{H_2}Ph$), 4.08 (ddd, *J* = 10.2, 6.0, 2.2 Hz, 1H, H-5), 4.02 (t, *J* = 8.5 Hz, 1H, H-3), 3.96 (s, 3H, $OC\underline{H_3}$), 3.95 – 3.89 (m, 2H, H-4 and H-6), 3.81 (dd, *J* = 10.5, 2.2 Hz, 1H, H-6), 3.04 (s, 3H, $C\underline{H_3}$), 2.47 (s, 3H, $C\underline{H_3}$), 1.95 (s, 3H, $C\underline{H_3}$).

^{13}C NMR (125 MHz, Chloroform-*d*) *δ* 153.9 (C-4´), 138.3 (C-1´), 138.1 (CqAr), 137.8 (CqAr), 137.77 (CqAr), 131.8 (CqAr), 129.2 (CqAr), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 128.07 (C_{Ar}), 127.9 (C_{Ar}), 127.85 (C_{Ar}), 127.8 (C_{Ar}), 126.8 (CqAr), 123.5(C-8´), 122.1(C-5´), 103.8(C-3´), 82.6 (C-2), 81.9 (C-3), 79.0 (C-4), 78.9 (C-1), 75.2 ($O\underline{C}H_2Ph$), 74.9 ($O\underline{C}H_2Ph$), 73.5 ($O\underline{C}H_2Ph$ and C-5), 69.5 (C-6), 55.9 ($O\underline{C}H_3$), 38.7 ($\underline{C}H_3$), 38.1 ($\underline{C}H_3$), 18.9 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{41}H_{44}O_{11}S_2K$ [M+K]$^+$: 815.20; found 815.20.

(3S,4S,5R)-2-Allyl-3,4,5-tris(benzyloxy)-6-methoxy-2-methyltetrahydro-2H-pyran **(208)**



Compound **208** was obtained as a by-product in mechanistic studies of cyclization reactions (see **Scheme 107**).

R_f 0.66 (Cyclohexane/ EtOAc: 5/1);

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.52 – 7.11 (m, 15H, H_{Ar}), 5.97 – 5.77 (m, 1H, $C\underline{H}=CH_2$), 5.20 – 5.12 (m, 2H, $CH=C\underline{H_2}$), 4.95 – 4.89 (m, 3H, $OC\underline{H_2}Ph$), 4.77 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.71 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.65 (d, *J* = 11.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.51 (d, *J* = 8.0 Hz, 1H, H-5), 3.80 (t, *J* = 9.4 Hz, 1H, H-3), 3.52 (s, 3H, $OC\underline{H_3}$), 3.42 (dd, *J* = 9.3, 8.0 Hz, 1H, H-4), 3.38 (d, *J* = 9.5 Hz, 1H, H-2), 2.56

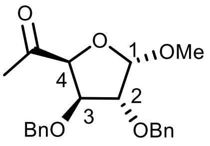
(dd, *J* = 15.4, 7.3 Hz, 1H, $C\underline{H}_2CH=CH_2$), 2.37 (ddt, *J* = 15.4, 7.0, 1.5 Hz, 1H, $C\underline{H}_2CH=CH_2$), 1.29 (s, 3H, $C\underline{H}_3$).

^{13}C NMR (125 MHz, Chloroform-*d*) *δ* 138.74 (CqAr), 138.67 (CqAr), 138.66 (CqAr), 132.6 ($CH_2=\underline{C}H$), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 118.4 ($\underline{C}H_2=CH$), 100.0 (C-5), 85.8 (C-2), 83.5 (C-4), 82.1 (C-3), 75.92 ($O\underline{C}H_2Ph$ and C-1), 75.9 ($O\underline{C}H_2Ph$), 75.0 ($O\underline{C}H_2Ph$), 57.2 ($O\underline{C}H_3$), 35.2 ($CH_2=CH\underline{C}H_2$), 25.2 ($\underline{C}H_3$).

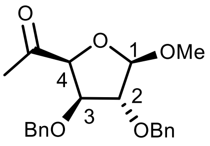
HRMS (ESI) m/z: calcd for $C_{31}H_{36}NaO_5$ $[M+Na]^+$: 511.24; found 511.24.

IR (film): 3031, 2931, 1454, 1201, 1134, 1070, 1043, 1029, 1011, 914, 734, 697 cm^{-1}.

1-((2S,3R,4R,5S)-3,4-Bis(benzyloxy)-5-methoxytetrahydrofuran-2-yl)ethan-1-one **(202)** *1-((2S,3R,4R,5R)-3,4-bis(benzyloxy)-5-methoxytetrahydrofuran-2-yl)ethan-1-one* **(202')**



202



202'

Compounds **202** were obtained as a by-product in cyclization reaction dr=**202**/**202'**=1/2 (see **Table 5**, **entry 9**).

Compound 202:

***R*$_f$** 0.43 (Cyclohexane/ EtOAc: 5/1);

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.39 – 7.19 (m, 10H, H_{Ar}), 5.00 (d, *J* = 4.2 Hz, 1H, H-1), 4.67 – 4.61 (m, 2H, H-4 and $OC\underline{H}_2Ph$), 4.57 (d, *J* = 12.0 Hz, 1H, $OC\underline{H}_2Ph$), 4.52 (s, 2H, $OC\underline{H}_2Ph$), 4.45 (dd, *J* = 7.1, 4.8 Hz, 1H, H-3), 4.05 (t, *J* = 4.5 Hz, 1H, H-2), 3.42 (s, 3H, $OC\underline{H}_3$), 2.17 (s, 3H, $C\underline{H}_3$).

^{13}C NMR (125 MHz, Chloroform-*d*) *δ* 206.1 ($\underline{C}=O$), 137.4 (CqAr), 137.5 (CqAr), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 102.0 (C-1), 83.6 (C-2), 82.7 (C-3), 82.3 (C-4), 72.9 ($O\underline{C}H_2Ph$), 72.6 ($O\underline{C}H_2Ph$), 55.8 ($O\underline{C}H_3$), 28.0 ($\underline{C}H_3$).

HRMS (ESI) m/z: calcd for $C_{21}H_{24}KO_5$ $[M+K]^+$: 395.1255; found 395.1257.

IR (film): 2927, 1718, 1454, 1356, 1207, 1193, 1115, 1053, 1028, 737, 698 cm^{-1}.

Compound 202':

***R*$_f$** 0.50 (Cyclohexane/ EtOAc: 5/1);

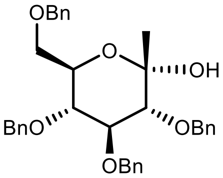
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.35 – 7.07 (m, 10H, H_{Ar}), 4.99 (s, 1H, H-1), 4.59 (d, *J* = 5.6 Hz, 1H, H-4), 4.45 – 4.31 (m, 4H, OC<u>H</u>$_2$Ph), 4.14 (dd, *J* = 5.6, 1.0 Hz, 1H, H-3), 3.90 (d, *J* = 0.9 Hz, 1H, H-2), 3.45 (s, 3H, OC<u>H</u>$_3$), 2.20 (s, 3H, C<u>H</u>$_3$).

^{13}C NMR (125 MHz, Chloroform-*d*) δ 208.6 (<u>C</u>=O), 137.3 (CqAr), 137.2 (CqAr), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 109.8 (C-1), 87.5 (C-O), 85.1 (C-O), 82.1 (C-O), 72.5 (O<u>C</u>H$_2$Ph), 72.1 (O<u>C</u>H$_2$Ph), 56.2 (O<u>C</u>H$_3$), 28.4 (<u>C</u>H$_3$).

HRMS (ESI) m/z: calcd for $C_{21}H_{24}KO_5$ [M+K]$^+$: 395.13; found 395.13.

IR (film): 2917, 1714, 1454, 1354, 1210, 1111, 1060, 1028, 947, 736, 697 cm^{-1}.

(2S,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran-2-ol **(178)**



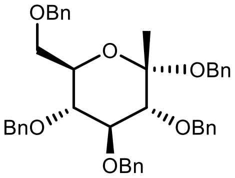
Compounds were obtained as a by-product in Fries rearrangement (see **Table 4**).

R_f 0.33 (Cyclohexane/EtOAc: 6/1);

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.21 (m, 18H, H_{Ar}), 7.15 (dd, *J* = 7.2, 2.4 Hz, 2H, H_{Ar}), 4.94 – 4.86 (m, 2H, OC<u>H</u>$_2$Ph), 4.81 (d, *J* = 10.9 Hz, 1H, OC<u>H</u>$_2$Ph), 4.69 (d, *J* = 11.1 Hz, 1H, OC<u>H</u>$_2$Ph), 4.61 (d, *J* = 12.3 Hz, 1H, OC<u>H</u>$_2$Ph), 4.58 – 4.47 (m, 2H, OC<u>H</u>$_2$Ph), 4.01 – 3.97 (m, 1H, H-5), 3.95 (t, *J* = 9.3 Hz, 1H, H-3), 3.72 (dd, *J* = 10.9, 4.0 Hz, 1H, H-6), 3.68 – 3.61 (m, 2H, H-4 and H-6), 3.36 (d, *J* = 9.3 Hz, 1H, H-2), 2.53 (s, 1H, O<u>H</u>), 1.40 (s, 3H, C<u>H</u>$_3$).

This data is consistent with the known literature.[233]

(2S,3R,4S,5R,6R)-2,3,4,5-Tetrakis(benzyloxy)-6-((benzyloxy)methyl)-2-methyltetrahydro-2H-pyran **(179)**



Compounds were obtained as a by-product in Fries rearrangement (see **Table 4**).

R_f 0.50 (Cyclohexane/EtOAc: 5/1);

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.40 – 7.22 (m, 23H, H_{Ar}), 7.19 – 7.12 (m, 2H, H_{Ar}), 4.96 (d, *J* = 11.5 Hz, 1H, $OC\underline{H_2}Ph$), 4.92 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.87 (d, *J* = 11.0 Hz, 1H, $OC\underline{H_2}Ph$), 4.83 (d, *J* = 10.8 Hz, 1H, $OC\underline{H_2}Ph$), 4.72 (d, *J* = 11.5 Hz, 1H, $OC\underline{H_2}Ph$), 4.61 (d, *J* = 12.2 Hz, 1H, $OC\underline{H_2}Ph$), 4.58 – 4.49 (m, 4H, $OC\underline{H_2}Ph$), 4.13 (t, *J* = 9.3 Hz, 1H, H-3), 3.75 (ddd, *J* = 9.8, 4.2, 1.9 Hz, 1H, H-5), 3.72 – 3.60 (m, 3H, H-4 and H-6), 3.40 (d, *J* = 9.6 Hz, 1H, H-2), 1.40 (s, 3H, $C\underline{H_3}$).

This data is consistent with the known literature.[233]

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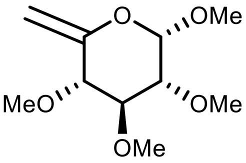

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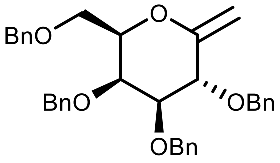

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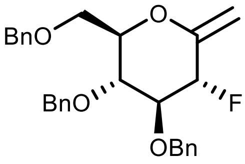

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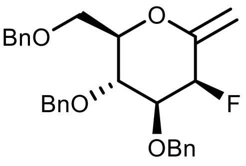

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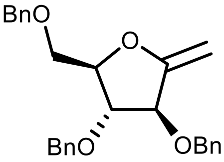

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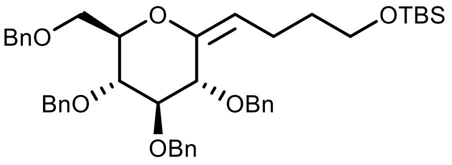

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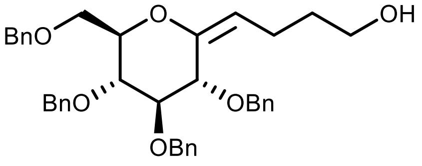

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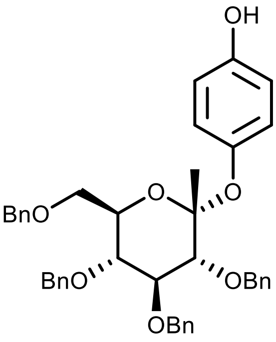

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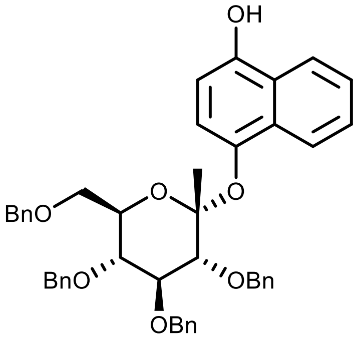

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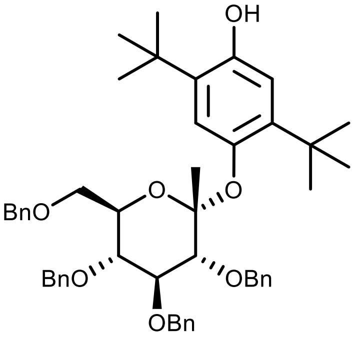

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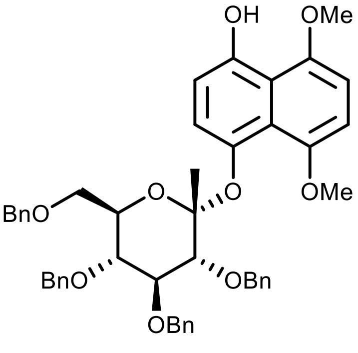

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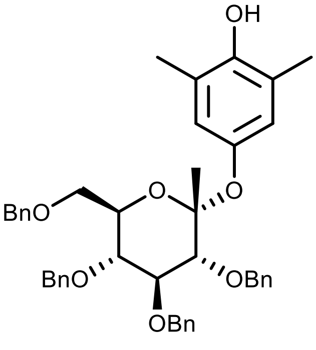

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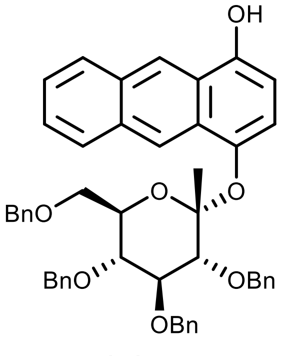

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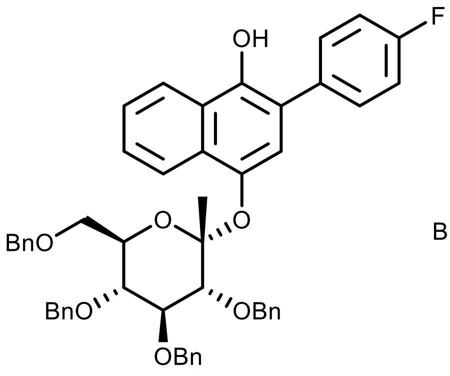

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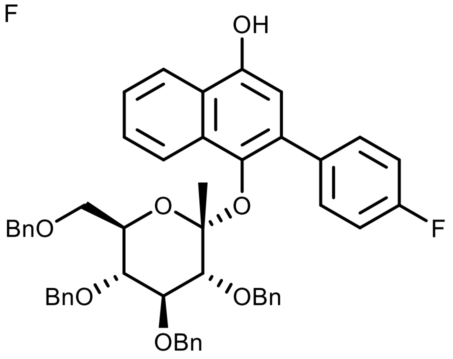

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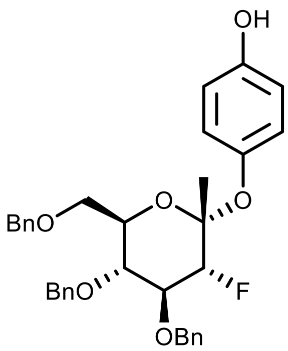

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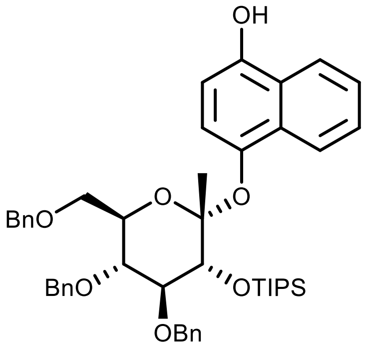

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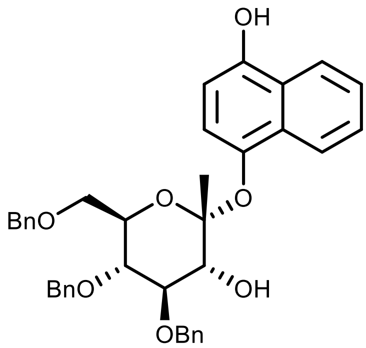

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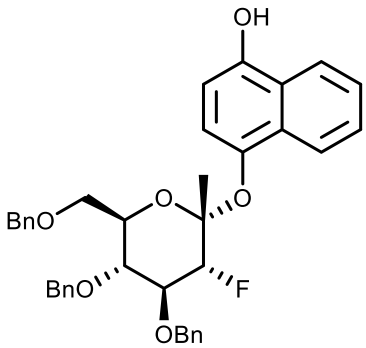

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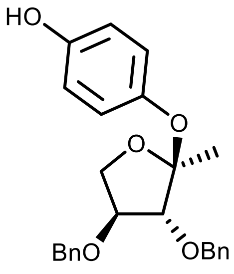

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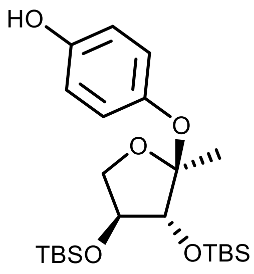

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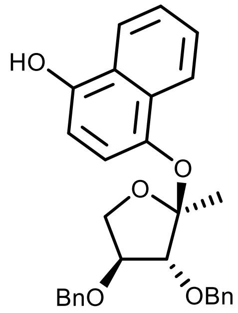

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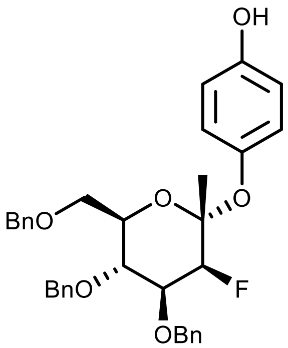

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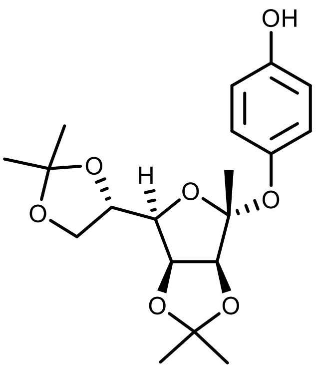

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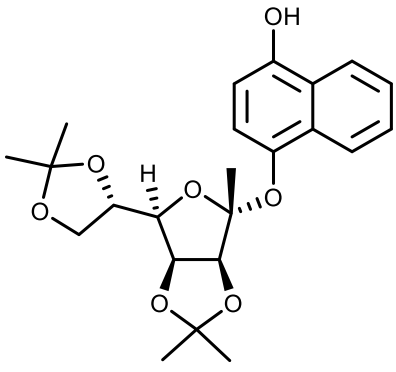

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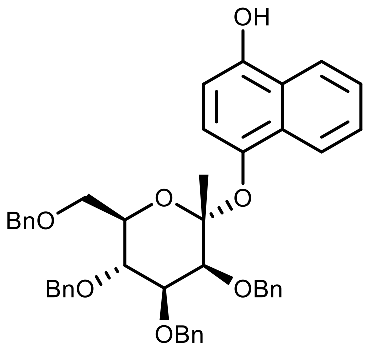

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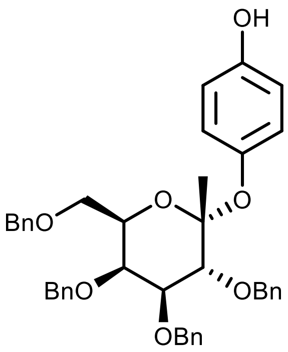

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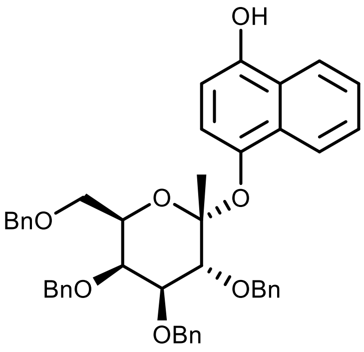

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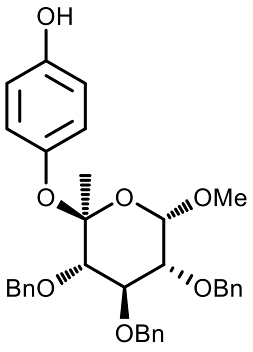

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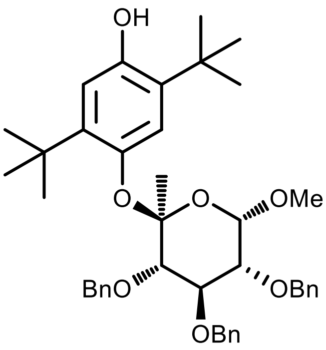

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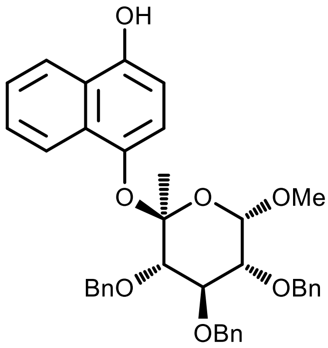

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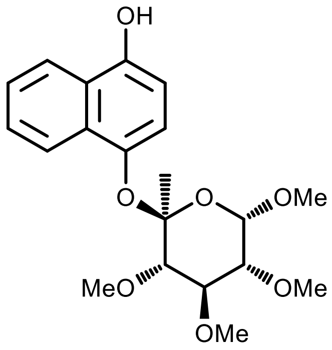

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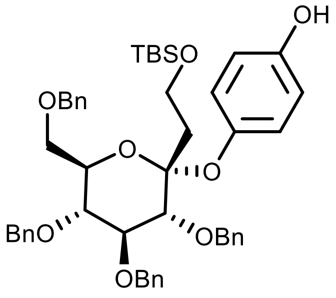

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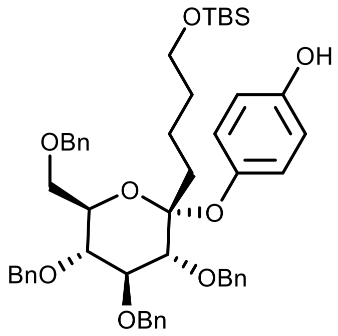

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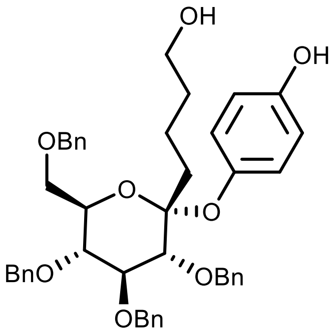

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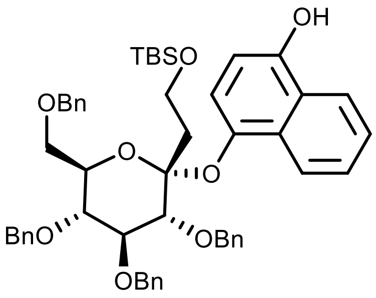

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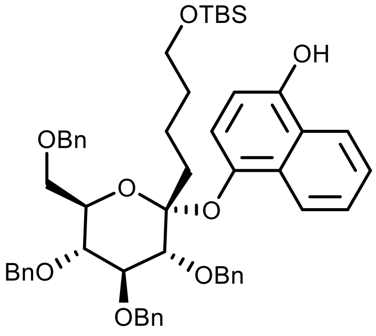

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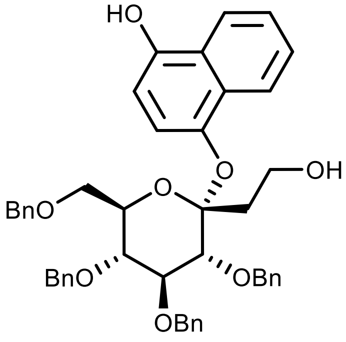
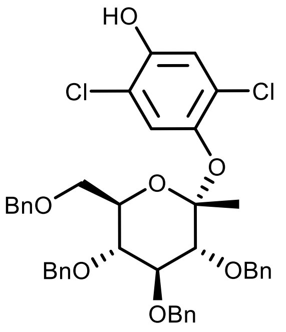
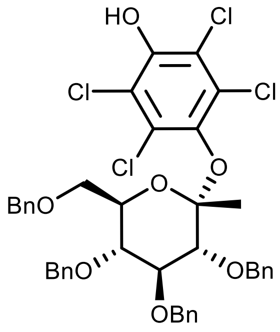


151o (77; 213)


151ai (79; 160)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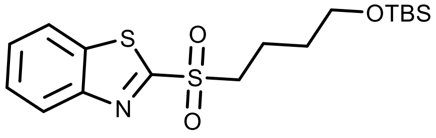
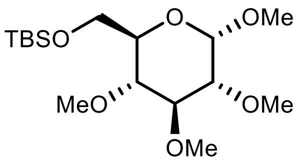
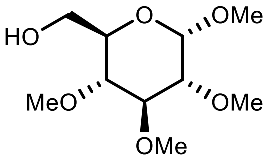
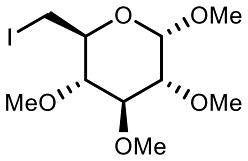
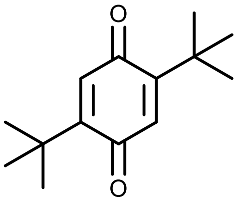
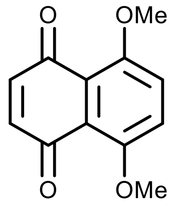

154 (67; 206)

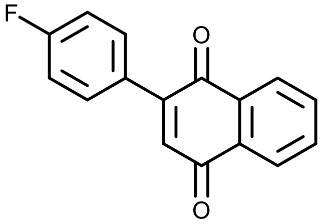

160a (; 173)

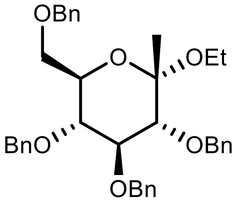

161a (; 173)

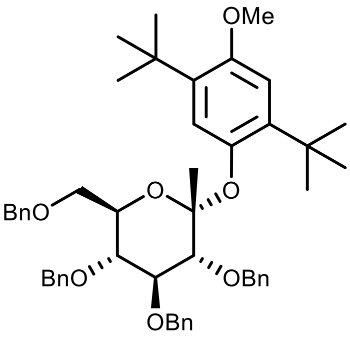

163 (69; 174)

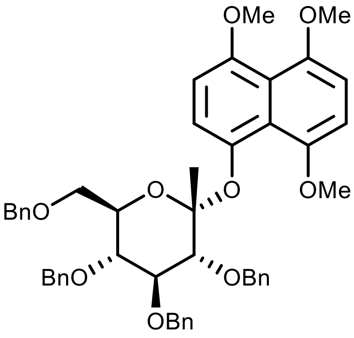

165 (70; 148)

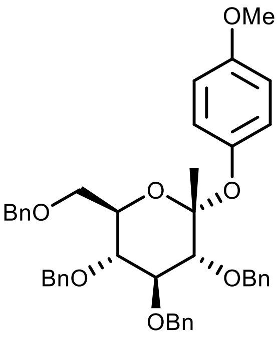

170 (71; 151)

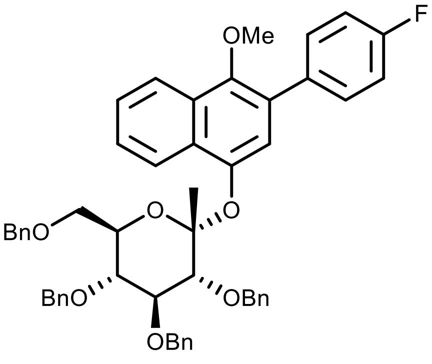

171 (71; 155)


175 (79; 162)


177ac (91; 149)


177ad (91; 152)


177a (91; 141)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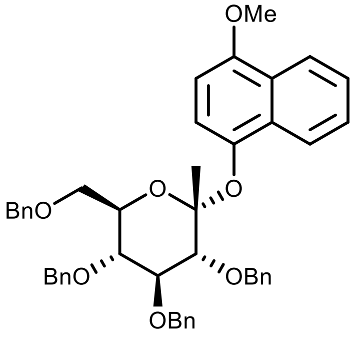
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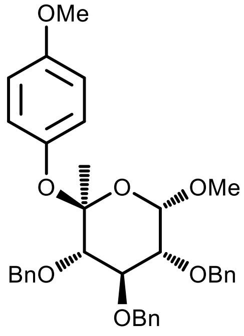
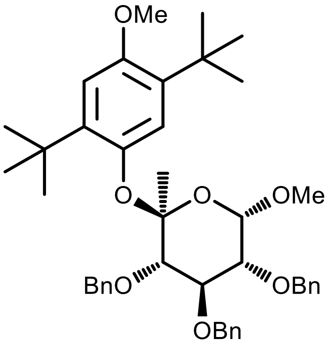

177ba (91; 163)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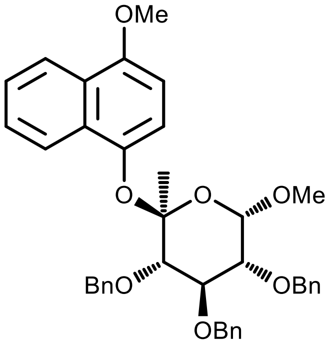
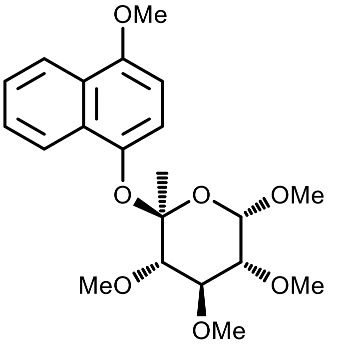
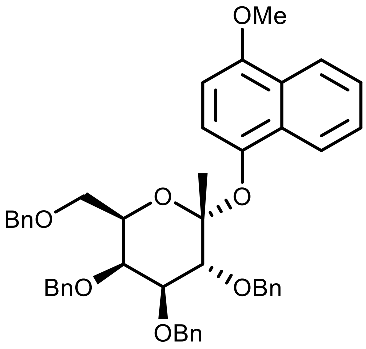

177bc (91; 167)


177c (91; 176)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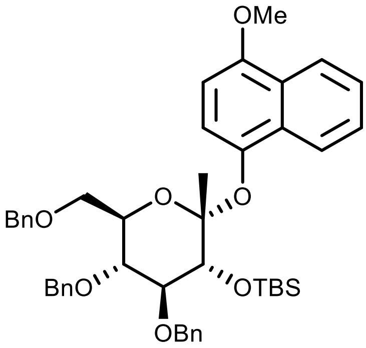
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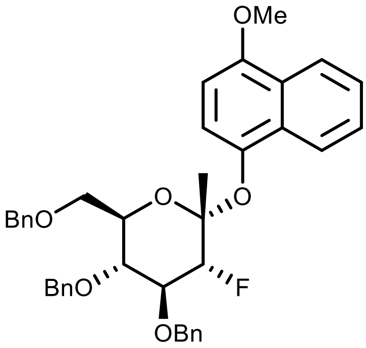
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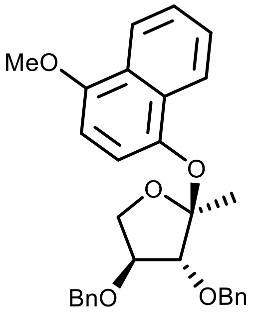
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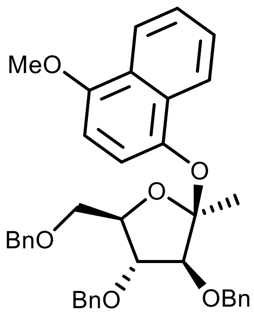
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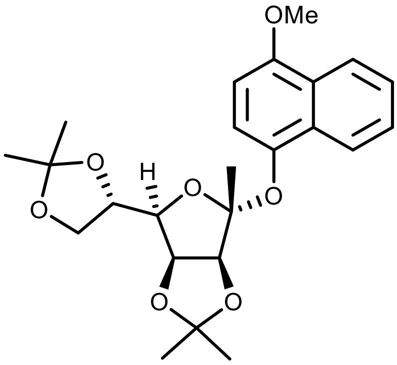
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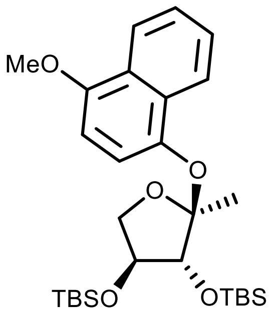
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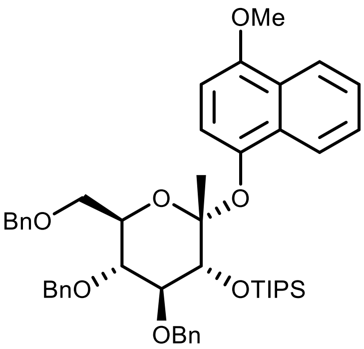
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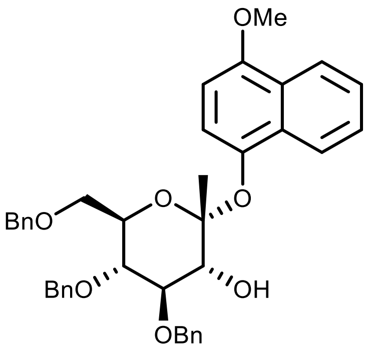
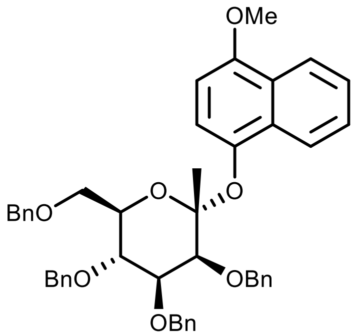
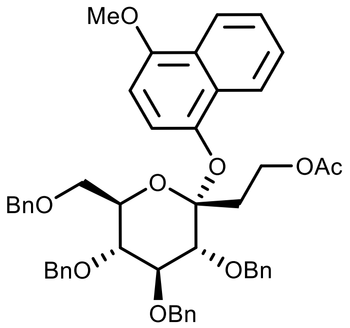

177h (92; 217)



177e (92; 226)



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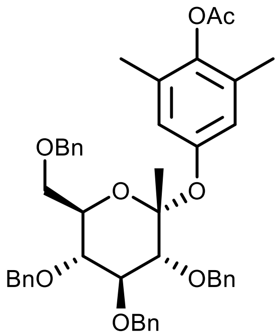
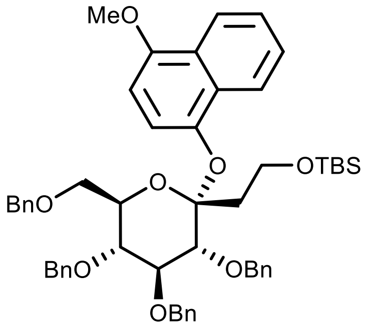
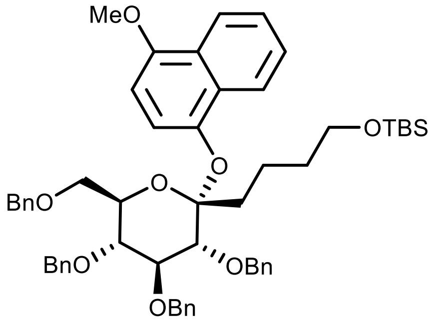


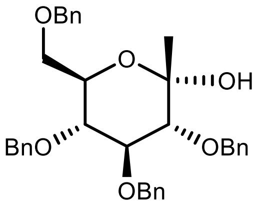
177ae (94; 154)



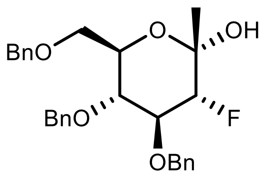
177pb (92; 205)



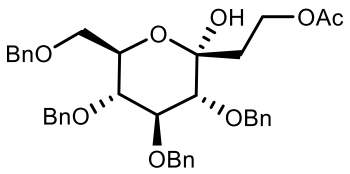
177qb (92; 212)



178 (93; 230)



178b (98; 186)



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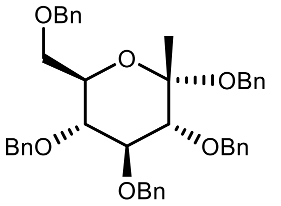

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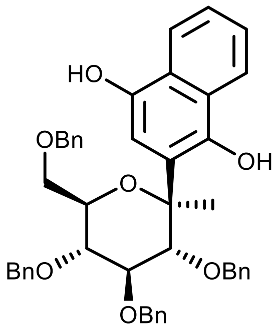
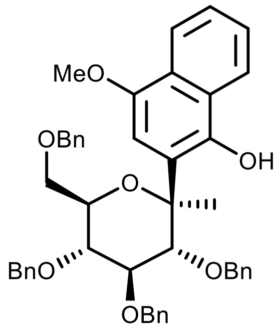
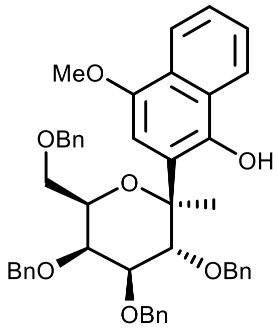


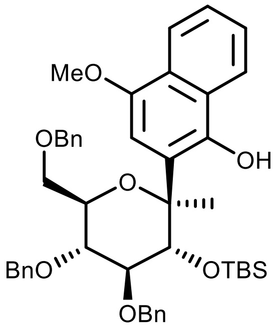
182 (95; 144)



183 (95; 145)



184 (96; 182)



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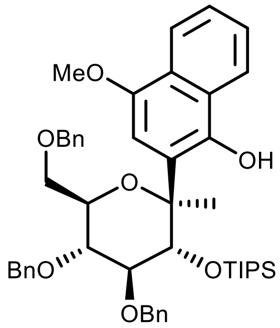
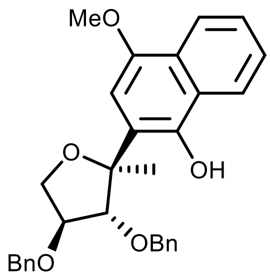
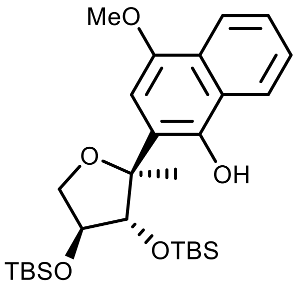


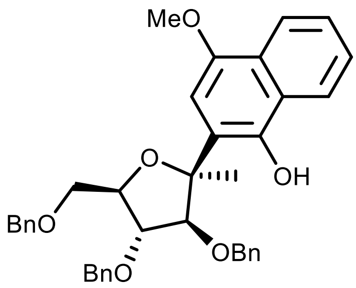
186 (96; 220)



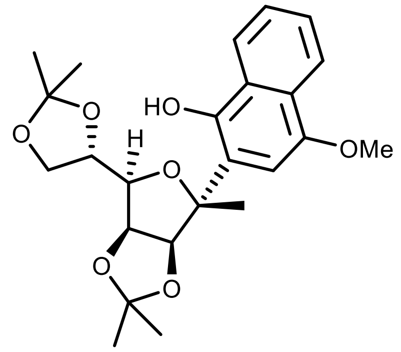
187 (97; 191)



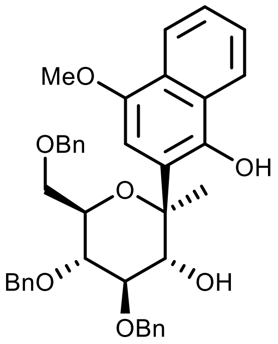
188 (97; 194)



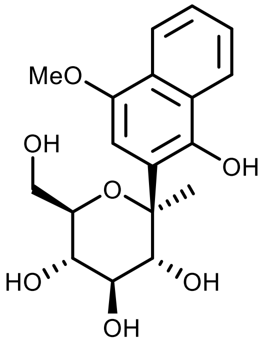
189 (97; 201)



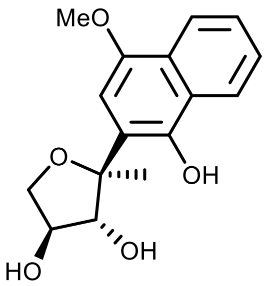
190 (97; 198)



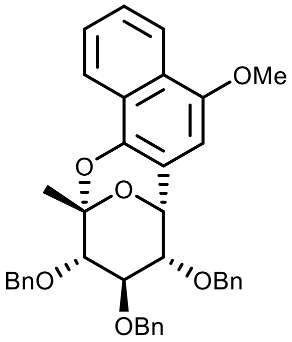
191 (110; 221)



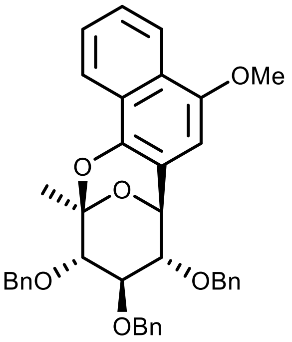
199 (101; 146)



200 (101; 195)



201α (103; 169)



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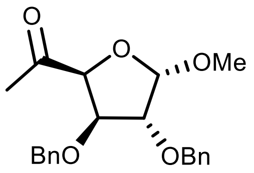
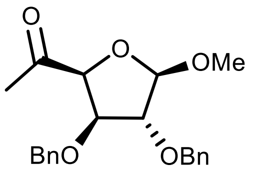
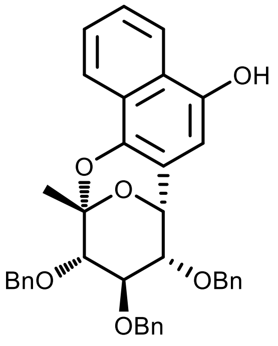


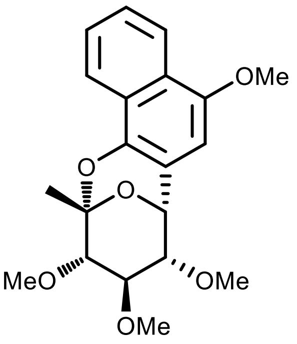
202 (104; 229)



202' (104; 229)



203 (105; 168)



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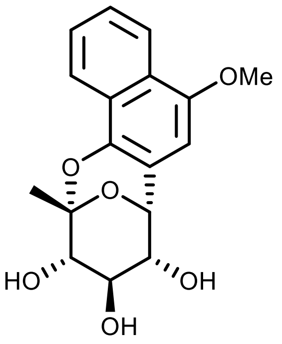
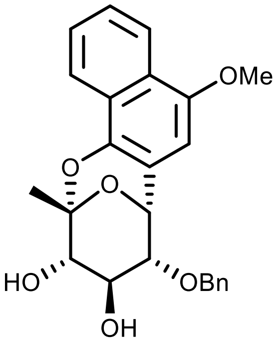
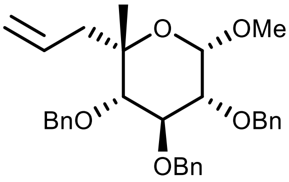


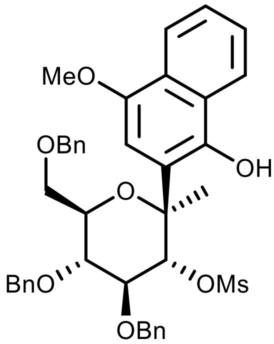
207 (107; 171)



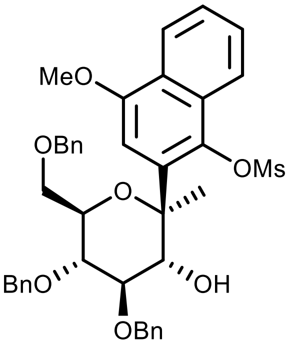
207' (107; 172)



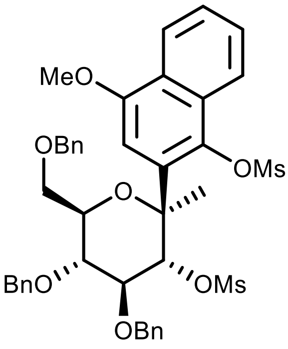
208 (108; 228)



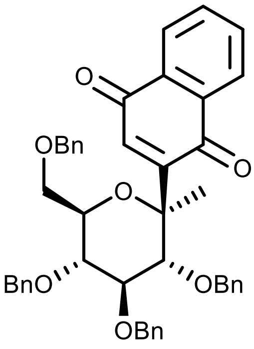
210 (111; 227)



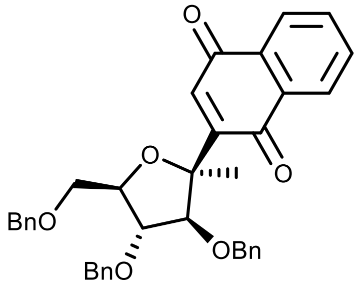
212 (111; 227)



213 (111; 228)



214 (112; 147)



215 (112; 202)

Haijuan LIU

Glycosylation Formelle de Quinones à partir d'*exo*-Glycals par Transfert d'Atome d'Hydrogène. Application à la synthèse de *C*,*C*-aryl glycosides *via* un réarrangement de type Fries

Résumé

Les glycoconjugués représentent une source féconde de composés bioactifs. Au fil des décennies, les chimistes de synthèse ont été attirés par les structures dans lesquels un groupement aromatique est lié de façon covalente à un sucre densément fonctionnalisée *via* une liaison *O*- ou *C*-glycosidique. Bien que de nombreuses méthodes aient été développées pour la synthèse de *O*- et *C*-aryl glycosides, très peu ont été décrites concernant des analogues portant un carbone quaternaire (pseudo)anomérique.

L'objectif de ce travail de thèse était de développer une nouvelle stratégie pour la construction du cycle DEF-benzoxocine du produit naturel nogalamycine à partir d'*exo*-glycals et de quinones par transfert d'atome d'hydrogène (HAT) catalysé par le fer. Une première étude nous a conduit à la préparation de *O*-aryl glycosides à partir d'*exo*-glycals par l'intermédiaire de radicaux pseudo-anomères tertiaires générés par HAT. Une série de *O*-aryl glycosides a été obtenue avec une stéréosélectivité faible à élevée. Par la suite, la synthèse de *C*-aryl glycosides *via* un réarrangement de type Fries catalysé par un acide de Lewis a également été étudiée, ouvrant la voie à une stratégie unifiée pour la construction de motifs *C*-glycosides caractérisés par un centre pseudoanomérique quaternaire stéréodéfini portant un substituant *O*- ou *C*-aryl exocyclique.

Mots-clés : Glycoconjugués, glycomimétiques, produits naturels, composés bioactifs, *O*-aryl glycosides, *C*-aryl glycosides, radicaux anomériques, nogalamycine, *exo*-glycals, quinones, MHAT, réarrangement de type Fries

Abstract

Glycoconjugates represent a prolific source of bioactive compounds. Over decades, synthetic chemists have been attracted by glycoconjugates in which an aromatic moiety is covalently linked to a densely functionalized sugar unit via a *O*- or *C*-glycosidic bond. Although many methods have been developed for the synthesis of *O*- and *C*-aryl glycosides, only few precedents have been published so far concerning analogues bearing a (pseudo)anomeric quaternary carbon centre.

The aim of this PhD work was to develop a new strategy for the construction of DEF- benzoxocin ring of natural product nogalamycin from *exo*-glycals and quinones under iron-mediated hydrogen atom transfer (HAT) conditions. A first study led us to the preparation of *O*-aryl ketosides from *exo*-glycals *via* the intermediacy of HAT-generated tertiary pseudo-anomeric radicals. A series of *O*-aryl glycosides were obtained with low to high stereoselectivity. Subsequently, the synthesis of *C*-aryl ketosides *via* an unprecedented Lewis acid-catalyzed *O* → *C* glycoside rearrangement was also demonstrated, opening the way to a unified strategy for the construction of *C*-glycoside motifs characterized by a stereodefined quaternary pseudoanomeric center bearing an exocyclic *O*- or *C*-aryl substituent.

Key words: Glycoconjugates, glycomimetics, natural products, bioactive compounds, *O*-aryl ketosides, *C*-aryl ketosides, anomeric radicals, nogalamycin, *exo*-glycals, quinones, MHAT, Fries-type rearrangement