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**Aluminium triflate-mediated reactions of glycals:
towards chiral multicyclic products**

by

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Thesis submitted in fulfilment of the requirements for the degree

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Chemistry

in the



Faculty of Science

of the

University of Johannesburg

Promoter: Prof. D. B. G. Williams

co-Promoter: Prof. H. H. Kinfe

August 2014

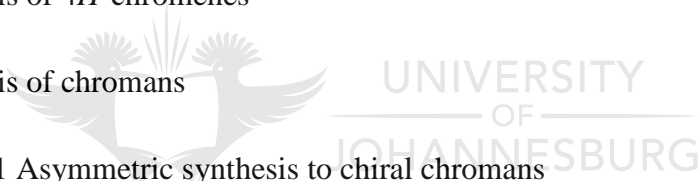
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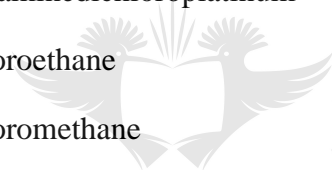
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I DEDICATE THIS THESIS TO MY LOVING MOTHER **IRENE JOYCE NHLAPHO**



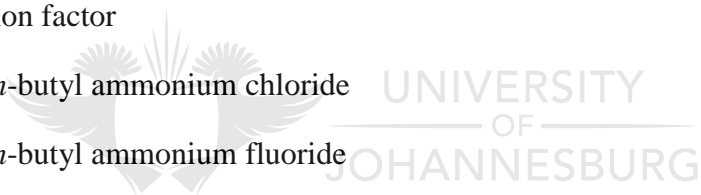
II. Abbreviations

Aq	aqueous
Ar	aryl
ATP	adenosine triphosphate
B3LYP	Becke, three-parameter, Lee-Yang-Parr
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BOC	<i>tert</i> -butyloxycarbonyl
BUS	<i>tert</i> -butylsulfonyl
CHD	coronary heart disease
COSY	correlation spectroscopy
<i>cis</i> -DDP	<i>cis</i> -diaminedichloroplatinum
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DMSO	dimethyl sulfoxide
dppp	bis(diphenylphosphino) propane
EDG	electron donating group
EWG	electron withdrawing group
HMBC	heteronuclear multiple bond correlation
HSAB	hard soft acid base
HSQC	heteronuclear single quantum correlation
LA	L-lactide



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LDL	low density lipoprotein
MCR	multi-component reaction
Mp	melting point
MRSA	methicillin-resistant <i>staphylococcus aureus</i>
NIS	<i>N</i> -iodosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
ORTEP	Oak Ridge thermal ellipsoid plot
PLA	poly(lactic acid)
PTC	phase transfer catalyst
RCM	ring closing metathesis
R _f	retention factor
TBACl	<i>tetra-n</i> -butyl ammonium chloride
TBAF	<i>tetra-n</i> -butyl ammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
TES	triethylsilyl
THF	tetrahydrofuran
TIPS	triisopropyl
TMS	trimethylsilyl



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VI. Research Outputs

Research Papers

Williams, D. B. G.; Simelane, S. B.; Kinfe, H. H. *Org. Biomol. Chem.* **2012**, *10*, 5636.

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Oral presentations at conferences

Young chemist symposium, University of Pretoria, **2012**

SACI Conference, East London, **2013**

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Frank Warren Conference, Bloemfontein, **2012**



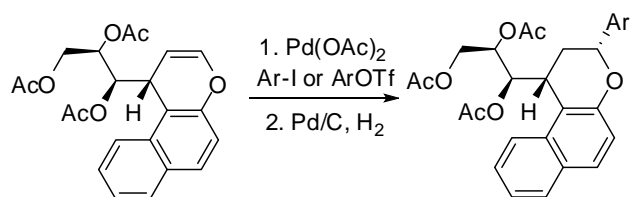
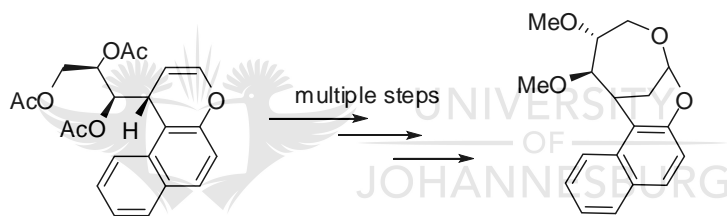
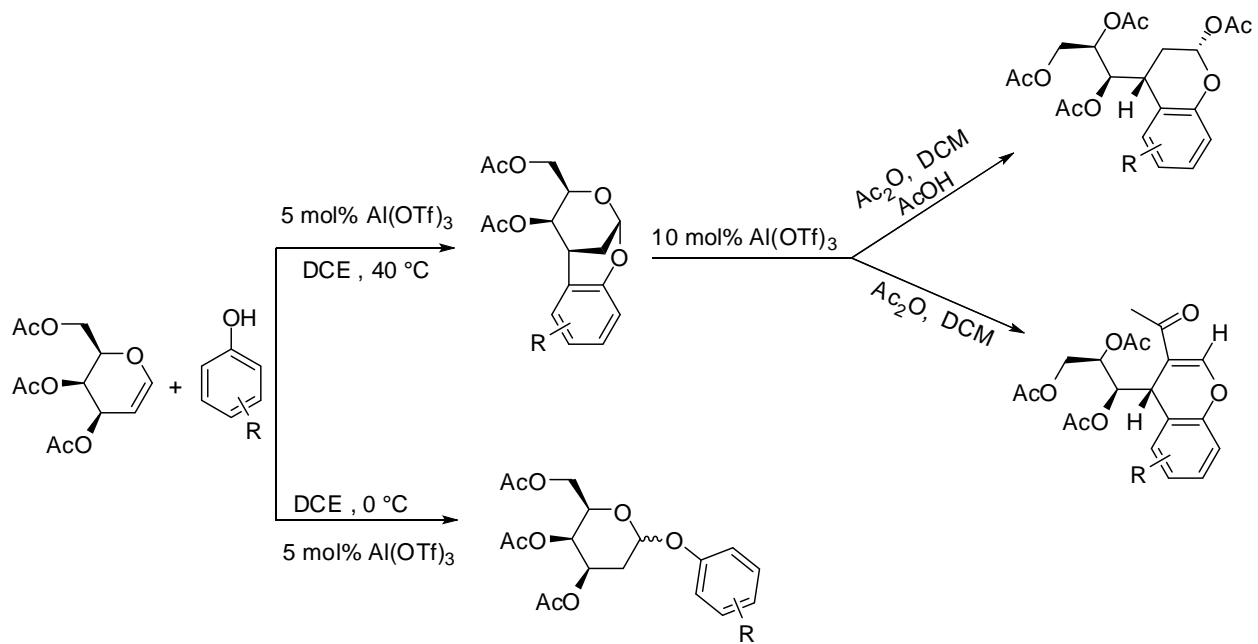
VII. Synopsis

The work described in this thesis involves the use of aluminium triflate as a Lewis acid catalyst for the synthesis of novel highly functionalised carbohydrate derivatives using 3,4,6-*tri-O*-acetyl-D-galactal as a substrate (summarised in Scheme I, below). This study initially focused on the synthesis of 1-*O*-aryl-2-deoxygalactosides by using a range of phenols as glycosyl acceptors. The galactosides were readily afforded in high yields at low temperatures using 5 mol% aluminium triflate. By merely increasing the temperature from 0 °C to 40 °C the reaction yielded a different set of tricyclic structures known as bridged chiral benzopyrans.

The bridged chiral benzopyrans were strategically ring opened *via* acetolysis to yield either galactose based chromenes or chromans, depending on the reaction conditions. A proposal relating to the mechanism of this selective ring opening acetolysis is discussed. The benzopyrans (chromenes, chromans and bridged chiral benzopyrans) were de-acetylated *via* triethyl amine catalysed transesterification. Interestingly, the chromenes did not yield the anticipated hydrolysis product (triol) but a new class of bridged chiral benzopyrans which were a result of intramolecular oxa-Michael addition.

A chromene that formed during the selective ring opening of the bridged chiral benzopyrans was employed to develop a method for the synthesis of a carbohydrate derived oxepane. The oxepane synthesis was achieved, albeit in the face of numerous challenges from side reactions. The difficulties encountered in the synthesis are discussed.

The chromenes are also shown to provide immediate access to carbohydrate derived flavonoid compounds. The Heck reaction with Pd(OAc)₂ and a range of aryl halides were employed for the cross-coupling and subsequent hydrogenation of the product with Pd/C afforded chiral flavonoids in high yields. Hydrolysis of the acetates on the flavonoids results into a triol dangling arm which provides a reactive site for further manipulations.



Scheme I. Reactions discussed in the thesis

Chapter 1

Aluminium triflate as a Lewis acid – A Literature survey

1.1 Introduction to Lewis acids

Metal triflates are emerging as Lewis acids of choice in organic transformations, as a replacement for traditional Lewis acids due to their increased activity and stability to moisture. They have recently shown activity in driving a number of well-known organic transformations, but this review will focus mainly on the use of $\text{Al}(\text{OTf})_3$ as a Lewis acid catalyst. Specifically aryl glycosidation reactions as well as synthesis of benzopyran derivatives will be reviewed.

1.1.1 Acid/base definitions

Acids and bases play a significant role in organic chemistry. They promote a wide range of organic transformations.¹ There has been a number of definitions that have been employed to explain what type of compound constitutes an acid or a base. The Arrhenius definition states that a species that dissolves in water and increase the concentration of hydrogen ions, H^+ (aq), is an acid. Conversely, one that dissolves in water and increases the concentration of hydroxide ions, OH^- (aq), is a base.² Brønsted and Lowry also defined an acid as a proton donor and a base as a proton acceptor.³ After the Brønsted-Lowry acid-base definition, Lewis proposed his own definition of acids and bases, defining an acid as an electron pair acceptor and a base as an electron pair donor.⁴ This is one of the most widely used definitions due to its simplicity and applicability.³

Pearson⁵ conceived the hard-soft acid-base theory which was pioneered by the realisation that certain metal ions (acids) displayed an affinity for non-metal ligands (bases). He defines hard acids as small non-polarisable species carrying a large positive charge and soft acids as large polarisable species carrying a diffuse positive charge. Although this hard-soft acid-base theory can explain stability on some acid-base interactions, it should be noted that relative acid/base strengths should be taken into account and this depends on the 'match' between the acid and base.

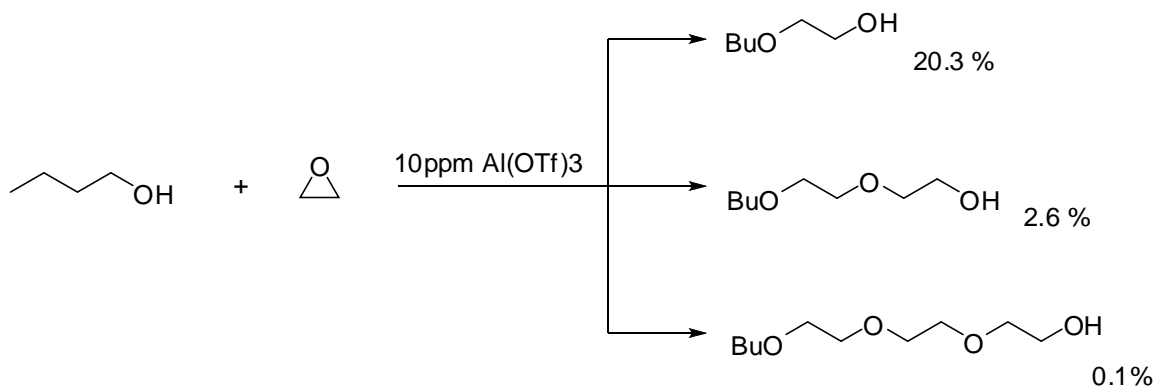
Lewis acid-catalysed reactions are of great interest because of their unique reactivities, selectivities and mild reaction conditions used.⁶ Traditional Lewis acids normally used to catalyse these reactions are AlCl_3 , BF_3 , TiCl_4 , SnCl_4 , etc. However, most of these Lewis acids require stoichiometric amounts, are moisture sensitive and easily decompose in the presence of small amounts of water.⁷ Furthermore, these Lewis acids cannot be recovered and reused upon completion of a reaction. In the early 1990's lanthanide triflates $[\text{Ln}(\text{OTf})_3]$ ("triflate" is a contraction of "trifluoromethane sulfonate", and will be used throughout this thesis) were introduced to organic synthesis boasting their characteristic feature of being stable and being able to work as a Lewis acid in water. Since then, these triflate salts have provided an alternative to the traditional Lewis acids. The most common triflate salts are the lanthanide triflates of the type $\text{Ln}(\text{OTf})_3$ (where $\text{Ln} = \text{La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Y}$), but the popular one is $\text{Sc}(\text{OTf})_3$, which has been used in reactions such as Friedel-Crafts acylation,⁸ aldol and Michael reactions,⁹ alongside many other organic transformations. The metal triflates as catalysts in organic synthesis have been extensively reviewed by Kobayashi.⁷

Recently there has been an increased interest in the use of metal triflates as Lewis acids. The use of aluminium triflate, however, has often been overlooked in favour of the lanthanide triflates. Nonetheless, recent literature reports have shown the competency of aluminium triflate with other Lewis acids, as will be discussed in the next section.

1.1.2 Aluminium triflate as a Lewis acid

According to Pearson's hard-soft acid-base theory,⁵ aluminium triflate is a hard acid since it is small and not easily polarisable. Like most triflates it is used as a Lewis acid (electron pair acceptor) in organic synthesis. Its use as a catalyst was first reported in 1985 by Daniel Falgoux *et al.* who invented a process for the preparation of addition products of epoxides and hydroxylated compounds.¹⁰ They first prepared the catalyst by reacting aluminium powder with 0.57 N triflic acid in water. They then isolated aluminium triflate by filtering off excess aluminium and evaporating the water at 100 °C under atmospheric pressure. The triflate salt was obtained as a white powder and was then used in 10 ppm concentration to catalyse the reaction between *n*-butanol and ethylene oxide, yielding monobutylethers of monoethylene glycol,

diethylene glycol and triethylene glycol in 20.3%, 2.6% and 0.1% (expressed as a percent by weight of the reaction medium), respectively.



Scheme 1.1. Reaction of *n*-butanol and ethylene oxide

The efficacy of aluminium triflate as catalyst was compared with others; namely potassium acetate, CH₃COOK, magnesium perchlorate, Mg(ClO₄)₂, zinc perchlorate, Zn(ClO₄)₂ and zinc triflate, Zn(OTf)₂. Al(OTf)₃ displayed the best catalytic activity as can be seen in Table 1.1. Then production of the monobutylethers of ethylene glycol with all the catalysts was performed under the same reaction conditions (T 200 °C, P 3 MPa, 1 h). With the same temperature, pressure and time applied with all catalyst systems evaluated, it implies that the measure of each catalyst's activity was based on the conversion rate of ethylene oxide, selectivity and catalyst loading.

An examination of Table 1.1 below, shows aluminium triflate to be very active and converts the substrates to product with good selectivity at low concentrations compared to the other catalysts. In turn the activity of potassium acetate, measured by the conversion rate of ethylene oxide, is satisfactory from catalyst concentrations of 50 ppm, but the selectivity, *S*, of the reaction is comparatively low. The perchlorates of both zinc and magnesium are selective catalysts but their activity leaves a lot to be desired. A year later another group then reported the synthesis of a few amino alcohols from amines and epoxides using catalytic amounts of aluminium triflate.¹¹

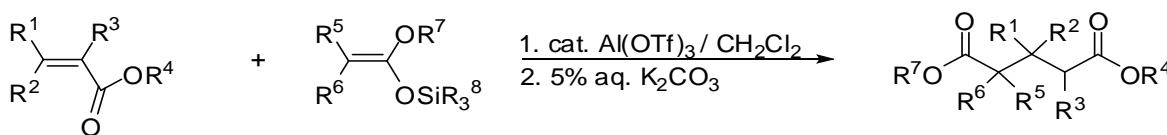
Table 1.1. Production of monobutylether of ethylene glycol with different catalysts.

Catalyst	Conc. (ppm)	Conversion rate of ethylene oxide ^a	Content of C ₄ H ₉ O-(CH ₂ CH ₂ O) _n H by weight			Selectivity S ^b
			n=1	n=2	n=3	
Al(OTf) ₃	10	1.00	20.3	2.6	0.1	7.8
CH ₃ COOK	50	0.93	16.3	4.3	-	3.8
CH ₃ COOK	100	1.00	16.6	4.6	-	3.6
CH ₃ COOK	300	1.00	15.3	4.3	3.5	3.5
Mg(ClO ₄) ₂	100	0.78	17.0	1.4	-	12.1
Mg(ClO ₄) ₂	300	0.98	23.4	1.8	-	13.0
Zn(ClO ₄) ₂	100	0.67	16.3	1.1	-	14.8
Zn(ClO ₄) ₂	300	1.00	22.5	2.5	0.1	9.0
Zn(OTf) ₂	50	1.00	17.8	2.5	-	7.1

^aConversion rate is standardised onto that for Al(OTf)₃ at 1.00.

^bSelectivity, defined by: $S = \frac{\text{weight of monobutyl ether of monoethyleneglycol produced}}{\text{weight of monobutylether of diethyleneglycol produced}}$

Nobutho *et al.* also reported the use of Al(OTf)₃ in a Michael reaction of *O*-silylated ketene acetals to α,β -unsaturated esters.¹² They found that the ester reacted smoothly with *O*-silylated ketene acetals to afford the corresponding glutarate in good yields in the presence of only catalytic amounts of aluminium triflate.



Scheme 1.2. Michael reaction of *O*-silylated ketene acetals with α,β -unsaturated esters

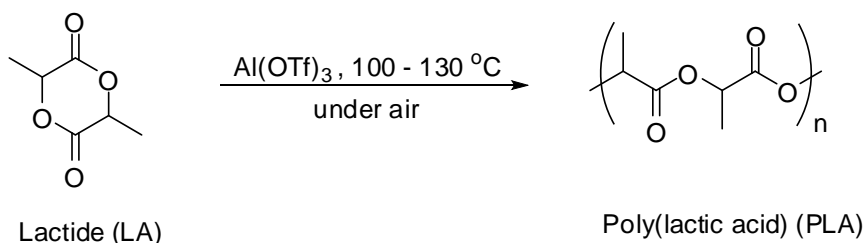
Al(OTf)₃, together with Ga(OTf)₃ and B(OTf)₃, were used by Olah and co-workers for the Friedel-Crafts acylation and alkylation of benzene and toluene.¹³ However, they found that

aluminium triflate's catalytic activity was inferior compared to that of gallium and boron triflates.

Early in 1990 Messina *et al.* reported the oligomerisation of olefins containing 3 to 6 carbon atoms ($C_3 - C_6$ olefins) using triflic acid salts of metals from group two, three, four and five of the periodic table as acid heterogeneous catalysts.¹⁴ The triflate salts were found to be efficient in driving the oligomerisation. Compared to previously used catalysts such as chloride salts and boron trifluoride etherate, they had greater thermal stability. Olah's group investigated the efficiency of these triflate salts, including $Al(OTf)_3$ in the cationic polymerisation of tetrahydrofuran.¹⁵ High molecular-weight polytetrahydrofuran was obtained in good yields with all three catalysts, further demonstrating the catalytic efficiency of these triflates.

Aluminium triflate has also been reported to effect the epoxidation of olefins with iodosylbenzene,¹⁶ as well as ring enlargement of 3-hydroxy-3-propargylisindolin-1-ones.¹⁷ Apart from Kobayashi's aldol reactions,¹⁸ aluminium triflate was little explored in this decade (1990-1999) in organic synthesis, but was more popular in polymerisation reactions since it was also reported to initiate the polymerisation of 1,3-pentadiene.¹⁹

In the previous decade (2000-2009), the amount of work done with aluminium triflate increased drastically. Its popularity in polymerisation reactions also gained momentum, with Kunioka *et al.* reporting the catalyst as an initiator for ring-opening polymerisation of L-lactide (LA).²⁰ The bulk polymerisation of LA to poly(lactic acid) (PLA) was done under air (Scheme 1.3) further showing the stability of the catalyst in moisture and air.



Scheme 1.3. Polymerisation of L-LA to PLA

In developing the method for PLA production the group was looking for a Lewis acid that could work in open air, based on efficiency and economics. Since metal triflates are known as Lewis acids that are stable in air and active in water,⁷ several metal triflates were investigated for their ability to drive the reaction and the superiority of Al(OTf)₃ is clear from the results summarized in Table 1.2.

Table 1.2. Poly(L-lactic acid) polymerised from L-lactide (LA) using metal triflate with H₂O as initiator at 100 °C.^a

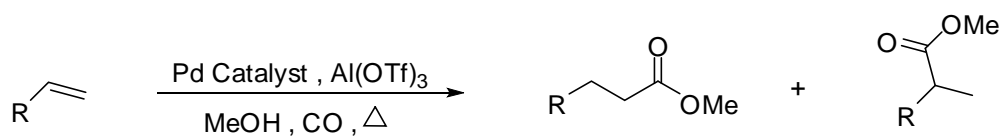
Entry	Catalyst	Reaction time (h)	Recovery ^b (%)	Molecular Weight ^c	
				M _n	M _w /M _n
1	Al(OTf) ₃	6	65	4,300	1.38
2	In(OTf) ₃	6	39	3,500	1.12
3	Sc(OTf) ₃	24	48	840	3.77
4	Cu(OTf) ₂	24	46	800	2.76
5	AgOTf	240	13	580	2.19
6	Mg(OTf) ₂	240	26	760	2.45
7	Y(OTf) ₃	240	47	940	3.18
8	La(OTf) ₃	240	31	900	2.57
9	Sm(OTf) ₃	240	40	760	3.86
10	Yb(OTf) ₃	240	45	1,160	2.94

^aPolymerisation conditions: 10 mmol LA monomer (1.44 g), 0.01 mmol metal triflate and 0.5 mmol H₂O (9 mg) in a 5 mL glass tube without a cap in air with no stirring at 100 °C. ^bRecovery was determined using the weight of the monomer and isolated dry polymer. ^cNumber average molecular weight distribution were determined by GPC.

Aluminium triflate and indium triflate, which are both group 13 metal triflates of the periodic table, had high activities for PLA polymerisation. Aluminium triflate also showed a high recoverability of 65%, and it was, therefore, the metal triflate of choice to catalyse the polymerisation of LA to PLA with different initiators namely; H₂O, alcohols and glycerol.

Since Kunioka *et al.* a number of articles have reported ring-opening polymerisation reactions with different cyclic monomers of varying ring sizes and a range of alcohols and diols.²¹ Aluminium triflate has also been used as a polymer supported Lewis acid, specifically polystyrene supported aluminium triflate [Ps-Al(OTf)₃].²² This heterogeneous catalyst has been used for reactions such as dithioacetylisation,²² Friedel-Crafts acylation,²³ sulfonylation of arenes²⁴ and a range of other organic transformations.

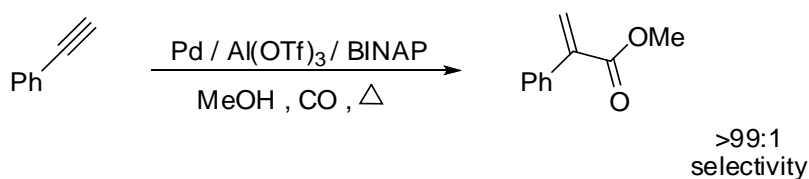
Aluminium triflate has also been used as a co-catalyst in Pd-catalysed methoxycarbonylation reactions,²⁵ where Brønsted acids are normally preferred. The alkenes, namely styrene,²⁵ pentene,²⁵ 1-octene²⁶ and vinyl acetate²⁷ were all methoxycarbonylated with high conversions in the presence of catalytic amounts of Al(OTf)₃ to their corresponding linear and branched esters. Williams *et al.* benchmarked the activity of Al(OTf)₃ with commonly used Brønsted acids and it was found to out-perform the Brønsted acids in all aspects of the reaction.²⁵



where R = Ph, nPropyl, nHexyl, OAc

Scheme 1.4. Methoxycarbonylation of alkenes

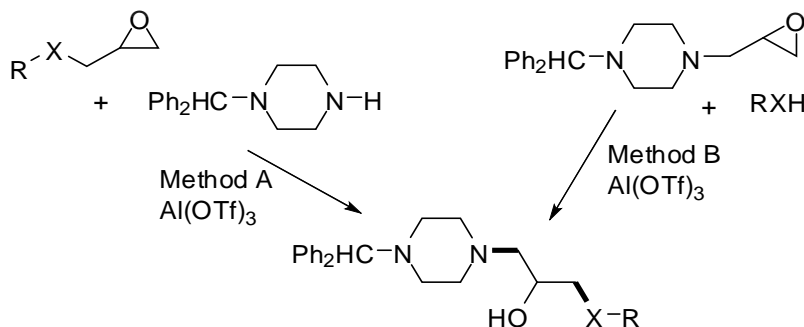
The Lewis acid catalyst aluminium triflate has also been reported to co-catalyse the methoxycarbonylation of the alkyne phenylacetylene.²⁸



Scheme 1.5. Methoxycarbonylation of phenylacetylene

The methoxycarbonylation proceeded smoothly to yield the branched ester product in high selectivity; however, the selectivity was attributed to the bidentate ligand, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), used in the reaction. The catalyst was recycled ten times without loss of activity.

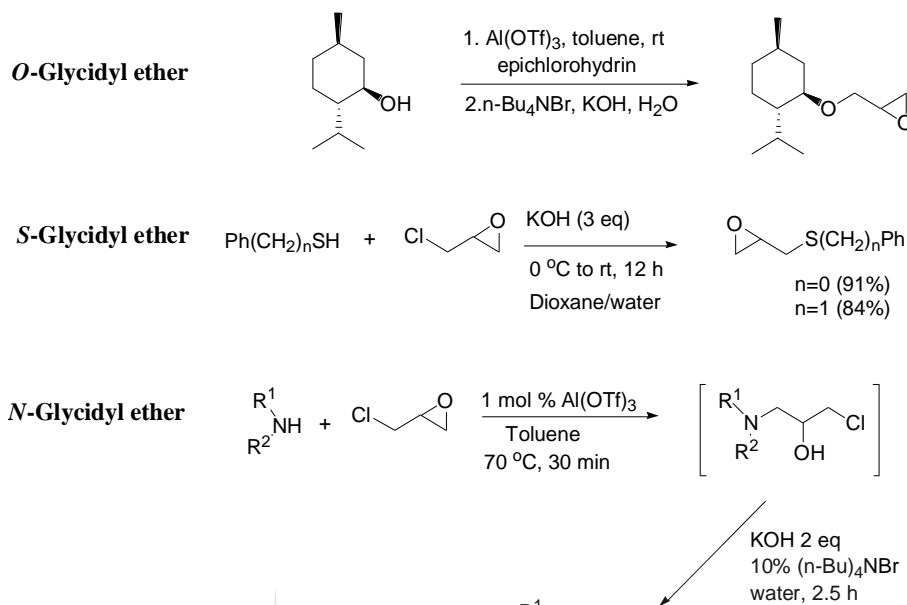
It is hard to ignore the fact that most of the work done with aluminium triflate is based on ring opening of epoxides with either alcohols,²⁹ thiols³⁰ or amines.³¹ One report that summarises this ring opening of epoxides with different nucleophiles was authored by Williams and Cullen.³⁰ Their report was based on epoxide ring opening towards piperazine-derived physiologically active compounds.



Scheme 1.6. Ring opening of epoxides

Aluminium triflate catalyses the ring opening of epoxides, forming β -amino alcohols bearing the piperazine motif.³⁰ Two different strategies were examined, where the glycidyl ether resided on either half of the molecule. Each half of the molecule contained a heteroatom that could be used either to attach the glycidyl moiety or as the nucleophile in the ring opening reaction, for the

same set of reagents, allowing each approach to be measured against the other. A range of glycidyl substrates were shown to be useful in this type of chemistry, and were synthesised as shown in Scheme 1.7.



Scheme 1.7. Synthesis of *O*-, *S*-, and *N*-glycidyl ethers

Inspection of the comparative results (Table 1.3) reveals that the use of piperazine-based amine to ring-open a heteroatom-linked glycidyl ether (method A) is the favoured method for the preparation of β -amino alcohols. This was explained by a proposal of the formation of a deactivated metal-glycidyl epoxide chelate species (Figure 1.1). The less deactivating the heteroatom X is, the more active the complex towards nucleophilic attack and *vice versa*. It therefore made sense to have the glycidyl ether riding on the softer Lewis basic heteroatom and to use the harder heteroatom as the nucleophile, than the other way around.

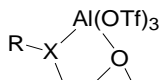
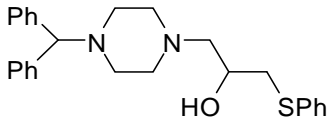
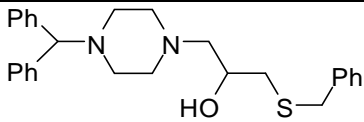
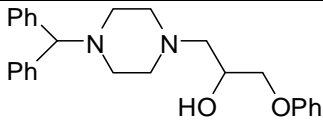
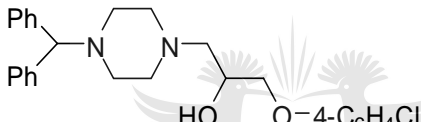
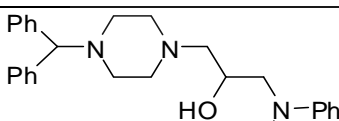


Figure 1.1. Proposed metal chelate structure of aluminium catalyst and heteroatom glycidyl ether

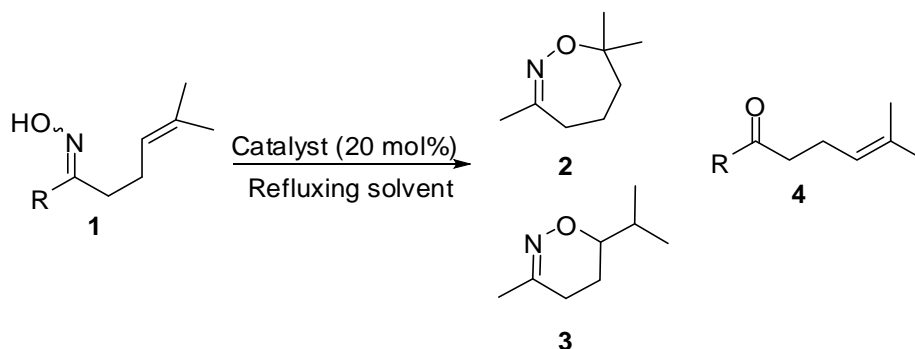
Table 1.3. Comparison of Methods A and B for obtaining β -amino alcohols

Entry	Product	Method	Yield (%)
1 ^a		A	82
2 ^a		B	48
3 ^a		A	86
4 ^a		B	30
5 ^b		A	73
6 ^b		B	0
7 ^b		A	85
8 ^b		B	0
9 ^b		A	78
10 ^b		B	33

^a10 mol % Al(OTf)₃ catalyst. ^b5 mol % Al(OTf)₃ catalyst.

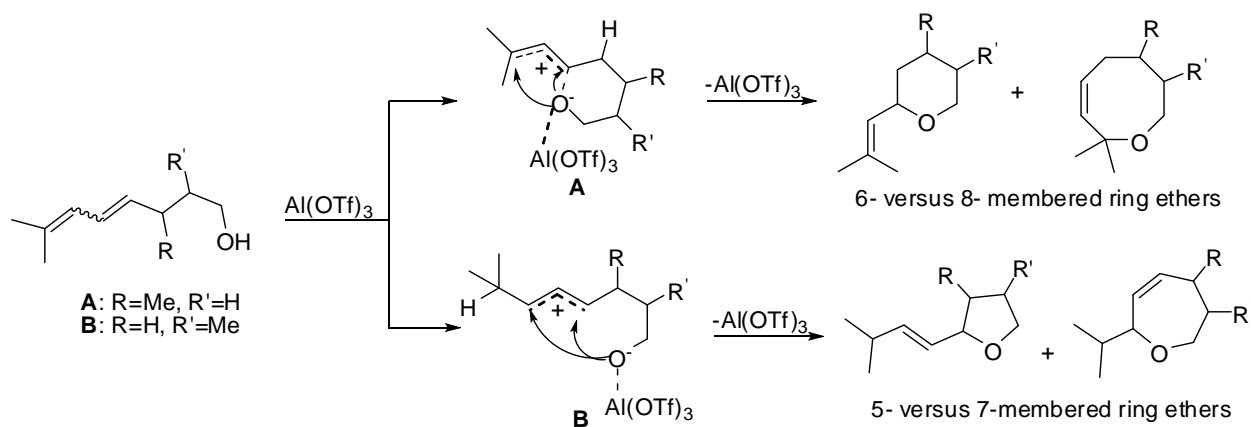
Aluminium triflate has also been reported to effect esterification reactions,³² acetal formation³³ as well as chemoselective thioacetalisation of carbonyl compounds.³⁴ Regioselective cycloisomerisation of non-activated unsaturated oximes catalysed by Al(OTf)₃ has also been reported (Scheme 1.8).³⁵ The reaction afforded 5-, 6-, 7-membered rings containing oxygen and nitrogen. A model reaction was used to compare aluminium triflate with Sn(OTf)₄, Fe(OTf)₃, Cu(OTf)₂ and TfOH, as well as to develop the method for the cycloisomerisation reaction. Aluminium triflate in nitromethane or dichloromethane proved to be the best conditions under

which to perform these reactions. Therefore, this catalyst was used with a variety of oximes to determine the scope of the reaction.



Scheme 1.8. Reaction of 7-methyl-1-phenyloct-6-en-3-one oxime (**1**) catalysed by aluminium triflate

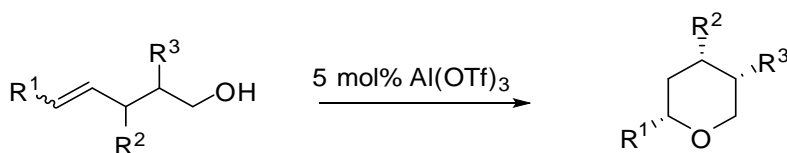
Aluminium triflate has also been shown to be an efficient catalyst for the cyclisation of non-activated unsaturated alcohols, leading quantitatively and regioselectively to the corresponding cyclic ethers (Scheme 1.9).³⁶ The mechanism explaining the regiochemical outcome of the reaction is explained by the scheme below.



Scheme 1.9. Mechanism for cyclisation of unsaturated alcohols

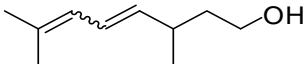
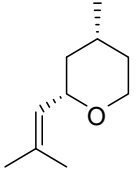
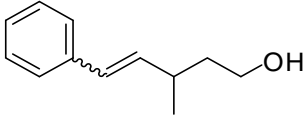
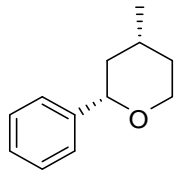
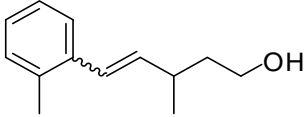
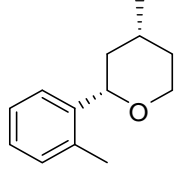
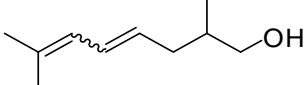
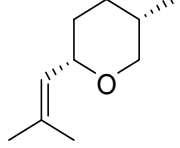
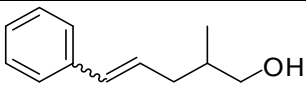
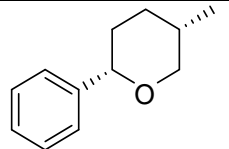
The mechanism of the reaction is explained by an initial coordination of Al^{3+} to the hydroxyl group of the alcohol leading to an increased acidity of the proton of the OH group, according to the results of theoretical calculations.³⁷ Proton addition to the diene unit may afford the formation of cationic allyl intermediates of type A and B (Scheme 1.9). Alkoxide addition can then either take place onto intermediate A to afford the formation of either 6- *versus* 8-membered ring ethers or into intermediate B leading to 5- *versus* 7-membered ring ethers. The cyclisation towards tetrahydrofuran and tetrahydropyran derivatives should be more favourable than seven or eight membered ring ethers. The experimental regioselectivity can be explained by the selective formation of a π -allyl carbocation intermediate A, which is more stable than B as a result of higher substitution and therefore additional stabilisation due to the presence of *gem*-dimethyl groups.

From a stereochemical point of view, the $\text{Al}(\text{OTf})_3$ -catalysed cycloisomerisation of differently 2- or 3-substituted alcohols formed the *cis* isomers of cyclic ethers as the main products (Scheme 1.10). For 3-methyl substituted alcohols, the cyclisation led to the thermodynamically more stable *cis*-1,3-diequatorial stereoisomer. Table 1.4 shows different unsaturated alcohols that were cycloisomerised with aluminium triflate.

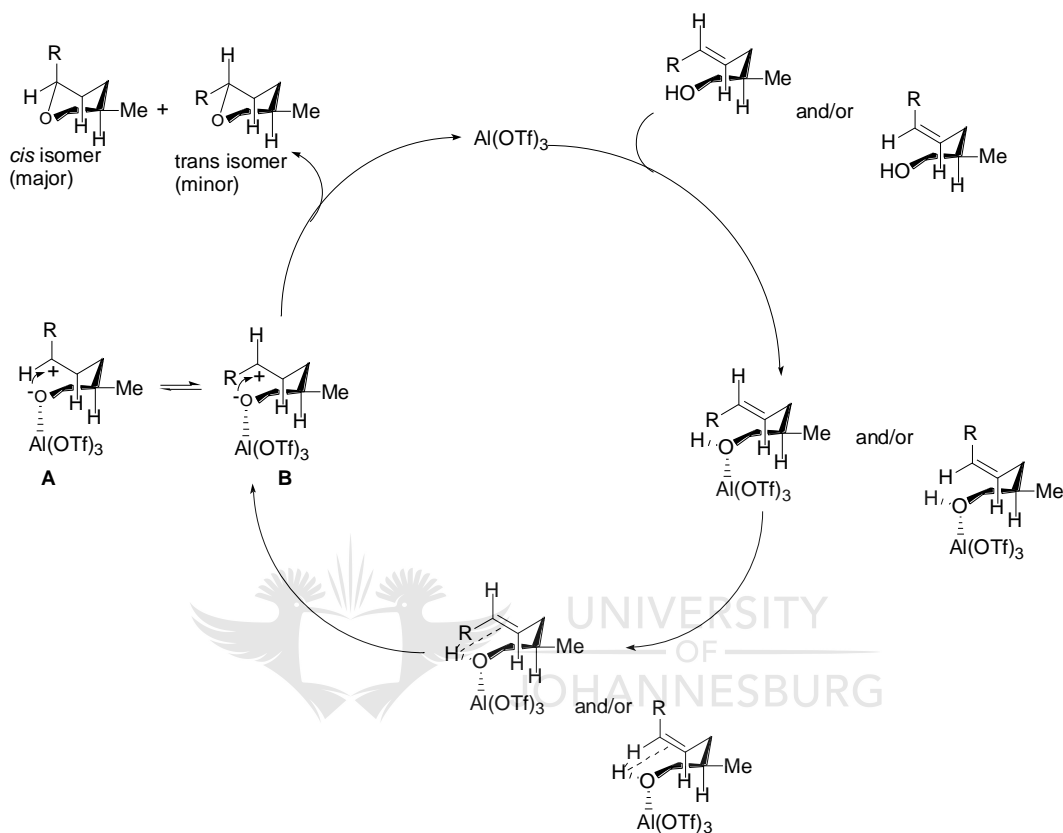


Scheme 1.10. Cycloisomerisation of alcohols

Table 1.4. Aluminium triflate catalysed cycloisomerisation of alcohols

Unsaturated alcohol (<i>Z/E</i>)	Conditions	Cyclic ethers	% isolated yield (<i>cis/trans</i>)
 (28:72)	CH ₂ Cl ₂ Reflux, 1 h		70 (82:18)
 (15:85)	ClCH ₂ CH ₂ Cl Reflux, 3 h		85 (90:10)
(0:100)			60 (95:5)
(28:72)			86 (90:10)
 (14:86)	ClCH ₂ CH ₂ Cl Reflux, 3 h		86 (92:8)
 (45:55)	CH ₂ Cl ₂ Reflux, 2 h		77 90:10
 (30:70)	ClCH ₂ CH ₂ Cl Reflux, 3 h		84 86:14

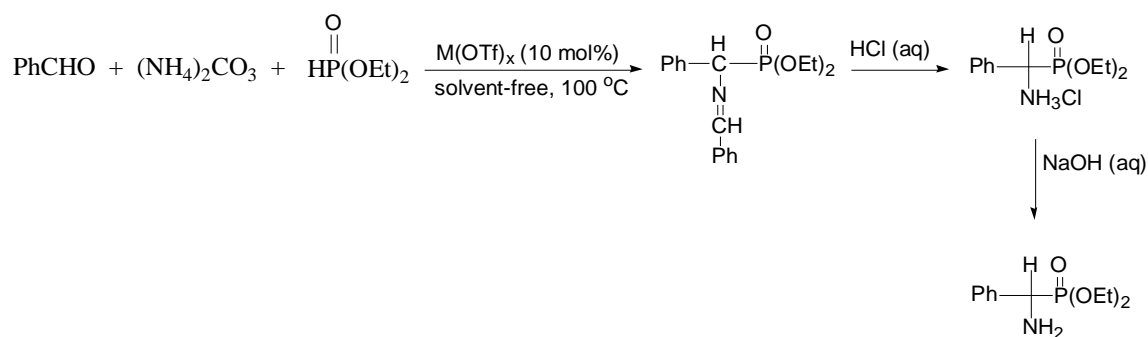
It was observed that alcohols bearing a phenyl group also favoured the *cis* product, which is also explained by the stabilisation of the benzylic-type cation intermediate formed in the presence of aluminium triflate. A general mechanism that would be applicable to a wide spectrum of unsaturated alcohols was then proposed (Scheme 1.11).



Scheme 1.11. General mechanism for cyclisation of unsaturated alcohols

Coordination of $\text{Al}(\text{OTf})_3$ to the hydroxyl group and the proton transfer to the double bond affords the formation of two carbocation-type intermediates **A** and **B** and in equilibrium as a result of the free rotation about the $\text{CH}_2\text{-CH}^+$ bond. In the more stable chair like conformation, carbocation **A** is less sterically hindered than **B** towards alkoxide addition. Simple calculations showed that carbocation **A** is slightly more stable than **B**, hence affording mainly the *cis* regioisomer.

Aluminium triflate has also been reported to catalyse the one-pot synthesis of primary diethyl 1-aminophosphonates under solvent-free conditions (Scheme 1.12, Table 1.5).³⁸ The feasibility of the reaction was examined by the reaction of benzaldehyde, ammonium carbonate and diethyl phosphate as a model in the presence of different metal triflates, including Al(OTf)₃.



Scheme 1.12. One-pot synthesis of diethyl 1-amino phenylmethylphosphonate

Table 1.5. Solvent-free, catalysed, one-pot synthesis of diethyl 1-aminophosphate

Entry	M(OTf) _x	Time (min)	Yield ^a (%)
1	Al(OTf) ₃	5	94
2	Ce(OTf) ₄	30	81
3	Cu(OTf) ₂	60	53
4	LiOTf	30	55
5	Mg(OTf) ₂	15	72

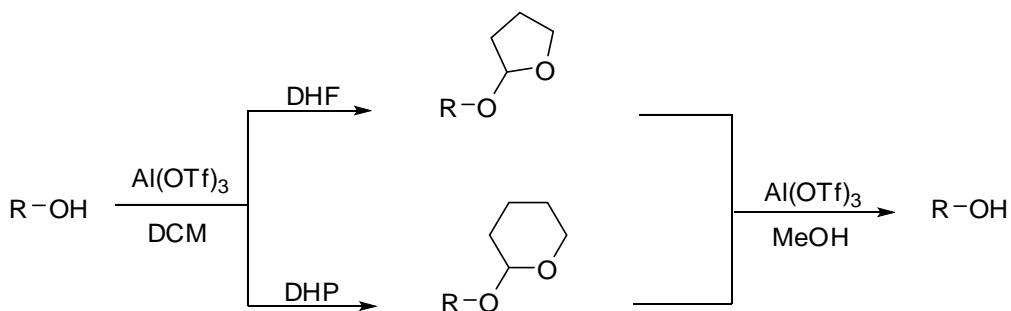
^aIsolated yield

Among the metal triflates tested Al(OTf)₃ turned out to be the most effective catalyst. Structurally diverse aldehydes and ketones were examined as substrates in this reaction in the presence of Al(OTf)₃. Differently substituted benzaldehydes were successfully converted to the

corresponding primary 1-aminophosphonates in high yields under solvent free conditions with ammonium carbonate and ammonium acetate.

Acetylations of alcohols, phenols and thiophenols could be carried out with a catalytic amount of $\text{Al}(\text{OTf})_3$.³⁹ A variety of primary, secondary, benzylic and cyclic alcohols were successfully acetylated using 0.1 mol % $\text{Al}(\text{OTf})_3$ with acetic anhydride under solvent-free conditions in excellent yields and short reaction times at room temperature. The reaction was further employed to successfully acetylate thiophenols. Aluminium triflate together with hexamethyldisilane converted α -hydroxyphosphonates, alcohols and phenols to their corresponding *O*-silylated products.⁴⁰

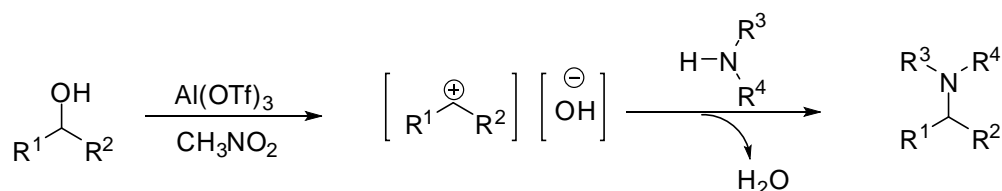
Ahmed Kamal *et al.* also reported the efficiency of $\text{Al}(\text{OTf})_3$ in tetrahydropyranylation of alcohols under solvent-free conditions as means of protecting hydroxyl groups.⁴¹ Another group further explored the catalyst in this reaction by protecting alcohols and phenols to their corresponding tetrahydropyranyl as well as tetrahydrofuranyl ethers.⁴² They also reported subsequent hydrolysis of the ethers back to alcohols using the same catalyst by changing the solvent system (Scheme 1.13.).



where R = aryl , alkyl

Scheme 1.13. Protection and deprotection of alcohols and phenols

This hard Lewis acid has also been reported to be a powerful catalyst in the direct amination of alcohols.⁴³ The reaction was proposed to proceed *via* a carbocation intermediate (Scheme 1.14). A number of allylic, benzylic, including benzhydrols were substituted using various nitrogen nucleophiles. They also showed that alcohols with electron donating (OMe and Me) substituents reacted faster than substituents bearing electron withdrawing groups (F, Br, I, NO₂ and CN).



Scheme 1.14. Direct amination of alcohols

Acid-sensitive functionalities such as *tert*-butyloxycarbonyl (BOC) and *tert*-butylsulfonyl (BUS) survived the reaction with 1 mol% Al(OTf)₃ further displaying the mildness of the otherwise hard Lewis acid.⁵ Figure 1.2 below show the different alcohol substrates that were used in the nucleophilic substitution reaction with various protected amines.

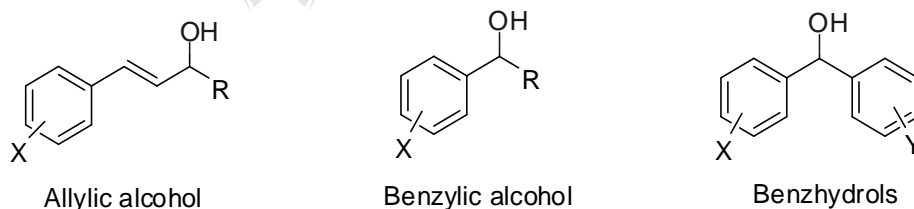
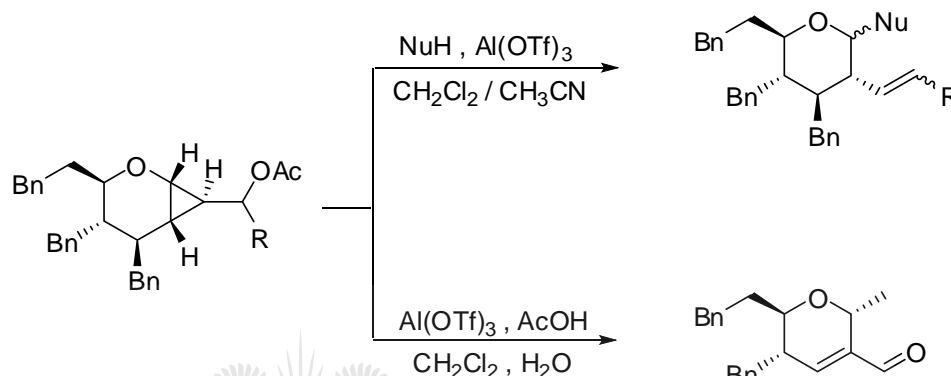


Figure 1.2. Substrates for Al(OTf)₃-catalysed direct nucleophilic substitution

In addition to the amination of alcohols which results into C-N bonds, Gohain *et al.*⁴⁴ expanded the nucleophilic substitution of the hydroxyl group with only propargylic alcohols using nucleophiles such as alcohols, aromatic compounds, amides, and thiols, leading to the construction of C-O, C-C, C-N and C-S bonds. The same group also reported propargylation of indoles using aluminium triflate.⁴⁵

Aluminium triflate has also recently been employed in synthesis and functionalisation of carbohydrate derivatives. It has been reported to catalyse a Ferrier-type rearrangement of 1,2-cyclopropanated glucose derivatives bearing an acetoxy group at the 1'-position (Scheme 1.15).⁴⁶ The cyclopropanated sugar was treated with various nucleophiles (alcohols, thiols, azide) and $\text{Al}(\text{OTf})_3$ to give *C*-vinyl glucosides in good yield and α -selectivity. On another reaction, they treated the cyclopropanated sugar with $\text{Al}(\text{OTf})_3$ and acetic acid which led to a novel fragmentation re-arrangement to form 2-3-dehydro-2-formyl-*C*-glycoside.



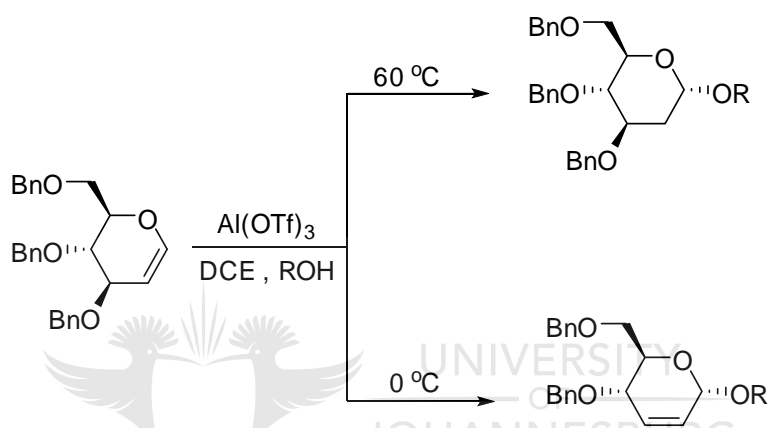
Scheme 1.15. Ferrier-type allylic rearrangement of cyclopropylcarbinyl acetate

Table 1.6. Treatment of cyclopropylcarbinyl acetate with nucleophiles in the presence of a Lewis acid and solvent at 40 °C.

Entry	Nucleophile	Catalyst	Solvent	Yield (%)	α : β
1	BnOH	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	CH_2Cl_2	41	1:0
2	BnOH	$\text{Al}(\text{OTf})_3$	CH_3CN	54	1:1
3	PhSH	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	CH_2Cl_2	72	1:1
4	PhSH	$\text{Al}(\text{OTf})_3$	CH_3CN	80	1.2:1
5	AlOH	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	CH_2Cl_2	30	1:0
6	AlOH	$\text{Al}(\text{OTf})_3$	CH_3CN	74	1:0
7	TMSN_3	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	CH_2Cl_2	80	2:1
8	TMSN_3	$\text{Al}(\text{OTf})_3$	CH_3CN	78	2.2:1

In this Ferrier type like rearrangement reaction Munyololo *et al.* compared $\text{Al}(\text{OTf})_3$ with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in different solvents (CH_2Cl_2 and CH_3CN).⁴⁶ Although comparable, aluminium triflate clearly outperforms the traditional Lewis acid (see Table 1.6).

Meanwhile Williams *et al.* reported the synthesis of *O*-glycosides from glycals.⁴⁷ They detailed a temperature-dependent mechanism towards either 2-deoxy glycosides *via* direct addition to the glycal substrate or 2,3-unsaturated pseudoglycals *via* Ferrier rearrangement. They did this by reacting 3,4,6-*tri-O*-benzyl-D-glucal with a range of alkyl alcohols catalysed by aluminium triflate in 1,2-dichloroethane (Scheme 1.16).



Scheme 1.16. Temperature controlled *O*-glycosidation

The reaction proceeded smoothly to give the temperature controlled products in moderate to high yields with high stereoselectivity for the α -*O*-glycoside. They extended their search on the abilities of the Lewis acid in glycosidation reactions by using 3,4,6-*tri-O*-acetyl-D-glucal and 3,4,6-*tri-O*-acetyl-D-galactal for the synthesis of *O*-aryl glycosides. Aromatic glycosides are of interest in this review and for aspects of the work covered in this thesis, and are briefly discussed in the next section.

1.2 Aromatic glycosides

Carbohydrates are the most abundant biomolecules on earth and they constitute an important class of natural products. Carbohydrates play important roles in many biological processes including cell recognition, cell migration, inflammation, bacterial and viral infections⁴⁸ and this has made them attractive synthetic targets. In particular, carbohydrates bearing aromatic

aglycons have been observed in complex naturally occurring drugs, such as vancomycin⁴⁹ and kendomycin.⁵⁰ Though the first reported glycosidic linkage in 1879 by Michael⁵¹ was the synthesis of an aryl glycoside from glucosyl chloride and potassium phenolate, their synthesis has been lagging behind compared to the attention given to their alkyl counterparts. Aryl *N*- and *S*-glycosides are known,⁵² but this review will concentrate mainly on the *O*- and *C*-aryl glycoside derivatives.

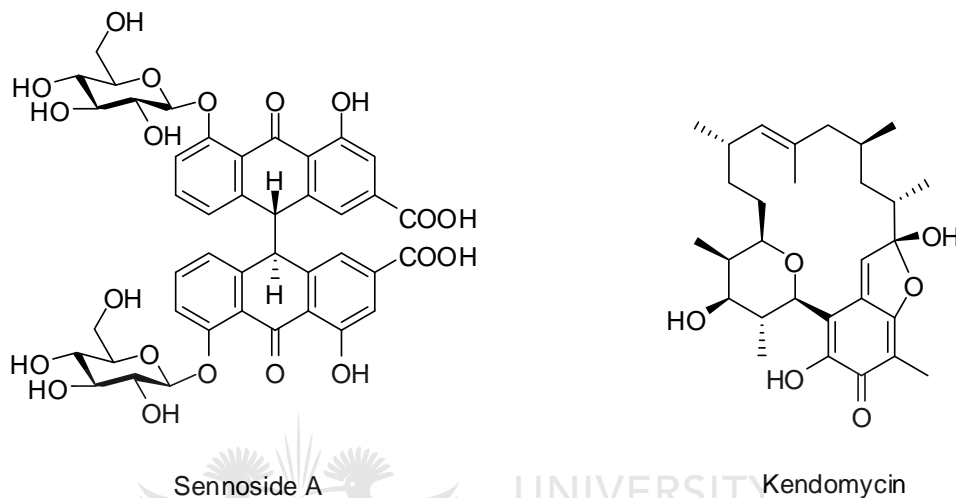


Figure 1.3. Biologically active glycosylated aromatic compounds

O- and *C*-glycosides may look structurally similar but they exhibit different biological and pharmacological potencies. This explains their equal importance in the field of carbohydrate chemistry, which arises solely from their differing glycosidic linkages. In the following discussion of this review the similarities and differences in physical properties of the *O*- and *C*-glycosides are summarised.

1.2.1 *O*-Glycosides vs *C*-glycosides: comparison of physical properties, anomeric effects, H-bonding abilities, stabilities and conformations

O- and *C*-glycosides have prevalent structural and chemical properties relating to bond lengths, van der Waals radii, electronegativities and bond rotational barriers being similar in both *O* and *C*-glycosides.⁵³ The largest difference between the physical constants of these two forms of glycosides is found in their dipole moments, where *O*-glycosides appear to be more polar than

their *C*-glycoside analogues. However, as minor differences do exist, the conformations of both *O*- and *C*-glycosides are represented by similar anti-periplanar rearrangements. Table 1.7 below lists some of the physical properties of the *O*- and *C*-glycosides.

Table 1.7. Physical properties of *O* and *C*-glycosides

Parameter	<i>O</i> -Glycoside	<i>C</i> -Glycoside
Bond length	O-C = 1.43 Å	O-C = 1.54 Å
Van der Waals radius	O = 1.52 Å	O = 2.0 Å
Electronegativity	O = 3.51	C = 2.35
Dipole moment	C-O = 0.74 D	C-C = 0.3 D
Bond rotational barrier	CH ₃ -O-CH ₃ = 2.7 kCal/mol	CH ₃ -O-CH ₃ = 2.88 kCal/mol
H-Bonding	Two	None
Anomeric effect	Yes	No
Exoanomeric effect	Yes	No
Stability	Cleaved by acids and enzymes	Stable to acids and enzymes
Conformation	C _{1'} -C _{2'} , antiperiplanar to O ₁ -C ₁	C _{1'} -C _{2'} , antiperiplanar to C ₁ -C ₂

Perhaps the major difference between *C* and *O*-glycosides is found within their chemical activities. *C*-glycosides are stable to acid hydrolysis and within the realm of physical properties, the anomeric protons of the *O* and *C*-glycosides exhibit similar coupling constants in their respective ¹H NMR spectra. A summary of the respective average coupling constants is presented and explained by Wang *et al.*⁵⁴ who discussed the preferred conformations of *C*-glycosides. It is perhaps due to these differences that the synthesis of *O* and *C*-aryl glycosides differs, especially with the glycosyl acceptor.

1.2.2 Synthesis of aryl *O*-glycosides

Aromatic *O*-glycosides are formed when a carbohydrate derivative reacts with a phenol derivative through the phenol oxygen atom. The glycosides are divided into two major sub-groups depending on the orientation of the aglycon into α - and β -glycosides.⁵⁵ The stereochemical outcome is influenced by several factors, but mainly the anomeric effect and

neighbouring group participation. The glycosidation reaction can proceed *via* an S_N1 (in acidic conditions) or S_N2 (in basic conditions) mechanism. Since Michael's first glycosidation reaction, a range of glycosyl donors have been developed for the synthesis of aryl *O*-glycosides (Fig. 1.4).

Researchers have found it difficult to synthesise aryl *O*-glycosides in high yield for a number of reasons. 1. The electron withdrawing nature of the aromatic ring makes the hydroxyl group of the phenol a relatively weak nucleophile under acidic conditions.⁴⁷ 2. Aromatic rings bearing electron donating groups tend to be ambident nucleophiles and give *C*-glycoside by-products at elevated temperatures.⁵⁶ 3. Steric hindrance from substituents of the aromatic ring, especially *ortho*-substituted phenols, can lead to slow reactions and the formation of by-products.⁵⁷ As a consequence, there is to date a need to develop high yielding chemistry with a wide scope of relevance for the synthesis of aryl *O*-glycosides.

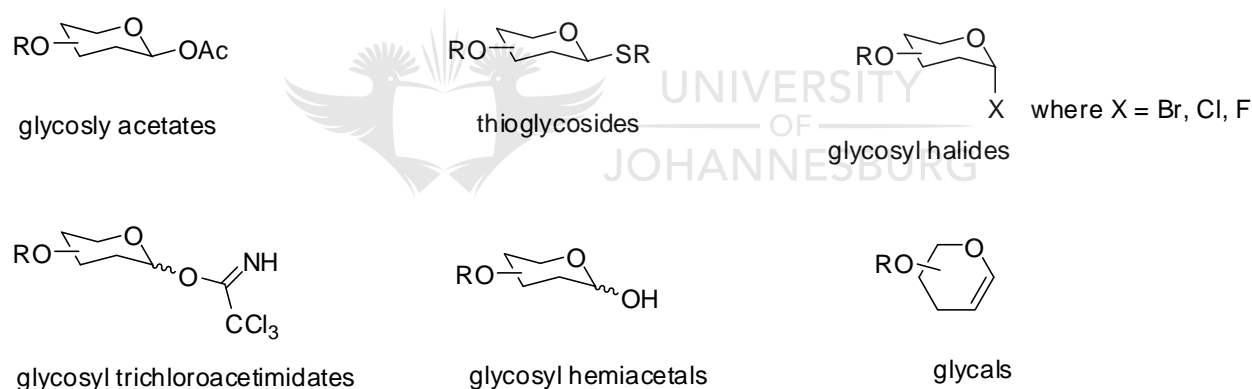
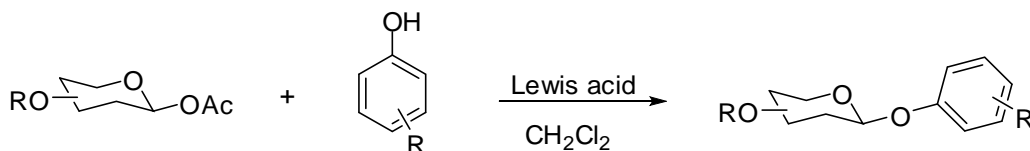


Figure 1.4. Glycosyl donors in synthesis of aryl *O*-glycosides

1.2.2.1 Glycosyl acetates

Glycosyl acetates can be activated with Lewis acids as well as Brønsted acids. The popularity of these anomeric acetates is due to the fact that they are easily accessible, being available in only one reaction step from the corresponding free sugar. The reactions are normally performed in dichloromethane, and generally phenols bearing an electron donating group (EDG) tend to give higher yields compared to ones with electron withdrawing groups (EWG). When present, a

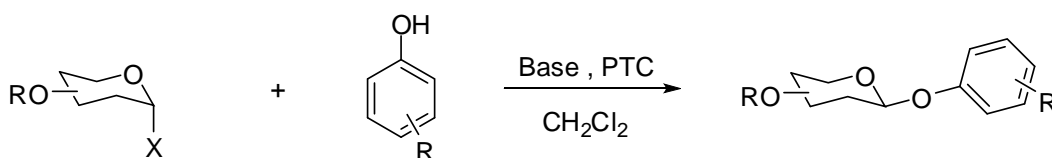
participating ester in the C-2 position leads glycosyl acetates to give β -glycosides. However, α -glycoside by-products can be formed due to anomerisation. This can be prevented by adding sub-equimolar amounts of a base.⁵⁸ Anomeric trifluoroacetates⁵⁹ and benzoates⁶⁰ have also been used as alternatives to glycosyl acetates for the synthesis aromatic *O*-glycosides.



Scheme 1.17. Glycosyl acetates as glycosyl donors

1.2.2.2 Glycosyl halides

Glycosyl halides are by far the most widely used glycosyl donors in the synthesis of *O*-aryl glycosides. Of these, glycosyl bromides are the most widely used halides because of their high reactivity, though unstable compared to glycosyl chlorides and iodides.⁶¹ Generally, glycosyl halides give moderate yields, but their advantage lies in the well documented reactions and their use under basic conditions. The glycosyl halides are normally isolated as the thermodynamically stable α -halide, but, since glycosidation proceeds *via* S_N2 mechanism under basic conditions, the β -glycoside product is normally obtained.



where X = Br, Cl, F

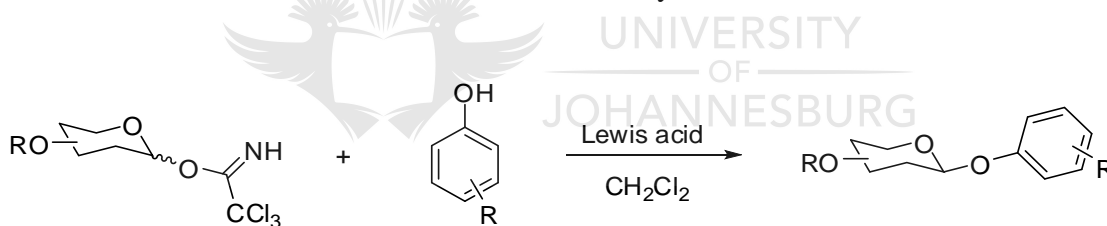
Scheme 1.18. Glycosyl halides as glycosyl donors

The original Michael⁵¹ and Koenings-Knorr⁶² methods for aryl *O*-glycosidation with glycosyl halides have been improved in the intervening years. The most striking and widely used approach being the use of *tetra*-butyl ammonium (TBA) salts as phase transfer catalysts (PTC). Also worth mentioning is that aromatic residues with electron-withdrawing groups (EWG) tend

to give better yields, possibly due to easier deprotonation of their acidic OH groups, and subsequent phase transfer of the phenolates.⁶³ Mukaiyama also showed that reaction of glycosyl halides can proceed under acidic conditions where reaction of the stable glycosyl fluorides was promoted by $\text{BF}_3 \cdot \text{OEt}_2$. Though unsatisfactory stereoselectivity was obtained, it could be controlled or improved upon by the use of a hindered nucleophile.⁶⁴

1.2.2.3 Glycosyl trichloroacetimidates

Trichloroacetimidates can be activated at low temperatures by a catalytic amount of Lewis acid, and it is thus a method of choice when working with sensitive or complex compounds. They normally give β -glycosides in high yields.⁶⁵ Trichloroacetimidates can be synthesised in anomerically pure forms by suitable treatment of the hemiacetal with trichloroacetonitrile in dichloromethane with an appropriate base⁵⁵ (K_2CO_3 for β -imidate, NaH for α -imidate). The major difference between trichloroacetimidates and glycosyl acetates is the rate of the reaction, where the imidates react faster than the acetates in catalytic amounts of Lewis acids.



Scheme 1.19. Glycosyl trichloroacetimidates as glycosyl donors

Recently Chang *et al.*⁶⁶ reported an α -selective synthesis of aromatic *O*-glycosides using different per-*O*-acetyl glycopyranosyl trichloroacetimidates. The method works well with phenols bearing electron withdrawing groups, and the methodology was demonstrated in the stereoselective synthesis of 4-methylumbelliferyl α -T-antigen (Figure 1.5).

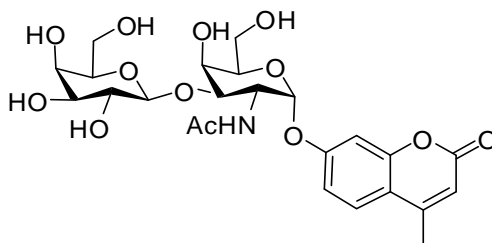


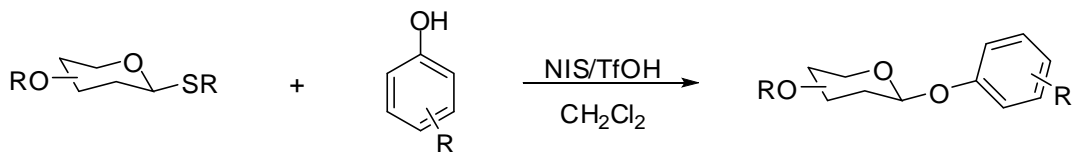
Figure 1.5. 4-Methylumbelliferyl α -T-antigen

Table 1.8. Selective synthesis of α -glycosides with glycosyl trichloroacetimidates

Glycosyl donor	Glycosyl acceptor	Product	Yield (%)
			60
			45
			55

1.2.2.4 Thioglycosides

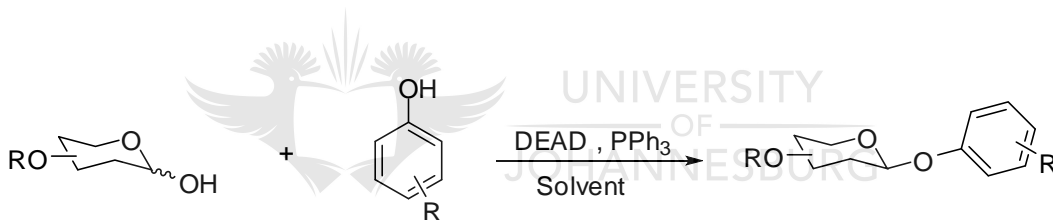
Thioglycosides are relatively stable carbohydrate derivatives, but they can be activated by thiophilic reagents such as iodonium species generated *in situ*. The combination of *N*-iodosuccinimide and triflic acid is a typical example of promoters of *O*-glycosidation using thioglycosides as glycosyl donors (Scheme 1.20). Generally, thioglycosides do not give appreciable yields compared to other donors, hence they are not frequently used for the synthesis of *O*-aryl glycosides. A reason for this might be due to the incompatibility of the promoters and the aromatic residues, which results in the formation of a host of by-products.⁶⁷ This resulted in the introduction of glycosyl sulfoxides,⁶⁸ which can be easily activated with triflic anhydride (Tf₂O), as glycosyl donors. Albeit circuitous, thioglycosides can be hydrolysed into their corresponding glycosyl hemiacetals which can be used for glycosidation using the Mitsunobu reaction.



Scheme 1.20. Thioglycosides as glycosyl donors

1.2.2.5 Glycosyl hemiacetals

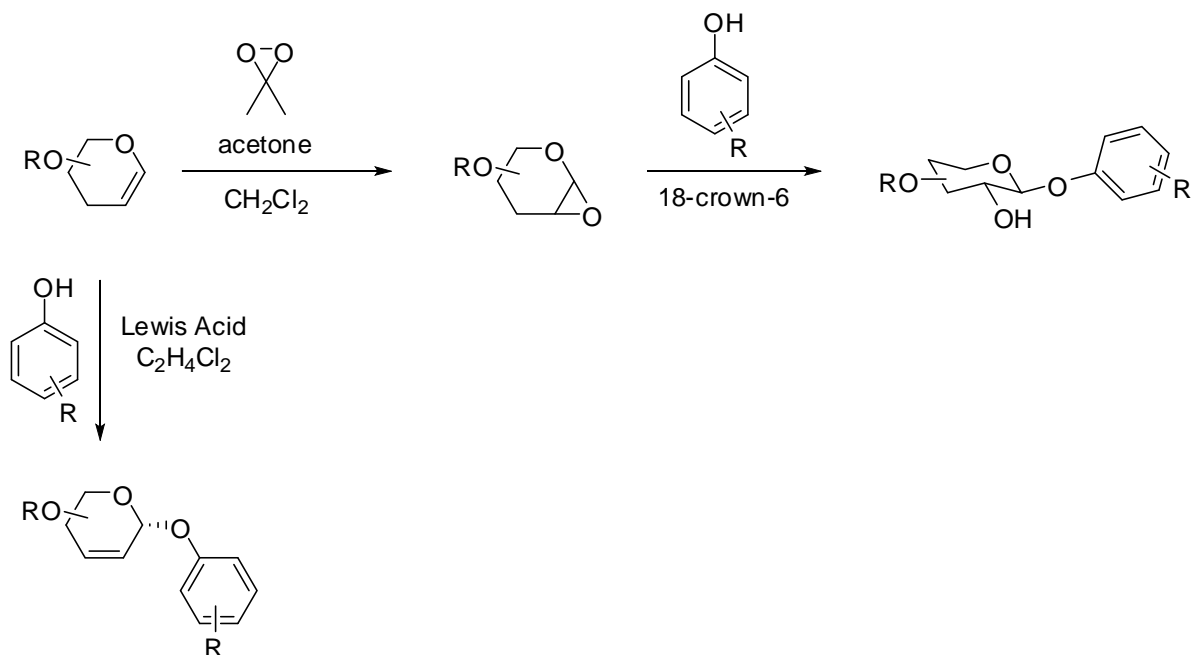
Carbohydrate derivatives unsubstituted at the anomeric position can be used directly as glycosyl donors by either *in situ* activation of the hydroxyl group or using the carbohydrates as a nucleophile.⁴⁹ The carbohydrate hemiacetals can be activated *in situ* by using Mitsunobu conditions, where the sugar hemiacetal and a suitable phenol are stirred with triphenylphosphine (PPh₃) and diethyl azodicarboxylate (DEAD) to give aromatic *O*-glycosides.⁶⁹ Alternatively, the hemiacetal carbohydrate can be used as a nucleophile to react with aromatic halides under basic conditions to provide aromatic *O*-glycosides.⁷⁰



Scheme 1.21. Mitsunobu reaction in aromatic *O*-glycosidation

1.2.2.6 Glycols as donors

Glycols are not very popular as glycosyl donors because they cannot be readily stereocontrolled, given the absence of a neighbouring group at C-2 of the saccharide. However, aromatic *O*-glycosidation recently has been reported with *tri-O*-acetylated glycols to give either 2,3-unsaturated pseudoglycosides or 2-deoxyglycosides in high stereoselectivity.⁴⁷ Glycols also can be oxidised to the corresponding α -1,2-anhydroglycoside by treatment with 3,3-dimethyldioxirane. The anhydrosugar can then react with nucleophiles such as phenols.⁷¹ In this way, the glycol is used as a source of the reactive glycosyl donor.



Scheme 1.22. Glycals as glycosyl donors

1.2.3 Synthesis of aryl C-glycosides

Aryl *C*-glycosides are formed when a carbon atom replaces the glycosidic oxygen atom in an aryl *O*-glycoside. Generally *C*-glycosides are hydrolytically stable compared to *O*-glycosides and are therefore referred to as stable analogues of *O*-glycosides.⁵³ Because of this stability aryl *C*-glycosides have improved pharmacological profiles and have thus gained increasing popularity as drug candidates. This has led to a great deal of work done towards assembling aryl *C*-glycosides. There have been a number of methods developed and/or employed for the synthesis of *C*-glycosides, ranging from those similar to *O*-glycosidation electrophilic reactions to the serendipitously discovered intramolecular *O*-*C* migrations.⁷² This part of the review will discuss only those electrophilic reactions where the electrophilic species are derived from the sugar component. Common glycosyl donors in the formation of aryl *C*-glycosides are shown in Figure 1.6.

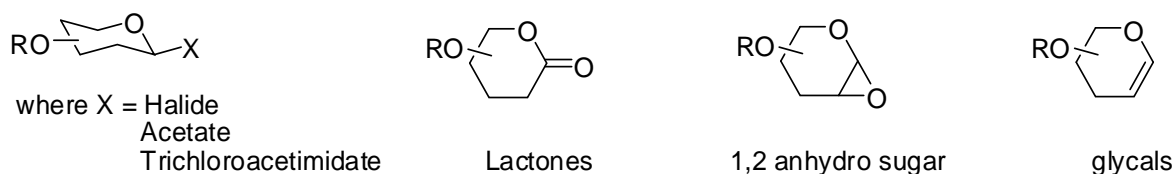


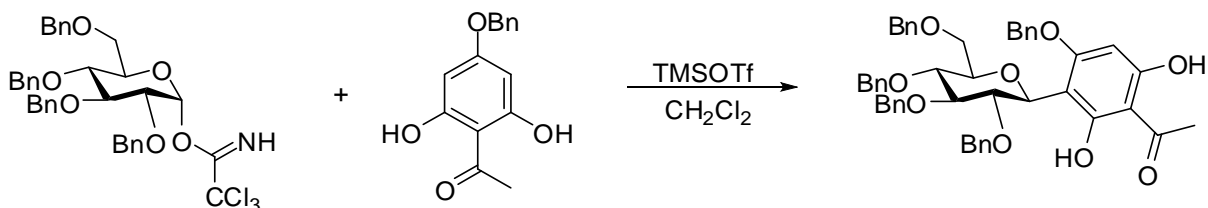
Figure 1.6. Glycosyl donors in electrophilic synthesis of aryl *C*-glycosides

The synthesis of aryl *C*-glycosides using electrophilic substitution has several similarities to the synthesis of the corresponding aryl *O*-glycosides. This is mainly due to the fact that the glycosidation proceeds *via* the same mechanism (S_N1). Though carbon is less nucleophilic compared to oxygen, it is believed that most activators of the aromatic *O*-glycosidation can catalyse the *C*-glycosidation reaction.⁵³

1.2.3.1 Glycosyl halides, acetates and trichloroacetimidates

Hurd and Bonner⁷³ reported the first synthesis of aryl *C*-glycosides in 1945, 66 years after the first report for the synthesis of aryl *O*-glycosides. They reacted a glycosyl chloride with benzene catalysed by aluminium chloride to give the corresponding aryl *C*-glycoside. Since then the halides (Cl, Br, I, F) have been shown to be good leaving groups in *C*-glycoside synthesis in the presence of Lewis acids.⁵³ Metal catalysed aryl *C*-glycosidation has also been reported using nickel and most recently cobalt.⁷⁴

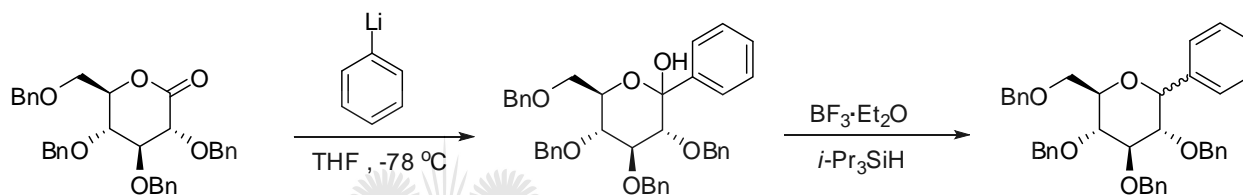
Hurd and Bonner⁷⁵ in the same year (1945) also reported the use of glycosyl acetates as glycosyl donors in aryl *C*-glycosidation. However, glycosyl acetates are infamous for their unsatisfactory stereoselectivity in aryl *C*-glycosidation, and they therefore have not been employed much as glycosyl donors for this reaction.⁷⁶ Instead, glycosyl trichloroacetimidates have been employed as glycosyl donors, an example being in the *C*-glycosidation step in the synthesis of an anti-inflammatory flavone by Tinaka *et al.* (Scheme 1.23).⁷⁷ Schmidt⁷⁸ *et al.* also demonstrated that glycosyl trichloroacetimidates were useful for the synthesis of aryl β -*C*-glycosides, especially with electron rich aromatic compounds.



Scheme 1.23. Glycosyl trichloroacetimidate in aryl *C*-glycosidation

1.2.3.2 Lactones as glycosyl donors

Glyconic lactones serve as alternatives to the direct methods for the synthesis of aryl *C*-glycosides. The use of glyconic acid lactones as electrophiles is a two-step process which proceeds by nucleophilic attack on the lactone by an organometallic reagent followed by reduction of the resulting lactol. Though Grignard reagents have been reported for the synthesis of alkyl *C*-glycosides,⁷⁹ organolithium reagents are normally employed in the synthesis of aryl *C*-glycosides.⁸⁰ Though not often used, this 2-step glycosidation is amongst the key steps in the synthesis of galtamycinone. A representative example of the use of glyconic lactones as glycosyl donors in the synthesis of aryl *C*-glycosides is shown in Scheme 1.24. This approach is non-stereoselective and is thus somewhat restricted where high enantiomeric excess is desirable.



Scheme 1.24. Lactones in aryl *C*-glycosidation

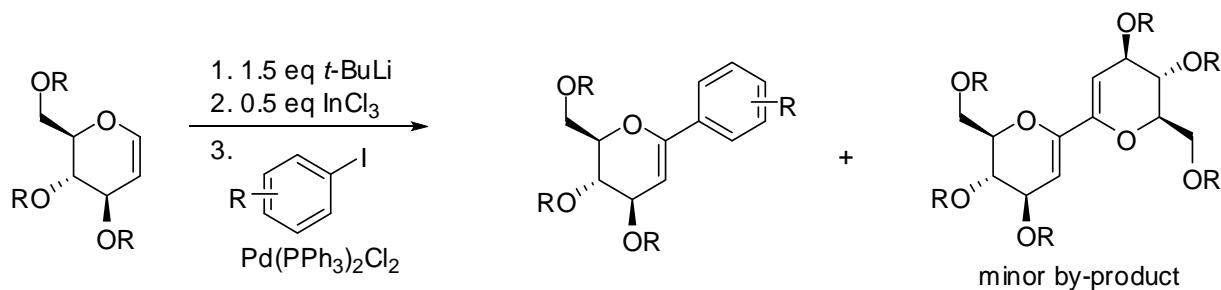
1.2.3.3 1,2-Anhydro sugars as donors

When using 1,2-anhydro sugars as glycosyl donors the *C*-glycosylation is achieved through a carbon nucleophilic attack on a cyclic species to give *C*-glycosides with defined stereochemistry. Improved stereoselectivities were obtained using epoxides or other three-membered cyclic intermediates as glycosyl donors.⁸¹ Though the yields are generally lower than their alkyl counterparts, aryl organocuprates react with glycal epoxides to give aryl *C*-glycosides.⁸²

1.2.3.4 Glycals as donors

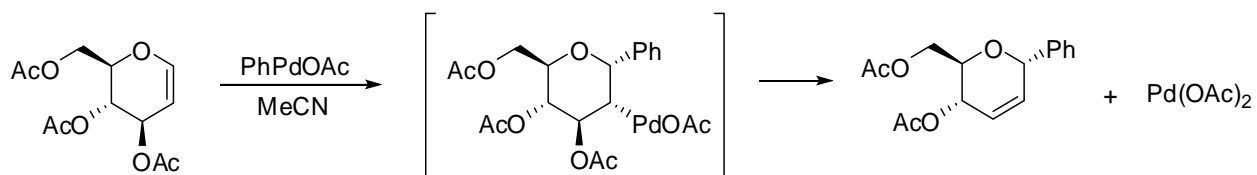
Since their first synthesis by Fischer⁸³ and Zach in 1913, glycals have been versatile intermediates in the synthesis of *O*- and *C*-glycosides. Organozinc reagents have been employed in the synthesis of alkyl and aryl *C*-glycosides from glycals in the presence of an acid.⁸⁴ The

reaction was reported to proceed with high stereoselectivity favouring the α -C-glycosides. Organoindium reagents have also been employed in the synthesis of C-aryl glycosides *via* palladium(0) catalysed cross-coupling reactions.⁸⁵ Electron-deficient aryl iodides coupled efficiently with the *in situ* generated indium reagents in the presence of $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ to produce aryl C-glycosides with minimal dimer formation (Scheme 1.25).



Scheme 1.25. Cross coupling reactions with glycals

Aryl boronic acids are also reported to add to per-acetylated glycals in the presence of a catalytic amount of $\text{Pd}(\text{OAc})_2$ (Scheme 1.26). Maddaford *et al.*⁸⁶ reported that the reaction proceeds *via* the *syn* addition of a σ -aryl-palladium complex to the glycal double bond followed by *anti*-elimination of palladium acetate to provide a pseudoglycal product. This may possibly be the case when the authors used stoichiometric amounts of palladium acetate. However, when using catalytic amounts of $\text{Pd}(\text{OAc})_2$, it is more likely that the reaction proceeds via a π -allyl Pd species generated from the allylic acetate in reaction with Pd(0). The authors do not mention this possibility. It is very unlikely that the Pd remains in the (II) oxidation state for the duration of the reaction, and turnover of the catalyst would therefore require a mechanism that relies upon Pd(0) species. Since the first step in the formation of the π -allyl Pd species gives an inversion of stereochemistry,⁸⁷ the Pd would be found on the lower (α) face of the ring. The η^3 π -allyl Pd species is in equilibrium with its η^1 σ -alkyl palladium counterpart,⁸⁸ which is the form usually implicated in transmetallation reactions. This interconversion is configurationally stable in ring systems, and the incoming aryl group would thus be transferred to the Pd, and through the Pd to the α face of the carbohydrate ring, accounting for the observed stereochemistry. This mechanism would consistently account for all products noted in the manuscript in question.



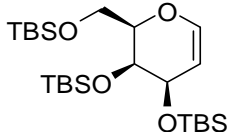
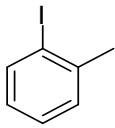
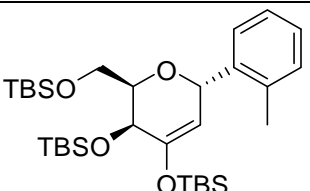
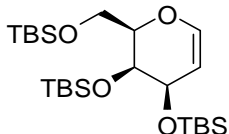
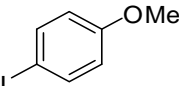
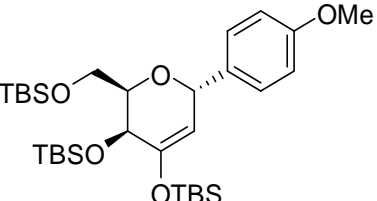
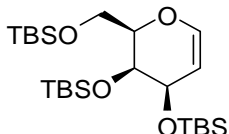
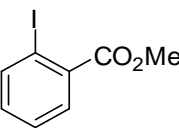
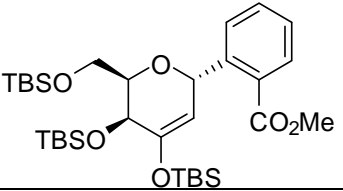
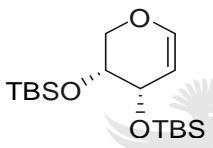
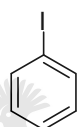
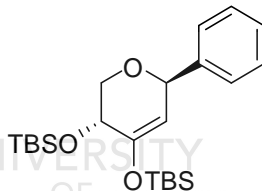
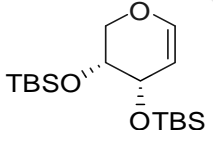
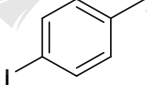
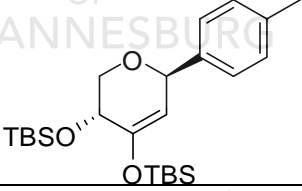
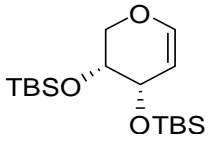
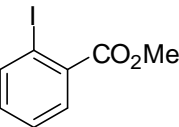
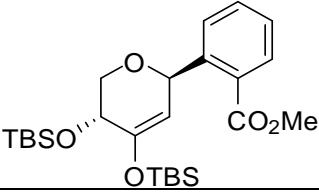
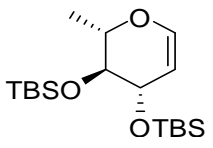
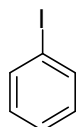
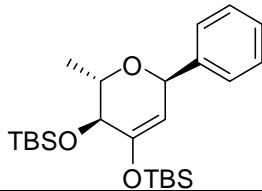
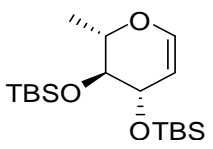
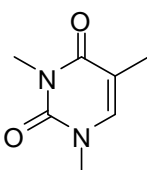
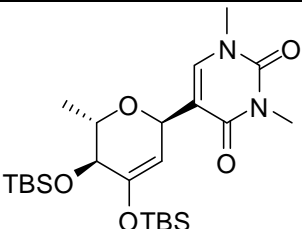
Scheme 1.26. Pd(OAc)₂ mediated C-glycosidation of 3,4,6-*tri-O*-acetyl-D-glucal

Such 2,3-unsaturated aryl C-glycosides have also been reported to be available via Lewis acid mediated carbon Ferrier re-arrangement.⁸⁹ This re-arrangement, when carried out with 5-membered aromatic ring nucleophiles such as thiophene, furan and pyrrole rings, was found to proceed smoothly with high stereoselectivity.

The Heck reaction has been used mostly for the synthesis of C-nucleosides where different furanoid glycols were coupled with a range of heterocyclic aromatic rings.⁹⁰ However, Lee and Ye⁹¹ recently reported an efficient and highly stereoselective Heck coupling reaction of different TBS-protected paranoid glycols with a range of aryl iodides (Table 1.9). The determining factor for the stereochemical outcome seems to be the stereochemistry of the OTBS group at C-3. In all cases, the incoming aryl group is delivered *trans* with respect to this group, regardless of the stereochemistry at C-4 or C-5.

Yadav⁹³ *et al.* reported aryl C-glycosidation of different glycols with aryl amines promoted by indium halides (InBr₃ and InCl₃). Indium halides have advantages over the traditional Lewis acids, such as low catalyst loading, moisture stability and recyclability.⁹³ In their glycosidation they observed an unusual formation of benzo-fused heterobicycles in the aminoglycosidation. A similar benzo-fused structure was also observed by Balasubramanian⁹⁴ *et al.* when they attempted to synthesise aryl C-glycosides from O-glycosides via O-C migration with boron trifluoride etherate. They called these benzo-fused structures bridged chiral benzopyrans. Benzopyrans and aryl O- and C-glycosides are core structures for a range of natural products, an example being Isoorientin-7-O-rutinoside (Figure 1.7) which is a flavonoid extracted from *Dianthus versicolor*, a plant used in traditional Mongolian medicine against liver diseases.⁹⁵

Table 1.9. Pd-catalysed Heck reactions of aryl iodides with different pyranoid glycols

Entry	Substrate	Aryl iodide	Product	Yield (%)
1				94
2				78
3				81
4				95
5				98
6				71
7				88
8				84

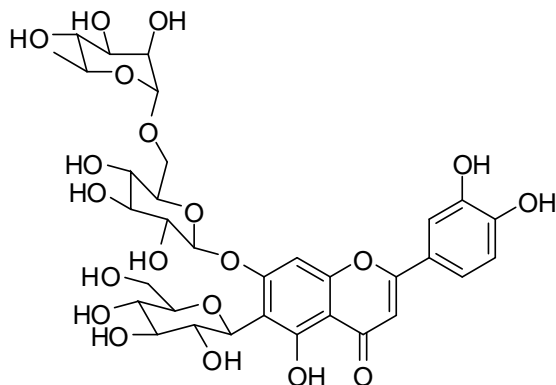


Figure 1.7. Isoorientin-7-*O*-rutinoside

1.3 Benzopyrans

Polycyclic molecules in which a benzene ring and a pyran ring are fused together with various levels of saturation are called benzopyrans.⁹⁶ The name benzopyran is widely used to refer to polycycles fused with a pyran ring (chromenes), but applies also to heterocycles bearing a dihydropyran ring (chromans) and some of the scaffolds are shown in Figure 1.8.

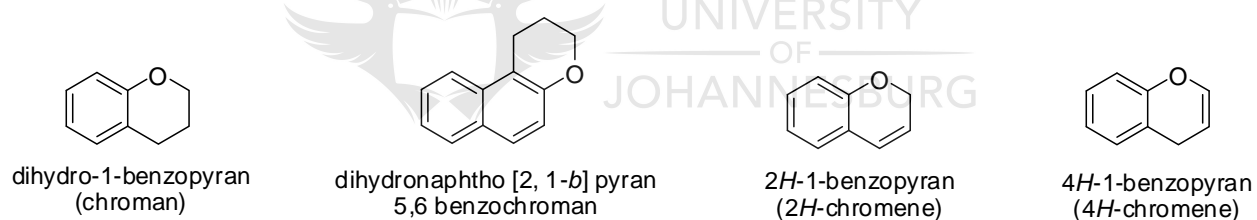


Figure 1.8. Structural skeletons of 1-benzopyrans

The benzopyran structure frequently appears in many natural products and artificial bioactive molecules which exhibit a wide range of biological activities.⁹⁷ It has thus been labeled as a *privileged structure* by Nicolaou⁹⁸ and others, though the term was initially used by Evans *et al.*⁹⁹ referring to benzodiazepines and benzazepines as structural motifs that bind as high affinity ligands to a wide range of protein receptors.

The occurrence of benzopyran derivatives in many natural products has been partly attributed to numerous prenylation and cyclisation reactions in many polyketide biosynthesis pathways.⁹⁸

There has been a great deal of work done around the synthesis of these privileged benzopyran structures with some groups making libraries with thousands of compounds containing the benzopyran scaffold. However, besides the recently reported synthesis of chromans and isochromans *via* the Pd-catalysed domino reaction,¹⁰⁰ researchers have not been using the ubiquitous carbohydrates as starting materials for the synthesis of benzopyran derivatives. This review will discuss general methods for the synthesis of 4*H*-chromenes and chromans.

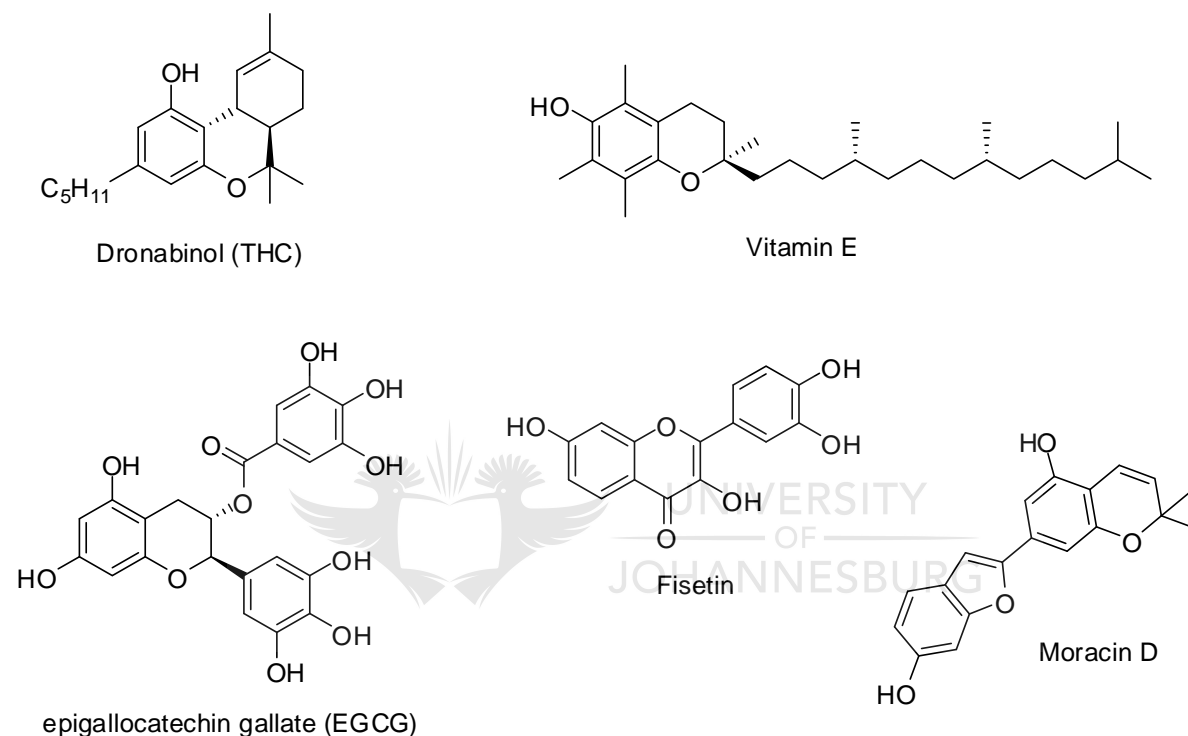
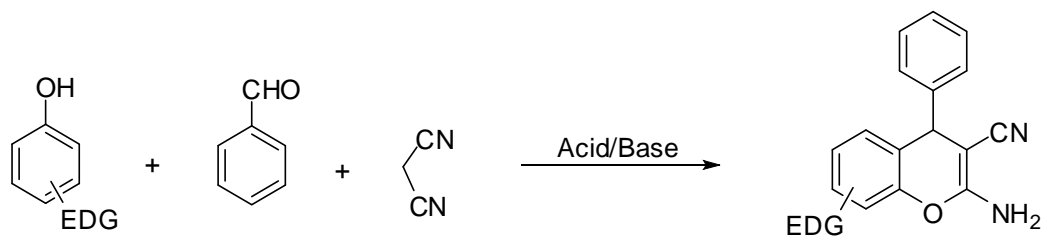


Figure 1.9. Benzopyran-containing bioactive molecules

1.3.1 Synthesis of 4*H*-chromenes

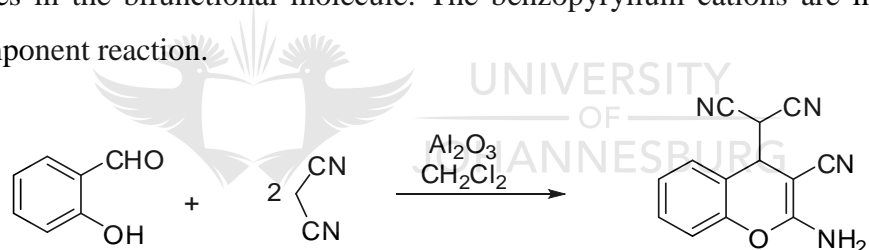
This section of the review discusses well established and widely employed methods for the synthesis of 4*H*-chromenes. In fact, each one of them has been used for combinatorial library synthesis of a range of 4*H*-chromene derivatives. One of the first and the most widely used methods is the multi-component reaction (MCR) involving electron rich phenols, aromatic aldehydes and malononitrile to generate 2-amino-3-cyano-4-aryl-4*H*-chromenes (Scheme 1.27).¹⁰¹ A variety of reagents have been reported to promote this multi-component reaction.¹⁰² The reaction proceeds through the initial formation of the Knoevenagel product from the

malononitrile and the aromatic aldehyde, followed by a click reaction involving the phenol and the Knoevenagel product to yield the aryl *4H*-chromene.



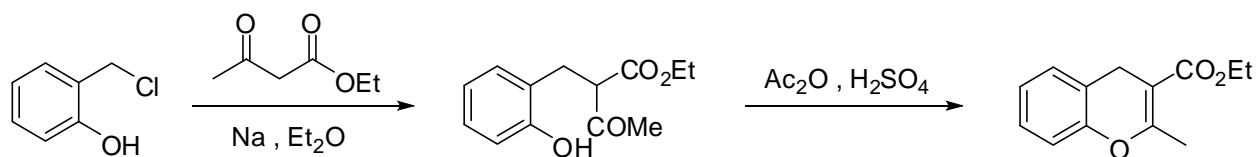
Scheme 1.27. Synthesis of *4H*-chromenes via a MCR

2-Hydroxybenzaldehyde (salicylaldehyde) and its derivatives are also widely employed for the synthesis of *4H*-chromenes, without phenols. In this protocol one 2-hydroxybenzaldehyde unit reacts with two units of malononitrile to provide a *4H*-chromene.¹⁰³ A two-bond formation between the 2-hydroxybenzaldehyde and the malononitrile proceeds in a domino fashion, where the 2-hydroxybenzaldehyde contributes both nucleophilic (phenolic hydroxyl) and electrophilic (aldehyde) sites in the bifunctional molecule. The benzopyrylium cations are intermediates in this multi-component reaction.



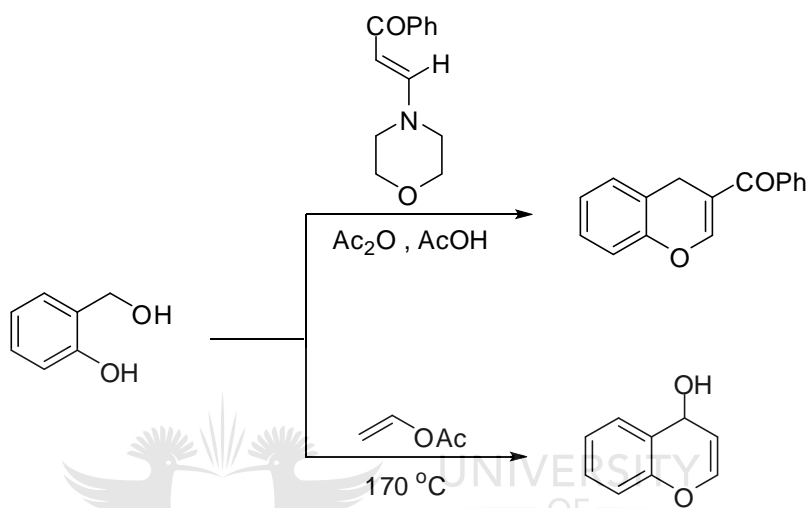
Scheme 1.28. 2-hydroxybenzaldehyde in *4H*-chromene synthesis

4H-Chromenes can also be synthesised by a two-step condensation reaction of ethyl acetoacetate with 2-hydroxybenzyl chlorides (Scheme 1.29).¹⁰⁴ This reaction involves initial alkylation of the ethyl acetoacetate with the benzyl chloride to yield a hydroxyphenyl propanone. Then cyclisation followed by subsequent dehydration under acidic conditions to furnish the *4H*-chromene.



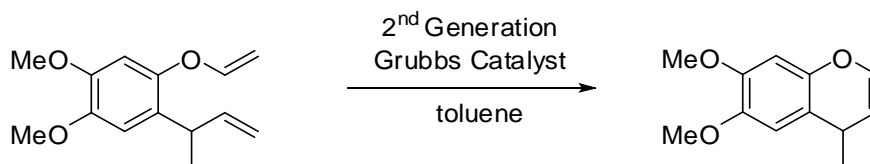
Scheme 1.29. Two-step synthesis of *4H*-chromene

2-Hydroxybenzyl alcohols react with functionalised enamines in a mixture of acetic acid and acetic anhydride at elevated temperatures to afford 3-aryl-4*H*-chromenes.¹⁰⁵ This reaction proceeds via hetero-Diels Alder reaction between an *in situ* generated *O*-quinone methide and the enamine. Though the Diels Alder reaction is not so popular in the synthesis of 4*H*-chromenes, at high temperatures and pressures dehydrated intermediates from 2-hydroxybenzyl alcohols (a quinone methide intermediate) react with excess vinyl acetate to give 4*H*-chromenes in moderate yields.¹⁰⁶



Scheme 1.30. 2-Hydroxy benzyl alcohol in the synthesis of 4*H*-chromenes

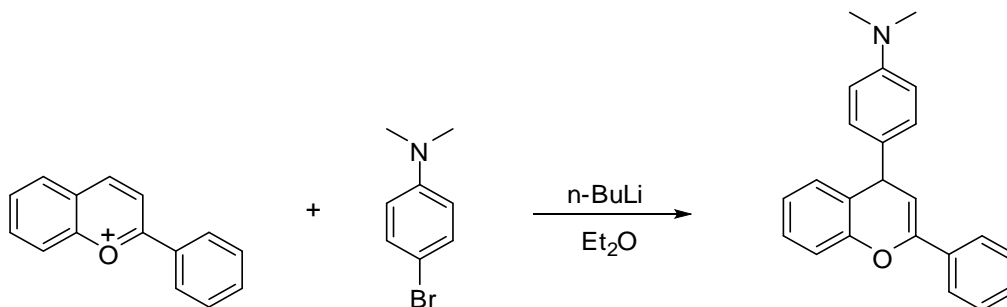
Ring closing olefin metathesis (RCM) has been used on *O*-vinylated 2-allylphenols to synthesise 4*H*-chromenes (Scheme 1.31).¹⁰⁷ Van Otterlo *et al.*¹⁰⁸ reported a detailed study of this reaction synthesising a wide variety of ring substituted 4*H*-chromenes as well as 2*H*-chromenes. The Grubbs first generation catalyst did not work well, however the second generation catalyst provided the chromenes in quantitative yields.



Scheme 1.31. Ring-Closure Metathesis in synthesis of 4*H*-chromenes

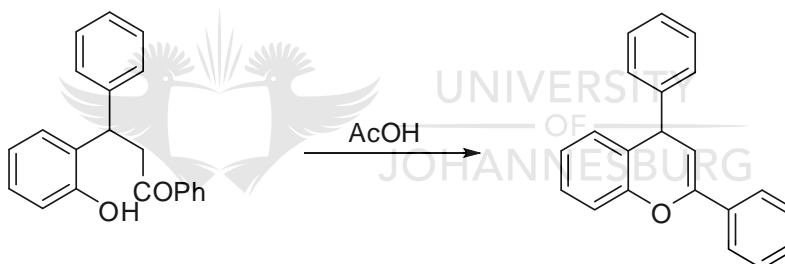
Occasionally, 4*H*-chromenes have been prepared by modifications of closely related compounds and/or heterocycles. One example is the benzpyrilium cation which reacts with soft aryl halides

to afford a C4-substituted aryl 4*H*-chromenes. A variety of nucleophiles (carbon, heteroatom, hydrides) have been employed in this reaction.¹⁰⁹



Scheme 1.32. Benzpyrilium cations as precursors for 4*H*-chromenes

Similarly 2,4-diaryl-4*H*-chromenes (Scheme 1.33) have been prepared by acid catalysed cyclisation of 3-(2-hydroxyphenyl)propan-1-ones. The cyclised keto-phenol precursors were synthesised by reacting aryl magnesium bromides with coumarins.¹¹⁰ Coumarins are chromene derivatives bearing a carbonyl functional group on the pyran ring.

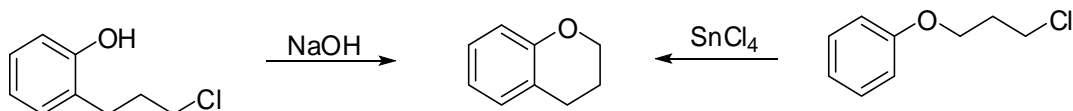


Scheme 1.33. Synthesis of 4*H*-chromenes from hydroxyl carbonyls

1.3.2 Synthesis of chromans

Chromans were first synthesised in 1905 by heating an aqueous sodium hydroxide solution with 2-(3-chloropropyl)phenol.¹⁰⁹ Normant and Maitte¹¹² later reported a much higher yielding reaction, where they prepared the chroman by cyclisation of phenyl 3-chloropropyl ether using tin tetrachloride (Scheme 1.34). The chroman moiety is present in a number of biologically active natural products such as tetrahydrocannabinol and Vitamin E. Actually it has been reported that the chroman moiety is responsible for the antiandrogenic properties of vitamin E.¹¹³ It is for this reason and the fact that chromans are not very reactive (since the heterocyclic ring is saturated) that researchers have focused mostly on the synthesis of substituted chroman

derivatives rather than the saturated scaffold. This report will discuss the most common methods for the synthesis of chroman derivatives. In principle, chromans can be prepared from chromenes by mere hydrogenation on the heterocyclic ring.



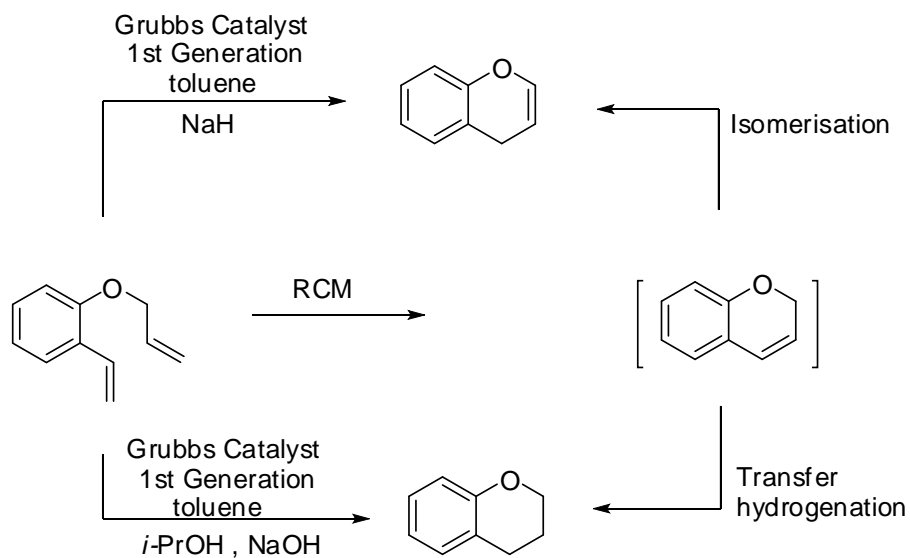
Scheme 1.34. Synthesis of dihydro-1-benzopyran (chroman)

1.3.2.1 Asymmetric synthesis to chiral chromans

The synthesis of chiral chromans was prompted by α -tocopherol (has 3 chiral centres), which is the most significant member of the vitamin E family serving as a natural lipophilic antioxidant and radical scavenger.¹¹⁴ Several methods have been employed for asymmetric synthesis namely: the use of chiral building blocks, kinetic resolution of enantiomers, desymmetrisation of prochiral compounds, use of chiral auxiliaries as well as the widely employed asymmetric catalysis. The asymmetric synthesis of chiral chromans has been recently reviewed by Shen.¹¹⁵ In addition, chromans are structurally related to chromenes and flavonoid compounds and the methods described by Shen¹¹⁵ readily apply to their synthesis as well.

1.3.2.2 Ring-closing metathesis

Ring-closing metathesis has been employed for the synthesis of numerous five- to eight-membered cyclic enol ethers. This normally involves the formation of a double bond which eventually isomerises and if saturated oxacycles are required, hydrogenated. However, Schmidt *et al.* reported a sequential ruthenium-catalysed ring-closing metathesis-transfer hydrogenation sequence for synthesis of chromanes from 2-(allyloxy)styrenes (Scheme 1.35), with the allyloxy styrenes synthesised from readily available salicylaldehydes.¹¹⁶ Ring-closing metathesis (RCM) has been used for the synthesis of chromenes, by cyclisation of enol ethers.¹⁰⁸



Scheme 1.35. RCM in synthesis of chromans

In this RCM-transfer hydrogenation, isopropanol in the presence of sodium hydroxide was employed to serve as a chemical trigger for the *in situ* formation of the transfer hydrogenation catalyst and also as a hydrogen transfer reagent to yield chromans, thereby circumventing ring-closing isomerisation which would otherwise result in an unsaturated pyran ring (chromene). Schmidt explored the generality of the method by using a variety of aryl substituted 2-(allyloxy)styrenes (Table 1.10) affording substituted chromene derivatives in one pot without the use of hydrogen gas.¹¹⁶

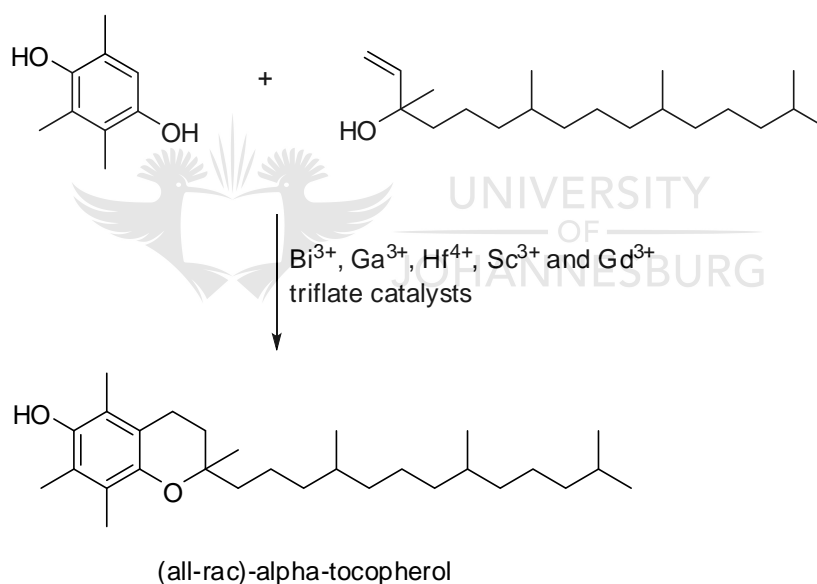
Table 1.10. Synthesis of chromans through RCM-transfer hydrogenation^a

Entry	RCM Precursor	Product	Yield (%)
1			66
2			82
3			98
4			65
5			75
6			62
7			83
8			33
9			76

^aPrecursor (0.1 M in toluene), Grubbs first generation catalyst (5 mol%), 40 °C; then add *i*-PrOH (10 vol%), NaOH (s, 0.5 equiv), 110 °C.

1.3.2.3 Friedel-Crafts alkylation

Friedel-Crafts alkylation is one of the oldest known reliable methods for C-C bond formation, and the development of milder protocols with a variety of Lewis acids for the alkylation of arenes and heteroarenes has been given lots of attention by researchers.¹¹⁷ Rare earth metal triflates [Bi(OTf)₃, Ga(OTf)₃, Hf(OTf)₄, Sc(OTf)₃ and Gd(OTf)₃] were employed by Bonrath *et al.* in the Friedel-Crafts synthesis of (all-*rac*)- α -tocopherol,¹¹⁸ a mixture of all eight stereoisomers of α -tocopherol (Scheme 1.36). The triflates showed high reactivity giving the desired substituted chromans in greater than 90% yield at low catalyst loadings. Recently triflate salts have been used with chiral ligands in enantioselective tandem Friedel-Crafts alkylations for the synthesis of chiral substituted chromans.¹¹⁹

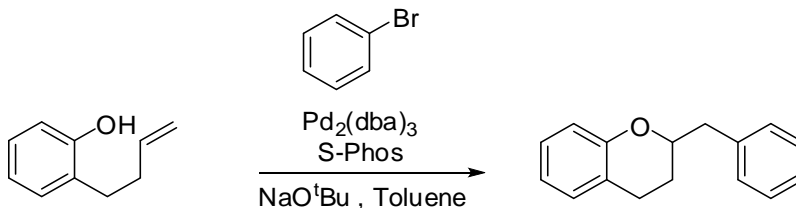


Scheme 1.36. Friedel-Crafts synthesis of (all-*rac*)- α -tocopherol

1.3.2.4 Palladium-catalysed cyclisation

Metal catalysts, especially palladium and ruthenium, are becoming popular in C-C forming cyclisations for the synthesis of heterocycles.¹²⁰ The synthesis of 2-substituted chroman derivatives has been reported to proceed smoothly *via* Pd-catalysed carboetherification of aryl

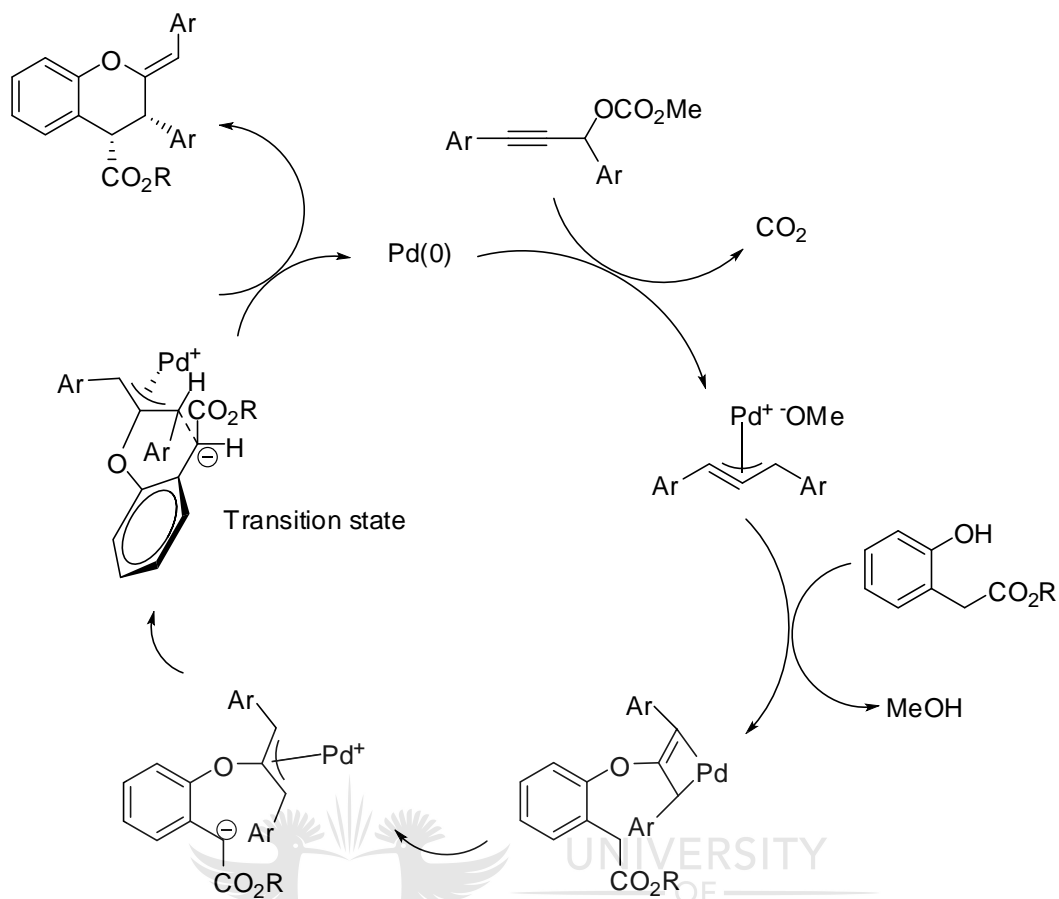
halides and 2-(but-3-en-1-yl)phenols.¹²¹ The palladium catalyst, Pd₂(dba)₃ was used in combination with the biaryl monophosphine ligand *S*-Phos to yield the 2-benzyl substituted chromans in high yield (Scheme 1.37).



Scheme 1.37. Pd-catalysed carboetherification

Tris(dibenzylideneacetone)dipalladium(0) has also been reported to catalyse the cyclisation of propargylic carbonates with 2-(2-hydroxyphenyl)-esters in a highly stereoselective process to give functionalised chromans (Scheme 1.38).¹²² Dimethyl sulfoxide (DMSO) and 1,1'-bis(diphenylphosphino)-ferrocene were employed as solvent and ligand of choice, respectively.

The reaction was proposed to proceed *via* initial decarboxylation to give a π -propargylpalladium complex. This complex further reacts with the 2-(2-hydroxyphenyl) ester leading to an anti- π -allylpalladium intermediate. This complex is then subjected to intramolecular attack of the enolate to produce chiral chroman (Scheme 1.38). The observed high diastereoselectivity was attributed to steric effects, where a lower energy transition state was one with less steric repulsions between ester and aryl substituents. Chromans directly substituted with aryl substituents on the heterocyclic ring are a class of flavonoid compounds.



Scheme 1.38. Proposed Mechanism for Pd(0)-catalysed cyclisation

1.4 Flavonoids

Generally the term “flavonoids” refers to the large class of polyphenolic compounds with a common diphenylpropane (C₆-C₃-C₆) carbon frame work consisting two aromatic rings linked through three carbon atoms, or more specifically a phenyl benzopyran skeleton.¹²³ Depending on the linkage of the phenyl ring on the benzopyrano (chromano) moiety, this group of natural products can be divided into three subclasses namely; flavonoids (2-phenylbenzopyrans), isoflavonoids (3-phenylbenzopyrans), and the neoflavonoids (4-phenylbenzopyrans).

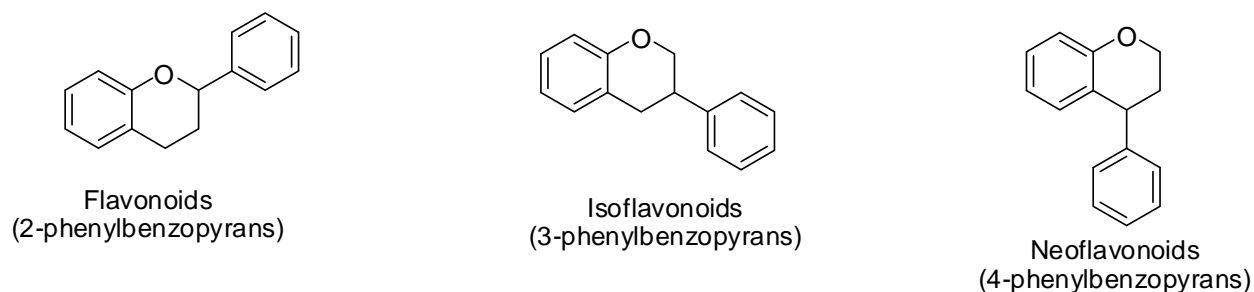


Figure 1.10. Structural backbones of flavonoid compounds

Based on the degree of oxidation and saturation in the heterocyclic ring the 2-phenylbenzopyrans (flavonoids) can further be subdivided into flavans, flavanols, flavanones, flavones, flavanonols, flavonols and anthocyanidins (Figure 1.11). From now on in the present manuscript, the term “flavonoids” will be used to refer to compounds bearing the 2-phenylbenzopyran skeleton.

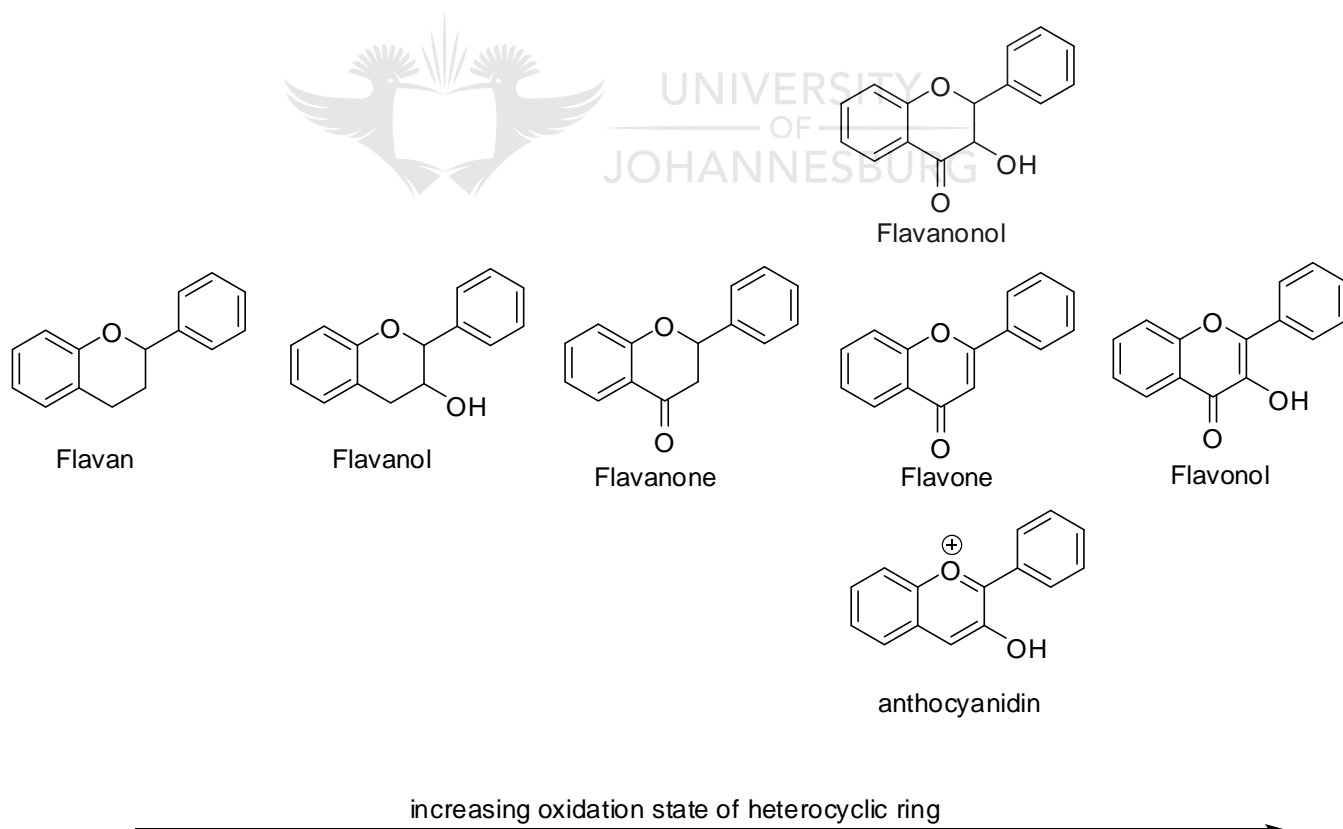


Figure 1.11. Sub-classes of flavonoids (2-phenylbenzopyrans)

Flavonoids occur naturally in fruits, vegetables and are also found in beverages such as tea and wine. They are plant pigments produced biosynthetically from phenylalanine.¹²⁴ Their chemical synthesis has been overlooked due to a lack of naturally occurring chiral substrates, hence most researchers have focussed on efficient extraction protocols since they are ubiquitous natural products.¹²³ Flavonoids are major nutraceutical ingredients found in plants. The term nutraceutical was coined by Stephen DeFelice¹²⁵ in 1979 meaning nontoxic food extract supplement that has scientifically proven health benefits for both the treatment and prevention of disease. Some of the major classes of flavonoids, with their bioactive compounds and the respective sources are presented in Table 1.11. There are many biological properties associated with flavonoids and these will be briefly highlighted, with special preference to the abundant green tea catechins and widely investigated and pharmaceutically employed quercetin.

1.4.1 Flavonoids in Health and Disease

Szent-Gyorgyi¹²⁶ isolated the flavonoid compound citrin from lemon and named it Vitamin P because of the permeability effect they had on vascular capillaries. However, the classification of flavonoids as Vitamin P was later revoked because a lack of dietary flavonoids did not result in an obvious deficiency syndrome.¹²⁷ The therapeutic effects of Vitamin P were, however, enough to draw interest in bio-assaying of flavonoid compounds. Also the “French paradox”—which is the observation of low coronary heart disease (CHD) death rates despite high intake of dietary cholesterol and saturated fat, has significantly contributed to biological investigations of flavonoid compounds especially in cardio-vascular diseases.¹²⁸ It is, therefore, not a surprise that modern orthodox physicians are increasing their use of pure flavonoids to treat many important common diseases, because of their proven ability to inhibit specific enzymes, to simulate some hormones and neurotransmitters, and to scavenge free radicals.¹²⁹ Quercetin (flavonol) and its derivatives/glycosides together with catechins (flavanols) and their corresponding gallates have received incredible attention from researchers in terms of investigating their biological properties. Some of the potencies of flavonoids against the world’s leading human killer diseases are outlined in this review.

Table 1.11. Main groups of flavonoids, compounds and food sources

Groups	Compounds	Food sources
Flavonols	Quercetin Kaempferol Myricetin Isorhamnetin Querctagetin	Yellow onion, Curly kale, Leek, Cherry tomato, Broccoli, Apple, Green and black tea, Black grapes, Blueberry.
Flavones	Tangeretin Heptamethoxyflavone Nobiletin Sinensetin Quercetogetin Chrysin Apegenin Luteolin Disometin Tricetin	Parsley, Celery, Capsicum pepper.
Flavanones	Naringenin Eriodictyol Hesperetin Dihydroquercetin Dihydrofisetin Dihydrobinetin	Orange juice, Grapefruit juice, Lemon juice.
Flavanols	Silibinin Silymarin Taxifolin Pinobanksin	Cocoa, Cocoa beverages, Chocolates.
Catechins (Proanthocyanidins)	(+) Catechin Gallocatechin (-) Epicatechin Epigallocatechin Epicatechin 3-gallate Epigallocatechin 3-gallate	Chocolate, Beans, Apricot, Cherry, Grapes, Peach, Red wine, Cider, Green tea, Black tea, Blackberry.
Anthocyanins	Cyanidin Delphinidin Malvidin Pelargonidin Peonidin Petunidin	Blue berry, Blackcurrant, Black grapes, Cherry, Rhubarb, Plum, Strawberry, Red wine, Red cabbage.

1.4.1.1 Flavonoids as antioxidants

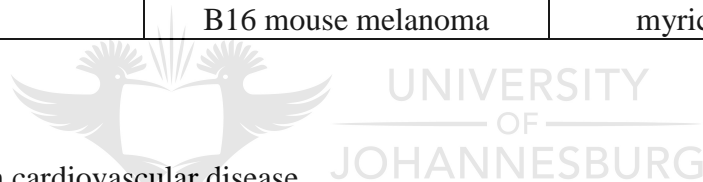
The best-described property of almost every group of flavonoids is their capacity to act as antioxidants. The flavones and catechins seem to be the most powerful flavonoids for protecting the body against reactive oxygen species.¹³⁰ Flavan-3-ols have been shown to behave as antioxidants via several mechanisms including the scavenging of free radicals, chelation of transition metals, as well as the mediation and inhibition of enzymes.¹³¹ Flavanols have been suggested to be superior to flavonols in their antioxidant capacity because oxidation of flavanols predominantly produces semiquinone radicals that couple to produce oligomeric compounds through nucleophilic addition.¹³² Coupling in this manner retains the number of reactive catechol/pyrogallol structures and effectively preserves scavenging ability.¹³³ Flavonols on the other hand form quinones that are more prone to redox-cycle with potential to behave as pro-oxidants. Though not recognised as principal dietary antioxidants like vitamin C and E, flavonoids have been shown to act synergistically with vitamins C and E to enhance hamster and human low density lipoprotein (LDL) resistance to oxidation.¹³⁴

1.4.1.2 Flavonoids in cancer

Flavonoids greatly influence the cascade of immunological events associated with the development and progression of cancer. By virtue of being antioxidants, they prevent reactive oxygen species induced DNA damage, which would otherwise lead to mutational changes.¹³⁰ Many other mechanisms of action have been identified, including carcinogen inactivation, antiproliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis and reversal of multidrug resistance or a combination of these mechanisms.¹³⁵ However, there is still room for a greater understanding of how flavonoids work in cellular organelles and tissues. Flavonoids have exhibited synergistic interactions with the routinely applied chemotherapeutic drug *cis*-diamminedichloroplatinum(II) (*cis*-DDP).¹³⁶ *In vitro* studies on the inhibitory properties of flavonoids against carcinogenesis in diverse cell systems are summarised in Table 1.12.¹³⁷

Table 1.12. Anticancer activities of flavonoids in various cancer cell lines

Cancer	Cell	Flavonoid
Human oral cancer	HSC-2, HSG, SCC-25	Flavanones, Isoflavones, EGC, chalcones, EGCG, curcumin, genistein, ECG, quercetin, cisplatin
Human breast cancer	MCF-7	Flavanones, quercetin, genistein, daidzein, luteolin
Human thyroid cancer	ARO, NPA, WRO	Genistein, apigenin, kaempferol, chrysin, luteolin, biochanin A
Human lung cancer	SK-LU1, SW900, H441, H661, haGo-K-1, A549	Flavone, quercetin
Human prostate	LNCaP, PC3, DU145	Catechin, quercetin, epicatechin, kaempferol, apigenin, luteolin, genistein, myricetin, sylimarin
Human colon	Caco-2, HT-29, IEC-6, HCT-15	Flavone, quercetin, genistein, anthocyanin
Human leukemia	HL-60, K562, 4A5, B16 mouse melanoma	Jurkat Apigenin, quercetin, myricetin, Chalcones



1.4.1.3 Flavonoids in cardiovascular disease

The *French paradox* summarises the effects of flavonoids in heart diseases. Generally a high cholesterol level and a high ratio of saturated and monounsaturated to polyunsaturated fatty acids in the blood predisposes patients to vascular diseases, whereas a high dietary content of vegetables and fruits (which are rich in flavonoids) has the opposite effect.¹³⁸ Because of their antioxidative effects flavonoids prevent the oxidation of low density lipoprotein (LDL). Oxidised LDL encourages deposits into the inner lining (endothelium) of arteries leading to narrowing which restricts blood flow resulting into heart failure. Clinical studies have shown that a high intake of flavonoids protects against coronary heart disease (CHD).¹³⁹

1.4.1.4 Flavonoids in diabetes mellitus

Flavonoids can ameliorate some of the consequences of diabetes mellitus.¹²⁹ Diabetes mellitus is a result of anomalies in carbohydrate metabolism which do not only result in a high glucose

concentration in the blood and urine, but also severe perturbation of lipid metabolism which leads to life-threatening physiological disorders and ultimately death. Flavonoids have been reported to be good inhibitors of aldose reductase,¹⁴⁰ an enzyme responsible for diabetic complications. Quercetin has been reported to possess antidiabetic activity and it has been found that it brings about regeneration of pancreatic islets and increases insulin release in streptozotocin-induced diabetes. It was also reported to stimulate Ca^{2+} uptake from isolated islet cells thus suggesting it to be effective even in non-insulin dependent diabetes.¹⁴¹ Sriram *et al.*¹⁴² reported fisetin to be a therapeutic agent for treatment of diabetes mellitus.

1.4.1.5 Antimicrobial activity of Flavonoids

The pharmaceutical and nutraceutical nature of flavonoids has led to research on its anti-infective effects. In an investigation into the antimicrobial action of propolis (bee glue), which has known healing properties dating back to biblical times, Mirzoeva *et al.*¹⁴³ showed that one of its constituent flavonoids, quercetin, caused an increase in permeability of the inner bacterial membrane and a dissipation of the membrane potential. The electrochemical gradient of protons across the membrane is essential for bacteria to maintain capacity for adenosine triphosphate (ATP) synthesis, membrane transport and motility. Mirzoeva *et al.* suggested that the effect of propolis on membrane permeability and membrane potential may contribute enormously to its overall antibacterial activity and may decrease the resistance of cells to other antibacterial agents. Propolis has also been reported to exhibit synergistic effects with other antibiotics such as tetracycline¹⁴³ and ampicillin.¹⁴⁴ Green tea extracts containing catechins were reported to be able to reverse β -lactam resistance in methicillin-resistant *Staphylococcus aureus* (MRSA).¹⁴⁵ Flavonoids also exhibit antifungal and antiviral activity and possess a wide range of other pharmaceutical applications.¹⁴⁶

1.5. Oxepanes and their synthesis

An oxepane is a saturated heterocyclic 7-membered ring with the formula $\text{C}_6\text{H}_{12}\text{O}$. Oxepanes are less stable than their corresponding six-membered rings (pyrans) as a result of transannular, bond and torsional strains,¹⁴⁷ and their synthesis remains a challenge primarily because of both

entropic and enthalpic barriers which hamper cyclisation strategies.¹⁴⁸ These 7-membered heterocycles can be found in many biologically active natural products, such as heliannuol B and C (allelopathic and phytotoxic), sodwanone S (antitumor) and zoapatanol (contraceptive).¹⁴⁹ They have also been used to replace the furanose ring in the synthesis of oxepane nucleic acids.¹⁵⁰

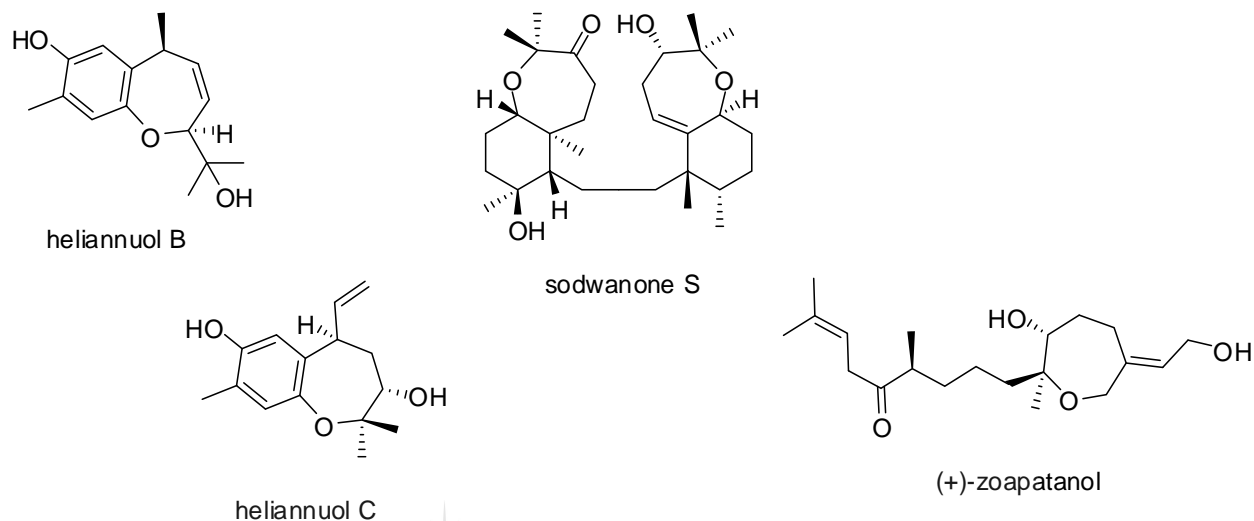
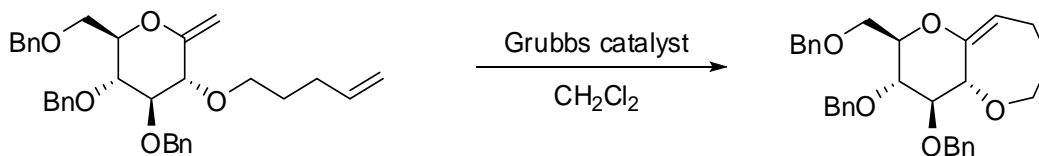


Figure 1.12. Bioactive natural products embodying the oxepane scaffold

1.5.1 Ring-closing metathesis (RCM) in oxepane synthesis

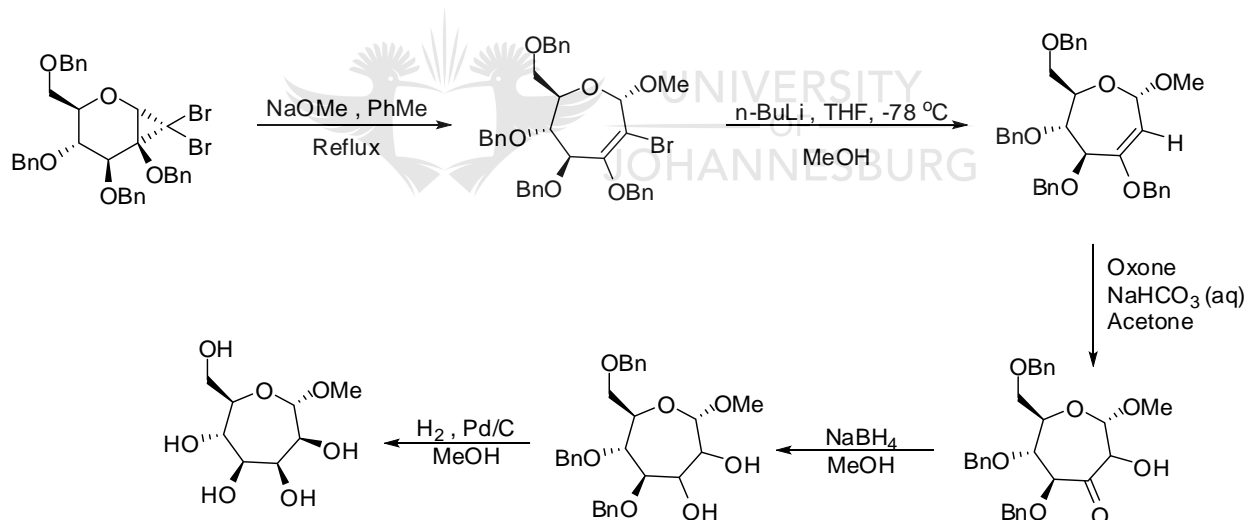
Ring-closing metathesis (RCM) has made it possible to cyclise substrates containing diverse functionalities leading to a wide range of carbo- and heterocycles of various ring sizes.¹⁴⁹ Schrock's molybdenum catalyst and Grubbs' first- and second-generation (ruthenium) catalysts have seen the most applications. These catalysts have been found to be compatible with many functional groups. Methylene glucose derivatives were reported to be cyclised into their corresponding C-glycosilidene compounds via RCM using Grubbs' catalyst.¹⁵² Enol ethers are usually not good substrates for a RCM reaction, but Dirat *et al.* demonstrated the mildness of the method in such cyclisations (Scheme 1.39).¹⁵² Grubbs and Fu also demonstrated¹⁵³ that the otherwise incompatible allyl ethers could be subjected to an RCM reaction using Schrock catalyst, leading to the formation of 5-8 membered cyclic ethers in good yield.



Scheme 1.39. Ring closure metathesis in synthesis of C-glycosilidene compounds

1.5.2 Cyclopropanated sugars in oxepane synthesis

The expansion of cyclopropane-fused carbohydrates to oxepanes has long been employed for the generation of a diverse range of septanoside carbohydrate mimics.¹⁵⁴ Ganesh *et al.*¹⁵⁵ reported a multi-step synthesis of D-glycero-D-talo-septanosides from *gem*-dihalocyclopropanes (Scheme 1.40). Generally, the use of cyclopropanated sugars, just like RCM, gives oxepenes which can be hydrogenated efficiently into oxepanes. Hoberg,¹⁵⁶ reported a high yielding synthesis of oxepenes from cyclopropanated sugars using a diverse range of silylated nucleophiles such as N₃, CN, SPh and allyl.

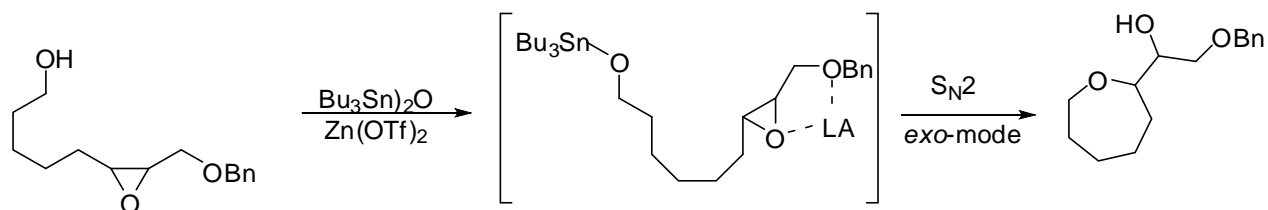


Scheme 1.40. Cyclopropanated sugars in synthesis of oxepanes

1.5.3 Hydroxy epoxides in oxepane synthesis

Intramolecular cyclisation of linear epoxy-alcohols is a well-established method for the preparation of five- and six-membered rings.¹⁵⁷ The scope of this reaction has been extended to the synthesis of oxepanes. This transformation has many benefits because the epoxide can be formed enantioselectively from an olefin and the resulting ring opening provides a new chiral

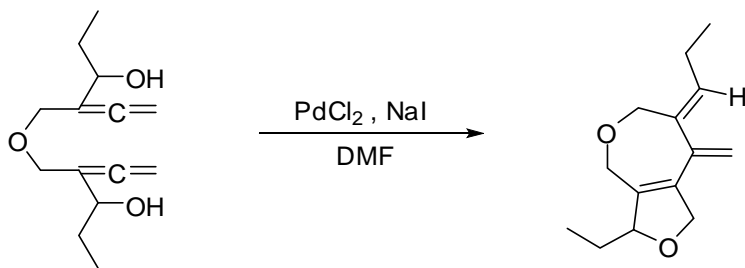
hydroxyl group for further functionalisation. Suzuki *et al.* have extensively investigated Lewis acid-mediated epoxide openings for the generation of a variety of medium ring ethers using a range of metal triflate catalysts (Scheme 1.41).¹⁵⁸ The group later applied the method in the synthesis of natural products.¹⁵⁹



Scheme 1.41. Synthesis of oxepanes from hydroxyl epoxides

1.5.4 Cyclisation through C-C bond formation

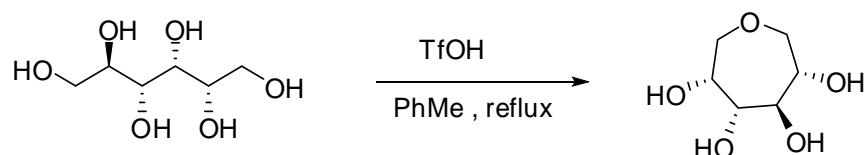
A general method for preparing cyclic ethers also has been applied in the synthesis of oxepanes. One approach uses the intramolecular attack of alkoxyallylstannanes onto aldehydes, a process which was developed by Yamamoto and co-workers and subsequently applied in the synthesis of hemibrevetoxin B.¹⁶⁰ Yamamoto *et al.*¹⁶¹ also reported intramolecular attack of allylstannanes on chiral acetals for the synthesis of oxepane derivatives. Ma and co-workers reported Pd(II)-mediated cyclisation for the generation of fused 5,7- and 5,8-membered ring systems.¹⁶² These cyclisation reactions include examples in which the tethering group contains a heteroatom, thereby generating fused heterocycles (Scheme 1.42).



Scheme 1.42. Palladium catalysed C-C cyclisation

1.5.5 Cyclisation through C-O bond formation

The ring-closure of linear alcohols to produce oxepanes was one of the first methods to be investigated and revealed the difficulties associated with this approach.¹⁶³ Despite these kinetic and thermodynamic challenges, researchers have continued to pursue this strategy owing to the benefits that a successful method would provide. Nicolaou reported the use of hydroxy ketone reductive C-O bond formation for the preparation of oxepanes.¹⁶⁴ Expanding on this powerful strategy for oxacycle formation, Kumar and co-workers reported the synthesis of (-)-*cis*-lauthisan and (+)-isolaurepan via reductive cyclisation.¹⁶⁵ Smith and co-workers reported the direct conversion of sorbitol into tetrahydroxyoxepane using catalytic amount of triflic acid.¹⁶⁶



Scheme.1.43. Cyclisation of sorbitol into tetrahydroxyoxepane

1.6 Summary

It is clear that aluminium triflate is an effective Lewis acid catalyst by which to effect many reactions. The chemistry of Al(OTf)₃ has been largely overlooked in favour of investigations relating to the lanthanide triflates, especially Sc(OTf)₃. However, recent work has shown that in many instances Al(OTf)₃ performs better than the traditional Lewis acids as well as many lanthanide triflates. It has in fact gained more popularity recently where it was involved in catalysis, Lewis acid-mediated protections and deprotections as well as in aminolysis and alcoholysis of epoxides. Aluminium triflate has also been shown to be recoverable and reusable without loss of activity. In addition, it is used in very low-sub-stoichiometric amounts.

This review also shows that metal triflates have recently been preferred in several well-known Lewis-acid mediated organic transformations ahead of traditional Lewis acids such as AlCl₃ and BF₃·OEt₂. However, aluminium triflate has not been extensively explored as a catalyst, especially in carbohydrate chemistry, despite carbohydrates representing an abundant group of

natural products, with diverse pharmacological and biological applications. Carbohydrates joined to an aromatic aglycon *via* an *O*- or *C*-glycosidic bond have gained popularity due to their availability in naturally occurring bioactive compounds.⁴⁹ General methods for the synthesis of these glycosides have been reported in this review.

This chapter also reviewed the synthesis of benzopyran derivatives. The benzopyran scaffold has been labelled as a *privileged* structure by Nicolaou⁹⁸ because it is found in a range of biologically active compounds, both synthetic and naturally occurring. The benzopyran can be found with either a saturated (chroman) or unsaturated (chromene) heterocyclic ring. A benzopyran joined with an aromatic ring on the pyran is called a flavonoid. These naturally occurring natural products are found in mostly fruit and vegetables and have also been labelled as nutraceuticals¹²⁵ because of their demonstrable health benefits. Some of the biological applications of these compounds have also been reviewed in this chapter. The synthesis of oxepanes, 7-membered oxacycles, also form part of this review chapter.

1.7 Present study

The present study shall involve an investigation into the efficacy of $\text{Al}(\text{OTf})_3$ as a Lewis acid catalyst for the synthesis of *O*-aryl-2-deoxyglycosides employing 3,4,6-tri-*O*-acetyl-D-galactal as the glycosyl donor. This reaction shall be followed by a temperature controlled Friedel-Crafts alkylation towards the synthesis of bridged chiral benzopyrans. The versatility of the catalyst will further be explored in the ring-opening acetolysis yielding highly functionalised chiral chromans and chromenes. Base-mediated de-acetylation of the chromenes would result into a new-class of chiral benzopyran which is anticipated to form *via* an intramolecular oxa-Michael addition.

The developed synthesis protocols will provide rapid access to the ubiquitous flavonoids which have well established health benefits. The synthesis of derivatives of these biologically active compounds will be reported, with special interest in catechins and quercetin-like compounds. To this end, Pd-catalysed Heck-type chemistry will be applied to unsaturated bi- and tricyclic

systems. A multi-step synthesis of an oxepane ring from a chromene derivative will also be discussed.

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Chapter 2

Synthesis of highly functionalised carbohydrate derivatives

2.1 Introduction

Carbohydrates are the most abundant group of natural products. Carbohydrates are the major nutrients which supply the body with energy. Moreover, polysaccharides such as cellulose, xylan and pectin determine the structure of plants, and chitin is the major component of the exoskeleton of insects, lobsters and crabs. Other polysaccharides, such as glycogen and starch serve as energy storage materials.

Carbohydrates are also involved in a wide range of biological processes,¹ such as cell-cell recognition, fertilisation, embryogenesis, neuronal development, hormone activities, the proliferation of cells and their organisation into specific tissues, viral and bacterial infections and tumour cell metastasis. It is therefore not surprising that carbohydrates are key biological molecules, since by virtue of different glycosidic linkages a diverse array of biologically active molecules can be synthesised.

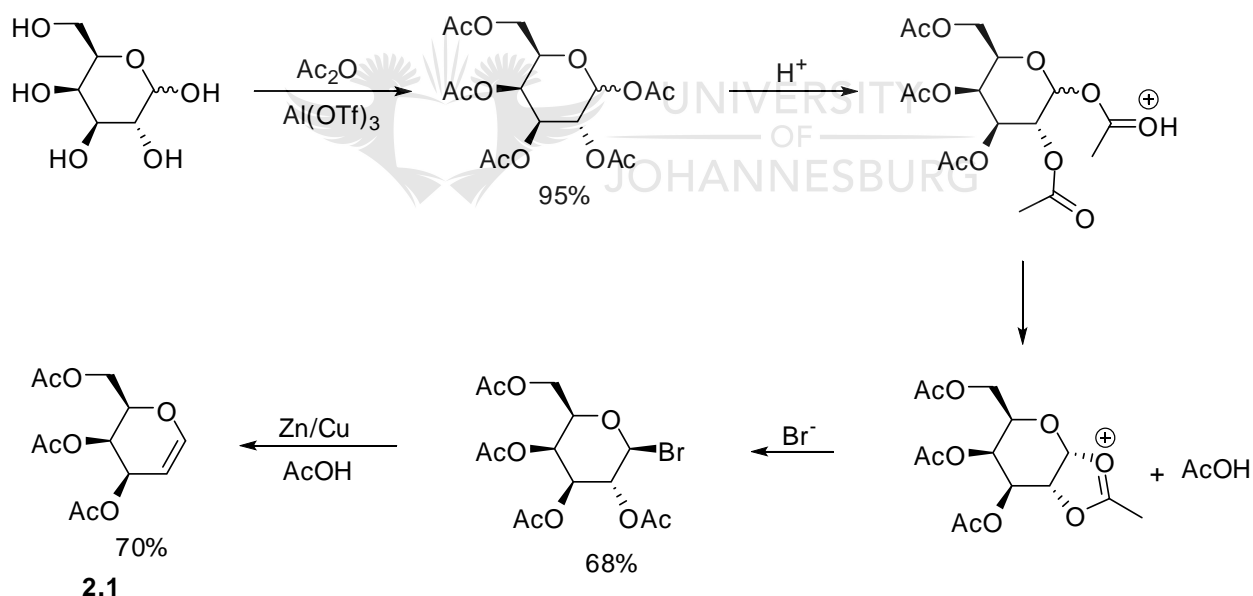
Carbohydrates (monosaccharides) owe their reactivity to the anomeric position, and to the other primary and secondary hydroxyl functions present. The synthesis of complex carbohydrate derivatives requires precise regioselectivity in various transformations. For many years this has been a prominent problem in carbohydrate chemistry due to the number and relative equivalence of the hydroxyl groups in carbohydrates. Protecting groups and protecting group strategies have therefore been of crucial importance to carbohydrate chemists in providing the broadest possible flexibility in synthetic avenues. Protecting group strategies also allow for ease of manipulation of carbohydrate derivatives into various other naturally occurring compounds.

Benzopyrans, just like carbohydrates, bear an oxygen-containing heterocyclic ring, which is fused to an aromatic ring. The benzopyran scaffold (chromenes and chromans) has been found in many naturally occurring bioactive molecules. Benzopyrans bearing a carbohydrate moiety have

not been given much attention by synthetic chemists. In this chapter, the synthesis of 2-deoxy-*O*-aryl glycosides starting from 3,4,6-*tri-O*-acetyl-D-galactal as well as the synthesis of bridged chiral benzopyrans and further manipulation thereof to chromenes and chromans is reported.

2.2 Synthesis of 3,4,6-*tri-O*-acetyl-D-galactal

Commercially available D-galactose was converted into 3,4,6-*tri-O*-acetyl-D-galactal through three reaction steps, reported by Emil Fischer and Karl Zach (Scheme 2.1).² In Fischer and Zach's reported method, the acetylation step was carried out using an excess of acetic anhydride. In the present instance, peracetylation conditions reported by Biezier *et al.*³ were adopted, with the exception that 5mol% Al(OTf)₃ was used as catalyst instead of In(OTf)₃. This step was generally high yielding, affording 95% yield of the peracetylated galactose within an hour.



Scheme 2.1. Multi-step synthesis of 3,4,6-*tri-O*-acetyl-D-galactal

After several optimisation attempts, the bromo-intermediate could be formed satisfactorily from HBr in acetic acid. The bromo-compound was labile and was thus used directly in the next step. The bromo intermediate is essentially exclusively the β -anomer because of neighbouring group

participation.⁴ Here, an ester, being in the α -position on C-2, reacts with the oxocarbenium intermediate shown (Scheme 2.1), to form a 5,6-bicyclic system in which the incoming bromide nucleophile is directed to the top face, thereby producing the β -product (Scheme 2.1). The final product was obtained in a yield of 70% by a reduction of the bromo-intermediate with a pre-mixed solution of CuSO_4 and zinc dust in acetic acid.² The overall yield in the three reaction steps from D-galactose to 3,4,6-*tri-O*-acetyl-D-galactal was 45%.

2.3 Synthesis of *O*-aryl 2-deoxy galactosides

Carbohydrates bearing an aromatic aglycone are key synthetic targets because of their presence in biologically active natural products. One of the simplest *O*-aryl glycosides is 4-hydroxyphenyl α -glucopyranoside (α -arbutin), which is an effective and safe ingredient for skin lightening.⁵ Due to the electron-withdrawing nature of the aromatic ring, phenols have been difficult to glycosylate. Additionally, most Lewis acid-promoted glycosylations with glycols tend to proceed *via* allylic rearrangement to provide the 2,3-unsaturated pseudo-glycosides.⁶ However, 3,4,6-*tri-O*-acetyl-D-galactal, unlike its glucose-derived 4-epimer, tends to favour direct addition to give 2-deoxy glycosides,⁷ and this phenomenon is discussed below.

The endocyclic double bond in a glycol, located between the C1 and C2 atoms of the pyranoid ring, forces O5, C1, C2, and C3 to lie in one plane, with the C4 and C5 carbon atoms being able to move above or below this plane. A glycol may adopt two opposite half-chair conformations – 4H_5 and 5H_4 and a change in configuration results in a change in the ${}^4H_5 \rightleftharpoons {}^5H_4$ conformational equilibrium. The vinylogous anomeric effect and the 1,3-diaxial interactions allow the glycols to adopt the half-chair conformations as shown in Figure 2.1.

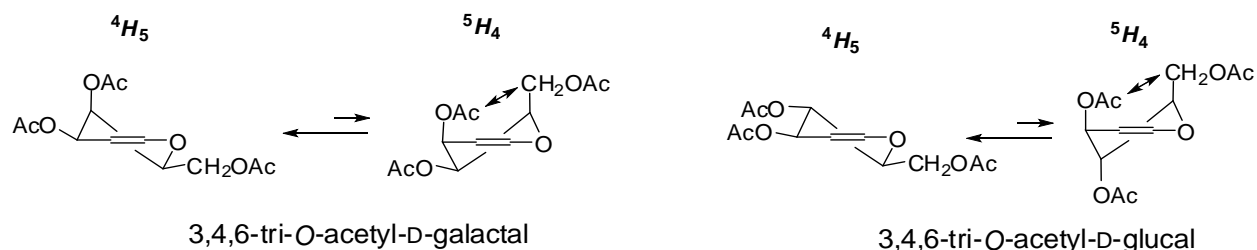
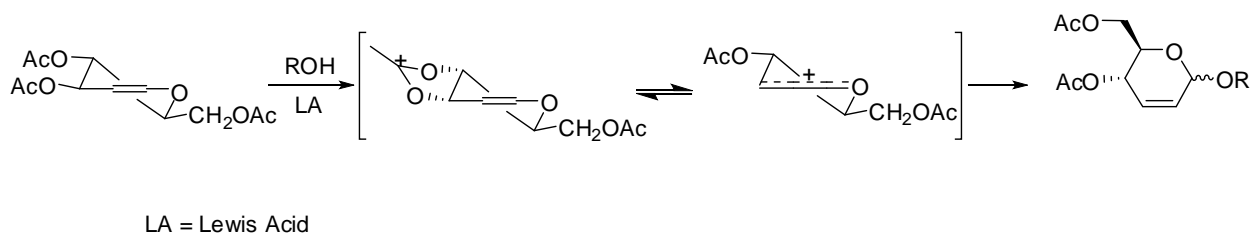


Figure 2.1. Conformational equilibria in 3,4,6-*tri-O*-acetyl-D-galactal and 3,4,6-*tri-O*-acetyl-D-glucal

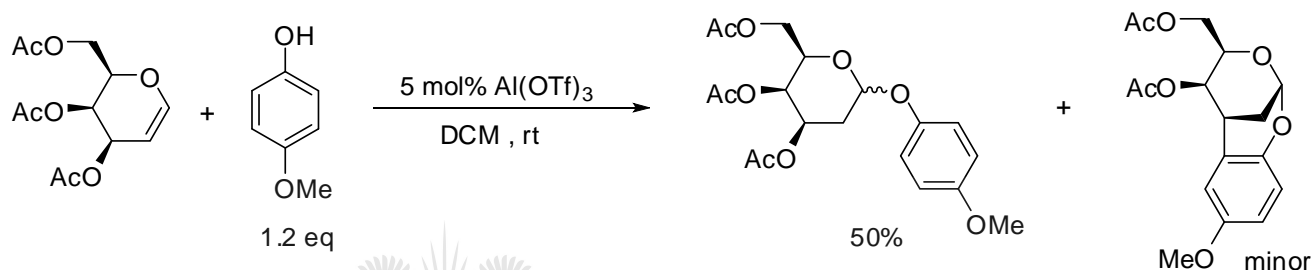
The difference between these two epimers (D-galactal and D-glucal) is the orientation of the homoallylic C-4 substituent with respect to its C-3 counterpart. The axial orientation of the C4 substituent in the galactal removes the possibility of anchimeric assistance towards the removal of the C-3 acetoxy function, while this remains possible with the glucal (Scheme 2.2), and this avoids allylic or Ferrier rearrangement and favours the direct addition to give 2-deoxy glycosides. Not all D-glucal derivatives require such neighbouring group participation from the C-4 substituent, because derivatives with non-participating groups at C-4 also undergo the Ferrier rearrangement.⁸



Scheme 2.2. Neighbouring group participation in the Ferrier reaction of 3,4,6-*tri-O*-acetyl-D-glucal

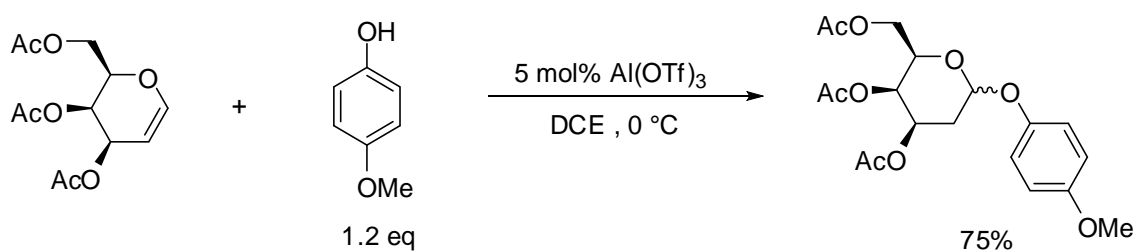
Initially the synthesis of *O*-aryl-2-deoxy galactosides was pursued by addition of 1.2 equivalents of phenol into a solution of 3,4,6-*tri-O*-acetyl-D-galactal and dichloromethane (DCM) at room temperature using 5 mol% aluminium triflate as catalyst. Phenols are known to be less nucleophilic compared to their alkyl alcohol counterparts, so to enhance the nucleophilicity

phenols bearing electron donating groups/substituents (EDG) were used. The reaction proceeded to completion within 1 hour giving the aryl 2-deoxy glycoside in an unsatisfactory yield of 50% and a minor by-product which was identified as a bridged chiral benzopyran (Scheme 2.3). Under optimised conditions, the formation of the bridged chiral benzopyran was suppressed in favour of the *O*-aryl-2-deoxyglycoside. (The formation of the *bridged chiral benzopyrans* was also optimised and is discussed in detail later in this chapter. This was achieved by altering the temperature between 0-40 °C and substituting DCM with DCE on account of the higher boiling point of DCE.)



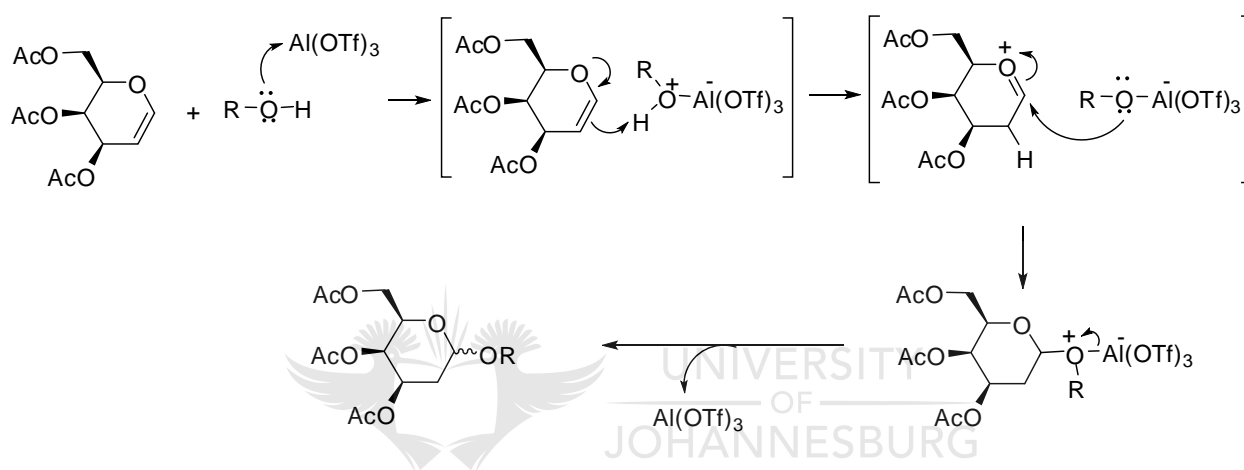
Scheme 2.3. Synthesis of *O*-aryl 2-deoxy glycosides

The same reaction was performed at 0 °C using 1,2-dichloroethane (DCE) as a solvent. The reaction proceeded much slower and more selectively towards the *O*-aryl-2-deoxyglycoside yielding an appreciable 75% of product.



Scheme 2.4. Optimised synthesis of *O*-aryl 2-deoxy galactosides

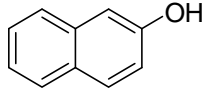
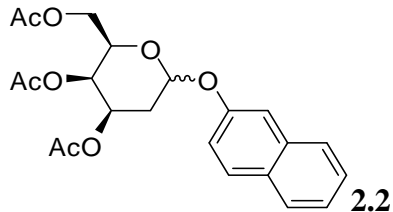
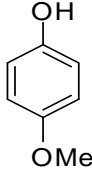
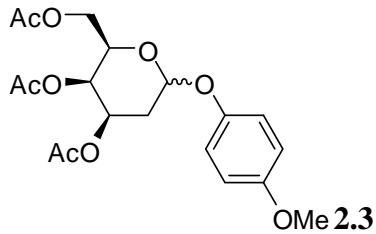
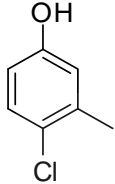
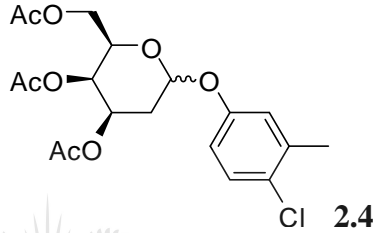
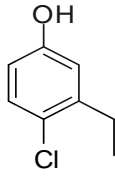
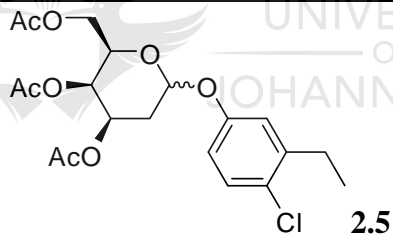
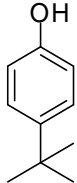
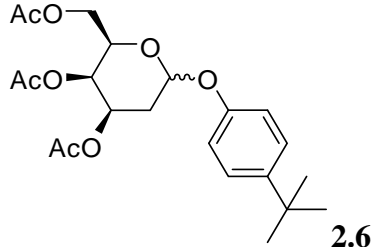
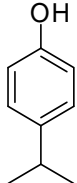
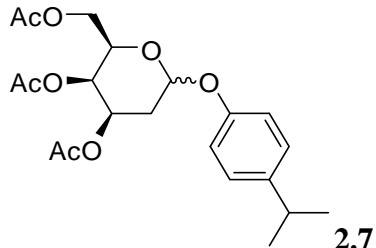
Under these partly optimised conditions (1.2 equivalents of phenol, 5 mol% $\text{Al}(\text{OTf})_3$, DCE, 0 °C) a range of phenols bearing electron-donating groups were employed to demonstrate the generality of the catalyst and/or the developed methodology (Table 2.1). The reactions gave good to high yields of product in short reaction times, as indicated by thin layer chromatography (TLC). The reaction is thought to proceed in a typical fashion, following an acid-catalysed (Lewis-assisted Brønsted acid)⁹ direct addition to the glycal double bond as shown in Scheme 2.5.



Scheme 2.5. Mechanism for synthesis of 1-*O*-aryl 2-deoxygalactosides

Reducing the temperature from ambient to 0 °C suppressed the formation of the bridged chiral benzopyran, although in some cases it was still observed as a minor by-product in trace amounts. The low temperature also ensured that the reaction proceeded slowly and stereoselectively towards the α -glycoside. Most of the reactions were highly stereoselective affording greater than 95% selectivity for the α -glycoside. The substrates bearing a chloride functional group in the *para* position did not give appreciable stereoselectivity. This may be attributed to the inductively electron-withdrawing nature of the chloride. Methyl phenols (cresols) were also investigated with respect to their ability to glycosylate with 3,4,6-*tri-O*-acetyl-D-galactal (Table 2.2). No significant difference in yields or stereochemistry was observed within the cresols as well as compared to the other phenols bearing electron-donating groups in the *para* positions.

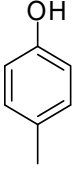
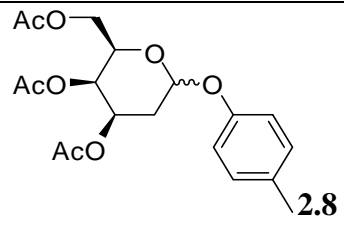
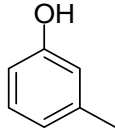
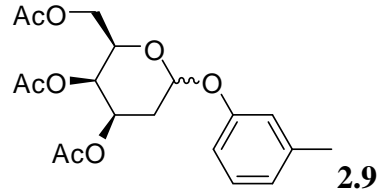
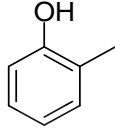
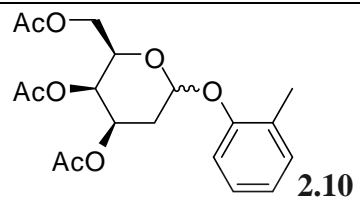
Table 2.1. Synthesis of 1-*O*-aryl-2-deoxy-D-galactosides using Al(OTf)₃^{a,b}

Entry	Substrate	Product	Time (h)	Yield (%)	α/β
1			3	63	>95 α
2			4	75	>95 α
3			5	83	7:1
4			5	81	9:1
5			3	78	>95 α
6			3	73	>95 α

^a0.735 mmol of galactal, 1.2 eq of phenol, 5 mol % Al(OTf)₃, 2 mL DCE, 0 °C.

^b α/β ratios determined by integration of anomeric signals in ¹H NMR spectra.

Table 2.2. Synthesis of 1-*O*-aryl-galactosides from cresols using Al(OTf)₃^{a,b}

Entry	Substrate	Product	Time (h)	Yield (%)	α/β
7			4	71	>95 α
8			4	74	>95 α
9			4	71	>95 α

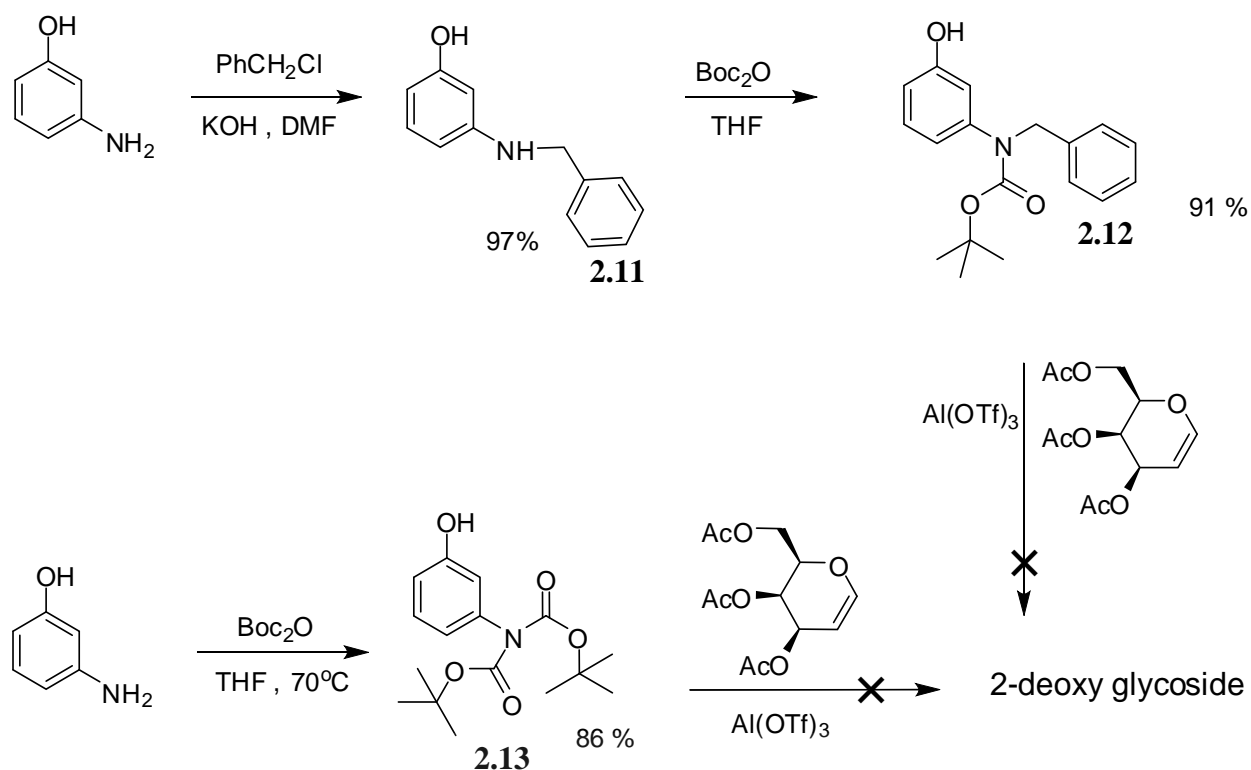
^a0.735 mmol of galactal, 1.2 eq of phenol, 5 mol % Al(OTf)₃, 2 mL DCE, 0 °C.

^b α/β ratios determined by integration of anomeric signals in ¹H NMR spectra.

The structures of the 2-deoxygalactosides were assigned on the following basis. Firstly, the absence of the characteristic olefinic signals downfield in the ¹H NMR spectra of the individual products implied that the Ferrier rearrangement did not take place. Ferrier rearrangement would have led to a double bond in the C2-C3 position. What the spectra did show was a signal at around 5.8 ppm that was allocated to the anomeric proton (presenting as a doublet, $J = 2.7$ Hz) and the presence of the three singlet resonances upfield at about 2.0 ppm, which were indicative of the presence of three acetates in the product. Furthermore, the ring CH₂ moiety resonated as an ABMX system manifesting as a triplet of doublets and a doublet of doublet resonances at 2.22 ppm ($J = 12.6$ and 3.0 Hz) and at 2.08 ppm ($J = 12.6$ and 5.4 Hz), respectively. The allocation of these signals was made unambiguous by extensive nOe, COSY, HSQC and H-H decoupling experiments. It is unusual for H-1 to demonstrate such limited coupling with the CH₂ moiety, where a doublet of doublets multiplicity would normally be anticipated. It is likely that the preferred conformation of the product brings the dihedral angles of the H-1 proton and the CH₂ protons to relative positions that preclude strong coupling. In contrast, the proton at H-3 demonstrated the anticipated multiplicity, i.e. resonating as a doublet of quartets, but it is in the α

position, while the H-1 proton is in the β -position, possibly accounting for this difference. This observation was made for all products of this study. Low field signals consistent with those expected of the aromatic moieties contained in each compound were also present in each spectrum. The use of ^{13}C NMR spectroscopy also helped in identifying the three carbonyl groups of the acetates and the aromatic signals downfield in the spectra. The diagnostic ring CH_2 group produced a resonance in the aliphatic region at about 30.0 ppm in the ^{13}C NMR spectrum of each compound. The presence of the carbonyl moieties was further identified with the use of infrared spectroscopy where there was a strong absorption around 1730 cm^{-1} , which is typical for ester groups.

Glycosylation of 3-aminophenol was unsuccessful, and the TLC plate showed many spots indicative of multiple product formation. Although phenyl amines are somewhat nucleophilic, their coupling with glycals is not well documented, except for the reported glycosylation of indolocarbazole with 3,4,6-*tri-O*-acetyl-D-galactal using *para*-toluene sulfonic acid (*p*-TsOH) in the synthesis of a *Tjipanazole* analogue.¹⁰ To avoid the formation of an *N*-glycoside and thereby reducing the number of by-products, the 3-aminophenol was *N*-protected using di-*tert*-butyl dicarbonate (Boc_2O) and benzyl chloride to produce **2.12** or **2.13**, depending on the reaction conditions (Scheme 2.6). The *N*-protected phenols also failed to yield the desired 1-*O*-aryl 2-deoxygalactosides. Alterations to the catalyst loading, reaction time and temperature did not improve the result. Possibly, the electron-withdrawing nature of the Boc group sufficiently reduces the nucleophilicity of the phenol to prevent reaction. Quite likely, though, the *N*-carbonyl lone pair of electrons might have been competing for complexation with $\text{Al}(\text{OTf})_3$, thereby reducing its Lewis acidity and ability to catalyse the desired reaction.



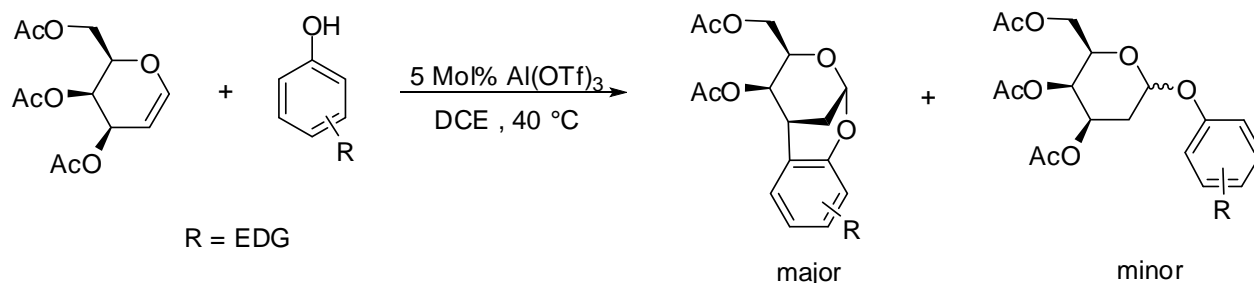
Scheme 2.6. Protection and attempted glycosidation with 3-aminophenol

2.4 Synthesis of bridged chiral benzopyrans

Glycosylation of 3,4,6-*tri-O*-acetyl-D-galactal has been less well-explored mainly because the galactal is less readily available compared to the glucal derivative. Another likely reason for it having been side-lined is that in many instances it does not give the anticipated results, instead producing by-products.¹¹ In support of the literature findings, and as already discussed in the previous section, when investigating the galactal in aromatic *O*-glycosylation reactions, some tricyclic substances were also obtained as by-products when using activated phenols as glycosyl acceptors.

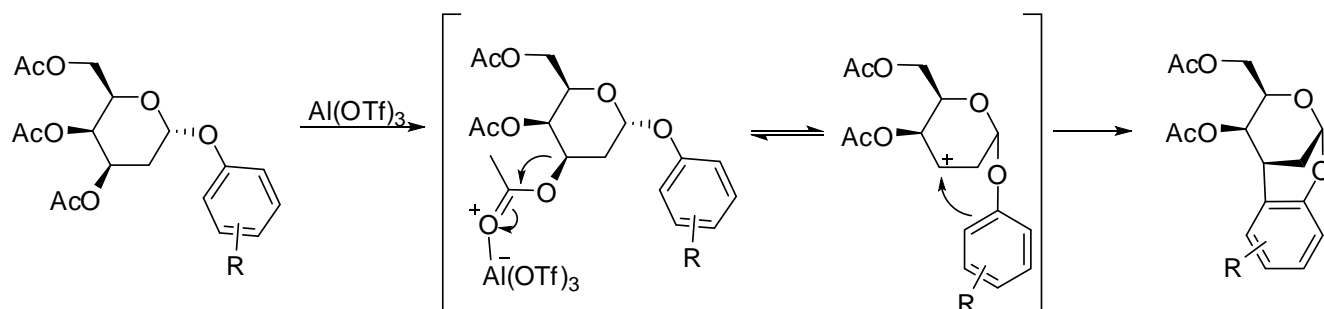
Due to continued interest in glycols as glycosyl donors in this laboratory, and recognising the opportunity to produce some interesting and relevant structures, it was hoped to optimise the method to *favour* the formation of these tricyclic structures, known as bridged chiral benzopyrans. As already indicated, such materials are rare and have been noted only as by-products in other work when attempting *O*-*C* migration with *O*-aryl-2-

deoxygalactopyranosides.¹² Several different reaction conditions were used in a bid to optimise the synthesis of these structures, eventually leading to conditions under which the tandem reaction is favoured (Scheme 2.7). These conditions were found to be mild and the bridged chiral tricyclic substances could be isolated in acceptable to good yields from the one-pot two-step method (Table 2.3).



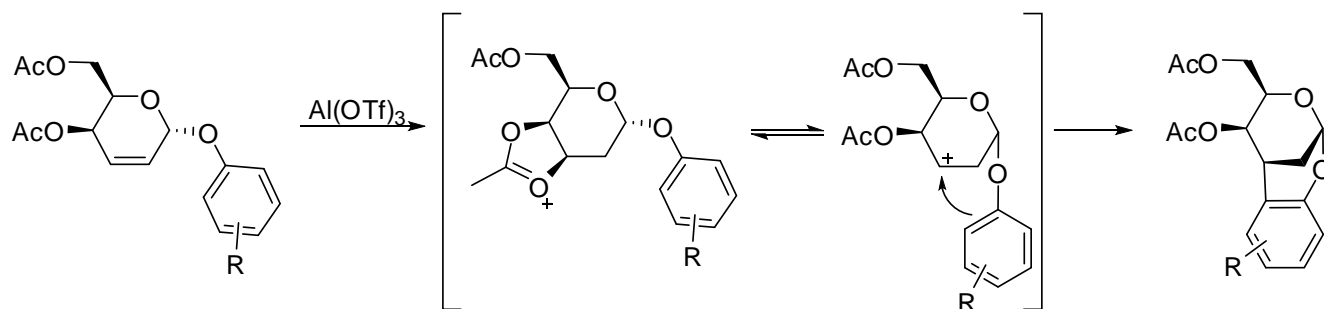
Scheme 2.7. Unusual Friedel-Crafts-type C-alkylation with triacetylgalactal

Attempts to synthesise the bridged chiral benzopyran from the 1-*O*-aryl-2-deoxygalactoside were unsuccessful, though it makes sense to think of the 1-*O*-aryl-2-deoxygalactoside as the kinetic product and the bridged chiral benzopyran as its derivative product. The reaction would be proposed to proceed with initial *O*-glycosylation to give the 1-*O*-aryl-2-deoxygalactoside. Then Al(OTf)₃ coordinates to the acyl moiety at C-3 making it a good leaving group. This is followed by an intramolecular C-alkylation, where the activated aromatic ring attacks the carbohydrate structure at C-3 (Scheme 2.8). This nucleophilic attack (Friedel-Crafts type reaction) results in an unusual C-alkylation in the *ortho* position of the aromatic ring yielding the unfamiliar tricyclic *O*-glycosides.



Scheme 2.8. Proposed mechanism for the synthesis of bridged chiral benzopyrans

However, the fact that the isolated *O*-aryl-2-deoxygalactoside failed to convert into the bridged product under various conditions in the presence of $\text{Al}(\text{OTf})_3$, may imply that it is not an intermediate on the path towards the tricycle. An alternative rationalisation is given below (Scheme 2.9), in which a Ferrier rearrangement is proposed to initiate the sequence. This is followed by creation of a charged intermediate, the formation of which may be facilitated by neighbouring group participation, as shown. Friedel-Crafts cyclisation would complete the sequence and produce the bridged tricyclic structure.



Scheme 2.9. Proposed alternative route for bridged chiral benzopyran synthesis

The developed protocol proved to be flexible with a diverse array of phenols bearing various substituents giving successful outcomes (Table 2.3). The results displayed in the table do not show any significant difference in the yields of the reaction in relation to the structure of the

aromatic moiety. The reactions are quite fast with the 2-naphthol proving to be the most reactive of the substrates. This may be due to the aryl cation intermediate usually formed during electrophilic aromatic substitution reactions being relatively stable for this bicyclic aryl system.

The presence of only 2 singlet resonances upfield at about 2.1 ppm were indicative of the presence of only two acetates in the product. Also the H-3 proton resonating at around 3.1 ppm showed direct correlation in the COSY spectrum with H-4 and H-2A and H-2B. The use of other NMR experiments such as ^{13}C NMR, HSQC, DEPT and HMBC were used to confirm the structure of the products as the bridged chiral benzopyrans. Single crystal X-ray crystallography of **2.18** unambiguously demonstrated the product to be the bridged tricyclic product, and the ORTEP diagram is shown in Figure 2.2.

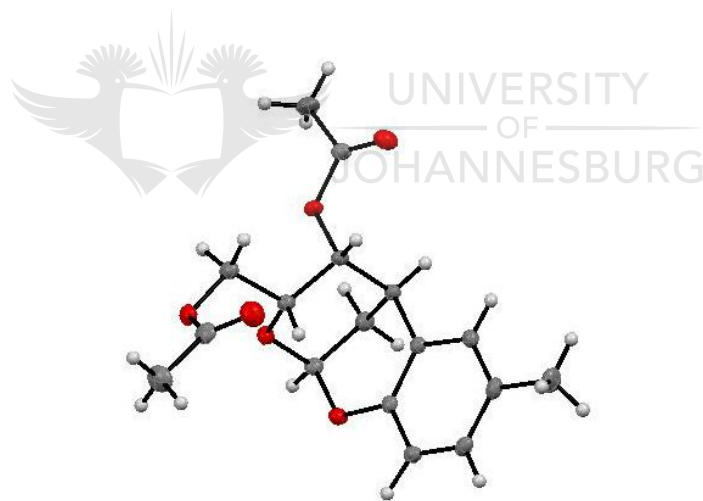
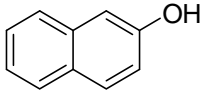
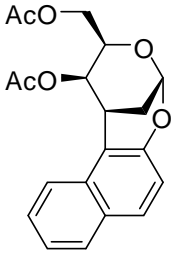
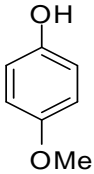
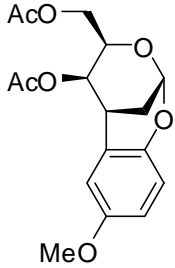
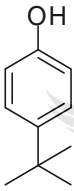
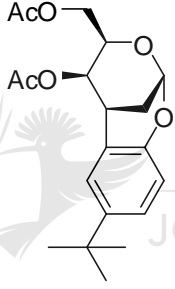
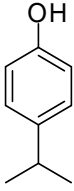
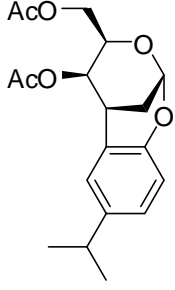
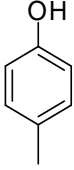
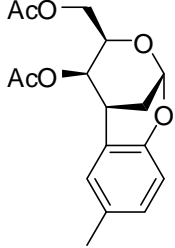


Figure 2.2 ORTEP diagram for tricyclic structure **2.18**

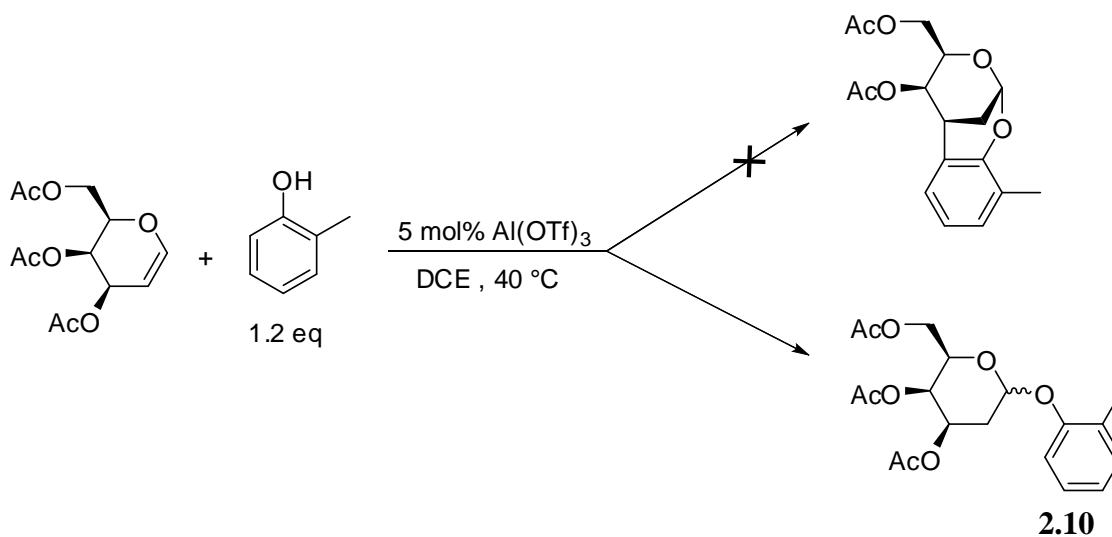
Table 2.3. Synthesis of bridged chiral benzopyrans using Al(OTf)₃^{a,b}

Entry	Substrate	Product	Yield (%)	[α] _D
1		 2.14	69	-134.2°
2		 2.15	71	-17.0°
3		 2.16	73	-48.0°
4		 2.17	70	-26.0°
5		 2.18	67	-27.0°

^a0.735 mmol of galactal, 1.2 eq of phenol, 5 mol % Al(OTf)₃, 2 mL DCE, 40 °C.

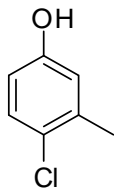
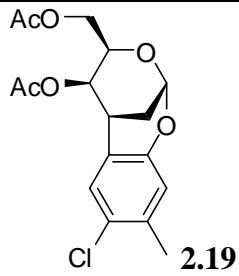
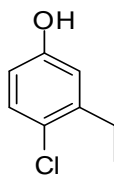
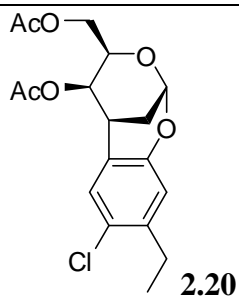
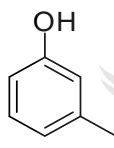
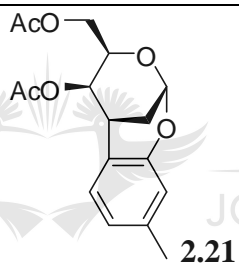
^bSpecific rotation was measured at *c* 0.5, CH₂Cl₂.

Meta-substituted phenols were also employed to show the generality of this tandem reaction (Table 2.4). The *meta*-substituted phenols gave an inseparable mixture of regioisomers, where the Friedel-Crafts alkylation step favoured the unhindered 6-position in the phenol. The formation of the regioisomers showed strong dependence on the group present in the *meta*-position, with the methyl-substituted substrate **2.19** giving a 5:1 ratio of products compared to the 15:1 ratio observed in the ethyl analogue **2.20**. This ratio was determined by assessment of the ¹H NMR spectrum and making use of those signals which are doubled up and well separated from each other. Interestingly, H-1 does not double up, providing coincident signals on the spectrum. Comparing the regioselectivity of the *meta*-cresol-derived bridged chiral benzopyran **2.21**, which is 5:2, to that of **2.19**, which is 5:1, it is clear that regioselectivity is also influenced by the electron-withdrawing group on the *para* position of **2.19**. This may be because the reaction proceeds much slower towards the synthesis of **2.19** as a consequence of a more weakly nucleophilic O group due to the inductive effects of the *p*-Cl group, allowing for improved regioselectivity compared to the faster reaction. Attempts to synthesise these interesting tricyclic structures with *o*-cresol were unsuccessful; instead the 1-*O*-aryl-2-deoxygalactoside was isolated (Scheme 2.10). That the Friedel-Crafts alkylation did not occur in this case may be due to steric hindrance preventing the formation of three contiguous substituent centres on the aromatic ring.



Scheme 2.10. Glycosidation with *o*-cresol

Table 2.4. Synthesis of bridged chiral benzopyrans with *meta*-substituted phenols^a

Entry	Substrate	Product	Yield (%)	Regeoisomers ^b
1			61	5:1
2			64	15:1
3			67	5:1

^a0.735 mmol of galactal, 1.2 eq of phenol, 5 mol % Al(Ot_f)₃, 2 mL DCE, 40 °C

^bRatio of regioisomers determined by integration of respective signals in ¹H NMR spectra

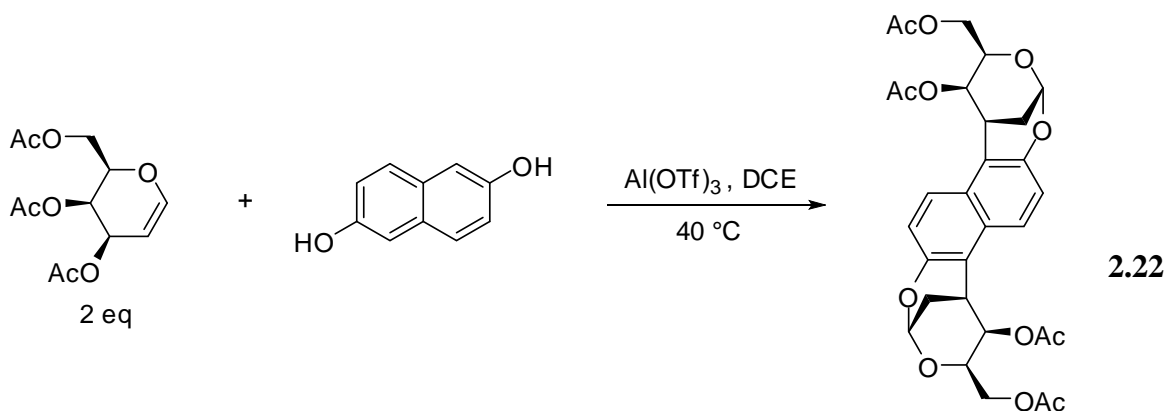
The NMR spectroscopic chemical shifts of the protons and carbons (H-1, C-1, H-3 and C-3) for each bridged chiral benzopyran were compared and tabulated (Table 2.5). For the regioisomers, data for the other regioisomer are also given and the data in parenthesis represent the multiplicity. The data show a high level of conservation of the chemical shift for H-1, H-3 and their associated carbon signals, indicating that the remote substitution exerts little influence on these centres (**2.14** being an obvious outlier due to the additional aromatic ring).

Table 2.5. Chemical shifts of *O*- and *C*-linkages to the pyranose ring (anomeric and 3rd position)

Structure no.	Proton δ_H		Carbon δ_C	
	H-1	H-3	C-1	C-3
2.14	5.74(s)	3.98(s)	92.6	27.7
2.15	5.60(s)	3.20(s)	92.8	32.8
2.16	5.61(s)	3.21(s)	92.9	32.8
2.17	5.62(s)	3.21(s)	92.9	32.7
2.18	5.66(s)	3.23(s)	92.9	32.4
2.19	5.62(s)	3.19(s) and 3.47(d)	92.3 and 92.9	29.7 and 31.9
2.20	5.62(s)	3.18(s) and 3.44(s)	93.0 and 94.4	29.8 and 31.9
2.21	5.63(s)	3.21(s) and 3.41(s)	92.6 and 92.9	29.0 and 32.1

NB: Data in parenthesis represent multiplicity

Using 2,6-dihydroxynaphthalene as a phenolic substrate, a hexacyclic bridged chiral benzopyran was synthesised. The 2,6-dihydroxynaphthalene was subjected to the same reaction conditions as the other phenols, except that 2 equivalents of the galactal were used to functionalise both ends of the phenolic substrate (Scheme 2.11). The product was also levorotatory with a specific rotation of $[\alpha]_D = -22.2^\circ$ (*c* 0.5, CH₂Cl₂) at room temperature. The hexacyclic bridged chiral benzopyran **2.22** was afforded in 64% yield, which is consistent with the yields from other phenols for this tandem reaction.



Scheme 2.11. Synthesis of hexacyclic bridged chiral benzopyran

The hexacyclic bridged chiral benzopyran has C_{2h} symmetry as is clearly visible on the ORTEP diagram shown in Figure 2.3. The symmetry is also evident from the 1H NMR and ^{13}C NMR spectra where each signal represents double the number of protons and carbons, respectively. For example the singlets representing the methyl for the acetates resonating at 2.21 and 1.97 ppm represent 4 methyl groups of the acetates. Also the ^{13}C NMR spectrum shows only 15 signals, also consistent with the symmetry of the molecule.

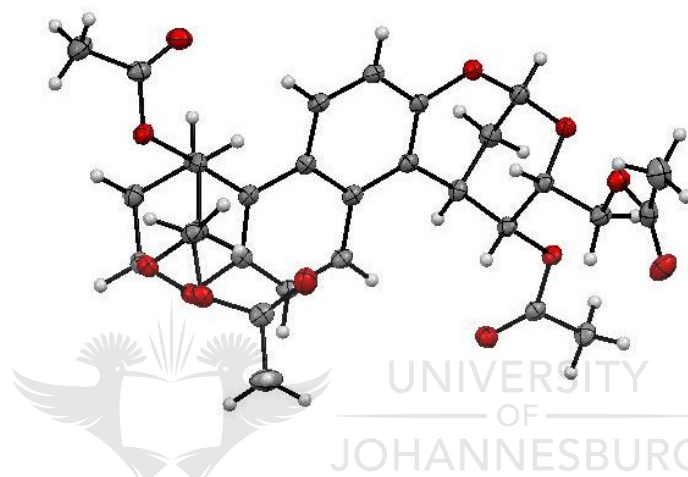
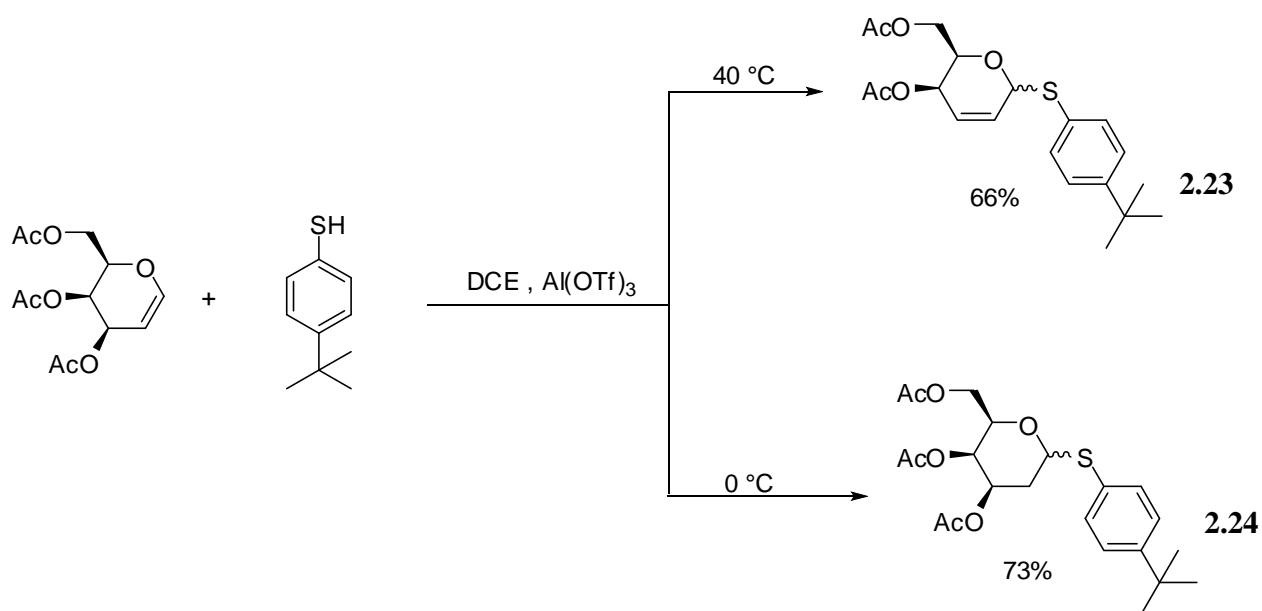


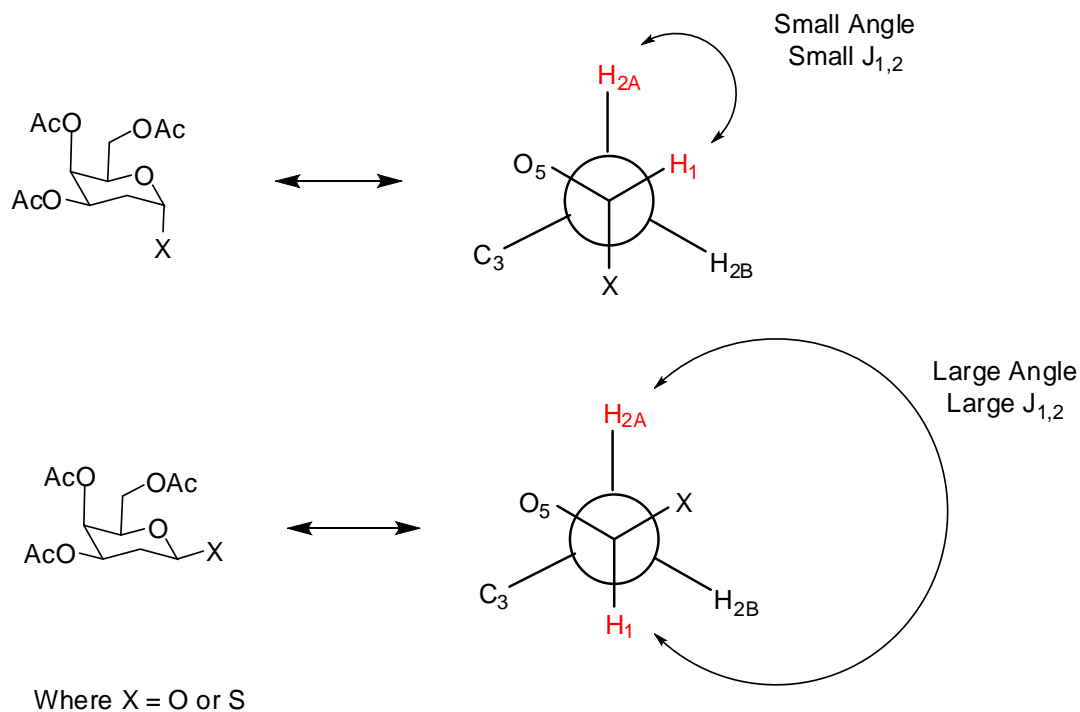
Figure 2.3. ORTEP diagram of the bridged chiral benzopyran **2.22**

Attempts to synthesise the bridged chiral benzopyrans using thiophenols bearing electron-donating groups instead of phenols were unsuccessful. The same reaction conditions as the phenols were employed, but only the 1-*S*-aryl-2,3-unsaturated pseudoglycoside **2.23** was obtained (Scheme 2.12) and no traces of the bridged chiral benzopyran were observed. Intrigued by this behaviour, the thiophenols were investigated to determine if they could afford the 1-*S*-aryl-2-deoxy galactoside under the same reaction conditions as those used with phenols. Interestingly, they behaved like the activated phenols and afforded the 1-*S*-aryl-2-deoxy galactoside **2.24**.



Scheme 2.12. Synthesis of thioglycosides

In the light of this intriguing outcome, the 2-deoxy thioglycoside was considered to possibly possess the β configuration, which would account for the absence of the Friedel-Crafts alkylation step. To investigate the proposition, the size of the coupling constant $J_{1,2}$ was compared with the analogous phenol product. For the *O*-galactoside it was found to be 2.8 Hz and for the *S*-galactoside 5.6 Hz. This difference is notable and worth explanation, but remains in the accepted range for α -glycosides. Since the size of the coupling constant has an inverse relationship with electronegativity, the difference in J values may be accounted for to some extent by this feature: oxygen is more electronegative ($EN = 3.44$) than sulfur ($EN = 2.58$), and so smaller J values would be expected for O-containing substances. β -galactosides, on the other hand, are usually expected to be accompanied by much larger coupling constants ($J_{1,2} = 8-10$ Hz) due to the larger dihedral angle as a result of axial-axial proton interactions (Scheme 2.13), than those observed for **2.24**. This dependence of the size of coupling constants on the dihedral angle φ of vicinal protons was first recognised by Karplus.¹³ According to Karplus, *trans*-diazial protons, with $\varphi = 180^\circ$ have a larger coupling constant, J , compared to axial-equatorial and equatorial-equatorial with $\varphi = 60^\circ$ which have a much smaller coupling constants.



Scheme 2.13. Newman projections of 4C_1 chair conformations

The size of the hetero-coupling constants $J_{C-1,H-1}$ was also probed. This was done through gated-decoupling experiments where all C-H hetero-coupling constants could be observed. The hetero-coupling constant for **2.6** was found to be $J_{C-1,H-1} = 170$ Hz whereas that of the thioglycoside **2.23** was found to be 168 Hz. The electronegativity of the substituent at C-1 affects the value of the hetero-coupling constant, hence thioglycosides generally have lower coupling constants than *O*-glycosides.¹⁴ For glycosides the difference between an α - and β -glycosides is approximately 10 Hz,¹⁵ and the anomer with an equatorially disposed H-1 has a larger coupling constant. This made it safe to conclude that the aryl thioglycoside is not β -oriented but is the α -anomer. This then meant the inherent differences in reactivity of the thiophenols and phenols could lie within the hard soft acid base (HSAB) theory. Aluminium triflate is a strong acid, hence it will complex stronger with the oxygen of the phenol than the sulfur of the thiophenol. The $[Al-O-R]H^+$ complex is a strong Brønsted acid that drives the cyclisation reaction, whereas the $[Al-S-R]H^+$ may not be strong enough to drive the tandem reaction, only ending at the Ferrier rearrangement

step which is supported by anchimeric assistance. Aluminium triflate ‘Brønsted activity’ has been reported in the methoxycarbonylation of alkenes.¹⁶

2.5 Ring-opening of bridged chiral benzopyrans

The successful synthesis of the range of bridged chiral benzopyrans, together with the fact that they have not been extensively investigated, led to the investigation of their ring-opening with the view to producing ring-opened benzopyrans. It was thought this reaction could be carried out *via* ring-opening acetolysis. Acetolysis by definition is the breakdown of an organic compound using either acetic acid or acetic anhydride. Aluminium triflate has demonstrated its potential as a Lewis acid catalyst in reactions catalysing the ring-opening of epoxides¹⁷ and oxetanes.¹⁸ However, the catalyst has not been reported to catalyse ring-opening of pyranose rings. The development of the ring-opening method was carried out by stirring the bridged chiral benzopyran in a mixture of acetic acid and acetic anhydride in the presence of a catalytic amount of Al(OTf)₃ and dichloromethane as a solvent. Interestingly, varying the ratios of acetic acid and acetic anhydride yielded different products, though these were all ring-opening products (Table 2.6).

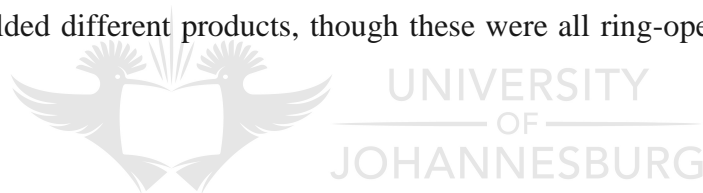
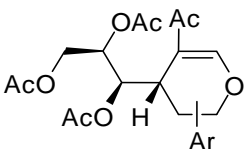
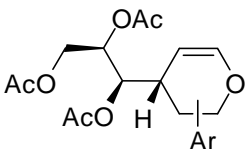
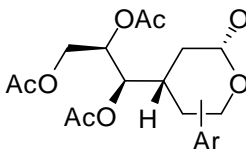


Table 2.6. Ring opening acetolysis, method development

Ac ₂ O : AcOH			
100% Ac ₂ O	exclusively	-	-
5:1	major	minor	trace
3:1	major	minor	trace
2:1	minor	minor	major
1:1	minor	minor	major
1:2	minor	-	minor ^a
100% AcOH	-	-	-

^aReaction did not go to completion

The ring-opening of these bridged chiral benzopyrans gave rise to a new class of chiral carbohydrate-derived benzopyrans, more generally known as chromenes and chromans. Chromenes can be either *4H* or *2H* depending on the position of the double bond in the pyranose ring and the current ring-opening reaction resulted in *4H*-chromenes as the product. Having developed the method with a series of varying reaction conditions, the conditions under which chromenes were formed exclusively were then employed in the synthesis of a range of chromene derivatives using bridged chiral benzopyrans derived from different phenolic substrates. Also, the conditions that favoured the formation of chromans over the chromenes were identified and different chromans were synthesised from an array of bridged chiral benzopyrans (see below).

2.5.1 Ring-opening towards chromenes

The *4H*-chromene structural motif is very important and has received considerable interest in the field of medicinal chemistry due to its wide range of biological activities.¹⁹ The bridged chiral benzopyrans were subjected to reaction with acetic anhydride and 10 mol% aluminium triflate in dichloromethane. The reaction proceeded smoothly to yield the chiral galactose-derived *4H*-chromenes in high yield (Table 2.7). The *4H*-chromenes were isolated and found to be enantiomerically pure with chirality preserved from the bridged chiral benzopyran.

The results displayed in the table show a high-yielding ring-opening methodology towards the synthesis of *4H*-chromenes. There is no significant difference in the yields with respect to substrate. Four tall singlets upfield in the ¹H NMR spectrum were indicative of the acetyl moieties. The anomeric proton resonates in the olefinic region of the ¹H NMR spectrum as a singlet which indicates the absence of H-2; there is also no long range coupling observed with H-3. From the DEPT spectrum only one CH₂ signal is observed, corresponding to C-6, as opposed to the two from the starting material (which correspond to C-2 and C-6). A single crystal was grown for chromene **2.28**, and X-ray crystallography was performed. The ORTEP diagram of the structure is shown in Figure 2.4, in which the C1-C2 double bond and overall structure are evident.

Table 2.7. Synthesis of chiral galactose-based chromenes using Al(OTf)₃^{a,b}

Entry	Substrate	Product	Yield (%)	[α] _D
1			87	-16.1°
2			83	-20.9°
3			90	-24.3°
4			80	-25.3°

^a200 mg of substrate, 10 mol % Al(OTf)₃, 2 mL DCM, 2 mL Ac₂O, rt

^bSpecific rotation was measured at (c 0.5, CH₂Cl₂)

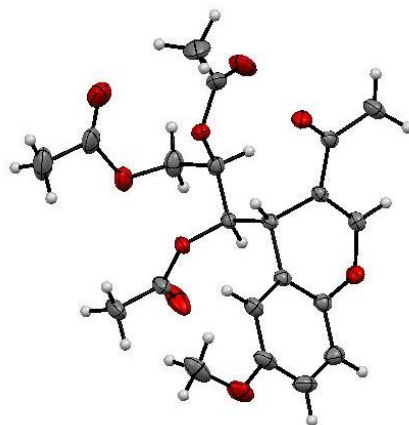
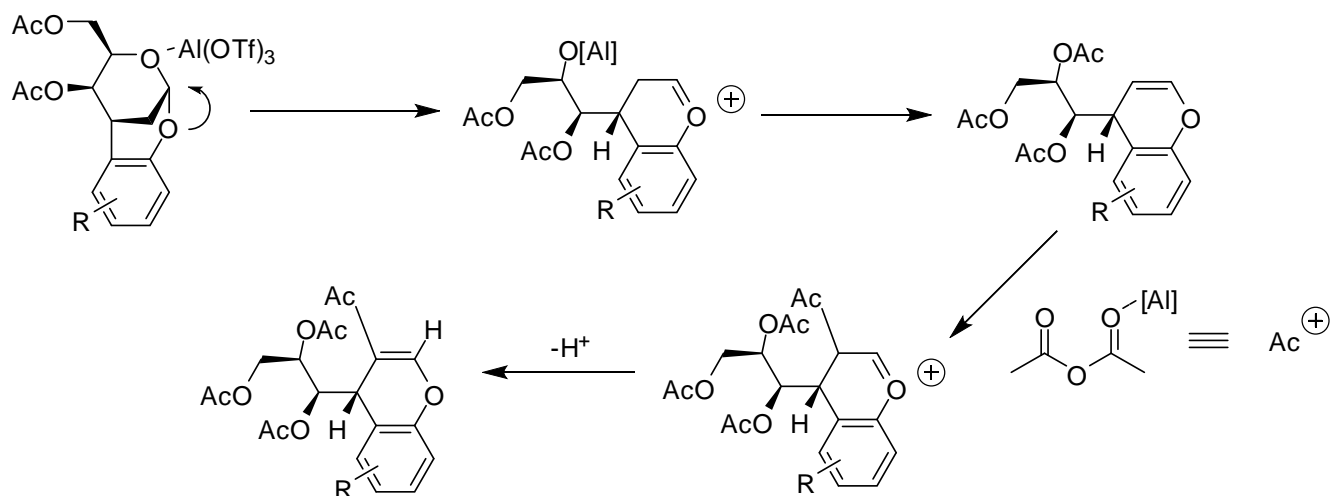


Figure 2.4. ORTEP diagram for chromene **2.28**

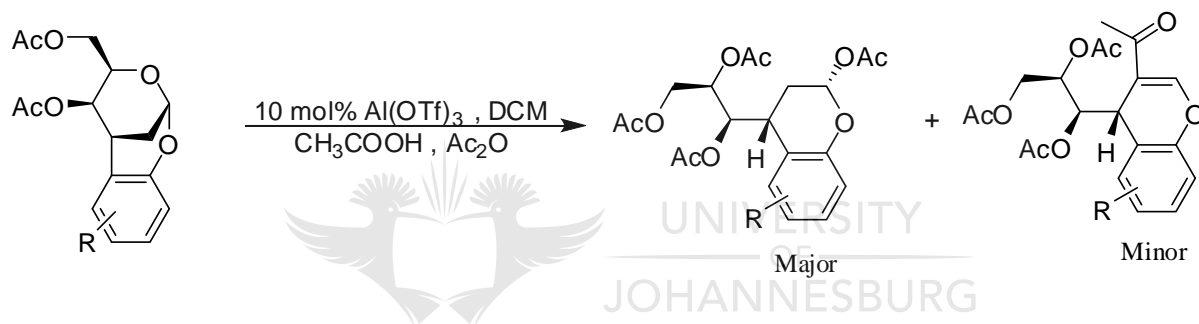
The mechanism of the reaction is proposed to proceed via the initial coordination of $\text{Al}(\text{OTf})_3$ on the hard oxygen of the ring system (Scheme 2.14). According to Pearson's hard-soft acid-base concept, $\text{Al}(\text{OTf})_3$ is a hard acid. Anchimeric assistance from the softer benzylic oxygen atom yields an oxocarbenium ion which rearranges to a $4H$ -chromene. Aluminium triflate is also proposed to activate the acetic anhydride, which acylates the chromene, eventually leading to the isolated keto product. An alternative, possibly more plausible mechanism is that the ring oxygen atom is acetylated during the ring-opening step by electrophilic attack of an Al-activated Ac_2O species, to produce the oxocarbenium cation. Thereafter, the mechanism is proposed to follow the same pathway described above.



Scheme 2.14. Proposed mechanism for synthesis of $4H$ -chromenes

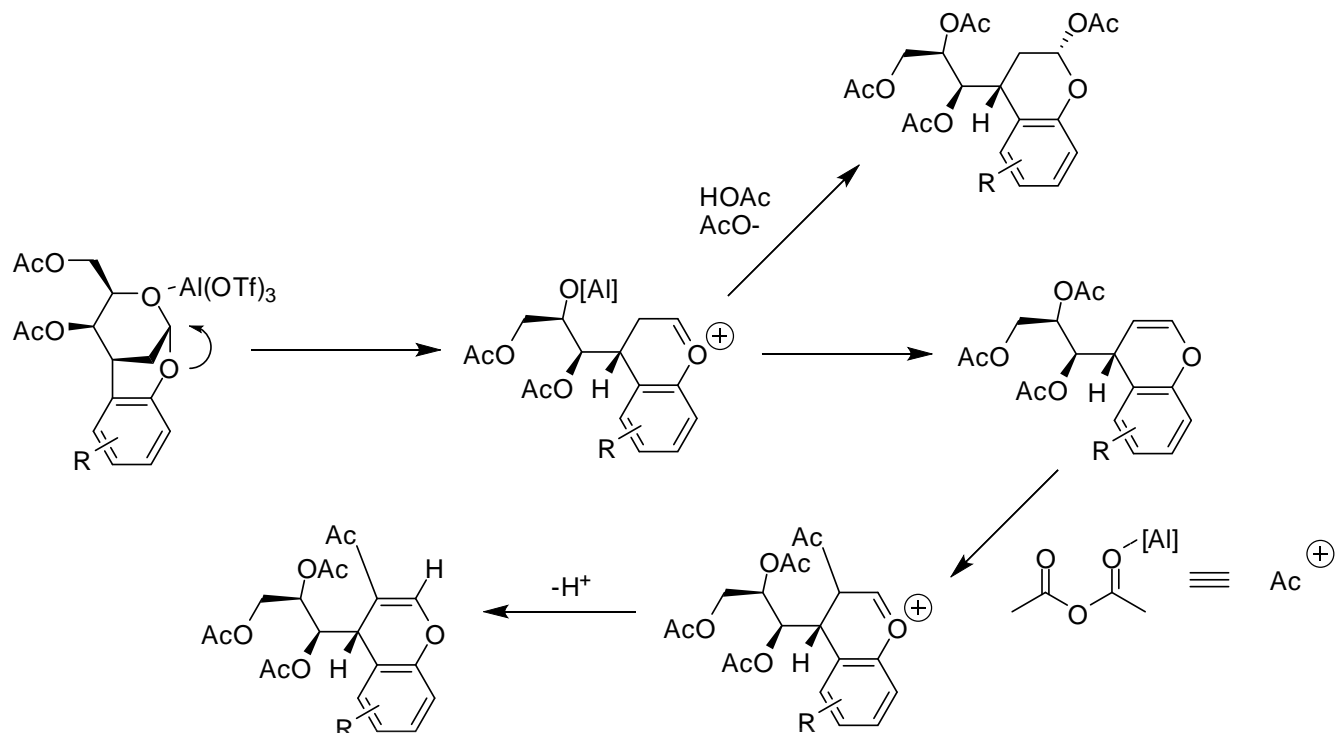
2.5.2 Ring-opening towards chromans

Chromans are another group of benzopyrans, structurally similar to chromenes, but with a saturated pyranose ring. The chroman moiety is also found in many natural products, a well-known example being vitamin E.²⁰ The synthesis of chromans was achieved in the present study by using equal volumes of acetic acid and acetic anhydride in dichloromethane, with 10 mol% of aluminium triflate as a catalyst (Scheme 2.15). The reaction did not proceed in the absence of either acetic anhydride or aluminium triflate, and only starting material was recovered in such instances. This means that both substances were essential for the ring opening to occur and the acetic acid creates a preference for whether a chromene or chroman is the major product.



Scheme 2.15. Synthesis of chromans

A plausible mechanism proceeds with initial coordination of aluminium triflate to the hard oxygen of the pyranose ring. Anchimeric assistance from the softer benzylic position oxygen atom produces the anticipated oxocarbenium ion intermediate. Alternatively, the aluminium centre binds to the Ac₂O and generates an activated electrophile, which initiates ring-opening and concomitant acetylation of the ring oxygen atom. The oxocarbenium intermediate is then subject to nucleophilic attack by the acetoxy group resident on the aluminium triflate and possibly from acetic acid to give the chroman (Scheme 2.16). The reaction also proceeds as explained previously to give the chromenes as minor by-products.



Scheme 2.16. Proposed mechanism for synthesis of chromenes and chromans

The optimised conditions for the ring-opening of the bridged chiral benzopyrans towards the formation of chromans were 2 mL acetic anhydride, 2 mL acetic acid, 2 mL dichloromethane and 10 mol% $\text{Al}(\text{OTf})_3$ for 200 mg of substrate.

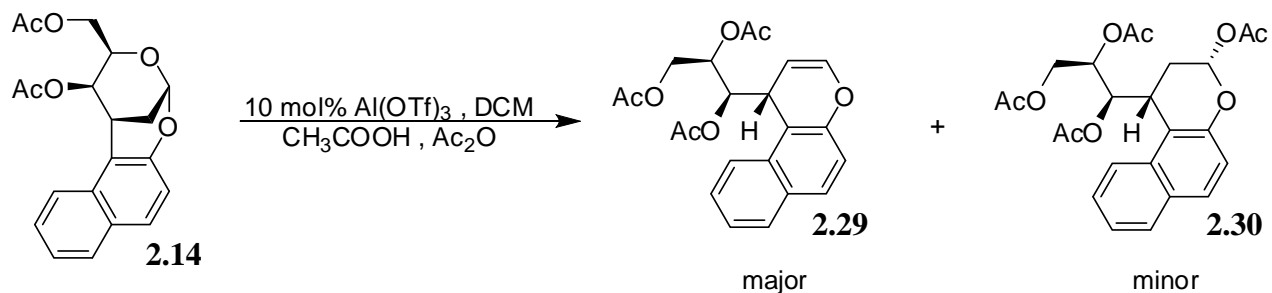
The chromans were recovered in acceptable yields, when considering that the chromenes also formed as minor by-products. The ring-opening protocol proved to be applicable to the synthesis of most benzopyrans (Table 2.8). An exception was found with the benzopyran bearing the naphthalene derivative, which gave the *4H*-chromene product as the major and the chroman as a minor product (Scheme 2.17), regardless of the reaction conditions.

Table 2.8. Synthesis of chiral galactose-based chromanes using $\text{Al}(\text{OTf})_3$ ^{a,b}

Entry	Substrate	Product	Yield (%)	$[\alpha]_D$
1			31 (minor)	-38.9°
2			63	-22.6°
3			67	-18.8°
4			58	-11.1°
5			66	-18.3°

^a200 mg of substrate, 10 mol % $\text{Al}(\text{OTf})_3$, 2 mL DCM, 2 mL Ac_2O , 2 mL AcOH , rt

^bSpecific rotation was measured at (c 0.5, CH_2Cl_2)



Scheme 2.17. Ring-opening of bridged chiral benzopyran **2.14**

The ^1H NMR spectrum of **2.30** presented an interesting phenomenon. While acetates typically resonate around 1.9-2.3 ppm, the acetate at C-4 resonated in the unusually highfield region of 1.23 ppm. This is likely due to the methyl moiety of the acetate falling within the shielding influence of the aromatic rings of the naphthalene residue. This is evident in the ORTEP diagram of **2.30** in Figure 2.5, where it can be seen that, in the solid state, the acetate lies over the naphthalene bicyclic structure and should thus experience NMR shielding. Also the anomeric proton, a doublet at 6.59 ppm, is a strongly deshielded acetal proton and this may be due to the electron withdrawing nature of the anomeric acetate and the ring oxygen depriving the anomeric proton of electron density. The coupling constant $J_{\text{H1-H2}} = 2.8$ Hz, which is characteristic of axial-equatorial and equatorial-equatorial interactions, means the acetate at the anomeric position is axially oriented. The four signals at around 170 ppm on the ^{13}C NMR spectrum are evidence of the presence of carbonyl groups and this is further confirmed by the strong absorbance at about 1730 cm^{-1} in the infrared spectrum, which is typical of esters. From the DEPT spectrum there are two CH_2 groups observed corresponding to C-2 and C-6 and this confirms that the pyranose ring bears no *endo* double bond, save being fused to the naphthalene ring.

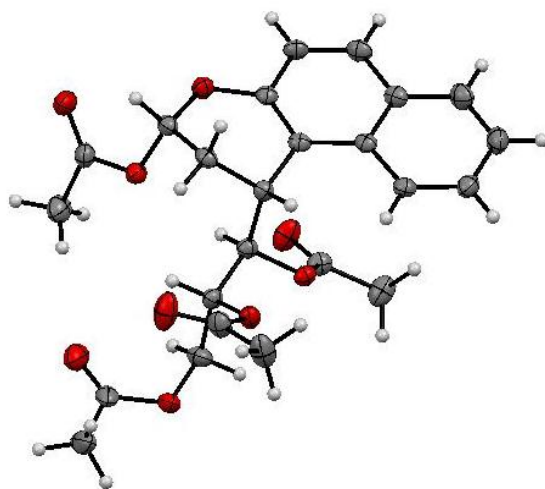


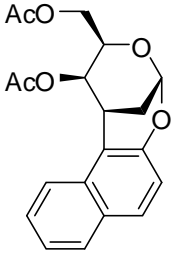
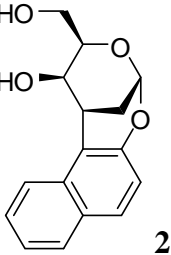
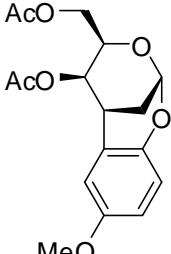
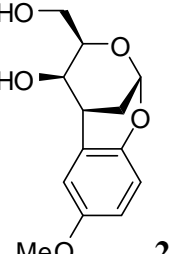
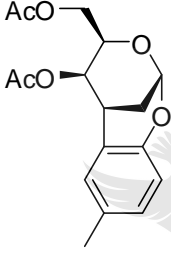
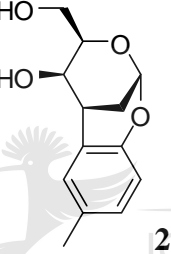
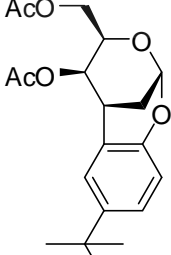
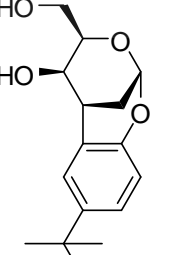
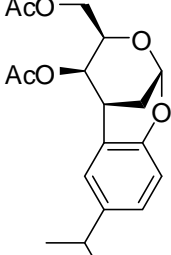
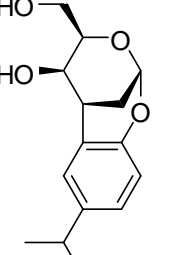
Figure 2.5. ORTEP diagram for chroman **2.30**

2.6 Deacetylation of chiral benzopyrans

The benzopyran scaffolds (including the bridged chiral benzopyrans, chromans and the chromenes), also known as ‘privileged structures’, were de-protected of their acetate groups. They were de-acetylated by stirring the benzopyran in a solution of methanol, triethyl amine and water (2:1:1), as discussed by Meier *et al.*²¹ This deprotection mechanism is consistent with that discussed by Marlier and co-workers for the alkaline hydrolysis of carboxylic esters.²²

The outcomes of the de-acetylation reactions of the bridged chiral benzopyrans are shown in Table 2.9. The observation of a more polar spot on the TLC plate as well as the disappearance of upfield methyl signals in the ^1H NMR spectrum and downfield carbonyl signals in the ^{13}C NMR spectrum gave evidence for the removal of the acetates.

Table 2.9. De-acetylation of bridged chiral benzopyrans^{a,b}

Entry	Substrate	Product	Yield (%)	$[\alpha]_D$
1		 2.35	92	-21.2°
2		 2.36	98	-31.2°
3		 2.37	94	-41.0°
4		 2.38	97	-28.2°
5		 2.39	93	-41.0°

^a200 mg of substrate, 2 mL of MeOH, 1 mL Et₃N, 1 mL H₂O, rt

^bSpecific rotation was measured at (*c* 0.5, MeOH)

The same reaction conditions were employed for the de-acetylation of chromans and the results are shown in Table 2.10.

Table 2.10. De-acetylation of chiral galactose-based chromans^{a,b}

Entry	Substrate	Product	Yield (%)	$[\alpha]_D$
1			86	-1.8°
2			92	-2.1°
3			88	-8.3°
4			90	-10.4°
5			93	-7.6°

^a200 mg of substrate, 2 mL of MeOH, 1 mL Et₃N, 1 mL H₂O, rt

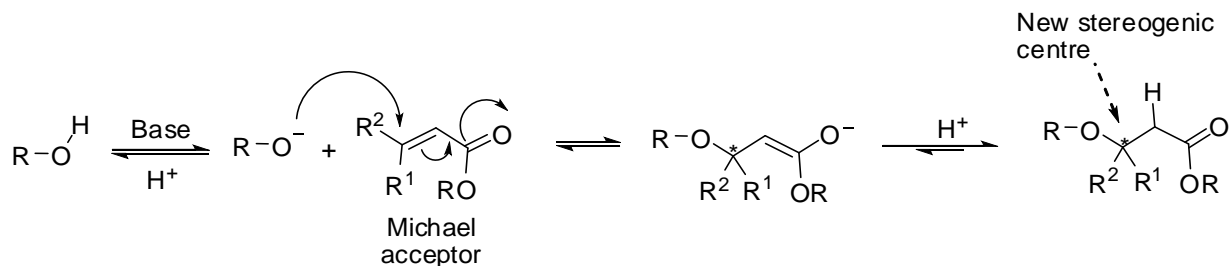
^bSpecific rotation was measured at (c 0.5, MeOH)

Again TLC monitoring was used to track progress of the reactions, and NMR spectroscopy was employed to identify the products of the de-acetylation reaction. Moreover, infrared spectroscopy was employed and the absorbance of the hydroxyl functions at around 3500 cm^{-1} was observed. No absorbance was observed around the ester region 1750 cm^{-1} that would normally be expected if esters are present. Attempts to de-acetylate chromenes of the form **2.25** as shown in Table 2.7 yielded rather unexpected products which are a result of intramolecular oxa-Michael addition and that chemistry is discussed in detail in the next section.

2.7. Intramolecular oxa-Michael addition

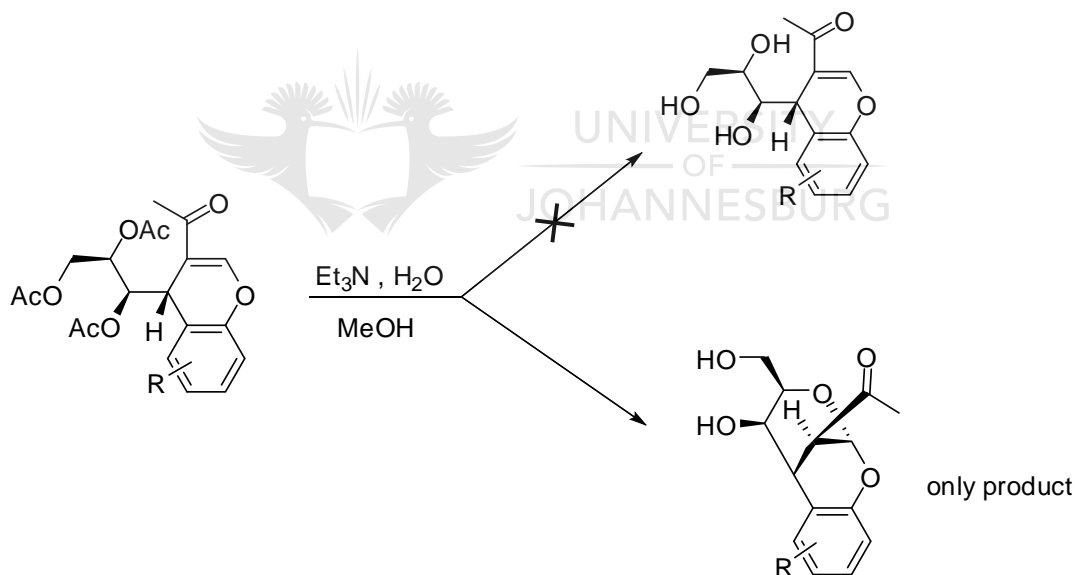
An oxa-Michael addition is the addition of oxygen nucleophiles to conjugate acceptor systems. Though reported earlier than the Michael addition by Loydl *et al.*²³ in 1878, this reaction is less popular than the addition of carbon nucleophiles to conjugated acceptor systems (Michael addition). This is mainly due to the fact that the oxa-Michael addition suffers from drawbacks such as low reactivity, reversibility problems as well as lack of control in stereoselectivity.²⁴ Two major approaches to substrate activation have been employed to effect this reaction, i.e. selected bases for the deprotonation of alcohols thereby enhancing their nucleophilicity, as well as Brønsted and Lewis acids for the activation of the conjugate acceptor.

Interestingly the addition of alcohols leads to intermediate enolates which could then serve as starting materials for further reactions (domino reactions)²⁵ or be protonated to give β -hydroxy carbonyl compounds.²⁶ The general mechanism for a base-catalysed oxa-Michael addition is shown in Scheme 2.18. This reaction has been used a number of times to provide access to natural products, an example being the quinine catalysed intramolecular oxa-Michael addition towards the synthesis of (+) calanolide A.²⁷



Scheme 2.18. General mechanism for oxa-Michael addition

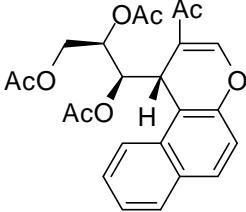
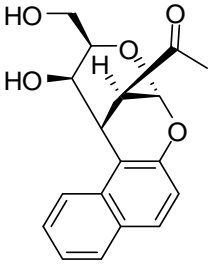
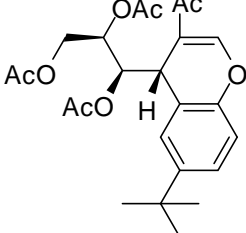
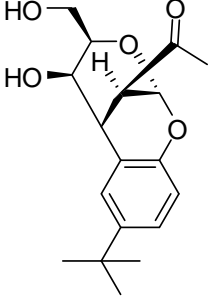
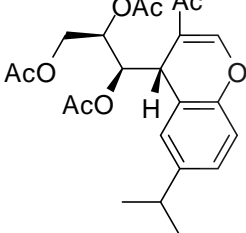
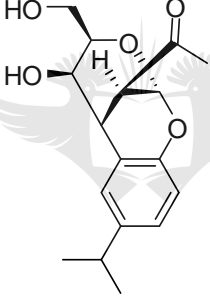
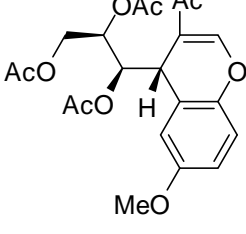
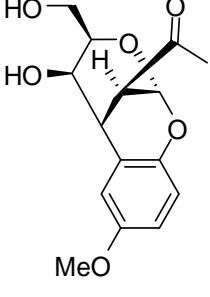
In the current discussion, galactose-derived chromenes were subjected to de-acetylation reactions in the presence of triethyl amine, methanol and water. Surprisingly, the expected product (triol) was not isolated, but upon further scrutiny it was realised that the product obtained was the result of an intramolecular oxa-Michael addition (Scheme 2.19).



Scheme 2.19. De-acetylation of chromenes

The chromenes were all converted into the chiral benzopyrans under the reaction conditions employed for de-acetylation (Et_3N , MeOH and H_2O). High yields were achieved in just 24 hours at room temperature and the results are shown in Table 2.11.

Table 2.11. De-acetylation of chiral galactose-based chromenes^{a,b}

substrate	Product	Yield (%)	$[\alpha]_D$
	 2.45	96	-1.8°
	 2.46	94	-8.9°
	 2.47	92	-10.9°
	 2.48	95	-2.8°

^a200 mg of substrate, 2 mL of MeOH, 1 mL Et₃N, 1 mL H₂O, rt

^bSpecific rotation was measured at (c 0.5, MeOH)

The appearance of only one methyl signal upfield in the NMR spectrum of the product **2.45** was an indication of a successful de-acetylation. However, a significant shift on the ‘anomeric proton’ from around 7.8 ppm in the starting material to around 5.9 ppm in the product was evidence that

de-acetylation was not the only reaction to take place. Upon closer scrutiny of the NMR spectra, it was evident that the product was a bridged chiral benzopyran (as shown in Table 2.11). The carbonyl carbon of the acetyl resonated around 207 ppm which is downfield compared to that of esters (170 ppm) and is more typical of ketone functionality. This shift is also downfield of the vinylogous ester in the substrate, where the carbonyl resonance was observed at 194 ppm. Also the presence of the hydroxyl functionality was confirmed using infrared spectroscopy, where the $-OH$ stretching bands were observed at around 3500 cm^{-1} . Single crystals of benzopyran **2.45** were grown and the ORTEP diagram is shown in Figure 2.6. This structure determination unambiguously demonstrated that the product was consistent with a deprotection/oxa-Michael set of reactions.

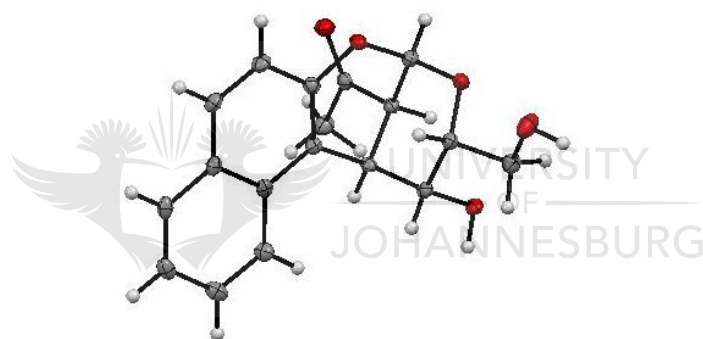
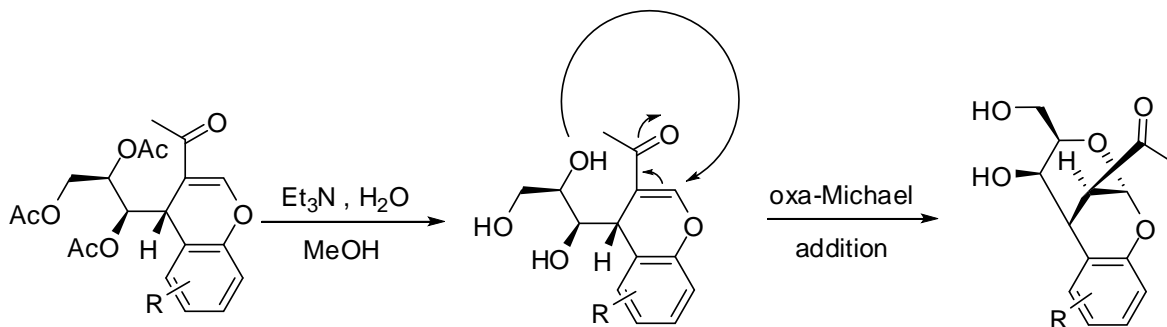


Figure 2.6. ORTEP diagram of benzopyran **2.45**

The mechanism of the reaction is proposed to proceed *via* the initial de-acetylation of the chromene as shown in Scheme 2.20. The triol intermediate undergoes an intramolecular oxa-Michael reaction to give the bridged chiral benzopyran. Though primary hydroxyl functions are known to be more reactive than secondary alcohols, the product is a result of nucleophilic attack by the secondary hydroxyl function at C-5 of the dangling arm on the starting material, showing a preference for the formation of the six-membered ring. This observation is explained in more detail in the next chapter.



Scheme 2.20. Mechanism for oxa-Michael addition

2.8 Conclusion

Aluminium triflate has been found to be a versatile catalyst in the synthesis of *O*-aryl-2-deoxy galactosides from 3,4,6-*tri-O*-acetyl-D-galactal. Phenols bearing nitrogen substituents did not glycosylate with the galactal glycosyl donor. Also, in the ‘Fischer-Zach’ synthesis of the 3,4,6-*tri-O*-acetyl-D-galactal, $\text{Al}(\text{OTf})_3$ was used as the Lewis acid catalyst for the acetylation of D-galactose. The catalyst also demonstrated its versatility in the temperature-controlled synthesis of bridged chiral benzopyrans. A range of activated phenols that were employed as glycosyl acceptors in the synthesis of *O*-aryl-2-deoxy galactosides were also used to achieve formation of the bridged chiral benzopyrans by merely increasing the temperature from 0 °C to 40 °C and keeping all other reaction conditions constant.

The bridged chiral benzopyrans could be ring-opened *via* acetolysis using aluminium triflate as the Lewis acid catalyst. This ring-opening would be selectively manipulated to yield either chromenes (by using only acetic anhydride) or chromans (by using a mixture of acetic acid and acetic anhydride). These galactal-derived chromenes and chromans together with the bridged chiral benzopyrans were de-acetylated *via* triethyl amine catalysed transesterification in aqueous methanol. Interestingly the chromenes yielded a new set of bridged chiral benzopyrans as a result of intramolecular oxa-Michael addition.

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Chapter 3

Synthesis of a galactose-based oxepane

3.1 Introduction

An oxepane is a saturated heterocyclic ether with six carbon atoms. Other members of saturated oxygen-containing heterocycles include; oxirane (2 carbon atoms), oxetane (3 carbon atoms), tetrahydrofuran (4 carbon atoms), tetrahydropyran (5C), oxepane (6C), oxocane (7C), oxonane (8C), etc. Cyclic ethers, including oxepanes, are found in both natural products and designed target molecules such as heliannol B and C (allelopathic and phytotoxic), sodwanone S (antitumour) and zoapatanol (contraceptive).¹ Artemisinin,² shown in Figure 3.1 is a potent antimalarial drug that bears the oxepane scaffold. The synthesis of seven membered ring ethers (oxepanes) and medium ring ethers has been a challenging endeavour due to the unfavourable enthalpic and entropic factors which make it difficult to employ traditional methods of ring formation.³

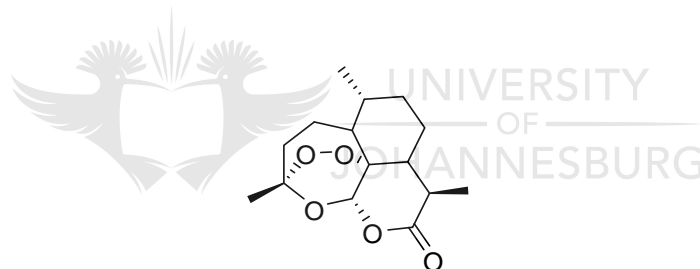


Figure 3.1. Diagram of artemisinin

Galactose-derived oxepanes (heptanosides) have been previously synthesised by employing cyclopropanated sugars.⁴ One other classical method employed for the synthesis of oxepanes and other medium ring ethers is ring closing metathesis (RCM).⁵ These protocols result in the formation of an alkene moiety which requires hydrogenation to afford the desired oxepane. Previous experience in our group with aluminium triflate has shown that this versatile catalyst promotes *O*-glycosidation.⁶ Hence, it was envisaged that it can be employed in intramolecular *O*-glycosidation chemistry towards the synthesis of an oxepane from a galactose-based chromene. Though benzoxepanes are known,⁷ oxepanes fused to the ‘privileged’ benzopyran scaffold have not been observed.

3.2 Oxepane synthesis

Acetolysis of the bridged chiral benzopyran derived from 2-naphthol (**2.14**, see Chapter 2) using a mixture of acetic acid and acetic anhydride had yielded the chromene (**2.29**) in 67% yield (Chapter 2). The ORTEP diagram based on a single-crystal X-ray structure determination is shown in Figure 3.2. This chromene was considered to be as a good building block for the synthesis of the desired oxepane. It was ought to de-acetylate the chromene and attempt to cyclise the resulting triol using the already developed method of aluminium triflate *O*-glycosidation⁶ to achieve the synthesis of the oxepane. When this work was started, it was not known that this would prove to be a long road to success.

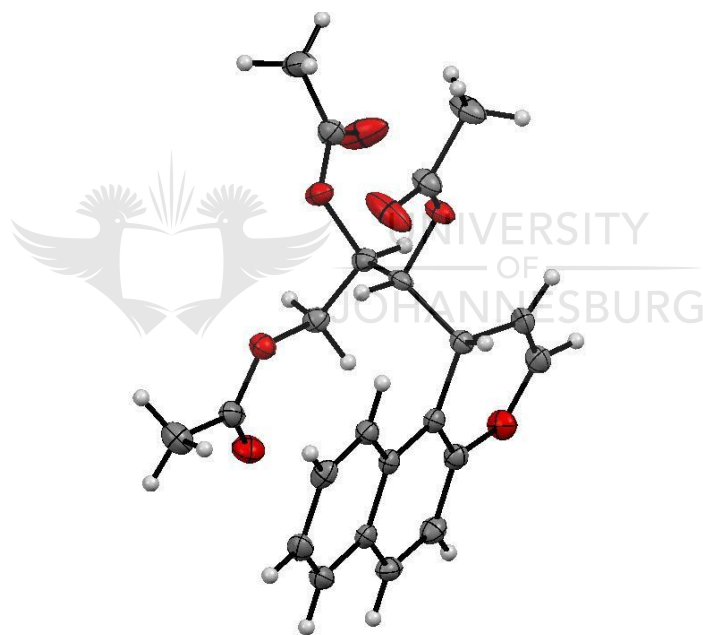
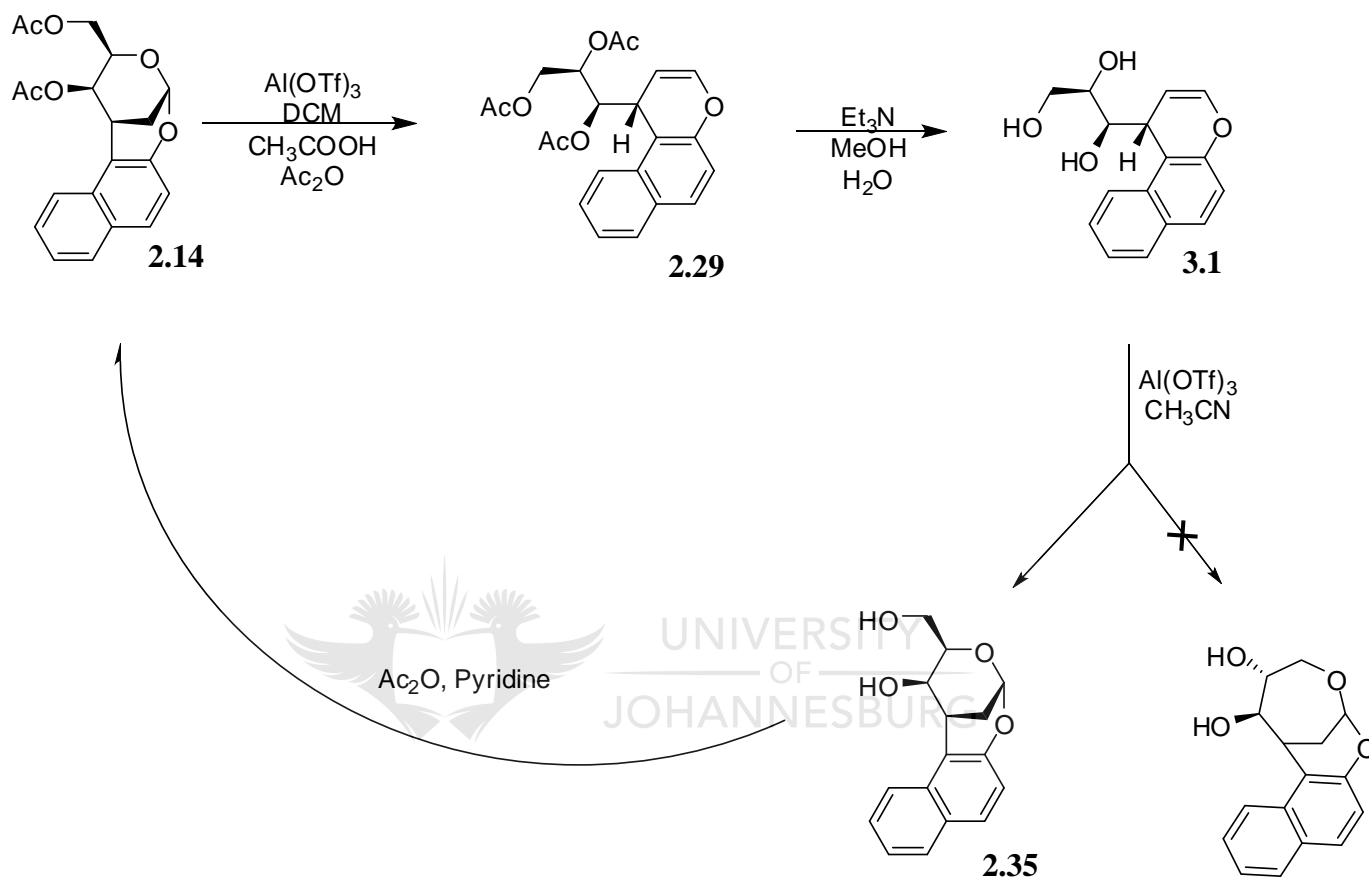


Figure 3.2. ORTEP diagram for chromene **2.29**

The solvent used was acetonitrile on account of the solubility profile of the substrate. Reaction of the triol in the presence of $\text{Al}(\text{OTf})_3$ facilitated intramolecular *O*-glycosidation, but cyclisation afforded the more preferred pyranose ring⁸ as opposed to the 7-membered ring oxepane as shown in Scheme 3.1. This was confirmed by acetylation of the diol product (**2.35**) and comparing the

NMR data of the resulting product to that of the bridged chiral benzopyran starting material (2.14).



Scheme 3.1. Attempted protecting group-free synthesis of an oxepane

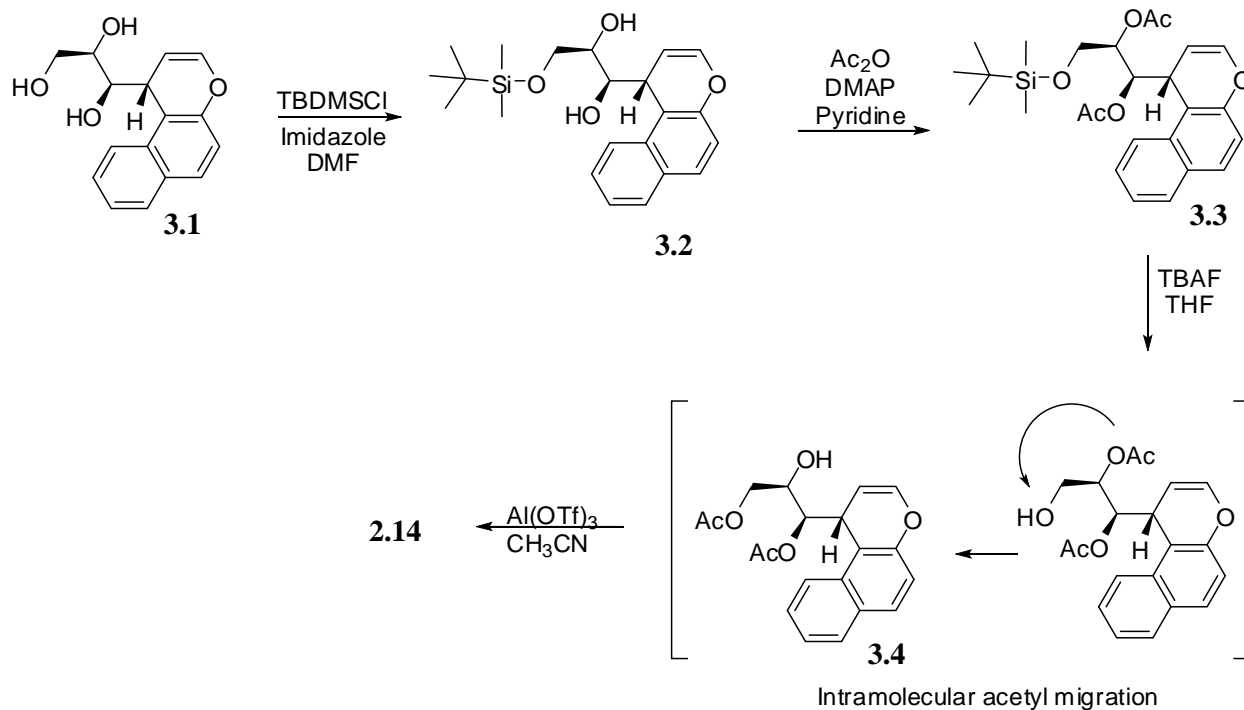
Primary hydroxyl groups are known to be more reactive than secondary alcohols and the hope was that the primary hydroxyl function on the chromene dangling arm would react ahead of the secondary alcohols to yield the oxepane. However, this was clearly not the case. According to Baldwin's rules for ring closure, if the carbon undergoing ring closure is sp^2 hybridised and the breaking bond is within the newly formed 6-membered ring (6-*Endo*-Trig), the reaction is favoured.⁹ A 7-*Endo*-Trig cyclisation is also favourable, but a 6-membered ring is more stable than a 7-membered ring. To substantiate these postulates a Density Functional Theory (DFT

B3LYP) computational method was employed to calculate the relative energies of the constitutional isomers that ‘could’ have formed as a result of the intramolecular *O*-glycosidation. The basis set chosen was 6-31+g (d,p). In studies using B3LYP, it has been shown¹⁰ that for relatively simple structures such as those of this study and with rather simple basis sets, a high level of accuracy is obtained, similar to those of much larger Dunning-type basis sets such as cc-pVDZ, cc-pVTz, aug-cc-pVDZ, and aug-cc-pVTZT.¹⁰

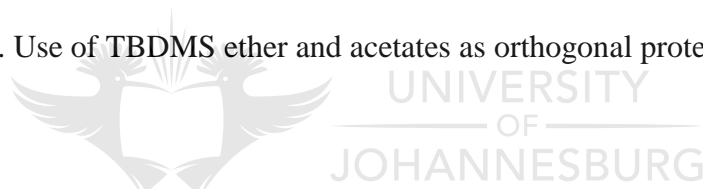
The relative energies were used to establish the most thermodynamically stable isomer which the triol would prefer to cyclise towards. The relative energy calculation for the bridged chiral benzopyran **2.35** and its 7-membered ring isomer showed the latter to be less stable by about 8 kJ/mol. This is not a significant difference,¹¹ but the combination of kinetic preference and thermodynamic stability dominated OH reactivity differences, proving sufficient to drive the cyclisation towards the preferred lower energy product. The next option was to use orthogonal protecting groups which would mask the secondary alcohols but provide a free primary hydroxyl function which would then cyclise to give the desired oxepane. These endeavours are detailed below.

3.2.1 Use of acetates and silyl ethers as orthogonal protecting groups

Acetates have gained popularity to mask hydroxyl groups in sugars by conversion into their corresponding esters, due to the ease of installation and removal.¹² The same applies with silyl ethers, but the bulky ones also boast the ability to selectively protect a primary hydroxyl group ahead of secondary alcohols. Moreover, silyl ethers can be selectively deprotected by employing fluoride sources, for example.¹² A very common silyl ether is the *tert*-butyldimethylsilyl ether (TBS) group. In the present case TBDMS-chloride was used in DMF for selective protection of the primary hydroxyl group using imidazole as a promoter and base to neutralise the HCl produced (Scheme 3.2).



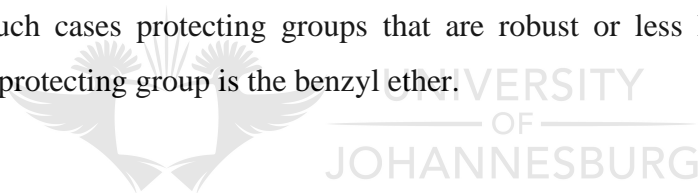
Scheme 3.2. Use of TBDMS ether and acetates as orthogonal protecting groups



The successful installation of the silyl ether was observed in the proton NMR spectra of the compound where the *tert*-butyl group was observed to resonate at 0.71 ppm as a singlet integrating for 9 protons. The two methyl groups covalently bonded to the silicon also resonate as singlets at -0.13 ppm and -0.21 ppm. Interestingly, the signals are split and this is likely due to their intrinsic diastereotopic relationship. The diol **3.2** was acetylated using acetic anhydride in pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP). NMR spectroscopy was used to confirm the identity and purity of the product after flash chromatography. Selective deprotection of the chromene **3.3** of its TBDMS group to give a free hydroxyl function was achieved by stirring the chromene in a solution of tertiary butyl ammonium fluoride (TBAF) and tetrahydrofuran (THF). The TLC plate showed the formation of a much more polar product compared to the starting material and ^1H NMR spectrum of the crude reaction mixture showed the disappearance of the signals corresponding to the TBDMS group. This compound was subjected to intramolecular *O*-glycosidation conditions in the presence of Al(OTf)_3 as discussed

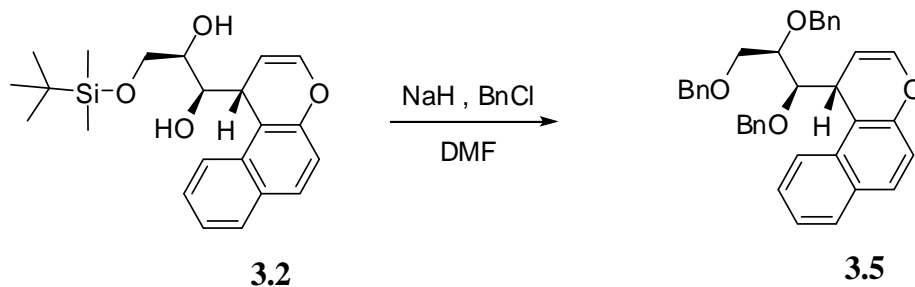
in the previous section. The NMR spectra of the product to those of the bridged chiral benzopyran **2.14** were superimposable.

Closer scrutiny of the NMR spectra of chromene **3.4** revealed that there was acetyl migration from C-5 to C-6. This unwanted migration completely removed any chance of obtaining the oxepane, instead promoting formation of the unwanted cyclisation product **2.14**. This was confirmed using both 1D and 2D NMR spectroscopy. The H-6 protons of chromene **3.4** were deshielded to around 4.0 ppm by the electron-withdrawing acetates as compared to the starting material where they resonate around 3.4 ppm due to the shielding experienced from the silicon. The H-5 proton was shielded from 4.5 ppm to 4.2 ppm after being freed from the acetate. More directly in the HMBC spectrum of **3.4**, the H-4 and H-6 protons show correlations to the carbonyl carbons of the acetates while H-5 does not, indicating that the hydroxyl group at C-5 is free of acetates. Migration of acetates from secondary to primary positions is known in organic synthesis¹³ and in such cases protecting groups that are robust or less likely to migrate are employed. One such protecting group is the benzyl ether.



3.2.2 Use of benzyl and silyl ethers as orthogonal protecting groups

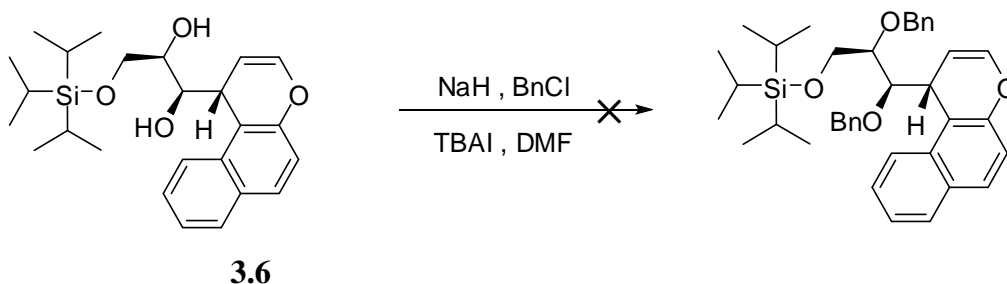
Benzyl ethers are quite useful in orthogonal protection of carbohydrate derivatives, mainly due to the fact that they are quite stable and can be selectively removed using catalytic hydrogenolysis, such as the use of palladium-charcoal (Pd-C, 10%) as a catalyst. Ethers, especially benzyl ethers, are less likely to migrate and hence were chosen to replace acetates as an orthogonal protecting group to the TBDMS group. The classical *Williamson ether synthesis*¹⁴ was employed for the benzylation of the diol **3.2** (Scheme 3.3).



Scheme 3.3. Williamson's benzylation of chromene **3.2**

The TBDMS group proved to be unstable under the strongly basic Williamson ether synthesis conditions; instead of obtaining a di-benzylated product a tri-benzylated product **3.5** was isolated. The stability of silyl ethers under basic conditions increases as follows: TMS < TES < TBDMS~TBDPS < TIPS with the TIPS being 100 000 times more stable than the TMS ethers.¹⁵

The TBDMS ethers were then substituted for triisopropyl silyl (TIPS) ethers on account of their enhanced stability under basic conditions. TIPSCl was used instead of TBDMSCl in DMF, again employing imidazole as promoter and base, and the primary hydroxyl group of triol **3.1** was selectively masked over the secondary alcohols to give **3.6**. Benzylation of the diol under a range of different conditions was unsuccessful (Scheme 3.4).



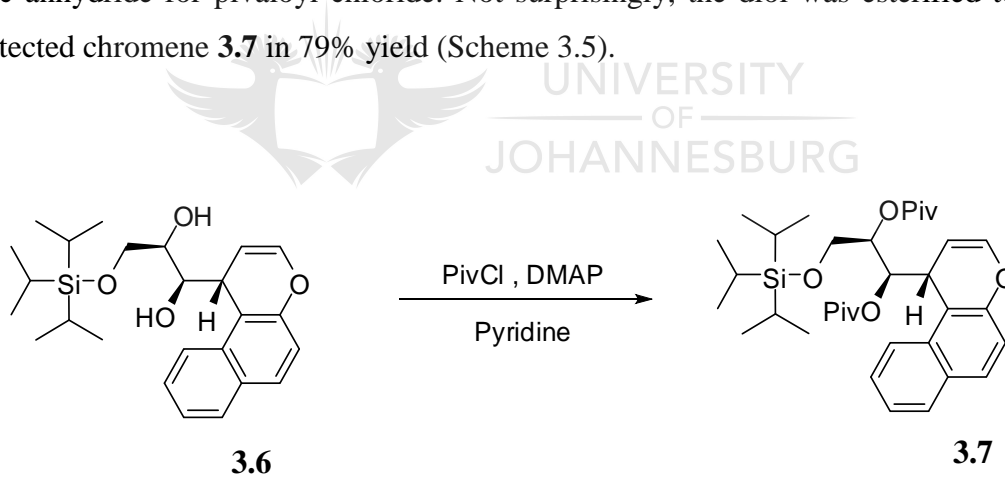
Scheme 3.4. Attempted benzylation of diol **3.6**

The TLC plate showed the formation of a less polar product with disappearance of the diol starting material **3.6**. However, numerous attempts to purify the resulting product of the reaction

using flash column chromatography were unsuccessful. Bulb-to-bulb distillation of the product under vacuum gave glassy crystals that did not dissolve in commonly used deuterated organic solvent such as CDCl_3 , methanol- d_4 , D_2O , DMSO, THF, $\text{C}_3\text{D}_6\text{O}$ and pyridine. It is possible that the product polymerised during the distillation, explaining the insolubility. An alternative orthogonal protecting group was thus to be employed to achieve the desired goal.

3.2.3 Use of pivaloates and silyl ethers as orthogonal protecting groups

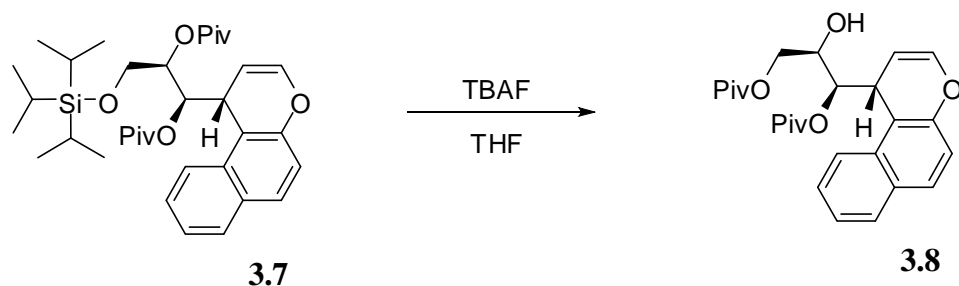
The sterically demanding 2,2-dimethylpropanoyl (pivaloyl) protecting group is substantially more stable than other acyl protecting groups and is normally employed when acyl migrations have to be avoided and also when carbohydrate derivatives are to be used as chiral auxiliaries.¹⁶ Pivaloates were thus chosen as the next orthogonal protecting group to the TIPS ether. The diol **3.6** was esterified using the same reaction conditions employed for acetylation, but substituting the acetic anhydride for pivaloyl chloride. Not surprisingly, the diol was esterified to give the fully protected chromene **3.7** in 79% yield (Scheme 3.5).



Scheme 3.5. Esterification of diol **3.6** using pivaloyl chloride

Next was the de-silylation of the fully protected chromene **3.7**, and this was done by stirring the chromene for 1 hour in a solution of TBAF and THF at ambient temperature. Formation of a more polar product than the starting material was observed by TLC analysis and ^1H NMR spectroscopy confirmed the removal of the TIPS group. However, closer scrutiny of the 1D and

2D NMR spectra indicated that there was acyl migration from C-5 to C-6 giving the resulting chromene **3.8** (Scheme 3.6).



Scheme 3.6. De-silylation of fully protected chromene **3.7**

The HMBC spectrum of chromene **3.7** clearly shows the H-4 and H-5 correlating to the carbonyls of the pivaloyl protecting group (Figure 3.3), as would be anticipated for such a structure.

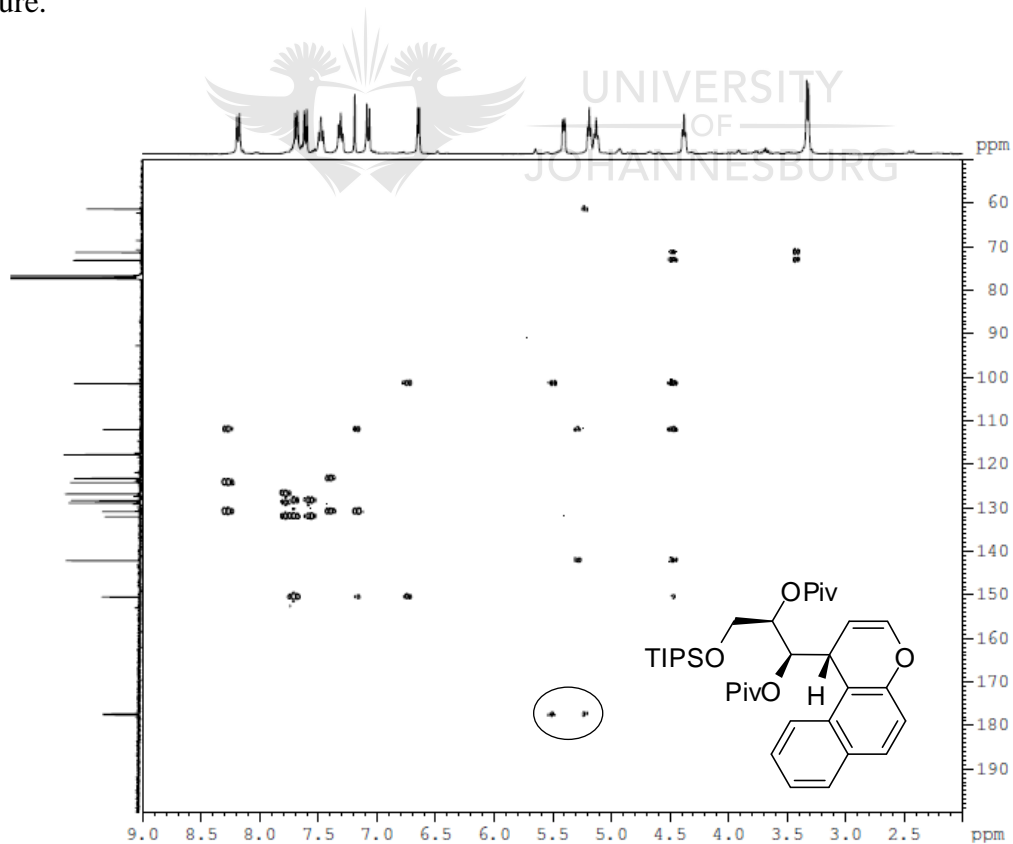


Figure 3.3. HMBC spectrum of chromene **3.7**

The H-6 protons (H_A and H_B) are clearly visible on the spectrum resonating as a doublet at 3.38 ppm and $J = 6.8$ Hz. H-4 and H-5 resonate downfield as a doublet and triplet respectively. Consider now the HMBC spectrum (Figure 3.4) of the deprotected chromene **3.8**; firstly, the H-6 protons are non-equivalent and split into two doublet of doublets and they are also de-shielded from 3.38 ppm in the starting material (**3.7**) to 3.80 ppm. Silicon has a lower electronegativity value ($EN = 1.9$) compared to that of hydrogen ($EN = 2.1$) and this might explain the downfield shift which is rather large. Secondly, the H-5 proton was also shielded from 5.18 ppm to 4.01 ppm in the deprotected chromene **3.8**. Lastly and more directly, the H-4 and the H-6 signals correlate to the carbonyl carbon signals of the pivaloyl protecting groups, providing a direct indication that the oxygen atoms attached to those carbon centres are esterified.

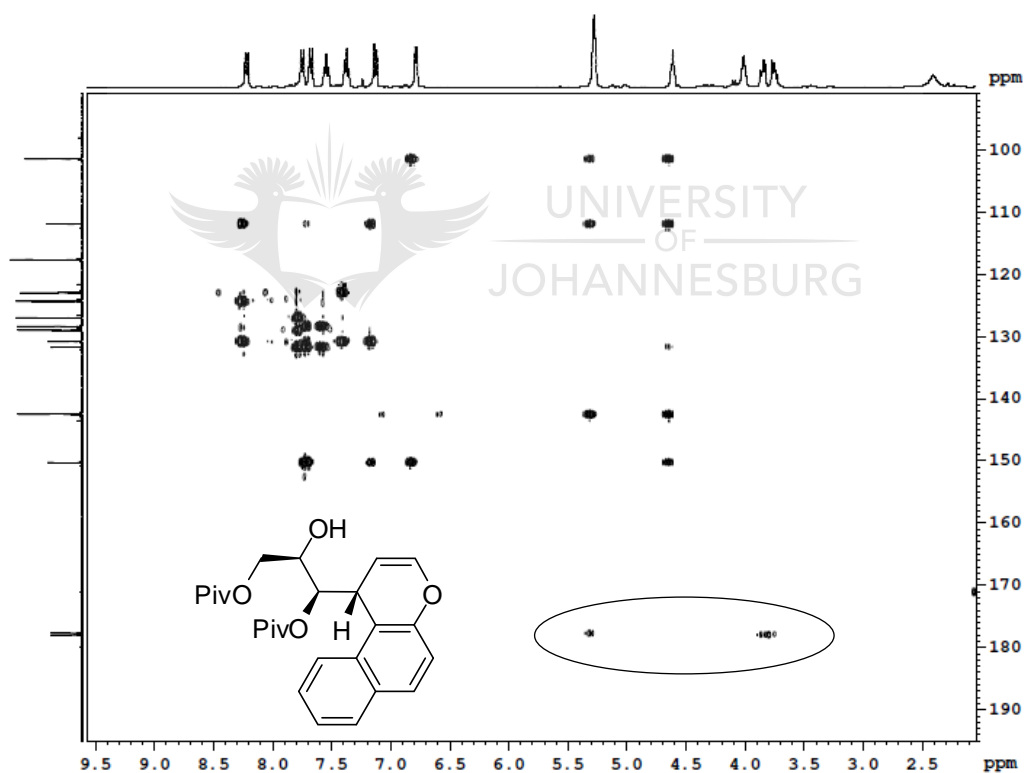
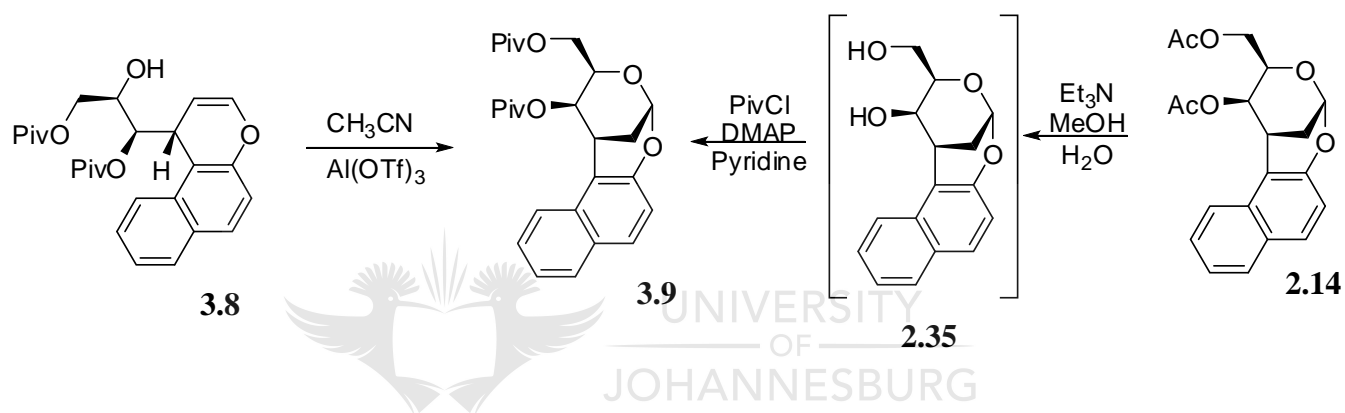


Figure 3.4. HMBC spectrum of de-silylated chromene **3.8**

The de-silylated chromene **3.8** was, however, subjected to ring closure conditions which proceeded successfully as shown in Scheme 3.7 (**3.8** provides **3.9**). It would be useful to effect a direct comparison of spectral data of the product with an authentic samples of the pivaloylated benzopyran. To this end, the bridged chiral benzopyran **2.14** was deprotected and the resulting diol was subsequently protected with pivaloyl groups. The NMR spectra of the two (cyclised product and protected product) compounds were identical in all respects. Single crystals were grown from product synthesised by each route and the ORTEP diagrams of both compounds were identical.



Scheme 3.7. Synthesis and comparing of cyclisation and protected products

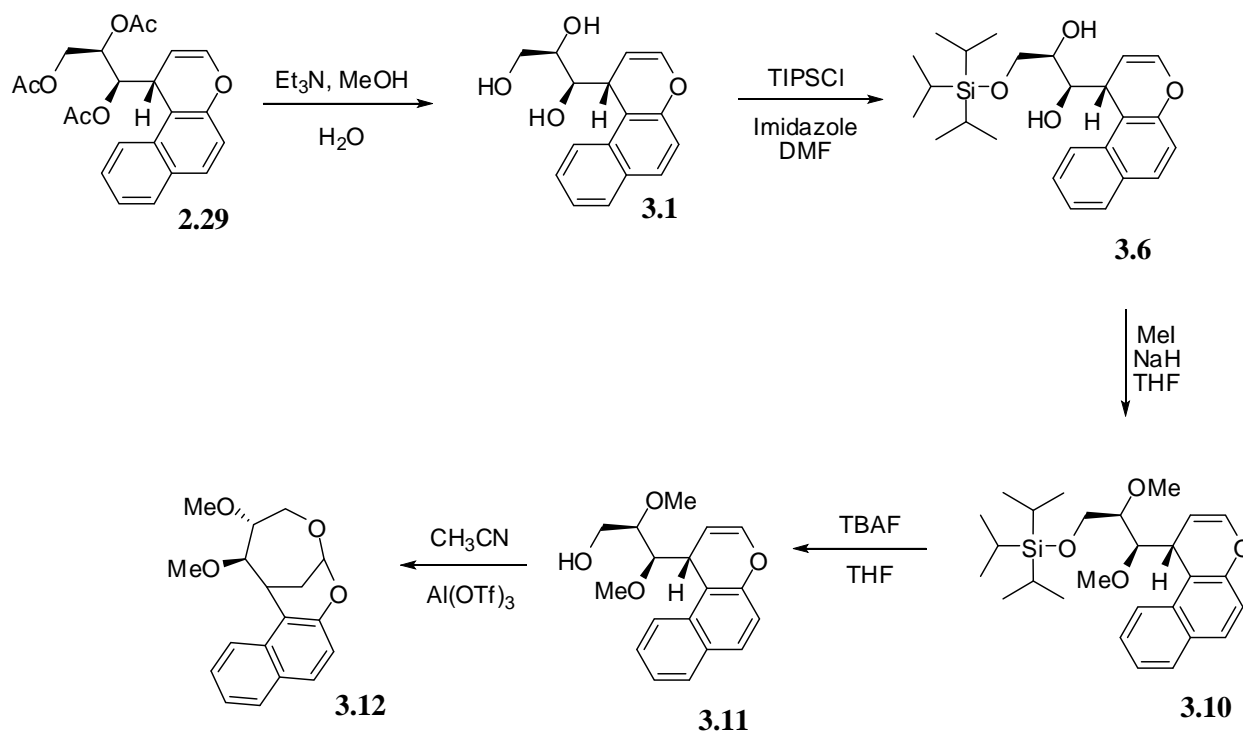
Clearly acyl protecting groups failed as orthogonal protecting groups due to acyl migration, even those known to be less prone to this issue. There was no choice but to revert back to ethers as protecting groups, even though benzyl ethers gave problems with purification amongst others. Ethers vary from the simple stable methyl ether to the more elaborate, substituted trityl ethers.¹⁷

3.2.4 Use of methyl and silyl ethers as orthogonal protecting groups

Methyl ethers are not ideal protecting groups for temporal masking of hydroxyl functions because of their high stability and the harsh reaction conditions required to cleave them.¹⁸ Methyl ethers are therefore hardly used as removable protecting groups (more common in

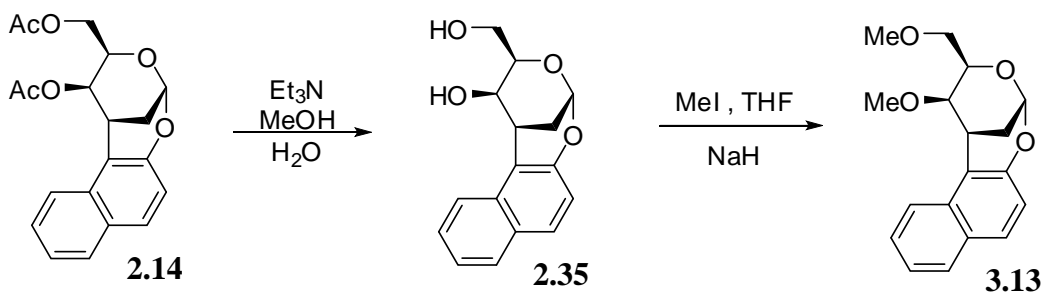
aromatic chemistry), but mostly for polysaccharide analysis.¹⁹ However, the elusiveness of the oxepane propelled the idea of using the methyl ethers on account of their stability. At this stage, it became important to consider demonstrating the proof of concept of being able to produce oxepanes using this type of chemistry.

When substituting the pivaloates for methyl ethers, the chromene diol **3.6** was methylated using iodomethane and sodium hydride in THF. The presence of methoxy groups in the product **3.10** was clearly evident in the ¹H NMR spectrum of the product, with distinct singlets resonating at 3.47 ppm and 3.06 ppm, both integrating for 3 protons. The resulting fully protected chromene **3.10** was successfully deprotected under the same reaction conditions as in previous cases (TBAF and THF) to give the free primary hydroxyl function in chromene **3.11**. Methyl ethers are quite stable and no known methyl migrations from secondary to primary hydroxyl functions have been reported; hence no migrations were anticipated under the cyclisation reaction conditions. Also, when comparing the NMR spectra of the starting material **3.10** and those of the product **3.11**, no significant shifts were observed with both H-4 and H-5 and not surprisingly also with signals ascribed to the H-6 protons. The chromene **3.11** was then subjected to ring closing conditions in the presence of Al(OTf)₃. Gratifyingly, and the galactose-derived oxepane was isolated in 88% yield. The overall yield for the oxepane synthesis from 3,4,6-*tri-O*-acetyl-D-galactal over 7-steps was 31%.



Scheme 3.8. Synthesis of D-(+)-galactose derived oxepane

The oxepane **3.12** was also compared to its 6-membered ring constitutional isomer. To do this, the bridged chiral benzopyran **2.14** was de-acetylated using triethyl amine in aqueous methanol (Scheme 3.9) and the resulting diol **2.35** was methylated using iodomethane and sodium hydride in THF. The bridged chiral benzopyran **3.13**, a constitutional isomer to the oxepane **3.12**, was isolated in a yield of 82%. More importantly, when comparing the NMR spectra of the two isomers, it was clear that they are quite distinct, as shown in Figures 3.5 and 3.6.



Scheme 3.9. Two-step acetyl/methyl exchange on bridged chiral benzopyran

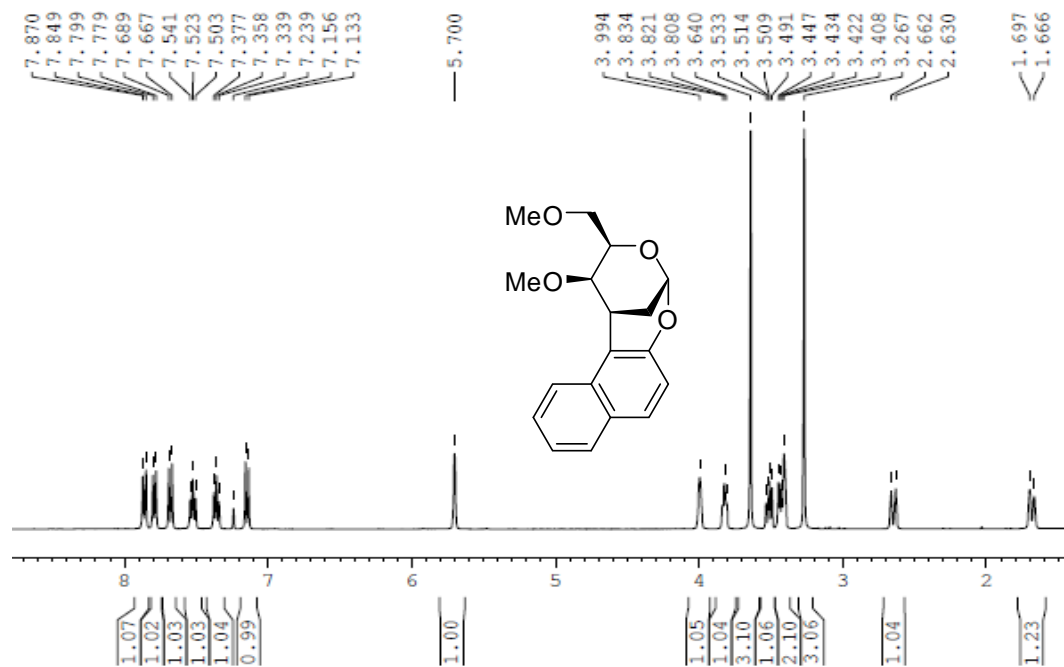


Figure 3.5. ^1H NMR spectrum of bridged chiral benzopyran **3.13**

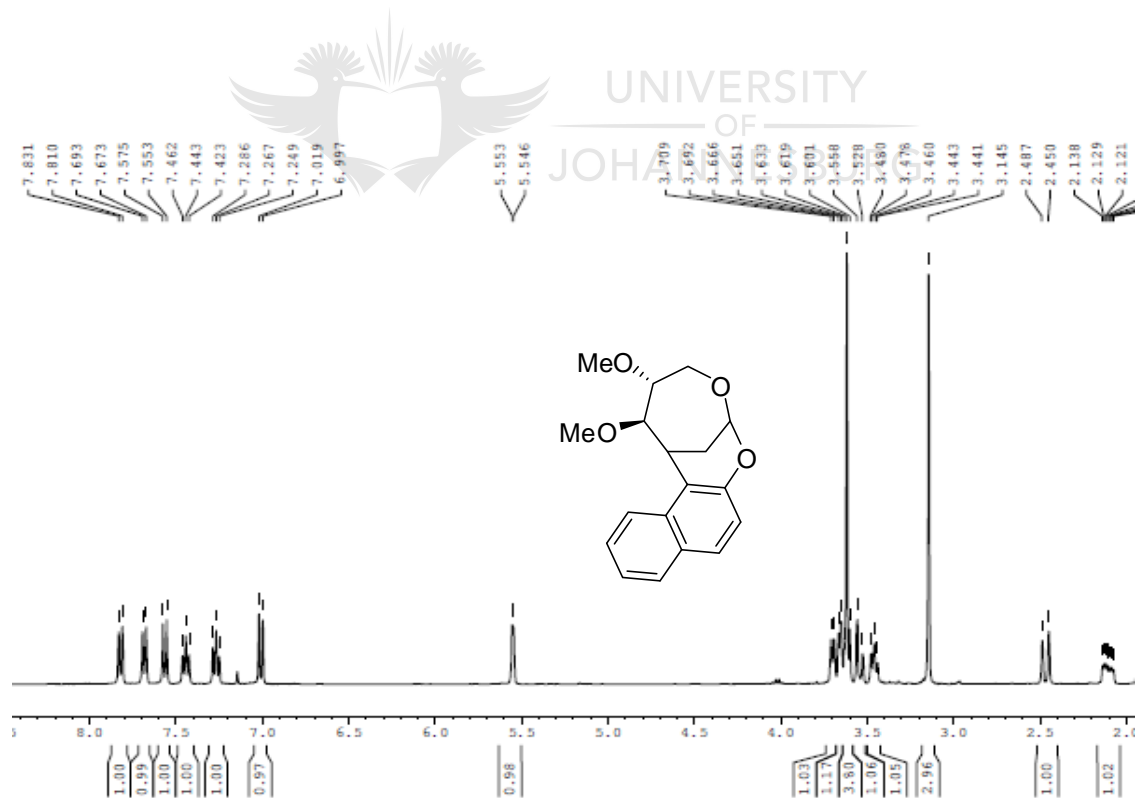


Figure 3.6. ^1H NMR spectrum of oxepane **3.12**

Not much information could be derived from the anomeric signal around 5.7 ppm and the aromatic protons downfield. Comparing the high-field signals generated by the H-2 proton, the chemical shift between the two isomers differs significantly, as does the appearance of the signals. On the bridged chiral benzopyran **3.13**, the H-2 protons resonate as doublets (with unresolved fine coupling) at 2.65 ppm (12.8 Hz) and 1.68 ppm (12.4 Hz), whereas on the oxepane **3.12** they resonate as a doublet (d) and doublet of doublet of doublets (ddd) at 2.56 (15.2 Hz) and 2.20 ($J = 14.8$ Hz, 7.2 Hz and 4.0 Hz). Equatorial protons are known to resonate at a lower field than chemically equivalent axial protons.²⁰ This means the difference in multiplicity is observed for the axially oriented protons. Also from the DEPT spectra of both compounds, the -OCH₂ (C-6) resonates at 72.3 ppm for the bridged chiral benzopyran **3.13** and at 61.5 ppm for the oxepane **3.12**. This clearly indicated that the carbons are not chemically equivalent. Moreover, in the HMBC spectra, correlations between C-6 and the anomeric proton were observed for the oxepane **3.12**, but not observed for the bridged chiral benzopyran **3.13**. This aspect was diagnostic for the oxepane. Also, the bridged chiral benzopyran is a solid at room temperature as opposed to the oxepane which is viscous oil. Single crystals were grown for the bridged chiral benzopyran **3.13** and the ORTEP diagram is shown in Figure 3.7.

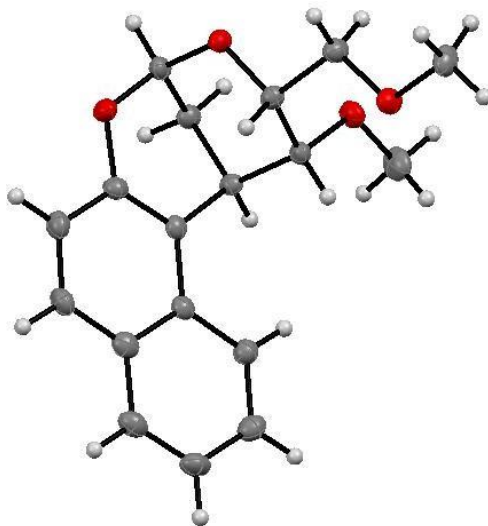
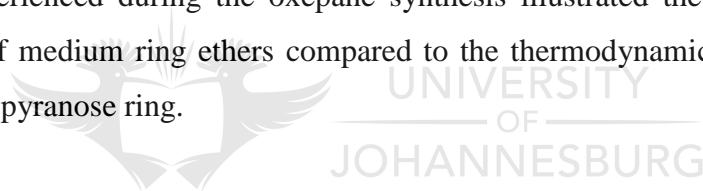


Figure 3.7. ORTEP diagram of bridged chiral benzopyran **3.13**

3.3 Conclusion

Aluminium triflate, a versatile Lewis acid catalyst, has been recently reported to efficiently catalyse *O*-glycosidation of glycals using alkyl and aromatic aglycons.⁶ In the previous chapter the catalyst was also shown to ring-open bridged chiral benzopyrans. In the current chapter the catalyst was employed in the intramolecular *O*-glycosidation towards the synthesis of an oxepane derivative. The route was fraught with troublesome side-reactions, which were eventually solved with a limiting protecting group strategy. Nevertheless, it has been successfully demonstrated that oxepanes can be prepared when the molecular architecture is appropriate to the cause. Future work in this area could be a search for mild conditions under which cyclisation can be effected in the presence of removable protecting groups. This would render the outcomes particularly useful in, for example, medicinal chemistry.

The difficulties experienced during the oxepane synthesis illustrated the problems associated with the synthesis of medium ring ethers compared to the thermodynamically more stable and kinetically preferred pyranose ring.



3.4 References

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Chapter 4

Synthesis of galactose based flavonoids

4.1 Introduction

Flavonoids are naturally occurring molecules found in fruits, vegetables as well as in beverages such as tea and wine. They also serve as plant pigments and are usually biosynthesised from phenylalanine.¹ Flavonoids have diverse biological applications mostly derived from their ability to serve as antioxidants by scavenging free radicals.² One flavonoid that has received a lot of attention from researchers in terms of investigating its biological properties is quercetin, because of its many health benefits. These include improvement of cardiovascular health, eye diseases, allergic disorders, arthritis, reducing risk of cancers and many more.³ The unavailability of suitable substrates has been a serious impediment towards the synthesis of these nutraceuticals, so researchers rely upon extraction methods⁴ rather than synthesis to obtain useful quantities of such substances.

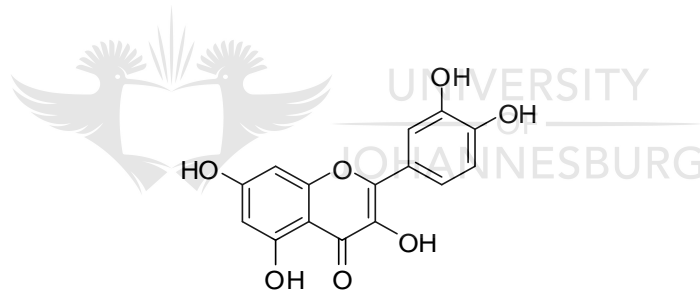


Figure 4.1. Structure of quercetin

Carbohydrates are ubiquitous chiral substrates towards the synthesis of many naturally occurring bioactive compounds.⁵ The use of these abundant natural products for the synthesis of flavonoid derivatives is appealing. In the previous sections the synthesis of chiral benzopyrans from D-(+)-galactose was reported. These chiral chromenes were envisaged to provide facile access to flavonoid compounds *via* palladium catalysed arylation of the pyranose ring of the benzopyran. Palladium is a versatile catalyst in organic synthesis and can facilitate myriad transformations with organic molecules, examples being hydrogenation, hydrogenolysis, carbonylation and the formation of C-C, C-O, C-N and C-S bonds.⁶ In fact, a number of well-known name reactions

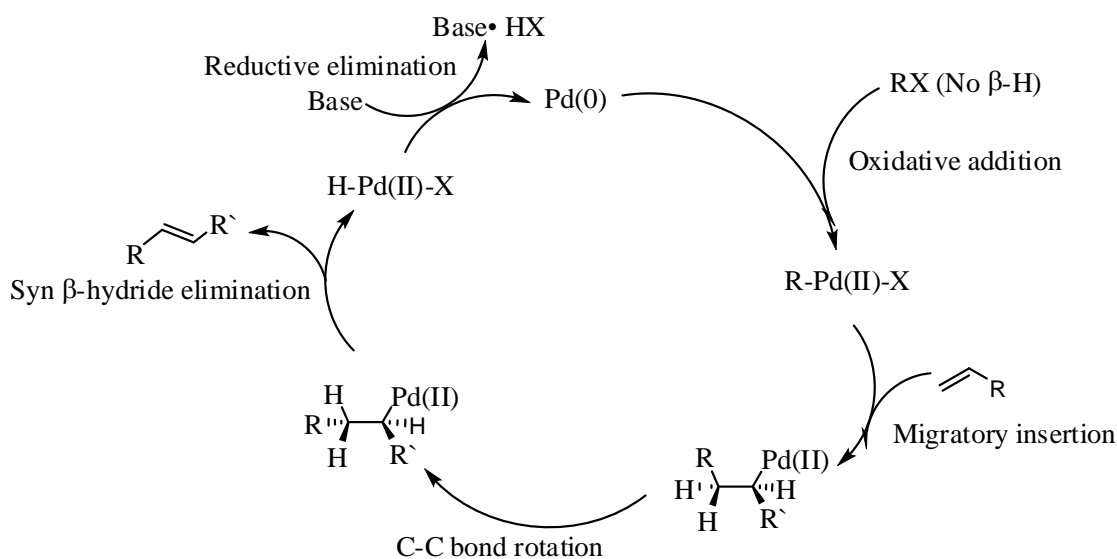
that feature palladium include: Heck, Suzuki, Stille, Sonogashira and Buchwald-Hartwig cross-couplings.⁷ Moreover, palladium protocols normally proceed under mild conditions affording high yields with excellent stereo-, regio- and chemoselectivity.⁷ The Heck reaction was employed in the cross-coupling of the chromenes and a range of aryl electrophiles to afford the galactose derived flavonoid compounds.

4.2 The Heck reaction

In 1968, Richard Heck introduced a new method for the arylation of olefinic compounds. Many synthetically useful applications have resulted from the introduction of this method.

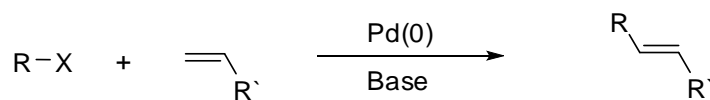
The Heck reaction generally proceeds through the following steps (Scheme 4.1):⁸

- ❖ Oxidative addition of the RX species to the palladium (0) catalyst.
- ❖ Formation of the π -complex.
- ❖ Bond formation *via* 1,2-addition of the σ -organopalladium reagent to the olefinic carbons (migratory insertion).
- ❖ *Syn* 1,2- β -hydride elimination of a palladium species (usually as hydridopalladium).



Scheme 4.1. Mechanism for the Heck reaction

The Heck reaction has emerged in recent years as a powerful and versatile method for carbon-carbon bond formation involving sp^2 carbons. This reaction is defined as a vinylic substitution reaction where a vinylic hydrogen atom is substituted by an aryl, vinyl, or benzyl group (Scheme 4.2). Traditional Heck couplings relied on aryl or vinyl iodides or bromides as the electrophilic partner, and later on triflates, chlorides, carbonyl and sulfonyl chlorides, diazonium salts, iodonium salts, and various leaving groups were introduced.^{6b} There are certain variable factors involved in the Heck reaction, and careful qualitative and quantitative optimisation of these factors is essential to achieve successful reactions. These are: ligands, solvents, halides, alkenes, bases, additives and temperature.



where R = aryl, vinyl, benzyl
X = I, Br, OTf, etc

Scheme 4.2. The Heck reaction



Oxidative addition is the first and often the rate determining step in the catalytic cycle. It is the addition of a covalent molecule to Pd(0) species with cleavage of its covalent bond and the formation of two new bonds to the Pd centre. In this process the palladium increases its formal oxidation state and its co-ordination number by two. The relative reactivity decreases in the order of $I > OTf > Br \gg Cl$. The high C-Cl bond dissociation energy makes aryl chlorides overall unsuitable substrates for Heck coupling, however the use of electron rich and bulky phosphine ligands circumvent this problem.⁹ The oxidative addition of aryl halides to Pd(0) is a kinetically disfavoured step when powerful electron donors such as -OH and -NH₂ reside on aromatic rings.^{6b}

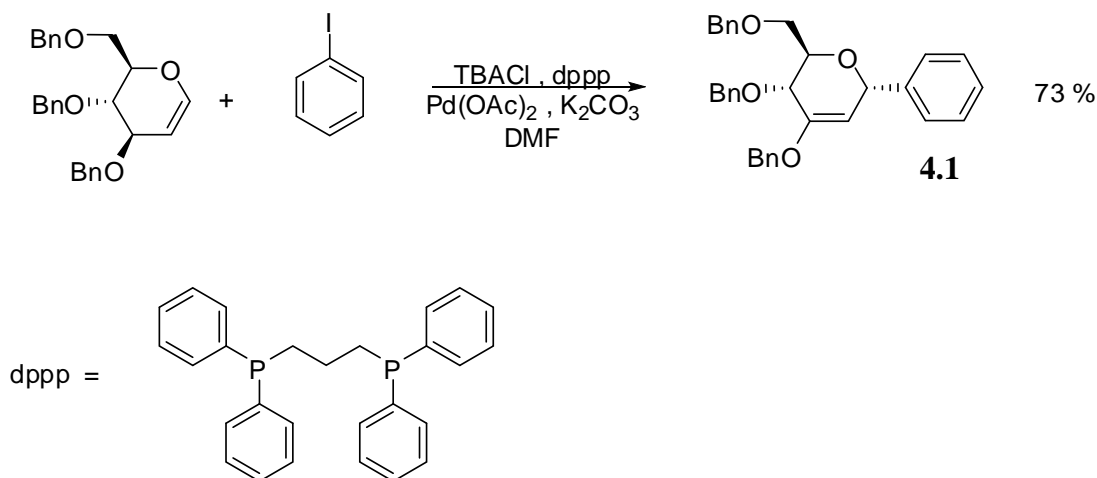
The Heck reaction of monosubstituted alkenes usually proceeds satisfactorily. The intermolecular Heck reaction is sensitive to steric factors of alkenes,¹⁰ and reactions of 1,1- and 1,2-disubstituted alkenes are slower than those of monosubstituted alkenes. Although

intermolecular reactions of congested double bonds are slow, intramolecular reactions of even very hindered double bonds proceed smoothly.¹¹ Alkenes bearing EWGs are most reactive.¹⁰ The reactivity of alkenes bearing electron donating groups such as vinyl ethers, vinyl esters, enamides, and enamines, is lower than that of alkenes with EWGs.

4.3 Cross-coupling reactions

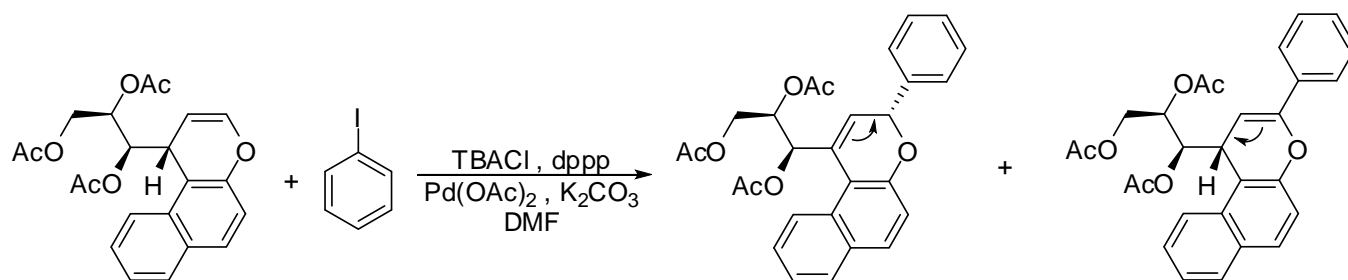
Though the Heck reaction is known to form C-C bonds with ease, it has not been popular in the synthesis of aryl C-glycosides. Accordingly, it lags behind methods such as electrophilic aromatic substitution of activated glycosyl donors such as glycosyl halides and glycosyl trichloroacetimidates with aromatic species,¹² and Lewis acid promoted O-C glycoside rearrangements.¹³ Some authors have reported the Heck-type coupling of furanoid and pyranoid glycols with iodo aglycons for the synthesis of C-nucleosides and C-glycoside antibiotics.¹⁴ Also, the use of oxidants¹⁵ to improve the reaction outcomes as well as microwave assisted palladium catalysed cross-coupling of pyranoid glycols have been reported.¹⁶ The method used in the current work for the cross-coupling reactions is that of Tao *et al.*¹⁷ who cross-coupled halo-*exo*-glycols and *endo*-glycols to achieve C-glycosidic disaccharides.

To test the compatibility and efficiency of Tao's method on the current chromene substrates; 3,4,6 *tri-O*-benzyl-D-glucal was reacted with two equivalents of iodobenzene, one equivalent of TBACl, 10 mol% Pd(OAc)₂, 10 mol% dppp in DMF. The reaction proceeded smoothly in 7 hours to give the aryl C-glycoside **4.1** in 73% yield as shown in Scheme 4.3. The reaction was stereoselective towards the α -glycoside, in agreement with the results reported by Tao *et al.*¹⁷



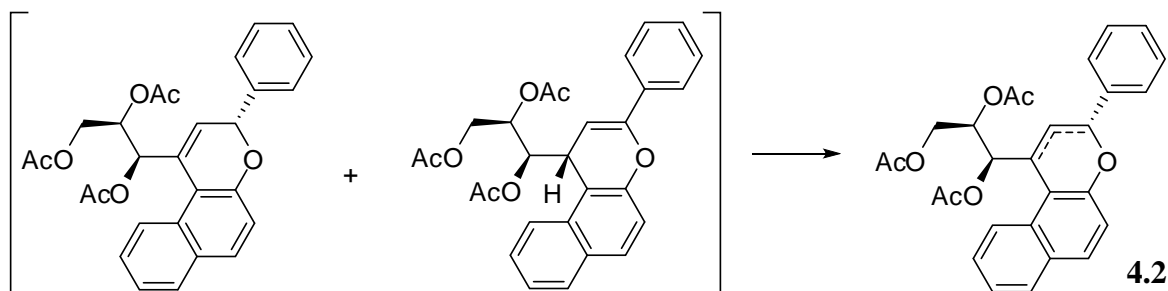
Scheme 4.3. Heck cross coupling with 3,4,6-*tri-O*-benzyl-D-glucal

The method was then extended to arylation reactions of chromene **2.29**, initially using iodobenzene as the aryl electrophile. Disappearance of the chromene limiting reagent and formation of new products was observed on the TLC plate and upon completion (10 hours) the reaction mixture was subjected to work up and the crude reaction mixture was purified using flash column chromatography. Two spots with relatively close retention factors were separated and characterised. Interestingly, the ^1H NMR spectra of the two compounds were similar, both showing doubling of signals in a 4:1 ratio. Analysis of the spectra revealed that the two compounds were double bond isomers, as shown in Scheme 4.4. It was anticipated that these isomers should be separable. Re-spotting the contents of the two NMR tubes onto a TLC plate, showed two separable spots again. Attempts to separate the two compounds by re-subjecting them to column chromatography and allowing the solvent to evaporate at room temperature, thereby avoiding heat, afforded the same result. This interesting observation was thought to be a result of spontaneous double bond isomerisation (Scheme 4.4). If this event was proceeding at ambient temperature, as appears to be the case, then separation of the isomers would not be possible.



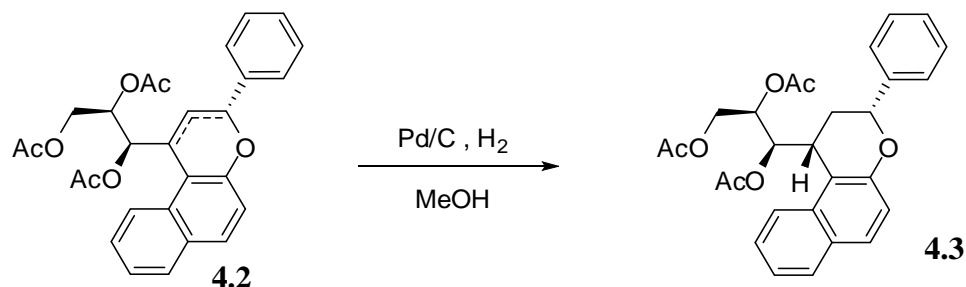
Scheme 4.4. Heck Coupling with iodobenzene

Palladium as a catalyst has been employed in isomerisation reactions and cases where the isomerisation compete with the Heck coupling have been reported.¹⁸ However, in the current case the isomerisation occurs even in the absence of palladium. Cyclic alkenes have also been observed to give a mixture of regio-isomers as a result of double bond migration after the arylation reaction, but addition of silver carbonate into the reaction mixture suppresses the double bond migration to give a typical Heck cross coupling product.¹⁹ The spontaneous reversible double bond migration in the present case might be favoured by the two regio-isomers having ‘similar’ or rather close relative energies, meaning that neither will act as a thermodynamic sink. Since in each isomer the double bond is conjugated with an aryl ring, it is reasonably expected that they would possess similar energies. Additionally, if the activation energy for this transformation is low, then it could proceed rapidly at ambient temperature. Since the isomerisation was noted to proceed rapidly and spontaneously at room temperature, and since the isomers could not be separated, the flavonoids are therefore represented as shown in Scheme 4.5.



Scheme 4.5. Representation of inseparable flavonoid regio-isomers

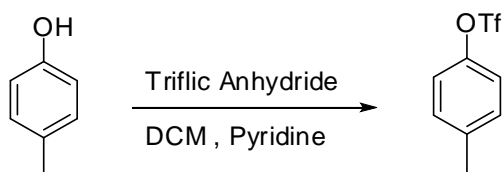
To circumvent this isomerisation problem, to aid in the analysis of the products and also to achieve the goal for synthesis of chiral flavonoid derivatives, the heterocyclic pyran ring was hydrogenated using palladium on carbon. To this end, Pd/C (20 mol%), methanol and hydrogen were employed for the hydrogenation reaction, and the *endo* double bond of the pyranose ring was hydrogenated overnight at 1 bar pressure of hydrogen (Scheme 4.6).



Scheme 4.6. Hydrogenation of flavonoids

The ^1H NMR spectrum of the isolated product **4.3** did not show doubling of signals, as was noted for spectra of the starting material **4.2**. Instead, only a single compound was present. Importantly, there was an absence of signals that would be consistent with the presence of a double bond. Instead, the presence of the reduced product with its new CH_2 group was evidenced by the resonances of the methylene protons with H-2A at 2.67 ppm resonating as a doublet of doublet of doublets ($J = 14.5$ Hz, 10.3 Hz and 7.6 Hz) and H-2B at 2.47 ppm resonating as a doublet of doublet of doublets ($J = 14.4$ Hz, 8.8 Hz and 3.6 Hz). This was the expected multiplicity of these geminal protons having two vicinal methine protons, in the present case being H-1 and H-3. Moreover, H-3 resonates at around 4.3 ppm as a quartet in the ^1H NMR spectrum ($J = 7.8$ Hz), which is a clear indication of having three neighbouring protons with coincidental coupling constants. Also from the DEPT spectrum there are two CH_2 groups observed, which correspond to C-2 and C-6, and this confirms that the pyranose ring bears no double bond additional to that of the naphthalene ring. The presence of the carbonyl moieties was further identified with the use of infrared spectroscopy where there was a strong absorption around 1730 cm^{-1} , which is typical for ester groups.

The success with this reaction led to interest in the use of other aryl electrophiles besides iodobenzene, to investigate the generality of the developed protocol. The order of reactivity of the aryl electrophiles in the Heck reaction is known to be as follows: I > OTf > Br >> Cl. It was envisaged that aryl triflates would be useful and could be readily prepared from the corresponding phenols. Accordingly, phenyl triflates were synthesised by stirring the phenol in a solution of pyridine and DCM with dropwise addition of triflic anhydride (Scheme 4.7), a method discussed by Zhiyan *et al.*²⁰

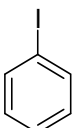
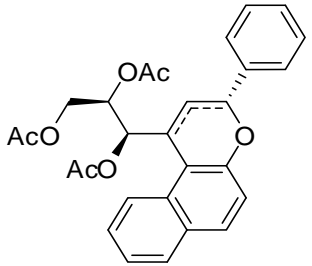
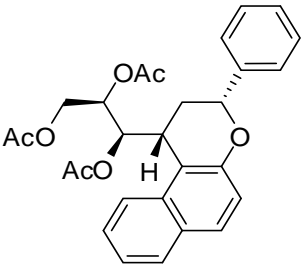
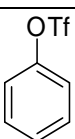
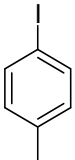
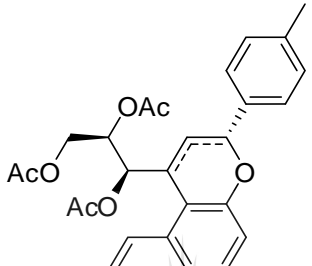
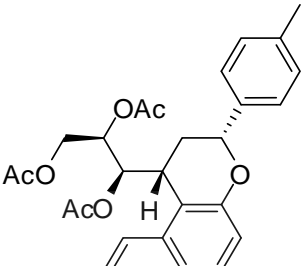
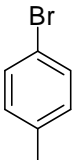
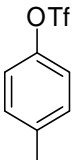
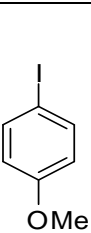
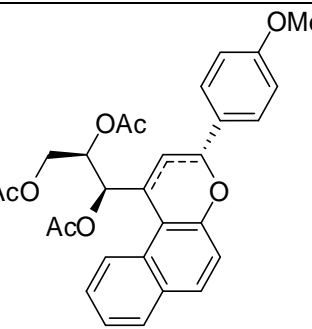
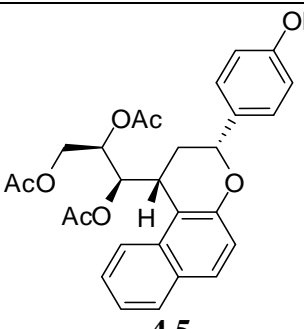
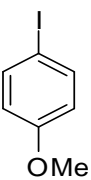
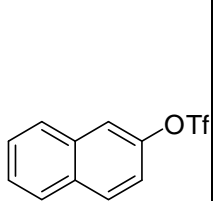
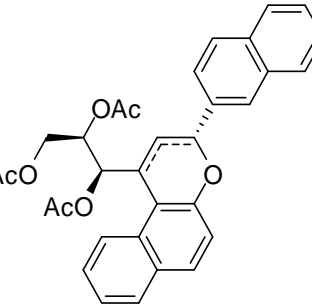
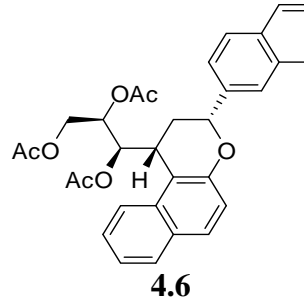


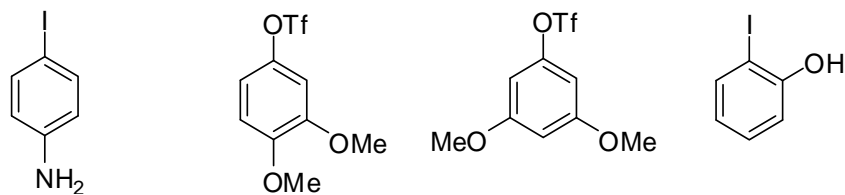
Scheme 4.7. Synthesis of phenyl triflates

The readily available phenyl triflates were then used as aryl electrophiles in the Heck reaction for the synthesis of flavonoid derivatives (Table 4.1), without any manipulations to the reaction conditions used for iodobenzene. The cross-coupling products were hydrogenated using Pd/C, MeOH and H₂. As a case in point, the NMR spectra of the hydrogenation product derived from phenyl triflate were compared to those of **4.3** and were found to be superimposable.

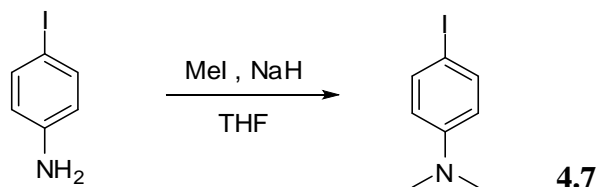
The yields of the cross coupling reactions were high with no significant difference in the outcomes or progress of the reactions noted in response to the nature of the aryl electrophile. 4-Iodo aniline and other highly activated aryl electrophiles such as the ones shown in Scheme 4.8 were either low yielding or no cross coupling product was observed during TLC analysis of the reaction mixtures. *Bis N*-methylation of 4-iodoaniline with the hope of improving the cross-coupling yield did not yield any better results. Due to time constraints, improvements to the catalyst system or deactivation of the N-group could not be investigated.

Table 4.1. Synthesis of flavonoids

Substrate	Product	Yield	Product	Yield	$[\alpha]_D$
		87%	 4.3	92%	-7.2°
		76%			
		83%	 4.4	85%	-2.6°
		81%			
		77%			
		75%	 4.5	86%	-1.0°
					
		73%	 4.6	79%	-9.2°

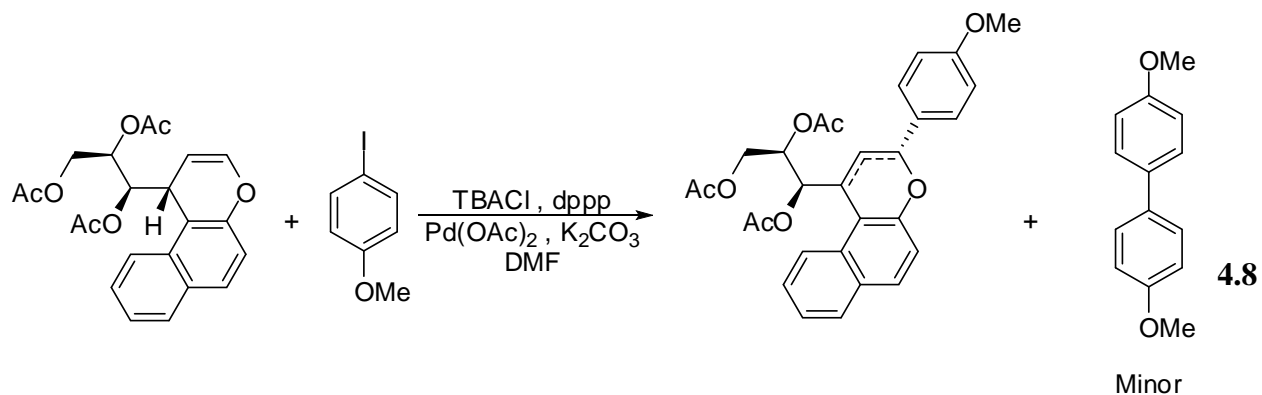


Scheme 4.8. Non-coupling aryl electrophiles



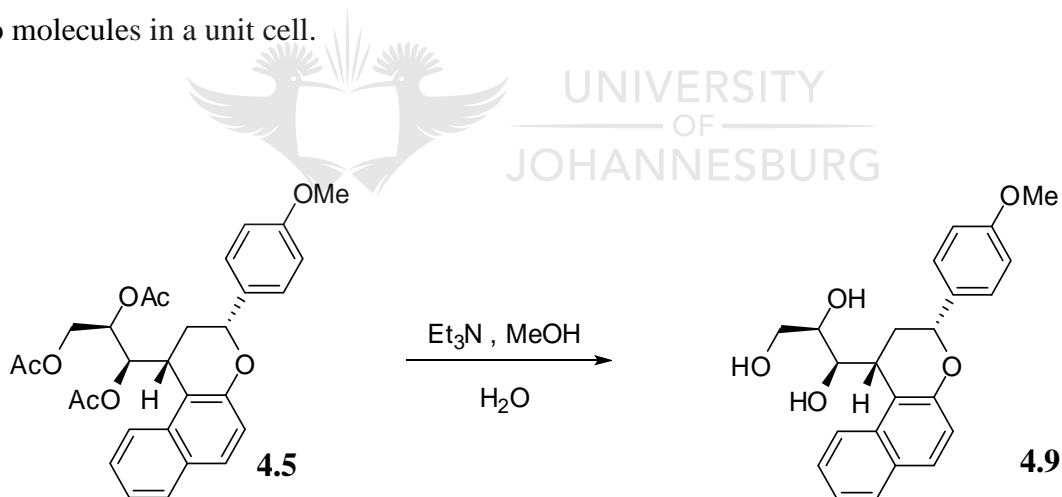
Scheme 4.9. Alkylation of 4-iodoaniline

Homo-coupling by-products were also observed and isolated as minor constituents. Although the competitive homo-coupling reaction is known with Heck coupling reactions,⁷ Tao *et al.* did not mention any observation of homo-coupled products when using this method for cross coupling of halo-*exo*-glycols with *endo*-glycols. Limberger's group used a similar method with a different ligand, $(P(o\text{-tol}))_3$, and observed substantial amounts of products of the homo-coupling reaction with aryl bromides bearing electron withdrawing groups at the *para*-position.²¹ In the present study homo-coupled products were observed as minor by-products on the TLC plate in all cross-coupling reactions, showing no dependence on the nature of the aryl electrophile. One of these by-products was isolated and characterised as biaryl **4.8** shown in Scheme 4.10.



Scheme 4.10. Heck coupling with 4-iodoanisole

The synthesised flavonoids bear acetates on the pyranose dangling arm which can be easily hydrolysed to a triol. This triol provides reactive sites which make the flavonoid available for further derivations. Flavonoid **4.5** was de-acetylated using triethylamine-catalysed hydrolysis in aqueous methanol. The reaction proceeded smoothly to give the solid triol product in 97% as a white solid (Scheme 4.11). The disappearance of the methyl signals at around 2.1 ppm belonging to acetates was evidence of the hydrolysis. The IR spectra also did not show strong absorptions around the ester region, but rather a strong broad absorption band was observed at 3461 cm^{-1} which is consistent with hydroxyl functions. Moreover, single crystals were grown for the triol product **4.9** and an ORTEP diagram is shown in Figure 4.2. The structure of the triol was thus unambiguously identified. This structure is useful because it confirms not only the hydrolysis product but also the absolute stereochemistry of the hydrogenation product. Specifically, it is evident that the dangling arm and the aryl group bear a *syn* relationship. Since the stereochemistry at the dangling arm is known with certainty based upon that of the starting chromene, the stereochemistry at C-1 can be directly determined. In the ORTEP diagram there are two molecules in a unit cell.



Scheme 4.11. De-acetylation of flavonoid **4.5**

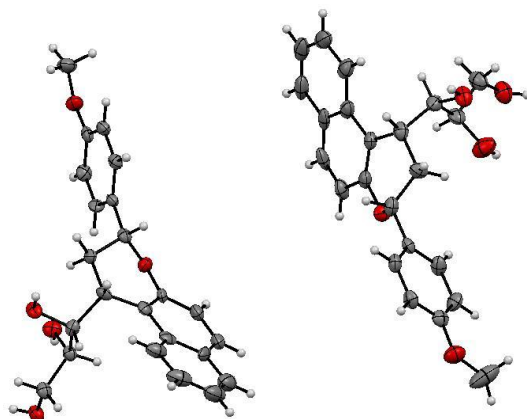


Figure 4.2. ORTEP diagram for triol **4.9**

4.4 Conclusion

The chromene **2.29** derived from aluminium triflate-catalysed ring-opening acetolysis of bridged chiral benzopyran **2.14** has once again proved to be a versatile and valuable product and intermediate towards the synthesis of other highly functionalised products. In the present case the chromene has been shown to provide immediate access to flavonoid derivatives. Flavonoids are naturally occurring compounds with high nutritional value and various health benefits, but their synthesis has been difficult to achieve due to the unavailability of suitable substrates.⁴ The use of a palladium catalyst for the Heck cross-coupling reaction and subsequent hydrogenation of the product so formed gave chiral flavonoids in high yields. Moreover, the dangling arm at the C-3 position of the pyranose ring bears easily cleaved acetates, which is a useful feature for further manipulations and to moderate solubility characteristics of the products.

4.5 Final summary

The current study has successfully introduced aluminium triflate into the diverse field of carbohydrate synthesis. Using 3,4,6-*tri-O*-acetyl-D-galactal as the glycosyl donor, a range of 1-*O*-aryl-2-deoxy galactosides were synthesised by using different activated phenols as glycosyl acceptors. The reaction proved to be temperature dependant because, by merely increasing the temperature of the reaction from 0 °C to 40 °C, a different set of products known as bridged chiral benzopyrans were obtained.

These bridged chiral benzopyrans were ring-opened *via* acetolysis using aluminium triflate as the Lewis acid catalyst. The ring opening was manipulated to be selective towards a novel class of chromenes (by using only acetic anhydride) and chromans (by using a mixture of acetic acid and acetic anhydride). The galactal-derived benzopyrans (chromenes, chromans and bridged chiral benzopyrans) were de-acetylated *via* triethyl amine catalysed transesterification in aqueous methanol. Interestingly the chromenes yielded a novel class of bridged chiral benzopyrans as a result of intramolecular oxa-Michael addition.

Aluminium triflate, a versatile Lewis acid catalyst also demonstrated that a carbohydrate derived oxepane can be synthesised using intramolecular *O*-glycosidation. Though the synthesis was hampered by troublesome side reactions, it was eventually solved with a limiting protecting group strategy. The difficulties experienced in the oxepane synthesis illustrated the problems associated with the synthesis of medium ring ethers compared to the thermodynamically more stable and kinetically preferred pyranose ring. Future work in this area could be a search for mild conditions under which cyclisation can be effected in the presence of removable protecting groups. This would render the outcomes particularly useful in, for example, medicinal chemistry.

The chromene formed from the selective ring opening of the bridged chiral benzopyrans proved to provide immediate access to carbohydrate derived flavonoid compounds. Different aryl halides and a palladium catalyst were employed for the Heck cross-coupling reaction and subsequent hydrogenation of the product so formed gave chiral flavonoids in high yields.

Hydrolysis of the acetates on the flavonoids make the flavonoids bioavailable and the triol also provide a reactive site for further manipulations.

The project has successfully introduced a novel class of carbohydrate derivatives starting from 3,4,6-*tri-O*-acetyl-D-galactal. It also provided an opening for substantial future studies in follow up work, especially biological screening of these and similar compounds.

4.6 References

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Chapter 5

Experimental Procedures

5.1 General

5.1.1 Chemical methods

All reactions were performed under an atmosphere of either nitrogen or argon. Unless otherwise stated, dry solvents were used in oven dried, flamed out glass apparatus with constant stirring with a magnetic stirrer. Room temperature refers to *ca.* 20-25 °C.

5.1.2 Chromatography

Qualitative thin layer chromatography (TLC) was conducted on “Merck GF254 precoated silica plates” (0.25 mm layer). The chromatograms were eluted using an appropriate solvent system as indicated for column chromatography. Compounds were visualised by their fluorescence under UV light (254 nm), as well as by spraying the plate with anisaldehyde spray followed by heating with a heat. “Flash chromatography” refers to column chromatography under nitrogen pressure using “Merck Kieselgel 60 (230-400 mesh), with eluents mixed in a volume per volume ratio. Solvents used as eluents, ethyl acetate and hexane were pre-distilled.

5.2 Spectroscopic data and methods

5.2.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were recorded by means of Bruker Ultrashield 400 MHz spectrometer in CDCl₃ unless otherwise indicated. ¹H NMR data are listed in the order: chemical shift (δ, reported in ppm and referred to the residual solvent peak of CDCl₃ [δ = 7.24 ppm] or in the case of aromatic compounds to TMS [δ = 0.00 ppm], multiplicity (s = singlet, d = doublet, q = quartet, br s = broad singlet, dd = doublet of doublets, dt = doublet of triplets, tt = triplet of triplets, dq = doublet of quartets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, p = pentet, sx = sextet, sp = septet.), number of protons, coupling

constants (J , in Hertz) and assignment. ^{13}C NMR data are listed in the order: Chemical shift (δ , reported in ppm and referred to the residual peak of CDCl_3 [$\delta = 77.0$ ppm]) and the specific carbon atom allocation. In most cases 2-dimensional NMR techniques; Correlation Spectroscopy (COSY), Heteronuclear Single Quantum Coherence (HSQC), Heteronuclear Multiple Bond Coherence (HMBC), Distortionless Enhancement by Polarisation Transfer (DEPT) and proton decoupling experiments were used to assist in the allocation of the spectra.

5.2.2 Mass spectrometry (m/z)

Mass spectrometry was performed on Thermo Double Focussing Sector high resolution mass spectrometer. Ionisation techniques include ESIMS and CIMS.

5.2.3 Infrared spectroscopy (IR)

A Tensor 27 spectrophotometer was used to record IR spectra using an ATR fitting. The data are listed with the characteristic peaks indicated in (cm^{-1}).

5.2.4 Melting points

Melting points were determined using a Gallencamp oil immersion apparatus and are uncorrected.

5.2.5 Optical Rotations

Optical rotations were determined on a Perkin-Elmer 141 polarimeter in chloroform/methanol solutions at $25\text{ }^\circ\text{C}$. The concentration c refers to $0.5\text{ g}/100\text{ mL}$.

5.3 Experimental methods

Per-acetylation of D-(+)-galactose

To a solution of D-(+)-galactose (0.5 g, 1 equivalent) and acetic anhydride (10 mL) at 0 °C, was added aluminium triflate (66 mg, 5 mol%). The reaction mixture was allowed to warm to room temperature and left stirring for 90 minutes. Ethyl acetate (10 mL) and sodium carbonate (1 g in 10 mL water) were added to the reaction mixture and the mixture was left stirring for an additional hour. Additional water (10 mL) and ethyl acetate (20 mL) were added, and the organic layer was isolated and washed with water (3 x 10 mL) and a saturated aqueous solution of sodium bicarbonate (5 mL). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. A white solid was obtained after drying, and was used directly in the next step.

Bromination

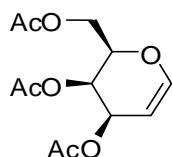
To a solution of the per-acetylated galactose (0.5 g, 1 equivalent) in dichloromethane (DCM, 30 mL) at 0 °C, was added hydrogen bromide (1 mL of 33% in acetic acid, 13 equivalents). The reaction mixture was stirred at 0 °C for 1 hour and thereafter warmed to room temperature. The progress of the reaction was monitored by TLC. After satisfactory conversion, the reaction mixture was diluted with dichloromethane (50 mL) and washed with ice water (5 mL), an aqueous solution of sodium bicarbonate (5 mL) and brine (5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was used without further purification in the last step.

Reduction

To a solution of the brominated product (0.7 g) in acetic acid (20 mL), were added copper(II) sulfate (0.18 g in 2 mL water) and zinc dust (3 g). The mixture was left stirring at 0 °C for 30 minutes and thereafter stirred at room temperature overnight. The solution was filtered under vacuum and the residue was rinsed with dichloromethane (50 mL). The filtrate was washed with

water (20 mL), an aqueous solution of sodium bicarbonate (10 mL) and brine (10 mL); dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography using a mixture of hexane and ethyl acetate (2:1) as eluent to give 324 mg of the protected galactal.

(2*R*,3*R*,4*R*)-2-(acetoxymethyl)-3,4-dihydro-2*H*-pyran-3,4-diyl diacetate (2.1)¹



Clear oil

Yield: 70%

R_f: 0.36 (Hexane:EtOAc, 2:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 6.41 (dd, 1H, *J* = 6.4 Hz and 1.6 Hz, *H*-1), 5.51-5.49 (m, 1H, *H*-3), 5.37 (dt, 1H, *J* = 4.7 Hz and 1.7 Hz, *H*-4), 4.67 (ddd, 1H, *J* = 6.4 Hz, 2.8 Hz and 1.2 Hz, *H*-2), 4.27 (tt, 1H, *J* = 6.2 Hz and 1.2 Hz, *H*-5), 4.24-4.14 (m, 2H, *H*-6_A and *H*-6_B), 2.07 (s, 3H, -COCH₃), 2.03 (s, 3H, -COCH₃), 1.97 (s, 3H, -COCH₃).

¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.4 (-C=O), 170.1 (-C=O), 170.0 (-C=O), 145.3 (*C*-1), 98.8 (*C*-2), 72.7 (*C*-5), 63.8 (*C*-3), 63.7 (*C*-4), 61.8 (*C*-6), 20.7 (-COCH₃), 20.6 (-COCH₃), 20.5 (-COCH₃).

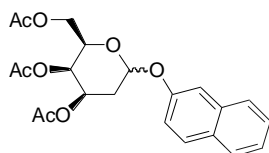
IR: 1737, 1650, 1370, 1213, 1079, 895 cm⁻¹

[α]_D: -4.7 (*c* 0.5, CH₂Cl₂)

5.3.1 Synthesis of *O*-aryl 2-deoxy galactosides

To a solution of 3,4,6-*tri-O*-acetyl-D-galactal (200 mg, 0.735 mmol) and DCE (2.0 mL), were added the phenol in question (1.2 equivalents, 0.882 mmol) and Al(OTf)₃ (5 mol%, 17 mg). The reaction mixture was stirred at 0 °C until it was judged to be complete by TLC analysis, at which time the reaction was quenched by the addition of concentrated aqueous sodium bicarbonate solution (2.0 mL). The resulting mixture was extracted with DCM (3×5 mL). The combined organic phases were dried over anhydrous magnesium sulfate. The volatile component was removed *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 3:1) was used as eluent.

2-Naphthalenyl-3,4,6-*tri-O*-acetyl-2-deoxy-D-lyxo-hexopyranoside (2.2)²



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Cream solid

Mp: 100-102 °C

Yield: 63%

R_f: 0.41 (Hexane:EtOAc, 3:1)

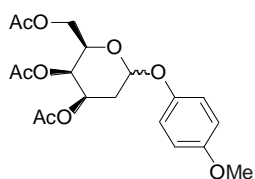
¹H NMR: (CDCl₃, 400 MHz): δ_H 7.76 (dd, 2H, *J* = 8.6 Hz and 3.4 Hz, *Ar*), 7.71 (d, 1H, *J* = 8.0 Hz, *Ar*), 7.45 (d, 1H, *J* = 2.4 Hz, *Ar*), 7.40 (t, 1H, *J* = 9.0 Hz, *Ar*), 7.34 (t, 1H, *J* = 7.4 Hz, *Ar*), 7.20 (dd, 1H, *J* = 8.8 Hz and 2.4 Hz, *Ar*), 5.87 (d, 1H, *J* = 2.8 Hz, *H*-1), 5.54 (dq, 1H, *J* = 11.4 Hz and 2.8 Hz, *H*-3), 5.40 (d, 1H, *J* = 2.8 Hz, *H*-4), 4.28 (t, 1H, *J* = 6.6 Hz, *H*-5), 4.07 (d, 2H, *J* = 6.4 Hz, *H*-6_A and *H*-6_B), 2.42 (td, 1H, *J* = 12.4 Hz and 2.4 Hz, *H*-2_A), 2.15 (dd, 4H, *J* = 11.0 Hz and 6.0 Hz, *H*-2_B and -COCH₃), 2.02 (s, 3H, -COCH₃), 1.78 (s, 3H, -COCH₃).

^{13}C NMR: (CDCl₃, 100 MHz): δ_{C} 170.4 (-C=O), 170.2 (-C=O), 170.0 (-C=O), 154.0 (*ipso*-Ph), 134.3 (*Ar*), 129.7 (*Ar*), 129.4 (*Ar*), 127.6 (*Ar*), 127.1 (*Ar*), 126.4 (*Ar*), 124.3 (*Ar*), 118.8 (*Ar*), 110.7 (*Ar*), 96.0 (*C-1*), 67.7 (*C-5*), 66.5 (*C-3*), 66.0 (*C-4*), 62.1 (*C-6*), 30.3 (*C-2*), 20.8 (-COCH₃), 20.7 (-COCH₃), 20.4 (-COCH₃).

IR: 2964, 1740, 1285, 1034, 811 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 439.1369, found: 439.1371

4-Methoxyphenyl-3,4,6-tri-*O*-acetyl-2-deoxy-D-lyxo-hexopyranoside (2.3)³



Cream solid

Mp: 60-62 °C

Yield: 75%

R_f: 0.36 (Hexane:EtOAc, 3:1)

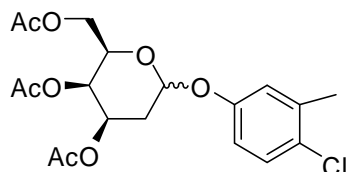
^1H NMR: (CDCl₃, 400 MHz): δ_{H} 6.95 (d, 2H, $J = 9.2$ Hz, *ortho*-Ph), 6.77 (d, 2H, $J = 10.8$ Hz, *meta*-Ph), 5.57 (d, 1H, $J = 2.8$ Hz, *H-1*), 5.43 (dq, 1H, $J = 12.4$ Hz and 2.7 Hz, *H-3*), 5.35 (s, 1H, *H-4*), 4.24 (t, 1H, $J = 6.6$ Hz, *H-5*), 4.07-3.98 (m, 2H, *H-6_A* and *H-6_B*), 3.71 (s, 3H, -OCH₃), 2.18 (td, 1H, $J = 12.6$ Hz and 3.5 Hz, *H-2_A*), 2.10 (s, 3H, -COCH₃), 2.04 (dd, 1H, $J = 12.8$ Hz and 5.2 Hz, *H-2_B*), 1.96 (s, 3H, -COCH₃), 1.90 (s, 3H, -COCH₃).

^{13}C NMR: (CDCl₃, 100 MHz): δ_{C} 170.2 (-C=O), 170.1 (-C=O), 169.9 (-C=O), 154.9 (*ipso*-Ph), 150.2 (*para*-Ph), 117.7 (*ortho*-Ph), 114.4 (*meta*-Ph), 96.6 (*C-1*), 67.3 (*C-5*), 66.4 (*C-3*), 65.9 (*C-4*), 62.1 (*C-6*), 55.5 (-OCH₃), 30.2 (*C-2*), 20.7 (-COCH₃), 20.5 (-COCH₃), 20.4 (-COCH₃).

IR: 2952, 1740, 1440, 1214, 1083, 879 cm^{-1}

HRMS (ESI+): calc. for $[\text{M}+\text{Na}]^+$: 419.1318, found: 419.1322

4-Chloro-3-methylphenyl-3,4,6-tri-O-acetyl-2-deoxy-D-lyxo-hexopyranoside (2.4)



Colourless oil

Yield: 83%

R_f : 0.41 (Hexane:EtOAc, 3:1)

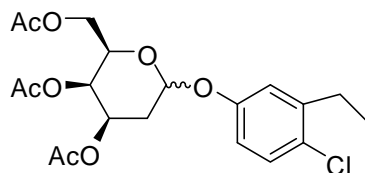
^1H NMR: (CDCl_3 , 400 MHz): δ_{H} 7.17 (d, 1H, $J = 8.8$ Hz, meta-Ph), 6.90 (d, 1H, $J = 2.8$ Hz, ortho-Ph), 6.79 (dd, 1H, $J = 8.8$ Hz and 2.8 Hz, ortho-Ph), 5.63 (d, 1H, $J = 2.8$ Hz, $H-1$), 5.42 (dq, 1H, $J = 12.3$ Hz and 2.7 Hz, $H-3$), 5.34 (d, 1H, $J = 2.4$ Hz, $H-4$), 4.18 (t, 1H, $J = 6.4$ Hz, $H-5$), 4.06-3.99 (m, 2H, $H-6_A$ and $H-6_B$), 2.28 (s, 3H, - CH_3), 2.19 (td, 1H, $J = 12.6$ Hz and 3.6 Hz, $H-2_B$), 2.10 (s, 3H, - COCH_3), 2.04 (dd, 1H, $J = 12.8$ Hz and 5.2 Hz, $H-2_B$), 1.96 (s, 3H, - COCH_3), 1.88 (s, 3H, - COCH_3).

^{13}C NMR: (CDCl_3 , 100 MHz): δ_{C} 170.2 (-C=O), 170.0 (-C=O), 169.8 (-C=O), 154.7 (*ipso*-Ph), 137.0 (*para*-Ph), 129.5 (*meta*-Ph), 127.5 (*ortho*-Ph), 119.0 (*meta*-Ph), 115.1 (*ortho*-Ph), 96.0 ($C-1$), 67.5 ($C-5$), 66.3 ($C-3$), 65.8 ($C-4$), 62.0 ($C-6$), 30.0 ($C-3$), 20.7 (- COCH_3), 20.5 (- COCH_3), 20.4 (- COCH_3), 20.1 (- CCH_3)

IR: 2596, 1742, 1480, 1221, 1018, 885 cm^{-1}

HRMS (ESI+): calc. for $[\text{M}+\text{Na}]^+$: 437.0979, found: 437.0991

4-Chloro-3-ethylphenyl-3,4,6-tri-*O*-acetyl-2-deoxy-D-*lyxo*-hexopyranoside (2.5)



Colourless oil

Yield: 81%

R_f: 0.45 (Hexane:EtOAc, 3:1)

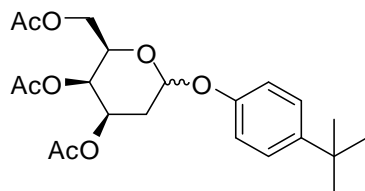
¹H NMR: (CDCl₃, 400 MHz): δ_H 7.19 (d, 1H, *J* = 8.8 Hz, *meta*-Ph), 6.91 (d, 1H, *J* = 3.2 Hz, *ortho*-Ph), 6.82 (dd, 1H, *J* = 8.6 Hz and 3.0 Hz, *ortho*-Ph), 5.67 (d, 1H, *J* = 2.8 Hz, *H*-1), 5.45 (dq, 1H, *J* = 12.3 Hz and 2.7 Hz, *H*-3), 5.36 (s, 1H, *H*-4), 4.20 (t, 1H, *J* = 6.6 Hz, *H*-5), 4.07-3.98 (m, 2H, *H*-6_A and *H*-6_B), 2.68 (q, 2H, *J* = 7.5 Hz, -CCH₂CH₃), 2.22 (td, 1H, *J* = 12.6 Hz and 3.5 Hz, *H*-2_A), 2.12 (s, 3H, -COCH₃), 2.06 (dd, 1H, *J* = 13.0 Hz and 5.0 Hz, *H*-2_B), 2.00 (s, 3H, -COCH₃), 1.90 (s, 3H, -COCH₃), 1.19 (t, 3H, *J* = 7.6 Hz, -CCH₂CH₃).

¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.3 (-C=O), 170.2 (-C=O), 170.0 (-C=O), 155.0 (*ipso*-Ph), 142.8 (*para*-Ph), 129.9 (*meta*-Ph), 127.0 (*ortho*-Ph), 117.6 (*meta*-Ph), 114.9 (*ortho*-Ph), 96.0 (*C*-1), 67.6 (*C*-5), 66.4 (*C*-3), 65.9 (*C*-4), 62.1 (*C*-6), 30.1 (*C*-2), 26.8 (-CCH₂CH₃), 20.8 (-COCH₃), 20.6 (-COCH₃), 20.5 (-COCH₃), 13.8 (-CCH₂CH₃).

IR: 2969, 1742, 1598, 1478, 1220, 1037, 883 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 451.1136, found: 451.1141

4-(1,1-Dimethylethyl)phenyl-3,4,6-tri-O-acetyl-2-deoxy-D-lyxo-hexopyranoside (2.6)⁴



Cream solid

Mp: 72-74 °C

Yield: 78%

R_f: 0.55 (Hexane:EtOAc, 3:1)

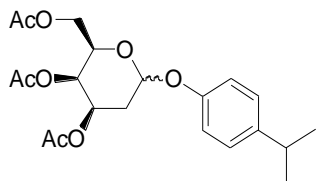
¹H NMR: (CDCl₃, 400 MHz): δ_H 7.28 (d, 2H, *J* = 8.8 Hz, *ortho*-Ph), 6.97 (d, 2H, *J* = 8.8 Hz, *meta*-Ph), 5.69 (d, 1H, *J* = 2.8 Hz, *H*-1), 5.48 (dq, 1H, *J* = 12.4 Hz and 2.7 Hz, *H*-3), 5.38 (s, 1H, *H*-4), 4.25 (t, 1H, *J* = 6.4 Hz, *H*-5), 4.10-4.03 (m, 2H, *H*-6_A and *H*-6_B), 2.22 (td, 1H, *J* = 12.6 Hz and 3.6 Hz, *H*-2_A), 2.14 (s, 3H, -COCH₃), 2.07 (dd, 1H, *J* = 12.0 Hz and 5.2 Hz, *H*-2_B), 2.00 (s, 3H, -COCH₃), 1.89 (s, 3H, -COCH₃), 1.27 (s, 9H, -C(CH₃)₃).

¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.4 (-C=O), 170.3 (-C=O), 170.1 (-C=O), 154.0 (*ipso*-Ph), 145.1 (*para*-Ph), 126.2 (*ortho*-Ph), 116.0 (*meta*-Ph), 95.9 (*C*-1), 67.4 (*C*-5), 66.5 (*C*-3), 66.1 (*C*-4), 62.0 (*C*-6), 34.1 (-C(CH₃)₃), 31.4 (-C(CH₃)₃), 30.3 (*C*-2), 20.9 (-COCH₃), 20.7 (-COCH₃), 20.6 (-COCH₃).

IR: 2962, 1742, 1513, 1226, 1003, 832 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 445.1839, found: 445.1850

4-(1-Methylethyl)phenyl-3,4,6-tri-*O*-acetyl-2-deoxy-D-lyxo-hexopyranoside (2.7)



Light yellow oil

Yield: 73%

R_f : 0.52 (Hexane:EtOAc, 3:1)

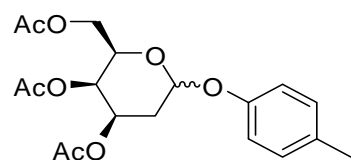
$^1\text{H NMR}$: (CDCl_3 , 400 MHz): δ_{H} 7.11 (d, 2H, $J = 8.4$ Hz, *ortho*-Ph), 6.95 (d, 2H, $J = 8.8$ Hz, *meta*-Ph), 5.67 (d, 1H, $J = 2.4$ Hz, *H*-1), 5.47 (dq, 1H, $J = 12.6$ Hz and 2.7 Hz, *H*-3), 5.37 (d, 1H, $J = 2.4$ Hz, *H*-4), 4.24 (t, 1H, $J = 6.6$ Hz, *H*-5), 4.09-4.00 (m, 2H, *H*-6_A and *H*-6_B), 2.83 (sp, 1H, $J = 6.8$ Hz, $-\text{CH}(\text{CH}_3)_2$), 2.21 (td, 1H, $J = 12.6$ Hz and 3.6 Hz, *H*-2_A), 2.12 (s, 3H, $-\text{COCH}_3$), 2.06 (dd, 1H, $J = 12.8$ Hz and 5.2 Hz, *H*-2_B), 1.98 (s, 3H, $-\text{COCH}_3$), 1.88 (s, 3H, $-\text{COCH}_3$), 1.19 (d, 6H, $J = 6.8$ Hz, $-\text{CH}(\text{CH}_3)_2$).

$^{13}\text{C NMR}$: (CDCl_3 , 100 MHz): δ_{C} 170.2 ($-\text{C}=\text{O}$), 170.1 ($-\text{C}=\text{O}$), 169.9 ($-\text{C}=\text{O}$), 154.3 (*ipso*-Ph), 142.8 (*para*-Ph), 127.2 (*ortho*-Ph), 116.3 (*meta*-Ph), 95.9 (*C*-1), 67.4 (*C*-5), 66.4 (*C*-3), 66.0 (*C*-4), 62.0 (*C*-5), 33.2 ($-\text{CH}(\text{CH}_3)_2$), 30.2 (*C*-2), 24.0 ($-\text{CH}(\text{CH}_3)_2$), 20.7 ($-\text{COCH}_3$), 20.6 ($-\text{COCH}_3$), 20.4 ($-\text{COCH}_3$).

IR: 2961, 1740, 1609, 1511, 1216, 1002, 831 cm^{-1}

HRMS (ESI⁺): calc. for $[\text{M}+\text{Na}]^+$: 431.1682, found: 431.1689

4-Methylphenyl-3,4,6-tri-*O*-acetyl-2-deoxy-D-lyxo-hexopyranoside (2.8)³



light yellow oil

Yield: 71%

R_f: 0.38 (Hexane:EtOAc, 3:1)

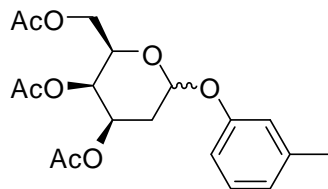
¹H NMR: (CDCl₃, 400 MHz): δ_H 7.06 (d, 2H, *J* = 8.0 Hz, *ortho*-Ph), 6.93 (d, 2H, *J* = 8.8 Hz, *meta*-Ph), 5.66 (d, 1H, *J* = 2.8 Hz, *H*-1), 5.48 (dq, 1H, *J* = 12.3 Hz and 2.7 Hz, *H*-3), 5.37 (d, 1H, *J* = 2.8 Hz, *H*-4), 4.25 (t, 1H, *J* = 6.6 Hz, *H*-5), 4.09-4.00 (m, 2H, *H*-6_A and *H*-6_B), 2.27 (s, 3H, -CCH₃), 2.22 (td, 1H, *J* = 12.8 Hz and 3.6 Hz, *H*-2_A), 2.13 (s, 3H, -COCH₃), 2.07 (dd, 1H, *J* = 12.8 Hz and 5.2 Hz, *H*-2_B), 2.00 (s, 3H, -COCH₃), 1.91 (s, 3H, -COCH₃).

¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.3 (-C=O), 170.2 (-C=O), 170.0 (-C=O), 154.2 (*ipso*-Ph), 131.7 (*para*-Ph), 129.9 (*ortho*-Ph), 116.4 (*meta*-Ph), 96.1 (*C*-1), 67.4 (*C*-5), 66.5 (*C*-3), 66.0 (*C*-4), 62.1 (*C*-6), 30.3 (*C*-2), 20.8 (-CCH₃), 20.7 (-COCH₃), 20.5(2x-COCH₃).

IR: 2927, 1741, 1509, 1217, 1015, 892 cm⁻¹

HRMS (ESI+) calc. for [M+Na]⁺: 403.1369, found: 403.1383

3-Methylphenyl-3,4,6-tri-*O*-acetyl-2-deoxy-D-lyxo-hexopyranoside (2.9)



Clear oil

Yield: 74%

R_f: 0.39 (Hexane:EtOAc, 3:1)

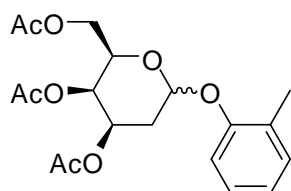
¹H NMR: (CDCl₃, 400 MHz): δ_H 7.13 (t, 1H, *J* = 7.8 Hz, *meta*-Ph), 6.85 (s, 1H, *ortho*-Ph), 6.81 (d, 2H, *J* = 8.0 Hz, *para*-Ph and *ortho*-Ph), 5.70 (s, 1H, *H*-1), 5.47 (dd, 1H, *J* = 8.2 Hz and 3.4 Hz, *H*-3), 5.37 (s, 1H, *H*-4), 4.24 (t, 1H, *J* = 6.4 Hz, *H*-5), 4.06-4.02 (m, 2H, *H*-6_A and *H*-6_B), 2.30 (s, 3H, -CCH₃), 2.12 (td, 1H, *J* = 12.8 Hz and 3.3 Hz, *H*-2_A), 2.13 (s, 3H, -COCH₃), 2.06 (dd, 1H, *J* = 13.0 Hz and 4.6 Hz, *H*-2_B), 1.99 (s, 3H, -COCH₃), 1.89 (s, 3H, -COCH₃).

^{13}C NMR: (CDCl_3 , 100 MHz): δ_{C} 170.3 (-C=O), 170.2 (-C=O), 170.0(-C=O), 156.2 (*ipso*-Ph), 139.4 (*meta*-Ph), 129.1 (*meta*-Ph), 123.1 (*para*-Ph), 117.2 (*ortho*-Ph), 113.3 (*ortho*-Ph), 95.7 (C-1), 67.4 (C-5), 66.4 (C-3), 65.9 (C-4), 62.0 (C-6), 30.2 (C-2), 21.3 (-CCH₃), 20.8 (-COCH₃), 20.6 (-COCH₃), 20.4 (-COCH₃).

IR: 2931, 1736, 1512, 1233, 1008, 823 cm^{-1}

HRMS (ESI+) calc. for $[\text{M}+\text{Na}]^+$: 403.1369, found: 403.1381

2-Methylphenyl-3,4,6-tri-*O*-acetyl-2-deoxy-D-lyxo-hexopyranoside (2.10)⁵



Clear oil

Yield: 71%

R_f : 0.38 (Hexane:EtOAc, 3:1)

^1H NMR: (CDCl_3 , 400 MHz): δ_{H} 7.13-7.07 (m, 3H, *ortho*-, *para*- and *meta*-Ph), 6.91 (td, 1H, $J = 7.2$ Hz and 2.4 Hz, *meta*-Ph), 5.71 (s, 1H, *H*-1), 5.48 (dt, 1H, $J = 12.4$ Hz and 3.8 Hz, *H*-3), 5.40 (s, 1H, *H*-4), 4.24 (t, 1H, $J = 6.4$ Hz, *H*-5), 4.10-4.05 (m, 2H, *H*-6_A and *H*-6_B), 2.28 (td, 1H, $J = 12.6$ Hz and 3.4 Hz, *H*-2_A), 2.22 (s, 3H, -CCH₃), 2.14 (s, 3H, -COCH₃), 2.11 (dd, 1H, $J = 13.2$ Hz and 4.2), 2.01 (s, 3H, -COCH₃), 1.91 (s, 3H, -COCH₃).

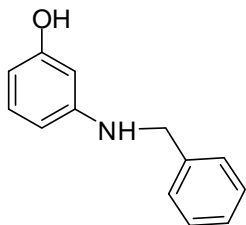
^{13}C NMR: (CDCl_3 , 100 MHz): δ_{C} 170.4 (-C=O), 170.2 (-C=O), 170.0(-C=O), 154.5 (*ipso*-Ph), 130.8 (*ortho*-Ph), 127.3 (*meta*-Ph), 126.8 (*para*-Ph), 122.1 (*meta*-Ph), 114.2 (*ortho*-Ph), 95.8 (C-1), 67.5 (C-5), 66.4 (C-3), 66.1 (C-4), 62.0 (C-6), 30.4 (C-2), 20.8 (-COCH₃), 20.7 (-COCH₃), 20.5 (-COCH₃), 16.2 (-CCH₃).

IR: 2923, 1740, 1381, 1223, 1032, 883 cm^{-1}

HRMS (ESI+) calc. for $[\text{M}+\text{Na}]^+$: 403.1369, found: 403.1365

5.3.2 Protection of aryl amines

3-(Benzylamino)phenol (2.11)⁶



To a solution of 3-amino phenol (1 g, 9.2 mmol) in DMF (15 mL) were added potassium hydroxide (1.55 g, 27.6 mmol) and benzyl chloride (1.58 mL, 13.8 mmol). The reaction mixture was allowed to stir at room temperature for 1 h, then warmed up to 80 °C and left to stir overnight. Upon completion the reaction mixture was extracted with DCM and washed with water (3×), dried in MgSO₄ (anhydrous). Volatiles were evaporated and the crude product purified through flash column chromatography (Hexane: EtOAc, 2:1).

Brown solid

Mp: 46-48 °C

Yield: 97 %

R_f: 0.46 (hexane/EtOAc, 2:1)

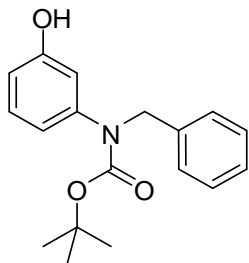
¹H NMR: (400 MHz, CDCl₃): δ_H 7.42-7.33 (m, 5H, *Ph*), 7.10 (t, 1H, *J* = 8.0 Hz, *H*-5), 6.44 (dd, 1H, *J* = 8.2 Hz and 2.2 Hz, *H*-6), 6.35 (dd, 1H, *J* = 4.0 Hz and 1.6 Hz, *H*-4), 6.32 (d, 1H, *J* = 2.0 Hz, *H*-2), 5.04 (s, 2H, -NHCH₂-), 3.68 (s, 2H, -NH and -OH).

¹³C NMR: (100 MHz, CDCl₃): δ_C 159.8 (*C*-3), 147.5 (*C*-1), 137.1 (*C*-1'), 130.0 (*C*-5), 128.4 (*meta*-Ph), 127.8 (*para*-Ph), 127.4 (*para*-Ph), 108.2 (*C*-2), 104.8 (*C*-6), 102.0 (*C*-4), 69.7 (-NHCH₂)

IR: 3436, 3362, 2878, 2360, 1764, 1582, 1178, 1025 cm⁻¹



3-Pivaloyloxy, 3-benzyl aminophenol (2.12)⁷



To a solution of phenol (500 mg, 2.5 mmol) in THF (10 mL) was added Boc_2O (821 mg, 3.76 mmol). The reaction mixture was allowed to stir at 40 °C for 16 hours. The THF was evaporated and the crude product was purified with flash column chromatography (Hexane: EtOAc, 7:1).

Cream solid

Mp: 84-86 °C

Yield: 91 %

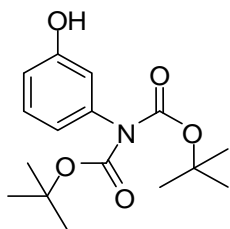
R_f : 0.57 (hexane/EtOAc, 7:1)

$^1\text{H NMR}$: (400 MHz, CDCl_3): δ_{H} 7.43-7.27 (m, 5H, *Ar*), 7.19 (br s, 1H, *Ar*), 7.16 (t, 1H, $J = 8.4$ Hz, *Ar*), 6.84 (dd, 1H, $J = 8.0$ Hz and 1.2 Hz, *Ph*), 6.64 (ddd, 1H, $J = 8.4$ Hz, 2.4 Hz and 0.8 Hz, *Ar*), 6.47 (br s, 1H, *OH*), 1.51 (s, 9H, $-\text{C}(\text{CH}_3)_3$).

$^{13}\text{C NMR}$: (75 MHz, CDCl_3): δ_{C} 159.5 ($-\text{C}=\text{O}$), 152.6 (*ipso-Ph*), 139.6 (*Ar*), 137.0 (*Ar*), 129.7 (*Ar*), 128.5 (*Ar*), 127.9 (*Ar*), 127.5 (*Ar*), 110.9 (*Ar*), 109.6 (*Ar*), 105.1 (*Ar*), 80.5 ($-\text{C}(\text{CH}_3)_3$), 69.9 ($-\text{CH}_2\text{Ph}$), 28.3 ($-\text{C}(\text{CH}_3)_3$).

IR: 3330, 2983, 1692, 1603, 1529, 1091, 771 cm^{-1}

3-Bis(pivaloyloxy)amino)phenol (2.13)



To solution of 3-amino phenol (500 mg, 4.6 mmol) in THF (10 mL) was added Boc_2O (3 eq, 3.01 g). The reaction mixture was allowed to heat under reflux at 70 °C for 10 hours. The solvent was evaporated and the crude product was purified using flash column chromatography (Hexane: EtOAc, 7:1).

Cream solid

Mp: 60-62 °C

Yield: 81 %

R_f : 0.63 (hexane/EtOAc, 7:1)

$^1\text{H NMR}$: (400 MHz, CDCl_3): δ_{H} 7.33 (br s, 1H, *H*-2), 7.20 (t, 1H, $J = 8.0$ Hz, *H*-5), 7.06 (dd, 1H, $J = 8.2$ Hz and 1.0 Hz, *H*-4), 6.79 (ddd, 1H, $J = 8.4$ Hz, 2.4 Hz and 1.2 Hz, *H*-6), 6.68 (br s, 1H, OH), 1.51 (s, 9H, $-\text{C}(\text{CH}_3)_3$), 1.47 (s, 9H, $-\text{C}(\text{CH}_3)_3$).

$^{13}\text{C NMR}$: (75 MHz, CDCl_3): δ_{C} 152.4 ($-\text{C}=\text{O}$), 151.8 ($-\text{C}=\text{O}$), 151.4 (*ipso*-Ph), 139.5 (*C*-3), 129.4 (*C*-5), 115.6 (*C*-6 and *C*-4), 111.6 (*C*-2), 83.4 ($-\text{C}(\text{CH}_3)_3$), 80.6 ($-\text{C}(\text{CH}_3)_3$), 28.3 ($-\text{C}(\text{CH}_3)_3$), 27.6 ($-\text{C}(\text{CH}_3)_3$).

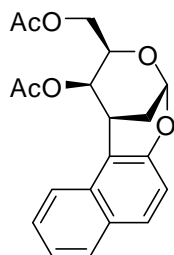
IR: 3560, 2972, 1758, 1698, 1546, 1140, 854 cm^{-1}

HRMS (ESI+): calc. for $[\text{M}+\text{Na}]^+$: 332.1474, found: 332.1477

5.3.3 Synthesis of bridged chiral benzopyrans with 3,4,6-*tri-O*-acetyl-D-galactal

To a solution of 3,4,6-*tri-O*-acetyl-D-galactal (200 mg, 0.735 mmol) and DCE (2.0 mL), were added the phenol in question (1.2 equivalents, 0.882 mmol) and $\text{Al}(\text{OTf})_3$ (5 mol%, 17 mg). The reaction mixture was stirred at 40 °C until it was judged to be complete by TLC analysis; the reaction was quenched by adding concentrated aqueous sodium bicarbonate solution (2 mL) and the mixture extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried over anhydrous magnesium sulfate. The volatile component was removed under vacuum leaving the crude product that was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 3:1) was used as eluent.

((1*R*,2*R*,3*R*,5*R*)-2-acetoxy-2,3-dihydro-1*H*-1,5-methanonaphtho[2,1-*d*][1,3]dioxocin-3-yl)methyl acetate (2.14)



Cream powder

Mp: 46-48 °C

Yield: 69%

R_f: 0.53 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 8.13 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.79 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.73 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.58 (t, 1H, *J* = 7.8 Hz, *H*-7'), 7.39 (t, 1H, *J* = 5.8 Hz, *H*-6'), 7.15 (d, 1H, *J* = 8.8 Hz, *H*-4'), 5.74 (s, 1H, *H*-1), 4.94 (s, 1H, *H*-4), 4.10 (d, 2H, *J* = 6.8 Hz, *H*-6_A and *H*-6_B), 3.98 (d, 2H, *J* = 4.0 Hz, *H*-3 and *H*-5), 2.56 (d, 1H, *J* = 13.2 Hz, *H*-2_A), 2.23 (s, 3H, -COCH₃), 1.96 (s, 3H, -COCH₃), 1.74 (d, 1H, *J* = 13.2 Hz, *H*-2_B).

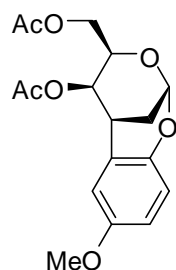
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.6(2x -C=O), 152.9 (*C*-2'), 131.8 (*C*-4'*a*), 129.4 (*C*-5'), 129.1 (*C*-8'*a*), 128.5 (*C*-3'), 127.5 (*C*-7'), 124.0 (*C*-8'), 121.7 (*C*-6'), 117.6 (*C*-4'), 114.2 (*C*-1'), 92.6 (*C*-1), 69.1 (*C*-4), 68.0 (*C*-5), 63.2 (*C*-6), 27.7 (*C*-3), 23.1 (*C*-2), 21.1 (-COCH₃), 20.8 (-COCH₃).

IR: 2945, 1748, 1729, 1372, 1087, 823 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 379.1158, found: 379.1160

[α]_D: -134.5 (c 0.5, CH₂Cl₂)

((2*R*,4*R*,5*R*,6*R*)-5-acetoxy-8-methoxy-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-4-yl)methyl acetate (2.15)³



White solid,

Mp: 90-92 °C

Yield: 71%

R_f: 0.52 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 6.84 (d, 1H, *J* = 9.2 Hz, *ortho*-Ph), 7.77 (dd, 1H, *J* = 8.8 Hz and 3.2 Hz, *meta*-Ph), 6.69 (d, 1H, *J* = 3.2 Hz, *meta*-Ph), 5.60 (s, 1H, *H*-1), 4.84 (s, 1H, *H*-4), 4.10-4.00 (m, 2H, *H*-6_A and *H*-6_B), 3.98 (t, 1H, *J* = 5.8 Hz, *H*-5), 3.75 (s, 3H, -OCH₃), 3.20 (s, 1H, *H*-3), 2.41 (dt, 1H, *J* = 13.2 Hz and 2.4 Hz, *H*-2_A), 2.14 (s, 3H, -COCH₃), 1.98 (s, 3H, -COCH₃), 1.67 (d, 1H, *J* = 12.0 Hz, *H*-2_B).

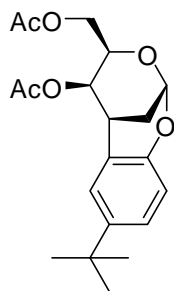
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.5 (-C=O), 170.2 (-C=O), 153.8 (*ipso*-Ph), 148.8 (*para*-Ph), 122.6 (*ortho*-Ph), 116.5 (*ortho*-Ph), 115.2 (*meta*-Ph), 113.4 (*meta*-Ph), 92.8 (*C*-1), 69.9 (*C*-4), 67.1 (*C*-5), 63.1 (*C*-6), 55.8 (-OCH₃), 32.8 (*C*-3), 23.4 (*C*-2), 21.0 (-COCH₃), 20.7 (-COCH₃).

IR: 2923, 1729, 1498, 1219, 1011, 861 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 359.1107, found: 359.1107

[α]_D: -17.0 (*c* 0.5, CH₂Cl₂)

((2*R*,4*R*,5*R*,6*R*)-5-acetoxy-8-(tert-butyl)-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-4-yl)methyl acetate (2.16)



Cream solid

Mp: 86-88 °C

Yield: 73%

R_f: 0.64 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 7.21 (dd, 1H, *J* = 8.4 Hz and 2.4 Hz, *meta*-Ph), 7.11 (d, 1H, *J* = 2.4 Hz, *meta*-Ph), 6.83 (d, 1H, *J* = 8.8 Hz, *ortho*-Ph), 5.61 (s, 1H, *H*-1), 4.84 (s, 1H, *H*-4), 4.10-4.00 (m, 2H, *H*-6_A and *H*-6_B), 3.97 (td, 1H, *J* = 6.1 Hz and 1.9 Hz, *H*-5), 3.21 (s, 1H, *H*-3), 2.42 (dt, 1H, *J* = 13.2 Hz and 2.4 Hz, *H*-2_A), 2.14 (s, 3H, -COCH₃), 1.97 (s, 3H, -COCH₃), 1.67 (d, 1H, *J* = 13.2 Hz, *H*-2_B), 1.27 (s, 9H, -C(CH₃)₃).

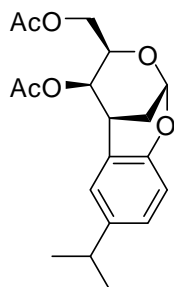
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.5 (-C=O), 170.1 (-C=O), 152.5 (*ipso*-Ph), 143.9 (*para*-Ph), 126.1 (*ortho*-Ph), 125.6 (*meta*-Ph), 121.3 (*ortho*-Ph), 115.1 (*meta*-Ph), 92.9 (*C*-1), 70.1 (*C*-4), 67.0 (*C*-5), 63.2 (*C*-6), 34.0 (-C(CH₃)₃), 32.8 (*C*-3), 31.4 (-C(CH₃)₃), 23.5 (*C*-2), 20.9 (-COCH₃), 20.6 (-COCH₃).

IR: 2965, 1733, 1437, 1229, 1043, 989, 866 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 385.1627, found: 385.1637

[α]_D: -48.0 (*c* 0.5, CH₂Cl₂)

((2*R*,4*R*,5*R*,6*R*)-5-acetoxy-8-isopropyl-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-4-yl)methyl acetate (2.17)



Cream solid

Mp: 74-76 °C

Yield: 70%

R_f: 0.60 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 7.06 (dd, 1H, *J* = 8.4 Hz and 2.4 Hz, *meta*-Ph), 6.99 (d, 1H, *J* = 2.4 Hz, *meta*-Ph), 6.83 (d, 1H, *J* = 8.4 Hz, *ortho*-Ph), 5.62 (s, 1H, *H*-1), 4.84 (s, 1H, *H*-4), 4.11-4.01 (m, 2H, *H*-6_A and *H*-6_B), 3.97 (td, 1H, *J* = 6.1 Hz and 1.7 Hz, *H*-5), 3.21 (s, 1H, *H*-3), 2.83 (sp, 1H, *J* = 6.8 Hz, -CH(CH₃)₂), 2.42 (dt, 1H, *J* = 12.4 Hz and 2.4 Hz, *H*-2_A), 2.15 (s, 3H, -COCH₃), 1.98 (s, 3H, -COCH₃), 1.68 (d, 1H, *J* = 12.0 Hz, *H*-2_B), 1.21 (d, 6H, *J* = 6.8 Hz, -CH(CH₃)₂).

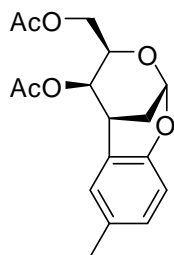
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.5 (-C=O), 170.2 (-C=O), 152.8 (*ipso*-Ph), 141.6 (*para*-Ph), 127.0 (*ortho*-Ph), 126.9 (*meta*-Ph), 121.8 (*ortho*-Ph), 115.5 (*meta*-Ph), 92.9 (*C*-1), 70.2 (*C*-4), 67.1 (*C*-5), 63.2 (*C*-6), 33.2 (-CH(CH₃)₂), 32.7 (*C*-3), 24.2 (-CHCH₃CH₃), 24.0 (-CHCH₃CH₃), 23.5 (*C*-2), 21.0 (-COCH₃), 20.7 (-COCH₃)

IR: 2959, 1730, 1590, 1227, 1047, 823 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 371.1471, found: 341.1476

[α]_D: -26.0 (*c* 0.5, CH₂Cl₂)

((2*R*,4*R*,5*R*,6*R*)-5-acetoxy-8-methyl-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-4-yl)methyl acetate (2.18)³



Cream solid

Mp: 122-124 °C

Yield: 67%

R_f: 0.56 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 7.04 (d, 1H, *J* = 8.4 Hz, *meta*-Ph), 7.02 (s, 1H, *ortho*-Ph), 7.85 (d, 1H, *J* = 8.0 Hz, *meta*-Ph), 5.67 (s, 1H, *H*-1), 4.87 (s, 1H, *H*-4), 4.13 (m, 2H, *H*-6_A and *H*-6_B), 4.01 (t, 1H, *J* = 3.6 Hz, *H*-5), 3.23 (s, 1H, *H*-3), 2.46 (d, 1H, *J* = 11.6 Hz, *H*-2_A), 2.31 (s, 3H, -CCH₃), 2.19 (s, 3H, -COCH₃), 2.03 (s, 3H, -COCH₃), 1.72 (d, 1H, *J* = 13.2 Hz, *H*-2_B).

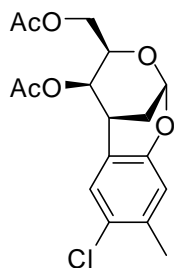
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.6 (-C=O), 170.2 (-C=O), 152.7 (*ipso*-Ph), 130.4 (*para*-Ph), 129.7 (*ortho*-Ph), 129.5 (*meta*-Ph), 121.8 (*ortho*-Ph), 115.5 (*meta*-Ph), 92.9 (*C*-1), 70.1 (*C*-4), 67.1 (*C*-5), 63.2 (*C*-6), 32.4 (*C*-3), 23.5 (*C*-2), 21.0 (-COCH₃), 20.8 (-CCH₃), 20.4 (-COCH₃)

IR: 2923, 1733, 1500, 1223, 1013, 877 cm⁻¹

HRMS (ESI+) calc. for [M+Na]⁺: 320.1260, found: 343.1165

[α]_D: -27.0 (*c* 0.5, CH₂Cl₂)

((2*R*,4*R*,5*R*,6*R*)-5-acetoxy-8-chloro-9-methyl-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-4-yl)methyl acetate (2.19)



Clear oil

Yield: 61%

R_f : 0.51 (Hexane: EtOAc, 3:1)

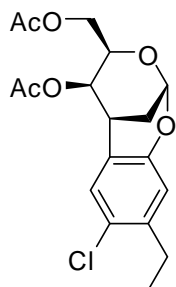
$^1\text{H NMR}$: (CDCl_3 , 400 MHz): Mixture of regioisomers (4:1), δ_{H} 7.19 (d, 0.2H, $J = 8.8$ Hz, *ortho*-Ph), 7.15 (s, 0.8H, *ortho*-Ph), 6.79 (s, 0.8H, *meta*-Ph), 6.73 (d, $J = 8.8$ Hz, 0.2H, *meta*-Ph), 5.62 (s, 1H, *H-1*), 4.80 (s, 0.8H, *H-4*), 4.73 (s, 0.2H, *H-4*), 4.10-4.00 (m, 2H, *H-6_A* and *H-6_B*), 3.92 (t, 1H, $J = 6.4$ Hz, *H-5*), 3.47 (d, 0.2H, $J = 2.0$ Hz, *H-3*), 3.19 (s, 0.8H, *H-3*), 2.41 (dt, 1H, $J = 13.2$ Hz and 2.4 Hz, *H-2_A*), 2.42 (s, 0.6H, - CCH_3), 2.29 (s, 2.4H, - CCH_3), 2.16 (s, 0.6H, - COCH_3), 2.14 (s, 2.4H - COCH_3), 1.99 (s, 3H, - COCH_3), 1.65 (d, 1H, $J = 14.0$ Hz, *H-2_B*).

$^{13}\text{C NMR}$: (CDCl_3 , 100 MHz): δ_{C} 170.5 (-C=O), 170.0 (-C=O), 153.2 (*ipso*-Ph), 137.0 (*para*-Ph), 128.9 (*ortho*-Ph), 126.1 (*meta*-Ph), 121.0 (*ortho*-Ph), 118.0 (*meta*-Ph), 92.9 (*C-1*), 69.6 (*C-4*), 67.0 (*C-5*), 62.9 (*C-6*), 31.9 (*C-3*), 23.3 (*C-2*), 21.0 (- COCH_3), 20.7 (- COCH_3), 19.9 (- CCH_3).

IR: 2943, 2365, 1737, 1370, 1220, 1030, 890 cm^{-1}

HRMS (ESI+) calc. for $[\text{M}+\text{Na}]^+$: 377.0768, found: 377.0781

((2*R*,4*R*,5*R*,6*R*)-5-acetoxy-8-chloro-9-ethyl-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-4-yl)methyl acetate (2.20)



Light yellow oil

Yield: 64%

R_f: 0.55 (Hexane: EtOAc, 3:1)

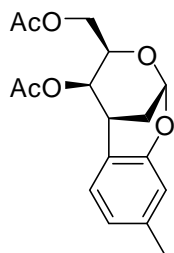
¹H NMR: (CDCl₃, 400 MHz): Mixture of regioisomers (9:1), δ_H 7.18 (d, 0.1H, *J* = 8.8 Hz, *ortho*-Ph), 7.15 (s, 0.9H, *ortho*-Ph), 6.79 (s, 0.9H, *meta*-Ph), 6.72 (d, 0.1H, *J* = 8.4 Hz, *meta*-Ph), 5.62 (s, 1H, *H*-1), 4.81 (s, 0.9H, *H*-4), 4.73 (s, 0.1H, *H*-4), 4.10-4.00 (m, 2H, *H*-6_A and *H*-6_B), 3.93 (td, 1H, *J* = 6.4 Hz and 1.7 Hz, *H*-5), 3.43 (s, 0.1H, *H*-3), 3.18 (s, 0.9H, *H*-3), 2.66 (q, 2H, *J* = 7.8 Hz, -CH₂CH₃), 2.41 (dt, 1H, *J* = 13.2 Hz and 2.4 Hz, *H*-2_A), 2.16 (s, 0.3H, -COCH₃), 2.14 (s, 2.7H, -COCH₃), 1.98 (s, 3H, -COCH₃), 1.65 (d, 1H, *J* = 13.2 Hz, *H*-2_B), 1.19 (t, 3H, *J* = 7.6 Hz, -CH₂CH₃).

¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.5 (-C=O), 170.0 (-C=O), 153.2 (*ipso*-Ph), 142.6 (*para*-Ph), 129.2 (*ortho*-Ph), 125.5 (*meta*-Ph), 121.0 (*ortho*-Ph), 116.5 (*meta*-Ph), 93.0 (*C*-1), 69.6 (*C*-4), 67.0 (*C*-5), 62.9 (*C*-6), 31.9 (*C*-3), 26.5 (-CH₂CH₃), 23.3 (*C*-2), 20.9 (-COCH₃), 20.7 (-COCH₃), 13.7 (-CH₂CH₃).

IR: 2970, 2936, 1739, 1340, 1220, 1032, 890 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 391.0925, found: 391.0930

((2*R*,4*R*,5*R*,6*R*)-5-acetoxy-9-methyl-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-4-yl)methyl acetate (2.21)



Colourless oil

Yield: 67%

R_f : 0.57 (Hexane: EtOAc, 3:1)

$^1\text{H NMR}$: (CDCl_3 , 400 MHz): Mixture of regioisomers (7:3), δ_{H} 7.10-7.04 (m, 1H, *Ar*), 6.80-6.74 (m, 1H, *Ar*), 5.63 (s, 1H, *H-1*), 4.81 (s, 0.7H, *H-4*), 4.78 (s, 0.3H, *H-4*), 4.09-4.01 (m, 2H, *H-6_A* and *H-6_B*), 3.96 (t, 1H, $J = 5.6$ Hz, *H-5*), 3.41 (s, 0.3H, *H-3*), 3.21 (s, 0.7H, *H-3*), 2.42 (d, 1H, $J = 13.2$ Hz, *H-2_A*), 2.38 (s, 0.9H, $-\text{CCH}_3$), 2.29 (s, 2.1H, $-\text{CCH}_3$), 2.16 (s, 0.9H, $-\text{COCH}_3$), 2.14 (s, 2.1H, $-\text{COCH}_3$), 1.98 (s, 3H, $-\text{COCH}_3$), 1.68 (d, 1H, $J = 12.8$ Hz, *H-2_B*).

$^{13}\text{C NMR}$: (CDCl_3 , 100 MHz): δ_{C} 170.6 ($-\text{C}=\text{O}$), 170.3 ($-\text{C}=\text{O}$), 154.6 (*ipso-Ph*), 139.3 (*meta-Ph*), 128.9 (*ortho-Ph*), 122.0 (*para-Ph*), 119.2 (*ortho-Ph*), 116.2 (*meta-Ph*), 92.9 (*C-1*), 70.1 (*C-4*), 67.0 (*C-5*), 63.2 (*C-6*), 32.1 (*C-3*), 23.6 (*C-2*), 21.2 ($-\text{COCH}_3$), 21.0 ($-\text{CCH}_3$), 20.7 ($-\text{COCH}_3$).

IR: 2947, 1737, 1624, 1439, 1221, 1093, 888 cm^{-1}

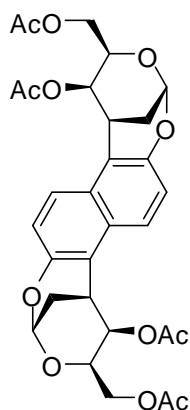
HRMS (ESI+): calc. for $[\text{M}+\text{Na}]^+$: 343.1158, found: 343.1149

5.3.4 Synthesis of Hexacyclic bridged chiral benzopyran with 3,4,6-*tri-O*-acetyl-D-galactal

To a solution of 3,4,6-*tri-O*-acetyl-D-galactal (200 mg, 0.735 mmol) in DCE (2.0 mL) were added 2,6-dihydroxynaphthalene (0.5 equivalents, 0.368 mmol) and $\text{Al}(\text{OTf})_3$ (5 mol%, 17 mg).

The reaction mixture was stirred at 40 °C until it was judged to be complete by TLC analysis, after which the reaction was quenched by adding saturated sodium bicarbonate (2 mL) solution and the mixture extracted with CH₂Cl₂ (3×5 mL). The combined organic phases were dried over anhydrous magnesium sulfate. The volatile component was removed under vacuum leaving the crude product that was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 1:1) was used as eluent.

(2*R*,4*R*,5*R*,6*R*,10*S*,12*R*,13*R*,14*S*)-4,12-bis(acetoxymethyl)-4,5,6,12,13,14-hexahydro-2,6:10,14-dimethanonaphtho[2,1-*d*:6,5-*d'*]bis([1,3]dioxocine)-5,13-diyl diacetate (2.22)



Cream solid

Mp: 208-210 °C

Yield: 64%

R_f: 0.37 (1:1, EtOAc:Hexane)

¹H NMR: (CDCl₃, 400 MHz): δ_H 8.03 (d, 2H, *J* = 9.2 Hz, *Ar*), 7.25 (d, 2H, *J* = 9.2 Hz, *Ar*), 5.72 (s, 2H, *H*-1), 4.90 (s, 2H, *H*-4), 4.09 (t, 4H, *J* = 3.4 Hz, *H*-6_A and *H*-6_B), 4.00 (d, 2H, *J* = 5.6 Hz, *H*-5), 3.92 (s, 2H, *H*-3), 2.54 (d, 2H, *J* = 13.2 Hz, *H*-2_A), 2.21 (s, 6H, -COCH₃), 1.97 (s, 6H, -COCH₃), 1.71 (d, 2H, *J* = 12.8 Hz, *H*-2_B).

^{13}C NMR: (CDCl₃, 100 MHz): δ_{C} 170.7(-C=O), 151.5 (*ipso*-Ph), 127.4 (*Ar*), 123.0 (*Ar*), 118.7 (*Ar*), 115.1 (*Ar*), 92.4 (*C-1*), 69.2 (*C-4*), 67.9 (*C-5*), 63.4 (*C-6*), 27.8 (*C-3*), 23.1 (*C-2*), 21.0 (-COCH₃), 20.7 (-COCH₃).

IR: 2982, 2361, 1733, 1599, 1403, 1220, 1007, 816

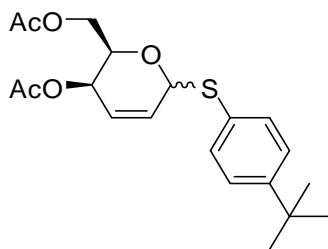
HRMS (ESI+) calc. for [M+Na]⁺: 607.1792, found: 607.1796

[α]_D: -22.0 (*c* 0.5, CH₂Cl₂)

5.3.5 Synthesis of *O*-aryl thiogalactosides

To a solution of 3,4,6-*tri-O*-acetyl-D-galactal (200 mg, 0.735 mmol) and DCE (2.0 mL), were added 4-*tert*-butylbenzenethiol (1.2 equivalents, 0.882 mmol) and Al(OTf)₃ (5 mol%, 17 mg). The reaction mixture was stirred at either 0 °C or 40 °C until it was judged to be complete by TLC analysis, at which time it was quenched by the addition of concentrated aqueous sodium bicarbonate solution (2.0 mL). The resulting mixture was extracted with DCM (3×5 mL). The combined organic phases were dried over anhydrous magnesium sulfate. The volatile component was removed *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 3:1) was used as eluent.

((2*R*,3*R*,6*R*)-3-acetoxy-6-(4-*tert*-butylphenylthio)-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate (2.23)



Light yellow oil

Yield: 66%

R_f: 0.57 (Hexane:EtOAc, 3:1)

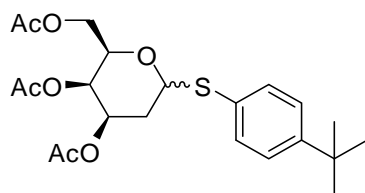
¹H NMR: (CDCl₃, 400 MHz): δ_H 7.47 (d, 2H, *J* = 8.0 Hz, *ortho*-Ph), 7.30 (d, 2H, *J* = 8.4 Hz, *meta*-Ph), 6.19 (dd, 1H, *J* = 10.0 Hz and 3.2 Hz, *H*-2), 6.06 (dd, 1H, *J* = 9.8 Hz and 5.4 Hz, *H*-3), 5.78 (s, 1H, *H*-1), 5.10 (t, 1H, *J* = 2.4 Hz, *H*-4), 4.69 (t, 1H, *J* = 6.0 Hz, *H*-5), 4.25 (d, 2H, *J* = 6.4 Hz, *H*-6_A and *H*-6_B), 2.05 (s, 3H, -COCH₃), 2.03 (s, 3H, -COCH₃), 1.23 (s, 9H, -C(CH₃)₃).

¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.5 (-C=O), 170.2 (-C=O), 150.9 (ipso), 131.9 (*ortho*-Ph), 131.4 (*C*-2), 130.9 (*para*-Ph), 125.9 (*meta*-Ph), 124.2 (*C*-3), 83.6 (*C*-1), 67.1 (*C*-5), 63.2 (*C*-4), 62.6 (*C*-6), 34.5 (-C(CH₃)₃), 31.2 (-C(CH₃)₃), 20.7(x2) (-COCH₃).

IR: 2960, 1741, 1490, 1368, 1223, 1072, 828 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 401.1399, found: 401.1384

(2*R*,3*R*,4*R*,6*R*)-2-(acetoxymethyl)-6-(4-*tert*-butylphenylthio)tetrahydro-2*H*-pyran-3,4-diyl diacetate (2.24)



Clear oil

Yield: 73%

R_f: 0.54 (Hexane:EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 7.38 (d, 2H, *J* = 8.0 Hz, *ortho*-Ph), 7.30 (d, 2H, *J* = 8.4 Hz, *meta*-Ph), 5.70 (d, 1H, *J* = 5.6 Hz, *H*-1), 5.35 (s, 1H, *H*-4), 5.26 (dd, 1H, *J* = 11.6

Hz and 3.6 Hz, *H*-3), 4.69 (t, 1H, *J* = 6.2 Hz, *H*-5), 4.08 (d, 2H, *J* = 6.4 Hz, *H*-6_A and *H*-6_B), 2.45 (td, 1H, *J* = 12.9 Hz and 5.7 Hz, *H*-2_A), 2.11 (s, 3H, -COCH₃), 2.04 (dd, 1H, *J* = 13.4 Hz and 5.0 Hz, *H*-2_B), 1.98 (s, 3H, -COCH₃), 1.96 (s, 3H, -COCH₃). 1.27 (s, 9H, -C(CH₃)₃).

¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.4 (-C=O), 170.2 (-C=O), 169.8 (-C=O), 150.7 (ipso), 131.6 (*ortho*-Ph), 130.2 (*para*-Ph), 126.0 (*meta*-Ph), 83.7 (*C*-1), 67.4 (*C*-5), 66.6 (x2) (*C*-4 and *C*-3), 62.3 (*C*-6), 34.5 (-C(CH₃)₃), 31.2 (-C(CH₃)₃), 30.6 (*C*-2), 20.8 (-COCH₃), 20.6 (-COCH₃).

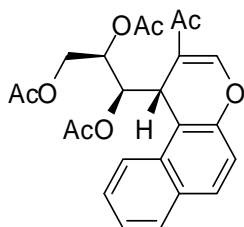
IR: 2958, 2926, 1744, 1491, 1461, 1219, 1015 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 461.1610, found: 461.1621

5.3.6 Acetolysis of bridged chiral benzopyrans towards 4*H*-chromenes

To a solution of the bridged chiral benzopyran (200 mg) in dichloromethane (2 mL) were added Al(OTf)₃ (10 mol%) and acetic anhydride (2mL) and the reaction solution was left to stir at room temperature under N₂ for 16 for hours. After completion, as determined by TLC, the product was extracted in diethyl ether and the organic layer washed with 1% NaHCO₃, saturated NaHCO₃ and brine. The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 2:1) was used as eluent.

(1*R*,2*R*)-1-(2-acetyl-1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triyl triacetate (2.25)



Cream solid

Mp: 125-127 °C

Yield: 87%

R_f: 0.36 (Hexane: EtOAc, 2:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 8.28 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.86 (s, 1H, *H*-1), 7.79 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.73 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.60 (td, 1H, *J* = 7.8 Hz and 1.6 Hz, *H*-7'), 7.44 (td, 1H, *J* = 8.0 Hz and 1.2 Hz, *H*-6'), 7.23 (d, 1H, *J* = 8.0 Hz, *H*-4'), 5.29 (d, 1H, *J* = 7.6 Hz, *H*-3), 5.17 (dd, 1H, *J* = 7.2 Hz and 2.8 Hz, *H*-4), 4.89 (td, 1H, *J* = 6.2 Hz and 2.8 Hz, *H*-5), 3.92 (dd, 1H, *J* = 11.4 Hz and 6.2 Hz, *H*-6_A), 3.80 (dd, 1H, *J* = 11.4 Hz and 6.2 Hz, *H*-6_B), 2.36 (s, 3H, -CCOCH₃), 2.13 (s, 3H, -OCOCH₃), 1.78 (s, 3H, -OCOCH₃), 1.54 (s, 3H, -OCOCH₃).

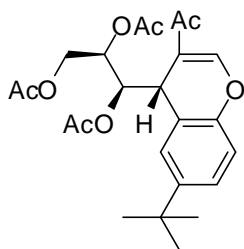
¹³C NMR: (CDCl₃, 100 MHz): δ_C 192.9 (-C=O), 170.2 (-C=O), 170.0 (-C=O), 169.9 (-C=O), 153.9 (*C*-1), 149.6 (*C*-2'), 131.6 (*C*-8'*a*), 131.3 (*C*-4'*a*), 129.3 (*C*-3'), 128.4 (*C*-5'), 127.1 (*C*-7'), 125.1 (*C*-6'), 123.5 (*C*-8'), 118.0 (*C*-2), 116.8 (*C*-4'), 113.8 (*C*-1'), 72.4 (*C*-4), 68.7 (*C*-5), 61.7 (*C*-6), 29.5 (*C*-3), 25.4 (-CCOCH₃), 20.8 (-OCOCH₃), 20.4 (-OCOCH₃), 20.2 (-OCOCH₃).

IR: 2961, 2360, 1742, 1664, 1206, 1043, 892 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 463.1369, found: 463.1378

[α]_D: -16.1 (*c* 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-(3-acetyl-6-*tert*-butyl-4*H*-chromen-4-yl)propane-1,2,3-triyl triacetate (2.26)



Light yellow oil

Yield: 83%

R_f: 0.40 (Hexane: EtOAc, 2:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 7.72 (s, 1H, *H-1*), 7.25 (d, 1H, *J* = 8.2 Hz, *meta*-Ph), 7.24 (s, 1H, *meta*-Ph), 6.97 (d, 1H, *J* = 8.4 Hz, *ortho*-Ph), 5.13 (td, 1H, *J* = 6.4 Hz and 4.4 Hz, *H-5*), 5.01 (dd, 1H, *J* = 6.4 Hz and 4.4 Hz, *H-4*), 4.41 (dd, 1H, *J* = 11.8 Hz and 4.2 Hz, *H-6_A*), 4.26 (d, 1H, *J* = 4.4 Hz, *H-3*), 4.13 (dd, 1H, *J* = 11.8 Hz and 6.2 Hz, *H-6_B*), 2.27 (s, 3H, -CCOCH₃), 2.06 (s, 3H, -OCOCH₃), 2.03 (s, 3H, -OCOCH₃), 1.85 (s, 3H, -OCOCH₃), 1.30 (s, 9H, -C(CH₃)₃).

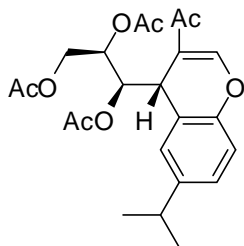
¹³C NMR: (CDCl₃, 100 MHz): δ_C 194.8 (-C=O), 170.6 (-C=O), 170.0 (-C=O), 169.8 (-C=O), 154.3 (*C-1*), 149.4 (*ipso*-Ph), 148.1 (*para*-Ph), 126.5 (*meta*-Ph), 125.4 (*meta*-Ph), 118.8 (*ortho*-Ph), 117.6 (*C-2*), 115.8 (*ortho*-Ph), 73.0 (*C-4*), 69.4 (*C-5*), 62.2 (*C-6*), 34.4 (-C(CH₃)₃), 33.8 (*C-3*), 31.4 (-C(CH₃)₃), 25.0 (-CCOCH₃), 20.8 (-OCOCH₃), 20.6 (-OCOCH₃), 20.5 (-OCOCH₃).

IR: 2963, 2330, 1735, 1223, 1043, 876 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 469.1839, found: 469.1848

[α]_D: -20.9 (*c* 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-(3-acetyl-6-isopropyl-4*H*-chromen-4-yl)propane-1,2,3-triyl triacetate (2.27)



Light yellow oil

Yield: 90%

R_f: 0.37 (Hexane: EtOAc, 2:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 7.71 (s, 1H, *H*-1), 7.09 (dd, 2H, *J* = 11.8 Hz and 1.8 Hz, *meta*-Ph), 6.95 (d, 1H, *J* = 8.0 Hz, *ortho*-Ph), 5.11 (td, 1H, *J* = 6.4 Hz and 4.4 Hz, *H*-5), 5.01 (dd, 1H, *J* = 6.4 Hz and 4.4 Hz, *H*-4), 4.40 (dd, 1H, *J* = 12.0 Hz and 4.4 Hz, *H*-6_A), 4.25 (d, 1H, *J* = 4.4 Hz, *H*-3), 4.12 (dd, 1H, *J* = 12.0 Hz and 6.0 Hz, *H*-6_B), 2.88 (sp, 1H, *J* = 7.2 Hz, -CH(CH₃)₂), 2.26 (s, 3H, -CCOCH₃), 2.05 (s, 3H, -OCOCH₃), 2.01 (s, 3H, -OCOCH₃), 1.85 (s, 3H, -OCOCH₃), 1.22 (d, 6H, *J* = 6.8 Hz, -CH(CH₃)₂).

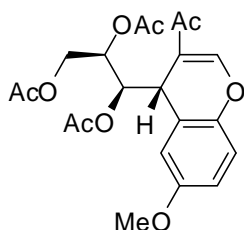
¹³C NMR: (CDCl₃, 100 MHz): δ_C 194.7 (-C=O), 170.6 (-C=O), 170.0 (-C=O), 169.8 (-C=O), 154.2 (*C*-1), 149.7 (*ipso*-Ph), 145.8 (*para*-Ph), 127.3 (*meta*-Ph), 126.5 (*meta*-Ph), 119.1 (*ortho*-Ph), 117.5 (*C*-2), 116.2 (*ortho*-Ph), 72.9 (*C*-4), 69.4 (*C*-5), 62.2 (*C*-6), 33.7 (-CH(CH₃)₂), 33.5 (*C*-3), 25.0 (-CCOCH₃), 24.0 (-CH(CH₃)₂), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 20.5 (-OCOCH₃).

IR: 2961, 2360, 1742, 1206, 1043, 892 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 455.1682, found: 455.1697

[α]_D: -24.3 (c 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-(3-acetyl-6-methoxy-4*H*-chromen-4-yl)propane-1,2,3-triyl triacetate (2.28)



Cream solid

Mp: 50-52°C

Yield: 80%

R_f: 0.31 (Hexane: EtOAc, 2:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 7.70 (s, 1H, *H-1*), 6.96 (d, 1H, *J* = 8.8 Hz, *ortho*-Ph), 6.77 (dd, 2H, *J* = 11.2 Hz and 2.6 Hz, *meta*-Ph), 5.14 (td, 1H, *J* = 6.6 Hz and 4.2 Hz, *H-5*), 5.03 (dd, 1H, *J* = 6.8 Hz and 4.0 Hz, *H-4*), 4.42 (dd, 1H, *J* = 12.0 Hz and 4.0 Hz, *H-6_A*), 4.23 (d, 1H, *J* = 3.6 Hz, *H-3*), 4.09 (dd, 1H, *J* = 11.8 Hz and 6.6 Hz, *H-6_B*), 3.78 (s, 3H, -OCH₃), 2.26 (s, 3H, -CCOCH₃), 2.04 (s, 3H, -OCOCH₃), 2.00 (s, 3H, -OCOCH₃), 1.87 (s, 3H, -OCOCH₃).

¹³C NMR: (CDCl₃, 100 MHz): δ_C 194.8 (-C=O), 170.6 (-C=O), 170.0 (-C=O), 169.9 (-C=O), 156.7 (*C-1*), 154.3 (*ipso*-Ph), 145.6 (*para*-Ph), 120.1 (*meta*-Ph), 117.2 (*C-2*), 116.7 (*ortho*-Ph), 114.5 (*ortho*-Ph), 113.6 (*meta*-Ph), 72.9 (*C-4*), 69.6 (*C-5*), 62.3 (*C-6*), 55.8 (-OCH₃), 34.1 (*C-3*), 25.0 (-CCOCH₃), 20.7 (-OCOCH₃), 20.6 (-OCOCH₃), 20.5 (-OCOCH₃).

IR: 2924, 1733, 1633, 1371, 1223, 1033, 826 cm⁻¹

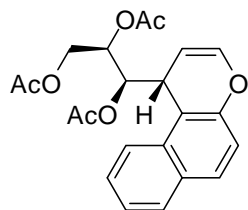
HRMS (ESI+): calc. for [M+Na]⁺: 443.1318, found: 443.1328

[α]_D: -25.3 (*c* 0.5, CH₂Cl₂)

5.3.7 Acetolysis of bridged chiral benzopyrans towards chromans

To a solution of the bridged chiral benzopyran (200 mg) in dichloromethane (2 mL) were added Al(OTf)₃ (10 mol%), acetic acid (2 mL) and acetic anhydride (2mL) and the reaction mixture was left to stir at room temperature under N₂ for 16 hours. After completion, as assessed by TLC, the product was extracted with diethyl ether and the organic layer washed with 1% NaHCO₃, saturated NaHCO₃ and brine. The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 3:1) was used as eluent.

(1*R*,2*R*)-1-(1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triyl triacetate (2.29)



Cream solid

Mp: 152-154 °C

Yield: 67%

R_f: 0.37 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 8.15 (d, 1H, *J* = 8.8 Hz, *H*-8'), 7.76 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.68 (d, 1H, *J* = 9.2 Hz, *H*-3'), 7.55 (t, 1H, *J* = 8.0 Hz, *H*-7'), 7.38 (t, 1H, *J* = 7.6 Hz, *H*-6'), 7.11 (d, 1H, *J* = 8.8 Hz, *H*-4'), 6.79 (d, 1H, *J* = 5.6 Hz, *H*-1), 5.47-5.42 (m, 2H, *H*-4 and *H*-5), 5.22 (t, 1H, *J* = 5.6 Hz, *H*-2), 4.43 (t, 1H, *J* = 6.0 Hz, *H*-3), 3.99 (dd, 1H, *J* = 12.0 Hz and 4.0 Hz, *H*-6_A), 3.80 (dd, 1H, *J* = 12.0 and 5.6 Hz, *H*-6_B), 2.13 (s, 3H, -COCH₃), 2.68 (s, 3H, -COCH₃), 1.60 (s, 3H, -COCH₃).

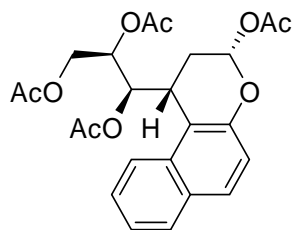
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.0 (2x, -C=O), 169.8 (-C=O), 150.2 (*C*-2'), 142.7 (*C*-1), 132.0 (*C*-4'*a*), 130.8 (*C*-8'*a*), 129.2 (*C*-5'), 128.4 (*C*-3'), 126.5 (*C*-7'), 124.2 (*C*-8'), 123.1 (*C*-6'), 117.8 (*C*-4'), 111.9 (*C*-1'), 100.4 (*C*-2), 73.6 (*C*-4), 69.3 (*C*-5), 62.5 (*C*-6), 32.0 (*C*-3), 20.8 (-COCH₃), 20.3 (-COCH₃), 20.0(-COCH₃) .

IR: 2963, 2357, 1741, 1654, 1201, 1039, 885 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 421.1264, found: 421.1273

[α]_D: -27.3 (*c* 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-((3*S*)-3-acetoxy-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triyl triacetate (2.30)



Cream solid

Mp: 150-152 °C

Yield: 31%

R_f: 0.33 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 8.02 (d, 1H, *J* = 8.0 Hz, *H*-8'), 7.71 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.65 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.48 (t, 1H, *J* = 7.6 Hz, *H*-7'), 7.32 (t, 1H, *J* = 7.4 Hz, *H*-6'), 7.08 (d, 1H, *J* = 8.8 Hz, *H*-4'), 6.60 (d, 1H, *J* = 2.4 Hz, *H*-1), 5.93 (d, 1H, *J* = 10.8 Hz, *H*-4), 5.74 (t, 1H, *J* = 6.2 Hz, *H*-5), 4.29 (dd, 1H, *J* = 11.6 and 4.4 Hz, *H*-6_A), 3.91-3.83 (m, 2H, *H*-6_B and *H*-3), 2.40 (d, 1H, *J* = 15.4 Hz, *H*-2_A), 2.30 (s, 3H, -COCH₃), 2.22 (s, 3H, -COCH₃), 2.13 (dd, 1H, *J* = 10.8 Hz and 4.4 Hz, *H*-2_B), 1.97 (s, 3H, -COCH₃), 1.23 (s, 3H, -COCH₃).

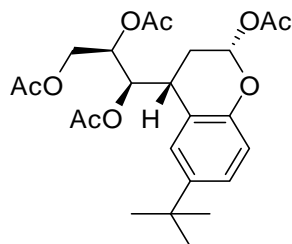
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.6 (-C=O), 170.4 (-C=O), 169.4(-C=O), 169.3(-C=O), 149.6 (*C*-2'), 132.5 (*C*-4'*a*), 129.5(x2) (*C*-8'*a* and *C*-5'), 128.3 (*C*-3'), 125.8 (*C*-7'), 123.5 (*C*-8'), 123.4 (*C*-6'), 118.7 (*C*-4'), 113.1 (*C*-1'), 89.2 (*C*-1), 72.3 (*C*-4), 69.4 (*C*-5), 62.7 (*C*-6), 28.1 (*C*-3), 26.5 (*C*-2), 21.2 (-COCH₃), 20.9 (-COCH₃), 20.6 (-COCH₃), 19.8 (-COCH₃).

IR: 2931, 1741, 1730, 1212, 1083, 1005, 926 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 481.1475, found: 481.1485

[α]_D: -38.9 (*c* 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-((2*S*)-2-acetoxy-6-*tert*-butylchroman-4-yl)propane-1,2,3-triyl triacetate (2.31)



Cream solid

Mp: 130-132 °C

Yield: 63%

R_f: 0.42 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 7.19 (d, 1H, *J* = 8.8 Hz, *meta*-Ph), 7.02 (s, 1H, *meta*-Ph), 6.81 (d, 1H, *J* = 8.8 Hz, *ortho*-Ph), 6.50 (s, 1H, *H*-1), 5.76 (d, 1H, *J* = 10.4 Hz, *H*-4), 5.61 (t, 1H, *J* = 6.2 Hz, *H*-5), 4.32 (dd, 1H, *J* = 11.6 Hz and 4.8 Hz, *H*-6_A), 3.83 (dd, 1H, *J* = 11.2 Hz and 8.0 Hz, *H*-6_B), 3.02 (dd, 1H, *J* = 10.0 Hz and 6.0 Hz, *H*-3), 2.4-2.16 (m, 7H, *H*-2_A and -COCH₃), 2.12-2.03 (m, 4H, *H*-2_B and -COCH₃), 1.98 (s, 3H, -COCH₃), 1.25 (s, 9H, -C(CH₃)₃).

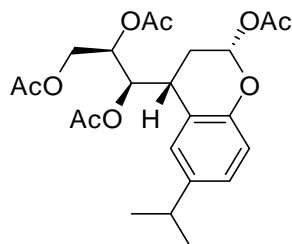
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.4 (-C=O), 169.5 (-C=O), 169.4 (-C=O), 148.9 (*ipso*-Ph), 143.6 (*para*-Ph), 126.8 (*meta*-Ph), 126.2 (*meta*-Ph), 119.4 (*ortho*-Ph), 117.0 (*ortho*-Ph), 89.3 (*C*-1), 72.4 (*C*-4), 69.3 (*C*-5), 62.7 (*C*-6), 34.1 (-C(CH₃)₃), 32.6 (*C*-3), 31.6 (-C(CH₃)₃), 26.3 (*C*-2), 21.2 (-COCH₃), 21.0 (-COCH₃), 20.9 (-COCH₃), 20.6 (-COCH₃).

IR: 2931, 1738, 1370, 1214, 1044, 914, 895

HRMS (ESI⁺) calc. for [M+Na]⁺: 487.1944, found: 487.1944

[α]_D: -22.6 (*c* 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-((2*S*)-2-acetoxy-6-isopropylchroman-4-yl)propane-1,2,3-triyl triacetate (2.32)



Cream solid

Mp: 110-112 °C

Yield: 67%

R_f: 0.37 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 7.01 (dd, 1H, *J* = 8.4 Hz and 2.0 Hz, *meta*-Ph), 6.89 (d, *J* = 2.0 Hz, *meta*-Ph), 6.79 (d, 1H, *J* = 8.0 Hz, *ortho*-Ph), 6.49 (s, 1H, *H*-1), 5.75 (d, *J* = 10.8 Hz, *H*-4), 5.60 (t, 1H, *J* = 5.8 Hz, *H*-5), 4.31 (dd, 1H, *J* = 11.4 Hz and 4.6 Hz, *H*-6_A), 3.83 (dd, 1H, *J* = 11.6 Hz and 8.0 Hz, *H*-6_B), 3.02-2.98 (m, 1H, *H*-3), 2.78 (sp, 1H, *J* = 6.8 Hz, -CH(CH₃)₂), 2.17 (d, 7H, *J* = 8.0 Hz, *H*-2_A and -COCH₃), 2.11 (dd, 1H, *J* = 6.0 Hz and 3.2 Hz, *H*-2_B), 2.04 (s, 3H, -COCH₃), 1.98 (s, 3H, -COCH₃), 1.17 (d, 6H, *J* = 6.8 Hz, -CH(CH₃)₂).

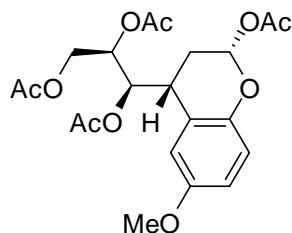
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.4 (-C=O), 169.4(2x -C=O), 149.1 (*ipso*-Ph), 141.2 (*para*-Ph), 127.9 (*meta*-Ph), 127.1 (*meta*-Ph), 119.7 (*ortho*-Ph), 117.2 (*ortho*-Ph), 89.2 (*C*-1), 72.4 (*C*-4), 69.2 (*C*-5), 62.7 (*C*-6), 33.4 (-CH(CH₃)₂), 32.4 (*C*-3), 26.1 (*C*-2), 24.4 (-CHCH₃CH₃), 24.1 (-CHCH₃CH₃), 21.1, (-COCH₃), 20.9 (-COCH₃), 20.8 (-COCH₃), 20.6 (-COCH₃),.

IR: 2292, 1738, 1496, 1215, 1082, 897 cm⁻¹

HRMS (ESI+) calc. for [M+Na]⁺: 473.1788, found: 473.1788

[α]_D: -18.8 (*c* 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-((2*S*)-2-acetoxy-6-methoxychroman-4-yl)propane-1,2,3-triyl triacetate (2.33)



Cream solid

Mp: 126-128 °C

Yield: 58%

R_f: 0.25 (Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 6.80 (d, 1H, *J* = 9.2 Hz, *meta*-Ph), 6.73 (d, 1H, *J* = 8.8 Hz, *ortho*-Ph), 6.60 (s, 1H, *meta*-Ph), 6.48 (s, 1H, *H-1*), 5.74 (d, 1H, *J* = 10.4 Hz, *H-4*), 5.59 (t, 1H, *J* = 5.8 Hz, *H-5*), 4.30 (dd, 1H, *J* = 11.4 Hz and 4.6 Hz, *H-6_A*), 3.84 (dd, 1H, *J* = 11.2 Hz and 8.0 Hz, *H-6_B*), 3.71 (s, 3H, -OCH₃), 3.00-2.96 (m, 1H, *H-3*), 2.17 (d, 6H, *J* = 5.6 Hz, -COCH₃), 2.17-2.02 (m, 5H, *H-2_A*, *H-2_B* and -COCH₃), 1.99 (s, 3H, -COCH₃).

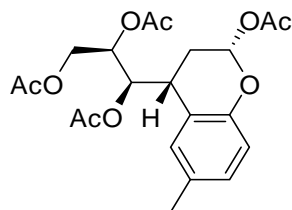
¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.4 (-C=O), 169.6 (-C=O), 169.4 (-C=O), 153.5 (*ipso*-Ph), 145.0 (*para*-Ph), 120.8 (*meta*-Ph), 118.0 (*ortho*-Ph), 115.4 (*ortho*-Ph), 114.4 (*meta*-Ph), 89.3 (*C-1*), 72.3 (*C-4*), 69.1 (*C-5*), 62.8 (*C-6*), 55.7 (-OCH₃), 32.6 (*C-3*), 26.0 (*C-2*), 21.2 (-COCH₃), 20.8 (-COCH₃), 20.6 (-COCH₃).

IR: 2917, 1731, 1495, 1372, 1185, 930, 893 cm⁻¹

HRMS (ESI+) calc. for [M+Na]⁺: 461.1424, found: 461.1433

[α]_D: -11.1 (*c* 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-((2*S*)-2-acetoxy-6-methylchroman-4-yl)propane-1,2,3-triyl triacetate (2.34)



Cream solid

Mp: 124-126 °C

Yield: 66%

R_f: 0.31(Hexane: EtOAc, 3:1)

¹H NMR: (CDCl₃, 400 MHz): δ_H 6.95 (d, 1H, *J* = 8.0 Hz, *meta*-Ph), 6.86 (s, 1H, *meta*-Ph), 6.76 (d, 1H, *J* = 8.4 Hz, *ortho*-Ph), 6.49 (s, 1H, *H-1*), 5.74 (d, 1H, *J* = 10.8 Hz, *H-4*), 5.59 (t, 1H, *J* = 6.0 Hz, *H-5*), 4.30 (dd, *J* = 11.6 and 4.8 Hz, *H-6_A*), 3.85 (dd, 1H, *J* = 11.2 Hz and 8.4 Hz, *H-6_B*), 2.99-2.95 (m, 1H, *H-3*), 2.22 (s, 3H, -CCH₃), 2.17 (d, 6H, *J* = 5.6 Hz, -COCH₃), 1.12-2.06 (m, 2H, *H-2_A* and *H-2_B*), 2.02 (s, 3H, -COCH₃), 1.99 (s, 3H, -COCH₃).

¹³C NMR: (CDCl₃, 100 MHz): δ_C 170.4 (-C=O), 169.5 (-C=O), 169.4 (-C=O), 148.9 (*ipso*-Ph), 130.7 (*meta*-Ph), 129.9 (*para*-Ph), 129.6 (*meta*-Ph), 119.7 (*ortho*-Ph), 117.2 (*ortho*-Ph), 89.2 (*C-1*), 72.3 (*C-4*), 69.1 (*C-5*), 62.8 (*C-6*), 32.3 (*C-3*), 26.1 (*C-2*), 21.2 (-CCH₃), 20.8 (-COCH₃), 20.7 (-COCH₃), 20.6 (-COCH₃), 20.4 (-COCH₃).

IR: 2956, 2853, 2360, 1734, 1594, 1294, 1049, 881 cm⁻¹

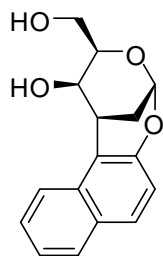
HRMS (ESI+) calc. for [M+Na]⁺: 445.1475, found: 445.1483

[α]_D: -18.3 (*c* 0.5, CH₂Cl₂)

5.3.8 De-acetylation of bridged chiral benzopyrans

To a solution (4 mL) of MeOH, Et₃N and H₂O in a ratio 2:1:1 respectively, was added 200 mg of the bridged chiral benzopyran. The reaction mixture was allowed to stir at room temperature for 24 hours and upon completion, the volatiles were evaporated. The crude product was subjected to column chromatography on flash silica for purification, and a mixture of ethyl acetate and hexane (2:1) was used as an eluent.

(1*R*,2*R*,3*R*,5*R*)-3-(hydroxymethyl)-2,3-dihydro-1*H*-1,5-methanonaphtho[2,1-*d*][1,3]dioxocin-2-ol (2.35)



Cream solid

Mp: 102-104 °C

Yield: 92%

R_f: 0.40 (Hexane:EtOAc, 1:2)

¹H NMR: (MeOD, 400 MHz): δ_H 7.91 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.75 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.67 (d, 1H, *J* = 9.2 Hz, *H*-3'), 7.48 (t, 1H, *J* = 7.6 Hz, *H*-7'), 7.30 (t, 1H, *J* = 7.4 Hz, *H*-6'), 7.07 (d, 1H, *J* = 8.8 Hz, *H*-4'), 5.62 (s, 1H, *H*-1), 3.81 (s, 1H, *H*-4), 3.73 (s, 1H, *H*-3), 3.61-3.53 (m, 3H, *H*-5, *H*-6_A and *H*-6_B), 2.73 (d, 1H, *J* = 12.8 Hz, *H*-2_A), 1.64 (d, 1H, *J* = 12.8 Hz, *H*-2_B).

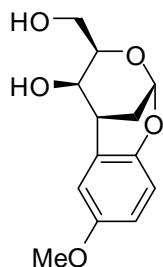
¹³C NMR: (MeOD, 100 MHz): δ_C 154.4 (*C*-2'), 133.2 (*C*-4'*a*), 130.6 (*C*-8'*a*), 129.8 (*C*-5'), 127.7 (*C*-3'), 127.9 (*C*-7'), 124.5 (*C*-8'), 122.2 (*C*-6'), 118.4 (*C*-4'), 117.0 (*C*-1'), 94.5 (*C*-1), 73.2 (*C*-5), 68.2 (*C*-4), 63.4 (*C*-6), 32.4 (*C*-3), 23.0 (*C*-2).

IR: 3343, 2900, 2355, 1621, 1514, 1258, 1002, 904 cm^{-1}

HRMS (ESI+) calc. for $[\text{M}+\text{Na}]^+$: 295.0947, found: 295.0948

$[\alpha]_{\text{D}}$: -21.2 (*c* 0.5, MeOH)

(2*R*,4*R*,5*R*,6*R*)-4-(hydroxymethyl)-8-methoxy-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-5-ol (2.36)



Cream solid

Mp: 112-114 °C

Yield: 98%

R_f : 0.32 (Hexane:EtOAc, 1:2)

^1H NMR: (MeOD, 400 MHz): δ_{H} 6.72 (s, 2H, *meta*-Ph), 6.68 (s, 1H, *ortho*-Ph), 5.49 (s, 1H, *H*-1), 3.70 (s, 4H, *H*-4 and $-\text{OCH}_3$), 3.58-3.56 (m, 3H, *H*-5, *H*-6_A and *H*-6_B), 3.01 (s, 1H, *H*-3), 2.54 (d, 1H, $J = 12.4$ Hz, *H*-2_A), 1.56 (d, 1H, $J = 13.2$ Hz, *H*-2_B).

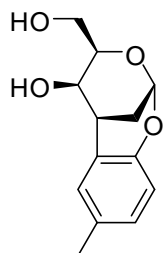
^{13}C NMR: (MeOD, 100 MHz): δ_{C} 155.0 (*ipso*-Ph), 150.5 (*para*-Ph), 126.1 (*ortho*-Ph), 116.8 (*ortho*-Ph), 115.2 (*meta*-Ph), 114.7 (*meta*-Ph), 94.6 (*C*-1), 72.2 (*C*-5), 70.1 (*C*-4), 63.4 (*C*-6), 56.2 ($-\text{OCH}_3$) 37.6 (*C*-3), 24.1 (*C*-2).

IR: 3365, 2972, 2919, 2362, 1621, 1462, 1062, 971 cm^{-1}

HRMS (ESI+) calc. for $[\text{M}+\text{Na}]^+$: 275.0896, found: 275.0883

$[\alpha]_{\text{D}}$: -31.2 (*c* 0.5, MeOH)

(2*R*,4*R*,5*R*,6*R*)-4-(hydroxymethyl)-8-methyl-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-5-ol (2.37)



Cream solid

Mp: 170-172 °C

Yield: 94%

R_f: 0.36 (Hexane:EtOAc, 1:2)

¹H NMR: (MeOD, 400 MHz): δ_H 6.85 (d, 1H, *J* = 8.4 Hz, *meta*-Ph), 6.82 (s, 1H, *meta*-Ph), 6.62 (d, 1H, *J* = 8.0 Hz, *ortho*-Ph), 5.42 (s, 1H, *H*-1), 3.57 (s, 1H, *H*-4), 3.52-3.47 (m, 3H, *H*-5, *H*-6_A and *H*-6_B), 2.91 (s, 1H, *H*-3), 2.47 (d, 1H, *J* = 13.2 Hz, *H*-2_A), 2.14 (s, 3H, -CH₃), 1.49 (d, 1H, *J* = 12.4 Hz, *H*-2_B).

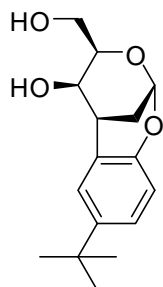
¹³C NMR: (MeOD, 100 MHz): δ_C 154.5 (*ipso*-Ph), 131.0 (*para*-Ph), 130.3 (*meta*-Ph), 129.9 (*meta*-Ph), 125.2 (*ortho*-Ph), 116.0 (*ortho*-Ph), 94.7 (*C*-1), 72.2 (*C*-5), 70.2 (*C*-4), 63.4 (*C*-6), 37.3 (*C*-3), 24.2 (*C*-2), 20.5 (-CH₃).

IR: 3362, 2972, 2906, 2488, 1738, 1491, 1095, 980 cm⁻¹

HRMS (ESI+) calc. for [M+Na]⁺: 236.1049, found: 236.1043

[α]_D: -41.0 (*c* 0.5, MeOH)

(2*R*,4*R*,5*R*,6*R*)-8-(*tert*-butyl)-4-(hydroxymethyl)-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-5-ol (2.38)



White solid

Mp: 124-126 °C

Yield: 97%

R_f: 0.44 (Hexane:EtOAc, 1:2)

¹H NMR: (MeOD, 400 MHz): δ_H 7.16 (d, 1H, *J* = 8.4 Hz, *meta*-Ph), 7.12 (s, 1H, *meta*-Ph), 6.74 (d, 1H, *J* = 8.4 Hz, *ortho*-Ph), 5.51 (s, 1H, *H*-1), 3.69 (s, 1H, *H*-4), 3.65-3.58 (m, 3H, *H*-5, *H*-6_A and *H*-6_B), 3.04 (s, 1H, *H*-3), 2.56 (d, 1H, *J* = 12.8 Hz, *H*-2_A), 1.56 (d, 1H, *J* = 12.8 Hz, *H*-2_B), 1.25 (s, 9H, -C(CH₃)₃).

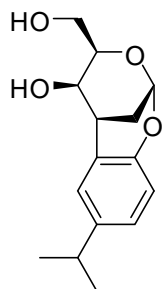
¹³C NMR: (MeOD, 100 MHz): δ_C 154.3 (*ipso*-Ph), 144.5 (*para*-Ph), 126.6 (*meta*-Ph), 126.4 (*meta*-Ph), 124.7 (*ortho*-Ph), 115.7 (*ortho*-Ph), 94.7 (*C*-1), 72.0 (*C*-5), 70.2 (*C*-4), 63.3 (*C*-6), 37.5 (*C*-3), 34.8 (-C(CH₃)₃), 32.0 (-C(CH₃)₃), 24.2 (*C*-2).

IR: 3293, 2956, 2906, 2362, 1615, 1494, 1062, 909 cm⁻¹

HRMS (ESI+) calc. for [M+Na]⁺: 301.1416, found: 301.1403

[α]_D: -28.2 (*c* 0.5, MeOH)

(2*R*,4*R*,5*R*,6*R*)-4-(hydroxymethyl)-8-isopropyl-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-5-ol (2.39)



Cream Solid

Mp: 128-130 °C

Yield: 93%

R_f: 0.41 (Hexane:EtOAc, 1:2)

¹H NMR: (MeOD, 400 MHz): δ_H 6.91 (dd, 1H, *J* = 8.4 Hz and 2.0 Hz, *meta*-Ph), 6.87 (d, 1H, *J* = 2.0 Hz, *meta*-Ph), 6.65 (d, 1H, *J* = 8.0 Hz, *ortho*-Ph), 5.42 (s, 1H, *H*-1), 3.58 (d, 1H, *J* = 3.6 Hz, *H*-4), 3.52-3.46 (m, 3H, *H*-5, *H*-6_A and *H*-6_B), 2.94 (d, 1H, *J* = 1.6 Hz, *H*-3), 2.70 (sp, 1H, *J* = 6.8 Hz, -CH(CH₃)₂), 2.47 (dt, 1H, *J* = 13.1 Hz and 2.5 Hz, *H*-2_A), 1.48 (d, 1H, *J* = 13.2 Hz, *H*-2_B), 1.09 (d, 6H, *J* = 6.8 Hz, -CH(CH₃)₂).

¹³C NMR: (MeOD, 100 MHz): δ_C 154.6 (*ipso*-Ph), 142.4 (*para*-Ph), 127.7 (*meta*-Ph), 127.3 (*meta*-Ph), 125.2 (*ortho*-Ph), 116.0 (*ortho*-Ph), 94.7 (*C*-1), 72.1 (*C*-5), 70.2 (*C*-4), 63.3 (*C*-6), 37.4 (*C*-3), 34.6 (-CH(CH₃)₂), 24.7 (-CH(CH₃)₂), 24.6 (-CH(CH₃)₂), 24.2 (*C*-2).

IR: 3333, 2955, 2919, 2478, 1492, 1209, 1001, 871 cm⁻¹

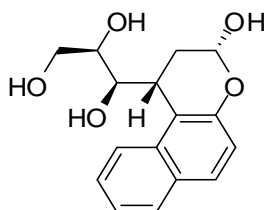
HRMS (ESI+) calc. for [M+Na]⁺: 287.1260, found: 287.1250

[α]_D: -41.0 (*c* 0.5, MeOH)

5.3.9 De-acetylation of chromans

To a solution (4 mL) of MeOH, Et₃N and H₂O in a ratio 2:1:1 respectively, was added 200 mg of the galactose based chroman. The solution was allowed to stir at room temperature for 24 hours and upon completion, the volatile components were evaporated. The crude product was subjected to column chromatography on flash silica for purification, and a mixture of ethyl acetate and methanol (EtOAc:MeOH, 9:1) was used as an eluent.

(1*R*,2*R*)-1-((3*S*)-3-hydroxy-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triol (2.40)



White solid

Mp: 106-108 °C

R_f: 0.29 (EtOAc:MeOH, 9:1)

¹H NMR: (MeOD, 400 MHz): δ_H 8.05(d, 1H, *J* = 8.4Hz, *H*-8'), 7.60 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.54 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.31 (t, 1H, *J* = 7.4 Hz, *H*-7'), 7.16 (t, 1H, *J* = 7.6 Hz, *H*-6'), 6.94 (d, 1H, *J* = 8.8 Hz, *H*-4'), 5.64 (dd, 1H, *J* = 10.0 Hz and 3.6 Hz, *H*-1), 3.83 (dd, 1H, *J* = 9.0 Hz and 1.0 Hz, *H*-4), 3.79 (dd, 1H, *J* = 4.6 Hz and 1.8 Hz, *H*-3), 3.75 (t, 1H, *J* = 6.4 Hz, *H*-5), 3.48 (dd, 2H, *J* = 6.2 Hz and 1.8 Hz, *H*-6_A and *H*-6_B), 2.37 (dt, 1H, *J* = 12.9 Hz and 2.3 Hz, *H*-2_A), 1.72 (ddd, 1H, *J* = 14.8 Hz, 10.0 Hz and 4.8 Hz, *H*-2_B).

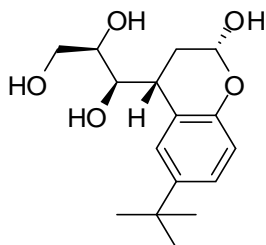
¹³C NMR: (MeOD, 100 MHz): δ_C 152.8 (*C*-2'), 135.1 (*C*-4'*a*), 130.7(*C*-8'*a*), 129.6 (*C*-5'), 129.0 (*C*-3'), 126.8 (*C*-7'), 125.2 (*C*-8'), 124.0 (*C*-6'), 119.9 (*C*-4'), 117.2 (*C*-1'), 93.0 (*C*-1), 73.7 (*C*-4), 72.1 (*C*-5), 65.0 (*C*-6), 35.3 (*C*-3), 32.2 (*C*-2).

IR: 3363, 2881, 2360, 1619, 1596, 1207, 1024 cm⁻¹

HRMS (ESI+): calc. for $[M+Na]^+$: 313.1052, found: 313.1046

$[\alpha]_D$: -1.8 (*c* 0.5, MeOH)

(1*R*,2*R*)-1-((2*S*)-6-*tert*-butyl-2-hydroxychroman-4-yl)propane-1,2,3-triol (2.41)



Cream solid

Mp: 82-84 °C

R_f : 0.34 (EtOAc:MeOH, 9:1)

$^1\text{H NMR}$: (MeOD, 400 MHz): δ_{H} 6.94 (d, 1H, $J = 8.4$ Hz, *meta*-Ph), 6.81 (s, 1H, *meta*-Ph), 6.67 (d, 1H, $J = 8.2$ Hz, *ortho*-Ph), 5.53 (d, 1H, $J = 2.8$ Hz, *H*-1), 3.97 (dd, 1H, $J = 9.4$ Hz and 3.2 Hz, *H*-5), 3.58 (dd, 1H, $J = 11.4$ Hz and 5.2 Hz, *H*-4), 3.48 (dd, 2H, $J = 6.2$ Hz and 1.8 Hz, *H*-6_A and *H*-6_B), 3.19 (s, 1H, *H*-3), 2.43 (dt, 1H, $J = 12.2$ Hz and 2.8 Hz, *H*-2_A), 1.52 (d, 1H, $J = 12.2$ Hz, *H*-2_B), 1.27 (s, 9H, -C(CH₃)₃).

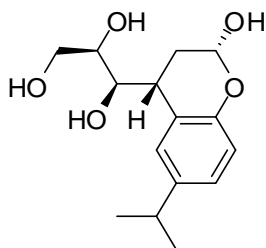
$^{13}\text{C NMR}$: (MeOD, 100 MHz): δ_{C} 154.4 (*ipso*-Ph), 142.2 (*para*-Ph), 128.1 (*meta*-Ph), 127.4 (*meta*-Ph), 125.3 (*ortho*-Ph), 115.7 (*ortho*-Ph), 98.9 (*C*-1), 80.1 (*C*-5), 72.1 (*C*-4), 64.5 (*C*-6), 38.3 (*C*-3), 34.9 (-C(CH₃)₃), 31.7 (-C(CH₃)₃), 26.5 (*C*-2).

IR: 3304, 2953, 2361, 2342, 1497, 1227, 1022, 819 cm^{-1}

HRMS (ESI+): calc. for $[M+Na]^+$: 319.1522, found: 319.1501

$[\alpha]_D$: -2.1 (*c* 0.5, MeOH)

(1*R*,2*R*)-1-((2*S*)-2-hydroxy-6-isopropylchroman-4-yl)propane-1,2,3-triol (2.42)



White solid

Mp: 93-95 °C

R_f: 0.32 (EtOAc:MeOH, 9:1)

¹H NMR: (MeOD, 400 MHz): δ_H 6.83 (d, 1H, *J* = 8.2 Hz, *meta*-Ph), 6.71 (s, 1H, *meta*-Ph), 6.53 (d, 1H, *J* = 8.0 Hz, *ortho*-Ph), 5.58 (d, 1H, *J* = 3.0 Hz, *H*-1), 4.01 (dd, 1H, *J* = 9.0 Hz and 3.1 Hz, *H*-5), 3.62 (dd, 1H, *J* = 11.6 Hz and 5.4 Hz, *H*-4), 3.51-3.46 (m, 3H, *H*-3, *H*-6_A and *H*-6_B), 2.81 (sp, 1H, *J* = 6.8 Hz, -CH(CH₃)₂), 2.47 (dt, 1H, *J* = 12.2 Hz and 2.8 Hz, *H*-2_A), 1.48 (d, 1H, *J* = 12.2 Hz, *H*-2_B), 1.11 (d, 6H, *J* = 6.8 Hz, -CH(CH₃)₂).

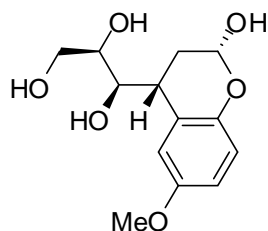
¹³C NMR: (MeOD, 100 MHz): 154.3 (*ipso*-Ph), 140.8 (*para*-Ph), 127.0 (*ortho*-Ph), 126.7 (*ortho*-Ph), 125.9 (*meta*-Ph), 115.5 (*meta*-Ph), 98.9 (*C*-1), 80.8 (*C*-5), 74.4 (*C*-4), 65.0 (*C*-6), 39.7 (*C*-3), 33.9 (-CH(CH₃)₂), 29.2 (*C*-2), 25.4 -CH(CH₃)₂, 25.3 -CH(CH₃)₂.

IR: 3307, 2946, 2349, 1484, 1221, 1017, 997, 894 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 305.1365, found: 305.1353

[α]_D: -8.3 (*c* 0.5, MeOH)

(1*R*,2*R*)-1-((2*S*)-2-hydroxy-6-methoxychroman-4-yl)propane-1,2,3-triol (2.43)



Cream solid

Mp: 72-74 °C

R_f: 0.16 (EtOAc:MeOH, 9:1)

¹H NMR: (MeOD, 400 MHz): δ_H 6.60 (d, 1H, *J* = 6.2 Hz, *meta*-Ph), 6.56 (s, 1H, *meta*-Ph), 6.54 (d, 1H, *J* = 6.8 Hz, *ortho*-Ph), 5.60 (d, 1H, *J* = 3.2 Hz, *H*-1), 3.98 (dd, 1H, *J* = 9.2 Hz and 3.2 Hz, *H*-5), 3.63 (br s, 5H, -OCH₃ and -OH), 3.56 (d, 1H, *J* = 3.2 Hz, *H*-3), 3.44 (dd, 1H, *J* = 12.0 Hz and 6.0 Hz, *H*-4), 3.06 (dd, 2H, *J* = 6.4 Hz and 3.2 Hz, *H*-6_A and *H*-6_B), 2.18 (dt, 1H, *J* = 11.6 and 3.6 Hz, *H*-2_A), 2.05 (d, 1H, *J* = 11.2 Hz, *H*-2_B)

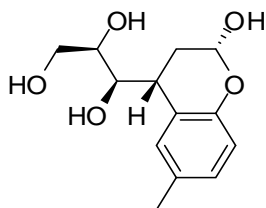
¹³C NMR: (MeOD, 100 MHz): 154.9 (*ipso*-Ph), 146.7 (*para*-Ph), 127.1 (*ortho*-Ph), 117.5 (*ortho*-Ph), 114.8 (*meta*-Ph), 114.7 (*meta*-Ph), 100.2 (*C*-1), 90.2 (*C*-5), 74.4 (*C*-4), 64.0 (*C*-6), 56.1 (-OCH₃) 39.3 (*C*-3), 34.7 (*C*-2).

IR: 3429, 2927, 2361, 1491, 1197, 1041, 869 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 293.1001, found: 293.1036

[α]_D: -10.4 (*c* 0.5, MeOH)

(1*R*,2*R*)-1-((2*R*)-2-hydroxy-6-methylchroman-4-yl)propane-1,2,3-triol (2.44)



Cream solid

Mp: 78-80 °C

Rf: 0.27 (EtOAc:MeOH, 9:1)

¹H NMR: (MeOD, 400 MHz): δ_{H} 6.85 (d, 1H, $J = 8.0$ Hz, *meta*-Ph), 6.74 (s, 1H, *meta*-Ph), 6.51 (d, 1H, $J = 8.0$ Hz, *ortho*-Ph), 5.54 (d, 1H, $J = 2.8$ Hz, *H-1*), 4.05 (dd, 1H, $J = 9.2$ Hz and 3.2 Hz, *H-5*), 3.64 (dd, 1H, $J = 11.8$ Hz and 5.6 Hz, *H-4*), 3.12 (dd, 2H, $J = 6.4$ Hz and 3.2 Hz, *H-6_A* and *H-6_B*), 3.05 (s, 1H, *H-3*), 2.47 (dt, 1H, $J = 12.6$ Hz and 3.0 Hz, *H-2_A*), 2.15 (s, 3H, -CH₃), 1.48 (d, 1H, $J = 12.4$ Hz, *H-2_B*),

¹³C NMR: (MeOD, 100 MHz): δ_{C} 154.3 (*ipso*-Ph), 130.8 (*para*-Ph), 129.8 (*ortho*-Ph), 128.7 (*ortho*-Ph), 117.6 (*meta*-Ph), 115.4 (*meta*-Ph), 100.2 (*C-1*), 80.7 (*C-5*), 74.4 (*C-4*), 65.1 (*C-6*), 39.1 (*C-3*), 34.7 (*C-2*), 20.8 (-CH₃).

IR: 3433, 2918, 2353, 1482, 1181, 1097, 879 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 277.1052, found: 277.1073

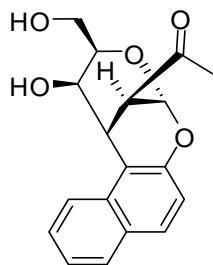
[α]_D: -7.6 (*c* 0.5, MeOH)

5.3.10 De-acetylation of chiral galactose based chromenes (Intramolecular oxa-Michael addition)

To a solution (4 mL) of MeOH, Et₃N and H₂O in a ratio 2:1:1 respectively, was added 200 mg of the galactose based chromene. The reaction was allowed to stir at room temperature for 24 hours and upon completion, all volatiles were evaporated. The crude product was subjected to column

chromatography on flash silica for purification, and a solution of ethyl acetate and hexane (Hexane: EtOAc, 1:2) was used as an eluent.

1-((1*R*,2*R*,3*R*,5*R*,13*R*)-2-hydroxy-3-(hydroxymethyl)-2,3-dihydro-1*H*-1,5-methanonaphtho[2,1-*d*][1,3]dioxocin-13-yl)ethanone (2.45)



Cream solid

Mp: 202-204 °C

Yield: 96 %

R_f: 0.25 (Hexane: EtOAc, 1:2)

¹H NMR: (400 MHz, MeOD): δ_H 8.03 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.80 (d, 1H, *J* = 8.4 Hz, *H*-5'), 7.71 (d, 1H, *J* = 9.2 Hz, *H*-3'), 7.56 (t, 1H, *J* = 7.8 Hz, *H*-7'), 7.37 (t, 1H, *J* = 7.4 Hz, *H*-6'), 7.06 (d, 1H, *J* = 9.0 Hz, *H*-4'), 5.89 (s, 1H, *H*-1), 4.62 (s, 1H, OH), 4.28 (p, 1H, *J* = 2.2 Hz, *H*-3), 3.96 (dd, 1H, *J* = 3.9 Hz and 1.9 Hz, *H*-4), 3.66-3.60 (m, 3H, *H*-6_A, *H*-6_B and *H*-2), 3.51 (t, 1H, *J* = 5.8 Hz, *H*-5), 1.89 (s, 3H, -COCH₃).

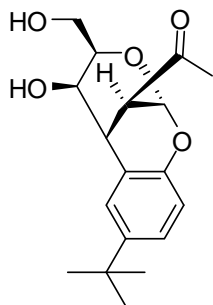
¹³C NMR: (100 MHz, MeOD) δ_C 207.8(-C=O), 154.0 (*C*-2'), 133.2 (*C*-4'*a*), 130.8 (*C*-8'*a*), 130.4 (*C*-3'), 129.8 (*C*-5'), 128.4 (*C*-7'), 124.9 (*C*-6'), 121.9 (*C*-8'), 118.2 (*C*-4'), 114.3 (*C*-1'), 94.1 (*C*-1), 73.0 (*C*-5), 68.5 (*C*-4), 63.0 (*C*-6), 45.5 (*C*-2), 35.8 (*C*-3), 27.1 (-COCH₃)

IR: 3433, 2921, 2547, 1700, 1597, 1439, 1225, 1075 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 338.1130, found: 338.1094

$[\alpha]_D$: -1.8 (*c* 0.5, MeOH)

1-((2*R*,4*R*,5*R*,6*R*,11*R*)-8-(*tert*-butyl)-5-hydroxy-4-(hydroxymethyl)-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-11-yl)ethanone (2.46)



Cream solid

Mp: 140-142 °C

Yield: 94 %

R_f : 0.29 (Hexane: EtOAc, 1:2)

$^1\text{H NMR}$: (400 MHz, CDCl_3): δ_{H} 7.17 (dd, 1H, $J = 8.4$ Hz and 2.4 Hz, *meta*-Ph), 7.06 (d, 1H, $J = 2.4$ Hz, *meta*-Ph), 6.78 (d, 1H, $J = 8.4$ Hz, *ortho*-Ph), 5.97 (s, 1H, *H*-1), 4.03 (dd, 1H, $J = 4.0$ Hz and 1.6 Hz, *H*-4), 3.96 (dd, 1H, $J = 12.4$ Hz and 3.6 Hz, *H*-6_A), 3.83 (dd, 1H, $J = 12.2$ Hz and 2.6 Hz, *H*-6_B), 3.56 – 3.52 (m, 2H, *H*-3 and *H*-5), 3.49 (t, 1H, $J = 2.2$ Hz, *H*-2), 2.06 (s, 3H, $-\text{COCH}_3$), 1.25 (s, 9H, $-\text{C}(\text{CH}_3)_3$).

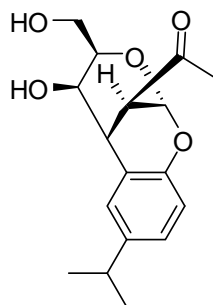
$^{13}\text{C NMR}$: (100 MHz, CDCl_3) δ_{C} 205.5 ($-\text{C}=\text{O}$), 152.0 (*ipso*-Ph), 144.4 (*para*-Ph), 126.3 (*meta*-Ph), 125.6 (*meta*-Ph), 119.6 (*ortho*-Ph), 115.2 (*ortho*-Ph), 93.4 (*C*-1), 72.6 (*C*-4), 68.2 (*C*-5), 64.2 (*C*-6), 45.6 (*C*-2), 39.1 (*C*-3), 34.1 ($-\text{C}(\text{CH}_3)_3$), 31.5 ($-\text{C}(\text{CH}_3)_3$), 27.2 ($-\text{COCH}_3$)

IR: 3353, 2947, 2928, 1701, 1493, 1201, 1006, 847 cm^{-1}

HRMS (ESI⁺): calc. for $[\text{M}+\text{Na}]^+$: 344.1600, found: 344.1548

$[\alpha]_D$: -8.9 (*c* 0.5, MeOH)

1-((2*R*,4*R*,5*R*,6*R*,11*R*)-5-hydroxy-4-(hydroxymethyl)-8-isopropyl-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-11-yl)ethanone (2.47)



Cream solid

Mp: 118-120 °C

Yield: 92 %

R_f : 0.23 (Hexane: EtOAc, 1:2)

$^1\text{H NMR}$: (400 MHz, CD_2Cl_2): δ_{H} 7.05 (dd, 1H, $J = 8.4$ Hz and 2.0 Hz, *meta*-Ph), 6.99 (d, 1H, $J = 2.0$ Hz, *meta*-Ph), 6.77 (d, 1H, $J = 8.4$ Hz, *ortho*-Ph), 5.92 (s, 1H, *H-1*), 4.15 (br s, 1H, *OH*), 4.02 (q, 1H, $J = 2.0$ Hz, *H-4*), 3.90 (dd, 1H, $J = 12.0$ Hz and 4.0 Hz, *H-6_A*), 3.80 (dd, 1H, $J = 12.0$ Hz and 2.8 Hz, *H-6_B*), 3.51 (m, 3H, *H-2*, *H-3*, *H-5*), 2.83 (sp, 1H, $J = 6.8$ Hz, $-\text{CH}(\text{CH}_3)_2$), 2.07 (s, 3H, $-\text{COCH}_3$), 1.20 (d, $J = 6.8$ Hz, $-\text{CH}(\text{CH}_3)_2$).

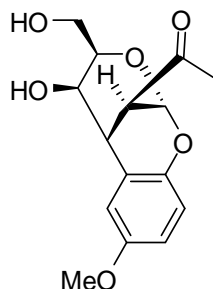
$^{13}\text{C NMR}$: (100 MHz, CD_2Cl_2) δ_{C} 206.0 ($-\text{C}=\text{O}$), 153.0 (*ipso*-Ph), 142.6 (*para*-Ph), 127.6 (*meta*-Ph), 127.5 (*meta*-Ph), 120.9 (*ortho*-Ph), 115.7 (*ortho*-Ph), 93.9 (*C-1*), 72.7 (*C-4*), 69.2 (*C-5*), 64.5 (*C-6*), 45.1 (*C-2*), 39.5 (*C-3*), 33.8 [$-\text{CH}(\text{CH}_3)_2$], 27.6 ($-\text{COCH}_3$), 24.5 [$-\text{CH}(\text{CH}_3)(\text{CH}_3)$], 24.4 [$-\text{CH}(\text{CH}_3)(\text{CH}_3)$].

IR: 3357, 2959, 2923, 1702, 1497, 1224, 1024, 866 cm^{-1}

HRMS (ESI⁺): calc. for $[\text{M}+\text{Na}]^+$: 330.1443, found: 330.1407

$[\alpha]_{\text{D}}$: -10.9 (c 0.5, MeOH)

1-((2*R*,4*R*,5*R*,6*R*,11*R*)-5-hydroxy-4-(hydroxymethyl)-8-methoxy-5,6-dihydro-4*H*-2,6-methanobenzo[*d*][1,3]dioxocin-11-yl)ethanone (2.48)



Cream solid

Mp: 152-154 °C

Yield: 95 %

R_f: 0.19 (Hexane: EtOAc, 1:2)

¹H NMR: (400 MHz, CD₂Cl₂): δ_H 6.76 (s, 1H, *meta*-Ph), 6.75 (d, 1H, *J* = 3.2 Hz, *meta*-Ph), 6.69 (d, 1H, *J* = 2.8 Hz, *ortho*-Ph), 5.92 (s, 1H, *H*-1), 4.19 (d, 1H, *J* = 4.8 Hz, OH), 4.04 (dd, 1H, *J* = 4.0 Hz and 1.6 Hz, *H*-4), 3.89 (dd, 1H, *J* = 12.2 Hz and 3.2 Hz, *H*-6_A), 3.80 (dd, 1H, *J* = 12.2 Hz and 3.2 Hz, *H*-6_B), 3.74 (s, 3H, -OCH₃), 3.51-3.48 (m, 3H, *H*-2, *H*-3 and *H*-5), 2.65 (br s, 1H, OH) 2.07 (s, 3H, -COCH₃).

¹³C NMR: (100 MHz, CD₂Cl₂) δ_C 205.9(-C=O), 154.6 (*para*-Ph), 148.9 (*ipso*-Ph), 122.0 (*ortho*-Ph), 116.6 (*meta*-Ph), 115.2 (*meta*-Ph), 114.3 (*ortho*-Ph), 93.8 (*C*-1), 72.5 (*C*-4), 69.3 (*C*-5), 64.4 (*C*-6), 56.2 (-OCH₃), 45.0 (*C*-2), 39.5 (*C*-3), 27.7 (-COCH₃).

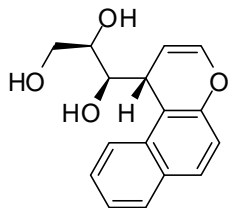
IR: 3375, 2393, 2852, 2361, 1686, 1493, 1094, 912

HRMS (ESI⁺): calc. for [M+Na]⁺: 318.1080, found: 318.1035

[α]_D: -2.8 (*c* 0.5, MeOH)

5.4. Oxepane synthesis (Chapter 3 compounds)

(1*R*,2*R*)-1-(1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triol (3.1)



To a solution of methanol, triethyl amine and water (10:5:2.5), was added 1 g (2.51 mmol) of tri-*O*-acetylated chromene **2.29** and the mixture allowed to stir at room temperature for 24 hours. Upon completion, as deduced by TLC, the volatiles were evaporated and the product purified using flash column chromatography using 100 % ethyl acetate as the eluent to give 660 mg of triol **3.1**.

White solid

Mp: 132-134 °C

Yield: 97 %

R_f: 0.57 (100% EtOAc)

¹H NMR: (400 MHz, DMSO-*d*₆): δ_H 8.12 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.83 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.77 (d, 1H, *J* = 11.6 Hz, *H*-3'), 7.47 (t, 1H, *J* = 7.4 Hz, *H*-7'), 7.39 (t, 1H, *J* = 7.4 Hz, *H*-6'), 7.18 (d, 1H, *J* = 8.8 Hz, *H*-4'), 6.86 (d, 1H, *J* = 5.6 Hz, *H*-1), 5.33 (t, 1H, *J* = 5.8 Hz, *H*-2), 4.51 (d, 1H, *J* = 6.8 Hz, -OH), 4.36 (d, 1H, *J* = 6.8 Hz, -OH), 4.32 (t, 1H, *J* = 5.6 Hz, -OH), 4.24 (t, 1H, *J* = 6.8 Hz, *H*-3), 3.64 (q, 1H, *J* = 5.4 Hz, *H*-5), 3.48 (t, 1H, *J* = 7.0 Hz, *H*-4), 3.23-3.19 (m, 2H, *H*-6_A and *H*-6_B).

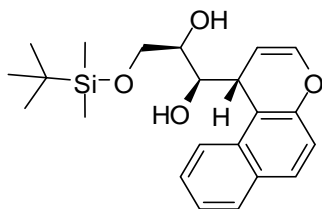
¹³C NMR: (100 MHz, DMSO-*d*₆) δ_C 149.7 (*C*-2'), 141.3 (*C*-1), 132.8 (*C*-4'*a*), 130.4 (*C*-8'*a*), 127.8(x2, *C*-5' and *C*-3'), 125.7 (*C*-7'), 124.4 (*C*-8'), 123.9 (*C*-6'), 117.3 (*C*-4'), 116.4 (*C*-1'), 104.1 (*C*-2), 74.9 (*C*-4), 70.2 (*C*-5), 63.0 (*C*-6), 33.3 (*C*-3).

IR: 3366, 2893, 2361, 1668, 1595, 1251, 1023, 748 cm⁻¹

HRMS (ESI+): calc. for $[M+Na]^+$: 295.0947, found: 295.0983

$[\alpha]_D$: -75.8 (*c* 0.5, MeOH)

(1*R*,2*R*)-1-(1*H*-benzo[*f*]chromen-1-yl)-3-(*tert*-butyldimethylsilyloxy)propane-1,2-diol (3.2)



To a solution of triol **3.1** (200 mg, 0.735 mmol) and DMF (5 mL), were added TBDMSCl (1.2 eq) and imidazole (2.5 eq) and the mixture allowed to stir at 50 °C for 4 hours as traced by TLC. Upon completion the product was extracted with ethyl acetate and the organic layer washed three (3) times with H₂O. The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 3:1) was used as eluent, providing 230 mg of the diol **3.2**.

Cream solid

Mp: 62-64 °C

Yield: 81 %

R_f : 0.51 (Hexane: EtOAc, 3:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.02 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.77 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.68 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.50 (t, 1H, *J* = 7.8 Hz, *H*-7'), 7.39 (t, 1H, *J* = 7.2 Hz, *H*-6'), 7.13 (d, 1H, *J* = 8.8 Hz, *H*-4'), 6.75 (d, 1H, *J* = 6.0 Hz, *H*-1), 5.38 (t, 1H, *J* = 5.6 Hz, *H*-2), 4.47 (t, 1H, *J* = 5.2 Hz, *H*-3), 3.98 (t, 1H, *J* = 4.2 Hz, *H*-4), 3.77 (q, 1H, *J* = 4.4 Hz, *H*-5), 3.42 (dd, 1H, *J* = 10.0 Hz and 4.4 Hz, *H*-6_A), 3.21 (dd, 1H, *J* = 10.0 Hz and 5.6 Hz, *H*-5), 2.99 (br s, 1H, -OH), 2.73 (br s, 1H, -

OH, 0.71 (s, 9H, -Si-C(CH₃)₃), -0.12 (s, 3H, -Si-C(CH₃)₂), -0.21 (s, 3H, -Si-C(CH₃)₂).

¹³C NMR: (100 MHz, CDCl₃) δ_C 150.1 (C-2'), 141.6 (C-1), 131.9 (C-4'a), 130.9 (C-8'a), 128.7 (C-5'), 128.5 (C-3'), 126.6 (C-7'), 124.3 (C-8'), 122.9 (C-6'), 117.7 (C-4'), 113.6 (C-1'), 102.3 (C-2), 73.8 (C-4), 70.2 (C-5), 65.0 (C-6), 34.7 (C-3), 25.6 (-Si-C(CH₃)₃), 18.0 (-Si-C(CH₃)₃), -5.70 (-SiCH₃CH₃), -5.81 (-SiCH₃CH₃).

IR: 3512, 3413, 2953, 2360, 1623, 1220, 815 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 409.1811, found: 409.1804

[α]_D: -7.2 (c 0.5, CH₂Cl₂)

(1R,2R)-1-(1H-benzof[*f*]chromen-1-yl)-3-(*tert*-butyldimethylsilyloxy)propane-1,2-diol diacetate (3.3)



To a solution of diol **3.2** (200 mg, 0.517 mmol) and pyridine (3 mL), was added 0.3 mL of acetic anhydride and the mixture was allowed to stir at room temperature overnight. Upon completion, as deduced by TLC, the product was washed four times with CuSO₄ (aq). The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 6:1) was used as eluent, providing 210 mg of the fully protected chromene **3.3**.

Clear oil

Yield: 86 %

R_f: 0.43 (Hexane: EtOAc, 6:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.13 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.75 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.68 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.52 (d, 1H, *J* = 7.4 Hz, *H*-7'), 7.10 (t, 1H, *J* = 7.2 Hz, *H*-6'), 7.12 (d, 1H, *J* = 8.8 Hz, *H*-4'), 6.75 (d, 1H, *J* = 6.0 Hz, *H*-1), 5.42 (dd, 1H, *J* = 7.2 Hz and 2.8 Hz, *H*-4), 5.26 (t, 1H, *J* = 5.6 Hz, *H*-2), 5.18 (td, 1H, *J* = 6.1 Hz and 2.9 Hz, *H*-5), 4.44 (t, 1H, *J* = 6.4 Hz, *H*-3), 2.14 (s, 3H, -COCH₃), 1.66 (s, 3H, -COCH₃), 0.69 (s, 9H, -Si-C(CH₃)₃), -0.15 (s, 3H, -Si-CCH₃CH₃), -0.21 (s, 3H, -Si-CCH₃CH₃).

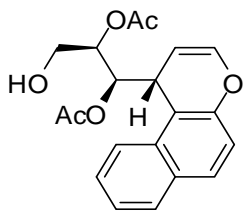
¹³C NMR: (100 MHz, CDCl₃) δ_C 170.2 (-C=O), 169.9 (-C=O), 150.4 (C-2'), 142.1 (C-1), 132.0 (C-4'a), 130.8 (C-8'a), 129.0 (C-5'), 128.3 (C-3'), 126.5 (C-7'), 124.1 (C-8'), 123.2 (C-6'), 117.7 (C-4'), 112.3 (C-1'), 101.3 (C-2), 73.5 (C-4), 71.7 (C-5), 61.1 (C-6), 31.9 (C-3), 25.5 (-Si-C(CH₃)₃), 21.0 (-COCH₃), 20.3 (-COCH₃), 17.9 (-Si-C(CH₃)₃), -5.8 (-Si(CH₃)₂).

IR: 2929, 1741, 1464, 1370, 1250, 1100, 835 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 493.2023, found: 493.1992

[α]_D: -69.9 (c 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-(1*H*-benzo[*f*]chromen-1-yl)-2-hydroxypropane-1,3-diyl diacetate (3.4)



To a solution of fully protected chromene **3.3** (200 mg, 0.425 mmol) and THF (5 mL), was added TBAF (2 eq) in THF and the mixture was allowed to stir at room temperature for one (1) hour. Upon completion, as deduced by TLC, H₂O (3 mL) was added and the product was extracted three (3) with ethyl acetate. The combined organic layers were dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to

column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 1:1) was used as eluent, providing 120 mg of the hydroxy chromene **3.4**.

Cream solid

Mp: 133-135 °C

Yield: 79 %

R_f: 0.32 (Hexane: EtOAc, 1:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.17 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.76 (d, 1H, *J* = 8.4 Hz, *H*-5'), 7.69 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.53 (t, 1H, *J* = 7.6 Hz, *H*-7'), 7.40 (t, 1H, *J* = 7.2 Hz, *H*-6'), 7.14 (d, 1H, *J* = 8.8 Hz, *H*-4'), 6.81 (d, 1H, *J* = 6.0 Hz, *H*-1), 5.27 (t, 1H, *J* = 5.6 Hz, *H*-4), 5.19 (dd, 1H, *J* = 7.0 Hz and 3.0 Hz, *H*-4), 4.63 (t, 1H, *J* = 6.4 Hz, *H*-3), 4.14 (t, 1H, *J* = 7.2 Hz, *H*-5), 3.92-3.82 (m, 2H, *H*-6_A and *H*-6_B), 2.39 (br s, 1H, -OH), 1.73 (s, 3H, -COCH₃), 1.67 (s, 3H, -COCH₃).

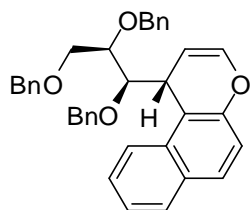
¹³C NMR: (100 MHz, CDCl₃) δ_C 170.8 (-C=O), 170.0 (-C=O), 150.4 (C-2'), 142.9 (C-1), 132.0 (C-4'*a*), 130.8 (C-8'*a*), 129.0 (C-5'), 128.4 (C-3'), 126.5 (C-7'), 124.3 (C-8'), 123.3 (C-6'), 117.7 (C-4'), 112.6 (C-1'), 101.2 (C-2), 75.6 (C-4), 68.2 (C-5), 65.6 (C-6), 31.8 (C-3), 20.4 (-COCH₃), 20.3 (-COCH₃).

IR: 3451, 2360, 1735, 1713, 1466, 1238, 1102, 819 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 379.1158, found: 379.1158

[α]_D: -20.8 (c 0.5, CH₂Cl₂)

1-((1*R*,2*R*)-1,2,3-tris(benzyloxy)propyl)-1*H*-benzo[*f*]chromene (3.5)



To a solution of diol **3.2** (200 mg, 0.517 mmol) and DMF (5 mL), were added NaH (2.07 mmol, 50 mg) and BnCl (2.07 mmol, 0.24 mL) and the mixture was allowed to stir at room temperature overnight. Upon completion, water (3 mL) was added and the product extracted three (3) times with ethyl acetate. The organic layer was washed two (2) times with water and the organic layer dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 7:1) was used as eluent, providing 190 mg of the tri-benzylated chromene **3.5**.



Clear oil

Yield: 68 %

R_f: 0.45 (Hexane: EtOAc, 7:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.00 (d, 1H, *J* = 6.8 Hz, *Ar*), 7.78 (d, 1H, *J* = 6.8 Hz, *Ar*), 7.70 (d, 1H, *J* = 8.0 Hz, *Ar*), 7.45-7.25 (m, 11H, *Ar*), 7.18-7.10 (m, 6H, *Ar*), 6.69 (d, 1H, *J* = 7.2 Hz, *Ar*), 6.65 (d, 1H, *J* = 5.6 Hz, *H-1*), 4.83 (d, 1H, *J* = 12.0 Hz, -CH₂Ph), 4.78 (t, 1H, *J* = 5.6 Hz, *H-2*), 4.65 (d, 1H, *J* = 12.0 Hz, -CH₂Ph), 4.50 (t, 1H, *J* = 6.8 Hz, *H-3*), 4.24 (s, 2H, -CH₂Ph), 3.92 (d, 1H, *J* = 10.8 Hz, -CH₂Ph), 3.87 (s, 1H, *H-5*), 3.67 (d, 2H, *J* = 10.0 Hz, -CH₂Ph and *H-4*), 3.52 (dd, 1H, *J* = 9.4 Hz and 5.8 Hz, *H-6_A*), 3.42 (dd, 1H, *J* = 9.6 Hz and 5.6 Hz, *H-6_B*)

¹³C NMR: (100 MHz, CDCl₃) δ_C 152.4 (*Ar*), 142.0 (*C-1*), 138.5 (*Ar*), 138.0 (*Ar*), 137.6 (*Ar*), 132.8 (*Ar*), 130.8 (*Ar*), 128.8 (*Ar*), 128.6 (*Ar*), 128.2 (*Ar*), 127.9 (*Ar*), 127.8 (*Ar*), 127.7 (*Ar*), 127.6 (*Ar*), 127.5 (*Ar*), 126.3 (*Ar*), 124.1 (*Ar*), 117.3 (*Ar*), 115.2 (*Ar*),

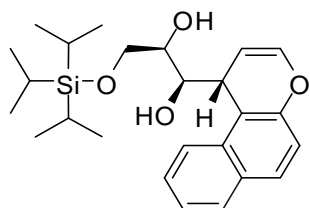
103.3 (C-2), 82.8 (C-4), 76.2 (C-5), 74.7 (-CH₂Ph), 73.1 (-CH₂Ph), 72.7 (-CH₂Ph), 70.2 (C-6), 32.2 (C-3).

IR: 3030, 2859, 1717, 1595, 1453, 1249, 1069, 695 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 565.2355, found: 565.2322

[α]_D: -14.4 (c 0.5, CH₂Cl₂)

(1R,2R)-1-(1H-benzo[f]chromen-1-yl)-3-(triisopropylsilyloxy)propane-1,2-diol (3.6)



To a solution of triol **3.1** (200 mg, 0.735 mmol) and DMF (5 mL), were added TIPSCl (2 eq) and imidazole (2.5 eq) and the reaction mixture allowed to stir at 50 °C for 14 hours as traced by TLC. Upon completion the product was extracted with ethyl acetate and the organic layer washed three (3) times with H₂O. The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 5:1) was used as eluent, providing 270 mg of the diol **3.6**

Light yellow oil

Yield: 86 %

R_f: 0.42 (Hexane: EtOAc, 5:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.01 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.77 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.67 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.50 (t, 1H, *J* = 7.0 Hz, *H*-7'), 7.38 (t, 1H, *J* = 7.0 Hz, *H*-6'), 7.11 (d, 1H, *J* = 9.2 Hz, *H*-4'), 6.75 (d, 1H, *J* = 6.0 Hz, *H*-1), 5.38 (t, 1H, *J* = 5.4 Hz, *H*-2), 4.47 (t, 1H, *J* = 4.8 Hz, *H*-3), 4.00 (d, 1H, *J* = 2.8 Hz, *H*-

4), 3.79 (br s, 1H, *H*-5), 3.47 (dd, 1H, *J* = 10.0 Hz and 4.4 Hz, *H*-6_A), 3.25 (dd, 1H, *J* = 10.0 Hz and 6.0 Hz, *H*-6_B), 3.01 (t, 1H, *J* = 1.8 Hz, -*OH*), 2.77 (d, 1H, *J* = 4.8 Hz, -*OH*), 0.88 (br s, 21H, -Si-[CH(CH₃)₂]₃)

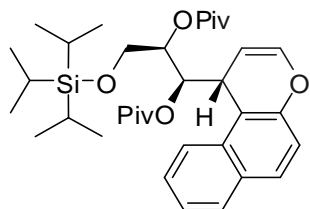
¹³C NMR: (100 MHz, CDCl₃) δ_C 150.1 (*C*-2'), 141.6 (*C*-1), 131.9 (*C*-4'*a*), 131.0 (*C*-8'*a*), 128.7 (*C*-5'), 128.5 (*C*-3'), 126.6 (*C*-7'), 124.3 (*C*-8'), 122.9 (*C*-6'), 117.7 (*C*-4'), 113.5 (*C*-1'), 102.3 (*C*-2), 73.9 (*C*-4), 70.4 (*C*-5), 65.2 (*C*-6), 34.8 (*C*-3), 17.7(-Si-[CH(CH₃)₂]₃), 11.6 (-Si-[CH(CH₃)₂]₃)

IR: 3511, 3403, 2947, 2368, 1617, 1224, 836 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 451.2281, found: 451.2268

[α]_D: -58.4 (c 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-(1*H*-benzo[*f*]chromen-1-yl)-3-(triisopropylsilyloxy)propane-1,2-diyl bis(2,2-dimethylpropanoate) (3.7)



To a solution of the diol **3.6** (200 mg, 0.466 mmol) and dry pyridine (3 mL), were added PivCl (5 eq, 0.29 mL) and a catalytic amount of DMAP. Reaction was allowed to stir at room temperature overnight. Upon completion, the reaction was extracted in ethyl acetate and washed four times with CuSO₄ (aq). The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 20:1) was used as eluent, providing 220 mg of the fully protected chromene **3.7**.

Clear Oil

Yield: 79 %

R_f: 0.65 (Hexane: EtOAc, 20:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.23 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.74 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.66 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.53 (t, 1H, *J* = 7.6 Hz, *H*-7'), 7.36 (t, 1H, *J* = 7.4 Hz, *H*-6'), 7.13 (d, 1H, *J* = 9.2 Hz, *H*-4'), 6.70 (d, 1H, *J* = 6.0 Hz, *H*-1), 5.46 (d, 1H, *J* = 6.0 Hz, *H*-4), 5.24 (t, 1H, *J* = 5.6 Hz, *H*-2), 5.18 (t, 1H, *J* = 6.6 Hz, *H*-5), 4.43 (t, 1H, *J* = 5.6 Hz, *H*-3), 3.38 (d, 2H, *J* = 6.8 Hz, *H*-6_A and *H*-6_B), 1.27 (s, 9H, -CO(CH₃)₃), 1.02 (s, 9H, -CO(CH₃)₃), 0.81 (br s, 21H, -Si-[CH(CH₃)₂]₃).

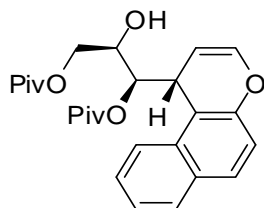
¹³C NMR: (100 MHz, CDCl₃) δ_C 177.6 (-C=O), 177.4 (-C=O), 150.5 (C-2'), 142.2 (C-1), 132.0 (C-4'a), 130.9 (C-8'a), 128.9 (C-5'), 128.3 (C-3'), 126.8 (C-7'), 124.2 (C-8'), 123.2 (C-6'), 117.8 (C-4'), 112.0 (C-1'), 101.4 (C-2), 73.1 (C-4), 71.3 (C-5), 61.3 (C-6), 39.0 (-C(CH₃)₃), 38.9 (-C(CH₃)₃), 32.3 (C-3), 27.4 (-C(CH₃)₃), 27.0 (-C(CH₃)₃), 17.7 (-Si-[CH(CH₃)₂]₃), 11.6 (-Si-[CH(CH₃)₂]₃).

IR: 2941, 2863, 2362, 1731, 1597, 1276, 1141, 883 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 619.3431, found: 619.3402

[α]_D: -12.8 (c 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-(1*H*-benzo[*f*]chromen-1-yl)-2-hydroxypropane-1,3-diyl bis(2,2-dimethylpropanoate) (3.8)



To a solution of fully protected chromene **3.7** (200 mg, 0.335 mmol) and THF (5 mL), was added TBAF (2 eq) in THF and the reaction mixture was allowed to stir at room temperature for two (2) hours. Upon completion, as deduced by TLC, H₂O (3 mL) was added and the product was extracted three (3) with ethyl acetate. The combined organic layers were dried with MgSO₄

(anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 5:1) was used as eluent, providing 110 mg of the hydroxy chromene **3.8**.

Cream solid

Mp: 83-85 °C

Yield: 74 %

R_f: 0.53 (Hexane: EtOAc, 5:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.22 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.75 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.68 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.55 (t, 1H, *J* = 7.4 Hz, *H*-7'), 7.37 (t, 1H, *J* = 7.4 Hz, *H*-6'), 7.13 (d, 1H, *J* = 9.2 Hz, *H*-4'), 6.79 (d, 1H, *J* = 5.6 Hz, *H*-1), 5.27 (d, 2H, *J* = 4.4 Hz, *H*-2 and *H*-4), 4.61 (t, 1H, *J* = 5.4 Hz, *H*-3), 4.01 (s, 1H, *H*-5), 3.85 (dd, 1H, *J* = 11.0 Hz and 5.8 Hz, *H*-6_A), 3.75 (dd, 1H, *J* = 11.0 Hz and 6.6 Hz, *H*-6_B), 2.41 (br s, 1H, -OH), 1.10 (s, 9H, -CO(CH₃)₃), 0.88 (s, 9H, -CO(CH₃)₃).

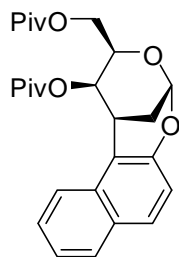
¹³C NMR: (100 MHz, CDCl₃) δ_C 178.0 (-C=O), 177.7 (-C=O), 150.2 (*C*-2'), 142.5 (*C*-1), 131.8 (*C*-4'_a), 130.8 (*C*-8'_a), 129.0 (*C*-5'), 128.4 (*C*-3'), 127.0 (*C*-7'), 124.4 (*C*-8'), 123.0 (*C*-6'), 117.7 (*C*-4'), 111.9 (*C*-1'), 101.5 (*C*-2), 73.7 (*C*-4), 68.5 (*C*-5), 64.1 (*C*-6), 39.0 (-C(CH₃)₃), 38.4 (-C(CH₃)₃), 32.2 (*C*-3), 27.0 (-C(CH₃)₃), 26.7 (-C(CH₃)₃).

IR: 3515, 2923, 2380, 1730, 1463, 1397, 1142, 815 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 463.2097, found: 463.2083

[α]_D: -19.3 (*c* 0.5, CH₂Cl₂)

((1*R*,2*R*,3*R*,5*R*)-2-(pivaloyloxy)-2,3-dihydro-1*H*-1,5-methanonaphtho[2,1-*d*][1,3]dioxocin-3-yl)methyl pivalate (3.9)



To a solution of the hydroxyl chromene **3.8** (100 mg, 0.227 mmol) and acetonitrile (2 mL), was added 5 mol% Al(OTf)₃ and the reaction allowed to stir at 50 °C for six (6) hours. Upon completion, the product was extracted in DCM and washed two (2) times with NaHCO₃ (aq) and once with brine. The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 7:1) was used as eluent, providing 84 mg of the cyclised product **3.9**.



Cream solid

Mp: 154-156 °C

Yield: 84 %

R_f: 0.56 (Hexane: EtOAc, 7:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.18 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.79 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.73 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.60 (t, 1H, *J* = 7.6 Hz, *H*-7'), 7.39 (t, 1H, *J* = 7.4 Hz, *H*-6'), 7.15 (d, 1H, *J* = 8.8 Hz, *H*-4'), 5.7 (s, 1H, *H*-1), 4.91 (s, 1H, *H*-4), 4.15 (dd, 1H, *J* = 9.2 Hz and 6.0 Hz, *H*-6_A), 4.08 – 4.01 (m, 2H, *H*-5 and *H*-6_B), 3.96 (s, 1H, *H*-3), 2.51 (d, 1H, *J* = 13.2 Hz, *H*-2_A), 1.74 (d, 1H, *J* = 13.2 Hz, *H*-2_B), 1.33 (s, 9H, -CO(CH₃)₃), 1.06 (s, 9H, -CO(CH₃)₃).

¹³C NMR: (100 MHz, CDCl₃) δ_C 178.0 (-C=O), 177.9 (-C=O), 152.8 (*C*-2'), 131.9 (*C*-4'a), 129.4 (*C*-8'a), 129.1 (*C*-5'), 128.4 (*C*-3'), 127.5 (*C*-7'), 123.9 (*C*-8'), 121.7 (*C*-6'), 117.5 (*C*-4'), 114.1 (*C*-1'), 92.5 (*C*-1), 68.6 (*C*-4), 67.9 (*C*-5), 62.6 (*C*-6),

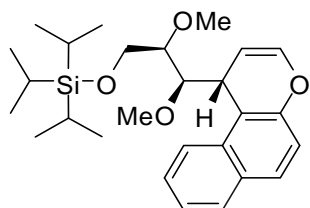
39.2 (-C(CH₃)₃), 38.6 (-C(CH₃)₃), 27.5 (C-3), 27.2 (-C(CH₃)₃), 27.0 (-C(CH₃)₃),
23.1 (C-2).

IR: 2963, 2936, 1726, 1623, 1468, 1339, 1221, 995 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 463.2097, found: 463.2100

[α]_D: -63.4 (c 0.5, CH₂Cl₂)

((2R,3R)-3-(1H-benzo[f]chromen-1-yl)-2,3-dimethoxypropoxy)triisopropylsilane (3.10)



To a solution of the diol **3.6** (400 mg, 0.932 mmol) and THF (5 mL), were added NaH (5 eq, 112 mg) and MeI (4 eq, 0.23 mL) and the reaction mixture allowed to stir at room temperature overnight. Upon completion, DCM (10 mL) was added and the reaction mixture washed with H₂O three (3) times. The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 9:1) was used as eluent, providing 387 mg of the fully protected chromene **3.10**.

Light yellow oil

Yield: 91 %

R_f: 0.48 (Hexane: EtOAc, 9:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.11 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.74 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.66 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.46 (t, 1H, *J* = 7.4 Hz, *H*-7'), 7.35 (t, 1H, *J* = 7.4 Hz, *H*-6'), 7.14 (d, 1H, *J* = 8.8 Hz, *H*-4'), 6.74 (d, 1H, *J* = 5.6 Hz, *H*-1), 5.26 (t, 1H, *J* = 5.8 Hz, *H*-2), 4.57 (t, 1H, *J* = 6.4 Hz, *H*-3), 3.74 (dd, 1H, *J* = 9.8 Hz

and 5.4 Hz, *H-6_A*), 3.67-3.62 (m, 2H, *H-4* and *H-6_B*), 3.46 (s, 3H, -OCH₃), 3.30 (t, 1H, *J* = 6.4 Hz, *H-5*), 3.06 (s, 3H, -OCH₃), 0.91 (br s, 21H, -Si-[CH(CH₃)₂]₃).

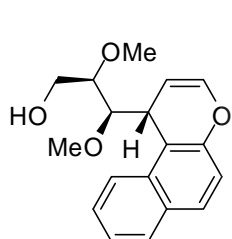
¹³C NMR: (100 MHz, CDCl₃) δ_C 150.4 (*C-2'*), 141.1 (*C-1*), 132.4 (*C-4'a*), 130.8 (*C-8'a*), 128.1 (*C-3'*), 127.9 (*C-5'*), 126.1 (*C-7'*), 123.9 (*C-8'*), 123.4 (*C-6'*), 117.4 (*C-4'*), 114.7 (*C-1'*), 103.4 (*C-2*), 83.5 (*C-4*), 80.4 (*C-5*), 61.1 (*C-6*), 59.7(-OCH₃), 58.9 (-OCH₃), 31.6 (*C-3*), 17.7 (-Si-[CH(CH₃)₂]₃), 11.7 (-Si-[CH(CH₃)₂]₃).

IR: 2948, 2842, 2371, 1653, 1328, 1226, 1043, 864 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 479.2594, found: 479.2598

[α]_D: -52.3 (c 0.5, CH₂Cl₂)

(2*R*,3*R*)-3-(1*H*-benzo[*f*]chromen-1-yl)-2,3-dimethoxypropan-1-ol (3.11)



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To a solution of fully protected chromene **3.10** (300 mg, 0.657 mmol) and THF (5 mL), was added TBAF (2 eq) in THF and the reaction mixture was allowed to stir at room temperature for two (2) hours. Upon completion, as deduced by TLC, H₂O (3 mL) was added and the product was extracted three (3) with ethyl acetate. The combined organic layers were dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 1:1) was used as eluent, providing 190 mg of the hydroxy chromene **3.11**.

Clear oil

Yield: 97 %

R_f: 0.26 (Hexane: EtOAc, 1:1)

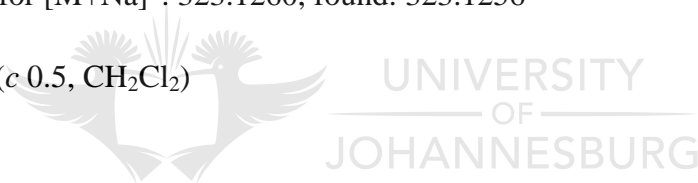
¹H NMR: (400 MHz, CDCl₃): δ_H 8.07 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.75 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.68 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.48 (t, 1H, *J* = 7.2 Hz, *H*-7'), 7.37 (t, 1H, *J* = 7.0 Hz, *H*-6'), 7.13 (d, 1H, *J* = 8.8 Hz, *H*-4'), 6.74 (d, 1H, *J* = 5.6 Hz, *H*-1), 5.23 (t, 1H, *J* = 5.6 Hz, *H*-2), 4.56 (t, 1H, *J* = 6.2 Hz, *H*-3), 3.60 (d, 1H, *J* = 5.2 Hz, *H*-6_A), 3.53 (d, 1H, *J* = 5.6 Hz, *H*-4), 3.48 (s, 4H, *H*-6_B and -OCH₃), 3.38 (d, 1H, *J* = 2.8 Hz, *H*-5), 3.03 (s, 3H, -OCH₃), 2.11 (br s, 1H, -OH).

¹³C NMR: (100 MHz, CDCl₃) δ_C 150.4 (*C*-2'), 141.7 (*C*-1), 132.3 (*C*-4'*a*), 130.8 (*C*-8'*a*), 128.5 (*C*-5'), 128.1 (*C*-3'), 126.3 (*C*-7'), 124.2 (*C*-8'), 123.3 (*C*-6'), 117.6 (*C*-4'), 114.3 (*C*-1'), 102.9 (*C*-2), 85.9 (*C*-4), 79.8 (*C*-5), 61.9 (*C*-6), 59.7(-OCH₃), 58.6 (-OCH₃), 32.0 (*C*-3).

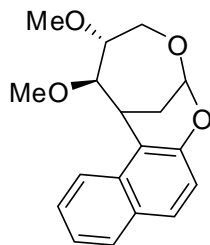
IR: 3493, 2894, 2383, 1642, 1459, 1226, 1039, 906 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 323.1260, found: 323.1256

[α]_D: -36.4 (*c* 0.5, CH₂Cl₂)



(2*R*,3*R*)-2,3-dimethoxy-1,2,3,4-tetrahydro-1,6-methanonaphtho[2,1-*d*][1,3]dioxinine (3.12)



To a solution of hydroxy chromene (150 mg, 0.499 mmol) and acetonitrile (3 mL), was added 10 mol % Al(OTf)₃ and the reaction was allowed to stir at room temperature for six (6) hours. Upon completion, as traced by TLC, the product was extracted in DCM and washed two (2) times with NaHCO₃ (aq) and once with brine. The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography

on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 2:1) was used as eluent, providing 132 mg of the oxepane **3.12**.

Light yellow oil

Yield: 88 %

R_f: 0.60 (Hexane: EtOAc, 2:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 7.92 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.78 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.66 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.54 (t, 1H, *J* = 7.6 Hz, *H*-7'), 7.36 (t, 1H, *J* = 7.6 Hz, *H*-6'), 7.10 (d, 1H, *J* = 8.8 Hz, *H*-4'), 5.65 (d, 1H, *J* = 2.8 Hz, *H*-1), 3.80 (d, 1H, *J* = 6.8 Hz, *H*-3), 3.75 (d, 1H, *J* = 5.6 Hz, *H*-4), 3.70 (s, 4H, *H*-6_A and -OCH₃), 3.64 (d, 1H, *J* = 12.4 Hz, *H*-6_B), 3.56 (t, 1H, *J* = 7.0 Hz, *H*-5), 3.24 (s, 3H, -OCH₃), 2.56 (d, 1H, *J* = 15.2 Hz, *H*-2_A), 2.20 (ddd, 1H, *J* = 14.8 Hz, 7.2 Hz and 4.0 Hz, *H*-2_B).

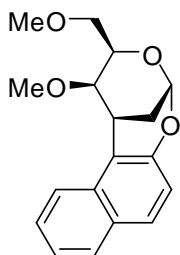
¹³C NMR: (100 MHz, CDCl₃) δ_C 152.4 (*C*-2'), 131.7 (*C*-4'*a*), 129.4 (*C*-8'*a*), 129.0 (*C*-5'), 128.9 (*C*-3'), 126.8 (*C*-7'), 123.4 (*C*-8'), 121.3 (*C*-6'), 118.1 (*C*-4'), 113.7 (*C*-1'), 93.5 (*C*-1), 85.9 (*C*-5), 84.6 (*C*-4), 61.5 (*C*-6), 58.6(-OCH₃), 57.0 (-OCH₃), 31.4 (*C*-3), 26.6 (*C*-2).

IR: 2928, 2821, 2359, 1623, 1427, 1270, 1068, 901 cm⁻¹

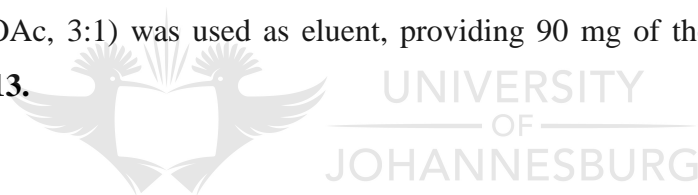
HRMS (ESI⁺): calc. for [M+Na]⁺: 323.1260, found: 323.1249

[α]_D: -34.6 (*c* 0.5, CH₂Cl₂)

(1*R*,2*R*,3*R*,5*R*)-2-methoxy-3-(methoxymethyl)-2,3-dihydro-1*H*-1,5-methanonaphtho[2,1-*d*][1,3]dioxocine (3.13)



To solution of the bridged chiral benzopyran diol **2.35** (100 mg, 0.367 mmol) and THF (3 mL), were added NaH (5 eq, 44 mg) and MeI (4 eq, 90 μ L) and the mixture allowed to stir at room temperature overnight. Upon completion, as traced by TLC, DCM (10 mL) was added and the reaction mixture washed with H₂O three (3) times. The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 3:1) was used as eluent, providing 90 mg of the methylated bridged chiral benzopyran **3.13**.



White solid

MP: 85-87 °C

Yield: 82 %

R_f: 0.39 (Hexane: EtOAc, 3:1)

¹H NMR: (400 MHz, CDCl₃): δ_{H} 7.86 (d, 1H, $J = 8.4$ Hz, *H*-8'), 7.79 (d, 1H, $J = 8.0$ Hz, *H*-5'), 7.68 (d, 1H, $J = 8.8$ Hz, *H*-3'), 7.52 (t, 1H, $J = 7.6$ Hz, *H*-7'), 7.36 (t, 1H, $J = 7.6$ Hz, *H*-6'), 7.14 (d, 1H, $J = 9.2$ Hz, *H*-4'), 5.70 (s, 1H, *H*-1), 3.99 (s, 1H, *H*-3), 3.82 (t, 1H, $J = 5.2$ Hz, *H*-5), 3.64 (s, 3H, -OCH₃), 3.51 (dd, 1H, $J = 9.4$ Hz and 7.4 Hz, *H*-6_A), 3.45-3.40 (m, 2H, *H*-4 and *H*-6_B), 3.27 (s, 3H, -OCH₃), 2.65 (d, 1H, $J = 12.8$ Hz, *H*-2_A), 1.68 (d, 1H, $J = 12.4$ Hz, *H*-2_B).

¹³C NMR: (100 MHz, CDCl₃) δ_{C} 153.5 (*C*-2'), 131.6 (*C*-4'*a*), 129.1 (*C*-8'*a*), 128.8 (*C*-5'), 128.7 (*C*-3'), 126.9 (*C*-7'), 123.4 (*C*-8'), 120.5 (*C*-6'), 117.8 (*C*-4'), 114.7 (*C*-1'),

92.9 (C-1), 76.2 (C-4), 72.3 (C-6), 70.2 (C-5), 59.1(-OCH₃), 57.6 (-OCH₃), 26.0 (C-3), 22.9 (C-2).

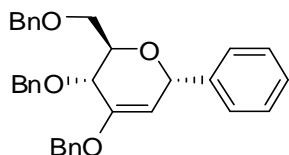
IR: 2911, 2381, 1621, 1463, 1221, 1042, 892 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 323.1260, found: 323.1251

[α]_D: -87.9 (c 0.5, CH₂Cl₂)

5.5 Chapter 4 (Flavonoid derivatives)

(2*R*,3*R*,6*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-6-phenyl-3,6-dihydro-2*H*-pyran (4.1)⁸



To a round bottom flask was added successively; 200 mg of 3,4,6-*tri-O*-benzyl-D-glucal, iodobenzene (2 eq, 0.11 mL), TBACl (1 eq, 133 mg), K₂CO₃ (2.5 eq, 166 mg), Pd(OAc)₂ (10 mol%, 11 mg), dppp (10 mol%, 20 mg) and DMF (5 mL). The reaction was allowed to stir at 80 °C for 7 hours. The reaction mixture was then diluted with water, extracted with diethyl ether, dried over anhydrous Na₂SO₄, and then concentrated. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 7:1) was used as an eluent, providing 172 mg of the C-glycoside **4.1**.

Light yellow oil

Yield: 73%

R_f: 0.53 (Hexane: EtOAc, 7:1)

¹H NMR: (400 MHz, CDCl₃): δ _H 4.46-7.21 (m, 20H, Ar), 5.29 (d, 1H, *J* = 3.2 Hz, *H*-1), 4.94 (d, 1H, *J* = 3.6 Hz, *H*-2), 4.80 (d, 2H, *J* = 5.2 Hz, -CH₂Ph), 4.77 (d, 1H, *J* = 11.6 Hz, -CH₂Ph), 4.47 (dd, 2H, *J* = 11.6 Hz and 6.0 Hz, -CH₂Ph), 4.35 (d, 1H, *J* = 12.4 Hz, -CH₂Ph), 4.12 (dd, 1H, *J* = 6.4 Hz and 1.2 Hz, *H*-4), 3.86-3.81 (m, 1H,

H-5), 3.58 (dd, 1H, *J* = 10.4 Hz and 4.8 Hz, *H*-6_A), 3.47 (dd, 1H, *J* = 10.4 Hz and 3.6 Hz, *H*-6_B).

¹³C NMR: (100 MHz, CDCl₃) δ_C 153.2 (*Ar*), 140.8 (*Ar*), 138.4 (*Ar*), 138.1 (*Ar*), 128.4 (*Ar*), 128.3 (*Ar*), 128.2 (x3) (*Ar*), 128.1 (*Ar*), 127.8 (*Ar*), 127.6 (*Ar*), 127.5 (*Ar*), 127.4 (*Ar*), 98.9 (*C*-2), 73.6 (*C*-1), 73.4 (-CH₂Ph), 73.2 (-CH₂Ph), 72.4 (*C*-5), 71.4 (*C*-4), 69.1 (-CH₂Ph), 68.8 (*C*-6).

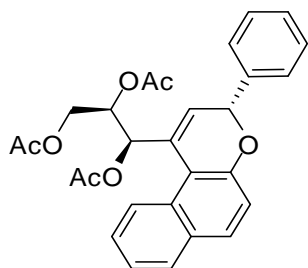
IR: 3402, 1063, 2865, 1724, 1585, 1312, 1095, 696 cm⁻¹

[α]_D: 10.0 (c 0.5, CH₂Cl₂)

Heck Cross-coupling

To a round bottom flask was added successively; 200 mg of tri-*O*-acetylated chromene **2.29**, aryl halide (2 eq), TBACl (1 eq), K₂CO₃ (2.5 eq), Pd(OAc)₂ (10 mol%), dppp (10 mol%) and DMF (5 mL). The reaction was allowed to stir at 80 °C for 14 hours. Upon completion the reaction mixture was then diluted with water, extracted with diethyl ether, dried over anhydrous Na₂SO₄, and then concentrated. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 4:1) was used as eluent, providing a mixture of unsaturated flavonoid regeoisomers in good yields.

(1*R*,2*R*)-1-((*R*)-3-phenyl-3*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triyl triacetate (4.2)



Thick yellow oil

Yield: 87 %

R_f: 0.40 (Hexane: EtOAc, 4:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.57 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.78 (d, 1H, *J* = 8.8 Hz, *H*-5'), 7.74 (d, 1H, *J* = 9.2 Hz, *H*-3'), 7.56-7.38 (m, 7H, *Ar*), 7.23 (d, 1H, *J* = 8.4 Hz, *H*-4'), 6.67 (d, 1H, *J* = 5.6 Hz, *H*-4), 6.03 (dd, 1H, *J* = 3.8 Hz and 1.0 Hz, *H*-2), 5.38 (d, 1H, *J* = 3.6 Hz, *H*-1), 4.92 (q, 1H, *J* = 4.4 Hz, *H*-5), 4.01 (dd, 1H, *J* = 12.2 Hz and 4.2 Hz, *H*-6_A), 3.61 (dd, 1H, *J* = 12.0 Hz and 5.2 Hz, *H*-6_B), 2.20 (s, 3H, -COCH₃), 1.83 (s, 3H, -COCH₃), 1.51 (s, 3H, -COCH₃).

¹³C NMR: (100 MHz, CDCl₃) δ_C 170.2 (-C=O), 170.0(-C=O), 169.6 (-C=O), 154.2 (*C*-2'), 139.3 (*Ar*), 133.6 (*Ar*), 131.5 (*Ar*), 130.0 (*Ar*), 128.4 (*Ar*), 127.7 (*Ar*) 126.9 (*Ar*), 126.7 (*Ar*), 125.0 (*C*-2), 124.9 (*Ar*), 122.3 (*Ar*), 117.6 (*Ar*), 115.8 (*C*-3), 77.3 (*C*-1), 72.3 (*C*-5), 71.2 (*C*-4), 61.7 (*C*-6), 21.0 (-COCH₃), 20.4 (-COCH₃), 19.9(-COCH₃).

IR: 2971, 2357, 1736, 1623, 1215, 1027, 814 cm⁻¹

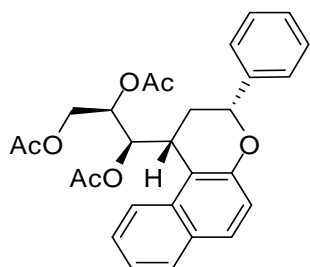
HRMS (ESI+): calc. for [M+Na]⁺: 497.1577, found: 497.1577



Hydrogenation of unsaturated flavonoids

To a solution of 100 mg of unsaturated flavonoid and methanol (3 mL), was added Pd/C (20 mol%) and the solution was allowed to stir under 1 bar hydrogen atmosphere at 50 °C for 8 hrs. Upon completion 10 mL of DCM was added and the reaction mixture was filtered through celite. The filtrate was concentrated and crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 4:1) was used as eluent, providing the flavonoid in high yields.

(1*R*,2*R*)-1-((3*R*)-3-phenyl-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triyl triacetate (4.3)



Thick yellow oil

Yield: 92 %

R_f : 0.38 (Hexane: EtOAc, 4:1)

$^1\text{H NMR}$: (400 MHz, CDCl_3): δ_{H} 8.10 (d, 1H, $J = 8.4$ Hz, $H-8'$), 7.77 (d, 1H, $J = 7.6$ Hz, $H-5'$), 7.67 (d, 1H, $J = 8.8$ Hz, $H-3'$), 7.54-7.49 (m, 3H, *Ar*), 7.43 (t, 2H, $J = 7.6$ Hz, *Ar*), 7.37-7.33 (m, 2H, *Ar*), 7.15 (d, 1H, $J = 8.8$ Hz, $H-4'$) 5.59 (dd, 1H, $J = 7.4$ Hz and 3.8 Hz, $H-4$), 4.97-4.94 (m, 2H, $H-5$ and $H-1$), 4.27 (q, 1H, $J = 8.8$ Hz, $H-3$), 3.77 (dd, 1H, $J = 11.6$ Hz and 5.2 Hz, $H-6_A$), 3.53 (dd, 1H, $J = 11.6$ Hz and 6.4 Hz, $H-6_B$), 2.67 (ddd, 1H, $J = 14.4$ Hz, 10.4 Hz and 7.6 Hz, $H-2_A$), 2.47 (ddd, 1H, $J = 14.4$ Hz, 8.8 Hz and 3.6 Hz, $H-2_B$), 2.11 (s, 3H, $-\text{COCH}_3$), 1.79 (s, 3H, $-\text{COCH}_3$), 1.70 (s, 3H, $-\text{COCH}_3$).

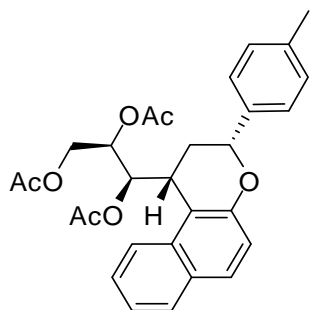
$^{13}\text{C NMR}$: (100 MHz, CDCl_3) δ_{C} 170.1 (2x, $-\text{C}=\text{O}$), 169.7 ($-\text{C}=\text{O}$), 155.5 ($\text{C}-2'$), 141.1 (*Ar*), 132.6 ($\text{C}-4'a$), 129.8 ($\text{C}-8'a$), 129.2 ($\text{C}-5'$), 128.8 ($\text{C}-3'$), 128.7 (*Ar*) 128.0 ($\text{C}-7'$), 126.4 ($\text{C}-8'$), 125.8 (*Ar*), 123.6 (*Ar*), 123.0 ($\text{C}-6'$), 119.4 ($\text{C}-4'$), 114.3 ($\text{C}-1'$), 77.6 ($\text{C}-1$), 73.0 ($\text{C}-4$), 69.0 ($\text{C}-5$), 61.9 ($\text{C}-6$), 33.4 ($\text{C}-2$), 32.6 ($\text{C}-3$), 20.9 ($-\text{COCH}_3$), 20.4 ($-\text{COCH}_3$), 20.3 ($-\text{COCH}_3$).

IR: 2958, 2923, 2362, 1743, 1631, 1211, 1033, 842 cm^{-1}

HRMS (ESI+): calc. for $[\text{M}+\text{Na}]^+$: 499.1733, found: 499.1734

$[\alpha]_{\text{D}}$: -7.2 (c 0.5, CH_2Cl_2)

(1*R*,2*R*)-1-((3*R*)-3-*p*-tolyl-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triyl triacetate (4.4)



Thick purple oil

Yield: 85 %

R_f: 0.41 (Hexane: EtOAc, 4:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 8.09 (d, 1H, *J* = 8.4 Hz, *H*-8'), 7.77 (d, 1H, *J* = 7.4 Hz, *H*-5'), 7.66 (d, 1H, *J* = 8.8 Hz, *H*-3'), 7.53 (t, 1H, *J* = 7.6 Hz, *H*-7'), 7.40 (d, 2H, *J* = 6.7 Hz, *Ar*), 7.35 (t, 1H, *J* = 7.6 Hz, *H*-6'), 7.23 (d, 2H, *J* = 6.8 Hz, *Ar*), 7.13 (d, 1H, *J* = 8.8 Hz, *H*-4'), 5.62 (dd, 1H, *J* = 7.6 Hz and 4.0 Hz, *H*-4), 4.94-4.88 (m, 2H, *H*-5 and *H*-1), 4.28 (q, 1H, *J* = 8.4 Hz, *H*-3), 3.78 (dd, 1H, *J* = 11.6 Hz and 5.2 Hz, *H*-6_A), 3.53 (dd, 1H, *J* = 11.6 Hz and 6.4 Hz, *H*-6_B), 2.66 (ddd, 1H, *J* = 14.4 Hz, 10.5 Hz and 7.7 Hz, *H*-2_A), 2.44 (ddd, 1H, *J* = 14.4 Hz, 9.0 Hz and 3.4 Hz, *H*-2_B), 2.36 (s, 3H, -CCH₃), 2.10 (s, 3H, -COCH₃), 1.81 (s, 3H, -COCH₃), 1.70 (s, 3H, -COCH₃).

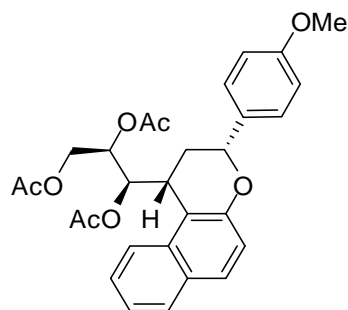
¹³C NMR: (100 MHz, CDCl₃) δ_C 170.1 (-C=O), 169.7 (-C=O), 155.7 (*C*-2'), 138.0 (*Ar*), 137.8 (*Ar*), 132.6 (*C*-4'*a*), 129.8 (*C*-8'*a*), 129.3 (*Ar*), 129.1 (*C*-5'), 128.8 (*C*-3'), 126.4 (*C*-7'), 125.9 (*Ar*), 123.6 (*C*-8'), 123.0 (*C*-6'), 119.5 (*C*-4'), 114.3 (*C*-1'), 77.7 (*C*-1), 73.0 (*C*-4), 69.0 (*C*-5), 61.9 (*C*-6), 33.4 (*C*-2), 32.7 (*C*-3), 21.2 (-CCH₃), 20.9 (-COCH₃), 20.4 (-COCH₃), 20.3(-COCH₃).

IR: 2962, 2924, 2358, 1738, 1620, 1369, 1209, 1020 cm⁻¹

HRMS (ESI⁺): calc. for [M+Na]⁺: 513.1890, found: 513.1881

[α]_D: -2.6 (*c* 0.5, CH₂Cl₂)

(1*R*,2*R*)-1-((3*R*)-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triyl triacetate (4.5)



Thick purple oil

Yield: 86 %

R_f : 0.32 (Hexane: EtOAc, 4:1)

$^1\text{H NMR}$: (400 MHz, CDCl_3): δ_{H} 8.10 (d, 1H, $J = 8.4$ Hz, $H-8'$), 7.77 (d, 1H, $J = 7.6$ Hz, $H-5'$), 7.66 (d, 1H, $J = 8.8$ Hz, $H-3'$), 7.53 (t, 1H, $J = 7.6$ Hz, $H-7'$), 7.43 (d, 2H, $J = 6.4$ Hz, Ar), 7.35 (t, 1H, $J = 7.6$ Hz, $H-6'$), 7.13 (d, 1H, $J = 8.8$ Hz, $H-4'$), 6.96 (d, 2H, $J = 6.4$ Hz, Ar) 5.63 (dd, 1H, $J = 7.2$ Hz and 4.0 Hz, $H-4$), 4.96 (q, 1H, $J = 5.6$ Hz, $H-5$), 4.88 (dd, 1H, $J = 10.6$ Hz and 3.0 Hz, $H-1$), 4.28 (q, 1H, $J = 8.4$ Hz, $H-3$), 3.81 (s, 3H, $-\text{OCH}_3$), 3.79 (dd, 1H, $J = 11.6$ Hz and 5.2 Hz, $H-6_A$), 3.52 (dd, 1H, $J = 11.6$ Hz and 6.4 Hz, $H-6_B$), 2.67 (ddd, 1H, $J = 14.4$ Hz, 10.6 Hz and 7.8 Hz, $H-2_A$), 2.43 (ddd, 1H, $J = 14.4$ Hz, 9.0 Hz and 3.2 Hz, $H-2_B$), 2.10 (s, 3H, $-\text{COCH}_3$), 1.82 (s, 3H, $-\text{COCH}_3$), 1.70 (s, 3H, $-\text{COCH}_3$).

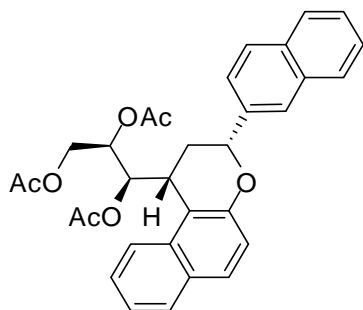
$^{13}\text{C NMR}$: (100 MHz, CDCl_3) δ_{C} 170.1 (x2) ($-\text{C}=\text{O}$), 169.7 ($-\text{C}=\text{O}$), 159.4 (Ar), 155.7 ($C-2'$), 133.0 (Ar), 132.6 ($C-4'a$), 129.7 ($C-8'a$), 129.1 ($C-5'$), 128.8 ($C-3'$), 127.3 (Ar), 126.4 ($C-7'$), 123.5 ($C-8'$), 123.0 ($C-6'$), 119.4 ($C-4'$), 114.3 ($C-1'$), 114.0 (Ar), 77.5 ($C-1$), 73.0 ($C-4$), 69.0 ($C-5$), 61.9 ($C-6$), 55.3 ($-\text{OCH}_3$), 33.2 ($C-2$), 32.7 ($C-3$), 20.9 ($-\text{COCH}_3$), 20.4 ($-\text{COCH}_3$), 20.2 ($-\text{COCH}_3$).

IR: 2932, 2360, 1739, 1615, 1514, 1211, 1028, 816 cm^{-1}

HRMS (ESI+): calc. for $[\text{M}+\text{Na}]^+$: 529.1839, found: 529.1839

$[\alpha]_{\text{D}}$: -1.0 (c 0.5, CH_2Cl_2)

(1*R*,2*R*)-1-((3*R*)-3-(naphthalen-2-yl)-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triyl triacetate (4.6)



Thick red oil

Yield: 79%

R_f : 0.39 (Hexane: EtOAc, 4:1)

$^1\text{H NMR}$: (400 MHz, CDCl_3): δ_{H} 8.10 (d, 1H, $J = 8.4$ Hz, *Ar*), 7.74 (d, 1H, $J = 8.4$ Hz, *Ar*), 7.67 (d, 1H, $J = 8.8$ Hz, *Ar*), 7.64-7.31 (m, 8H, *Ar*), 7.15 (d, 1H, $J = 9.2$ Hz, *Ar*), 5.59 (dd, 1H, $J = 7.4$ Hz and 3.8 Hz, *H-4*), 4.97-4.93 (m, 2H, *H-1* and *H-5*), 4.27 (q, 1H, $J = 8.0$ Hz, *H-3*), 3.77 (dd, 1H, $J = 11.6$ Hz and 5.2 Hz, *H-6_A*), 3.53 (dd, 1H, $J = 11.6$ Hz and 6.0 Hz, *H-6_B*), 2.67 (ddd, 1H, $J = 14.8$ Hz, 7.2 Hz and 2.8 Hz, *H-2_A*), 2.43 (ddd, 1H, $J = 15.2$ Hz, 8.8 Hz and 3.2 Hz, *H-2_B*), 2.11 (s, 3H, -COCH₃), 1.78 (s, 3H, -COCH₃), 1.71 (s, 3H, -COCH₃).

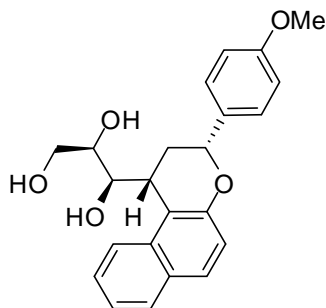
$^{13}\text{C NMR}$: (100 MHz, CDCl_3): δ_{C} 170.1 (x2) (-C=O), 169.7 (-C=O), 155.6 (*Ar*), 141.1 (*Ar*), 132.7 (*Ar*), 129.8 (*Ar*), 129.2 (*Ar*), 128.8 (*Ar*), 128.7 (*Ar*), 128.0 (*Ar*), 126.9 (*Ar*), 126.4 (*Ar*), 125.9 (*Ar*), 123.6 (*Ar*), 123.1 (*Ar*), 119.5 (*Ar*), 114.4 (*Ar*), 114.0 (*Ar*), 77.7 (*C-1*), 73.0 (*C-4*), 69.0 (*C-5*), 61.9 (*C-6*), 33.4 (*C-2*), 32.6 (*C-3*), 20.9 (-COCH₃), 20.4 (-COCH₃), 20.3 (-COCH₃).

IR: 2941, 2362, 1743, 1511, 1226, 1013, 804 cm^{-1}

HRMS (ESI⁺): calc. for $[\text{M}+\text{Na}]^+$: 549.1890, found: 549.1870

$[\alpha]_{\text{D}}$: -9.2 (*c* 0.5, CH_2Cl_2)

(1*R*,2*R*)-1-((3*R*)-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*f*]chromen-1-yl)propane-1,2,3-triol



To a solution (4 mL) of MeOH, Et₃N and H₂O in a ratio 2:1:1 respectively, was added 100 mg of the flavonoid **4.5**. The reaction was allowed to stir at room temperature for 24 hours and upon completion as deduced by TLC, volatiles were evaporated. The crude product was subjected to column chromatography on flash silica for purification, 100% ethyl acetate was used as an eluent, providing 73 mg of the triol flavonoid **4.9**.

Cream Solid



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Mp: 156-158 °C

Yield: 97 %

R_f: 0.28 (100% EtOAc)

¹H NMR: (400 MHz, CDCl₃): δ_H 7.92(d, 1H, *J* = 8.4 Hz, *H*-8'), 7.67 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.56 (d, 1H, *J* = 9.2 Hz, *H*-3'), 7.37 (t, 1H, *J* = 6.4 Hz, *H*-7'), 7.33 (d, 2H, *J* = 8.8 Hz, *Ar*), 7.23 (t, 1H, *J* = 7.2 Hz, *H*-6'), 7.02 (d, 1H, *J* = 8.8 Hz, *H*-4'), 6.85 (d, 2H, *J* = 8.4 Hz, *Ar*) 4.70 (dd, 1H, *J* = 10.8 Hz and 3.2 Hz, *H*-1), 4.09 (dd, 1H, *J* = 5.6 Hz and 2.1 Hz, *H*-5), 4.02 (dd, 1H, *J* = 5.8 Hz and 2.6 Hz, *H*-4), 3.26-3.22(m, 1H, *H*-5), 2.91 (dd, 1H, *J* = 11.2 Hz and 7.6 Hz, *H*-6_A), 2.83 (dd, 1H, *J* = 11.2 Hz and 4.8 Hz, *H*-6_B), 2.70 (ddd, 1H, *J* = 14.0 Hz, 10.8 Hz and 7.2 Hz, *H*-2_A), 2.39 (ddd, 1H, *J* = 14.0 Hz, 8.8 Hz and 3.2 Hz, *H*-2_B)

¹³C NMR: (100 MHz, CDCl₃) δ_C 160.8 (*Ar*), 157.2 (*C*-2'), 135.2 (*C*-4'*a*), 134.4 (*Ar*), 131.4 (*C*-8'*a*), 129.6 (*C*-5'), 129.3 (*C*-3'), 128.7 (*Ar*), 127.0 (*C*-7'), 124.5 (*C*-8'), 124.4

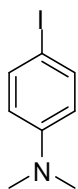
(C-6'), 120.3 (C-4'), 118.2 (C-1'), 114.8 (Ar), 79.8 (C-1), 73.3 (C-4), 71.5 (C-5), 65.7 (C-6), 55.7 (-OCH₃), 37.9 (C-3), 34.6 (C-2).

IR: 3429, 2932, 2886, 2360, 1713, 1597, 1174, 900 cm⁻¹

HRMS (ESI+): calc. for [M+Na]⁺: 403.1522, found: 403.1522

[α]_D: -1.2 (c 0.5, MeOH)

4-Iodo-N,N-dimethylaniline (4.7)⁹



To a solution of iodo aniline (1 g, 4.56 mmol) and THF (20 mL), were added NaH (5 eq, 547 mg) and MeI (4 eq, 1.13 mL) and reaction allowed to stir at room temperature overnight. Upon completion, as traced by TLC, DCM (20 mL) was added and the reaction mixture washed with H₂O three (3) times. The organic layer was dried with MgSO₄ (anhydrous) and the volatiles were evaporated *in vacuo*. The crude product was subjected to column chromatography on flash silica for purification, and a solution of hexane and ethyl acetate (Hexane: EtOAc, 6:1) was used as eluent, providing 90 mg of the N-methylated aryl iodide **4.7** in 82% yield.

Cream Solid

Mp: 73-75 °C

Yield: 82%

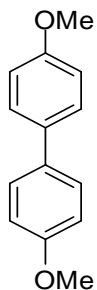
R_f: 0.48 (Hexane: EtOAc, 6:1)

¹H NMR: (400 MHz, CDCl₃): δ_H 7.46 (dd, 2H, *J* = 6.8 Hz and 2.4 Hz, *meta*-Ph), 6.49 (dd, 2H, *J* = 7.0 Hz and 1.8 Hz, *ortho*-Ph), 2.91 (s, 6H, -N(CH₃)₂)

^{13}C NMR: (100 MHz, CDCl_3) δ_{C} 149.9 (*para*-Ph), 137.5 (*meta*-Ph), 114.8 (*ortho*-Ph), 77.6 (*ipso*-Ph), 40.4 (-N(CH₃)₂)

IR: 2955, 2922, 1583, 1493, 1459, 1228, 800 cm^{-1}

4,4'-Dimethoxybiphenyl (4.8)¹⁰



Homo coupling by-product in the synthesis of flavonoid **4.5**.

Cream Solid

Mp: 168-170 °C

R_f: 0.63 (Hexane: EtOAc, 4:1)

^1H NMR: (400 MHz, CDCl_3): δ_{H} 7.46 (d, 4H, $J = 9.6$ Hz, *meta*-Ph), 6.94 (d, 4H, $J = 8.8$ Hz, *ortho*-Ph), 3.83 (s, 6H, -OCH₃)

^{13}C NMR: (100 MHz, CDCl_3) δ_{C} 158.6 (*ipso*-Ph), 133.4 (*para*-Ph), 127.7 (*meta*-Ph), 114.1 (*ortho*-Ph), 55.3 (-OCH₃)

IR: 3014, 2919, 2528, 2062, 1604, 1466, 1328, 1092, 822 cm^{-1}

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Appendix A

Table 1.1. Crystal data and structure refinement for structures in figure 2.2 and 2.3 respectively

Empirical formula	$C_{17}H_{20}O_6$	$C_{30}H_{33}O_{12}$
Formula weight	320.33	585.56
Temperature	100(2) K	100(2) K
Wavelength	0.71073 Å	1.54178 Å
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions	$a = 7.0361(7)$ Å $\alpha = 90^\circ$	$a = 9.1869(3)$ Å $\alpha = 90^\circ$
	$b = 14.3568(14)$ Å $\beta = 90^\circ$	$b = 9.6630(3)$ Å $\beta = 90^\circ$
	$c = 15.7212(16)$ Å $\gamma = 90^\circ$	$c = 30.2310(8)$ Å $\gamma = 90^\circ$
Volume	$1588.1(3)$ Å ³	$2683.70(14)$ Å ³
Z	4	4
Density (calculated)	1.340 Mg/m ³	1.449 Mg/m ³
Absorption coefficient	0.102 mm ⁻¹	0.949 mm ⁻¹
F(000)	680	1236
Crystal size	0.22 x 0.15 x 0.10 mm ³	0.31 x 0.28 x 0.27 mm ³
Theta range for data collection	1.92 to 28.33°	2.92 to 66.38°
Index ranges	$-9 \leq h \leq 9, -19 \leq k \leq 19, -21 \leq l \leq 21$	$-6 \leq h \leq 10, -11 \leq k \leq 11, -35 \leq l \leq 33$
Reflections collected	47669	32680
Independent reflections	3947 [R(int) = 0.0389]	4569 [R(int) = 0.0253]
Completeness to theta	99.9 %	97.8 %
Max. and min. transmission	0.9899 and 0.9780	0.7864 and 0.7561
Refinement method	Full-matrix least-squares on F ²	Full-matrix least-squares on F ²
Data / restraints / parameters	3947 / 0 / 211	4569 / 0 / 384
Goodness-of-fit on F ²	1.035	1.005
Final R indices [I > 2σ(I)]	R1 = 0.0294, wR2 = 0.0781	R1 = 0.0251, wR2 = 0.0703
R indices (all data)	R1 = 0.0315, wR2 = 0.0803	R1 = 0.0252, wR2 = 0.0704
Absolute structure parameter	0.0(6)	0.08(10)
Largest diff. peak and hole	0.252 and -0.175 e.Å ⁻³	0.215 and -0.196 e.Å ⁻³

Table 1.2. Crystal data and structure refinement for structures in figure 2.4 and 2.5 respectively

Empirical formula	$C_{21}H_{24}O_9$	$C_{20}H_{26}O_6$
Formula weight	420.40	362.41
Temperature	100(2) K	100(2) K
Wavelength	0.71073 Å	1.54178 Å
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions	a = 7.5952(8) Å $\alpha = 90^\circ$	a = 8.3895(2) Å $\alpha = 90^\circ$
	b = 13.8502(15) Å $\beta = 90^\circ$	b = 14.3785(3) Å $\beta = 90^\circ$
	c = 19.741(2) Å $\gamma = 90^\circ$	c = 19.2943(4) Å $\gamma = 90^\circ$
Volume	2076.6(4) Å ³	2327.44(9) Å ³
Z	4	4
Density (calculated)	1.345 Mg/m ³	1.034 Mg/m ³
Absorption coefficient	0.106 mm ⁻¹	0.625 mm ⁻¹
F(000)	888	776
Crystal size	0.568 x 0.539 x 0.523 mm ³	0.49 x 0.08 x 0.08 mm ³
Theta range for data collection	1.796 to 28.313°	5.52 to 66.59°
Index ranges	-10 ≤ h ≤ 8, -18 ≤ k ≤ 18, -22 ≤ l ≤ 26	-2 ≤ h ≤ 9, -17 ≤ k ≤ 17, -22 ≤ l ≤ 22
Reflections collected	20614	33204
Independent reflections	5158 [R(int) = 0.0475]	4018 [R(int) = 0.0298]
Completeness to theta	100.0 %	98.3 %
Max. and min. transmission	0.7457 and 0.6390	0.9499 and 0.7509
Refinement method	Full-matrix least-squares on F ²	Full-matrix least-squares on F ²
Data / restraints / parameters	5158 / 0 / 276	4018 / 0 / 302
Goodness-of-fit on F ²	1.029	1.017
Final R indices [I > 2σ(I)]	R1 = 0.0359, wR2 = 0.0894	R1 = 0.0235, wR2 = 0.0591
R indices (all data)	R1 = 0.0411, wR2 = 0.0932	R1 = 0.0242, wR2 = 0.0598
Absolute structure parameter	-0.4(4)	0.03(10)
Largest diff. peak and hole	0.181 and -0.257 e.Å ⁻³	0.132 and -0.153 e.Å ⁻³

Table 1.3. Crystal data and structure refinement for structures in figure 2.6 and 3.2 respectively

Empirical formula	$C_{18}H_{18}O_5$	$C_{22}H_{22}O_7$
Formula weight	314.32	398.40
Temperature	100(2) K	100(2) K
Wavelength	1.54178 Å	1.54178 Å
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions	$a = 6.96970(10)$ Å $\alpha = 90^\circ$	$a = 7.6131(2)$ Å $\alpha = 90^\circ$
	$b = 8.13260(10)$ Å $\beta = 90^\circ$	$b = 9.5089(3)$ Å $\beta = 90^\circ$
	$c = 25.6302(4)$ Å $\gamma = 90^\circ$	$c = 26.2854(8)$ Å $\gamma = 90^\circ$
Volume	$1452.77(4)$ Å ³	$1902.86(10)$ Å ³
Z	4	4
Density (calculated)	1.437 Mg/m ³	1.391 Mg/m ³
Absorption coefficient	0.867 mm ⁻¹	0.866 mm ⁻¹
F(000)	664	840
Crystal size	0.29 x 0.29 x 0.26 mm ³	0.21 x 0.19 x 0.13 mm ³
Theta range for data collection	5.71 to 66.54°	5.74 to 65.00°
Index ranges	$-5 \leq h \leq 8, -9 \leq k \leq 9, -30 \leq l \leq 28$	$-8 \leq h \leq 8, -11 \leq k \leq 8, -28 \leq l \leq 30$
Reflections collected	15986	20332
Independent reflections	2534 [R(int) = 0.0360]	3161 [R(int) = 0.0337]
Completeness to theta	99.0 %	98.4 %
Max. and min. transmission	0.8085 and 0.7870	0.8957 and 0.8390
Refinement method	Full-matrix least-squares on F ²	Full-matrix least-squares on F ²
Data / restraints / parameters	2534 / 0 / 215	3161 / 0 / 265
Goodness-of-fit on F ²	0.758	1.000
Final R indices [I > 2σ(I)]	R1 = 0.0263, wR2 = 0.0820	R1 = 0.0287, wR2 = 0.0793
R indices (all data)	R1 = 0.0276, wR2 = 0.0845	R1 = 0.0290, wR2 = 0.0797
Absolute structure parameter	-0.15(13)	0.02(14)
Largest diff. peak and hole	0.158 and -0.181 e.Å ⁻³	0.182 and -0.148 e.Å ⁻³

Table 1.4. Crystal data and structure refinement for structures in figure 3.7 and 4.2 respectively

Empirical formula	$C_{18}H_{20}O_4$	$C_{23}H_{24}O_5$
Formula weight	300.34	380.42
Temperature	100(2) K	293(2) K
Wavelength	1.54178 Å	0.71073 Å
Crystal system	monoclinic	monoclinic
Space group	$P12_11$	$P2_1$
Unit cell dimensions	a = 9.7808(10) Å $\alpha = 90^\circ$	a = 17.387(2) Å $\alpha = 90^\circ$
	b = 7.6912(8) Å $\beta = 91.318(4)^\circ$	b = 5.4236(6) Å $\beta = 96.356(4)^\circ$
	c = 10.1091(11) Å $\gamma = 90^\circ$	c = 20.197(3) Å $\gamma = 90^\circ$
Volume	760.27(14) Å ³	1892.8(4) Å ³
Z	2	4
Density (calculated)	1.312 Mg/m ³	1.335 Mg/m ³
Absorption coefficient	0.749 mm ⁻¹	0.093 mm ⁻¹
F(000)	320	808
Crystal size	0.50 x 0.36 x 0.23 mm ³	0.044x 0.048x0.434 mm ³
Theta range for data collection	11.56 to 66.44°	2.936 to 23.722°
Index ranges	-11 ≤ h ≤ 11, -6 ≤ k ≤ 9, -12 ≤ l ≤ 11	-19 ≤ h ≤ 19, -6 ≤ k ≤ 6, -22 ≤ l ≤ 22
Reflections collected	10564	33426
Independent reflections	2215 [R(int) = 0.0896]	5590 [R(int) = 0.1089]
Completeness to theta	95.2 %	82.6 %
Max. and min. transmission	0.8484 and 0.7058	0.9960 and 0.9610
Refinement method	Full-matrix least-squares on F ²	Full-matrix least-squares on F ²
Data / restraints / parameters	2215 / 1 / 201	5590 / 1 / 510
Goodness-of-fit on F ²	1.129	1.063
Final R indices [I > 2σ(I)]	R1 = 0.0221, wR2 = 0.0665	R1 = 0.0558, wR2 = 0.1262
R indices (all data)	R1 = 0.0912, wR2 = 0.0700	R1 = 0.1035, wR2 = 0.1527
Absolute structure parameter	-0.11(11)	-1.7(9)
Largest diff. peak and hole	0.169 and -0.172 e.Å ⁻³	0.330 and -0.419 e.Å ⁻³

Appendix B

Table 1.1 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for bridged chiral benzopyran (Figure 2.2). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	10564(3)	1789(1)	765(1)	26(1)
C(2)	11152(2)	2514(1)	1405(1)	17(1)
C(3)	4241(3)	6132(1)	2798(1)	30(1)
C(4)	5927(2)	5566(1)	2546(1)	20(1)
C(5)	6957(2)	4071(1)	2099(1)	18(1)
C(6)	8092(2)	3739(1)	2861(1)	14(1)
C(7)	10047(2)	3362(1)	2625(1)	14(1)
C(8)	10998(2)	2908(1)	3405(1)	14(1)
C(9)	9671(2)	2157(1)	3757(1)	15(1)
C(10)	7819(2)	2630(1)	3993(1)	15(1)
C(11)	11264(2)	3624(1)	4102(1)	14(1)
C(12)	9795(2)	3772(1)	4684(1)	14(1)
C(13)	9996(2)	4410(1)	5346(1)	16(1)
C(14)	11676(2)	4908(1)	5430(1)	18(1)
C(15)	13184(2)	4772(1)	4864(1)	18(1)
C(16)	12953(2)	4123(1)	4208(1)	16(1)
C(17)	15027(3)	5296(1)	4971(1)	28(1)
O(1)	12648(2)	2920(1)	1418(1)	24(1)
O(2)	9722(2)	2670(1)	1964(1)	16(1)
O(3)	7541(2)	5843(1)	2495(1)	26(1)
O(4)	5423(2)	4676(1)	2361(1)	18(1)
O(5)	6939(2)	3052(1)	3279(1)	15(1)
O(6)	8074(2)	3309(1)	4653(1)	16(1)

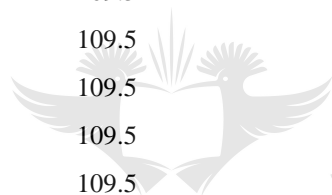
Table 1.2 Bond lengths [Å] and angles [°] for bridged chiral benzopyran (Figure 2.2).

C(1)-C(2)	1.505(2)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(1)-H(1D)	0.9800
C(1)-H(1E)	0.9800
C(1)-H(1F)	0.9800
C(2)-O(1)	1.203(2)
C(2)-O(2)	1.3547(19)
C(3)-C(4)	1.491(2)
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-O(3)	1.206(2)
C(4)-O(4)	1.3577(19)
C(5)-O(4)	1.4459(19)
C(5)-C(6)	1.517(2)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-O(5)	1.4363(17)
C(6)-C(7)	1.524(2)
C(6)-H(6)	1.0000
C(7)-O(2)	1.4558(16)
C(7)-C(8)	1.5413(19)
C(7)-H(7)	1.0000
C(8)-C(11)	1.514(2)
C(8)-C(9)	1.530(2)
C(8)-H(8)	1.0000
C(9)-C(10)	1.515(2)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-O(5)	1.4181(17)
C(10)-O(6)	1.4352(17)
C(10)-H(10)	1.0000



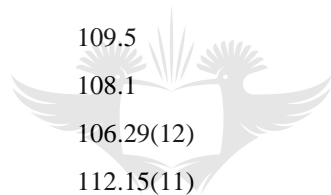
C(11)-C(12)	1.396(2)
C(11)-C(16)	1.398(2)
C(12)-O(6)	1.3819(18)
C(12)-C(13)	1.3938(19)
C(13)-C(14)	1.388(2)
C(13)-H(13)	0.9500
C(14)-C(15)	1.398(2)
C(14)-H(14)	0.9500
C(15)-C(16)	1.400(2)
C(15)-C(17)	1.508(2)
C(16)-H(16)	0.9500
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800

C(2)-C(1)-H(1A)	109.5
C(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
C(2)-C(1)-H(1D)	109.5
H(1A)-C(1)-H(1D)	141.1
H(1B)-C(1)-H(1D)	56.3
H(1C)-C(1)-H(1D)	56.3
C(2)-C(1)-H(1E)	109.5
H(1A)-C(1)-H(1E)	56.3
H(1B)-C(1)-H(1E)	141.1
H(1C)-C(1)-H(1E)	56.3
H(1D)-C(1)-H(1E)	109.5
C(2)-C(1)-H(1F)	109.5
H(1A)-C(1)-H(1F)	56.3
H(1B)-C(1)-H(1F)	56.3
H(1C)-C(1)-H(1F)	141.1
H(1D)-C(1)-H(1F)	109.5
H(1E)-C(1)-H(1F)	109.5



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O(1)-C(2)-O(2)	123.98(14)
O(1)-C(2)-C(1)	125.94(15)
O(2)-C(2)-C(1)	110.06(14)
C(4)-C(3)-H(3A)	109.5
C(4)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(4)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
O(3)-C(4)-O(4)	122.82(15)
O(3)-C(4)-C(3)	125.95(16)
O(4)-C(4)-C(3)	111.22(14)
O(4)-C(5)-C(6)	110.89(12)
O(4)-C(5)-H(5A)	109.5
C(6)-C(5)-H(5A)	109.5
O(4)-C(5)-H(5B)	109.5
C(6)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	108.1
O(5)-C(6)-C(5)	106.29(12)
O(5)-C(6)-C(7)	112.15(11)
C(5)-C(6)-C(7)	113.23(12)
O(5)-C(6)-H(6)	108.3
C(5)-C(6)-H(6)	108.3
C(7)-C(6)-H(6)	108.3
O(2)-C(7)-C(6)	105.94(11)
O(2)-C(7)-C(8)	110.33(11)
C(6)-C(7)-C(8)	110.39(11)
O(2)-C(7)-H(7)	110.0
C(6)-C(7)-H(7)	110.0
C(8)-C(7)-H(7)	110.0
C(11)-C(8)-C(9)	106.96(11)
C(11)-C(8)-C(7)	110.05(11)
C(9)-C(8)-C(7)	108.71(12)
C(11)-C(8)-H(8)	110.4
C(9)-C(8)-H(8)	110.4
C(7)-C(8)-H(8)	110.4



C(10)-C(9)-C(8)	107.34(11)
C(10)-C(9)-H(9A)	110.2
C(8)-C(9)-H(9A)	110.2
C(10)-C(9)-H(9B)	110.2
C(8)-C(9)-H(9B)	110.2
H(9A)-C(9)-H(9B)	108.5
O(5)-C(10)-O(6)	109.61(11)
O(5)-C(10)-C(9)	111.90(11)
O(6)-C(10)-C(9)	111.97(12)
O(5)-C(10)-H(10)	107.7
O(6)-C(10)-H(10)	107.7
C(9)-C(10)-H(10)	107.7
C(12)-C(11)-C(16)	118.23(13)
C(12)-C(11)-C(8)	119.09(13)
C(16)-C(11)-C(8)	122.64(13)
O(6)-C(12)-C(13)	115.54(13)
O(6)-C(12)-C(11)	123.49(13)
C(13)-C(12)-C(11)	120.96(14)
C(14)-C(13)-C(12)	119.69(14)
C(14)-C(13)-H(13)	120.2
C(12)-C(13)-H(13)	120.2
C(13)-C(14)-C(15)	120.99(14)
C(13)-C(14)-H(14)	119.5
C(15)-C(14)-H(14)	119.5
C(16)-C(15)-C(14)	118.24(15)
C(16)-C(15)-C(17)	120.95(15)
C(14)-C(15)-C(17)	120.80(14)
C(15)-C(16)-C(11)	121.87(14)
C(15)-C(16)-H(16)	119.1
C(11)-C(16)-H(16)	119.1
C(15)-C(17)-H(17A)	109.5
C(15)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(15)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5



C(2)-O(2)-C(7)	117.32(12)
C(4)-O(4)-C(5)	115.56(12)
C(10)-O(5)-C(6)	114.16(11)
C(12)-O(6)-C(10)	117.53(11)

Symmetry transformations used to generate equivalent atoms.

Table 1.3 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for bridged chiral benzopyran (Figure 2.2). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	28(1)	28(1)	22(1)	-10(1)	0(1)	3(1)
C(2)	21(1)	17(1)	15(1)	0(1)	2(1)	4(1)
C(3)	31(1)	23(1)	36(1)	3(1)	-1(1)	11(1)
C(4)	25(1)	15(1)	18(1)	6(1)	-2(1)	3(1)
C(5)	21(1)	18(1)	15(1)	0(1)	-2(1)	4(1)
C(6)	16(1)	13(1)	13(1)	1(1)	1(1)	0(1)
C(7)	15(1)	13(1)	12(1)	-2(1)	1(1)	0(1)
C(8)	13(1)	14(1)	14(1)	-1(1)	0(1)	1(1)
C(9)	18(1)	12(1)	16(1)	1(1)	-2(1)	0(1)
C(10)	17(1)	14(1)	15(1)	2(1)	1(1)	-3(1)
C(11)	15(1)	12(1)	13(1)	1(1)	-2(1)	2(1)
C(12)	14(1)	13(1)	14(1)	2(1)	-2(1)	1(1)
C(13)	18(1)	17(1)	14(1)	-1(1)	0(1)	4(1)
C(14)	21(1)	16(1)	16(1)	-3(1)	-5(1)	3(1)
C(15)	16(1)	17(1)	20(1)	0(1)	-6(1)	1(1)
C(16)	13(1)	18(1)	16(1)	1(1)	0(1)	1(1)
C(17)	21(1)	33(1)	30(1)	-9(1)	-5(1)	-7(1)
O(1)	23(1)	23(1)	25(1)	-1(1)	7(1)	-1(1)
O(2)	17(1)	17(1)	14(1)	-5(1)	1(1)	-1(1)
O(3)	26(1)	19(1)	33(1)	4(1)	2(1)	-4(1)
O(4)	17(1)	16(1)	19(1)	2(1)	-2(1)	2(1)
O(5)	14(1)	15(1)	16(1)	2(1)	0(1)	-2(1)
O(6)	16(1)	18(1)	15(1)	-2(1)	2(1)	-2(1)

Table 1.4 Hydrogen coordinates (x 10⁴) and isotropic displacement parameters (Å²x 10³) for bridged chiral benzopyran (Figure 2.2)

	x	y	z	U(eq)
H(1A)	9279	1569	899	39
H(1B)	11452	1264	787	39
H(1C)	10577	2061	194	39
H(1D)	11593	1694	355	39
H(1E)	9420	1999	466	39
H(1F)	10295	1201	1059	39
H(3A)	3598	6363	2287	45
H(3B)	4656	6661	3146	45
H(3C)	3362	5745	3127	45
H(5A)	7806	4411	1704	22
H(5B)	6430	3527	1792	22
H(6)	8267	4277	3257	17
H(7)	10864	3876	2401	16
H(8)	12248	2629	3242	16
H(9A)	9443	1671	3322	18
H(9B)	10244	1860	4264	18
H(10)	6937	2140	4214	18
H(13)	8987	4503	5739	20
H(14)	11803	5348	5878	21
H(16)	13972	4020	3823	19
H(17A)	15971	5053	4571	42
H(17B)	15492	5216	5554	42
H(17C)	14815	5959	4859	42

Table 1.5 Torsion angles [°] for bridged chiral benzopyran (Figure 2.2)

O(4)-C(5)-C(6)-O(5)	74.50(14)
O(4)-C(5)-C(6)-C(7)	-161.94(12)
O(5)-C(6)-C(7)-O(2)	67.96(14)

C(5)-C(6)-C(7)-O(2)	-52.32(15)
O(5)-C(6)-C(7)-C(8)	-51.48(15)
C(5)-C(6)-C(7)-C(8)	-171.76(12)
O(2)-C(7)-C(8)-C(11)	-177.88(11)
C(6)-C(7)-C(8)-C(11)	-61.13(15)
O(2)-C(7)-C(8)-C(9)	-61.04(15)
C(6)-C(7)-C(8)-C(9)	55.70(14)
C(11)-C(8)-C(9)-C(10)	59.60(14)
C(7)-C(8)-C(9)-C(10)	-59.19(14)
C(8)-C(9)-C(10)-O(5)	60.79(15)
C(8)-C(9)-C(10)-O(6)	-62.73(14)
C(9)-C(8)-C(11)-C(12)	-30.14(17)
C(7)-C(8)-C(11)-C(12)	87.77(16)
C(9)-C(8)-C(11)-C(16)	147.62(13)
C(7)-C(8)-C(11)-C(16)	-94.47(16)
C(16)-C(11)-C(12)-O(6)	-178.95(12)
C(8)-C(11)-C(12)-O(6)	-1.1(2)
C(16)-C(11)-C(12)-C(13)	0.7(2)
C(8)-C(11)-C(12)-C(13)	178.60(13)
O(6)-C(12)-C(13)-C(14)	179.96(12)
C(11)-C(12)-C(13)-C(14)	0.2(2)
C(12)-C(13)-C(14)-C(15)	-0.8(2)
C(13)-C(14)-C(15)-C(16)	0.3(2)
C(13)-C(14)-C(15)-C(17)	-178.30(14)
C(14)-C(15)-C(16)-C(11)	0.7(2)
C(17)-C(15)-C(16)-C(11)	179.33(15)
C(12)-C(11)-C(16)-C(15)	-1.2(2)
C(8)-C(11)-C(16)-C(15)	-179.02(13)
O(1)-C(2)-O(2)-C(7)	-1.0(2)
C(1)-C(2)-O(2)-C(7)	-179.45(12)
C(6)-C(7)-O(2)-C(2)	152.95(12)
C(8)-C(7)-O(2)-C(2)	-87.57(15)
O(3)-C(4)-O(4)-C(5)	0.1(2)
C(3)-C(4)-O(4)-C(5)	179.29(13)
C(6)-C(5)-O(4)-C(4)	78.77(15)
O(6)-C(10)-O(5)-C(6)	66.39(14)



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C(9)-C(10)-O(5)-C(6)	-58.44(15)
C(5)-C(6)-O(5)-C(10)	177.30(11)
C(7)-C(6)-O(5)-C(10)	53.06(15)
C(13)-C(12)-O(6)-C(10)	-178.54(12)
C(11)-C(12)-O(6)-C(10)	1.16(19)
O(5)-C(10)-O(6)-C(12)	-93.41(14)
C(9)-C(10)-O(6)-C(12)	31.38(16)

Symmetry transformations used to generate equivalent atoms:

Table 1.6 Hydrogen bonds for bridged chiral benzopyran (Figure 2.2) [\AA and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	\angle (DHA)	Symmetry Operator
No Classic Hydrogen Bonds Found					

Table 2.1 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for bridged chiral benzopyran (Figure 2.3). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	5107(1)	2303(1)	251(1)	34(1)
O(2)	6722(1)	684(1)	448(1)	24(1)
O(3)	771(1)	9196(1)	487(1)	25(1)
O(4)	-1228(1)	8062(1)	262(1)	34(1)
O(5)	7839(1)	1388(1)	1309(1)	22(1)
O(6)	6434(1)	2257(1)	1900(1)	22(1)
O(7)	9973(1)	3241(1)	926(1)	22(1)
O(8)	10713(1)	5451(1)	888(1)	31(1)
O(9)	4735(1)	9925(1)	1337(1)	22(1)
O(10)	2221(1)	10244(1)	1271(1)	22(1)
O(11)	412(1)	8422(1)	1846(1)	21(1)
O(12)	290(1)	6359(1)	2191(1)	24(1)
C(1)	5407(2)	1107(2)	310(1)	25(1)

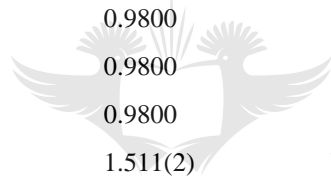
C(2)	7779(2)	1753(2)	531(1)	23(1)
C(3)	7546(2)	2419(1)	977(1)	21(1)
C(4)	8504(1)	3689(2)	1033(1)	19(1)
C(5)	8434(2)	4200(1)	1510(1)	19(1)
C(6)	6897(2)	4595(1)	1641(1)	19(1)
C(7)	6331(2)	5949(1)	1572(1)	18(1)
C(8)	4960(2)	6329(2)	1756(1)	19(1)
C(9)	4430(2)	7703(2)	1701(1)	19(1)
C(10)	3047(2)	8222(1)	1919(1)	19(1)
C(11)	1727(2)	7982(1)	1618(1)	19(1)
C(12)	1840(2)	8824(1)	1194(1)	19(1)
C(13)	433(2)	8818(2)	938(1)	23(1)
C(14)	-144(2)	8698(2)	176(1)	26(1)
C(15)	4406(2)	-78(2)	234(1)	34(1)
C(16)	7858(2)	1851(2)	1751(1)	23(1)
C(17)	6043(2)	3624(2)	1848(1)	20(1)
C(18)	10985(2)	4233(2)	868(1)	24(1)
C(19)	12444(2)	3626(2)	779(1)	33(1)
C(20)	8922(2)	3027(2)	1815(1)	23(1)
C(21)	4156(2)	5296(2)	1987(1)	21(1)
C(22)	4675(2)	3978(2)	2023(1)	21(1)
C(23)	5197(2)	8612(1)	1437(1)	19(1)
C(24)	3447(2)	10436(1)	1545(1)	22(1)
C(25)	3219(2)	9784(2)	1993(1)	24(1)
C(26)	-193(2)	7497(1)	2124(1)	20(1)
C(27)	-1533(2)	8092(2)	2337(1)	24(1)
C(28)	409(2)	9039(2)	-277(1)	35(1)
C(29)	6527(2)	8222(1)	1239(1)	21(1)
C(30)	7080(2)	6937(1)	1313(1)	20(1)

Table 2.2 Bond lengths [Å] and angles [°] for bridged chiral benzopyran (Figure 2.3).

O(1)-C(1)	1.202(2)
O(1)-H(1)	0.8400
O(2)-C(1)	1.3422(19)
O(2)-C(2)	1.4397(18)
O(3)-C(14)	1.3494(19)
O(3)-C(13)	1.4450(17)
O(4)-C(14)	1.199(2)
O(5)-C(16)	1.4077(17)
O(5)-C(3)	1.4390(17)
O(6)-C(17)	1.3784(17)
O(6)-C(16)	1.4382(17)
O(7)-C(18)	1.3473(18)
O(7)-C(4)	1.4535(16)
O(8)-C(18)	1.2049(19)
O(9)-C(23)	1.3717(17)
O(9)-C(24)	1.4277(17)
O(10)-C(24)	1.4104(17)
O(10)-C(12)	1.4355(17)
O(11)-C(26)	1.3461(17)
O(11)-C(11)	1.4543(16)
O(12)-C(26)	1.2035(18)
C(1)-C(15)	1.487(2)
C(2)-C(3)	1.5091(19)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.520(2)
C(3)-H(3)	1.0000
C(4)-C(5)	1.5282(19)
C(4)-H(4)	1.0000
C(5)-C(6)	1.5151(19)
C(5)-C(20)	1.527(2)
C(5)-H(5)	1.0000
C(6)-C(17)	1.374(2)
C(6)-C(7)	1.423(2)

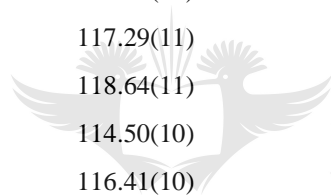


C(7)-C(30)	1.414(2)
C(7)-C(8)	1.4257(19)
C(8)-C(21)	1.424(2)
C(8)-C(9)	1.424(2)
C(9)-C(23)	1.380(2)
C(9)-C(10)	1.5160(19)
C(10)-C(11)	1.5329(18)
C(10)-C(25)	1.535(2)
C(10)-H(10)	1.0000
C(11)-C(12)	1.5203(19)
C(11)-H(11)	1.0000
C(12)-C(13)	1.5078(19)
C(12)-H(12)	1.0000
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-C(28)	1.496(2)
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-C(20)	1.511(2)
C(16)-H(16)	1.0000
C(17)-C(22)	1.405(2)
C(18)-C(19)	1.487(2)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-H(20A)	0.9900
C(20)-H(20B)	0.9900
C(21)-C(22)	1.364(2)
C(21)-H(21)	0.9500
C(22)-H(22)	0.9500
C(23)-C(29)	1.411(2)
C(24)-C(25)	1.509(2)
C(24)-H(24)	1.0000
C(25)-H(25A)	0.9900
C(25)-H(25B)	0.9900



C(26)-C(27)	1.5030(19)
C(27)-H(27A)	0.9800
C(27)-H(27B)	0.9800
C(27)-H(27C)	0.9800
C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800
C(28)-H(28C)	0.9800
C(29)-C(30)	1.361(2)
C(29)-H(29)	0.9500
C(30)-H(30)	0.9500

C(1)-O(1)-H(1)	109.5
C(1)-O(2)-C(2)	116.27(11)
C(14)-O(3)-C(13)	115.68(11)
C(16)-O(5)-C(3)	116.33(10)
C(17)-O(6)-C(16)	117.55(11)
C(18)-O(7)-C(4)	117.29(11)
C(23)-O(9)-C(24)	118.64(11)
C(24)-O(10)-C(12)	114.50(10)
C(26)-O(11)-C(11)	116.41(10)
O(1)-C(1)-O(2)	123.08(14)
O(1)-C(1)-C(15)	125.17(15)
O(2)-C(1)-C(15)	111.73(13)
O(2)-C(2)-C(3)	111.50(11)
O(2)-C(2)-H(2A)	109.3
C(3)-C(2)-H(2A)	109.3
O(2)-C(2)-H(2B)	109.3
C(3)-C(2)-H(2B)	109.3
H(2A)-C(2)-H(2B)	108.0
O(5)-C(3)-C(2)	107.55(11)
O(5)-C(3)-C(4)	111.95(11)
C(2)-C(3)-C(4)	111.14(11)
O(5)-C(3)-H(3)	108.7
C(2)-C(3)-H(3)	108.7
C(4)-C(3)-H(3)	108.7
O(7)-C(4)-C(3)	105.83(11)

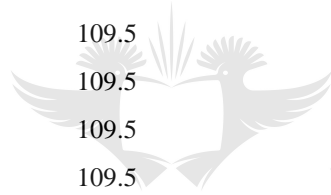


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O(7)-C(4)-C(5)	110.14(11)
C(3)-C(4)-C(5)	109.91(11)
O(7)-C(4)-H(4)	110.3
C(3)-C(4)-H(4)	110.3
C(5)-C(4)-H(4)	110.3
C(6)-C(5)-C(20)	107.68(11)
C(6)-C(5)-C(4)	111.55(11)
C(20)-C(5)-C(4)	108.54(11)
C(6)-C(5)-H(5)	109.7
C(20)-C(5)-H(5)	109.7
C(4)-C(5)-H(5)	109.7
C(17)-C(6)-C(7)	119.06(12)
C(17)-C(6)-C(5)	118.60(12)
C(7)-C(6)-C(5)	122.29(12)
C(30)-C(7)-C(6)	121.60(12)
C(30)-C(7)-C(8)	118.19(12)
C(6)-C(7)-C(8)	120.19(12)
C(21)-C(8)-C(9)	122.31(13)
C(21)-C(8)-C(7)	117.90(13)
C(9)-C(8)-C(7)	119.79(12)
C(23)-C(9)-C(8)	119.11(13)
C(23)-C(9)-C(10)	117.96(12)
C(8)-C(9)-C(10)	122.93(12)
C(9)-C(10)-C(11)	110.81(11)
C(9)-C(10)-C(25)	107.63(12)
C(11)-C(10)-C(25)	108.51(11)
C(9)-C(10)-H(10)	109.9
C(11)-C(10)-H(10)	109.9
C(25)-C(10)-H(10)	109.9
O(11)-C(11)-C(12)	107.48(11)
O(11)-C(11)-C(10)	109.38(10)
C(12)-C(11)-C(10)	111.36(11)
O(11)-C(11)-H(11)	109.5
C(12)-C(11)-H(11)	109.5
C(10)-C(11)-H(11)	109.5
O(10)-C(12)-C(13)	107.16(11)



O(10)-C(12)-C(11)	113.05(11)
C(13)-C(12)-C(11)	111.89(11)
O(10)-C(12)-H(12)	108.2
C(13)-C(12)-H(12)	108.2
C(11)-C(12)-H(12)	108.2
O(3)-C(13)-C(12)	107.48(11)
O(3)-C(13)-H(13A)	110.2
C(12)-C(13)-H(13A)	110.2
O(3)-C(13)-H(13B)	110.2
C(12)-C(13)-H(13B)	110.2
H(13A)-C(13)-H(13B)	108.5
O(4)-C(14)-O(3)	123.33(14)
O(4)-C(14)-C(28)	126.36(14)
O(3)-C(14)-C(28)	110.30(13)
C(1)-C(15)-H(15A)	109.5
C(1)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(1)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
O(5)-C(16)-O(6)	111.89(11)
O(5)-C(16)-C(20)	111.64(12)
O(6)-C(16)-C(20)	110.07(11)
O(5)-C(16)-H(16)	107.7
O(6)-C(16)-H(16)	107.7
C(20)-C(16)-H(16)	107.7
C(6)-C(17)-O(6)	123.89(12)
C(6)-C(17)-C(22)	121.05(13)
O(6)-C(17)-C(22)	115.07(12)
O(8)-C(18)-O(7)	123.00(14)
O(8)-C(18)-C(19)	125.61(14)
O(7)-C(18)-C(19)	111.39(13)
C(18)-C(19)-H(19A)	109.5
C(18)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5



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H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(16)-C(20)-C(5)	106.88(11)
C(16)-C(20)-H(20A)	110.3
C(5)-C(20)-H(20A)	110.3
C(16)-C(20)-H(20B)	110.3
C(5)-C(20)-H(20B)	110.3
H(20A)-C(20)-H(20B)	108.6
C(22)-C(21)-C(8)	120.88(13)
C(22)-C(21)-H(21)	119.6
C(8)-C(21)-H(21)	119.6
C(21)-C(22)-C(17)	120.61(13)
C(21)-C(22)-H(22)	119.7
C(17)-C(22)-H(22)	119.7
O(9)-C(23)-C(9)	123.88(12)
O(9)-C(23)-C(29)	114.92(12)
C(9)-C(23)-C(29)	121.18(13)
O(10)-C(24)-O(9)	110.98(11)
O(10)-C(24)-C(25)	111.19(12)
O(9)-C(24)-C(25)	111.51(11)
O(10)-C(24)-H(24)	107.7
O(9)-C(24)-H(24)	107.7
C(25)-C(24)-H(24)	107.7
C(24)-C(25)-C(10)	106.99(11)
C(24)-C(25)-H(25A)	110.3
C(10)-C(25)-H(25A)	110.3
C(24)-C(25)-H(25B)	110.3
C(10)-C(25)-H(25B)	110.3
H(25A)-C(25)-H(25B)	108.6
O(12)-C(26)-O(11)	124.04(13)
O(12)-C(26)-C(27)	125.40(13)
O(11)-C(26)-C(27)	110.56(12)
C(26)-C(27)-H(27A)	109.5
C(26)-C(27)-H(27B)	109.5
H(27A)-C(27)-H(27B)	109.5
C(26)-C(27)-H(27C)	109.5



H(27A)-C(27)-H(27C)	109.5
H(27B)-C(27)-H(27C)	109.5
C(14)-C(28)-H(28A)	109.5
C(14)-C(28)-H(28B)	109.5
H(28A)-C(28)-H(28B)	109.5
C(14)-C(28)-H(28C)	109.5
H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5
C(30)-C(29)-C(23)	119.85(13)
C(30)-C(29)-H(29)	120.1
C(23)-C(29)-H(29)	120.1
C(29)-C(30)-C(7)	121.68(13)
C(29)-C(30)-H(30)	119.2
C(7)-C(30)-H(30)	119.2

Symmetry transformations used to generate equivalent atoms:

Table 2.3 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for bridged chiral benzopyran (Figure 2.3). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	29(1)	33(1)	41(1)	1(1)	-7(1)	1(1)
O(2)	28(1)	21(1)	24(1)	-2(1)	-1(1)	-1(1)
O(3)	24(1)	30(1)	21(1)	2(1)	-2(1)	-2(1)
O(4)	25(1)	42(1)	36(1)	-8(1)	-4(1)	-4(1)
O(5)	26(1)	18(1)	22(1)	1(1)	1(1)	2(1)
O(6)	23(1)	19(1)	24(1)	3(1)	5(1)	1(1)
O(7)	18(1)	22(1)	25(1)	-1(1)	3(1)	1(1)
O(8)	29(1)	25(1)	39(1)	2(1)	7(1)	-4(1)
O(9)	20(1)	19(1)	27(1)	1(1)	1(1)	0(1)
O(10)	21(1)	19(1)	28(1)	1(1)	-3(1)	-1(1)
O(11)	18(1)	22(1)	23(1)	1(1)	5(1)	1(1)
O(12)	26(1)	22(1)	25(1)	0(1)	2(1)	1(1)
C(1)	25(1)	31(1)	18(1)	-2(1)	1(1)	-2(1)
C(2)	19(1)	24(1)	25(1)	-2(1)	2(1)	0(1)

C(3)	19(1)	22(1)	22(1)	2(1)	0(1)	2(1)
C(4)	16(1)	19(1)	23(1)	1(1)	1(1)	3(1)
C(5)	16(1)	20(1)	22(1)	1(1)	0(1)	-1(1)
C(6)	17(1)	22(1)	17(1)	-2(1)	0(1)	0(1)
C(7)	18(1)	20(1)	16(1)	-3(1)	-1(1)	-1(1)
C(8)	18(1)	23(1)	15(1)	-2(1)	0(1)	-1(1)
C(9)	17(1)	22(1)	17(1)	-1(1)	-1(1)	-1(1)
C(10)	19(1)	22(1)	18(1)	-2(1)	1(1)	2(1)
C(11)	16(1)	21(1)	21(1)	-2(1)	3(1)	1(1)
C(12)	17(1)	19(1)	21(1)	-2(1)	2(1)	0(1)
C(13)	20(1)	26(1)	22(1)	1(1)	0(1)	-1(1)
C(14)	26(1)	24(1)	26(1)	-6(1)	-5(1)	8(1)
C(15)	38(1)	39(1)	25(1)	-4(1)	-2(1)	-16(1)
C(16)	24(1)	22(1)	22(1)	3(1)	1(1)	3(1)
C(17)	23(1)	19(1)	17(1)	-2(1)	0(1)	0(1)
C(18)	23(1)	27(1)	21(1)	0(1)	2(1)	-3(1)
C(19)	22(1)	37(1)	41(1)	0(1)	4(1)	-1(1)
C(20)	20(1)	27(1)	21(1)	1(1)	-2(1)	2(1)
C(21)	18(1)	26(1)	19(1)	-2(1)	3(1)	-1(1)
C(22)	21(1)	24(1)	19(1)	1(1)	4(1)	-4(1)
C(23)	17(1)	19(1)	19(1)	-1(1)	-4(1)	-1(1)
C(24)	19(1)	19(1)	28(1)	-3(1)	-2(1)	1(1)
C(25)	23(1)	24(1)	23(1)	-6(1)	-2(1)	2(1)
C(26)	19(1)	24(1)	18(1)	-2(1)	-1(1)	-2(1)
C(27)	21(1)	29(1)	23(1)	1(1)	4(1)	2(1)
C(28)	41(1)	38(1)	24(1)	-2(1)	-5(1)	6(1)
C(29)	18(1)	22(1)	22(1)	1(1)	1(1)	-4(1)
C(30)	16(1)	23(1)	21(1)	-2(1)	1(1)	-2(1)

Table 3.1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for chromene (Figure 2.4). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(3)	6407(2)	5781(1)	7617(1)	42(1)
O(8)	-132(2)	3748(1)	10233(1)	38(1)
O(1)	3425(2)	7919(1)	9677(1)	26(1)
O(4)	2406(2)	4715(1)	9472(1)	22(1)
O(5)	55(3)	5279(1)	8911(1)	58(1)
O(6)	2853(2)	4470(1)	10924(1)	28(1)
O(7)	2190(3)	5069(2)	11955(1)	53(1)
O(2)	5785(2)	5804(1)	11281(1)	31(1)
C(1)	6839(3)	4795(2)	7707(1)	44(1)
C(2)	5617(3)	6242(2)	8146(1)	31(1)
C(12)	5356(2)	5834(1)	8785(1)	25(1)
C(11)	4567(2)	6374(1)	9301(1)	21(1)
C(10)	4147(2)	5951(1)	9987(1)	19(1)
C(13)	2285(2)	5492(1)	9960(1)	20(1)
C(16)	1589(2)	5126(1)	10635(1)	24(1)
C(17)	-209(3)	4635(2)	10617(1)	36(1)
C(20)	111(3)	2916(2)	10578(1)	44(1)
O(9)	142(4)	2861(1)	11181(1)	72(1)
C(5)	4110(2)	7320(1)	9169(1)	23(1)
C(6)	3763(2)	7649(1)	10328(1)	22(1)
C(7)	4216(2)	6749(1)	10508(1)	20(1)
C(14)	1231(3)	4706(1)	8962(1)	30(1)
C(15)	1583(4)	3902(2)	8476(1)	39(1)
C(18)	3005(3)	4508(2)	11610(1)	40(1)
C(8)	4978(2)	6552(1)	11182(1)	24(1)
C(9)	4798(3)	7290(2)	11738(1)	35(1)
C(4)	4349(3)	7737(2)	8535(1)	30(1)
C(3)	5081(3)	7190(2)	8024(1)	34(1)
C(21)	317(5)	2084(2)	10102(2)	60(1)
C(19)	4279(5)	3776(2)	11858(2)	65(1)

Table 3.2 Bond lengths [Å] and angles [°] for chromene (Figure 2.4).

O(3)-C(2)	1.364(3)
O(3)-C(1)	1.416(3)
O(8)-C(20)	1.350(3)
O(8)-C(17)	1.445(3)
O(1)-C(6)	1.364(2)
O(1)-C(5)	1.402(2)
O(4)-C(14)	1.345(2)
O(4)-C(13)	1.448(2)
O(5)-C(14)	1.199(3)
O(6)-C(18)	1.360(3)
O(6)-C(16)	1.440(2)
O(7)-C(18)	1.204(3)
O(2)-C(8)	1.220(2)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(3)	1.395(3)
C(2)-C(12)	1.396(3)
C(12)-C(11)	1.398(2)
C(12)-H(12)	0.9500
C(11)-C(5)	1.380(2)
C(11)-C(10)	1.510(2)
C(10)-C(7)	1.510(2)
C(10)-C(13)	1.551(2)
C(10)-H(10)	1.0000
C(13)-C(16)	1.521(3)
C(13)-H(13)	1.0000
C(16)-C(17)	1.526(3)
C(16)-H(16)	1.0000
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(20)-O(9)	1.193(3)
C(20)-C(21)	1.497(3)
C(5)-C(4)	1.391(3)



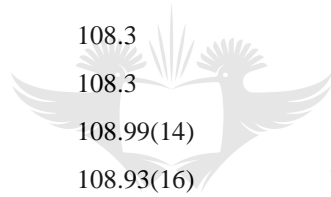
C(6)-C(7)	1.341(2)
C(6)-H(6)	0.9500
C(7)-C(8)	1.476(2)
C(14)-C(15)	1.494(3)
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(18)-C(19)	1.484(4)
C(8)-C(9)	1.506(3)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(4)-C(3)	1.377(3)
C(4)-H(4)	0.9500
C(3)-H(3)	0.9500
C(21)-H(21A)	0.9800
C(21)-H(21B)	0.9800
C(21)-H(21C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800



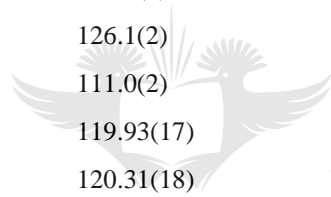
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C(2)-O(3)-C(1)	117.23(18)
C(20)-O(8)-C(17)	117.81(18)
C(6)-O(1)-C(5)	116.22(14)
C(14)-O(4)-C(13)	117.55(14)
C(18)-O(6)-C(16)	115.26(17)
O(3)-C(1)-H(1A)	109.5
O(3)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(3)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(3)-C(2)-C(3)	115.93(18)
O(3)-C(2)-C(12)	124.4(2)
C(3)-C(2)-C(12)	119.66(18)

C(2)-C(12)-C(11)	120.19(18)
C(2)-C(12)-H(12)	119.9
C(11)-C(12)-H(12)	119.9
C(5)-C(11)-C(12)	118.54(17)
C(5)-C(11)-C(10)	118.93(16)
C(12)-C(11)-C(10)	122.50(16)
C(11)-C(10)-C(7)	108.65(14)
C(11)-C(10)-C(13)	108.67(14)
C(7)-C(10)-C(13)	110.76(14)
C(11)-C(10)-H(10)	109.6
C(7)-C(10)-H(10)	109.6
C(13)-C(10)-H(10)	109.6
O(4)-C(13)-C(16)	110.95(13)
O(4)-C(13)-C(10)	105.64(13)
C(16)-C(13)-C(10)	115.04(14)
O(4)-C(13)-H(13)	108.3
C(16)-C(13)-H(13)	108.3
C(10)-C(13)-H(13)	108.3
O(6)-C(16)-C(13)	108.99(14)
O(6)-C(16)-C(17)	108.93(16)
C(13)-C(16)-C(17)	116.03(17)
O(6)-C(16)-H(16)	107.5
C(13)-C(16)-H(16)	107.5
C(17)-C(16)-H(16)	107.5
O(8)-C(17)-C(16)	110.86(16)
O(8)-C(17)-H(17A)	109.5
C(16)-C(17)-H(17A)	109.5
O(8)-C(17)-H(17B)	109.5
C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	108.1
O(9)-C(20)-O(8)	124.1(2)
O(9)-C(20)-C(21)	125.2(3)
O(8)-C(20)-C(21)	110.8(2)
C(11)-C(5)-C(4)	122.08(18)
C(11)-C(5)-O(1)	121.41(16)
C(4)-C(5)-O(1)	116.49(16)



C(7)-C(6)-O(1)	123.59(17)
C(7)-C(6)-H(6)	118.2
O(1)-C(6)-H(6)	118.2
C(6)-C(7)-C(8)	120.72(16)
C(6)-C(7)-C(10)	119.41(16)
C(8)-C(7)-C(10)	119.46(15)
O(5)-C(14)-O(4)	123.49(18)
O(5)-C(14)-C(15)	124.87(19)
O(4)-C(14)-C(15)	111.64(17)
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
O(7)-C(18)-O(6)	122.9(2)
O(7)-C(18)-C(19)	126.1(2)
O(6)-C(18)-C(19)	111.0(2)
O(2)-C(8)-C(7)	119.93(17)
O(2)-C(8)-C(9)	120.31(18)
C(7)-C(8)-C(9)	119.74(17)
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(3)-C(4)-C(5)	118.84(19)
C(3)-C(4)-H(4)	120.6
C(5)-C(4)-H(4)	120.6
C(4)-C(3)-C(2)	120.63(18)
C(4)-C(3)-H(3)	119.7
C(2)-C(3)-H(3)	119.7
C(20)-C(21)-H(21A)	109.5
C(20)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5



C(20)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
C(18)-C(19)-H(19A)	109.5
C(18)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 3.3 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for chromene (Figure 2.4). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(3)	44(1)	58(1)	23(1)	-9(1)	10(1)	-2(1)
O(8)	41(1)	35(1)	37(1)	-6(1)	4(1)	-17(1)
O(1)	30(1)	22(1)	26(1)	1(1)	-3(1)	5(1)
O(4)	26(1)	19(1)	20(1)	-3(1)	-4(1)	1(1)
O(5)	63(1)	49(1)	60(1)	-22(1)	-40(1)	24(1)
O(6)	40(1)	23(1)	20(1)	2(1)	-1(1)	-2(1)
O(7)	69(1)	68(1)	22(1)	-9(1)	10(1)	-18(1)
O(2)	37(1)	30(1)	26(1)	5(1)	-11(1)	-2(1)
C(1)	40(1)	63(2)	31(1)	-21(1)	5(1)	3(1)
C(2)	27(1)	47(1)	19(1)	-5(1)	2(1)	-6(1)
C(12)	25(1)	29(1)	21(1)	-4(1)	0(1)	0(1)
C(11)	19(1)	25(1)	18(1)	0(1)	-3(1)	-2(1)
C(10)	21(1)	18(1)	17(1)	-1(1)	-3(1)	2(1)
C(13)	22(1)	16(1)	20(1)	-3(1)	-2(1)	0(1)
C(16)	28(1)	21(1)	24(1)	-3(1)	5(1)	-2(1)
C(17)	31(1)	32(1)	45(1)	-6(1)	10(1)	-7(1)
C(20)	54(1)	32(1)	47(1)	-3(1)	11(1)	-21(1)
O(9)	127(2)	44(1)	45(1)	5(1)	12(1)	-27(1)
C(5)	20(1)	26(1)	22(1)	0(1)	-2(1)	-2(1)

C(6)	20(1)	23(1)	23(1)	-3(1)	-1(1)	0(1)
C(7)	18(1)	24(1)	18(1)	-3(1)	0(1)	-3(1)
C(14)	38(1)	26(1)	24(1)	-2(1)	-10(1)	-1(1)
C(15)	58(1)	34(1)	26(1)	-10(1)	-10(1)	0(1)
C(18)	58(1)	38(1)	22(1)	6(1)	-2(1)	-20(1)
C(8)	23(1)	29(1)	19(1)	0(1)	-1(1)	-7(1)
C(9)	41(1)	42(1)	21(1)	-8(1)	-2(1)	-1(1)
C(4)	29(1)	33(1)	27(1)	7(1)	-4(1)	-4(1)
C(3)	34(1)	46(1)	21(1)	7(1)	-1(1)	-7(1)
C(21)	76(2)	37(1)	69(2)	-14(1)	18(2)	-23(1)
C(19)	107(3)	46(2)	43(2)	19(1)	-28(2)	-10(2)

Table 3.4. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for chomene (Figure 2.4).

	x	y	z	U(eq)
H(1A)	7621	4727	8099	66
H(1B)	7436	4554	7300	66
H(1C)	5761	4423	7784	66
H(12)	5715	5188	8869	30
H(10)	5035	5444	10103	23
H(13)	1444	5986	9782	23
H(16)	1494	5694	10946	29
H(17A)	-598	4494	11085	43
H(17B)	-1080	5076	10408	43
H(6)	3672	8124	10674	27
H(15A)	498	3534	8402	59
H(15B)	2489	3475	8663	59
H(15C)	1991	4170	8044	59
H(9A)	5379	7052	12148	52
H(9B)	3548	7402	11832	52
H(9C)	5351	7896	11595	52
H(4)	4014	8388	8455	36

H(3)	5221	7461	7586	40
H(21A)	1106	1602	10303	91
H(21B)	816	2313	9673	91
H(21C)	-836	1790	10017	91
H(19A)	4558	3904	12334	98
H(19B)	5359	3809	11587	98
H(19C)	3760	3130	11817	98

Table 3.5 Torsion angles [°] for chromene (Figure 2.4).

C(1)-O(3)-C(2)-C(3)	-175.13(19)
C(1)-O(3)-C(2)-C(12)	6.0(3)
O(3)-C(2)-C(12)-C(11)	178.54(18)
C(3)-C(2)-C(12)-C(11)	-0.3(3)
C(2)-C(12)-C(11)-C(5)	-2.0(3)
C(2)-C(12)-C(11)-C(10)	176.05(16)
C(5)-C(11)-C(10)-C(7)	-30.8(2)
C(12)-C(11)-C(10)-C(7)	151.21(17)
C(5)-C(11)-C(10)-C(13)	89.83(18)
C(12)-C(11)-C(10)-C(13)	-88.19(19)
C(14)-O(4)-C(13)-C(16)	107.99(18)
C(14)-O(4)-C(13)-C(10)	-126.71(16)
C(11)-C(10)-C(13)-O(4)	63.39(16)
C(7)-C(10)-C(13)-O(4)	-177.33(14)
C(11)-C(10)-C(13)-C(16)	-173.88(14)
C(7)-C(10)-C(13)-C(16)	-54.60(19)
C(18)-O(6)-C(16)-C(13)	143.94(16)
C(18)-O(6)-C(16)-C(17)	-88.6(2)
O(4)-C(13)-C(16)-O(6)	65.62(17)
C(10)-C(13)-C(16)-O(6)	-54.21(19)
O(4)-C(13)-C(16)-C(17)	-57.7(2)
C(10)-C(13)-C(16)-C(17)	-177.57(15)
C(20)-O(8)-C(17)-C(16)	95.5(2)
O(6)-C(16)-C(17)-O(8)	-57.7(2)
C(13)-C(16)-C(17)-O(8)	65.7(2)

C(17)-O(8)-C(20)-O(9)	5.5(4)
C(17)-O(8)-C(20)-C(21)	-175.0(2)
C(12)-C(11)-C(5)-C(4)	2.4(3)
C(10)-C(11)-C(5)-C(4)	-175.67(16)
C(12)-C(11)-C(5)-O(1)	-175.63(16)
C(10)-C(11)-C(5)-O(1)	6.3(2)
C(6)-O(1)-C(5)-C(11)	20.8(2)
C(6)-O(1)-C(5)-C(4)	-157.40(16)
C(5)-O(1)-C(6)-C(7)	-20.3(2)
O(1)-C(6)-C(7)-C(8)	164.98(16)
O(1)-C(6)-C(7)-C(10)	-7.7(3)
C(11)-C(10)-C(7)-C(6)	31.9(2)
C(13)-C(10)-C(7)-C(6)	-87.39(19)
C(11)-C(10)-C(7)-C(8)	-140.90(15)
C(13)-C(10)-C(7)-C(8)	99.80(18)
C(13)-O(4)-C(14)-O(5)	-3.3(3)
C(13)-O(4)-C(14)-C(15)	176.41(17)
C(16)-O(6)-C(18)-O(7)	-2.3(3)
C(16)-O(6)-C(18)-C(19)	177.5(2)
C(6)-C(7)-C(8)-O(2)	-161.43(17)
C(10)-C(7)-C(8)-O(2)	11.3(3)
C(6)-C(7)-C(8)-C(9)	16.8(3)
C(10)-C(7)-C(8)-C(9)	-170.49(16)
C(11)-C(5)-C(4)-C(3)	-0.6(3)
O(1)-C(5)-C(4)-C(3)	177.57(17)
C(5)-C(4)-C(3)-C(2)	-1.8(3)
O(3)-C(2)-C(3)-C(4)	-176.73(19)
C(12)-C(2)-C(3)-C(4)	2.2(3)

Symmetry transformations used to generate equivalent atoms:

Table 3.6. Hydrogen bonds for chromene (Figure 2.4) [\AA and $^\circ$].

D-H...A	d(D-H)	d(H...A)	d(D...A)	\angle (DHA)
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Table 4.1 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for chroman (Figure 2.5). U_{eq} is defined as 1/3 of the trace of the orthogonalised U^{ij} tensor.

Atom	x	y	z	$U(eq)$
C1	5241.9(18)	3666.4(11)	8190.7(9)	22.5(3)
C2	4764.2(19)	3039.5(11)	7602.0(8)	22.1(3)
C3	4724.8(19)	2008.8(11)	7812.5(8)	20.0(3)
C4	3640.8(19)	1930.2(11)	8435.0(7)	19.5(3)
C5	3585.1(19)	2660.7(11)	8894.0(8)	20.7(3)
C6	2657(2)	2634.9(12)	9503.3(8)	23.9(3)
C7	1756(2)	1869.8(12)	9641.4(8)	26.0(4)
C8	1720(2)	1105.3(12)	9177.5(8)	24.1(3)
C9	2667.0(19)	1135.2(11)	8565.9(8)	20.6(3)
C10	2576.9(19)	360.3(11)	8106.7(8)	22.9(3)
C11	1632(2)	-388.7(12)	8252.9(9)	27.2(4)
C12	708(2)	-414.1(13)	8861.2(10)	32.6(4)
C13	751(2)	320.4(13)	9307.7(9)	31.2(4)
C14	7702(2)	4204.7(12)	8670.6(9)	26.8(4)
C15	9405(2)	3946.8(14)	8787.8(11)	36.0(4)
C16	6387.5(19)	1596.3(11)	7964.7(8)	20.8(3)
C17	6317(2)	415.5(12)	8838.5(8)	25.1(3)
C18	5989(2)	-591.0(12)	8960.5(9)	33.6(4)
C19	7494.2(19)	1644.2(11)	7346.5(8)	22.1(3)
C20	9094(2)	1189.2(13)	7480.5(9)	29.0(4)
C21	10809(2)	2037.9(12)	6728.0(11)	32.0(4)
C22	11565(3)	2016.0(14)	6029.7(12)	46.4(6)
C23	6844(2)	1586.8(13)	6144.8(9)	30.8(4)
C24	6210(3)	959.9(15)	5595.5(9)	40.8(5)
O1	4405.0(14)	3489.1(8)	8813.1(6)	25.2(3)
O2	6919.1(13)	3525.6(8)	8314.0(6)	24.7(3)
O3	7062.2(15)	4903.7(9)	8857.0(8)	36.7(3)
O4	6196.9(13)	624.3(7)	8153.5(5)	21.2(2)
O5	6642.6(18)	971.3(9)	9277.1(6)	36.5(3)
O6	6759.9(14)	1168.0(8)	6769.9(6)	24.8(3)
O7	7373(2)	2355.1(10)	6055.5(7)	46.0(4)
O8	10046.1(14)	1229.9(8)	6859.4(7)	30.7(3)
O9	10831.5(16)	2682.3(9)	7125.2(8)	39.9(3)

Table 4.2 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for chroman (Figure 2.5). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11} + \dots + 2hka \times b \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	18.8(8)	23.7(8)	25.1(8)	2.2(7)	1.4(6)	1.0(6)
C2	18.5(8)	27.0(8)	20.7(8)	2.8(7)	-0.2(6)	1.7(6)
C3	18.5(8)	23.7(8)	17.8(7)	-1.7(6)	-0.7(6)	-0.3(6)
C4	18.5(7)	23.1(8)	16.9(7)	1.1(6)	-2.3(6)	4.1(6)
C5	18.3(7)	22.8(7)	21.1(7)	0.6(6)	-1.8(6)	2.8(6)

C6	25.4(8)	26.8(8)	19.5(7)	-3.5(6)	1.2(6)	4.0(7)
C7	27.4(9)	32.0(9)	18.8(8)	2.0(7)	4.0(7)	3.8(7)
C8	24.0(8)	27.0(8)	21.4(8)	3.6(7)	1.0(6)	3.2(7)
C9	18.4(8)	23.1(8)	20.4(7)	2.4(6)	-1.2(6)	3.4(6)
C10	20.0(8)	25.8(8)	22.8(8)	-0.7(6)	-0.2(6)	3.2(6)
C11	26.4(8)	22.5(8)	32.6(9)	-1.5(7)	-2.5(7)	1.0(7)
C12	32.6(9)	26.3(9)	39(1)	6.1(8)	1.9(8)	-5.3(7)
C13	32.8(9)	32.5(9)	28.5(9)	6.2(8)	6.0(7)	-1.5(8)
C14	27.2(9)	23.6(8)	29.5(9)	-0.1(7)	0.2(7)	-5.0(7)
C15	27.7(9)	33.6(10)	46.6(11)	-4.1(9)	-8.5(8)	-2.9(8)
C16	21.3(8)	21.1(7)	20.0(7)	-2.5(6)	-0.9(6)	0.5(7)
C17	26.5(8)	28.7(8)	20.3(7)	-2.5(7)	-4.5(7)	2.3(7)
C18	45.3(11)	28.5(9)	27.1(9)	2.2(7)	-12.7(8)	-1.6(8)
C19	20.9(8)	23.1(8)	22.3(7)	-5.3(6)	-0.7(6)	-0.5(7)
C20	23.0(9)	33.3(9)	30.8(9)	-0.4(7)	5.7(7)	5.3(7)
C21	18.7(8)	25.4(9)	51.9(11)	2.8(8)	1.8(8)	5.0(7)
C22	44.1(12)	27.2(9)	67.8(14)	7.3(9)	26.8(11)	4.4(9)
C23	33.3(9)	35.8(10)	23.3(8)	-1.8(8)	4.1(7)	-5.8(8)
C24	46.7(12)	53.0(12)	22.6(9)	-6.5(8)	4.5(8)	-19.3(10)
O1	28.4(6)	22.8(6)	24.5(5)	-3.4(5)	3.5(5)	-2.2(5)
O2	21.1(6)	22.2(6)	30.9(6)	-3.0(5)	-2.4(5)	0.6(4)
O3	30.9(7)	26.4(6)	52.8(8)	-10.9(6)	1.3(6)	-2.2(5)
O4	23.3(5)	21.1(5)	19.0(5)	-2.4(4)	-2.3(4)	1.6(4)
O5	54.6(9)	32.5(7)	22.4(6)	-4.8(5)	-9.6(6)	-4.8(6)
O6	27.0(6)	26.7(6)	20.6(5)	-4.2(5)	3.5(5)	-5.2(5)
O7	69.3(10)	38.8(8)	30.1(7)	-3.5(6)	-2.6(7)	-20.0(7)
O8	25.1(6)	25.3(6)	41.8(7)	-1.1(5)	12.9(5)	2.6(5)
O9	28.6(7)	33.7(7)	57.3(8)	-7.6(7)	-6.6(6)	-1.8(6)

Table 4.3 Bond Lengths for chroman (Figure 2.5).

Atom Atom	Length/Å	Atom Atom	Length/Å
C1 C2	1.504(2)	C14 C15	1.493(3)
C1 O1	1.414(2)	C14 O2	1.363(2)
C1 O2	1.441(2)	C14 O3	1.195(2)
C2 C3	1.537(2)	C16 C19	1.513(2)
C3 C4	1.511(2)	C16 O4	1.4532(19)
C3 C16	1.544(2)	C17 C18	1.492(2)
C4 C5	1.375(2)	C17 O4	1.3592(19)
C4 C9	1.427(2)	C17 O5	1.196(2)
C5 C6	1.410(2)	C19 C20	1.515(2)
C5 O1	1.384(2)	C19 O6	1.4442(19)
C6 C7	1.361(2)	C20 O8	1.441(2)
C7 C8	1.418(2)	C21 C22	1.489(3)
C8 C9	1.423(2)	C21 O8	1.351(2)
C8 C13	1.414(3)	C21 O9	1.203(2)
C9 C10	1.426(2)	C23 C24	1.489(3)
C10 C11	1.366(2)	C23 O6	1.350(2)
C11 C12	1.407(3)	C23 O7	1.203(2)
C12 C13	1.363(3)		

Table 4.4 Bond Angles for chroman (Figure 2.5)

Atom Atom Atom	Angle/°	Atom Atom Atom	Angle/°
O1 C1 C2	113.63(13)	O2 C14 C15	111.06(15)
O1 C1 O2	108.61(13)	O3 C14 C15	126.37(17)
O2 C1 C2	107.50(13)	O3 C14 O2	122.56(16)
C1 C2 C3	112.57(13)	C19 C16 C3	112.77(12)
C2 C3 C16	113.65(13)	O4 C16 C3	108.53(12)
C4 C3 C2	107.17(13)	O4 C16 C19	107.99(12)
C4 C3 C16	111.34(13)	O4 C17 C18	110.73(13)
C5 C4 C3	118.39(14)	O5 C17 C18	125.38(15)
C5 C4 C9	118.58(14)	O5 C17 O4	123.89(15)
C9 C4 C3	123.02(14)	C16 C19 C20	112.92(13)
C4 C5 C6	122.39(15)	O6 C19 C16	108.90(13)
C4 C5 O1	124.60(14)	O6 C19 C20	107.73(13)
O1 C5 C6	113.01(13)	O8 C20 C19	109.37(14)
C7 C6 C5	119.40(15)	O8 C21 C22	110.71(16)
C6 C7 C8	120.98(15)	O9 C21 C22	125.88(18)
C7 C8 C9	119.22(15)	O9 C21 O8	123.40(18)
C13 C8 C7	121.27(15)	O6 C23 C24	110.32(15)
C13 C8 C9	119.51(15)	O7 C23 C24	125.84(17)
C8 C9 C4	119.36(14)	O7 C23 O6	123.84(16)
C8 C9 C10	117.52(15)	C5 O1 C1	119.84(12)
C10 C9 C4	123.12(14)	C14 O2 C1	116.94(13)
C11 C10 C9	121.23(15)	C17 O4 C16	116.62(12)
C10 C11 C12	120.81(16)	C23 O6 C19	117.03(13)
C13 C12 C11	119.51(16)	C21 O8 C20	116.99(14)
C12 C13 C8	121.41(16)		

Table 4.5 Torsion Angles for chroman (Figure 2.5)

A B C D	Angle/°	A B C D	Angle/°
C1 C2 C3 C4	54.81(17)	C9 C4 C5 O1	-176.75(14)
C1 C2 C3 C16	-68.64(17)	C9 C8 C13 C12	0.4(3)
C2 C1 O1 C5	16.44(19)	C9 C10 C11 C12	0.4(3)
C2 C1 O2 C14	160.69(13)	C10 C11 C12 C13	0.4(3)
C2 C3 C4 C5	-32.85(19)	C11 C12 C13 C8	-0.8(3)
C2 C3 C4 C9	146.79(14)	C13 C8 C9 C4	179.80(15)
C2 C3 C16 C19	-60.12(17)	C13 C8 C9 C10	0.4(2)
C2 C3 C16 O4	-179.73(12)	C15 C14 O2 C1	177.40(14)
C3 C4 C5 C6	-177.44(15)	C16 C3 C4 C5	92.01(17)
C3 C4 C5 O1	2.9(2)	C16 C3 C4 C9	-88.35(18)
C3 C4 C9 C8	177.89(14)	C16 C19 C20 O8	177.57(13)
C3 C4 C9 C10	-2.7(2)	C16 C19 O6 C23	136.30(15)
C3 C16 C19 C20	-176.62(14)	C18 C17 O4 C16	176.19(14)
C3 C16 C19 O6	-57.00(17)	C19 C16 O4 C17	134.19(14)
C3 C16 O4 C17	-103.26(15)	C19 C20 O8 C21	80.82(18)

C4C3 C16C19	178.73(13)	C20C19O6 C23	-100.91(16)
C4C3 C16O4	59.13(16)	C22C21O8 C20	-172.66(16)
C4C5 C6 C7	-1.2(2)	C24C23O6 C19	173.19(15)
C4C5 O1 C1	6.9(2)	O1 C1 C2 C3	-48.30(18)
C4C9 C10C11	179.80(15)	O1 C1 O2 C14	-75.97(16)
C5C4 C9 C8	-2.5(2)	O1 C5 C6 C7	178.43(15)
C5C4 C9 C10	176.91(15)	O2 C1 C2 C3	71.91(16)
C5C6 C7 C8	-0.9(3)	O2 C1 O1 C5	-103.13(15)
C6C5 O1 C1	-172.74(14)	O3 C14O2 C1	-2.4(2)
C6C7 C8 C9	1.2(2)	O4 C16C19C20	-56.71(17)
C6C7 C8 C13	-178.11(17)	O4 C16C19O6	62.91(15)
C7C8 C9 C4	0.5(2)	O5 C17O4 C16	-3.8(2)
C7C8 C9 C10	-178.93(15)	O6 C19C20O8	57.29(17)
C7C8 C13C12	179.71(17)	O7 C23O6 C19	-6.2(3)
C8C9 C10C11	-0.8(2)	O9 C21O8 C20	6.1(3)
C9C4 C5 C6	2.9(2)		

Table 4.6 Hydrogen Atom Coordinates ($\text{\AA}\times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2\times 10^3$) for chroman (Figure 2.5).

Atom	x	y	z	U(eq)
H1	5062	4328	8051	27
H2A	5526	3121	7215	26
H2B	3695	3225	7434	26
H3	4238	1647	7424	24
H6	2662	3147	9814	29
H7	1142	1848	10055	31
H10	3185	365	7691	27
H11	1599	-898	7940	33
H12	60	-939	8960	39
H13	115	304	9715	37
H15A	10030	4510	8875	54
H15B	9820	3630	8376	54
H15C	9480	3531	9189	54
H16	6879	1940	8362	25
H18A	6198	-742	9447	50
H18B	6682	-967	8663	50
H18C	4872	-725	8851	50
H19	7668	2311	7219	27
H20A	9649	1516	7862	35
H20B	8935	533	7620	35
H22A	10772	2179	5677	70
H22B	11977	1390	5938	70
H22C	12445	2464	6015	70
H24A	6164	1297	5154	61
H24B	5138	751	5723	61
H24C	6913	419	5547	61

Table 5.1 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for bridged chiral benzopyran (Figure 2.6). U_{eq} is defined as 1/3 of the trace of the orthogonalised U^{II} tensor.

Atom	x	y	z	U(eq)
C1	5571(3)	11363(2)	367.8(7)	19.0(4)
C2	4120(3)	10416(2)	687.1(7)	14.5(4)
C3	5047(3)	8877(2)	912.3(6)	14.3(4)
C4	3532(3)	7752(2)	1163.1(7)	13.1(4)
C5	2073(3)	7326(2)	732.6(7)	12.9(4)
C6	1133(3)	8931(2)	569.6(7)	13.9(4)
C7	669(3)	5994(2)	891.5(6)	14.5(4)
C8	1507(3)	4377(2)	1056.8(8)	20.0(4)
C9	2461(3)	8566(2)	1607.1(7)	12.6(4)
C10	813(3)	9438(2)	1496.3(7)	13.9(4)
C11	-322(3)	10174(2)	1886.3(7)	17.1(4)
C12	230(3)	10066(2)	2395.2(7)	17.3(4)
C13	1942(3)	9237(2)	2535.6(7)	15.0(4)
C14	3079(3)	8482(2)	2139.8(7)	13.0(4)
C15	4808(3)	7704(2)	2294.3(7)	16.5(4)
C16	5372(3)	7663(2)	2807.3(7)	19.5(4)
C17	4228(3)	8400(2)	3196.6(7)	18.5(4)
C18	2560(3)	9170(2)	3061.9(7)	17.2(4)
O1	4881(2)	12970.2(17)	261.2(6)	28.6(4)
O2	5992(2)	8035.8(16)	498.7(5)	17.1(3)
O3	2499.4(19)	10019.9(15)	352.2(5)	15.5(3)
O4	139.6(19)	9690.9(15)	995.8(5)	15.1(3)
O5	-1060.6(19)	6198.5(16)	881.2(5)	19.5(3)

Table 5.2 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for bridged chiral benzopyran (Figure 2.6). The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+\dots+2hka \times b \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	17.7(10)	18.9(9)	20.3(9)	0.3(7)	1.9(8)	0.5(8)
C2	13.2(9)	17.6(9)	12.7(8)	-0.3(7)	0.4(7)	1.1(7)
C3	12.3(9)	18.8(9)	11.7(8)	-5.1(7)	1.1(7)	2.5(8)
C4	14.0(9)	12.8(8)	12.7(8)	-0.8(7)	-2.4(7)	3.5(7)
C5	13.6(9)	13.6(8)	11.5(8)	-0.1(6)	0.2(7)	2.6(7)
C6	13.6(9)	14.6(8)	13.6(8)	0.5(7)	0.8(7)	0.4(7)
C7	16.2(10)	17.7(9)	9.7(8)	-1.0(7)	-0.6(7)	1.6(8)
C8	18.7(10)	16.9(9)	24.5(10)	2.5(8)	3.2(8)	2.0(8)
C9	13(1)	9.9(8)	14.9(8)	0.2(6)	0.5(7)	-0.5(7)
C10	14.2(9)	13.6(8)	13.9(8)	1.4(7)	-0.6(7)	-0.5(8)
C11	15.1(10)	15.8(9)	20.5(9)	0.0(7)	2.5(7)	4.0(8)
C12	15.4(10)	18.5(9)	17.9(9)	-2.1(7)	3.9(7)	1.1(8)
C13	16.4(10)	13.7(8)	14.8(8)	-0.5(7)	2.6(7)	-3.0(8)
C14	15.2(10)	9.5(8)	14.1(8)	0.0(7)	-0.1(7)	-3.3(7)
C15	17.8(10)	14.8(9)	16.7(9)	-2.8(7)	-0.5(8)	1.5(8)
C16	22.6(11)	16.4(9)	19.5(10)	0.0(7)	-6.3(8)	0.4(8)

C17	23.5(10)	18.0(9)	14.1(8)	0.9(7)	-3.0(8)	-8.0(8)
C18	22.4(11)	14.7(8)	14.6(8)	-1.2(6)	4.3(8)	-5.1(8)
O1	23.1(8)	22.2(7)	40.4(9)	13.0(6)	11.5(7)	2.9(7)
O2	14.5(7)	21.6(7)	15.1(6)	-1.0(5)	1.8(5)	6.6(6)
O3	13.9(7)	17.9(6)	14.6(6)	4.0(4)	-1.7(5)	-0.3(5)
O4	15.3(7)	17.5(6)	12.5(6)	0.3(5)	-1.5(5)	4.1(5)
O5	15.0(7)	21.3(7)	22.3(7)	3.7(6)	-0.5(5)	2.0(6)

Table 5.3 Bond Lengths for bridged chiral benzopyran (Figure 2.6).

Atom Atom	Length/Å	Atom Atom	Length/Å
C1 C2	1.512(3)	C7 O5	1.217(2)
C1 O1	1.419(2)	C9 C10	1.379(3)
C2 C3	1.522(2)	C9 C14	1.433(2)
C2 O3	1.455(2)	C10 C11	1.408(3)
C3 C4	1.538(3)	C10 O4	1.381(2)
C3 O2	1.423(2)	C11 C12	1.363(3)
C4 C5	1.540(2)	C12 C13	1.417(3)
C4 C9	1.513(2)	C13 C14	1.426(3)
C5 C6	1.519(2)	C13 C18	1.417(3)
C5 C7	1.515(2)	C14 C15	1.418(3)
C6 O3	1.415(2)	C15 C16	1.373(3)
C6 O4	1.433(2)	C16 C17	1.411(3)
C7 C8	1.499(2)	C17 C18	1.364(3)

Table 5.4 Bond Angles for bridged chiral benzopyran (Figure 2.6).

Atom Atom Atom	Angle/°	Atom Atom Atom	Angle/°
O1 C1 C2	110.27(16)	C10 C9 C14	118.09(16)
C1 C2 C3	109.91(15)	C14 C9 C4	123.18(16)
O3 C2 C1	108.24(14)	C9 C10 C11	122.68(16)
O3 C2 C3	111.76(14)	C9 C10 O4	123.42(16)
C2 C3 C4	110.90(15)	O4 C10 C11	113.89(16)
O2 C3 C2	108.01(13)	C12 C11 C10	119.58(18)
O2 C3 C4	110.07(14)	C11 C12 C13	120.76(18)
C3 C4 C5	106.72(13)	C12 C13 C14	119.47(16)
C9 C4 C3	113.11(14)	C12 C13 C18	121.10(17)
C9 C4 C5	108.14(15)	C18 C13 C14	119.42(18)
C6 C5 C4	106.77(14)	C13 C14 C9	119.35(17)
C7 C5 C4	113.23(14)	C15 C14 C9	122.86(17)
C7 C5 C6	114.20(16)	C15 C14 C13	117.77(16)
O3 C6 C5	110.84(15)	C16 C15 C14	121.42(18)
O3 C6 O4	110.81(14)	C15 C16 C17	120.38(18)
O4 C6 C5	111.66(14)	C18 C17 C16	119.82(17)
C8 C7 C5	116.84(16)	C17 C18 C13	121.18(17)
O5 C7 C5	122.39(17)	C6 O3 C2	115.42(13)
O5 C7 C8	120.76(18)	C10 O4 C6	118.65(14)

C10 C9 C4

118.73(15)

Table 5.5 Hydrogen Bonds for bridged chiral benzopyran (Figure 2.6).

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A
C6	H6	O2 ¹	1.00	2.53	3.172(2)	122.1
C8	H8A	O1 ²	0.98	2.36	3.316(3)	166.1
O1	H1	O3 ³	0.84	2.08	2.9111(19)	173.2
O2	H2A	O5 ⁴	0.84	1.88	2.7228(19)	178.0

Table 5.6 Torsion Angles for bridged chiral benzopyran (Figure 2.6)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C3	C4	-170.81(15)	C9	C10	O4	C6	3.8(2)
C1	C2	C3	O2	-50.12(19)	C9	C14	C15	C16	179.11(17)
C1	C2	O3	C6	171.31(14)	C10	C9	C14	C13	2.4(2)
C2	C3	C4	C5	58.36(17)	C10	C9	C14	C15	-176.16(15)
C2	C3	C4	C9	-60.44(18)	C10	C11	C12	C13	0.6(3)
C3	C2	O3	C6	50.14(19)	C11	C10	O4	C6	-177.06(16)
C3	C4	C5	C6	-63.22(17)	C11	C12	C13	C14	-1.2(3)
C3	C4	C5	C7	170.25(14)	C11	C12	C13	C18	177.78(17)
C3	C4	C9	C10	89.36(19)	C12	C13	C14	C9	-0.4(3)
C3	C4	C9	C14	-90.45(19)	C12	C13	C14	C15	178.28(16)
C4	C5	C6	O3	63.02(17)	C12	C13	C18	C17	-178.67(17)
C4	C5	C6	O4	-61.06(19)	C13	C14	C15	C16	0.5(3)
C4	C5	C7	C8	-57.5(2)	C14	C9	C10	C11	-3.1(3)
C4	C5	C7	O5	123.45(19)	C14	C9	C10	O4	175.96(15)
C4	C9	C10	C11	177.09(16)	C14	C13	C18	C17	0.3(3)
C4	C9	C10	O4	-3.9(2)	C14	C15	C16	C17	0.1(3)
C4	C9	C14	C13	-177.75(15)	C15	C16	C17	C18	-0.5(3)
C4	C9	C14	C15	3.7(3)	C16	C17	C18	C13	0.4(3)
C5	C4	C9	C10	-28.6(2)	C18	C13	C14	C9	-179.34(16)
C5	C4	C9	C14	151.58(16)	C18	C13	C14	C15	-0.7(2)
C5	C6	O3	C2	-57.03(18)	O1	C1	C2	C3	-166.10(15)
C5	C6	O4	C10	29.9(2)	O1	C1	C2	O3	71.59(19)
C6	C5	C7	C8	179.99(15)	O2	C3	C4	C5	-61.11(18)
C6	C5	C7	O5	1.0(2)	O2	C3	C4	C9	-179.90(14)
C7	C5	C6	O3	-171.03(14)	O3	C2	C3	C4	-50.62(18)
C7	C5	C6	O4	64.89(19)	O3	C2	C3	O2	70.08(19)
C9	C4	C5	C6	58.76(17)	O3	C6	O4	C10	-94.16(17)
C9	C4	C5	C7	-67.77(18)	O4	C6	O3	C2	67.53(18)
C9	C10	C11	C12	1.6(3)	O4	C10	C11	C12	-177.54(17)

Table 5.7 Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for bridged chiral benzopyran (Figure 2.6).

Atom	x	y	z	U(eq)
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H1A	6797	11434	562	23
H1B	5815	10778	36	23
H2	3665	11127	980	17
H3	6012	9202	1182	17
H4	4159	6722	1291	16
H5	2812	6906	426	15
H6	166	8673	293	17
H8A	2630	4128	841	30
H8B	545	3509	1014	30
H8C	1893	4439	1424	30
H11	-1465	10741	1795	21
H12	-541	10553	2659	21
H15	5595	7199	2037	20
H16	6538	7135	2901	23
H17	4618	8361	3552	22
H18	1800	9669	3326	21
H1	5709	13493	91	43
H2A	6913	7489	620	26

Table 6.1 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for chromene (Figure 3.2). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	5531(1)	4797(1)	1344(1)	24(1)
O(2)	6217(2)	6045(1)	646(1)	33(1)
O(3)	6060(2)	2094(1)	1827(1)	25(1)
O(4)	7821(2)	381(2)	1551(1)	55(1)
O(5)	2976(2)	1001(1)	1687(1)	25(1)
O(6)	1516(2)	2094(1)	2309(1)	53(1)
O(7)	3443(2)	2328(1)	-94(1)	28(1)
C(1)	44(2)	7529(2)	1097(1)	26(1)
C(2)	774(2)	7391(2)	624(1)	24(1)
C(3)	1477(2)	6097(2)	461(1)	21(1)
C(4)	1438(2)	4905(2)	790(1)	19(1)
C(5)	2160(2)	3594(2)	616(1)	19(1)
C(6)	2118(2)	2284(2)	946(1)	22(1)
C(7)	3326(2)	2312(2)	1420(1)	21(1)
C(8)	5304(2)	2274(2)	1323(1)	22(1)
C(9)	6072(2)	3556(2)	1070(1)	23(1)

C(10)	5683(2)	6014(2)	1073(1)	25(1)
C(11)	5095(2)	7253(2)	1380(1)	34(1)
C(12)	7158(2)	1004(2)	1896(1)	26(1)
C(13)	7413(2)	696(2)	2446(1)	36(1)
C(14)	2125(2)	1041(2)	2128(1)	28(1)
C(15)	2026(3)	-402(2)	2358(1)	37(1)
C(16)	2793(2)	3535(2)	127(1)	22(1)
C(17)	3147(2)	1085(2)	163(1)	28(1)
C(18)	2521(2)	1013(2)	627(1)	26(1)
C(19)	2834(2)	4711(2)	-199(1)	25(1)
C(20)	2199(2)	5963(2)	-35(1)	24(1)
C(21)	-32(2)	6351(2)	1423(1)	25(1)
C(22)	648(2)	5076(2)	1275(1)	21(1)

Table 6.2 Bond lengths [Å] and angles [°] for chromene (Figure 3.2)

O(1)-C(10)	1.3630(18)
O(1)-C(9)	1.4433(18)
O(2)-C(10)	1.1954(19)
O(3)-C(12)	1.3427(19)
O(3)-C(8)	1.4563(17)
O(4)-C(12)	1.194(2)
O(5)-C(14)	1.3282(19)
O(5)-C(7)	1.4551(17)
O(6)-C(14)	1.201(2)
O(7)-C(16)	1.3783(18)
O(7)-C(17)	1.378(2)
C(1)-C(2)	1.368(2)
C(1)-C(21)	1.412(2)
C(1)-H(1)	0.9500
C(2)-C(3)	1.409(2)
C(2)-H(2)	0.9500
C(3)-C(20)	1.420(2)
C(3)-C(4)	1.4265(19)
C(4)-C(22)	1.419(2)



C(4)-C(5)	1.436(2)
C(5)-C(16)	1.374(2)
C(5)-C(6)	1.5179(19)
C(6)-C(18)	1.503(2)
C(6)-C(7)	1.549(2)
C(6)-H(6)	1.0000
C(7)-C(8)	1.528(2)
C(7)-H(7)	1.0000
C(8)-C(9)	1.506(2)
C(8)-H(8)	1.0000
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(11)	1.496(2)
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-C(13)	1.488(2)
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-C(15)	1.500(2)
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(16)-C(19)	1.409(2)
C(17)-C(18)	1.313(2)
C(17)-H(17)	0.9500
C(18)-H(18)	0.9500
C(19)-C(20)	1.354(2)
C(19)-H(19)	0.9500
C(20)-H(20)	0.9500
C(21)-C(22)	1.374(2)
C(21)-H(21)	0.9500
C(22)-H(22)	0.9500

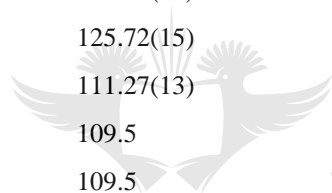
C(10)-O(1)-C(9) 114.15(11)



C(12)-O(3)-C(8)	117.28(11)
C(14)-O(5)-C(7)	119.12(11)
C(16)-O(7)-C(17)	116.74(11)
C(2)-C(1)-C(21)	119.45(14)
C(2)-C(1)-H(1)	120.3
C(21)-C(1)-H(1)	120.3
C(1)-C(2)-C(3)	121.03(14)
C(1)-C(2)-H(2)	119.5
C(3)-C(2)-H(2)	119.5
C(2)-C(3)-C(20)	120.35(13)
C(2)-C(3)-C(4)	120.07(13)
C(20)-C(3)-C(4)	119.57(13)
C(22)-C(4)-C(3)	117.56(13)
C(22)-C(4)-C(5)	123.16(13)
C(3)-C(4)-C(5)	119.27(13)
C(16)-C(5)-C(4)	117.81(13)
C(16)-C(5)-C(6)	120.54(13)
C(4)-C(5)-C(6)	121.53(12)
C(18)-C(6)-C(5)	109.70(12)
C(18)-C(6)-C(7)	109.96(12)
C(5)-C(6)-C(7)	115.64(11)
C(18)-C(6)-H(6)	107.0
C(5)-C(6)-H(6)	107.0
C(7)-C(6)-H(6)	107.0
O(5)-C(7)-C(8)	103.97(11)
O(5)-C(7)-C(6)	105.37(11)
C(8)-C(7)-C(6)	116.75(12)
O(5)-C(7)-H(7)	110.1
C(8)-C(7)-H(7)	110.1
C(6)-C(7)-H(7)	110.1
O(3)-C(8)-C(9)	110.10(12)
O(3)-C(8)-C(7)	103.88(11)
C(9)-C(8)-C(7)	115.93(12)
O(3)-C(8)-H(8)	108.9
C(9)-C(8)-H(8)	108.9
C(7)-C(8)-H(8)	108.9



O(1)-C(9)-C(8)	109.32(11)
O(1)-C(9)-H(9A)	109.8
C(8)-C(9)-H(9A)	109.8
O(1)-C(9)-H(9B)	109.8
C(8)-C(9)-H(9B)	109.8
H(9A)-C(9)-H(9B)	108.3
O(2)-C(10)-O(1)	122.74(15)
O(2)-C(10)-C(11)	126.04(15)
O(1)-C(10)-C(11)	111.21(13)
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
O(4)-C(12)-O(3)	123.01(14)
O(4)-C(12)-C(13)	125.72(15)
O(3)-C(12)-C(13)	111.27(13)
C(12)-C(13)-H(13A)	109.5
C(12)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(12)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
O(6)-C(14)-O(5)	123.84(14)
O(6)-C(14)-C(15)	125.73(14)
O(5)-C(14)-C(15)	110.43(13)
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
O(7)-C(16)-C(5)	123.63(13)
O(7)-C(16)-C(19)	113.40(13)
C(5)-C(16)-C(19)	122.97(14)



C(18)-C(17)-O(7)	123.94(14)
C(18)-C(17)-H(17)	118.0
O(7)-C(17)-H(17)	118.0
C(17)-C(18)-C(6)	123.46(14)
C(17)-C(18)-H(18)	118.3
C(6)-C(18)-H(18)	118.3
C(20)-C(19)-C(16)	119.76(13)
C(20)-C(19)-H(19)	120.1
C(16)-C(19)-H(19)	120.1
C(19)-C(20)-C(3)	120.55(13)
C(19)-C(20)-H(20)	119.7
C(3)-C(20)-H(20)	119.7
C(22)-C(21)-C(1)	120.84(14)
C(22)-C(21)-H(21)	119.6
C(1)-C(21)-H(21)	119.6
C(21)-C(22)-C(4)	121.03(14)
C(21)-C(22)-H(22)	119.5
C(4)-C(22)-H(22)	119.5



Symmetry transformations used to generate equivalent atoms:

Table 6.3 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for chromene (Figure 3.2). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^* U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	27(1)	22(1)	23(1)	2(1)	2(1)	-1(1)
O(2)	39(1)	32(1)	28(1)	7(1)	3(1)	-4(1)
O(3)	33(1)	24(1)	19(1)	-2(1)	-5(1)	9(1)
O(4)	70(1)	65(1)	30(1)	-9(1)	-6(1)	46(1)
O(5)	36(1)	17(1)	22(1)	5(1)	7(1)	2(1)
O(6)	87(1)	23(1)	49(1)	2(1)	39(1)	4(1)
O(7)	33(1)	27(1)	25(1)	-4(1)	3(1)	5(1)
C(1)	25(1)	20(1)	33(1)	-3(1)	-6(1)	4(1)
C(2)	24(1)	19(1)	30(1)	4(1)	-5(1)	-1(1)
C(3)	19(1)	21(1)	23(1)	2(1)	-7(1)	-2(1)

C(4)	17(1)	21(1)	20(1)	0(1)	-4(1)	-2(1)
C(5)	17(1)	20(1)	21(1)	0(1)	-3(1)	-2(1)
C(6)	23(1)	18(1)	25(1)	2(1)	-1(1)	0(1)
C(7)	29(1)	13(1)	20(1)	4(1)	1(1)	0(1)
C(8)	29(1)	21(1)	16(1)	-2(1)	-3(1)	4(1)
C(9)	23(1)	24(1)	21(1)	-1(1)	-1(1)	2(1)
C(10)	20(1)	23(1)	32(1)	4(1)	-3(1)	-3(1)
C(11)	37(1)	25(1)	38(1)	1(1)	5(1)	-1(1)
C(12)	30(1)	22(1)	28(1)	-2(1)	-3(1)	5(1)
C(13)	46(1)	32(1)	29(1)	2(1)	-10(1)	10(1)
C(14)	37(1)	22(1)	26(1)	3(1)	6(1)	0(1)
C(15)	55(1)	24(1)	32(1)	7(1)	11(1)	3(1)
C(16)	21(1)	23(1)	23(1)	-1(1)	-3(1)	2(1)
C(17)	31(1)	21(1)	32(1)	-5(1)	-6(1)	4(1)
C(18)	30(1)	17(1)	32(1)	-2(1)	-8(1)	-1(1)
C(19)	24(1)	31(1)	20(1)	1(1)	0(1)	-2(1)
C(20)	23(1)	26(1)	23(1)	7(1)	-3(1)	-3(1)
C(21)	22(1)	30(1)	22(1)	-5(1)	-2(1)	3(1)
C(22)	21(1)	22(1)	21(1)	1(1)	-2(1)	-1(1)

Table 7.1 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for bridged chiral benzopyran (Figure 3.7). $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	9660(1)	3652(1)	4073(1)	23(1)
O(2)	7613(1)	4867(1)	1242(1)	20(1)
O(3)	5271(1)	4297(1)	1006(1)	21(1)
O(4)	9435(1)	1740(1)	1252(1)	22(1)
C(1)	10747(2)	4493(2)	4771(1)	27(1)
C(2)	9247(1)	4609(2)	2939(1)	22(1)
C(3)	7982(1)	3757(2)	2340(1)	18(1)
C(4)	8192(1)	1865(2)	1937(1)	17(1)

C(5)	6969(1)	1255(1)	1076(1)	17(1)
C(6)	5638(1)	1354(2)	1803(1)	17(1)
C(7)	5134(1)	-43(2)	2598(1)	17(1)
C(8)	5902(1)	-1583(2)	2834(1)	21(1)
C(9)	5408(2)	-2877(2)	3623(1)	24(1)
C(10)	4119(2)	-2730(2)	4195(1)	25(1)
C(11)	6572(1)	4255(2)	381(1)	18(1)
C(12)	4857(2)	2838(2)	1686(1)	19(1)
C(13)	6860(1)	2447(2)	-133(1)	19(1)
C(14)	9926(2)	11(2)	1134(2)	32(1)
C(15)	3338(2)	-1283(2)	3962(1)	24(1)
C(16)	3826(1)	101(2)	3174(1)	21(1)
C(17)	3046(2)	1631(2)	2949(1)	22(1)
C(18)	3555(1)	2977(2)	2236(1)	23(1)

Table 7.2 Bond lengths [\AA] and angles [$^\circ$] for bridged chiral benzopyran (Figure 3.7).

O(1)-C(2)	1.4128(15)
O(1)-C(1)	1.4183(16)
O(2)-C(11)	1.4060(15)
O(2)-C(3)	1.4401(14)
O(3)-C(12)	1.3807(15)
O(3)-C(11)	1.4342(16)
O(4)-C(4)	1.4159(15)
O(4)-C(14)	1.4197(17)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(3)	1.5139(18)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.5258(17)
C(3)-H(3)	1.0000
C(4)-C(5)	1.536(2)
C(4)-H(4)	1.0000

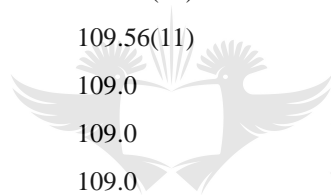
C(5)-C(6)	1.5123(18)
C(5)-C(13)	1.5292(16)
C(5)-H(5)	1.0000
C(6)-C(12)	1.3766(18)
C(6)-C(7)	1.4353(16)
C(7)-C(8)	1.4201(18)
C(7)-C(16)	1.4224(17)
C(8)-C(9)	1.3703(18)
C(8)-H(8)	0.9500
C(9)-C(10)	1.404(2)
C(9)-H(9)	0.9500
C(10)-C(15)	1.367(2)
C(10)-H(10)	0.9500
C(11)-C(13)	1.5129(18)
C(11)-H(11)	1.0000
C(12)-C(18)	1.4061(19)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-C(16)	1.4185(18)
C(15)-H(15)	0.9500
C(16)-C(17)	1.4182(19)
C(17)-C(18)	1.3622(19)
C(17)-H(17)	0.9500
C(18)-H(18)	0.9500

C(2)-O(1)-C(1)	111.29(10)
C(11)-O(2)-C(3)	116.33(9)
C(12)-O(3)-C(11)	118.27(10)
C(4)-O(4)-C(14)	113.64(10)
O(1)-C(1)-H(1A)	109.5
O(1)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
O(1)-C(1)-H(1C)	109.5

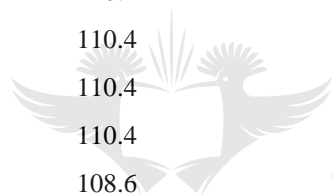


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H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
O(1)-C(2)-C(3)	108.34(10)
O(1)-C(2)-H(2A)	110.0
C(3)-C(2)-H(2A)	110.0
O(1)-C(2)-H(2B)	110.0
C(3)-C(2)-H(2B)	110.0
H(2A)-C(2)-H(2B)	108.4
O(2)-C(3)-C(2)	103.85(10)
O(2)-C(3)-C(4)	113.09(10)
C(2)-C(3)-C(4)	113.96(11)
O(2)-C(3)-H(3)	108.6
C(2)-C(3)-H(3)	108.6
C(4)-C(3)-H(3)	108.6
O(4)-C(4)-C(3)	108.55(10)
O(4)-C(4)-C(5)	111.59(10)
C(3)-C(4)-C(5)	109.56(11)
O(4)-C(4)-H(4)	109.0
C(3)-C(4)-H(4)	109.0
C(5)-C(4)-H(4)	109.0
C(6)-C(5)-C(13)	108.28(10)
C(6)-C(5)-C(4)	112.14(10)
C(13)-C(5)-C(4)	107.97(10)
C(6)-C(5)-H(5)	109.5
C(13)-C(5)-H(5)	109.5
C(4)-C(5)-H(5)	109.5
C(12)-C(6)-C(7)	118.18(12)
C(12)-C(6)-C(5)	118.79(11)
C(7)-C(6)-C(5)	123.02(11)
C(8)-C(7)-C(16)	118.24(11)
C(8)-C(7)-C(6)	122.11(12)
C(16)-C(7)-C(6)	119.65(11)
C(9)-C(8)-C(7)	120.77(12)
C(9)-C(8)-H(8)	119.6
C(7)-C(8)-H(8)	119.6
C(8)-C(9)-C(10)	120.89(12)



C(8)-C(9)-H(9)	119.6
C(10)-C(9)-H(9)	119.6
C(15)-C(10)-C(9)	119.88(11)
C(15)-C(10)-H(10)	120.1
C(9)-C(10)-H(10)	120.1
O(2)-C(11)-O(3)	110.93(10)
O(2)-C(11)-C(13)	112.46(11)
O(3)-C(11)-C(13)	110.29(10)
O(2)-C(11)-H(11)	107.6
O(3)-C(11)-H(11)	107.6
C(13)-C(11)-H(11)	107.6
C(6)-C(12)-O(3)	123.27(12)
C(6)-C(12)-C(18)	122.30(11)
O(3)-C(12)-C(18)	114.42(11)
C(11)-C(13)-C(5)	106.65(10)
C(11)-C(13)-H(13A)	110.4
C(5)-C(13)-H(13A)	110.4
C(11)-C(13)-H(13B)	110.4
C(5)-C(13)-H(13B)	110.4
H(13A)-C(13)-H(13B)	108.6
O(4)-C(14)-H(14A)	109.5
O(4)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
O(4)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(10)-C(15)-C(16)	120.90(13)
C(10)-C(15)-H(15)	119.6
C(16)-C(15)-H(15)	119.6
C(17)-C(16)-C(15)	121.73(12)
C(17)-C(16)-C(7)	118.97(11)
C(15)-C(16)-C(7)	119.29(12)
C(18)-C(17)-C(16)	120.91(12)
C(18)-C(17)-H(17)	119.5
C(16)-C(17)-H(17)	119.5
C(17)-C(18)-C(12)	119.81(12)



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C(17)-C(18)-H(18)	120.1
C(12)-C(18)-H(18)	120.1

Symmetry transformations used to generate equivalent atoms:

Table 7.3 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for bridged chiral benzopyran (Figure 3.7). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
O(1)	25(1)	24(1)	20(1)	0(1)	-8(1)	-5(1)
O(2)	21(1)	18(1)	19(1)	2(1)	-6(1)	-3(1)
O(3)	20(1)	17(1)	25(1)	4(1)	2(1)	1(1)
O(4)	18(1)	23(1)	26(1)	-2(1)	6(1)	2(1)
C(1)	27(1)	25(1)	27(1)	-4(1)	-11(1)	1(1)
C(2)	25(1)	20(1)	20(1)	1(1)	-5(1)	-4(1)
C(3)	20(1)	19(1)	14(1)	1(1)	-1(1)	0(1)
C(4)	14(1)	19(1)	18(1)	1(1)	1(1)	1(1)
C(5)	18(1)	15(1)	17(1)	-1(1)	1(1)	1(1)
C(6)	16(1)	19(1)	14(1)	-2(1)	-3(1)	-1(1)
C(7)	17(1)	18(1)	15(1)	-3(1)	-2(1)	-2(1)
C(8)	23(1)	19(1)	20(1)	-1(1)	-2(1)	0(1)
C(9)	31(1)	19(1)	22(1)	0(1)	-3(1)	0(1)
C(10)	30(1)	26(1)	20(1)	5(1)	1(1)	-8(1)
C(11)	16(1)	21(1)	17(1)	2(1)	-4(1)	-3(1)
C(12)	21(1)	18(1)	19(1)	-1(1)	-1(1)	-3(1)
C(13)	21(1)	19(1)	15(1)	0(1)	-2(1)	-2(1)
C(14)	23(1)	28(1)	43(1)	-6(1)	7(1)	8(1)
C(15)	24(1)	29(1)	19(1)	-2(1)	3(1)	-6(1)
C(16)	23(1)	24(1)	15(1)	-4(1)	-1(1)	-4(1)
C(17)	16(1)	25(1)	25(1)	-4(1)	3(1)	0(1)
C(18)	19(1)	23(1)	28(1)	-2(1)	-1(1)	3(1)

Table 8.1 Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for flavonoid (Figure 4.2). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2775(3)	6181(12)	6689(3)	24(2)
C(2)	3048(3)	4361(13)	7148(3)	34(2)
C(3)	2836(4)	4352(15)	7770(3)	38(2)
C(4)	2340(4)	6186(15)	7959(3)	38(2)
C(5)	2145(4)	6300(18)	8621(4)	54(2)
C(6)	1686(5)	8120(20)	8807(4)	59(3)
C(7)	1387(4)	9928(16)	8365(4)	52(2)
C(8)	1559(4)	9879(15)	7711(4)	41(2)
C(9)	2029(4)	8013(13)	7493(3)	32(2)
C(10)	2244(4)	7905(12)	6819(3)	27(2)
C(11)	1876(3)	9567(11)	6277(3)	24(2)
C(12)	1006(3)	9036(12)	6114(3)	26(2)
C(13)	777(3)	6351(12)	5982(3)	25(1)
C(14)	-91(3)	6121(11)	5979(3)	29(2)
C(15)	2308(3)	9492(12)	5653(3)	25(2)
C(16)	3110(3)	8506(11)	5797(3)	24(2)
C(17)	3545(3)	8294(11)	5199(3)	21(2)
C(18)	4059(3)	10096(11)	5068(3)	26(2)
C(19)	4452(3)	9999(12)	4509(3)	27(2)
C(20)	4315(3)	8056(12)	4074(3)	26(2)
C(21)	5030(4)	9913(14)	3270(3)	41(2)
C(22)	3804(3)	6240(12)	4200(3)	29(2)
C(23)	3420(3)	6343(12)	4754(3)	27(2)
C(24)	6952(4)	6404(14)	8447(3)	31(2)
C(25)	6662(4)	4623(14)	7970(3)	37(2)
C(26)	6923(4)	4645(16)	7360(4)	43(2)
C(27)	7428(4)	6483(15)	7189(3)	37(2)
C(28)	7652(4)	6654(18)	6534(4)	51(2)
C(29)	8118(4)	8471(18)	6362(4)	53(2)
C(30)	8386(4)	10248(17)	6824(4)	50(2)
C(31)	8196(4)	10175(15)	7467(4)	43(2)
C(32)	7710(4)	8275(14)	7670(3)	35(2)
C(33)	7497(4)	8111(13)	8336(3)	30(2)

C(34)	7877(4)	9694(13)	8900(3)	33(2)
C(35)	8752(4)	9170(13)	9018(3)	34(2)
C(36)	9000(4)	6538(13)	9128(4)	36(2)
C(37)	9839(4)	6225(14)	9018(4)	43(2)
C(38)	7489(3)	9337(13)	9544(3)	33(2)
C(39)	6670(4)	8480(13)	9418(3)	32(2)
C(40)	6286(3)	7961(12)	10033(3)	24(2)
C(41)	5734(3)	9519(12)	10236(3)	30(2)
C(42)	5379(3)	9046(12)	10803(3)	29(2)
C(43)	5580(4)	6998(12)	11172(3)	31(2)
C(44)	5358(6)	4541(16)	12124(4)	74(3)
C(45)	6128(4)	5389(13)	10980(3)	35(2)
C(46)	6474(4)	5892(14)	10415(3)	34(2)
O(1)	3073(2)	6088(8)	6090(2)	28(1)
O(2)	731(2)	10508(7)	5550(2)	29(1)
O(3)	1012(3)	5633(8)	5361(2)	33(1)
O(4)	-366(2)	3726(7)	5793(2)	31(1)
O(5)	4679(2)	7777(9)	3505(2)	34(1)
O(6)	6637(2)	6207(8)	9044(2)	34(1)
O(7)	9080(2)	10651(8)	9575(2)	40(1)
O(8)	8883(3)	5817(10)	9780(3)	55(2)
O(9)	10127(3)	3815(9)	9185(3)	47(1)
O(10)	5195(3)	6694(9)	11735(2)	44(1)

Table 8.2 Bond lengths [Å] and angles [°] for flavonoid (Figure 4.2).

C(1)-C(10)	1.360(9)
C(1)-O(1)	1.370(7)
C(1)-C(2)	1.400(9)
C(2)-C(3)	1.349(9)
C(3)-C(4)	1.397(10)
C(4)-C(5)	1.418(10)
C(4)-C(9)	1.431(10)
C(5)-C(6)	1.347(12)
C(6)-C(7)	1.388(12)
C(7)-C(8)	1.385(10)
C(8)-C(9)	1.403(10)
C(9)-C(10)	1.451(9)
C(10)-C(11)	1.506(9)
C(11)-C(15)	1.537(8)
C(11)-C(12)	1.540(8)
C(12)-O(2)	1.429(7)
C(12)-C(13)	1.525(9)
C(13)-O(3)	1.415(7)
C(13)-C(14)	1.514(8)
C(14)-O(4)	1.420(7)
C(15)-C(16)	1.493(8)
C(16)-O(1)	1.442(7)
C(16)-C(17)	1.498(9)
C(17)-C(18)	1.371(8)
C(17)-C(23)	1.390(9)
C(18)-C(19)	1.383(8)
C(19)-C(20)	1.375(9)
C(20)-C(22)	1.368(9)
C(20)-O(5)	1.381(8)
C(21)-O(5)	1.415(8)
C(22)-C(23)	1.367(9)
C(24)-C(33)	1.362(9)
C(24)-O(6)	1.381(8)
C(24)-C(25)	1.418(9)
C(25)-C(26)	1.358(9)

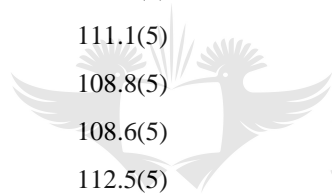


C(26)-C(27)	1.397(11)
C(27)-C(32)	1.422(10)
C(27)-C(28)	1.422(10)
C(28)-C(29)	1.346(12)
C(29)-C(30)	1.387(12)
C(30)-C(31)	1.375(10)
C(31)-C(32)	1.422(10)
C(32)-C(33)	1.437(9)
C(33)-C(34)	1.519(9)
C(34)-C(35)	1.540(9)
C(34)-C(38)	1.542(9)
C(35)-O(7)	1.447(8)
C(35)-C(36)	1.500(10)
C(36)-O(8)	1.410(8)
C(36)-C(37)	1.509(9)
C(37)-O(9)	1.427(8)
C(38)-C(39)	1.494(9)
C(39)-O(6)	1.443(8)
C(39)-C(40)	1.500(9)
C(40)-C(41)	1.376(9)
C(40)-C(46)	1.380(9)
C(41)-C(42)	1.383(9)
C(42)-C(43)	1.362(9)
C(43)-C(45)	1.379(9)
C(43)-O(10)	1.392(8)
C(44)-O(10)	1.418(9)
C(45)-C(46)	1.375(9)

C(10)-C(1)-O(1)	121.8(6)
C(10)-C(1)-C(2)	123.0(6)
O(1)-C(1)-C(2)	115.1(6)
C(3)-C(2)-C(1)	120.7(7)
C(2)-C(3)-C(4)	119.5(7)
C(3)-C(4)-C(5)	120.5(7)
C(3)-C(4)-C(9)	120.9(6)
C(5)-C(4)-C(9)	118.6(8)

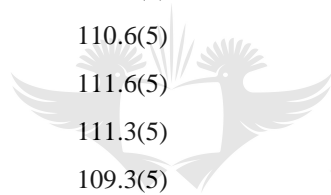


C(6)-C(5)-C(4)	120.4(8)
C(5)-C(6)-C(7)	122.0(8)
C(8)-C(7)-C(6)	119.6(8)
C(7)-C(8)-C(9)	120.5(8)
C(8)-C(9)-C(4)	118.9(6)
C(8)-C(9)-C(10)	122.9(7)
C(4)-C(9)-C(10)	118.1(6)
C(1)-C(10)-C(9)	117.4(6)
C(1)-C(10)-C(11)	120.9(6)
C(9)-C(10)-C(11)	121.7(6)
C(10)-C(11)-C(15)	112.0(5)
C(10)-C(11)-C(12)	111.8(5)
C(15)-C(11)-C(12)	112.2(5)
O(2)-C(12)-C(13)	109.6(5)
O(2)-C(12)-C(11)	107.4(5)
C(13)-C(12)-C(11)	116.5(5)
O(3)-C(13)-C(14)	111.1(5)
O(3)-C(13)-C(12)	108.8(5)
C(14)-C(13)-C(12)	108.6(5)
O(4)-C(14)-C(13)	112.5(5)
C(16)-C(15)-C(11)	112.3(5)
O(1)-C(16)-C(15)	108.8(5)
O(1)-C(16)-C(17)	108.0(5)
C(15)-C(16)-C(17)	114.4(5)
C(18)-C(17)-C(23)	118.4(6)
C(18)-C(17)-C(16)	120.0(6)
C(23)-C(17)-C(16)	121.5(5)
C(17)-C(18)-C(19)	121.5(6)
C(20)-C(19)-C(18)	118.9(6)
C(22)-C(20)-C(19)	120.2(6)
C(22)-C(20)-O(5)	116.2(6)
C(19)-C(20)-O(5)	123.5(6)
C(23)-C(22)-C(20)	120.5(6)
C(22)-C(23)-C(17)	120.3(6)
C(33)-C(24)-O(6)	123.2(6)
C(33)-C(24)-C(25)	123.5(6)



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O(6)-C(24)-C(25)	113.3(6)
C(26)-C(25)-C(24)	118.8(7)
C(25)-C(26)-C(27)	120.9(7)
C(26)-C(27)-C(32)	119.9(6)
C(26)-C(27)-C(28)	121.4(8)
C(32)-C(27)-C(28)	118.7(8)
C(29)-C(28)-C(27)	121.5(9)
C(28)-C(29)-C(30)	120.2(8)
C(31)-C(30)-C(29)	121.1(8)
C(30)-C(31)-C(32)	120.4(8)
C(31)-C(32)-C(27)	118.1(6)
C(31)-C(32)-C(33)	122.5(7)
C(27)-C(32)-C(33)	119.4(7)
C(24)-C(33)-C(32)	117.0(6)
C(24)-C(33)-C(34)	120.9(6)
C(32)-C(33)-C(34)	122.1(6)
C(33)-C(34)-C(35)	110.6(5)
C(33)-C(34)-C(38)	111.6(5)
C(35)-C(34)-C(38)	111.3(5)
O(7)-C(35)-C(36)	109.3(5)
O(7)-C(35)-C(34)	108.4(5)
C(36)-C(35)-C(34)	117.5(6)
O(8)-C(36)-C(35)	109.5(6)
O(8)-C(36)-C(37)	110.3(6)
C(35)-C(36)-C(37)	110.6(6)
O(9)-C(37)-C(36)	112.8(6)
C(39)-C(38)-C(34)	113.2(5)
O(6)-C(39)-C(38)	109.7(5)
O(6)-C(39)-C(40)	106.1(5)
C(38)-C(39)-C(40)	114.8(5)
C(41)-C(40)-C(46)	117.5(6)
C(41)-C(40)-C(39)	121.4(6)
C(46)-C(40)-C(39)	121.1(6)
C(40)-C(41)-C(42)	121.5(6)
C(43)-C(42)-C(41)	119.6(6)
C(42)-C(43)-C(45)	120.3(6)



C(42)-C(43)-O(10)	115.3(6)
C(45)-C(43)-O(10)	124.4(6)
C(46)-C(45)-C(43)	119.2(6)
C(45)-C(46)-C(40)	121.8(6)
C(1)-O(1)-C(16)	111.5(5)
C(20)-O(5)-C(21)	116.3(5)
C(24)-O(6)-C(39)	113.2(5)
C(43)-O(10)-C(44)	117.8(6)

Symmetry transformations used to generate equivalent atoms:

Table 8.3 Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for flavonoid (Figure 4.2). The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2}U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
C(1)	18(3)	30(4)	22(4)	5(3)	-7(3)	-2(3)
C(2)	21(3)	41(4)	38(4)	6(4)	-5(3)	-3(3)
C(3)	25(4)	49(5)	36(5)	13(4)	-6(3)	-8(4)
C(4)	36(4)	59(5)	16(4)	8(4)	-7(3)	-23(4)
C(5)	44(5)	79(6)	38(5)	3(5)	1(4)	-23(5)
C(6)	46(5)	95(7)	37(5)	-11(5)	9(4)	-30(6)
C(7)	44(5)	60(6)	54(6)	-25(5)	21(4)	-21(4)
C(8)	35(4)	51(5)	39(5)	-14(4)	11(4)	-17(4)
C(9)	23(4)	43(4)	31(4)	-10(4)	2(3)	-19(3)
C(10)	24(3)	27(4)	28(4)	-4(3)	-2(3)	-10(3)
C(11)	17(3)	25(4)	32(4)	-4(3)	6(3)	1(3)
C(12)	29(3)	24(3)	23(4)	-1(3)	3(3)	6(3)
C(13)	24(3)	23(4)	27(4)	-1(3)	0(3)	1(3)
C(14)	29(3)	24(4)	31(4)	-3(3)	-1(3)	-1(3)
C(15)	21(3)	27(4)	27(4)	7(3)	0(3)	4(3)
C(16)	23(3)	20(4)	29(4)	0(3)	-1(3)	-1(3)
C(17)	15(3)	23(4)	25(4)	1(3)	0(3)	-1(3)
C(18)	22(3)	22(4)	32(4)	0(3)	2(3)	3(3)
C(19)	19(3)	31(4)	32(4)	4(3)	1(3)	0(3)
C(20)	21(3)	24(4)	30(4)	2(3)	-7(3)	2(3)

C(21)	34(4)	55(5)	36(4)	-1(4)	12(3)	-12(4)
C(22)	34(4)	26(4)	27(4)	-6(3)	0(3)	-4(3)
C(23)	28(3)	21(4)	32(4)	2(3)	1(3)	-10(3)
C(24)	27(3)	39(4)	25(4)	1(3)	-3(3)	9(4)
C(25)	31(4)	48(5)	30(4)	-10(4)	-7(3)	1(3)
C(26)	25(4)	66(6)	34(4)	-14(4)	-11(3)	9(4)
C(27)	27(4)	59(5)	24(4)	-3(4)	-5(3)	20(4)
C(28)	42(5)	83(7)	26(4)	-2(4)	-3(4)	25(5)
C(29)	37(5)	88(7)	34(5)	9(5)	5(4)	31(5)
C(30)	32(4)	67(6)	52(5)	25(5)	10(4)	15(4)
C(31)	43(4)	48(5)	37(5)	12(4)	5(4)	15(4)
C(32)	29(4)	47(5)	29(4)	6(4)	2(3)	12(4)
C(33)	28(4)	34(4)	26(4)	3(3)	-5(3)	4(3)
C(34)	35(4)	29(4)	34(4)	-1(3)	-3(3)	3(3)
C(35)	38(4)	32(4)	31(4)	0(3)	-1(3)	-10(3)
C(36)	32(4)	29(4)	45(5)	2(4)	0(3)	-8(3)
C(37)	33(4)	37(4)	58(5)	4(4)	4(3)	5(4)
C(38)	31(4)	36(4)	32(4)	-7(3)	8(3)	-3(3)
C(39)	34(4)	33(4)	28(4)	0(3)	-2(3)	7(3)
C(40)	19(3)	25(4)	27(4)	-4(3)	-3(3)	-1(3)
C(41)	30(4)	30(4)	28(4)	0(3)	-6(3)	3(3)
C(42)	25(3)	26(4)	37(4)	-3(3)	1(3)	12(3)
C(43)	33(4)	30(4)	29(4)	-8(3)	1(3)	-7(3)
C(44)	138(9)	47(6)	44(5)	2(5)	36(6)	-14(6)
C(45)	46(4)	28(4)	31(4)	6(3)	2(3)	4(4)
C(46)	33(4)	40(5)	29(4)	-5(4)	3(3)	14(4)
O(1)	29(2)	29(3)	25(3)	3(2)	3(2)	1(2)
O(2)	29(2)	15(2)	43(3)	2(2)	-2(2)	0(2)
O(3)	36(3)	24(2)	39(3)	-5(2)	8(2)	-1(2)
O(4)	25(2)	28(3)	40(3)	0(2)	-2(2)	-2(2)
O(5)	30(2)	43(3)	29(3)	-1(2)	9(2)	-1(2)
O(6)	41(3)	35(3)	25(3)	-9(2)	4(2)	-9(2)
O(7)	44(3)	26(3)	49(3)	-2(2)	-7(2)	-1(2)
O(8)	65(3)	46(3)	59(4)	17(3)	22(3)	16(3)
O(9)	42(3)	43(3)	54(3)	-2(3)	-4(3)	7(3)
O(10)	53(3)	43(3)	38(3)	-3(3)	15(3)	-3(3)

Table 8.4 Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for flavonoid (Figure 4.2).

	x	y	z	U(eq)
H(2)	3380	3145	7022	41
H(3)	3018	3132	8071	45
H(5)	2334	5113	8929	64
H(6)	1565	8161	9244	71
H(7)	1074	11167	8507	62
H(8)	1360	11093	7415	49
H(11)	1922	11255	6449	29
H(12)	745	9604	6492	31
H(13)	1037	5310	6335	30
H(14A)	-229	6502	6420	34
H(14B)	-343	7318	5671	34
H(15A)	2021	8468	5317	30
H(15B)	2331	11145	5472	30
H(16)	3401	9594	6122	29
H(18)	4146	11415	5361	31
H(19)	4803	11227	4428	33
H(21A)	5487	10305	3563	61
H(21B)	4673	11267	3259	61
H(21C)	5167	9614	2830	61
H(22)	3718	4924	3906	35
H(23)	3073	5101	4834	33
H(25)	6300	3461	8072	44
H(26)	6763	3422	7053	52
H(28)	7472	5483	6218	61
H(29)	8260	8535	5932	64
H(30)	8700	11512	6698	60
H(31)	8387	11375	7771	51
H(34)	7810	11423	8765	40
H(35)	8978	9755	8623	41
H(36)	8683	5492	8810	43

H(37A)	9897	6553	8554	52
H(37B)	10147	7427	9286	52
H(38A)	7785	8143	9825	40
H(38B)	7503	10888	9784	40
H(39)	6368	9733	9154	38
H(41)	5596	10924	9987	36
H(42)	5005	10119	10931	35
H(44A)	5897	4514	12291	111
H(44B)	5235	3108	11854	111
H(44C)	5051	4543	12491	111
H(45)	6261	3980	11229	42
H(46)	6845	4809	10287	41
H(2A)	855	11950	5622	44
H(3A)	967	4135	5317	49
H(4)	-559	3743	5404	47
H(7A)	8946	12090	9515	61
H(8A)	9019	4378	9840	83
H(9)	10362	3833	9560	70

