Diastereoselectivity in Anomeric *O*-alkylation Glycosylation

Jørn Holm Naimak

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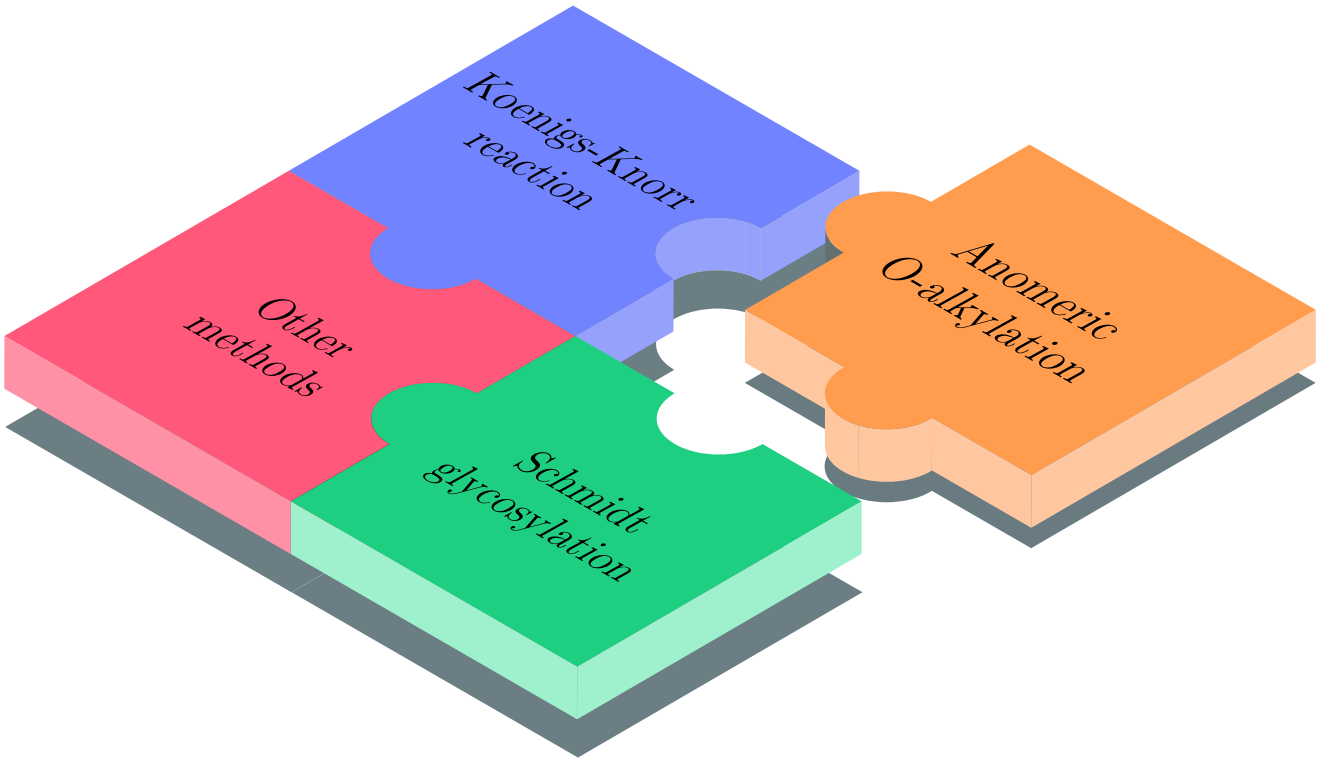

BiolinkGroup

University of Stavanger

1 Abstract

Biosynth AS used anomeric *O*-alkylation of α-haloacetophenones in their patented total synthesis of anthocyanins from 2006. There were, however, several challenges with stereoselectivity and yields when performing this glycosylation on a large scale. The goal of this Ph.D. has been to investigate anomeric *O*-alkylation. The first glycosylation method was developed in 1869, yet chemists still face challenges with glycosylation. An example of a popular glycosylation method widely utilized in chemical industries is the Schmidt glycosylation, a technique which does not necessarily provide high α-stereoselectivity and high yields in α-glycosylation. It is also not necessarily the most economically feasible glycosylation method. This work adds another piece to the puzzle of glycosylation. More insight into how solvents and bases influence strereoselectivity and yields in anomeric *O*-alkylation was uncovered in this work. Tetramethyl urea (TMU) was found to be a superior solvent for α-glycosylation compared to *N,N*-dimethylformamide (DMF). This finding could have wide applications, since DMF is the preferred solvent for many reactions that require a highly polar aprotic solvent. The advantage of TMU over DMF became less significant when larger amounts of solvent was used. For β-glycosylation, toluene was found to be a suitable alternative to dichloromethane (DCM), which also is more safe to use on large scale with strong bases. Of the bases that were investigated, Cs_2CO_3 and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were found to favor α-glycosylation, while LiH and NaH were found to favor β-glycosylation. Decreasing the temperature seemed to marginally increase β-glycosylation, but prevented the reaction from occurring altogether in less polar solvents. Raising the temperature increased α-glycosylation marginally, but unfortunately it more significantly increased the production of pentaacetate **34** as a byproduct. Halogenated acetophenones with electron donating groups (EDG) in the *para* position were shown to be more reactive in anomeric *O*-alkylation than halogenated acetophenones with electron withdrawing groups (EWG) in the *para* position. These results are in agreement with studies on nucleophilic substitution of α-haloketones, which indicates that the mechanistic pathway for producing glycosides is in competition with another mechanistic pathway for producing acyloins.

2 Acknowledgment

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Figure 1: Me and Adj. Prof. Dr. Einar Bakstad at the Houston Space Center, during our visit to Prof. Dr. K.C. Nicolaou's 70-year symposium.

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Abbreviations and acronyms

Ac	Acetyl
aq	Aqua
ATP	Adenosine triphosphate
Bn	Benzyl
BDE	Bond-dissociation energy
BSM	Benzenesulfinyl morpholine
BDNF	Brain-derived neurotrophic factor
CETP	Cholesteryl ester transfer protein
COX-2	Cyclooxygenase 2
Cyanidin 3-glc	Cyanidin 3-O-β-glucopyranoside chloride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMDO	Dimethyldioxirane (Murrayś reagent)
DMSO	Dimethyl sulfoxide
DMPU	*N*,*N*'-Dimethylpropyleneurea
DMTST	Dimethyl(methylthio)sulfonium trifluoromethanesulfonate
Delphinidin 3-glc	Delphinidin 3-O-β-glucopyranoside chloride
E	Electrophile
EDG	Electron donating group
ESI	Electrospray ionization
eNOS	Endothelial nitric oxide synthase
ETC	Electron transport chain
EWG	Electron withdrawing group
FC	Flash chromatography
GlcA	Glucuronic acid
GLUT4	Glucose transporter type 4
GSH	Glutathione
GST	Glutathione S-transferase
DFC	Dry flash chromatography
HbA1c	Hemoglobin A1C
HDL	High-density lipoprotein
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
IL-6	Interleukin 6
iNOS	Inducible nitric oxide synthase
IR	Infrared
KHMDS	Potassium bis(trimethylsilyl)amide
LDL	Low-density lipoprotein
Lit.	Literature
LRMS	Low resolution mass spectrometry
M.P.	Melting point
MPBT	*S*-(4-Methoxyphenyl)benzenethiosulfinate
MS	Molecular sieve
Malvidin 3-glc	Malvidin 3-O-β-glucopyranoside chloride

NA	Not available
NBS	*N*-Bromosuccinimide
NF-κB	Nuclear factor κ-light-chain-enhancer of activated B cells
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
NMP	*N*-Methyl-2-pyrrolidone
NO	Nitric oxide
NPG	*n*-Pentylglycoside
nNOS	Neuronal nitric oxide synthase
PE	Petroleum ether (mixture of pentanes, hexanes, and heptanes)
Pg	Protective group
Pelargonidin 3-glc	Pelargonidin 3-O-β-glucopyranoside chloride
Peonidin 3-glc	Peonidin 3-O-β-glucopyranoside chloride
Petunidin 3-glc	Petunidin 3-O-β-glucopyranoside chloride
R_f	Retardation factor
R.T.	Room temperature
ROS	Reactive oxygen species
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOD	Superoxide dismutase
TBME	*tert*-butyl-methyl ether
TFT	α,α,α-Trifluorotoluene
THF	Tetrahydrofuran
THTDPCI	Trihexyltetradecylphosphonium chloride
TMS	Trimethylsilyl
TMU	Tetramethylurea
TTBP	2,4,6-Tri-*tert*-butylpyrimidine
TLC	Thin-layer chromatography
TsOH	*p*-Toluenesulfonic acid

Contents

3 Introduction

The following work was conducted at one of the daughter companies of the Biolink Group AS, which formerly owned the company called MedPallett AS which produces the nutritional supplement Medox (Figure 5) from the exocarp of bilberries and blackcurrant. In 2016, MedPallett AS was bought by the German company Evonik Industries AG. The Biolink Group AS is currently divided into two different daughter companies: Polyphenols AS which extract polyphenols from natural compounds, and Biosynth AS which is working on the synthesis of natural compounds (Figure 2).

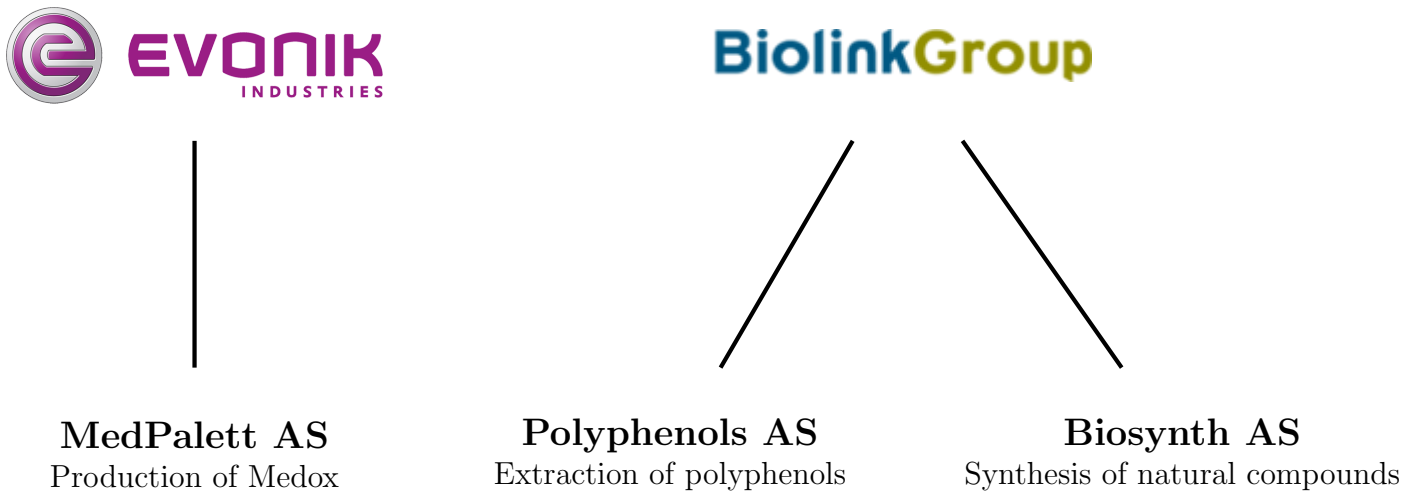


Figure 2: Organization of the Biolink Group AS (MedPallett AS was recently bought by the German company Evonik Industries AG).

3.1 Objectives

In 2006 Biosynth AS filed a patent for a method to synthesize anthocyanins[1]. In their patented total synthesis of anthocyanins they use anomeric *O*-alkylation of α-haloacetophenones. There were, however, several challenges with the stereoselectivity and yields of this reaction when performing it on a larger industrial scale. The goal of this Ph.D. project has been to investigate anomeric *O*-alkylation, and assess its performance and utility compared to other glycosylation methods. Since the first patent, Biosynth AS has been working with the Swiss corporation Solvias to upscale anthocyanins production. This work has been proceeding simultaneously with the Ph.D., and Biosynth AS is now in the process of publishing a new patent.

3.2 Anthocyanins

The word anthocyanin comes from two Greek phrases, "anthos" which means flower, and "kyáneos" which means blue. They belong to a group of molecules called flavonoids, which are a type of secondary metabolites used as as pigments in plants[2] and fungi[3]. There are six major subclasses of flavonoids: anthocyanins, flavan-3-ols, flavonols, flavones, flavanones, and isoflavones. Flavonoids are found in cacao beans, vegetables, fruit, tea, and red wine. Berries, in particular, tend to be rich in anthocyanins. There has been a great deal of attention to the health benefits of the flavonoids contained in fresh fruit and vegetables. Anthocyanins are water-soluble molecules that can appear with different colors depending on the pH (Scheme 1). Anthocyanins are mainly found as glycosides in nature. This might be to make them

more stable and increase their solubility, which also makes them more biologically available. Further, the aglycones can be produced synthetically and are called anthocyanidins.

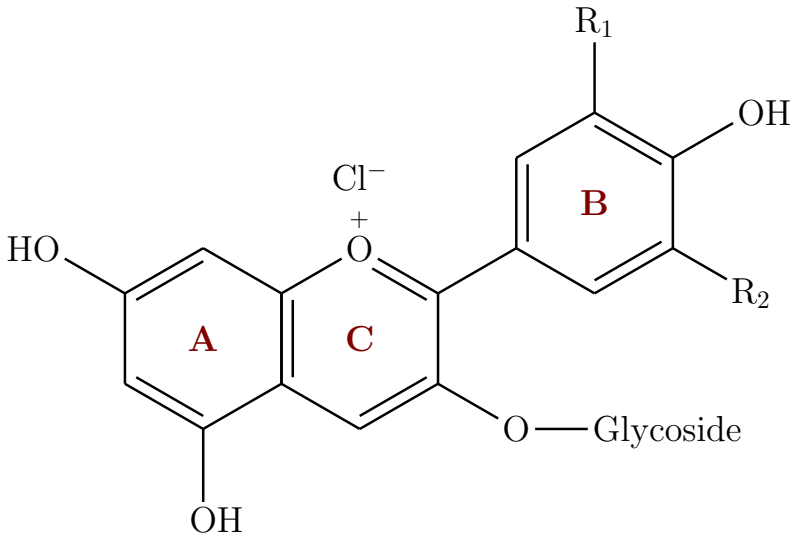
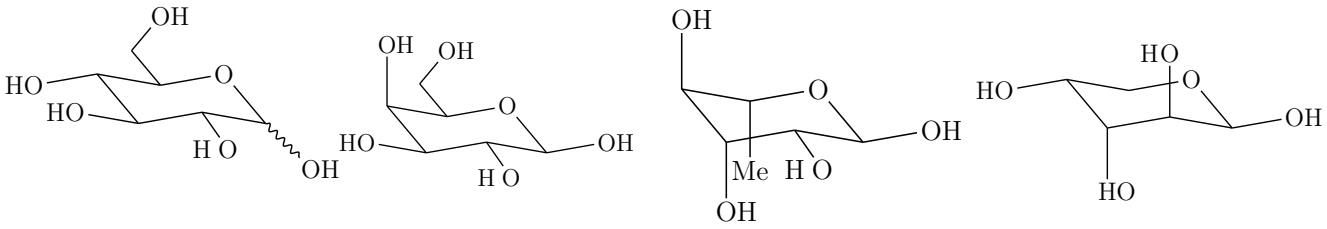


Figure 3: General structure of an anthocyanin.

Over 700 anthocyanins have been discovered in nature, but only 6 anthocyanidin motifs are present in more than 90% of all of them: cyanidin (50%), delphinidin (12%), pelargonidin (12%), malvidin (12%), peonidin (7%) and petunidin (7%)[4]. The only difference between these anthocyanidins is in the substituents (OH or OMe) linked to the phenolic B-ring (Figure 3). The substituents affects both color and antioxidant power of anthocyanins. The glycosides in anthocyanins can be mono-, di- or trisaccharides. Of these, monoglycosides are most commonly found in fruits and berries, and constitute more than 70% of the glycosides coupled to anthocyanins. The most common monoglycosides found in anthocyanidins are glucose, galactose, rhamnose, and arabinose (Figure 4).



Glucose **1** Galactose **2** Rhamnose **3** Arabinose **4**

Figure 4: The most common monoglycosides naturally occurring in anthocyanidins.[5]

Anthocyanins typically absorb light at $\lambda = 520$ and $\lambda = 280$ nm[6]. The colors of anthocyanins vary somewhat according to the substituents at the B-ring (Table 2). Hydroxyl groups and methoxy groups on the B-ring shift the absorption spectrum of anthocyanins towards a deep blue color.

Table 2: Common types of naturally occurring anthocyanins and their colors.

Name of anthocyanin	Abbreviation	R_1	R_2	Natural color
Pelargonidin 3-O-β-glucoside	Pelargonidin 3-glc (**5**)	H	H	Orange red
Peonidin 3-O-β-glucoside	Peonidin 3-glc (**6**)	MeO	H	Rosy red
Cyanidin 3-O-β-glucoside	Cyanidin 3-glc (**7**)	OH	H	Purple red
Malvidin 3-O-β-glucoside	Malvidin 3-glc (**8**)	MeO	MeO	Magenta
Petunidin 3-O-β-glucoside	Petunidin 3-glc (**9**)	MeO	OH	Purple
Delphinidin 3-O-β-glucoside	Delphinidin 3-glc (**10**)	OH	OH	Bluish purple

Several plants that contain anthocyanins have traditionally been used as herbal remedies[4]. In Scandinavian countries, bilberries have a long history of being used to promote health. Bilberries contain predominantly cyanidin 3-glc (**7**) and delphinidin (**10**), smaller amounts of malvidin 3-glc (**8**), petunidin 3-glc (**9**) and peonidin 3-glc (**6**)[7] (Figure 5).

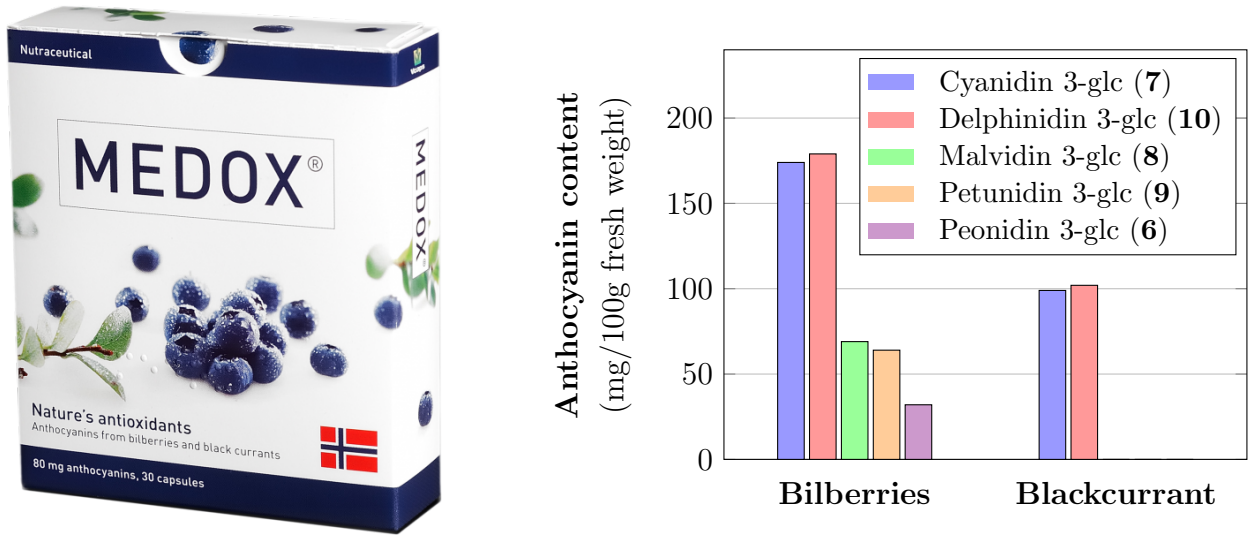
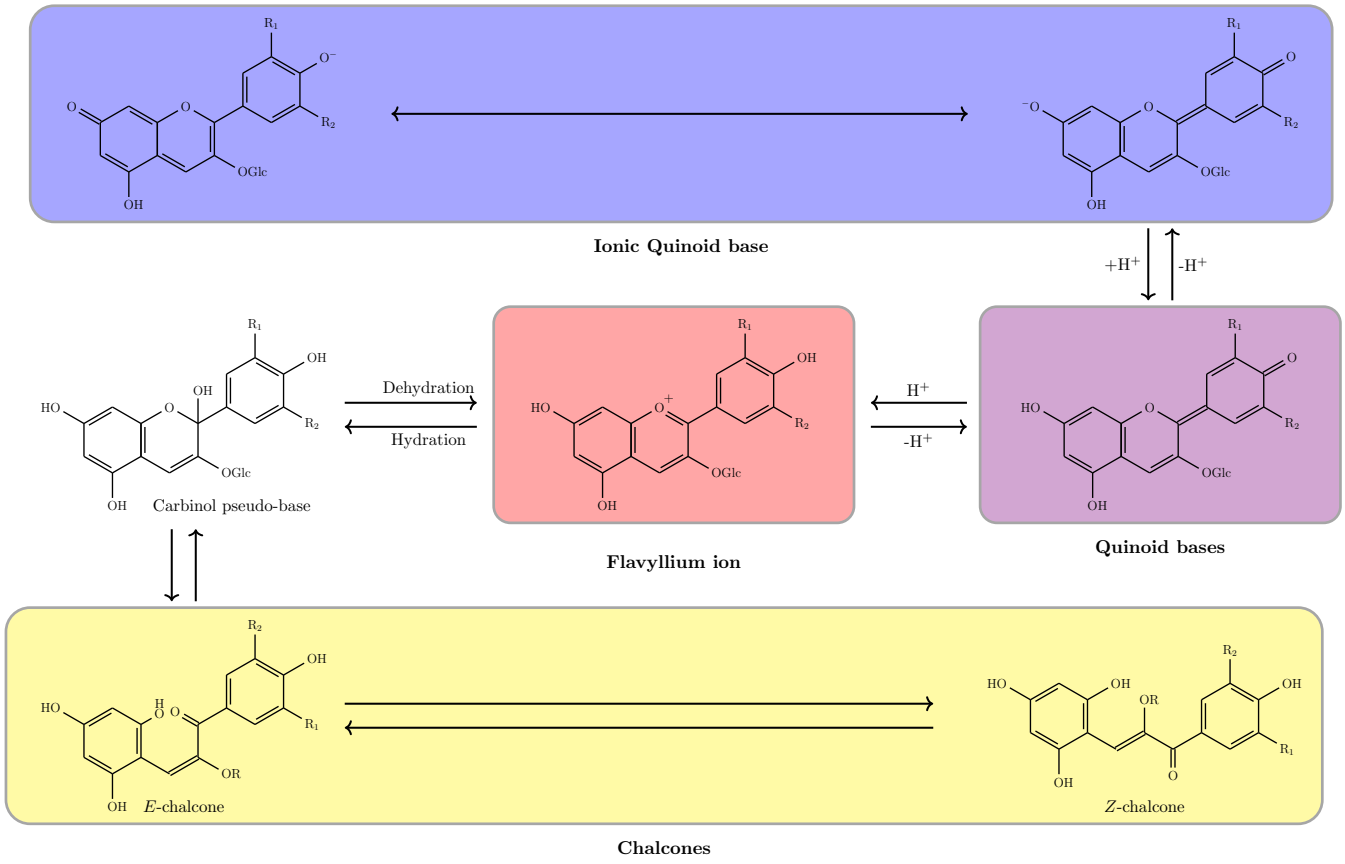


Figure 5: The Medox nutritional supplement, and the anthocyanin content in bilberries and blackcurrant[7], which are the two main ingredients in Medox.

In plants, anthocyanins are found together with copigments (mostly metal cations or other flavonoids), that stabilize them and protect them against degradation[8],. The stability of anthocyanins in purple potato peel in a solution was found to be increased by citric acid monohydrate and glucose, while ascorbic acid decreased the stability[9]. Copigments also affect the colors of anthocyanins, and the huge color variety found in the plant kingdom can partially be attributed to different anthocyanins with different copigments. The copigments found in the anthocyanins in wines may account for roughly 30-50% of their color[10].

3.3 pH related equilibrium forms of anthocyanins

In solution, anthocyanin molecules are present in an equilibrium between the colored cationic form and the colorless pseudo base. This equilibrium is directly influenced by pH, which is essential for the color of anthocyanins. There are several different pH related equilibrium forms of anthocyanins that have different colors[11]. The flavylium ion has a red color and is the most stable equilibrium form. A significant amount of this form is present at a pH of less than 3. If the pH is increased above 3, the flavylium ion can go either the kinetically favored pathway towards chalcone, or the thermodynamically favored pathway towards quinoidal bases. In the kinetically favored pathway, the flavylium ion is hydrated to produce a colorless carbinol base which can undergo ring-opening to produce yellow chalcone. In the thermodynamically favored pathway, a hydroxyl group on the A-ring or B-ring is deprotonated to produce a blue-colored quinoidal base. If the pH is sufficiently high, more than one hydroxyl group can be deprotonated simultaneously, which shifts the color towards an even deeper blue. Because the color of anthocyanins is pH dependent, they can act as pH indicators. Anthocyanins are stable at low pH and low temperatures, but become less stable when exposed to heat and bases.



Scheme 1: Molecular structures of anthocyanins at different pH[11].

3.4 Possible health benefits of anthocyanins

Adenosine triphosphate (ATP) is generated in a process known as oxidative phosphorylation, which entails the transportation of protons across the inner mitochondrial membrane through the electron transfer chain (ETC). Under ordinary conditions, oxygen is reduced through a collection of proteins in a series of redox reactions (Figure 7), to produce carbon dioxide and water; nonetheless, roughly 0.1-2% of electrons passing through the ETC is prematurely and incompletely reduced[12] to produce the superoxide radical ($O_2^{\cdot -}$),

which gives rise to many other reactive oxygen species. Several disorders are related to the proliferation of reactive oxygen species (Figure 6)[13].

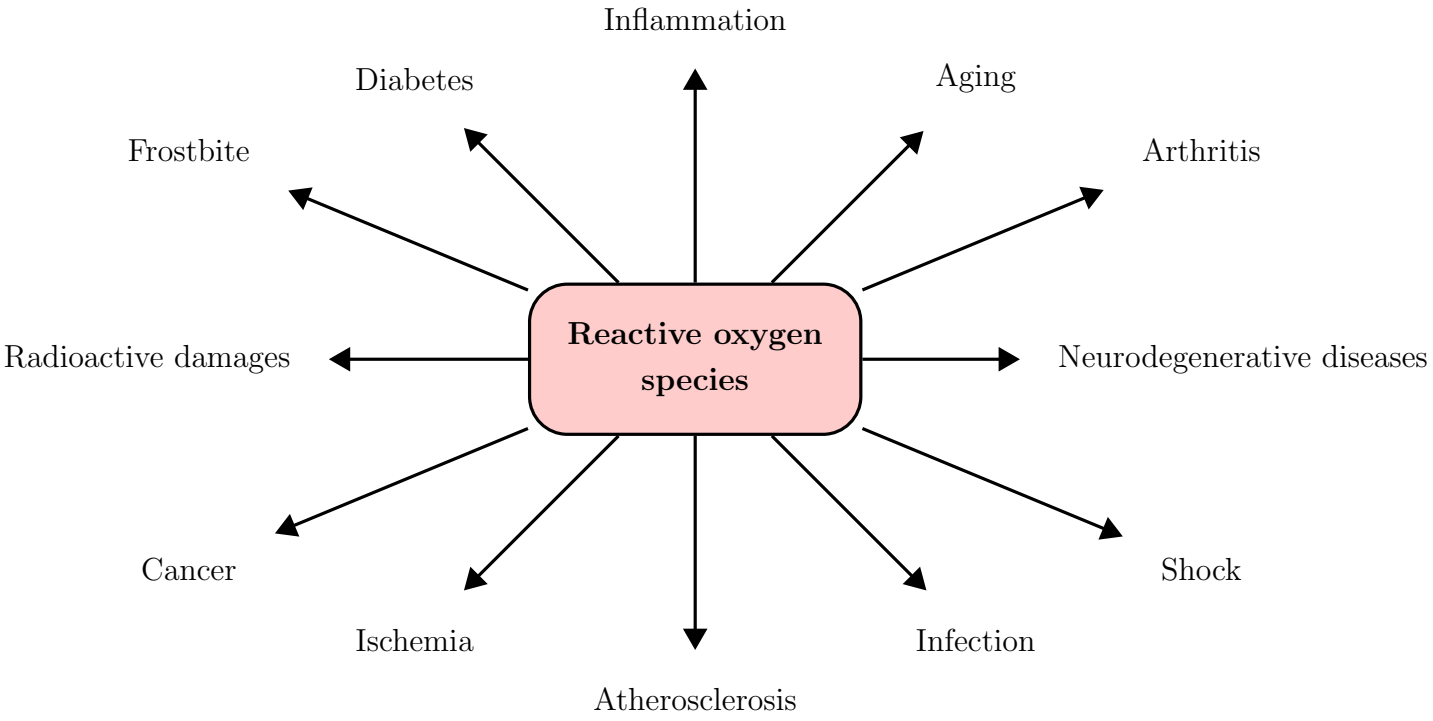


Figure 6: Reactive oxygen species impact many types of biological tissue, and are a main contributor to many diseases[14].

Anthocyanins are potent antioxidants[15,16,17], and it was first thought that the health benefits associated with anthocyanins came from their ability to scavenge oxygen radicals. Anthocyanins might also chelate copper and iron ions, which contribute to the production of oxygen radicals. However, more recent research has shown that anthocyanins are poorly absorbed into the bloodstream and that they are quickly metabolized into metabolites with a lower assumed antioxidant potential[18]. The intracellular concentration of anthocyanins is likely 100 to 1000 times lower than other antioxidants, such as glutathione, uric acid, and vitamin C[19]. Researchers at the Linus Pauling Institute have claimed that the main antioxidant effect from anthocyanins comes from increased concentrations of uric acid, rather than from the anthocyanins themselves.[20]. Anthocyanins have, however, also been shown to interact with many enzymes in the human body. These effects can be considerable, even if only trace amounts of anthocyanins are available, due to biochemical cascades that amplify the signal. Further, anthocyanin metabolites might also interact with enzymes[21].

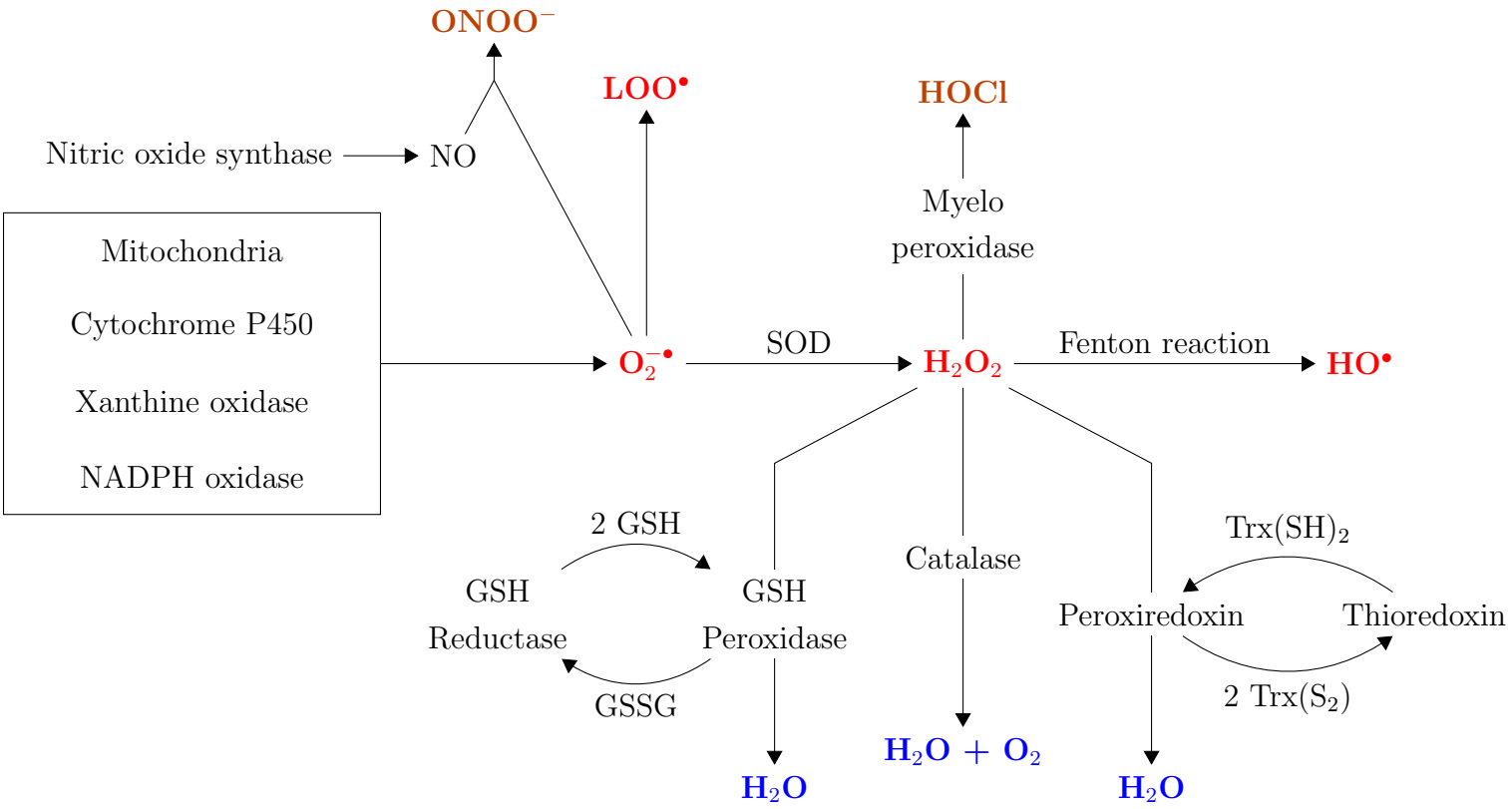


Figure 7: Different pathways with enzymes involved in the generation and neutralization of reactive oxygen species[22].

Superoxide might inactivate enzymes or commence lipid peroxidation in its protonated form (hydroperoxyl HO·). Superoxide dismutases (SODs) are a class of enzymes which catalyze the dismutation of superoxide into oxygen and hydrogen peroxide[13]. Catalases that are concentrated in peroxisomes situated alongside mitochondria catalyze the decomposition of hydrogen peroxide into water and oxygen[23]. Peroxiredoxins additionally hamper hydrogen peroxide within the mitochondria, cytosol, and the nucleus[24]. They reduce hydrogen peroxide by shifting the energy of the reactive peroxides into a sulfur-containing peptide known as glutathione, where sulfur functions as an electron acceptor.

Some of the enzymes involved in the neutralization of reactive oxygen species have been found to be upregulated by anthocyanins. SOD1, SOD2, GSH reductase, and thioredoxin were upregulated in mice fed with blueberry extracts[25]. Mice fed with blackberry extracts were found to have increased glutathione levels, and significantly upregulated glutathione peroxidase and catalase[26]. Rats given anthocyanin-rich extract from black rice showed a better profile of the antioxidant system with normal glutathione peroxidase (GSH-Px), SOD, and glutathione S-transferase (GST) activities[27]. A study on 18 male probands daily consumed 700 mL juice, and 9 consumed control juice, in a 4-week intervention, followed by a 3-week wash-out. An increase of glutathione ($p<0.05$) and reduced glutathione ($p<5\times10^{-4}$) was observed among the participants in the study[28].

The effect of anthocyanins on inflammation

Inflammation is a protective response to harmful stimuli, which helps to dispose of damaged cells and prevent the proliferation of pathogens[29]. Chronic inflammation can, however, lead to numerous diseases (Figure 8)[30].

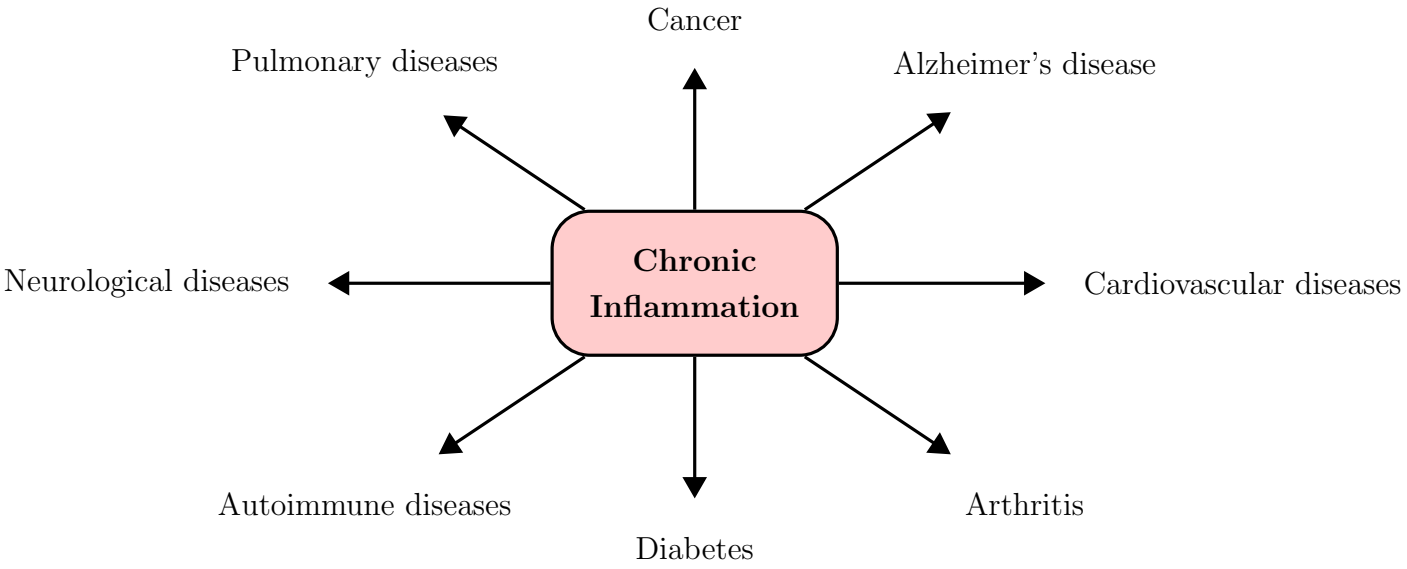


Figure 8: Chronic inflammation is related to several disorders[31].

Nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) is an enzyme involved in the inflammatory response[32]. Further, anthocyanins seem to downregulate NF-κB, and thereby reduce chronic inflammation[33]. Cyclooxygenase 2 (COX-2) is a protein involved in the synthesis of prostaglandins which increases pain and inflammation, and is presumably downregulated by anthocyanins. This might be beneficial against a whole range of diseases since chronic inflammation seems to be involved in worsening the condition of patients with cancer, cardiovascular diseases, and a whole range of other diseases. Neuronal nitric oxide synthase (nNOS) is an enzyme that releases nitric oxide into the nervous tissue, while inducible nitric oxide synthase (iNOS) is an enzyme that releases nitric oxide into the immune system. Excess nitric oxide can cause inflammation. Anthocyanins seem to downregulate nNOS and iNOS[34], and might thereby decrease inflammation in the nervous system and the immune system (Figure 9).

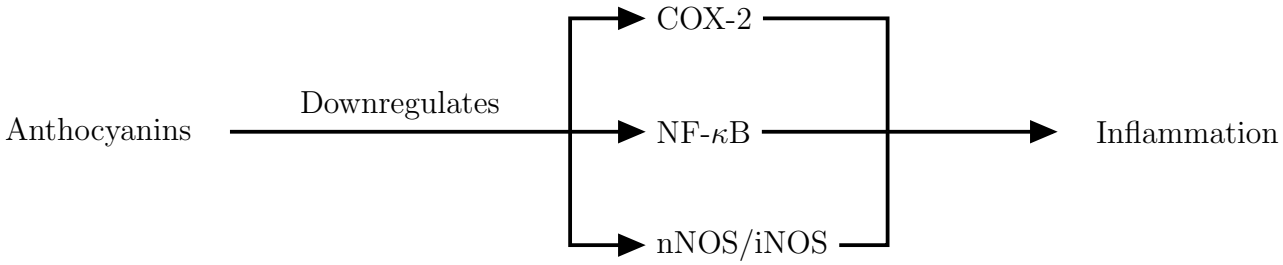


Figure 9: Enzymes related to inflammation that are downregulated by anthocyanins[33,34].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is believed to cause deaths by a cytokine storm, which is caused by a combination of several immune-active molecules[35]. Since anthocyanins downregulate several inflammatory enzymes, it might be interesting to investigate if they could reduce the likelihood to die from SARS-CoV-2 and other viruses which cause an overactivation of the immune system. One of the pro-inflammatory cytokines found in a high concentration is interleukin 6 (IL-6). Anthocyanin supplementation has been found to significantly decreases blood plasma levels of IL-6[36].

The effect of anthocyanins on cardiovascular diseases

Cardiovascular diseases are the leading cause of death worldwide, in every part of the world with the exception of Africa[37], mainly affecting the elderly[38]. Since chronic inflammation of arteries is related to cardiovascular diseases[39], the reduced inflammation caused by anthocyanins is beneficial against cardiovascular diseases. Endothelial nitric oxide synthase (eNOS) is an enzyme that releases nitric oxide into the bloodstream from the amino acid arginine[40]. Even though nitric oxide is toxic, recent research has found that nitric oxide and carbon monoxide are used as hormones/neurotransmitters[41]. Nitric oxide released into the bloodstream causes to vasodilation[42], and anthocyanins have been found to upregulate eNOS[43]. Increased vasodilation from anthocyanins might have a preventive effect against cardiovascular diseases. High-density lipoprotein (HDL) and low-density lipoprotein (LDL) are transport proteins, which transport cholesterol and a variety of other fat molecules in the bloodstream and around cells. LDL is commonly labeled as "bad cholesterol", as it increases the risk for cardiovascular diseases. HDL, on the other hand, is termed as the "good cholesterol", as it is associated with a lower risk for cardiovascular diseases. Cholesteryl ester transfer protein (CETP) is an enzyme that transports cholesterol and a variety of other fat molecules between LDL and HDL. Anthocyanins inhibit CETP which then has been shown to increase the concentration of HDL and decreases the concentration of LDL[44]. An extract of anthocyanins from bilberries and black currant has been found to have a positive influence on the lipid profile for individuals with an increased risk of developing cardiovascular diseases[45].

The effect of anthocyanins on diabetes

Diabetes mellitus type 2 is a chronic metabolic disease which is distinguished by elevated blood glucose, low blood concentration of insulin, along with comparative deficiency of insulin receptors[46]. Long-term complications include elevated blood glucose, cardiovascular diseases, strokes, diabetic retinopathy that may cause blindness, kidney failure, and inadequate blood circulation from the limbs that might result in amputations[47]. The number of individuals that have been diagnosed with type 2 diabetes has grown from 30 million in 1985 to 392 million in 2015[48]. Type 2 diabetes exerts a massive financial burden on the world economy[49]. It has been demonstrated that anthocyanins, and other flavonoids interfere with the digestion and absorption of carbohydrates. A study that compared how anthocyanins, flavones, flavonols, flavanones, and flavan-3-ols affect the risk of diabetes type 2, found a significantly reduced risk of diabetes type 2 with a high intake of anthocyanins, while no significant reduced risk for any of the other flavonoids and diabetes type 2[50]. A six-week randomized trial on people with diabetes demonstrated that daily supplementation with extracts from Cornelian cherry which contained 600 mg of anthocyanins reduced serum amounts of hemoglobin A1C (HbA1c) and triglycerides considerably and improved serum insulin concentrations[51]. Anthocyanins have also been found to upregulate the expression of glucose transporter type 4 (GLUT4)[52], which facilitates the diffusion of glucose into fat and muscular tissue[53].

Metabolic syndrome

Metabolic syndrome is a cluster of three of the five health problems: weight problems, high blood pressure, elevated blood sugar, higher serum triglycerides, and significantly lowered serum HDL[54]. Metabolic syndrome is linked with the possibility of establishing cardiovascular disease and to develop type 2 diabetes. In the U.S. roughly 1/4 of the adult population has metabolic syndrome, and the prevalence grows with age, and minorities are currently being overrepresented[55]. The syndrome is presumed to be caused by an inherent disorder of energy usage and storage, but this is currently an active area of research. Several studies show that anthocyanin-rich food, and anthocyanin extracts, might help against clinical manifestations of metabolic syndrome[56], however, no mechanism of action has been identified. The low bioavailability of

anthocyanins suggests that the effect might be facilitated by anthocyanin metabolites.

The effect of anthocyanins on cancer

Cancer is a set of illnesses that involve abnormal development of cells which enable them to grow uncontrollably and propagate into other regions of the body and disrupt bodily functions. More than 100 different kinds of cancers impact human beings[57]. In addition to the antioxidant and anti-inflammatory effects of anthocyanins which may aid against cancer, *in vitro* studies have discovered that anthocyanins downregulate cancer cell proliferation, with minimal disruption of the proliferation of normal cells[58]. Anthocyanins have also been found to downregulate cancer cell invasiveness and to induce cancer cell apoptosis[58]. In order to induce these effects the concentration of anthocyanins needed to be between 10^{-6} and 10^{-4} M. The blood concentration of anthocyanins after consumption of berries extract seems to be much lower (10^{-7} and 10^{-8}), and *in vivo* evidence against most types of cancer is lacking. *In vivo* studies have, however, shown that anthocyanins are effective against gastrointestinal tract cancer, and skin cancer when smeared on the skin. In order to make anthocyanins more effective against other forms of cancer, it might be necessary to find a way to increase the uptake of anthocyanins. The uptake of anthocyanins seems to depend upon which sugar it is attached to. Glucose is, for example, effectively metabolized by bacteria in the gut, while other sugars might not be metabolized at all. In an absorption study where anthocyanins were injected into the stomach of rats[59], anthocyanins attached to arabinose were found to be absorbed better than anthocyanins attached to glucose and galactose. Anthocyanins are, however, most stable in acidic solutions (like in the stomach). Copigments help to protect them from degradation in the more basic environment of the mouth and esophagus. So far, there is however not much proof that diets rich in anthocyanins protect against cancers. Further investigations and larger cohort studies are necessary to determine if there is an association and to ascertain whether supplementation with anthocyanins can be beneficial in cancer prevention.

Brain function

Even though some flavonoids and flavonoid-rich foods can improve cognitive functioning it is not yet clear if their ingestion could diminish the risk of dementia and cognitive impairments in humans. Flavonoids are believed to:

- Promote neurogenesis, synaptic development, and neuron survival from the learning and memory related to the hippocampus by stimulating the production of neurotrophins such as brain-derived neurotrophic factor (BDNF)[60].
- Protect hippocampal cells and striatal dopaminergic cells in cytotoxic molecules (pro-inflammatory mediators and reactive oxygen species (ROS)) published by abnormally activated microglia and hypertrophic astrocytes at bronchial ailments[61].
- Decrease neuroinflammation by inhibiting the creation of pro-inflammatory cytokines, lipid mediators, along with reactive oxygen species by astrocytes and microglial cells[33,34].
- Stimulate the creation of nitric oxide (NO)[43], which enhances adrenal function, raises cerebral blood circulation, and shields artery walls from the buildup of atherosclerotic plaques.

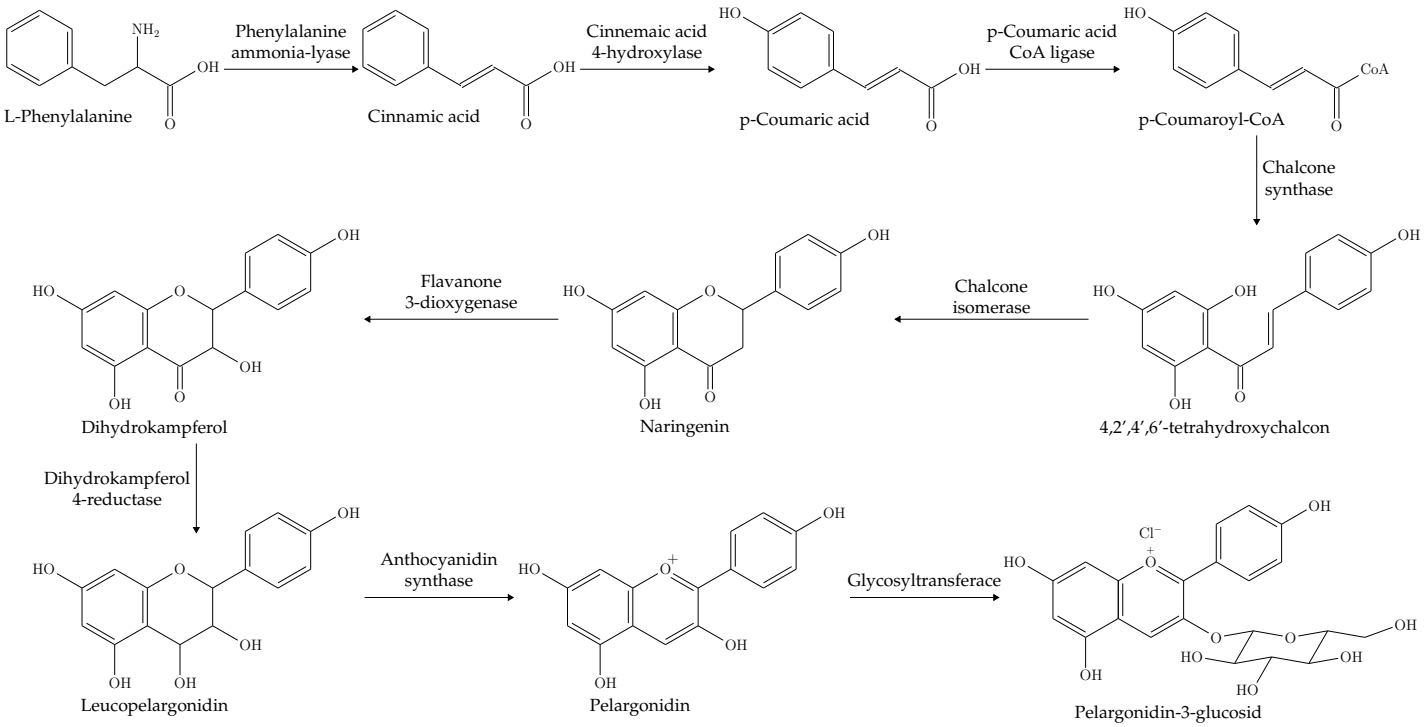
Possible effect of anthocyanins on metal absorption

As with many phenolic compounds, anthocyanins might function as chelators that decrease metal salt absorption. It has, for example, been shown that coffee decreases iron salt absorption if consumed together

with iron salt-rich food[62]. So for people with a low concentration of iron cations, zinc cations or other metal cations essential for human health, it is advisable to limit the consumption of anthocyanins, and other phenolic compounds together with metal salts. In pathological conditions of iron or copper surplus, it is not understood whether flavonoids or their metabolites function as effective metallic chelators *in vivo*. Metallic ions, for instance, iron along with copper, may catalyze the creation of free radicals. The ability of flavonoids to chelate metal ions appears to subscribe to their antioxidant exercise *in vitro*.

Biosynthesis of anthocyanins

The synthesis of flavonoids starts with the Shikimate pathway which synthesizes aromatic amino acids. The precursors for the forming of most of the anthocyanins is the aromatic amino acid L-phenylalanine[63]. The enzyme phenylalanine ammonia-lyase converts it into cinnamic acid, which is then converted into *p*-coumaric acid by the enzyme cinnamic acid 4-hydroxylase. Coenzyme A is then attached to *p*-coumaric acid by the enzyme *p*-Coumaric acid CoA ligase. The product *p*-coumaroyl-CoA is subsequently converted into 4,2',4','6-tetrahydroxychalcon by the enzyme chalcone synthase. The chalcone is then isomerized into naringenin, and a hydroxy group is attached by flavanone 3-dioxigenase. Dihydrokaempferol can now be made into dihydroquercetin, which gives rise to cyanidin and delphinidin, or it can be reduced into leucopelargonidin, which gives rise to pelargonidin. The last step attaches the sugar to the anthocyanidin (Scheme 2).



Scheme 2: Proposed biosynthesis of pelargonidin 3-glc (**5**)[63].

Chemical total synthesis of anthocyanins

Sir Robert Robinson was one of the 19th century's foremost contributors to the development of organic chemistry. His work with natural product synthesis led to him being awarded the Nobel Prize in chemistry in 1947[64]. He was also the first to synthesize anthocyanins. He synthesized several anthocyanidins (aglycons) from 1922 to 1928, and several glycosylated anthocyanidins from 1928 to 1934 (Figure 10).

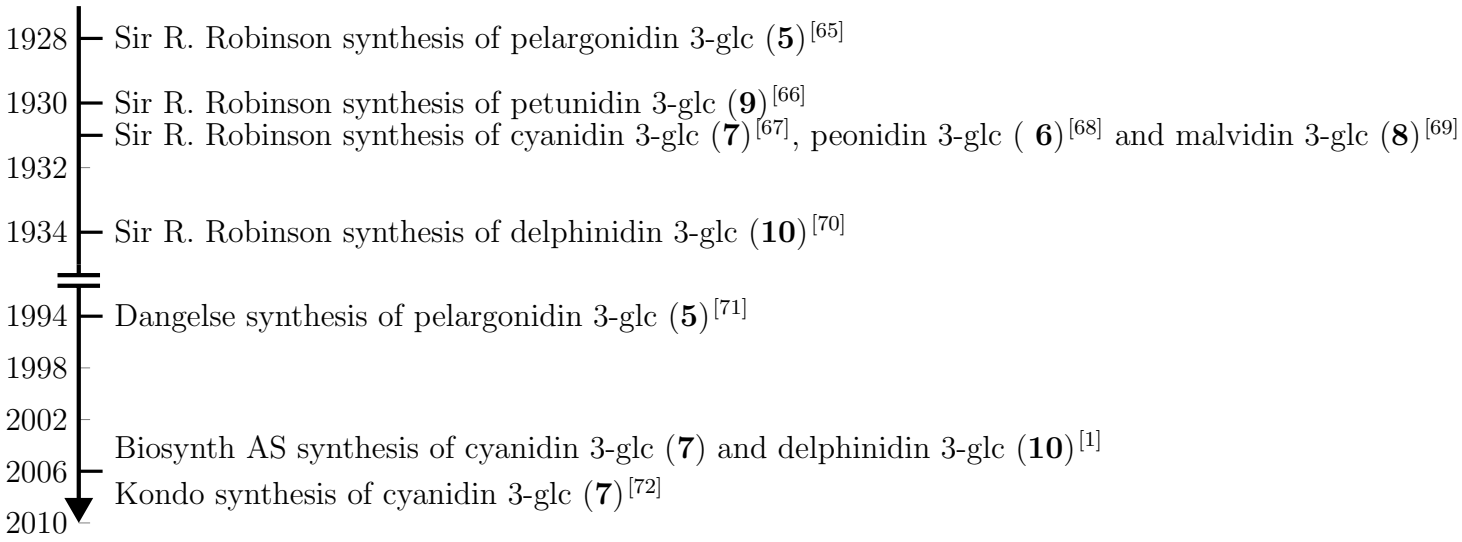
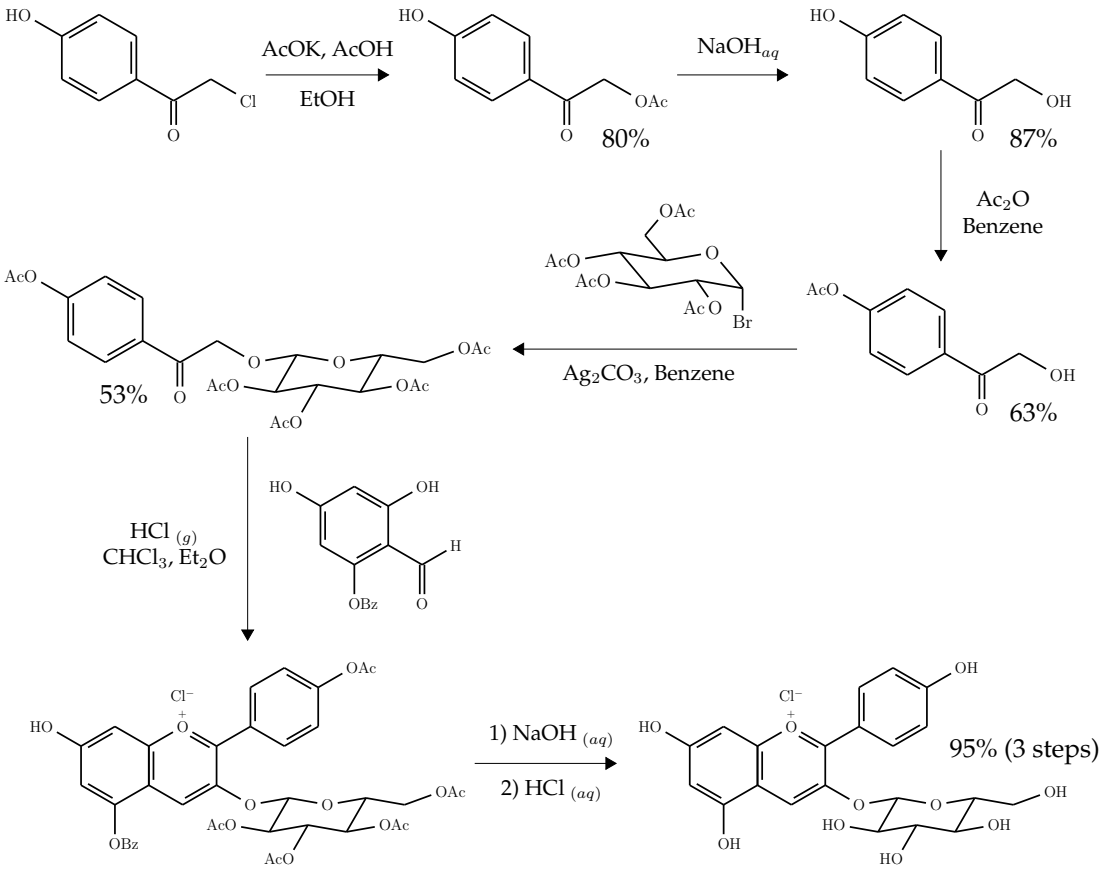


Figure 10: Timeline for total syntheses of anthocyanins

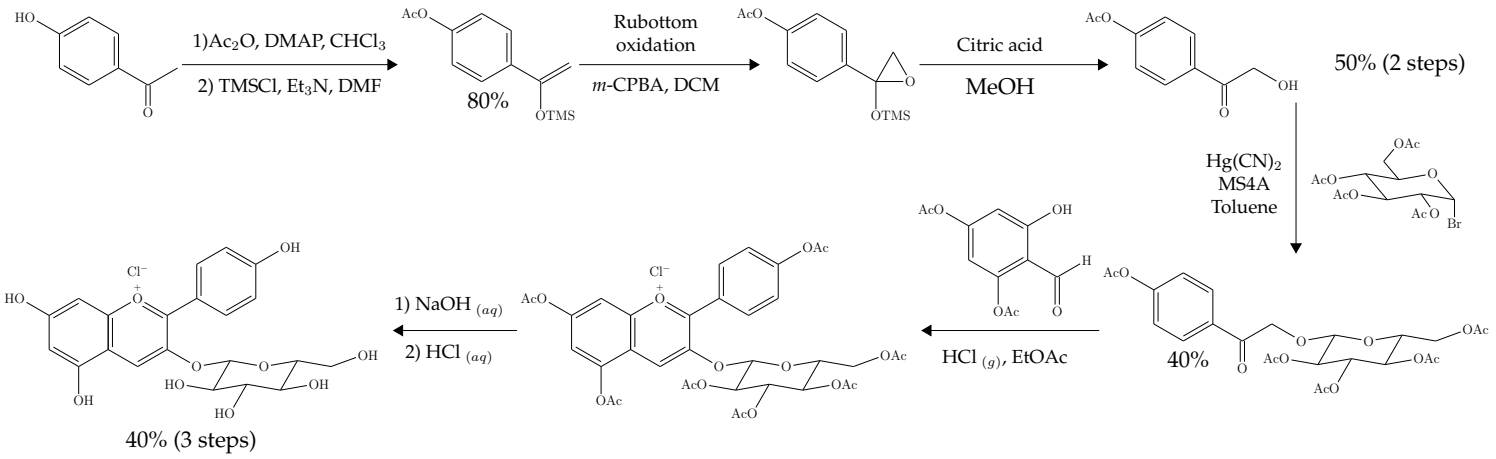
In Sir Robert Robinson's total synthesis of pelargonidin 3-glc (**5**) he used two steps to produce the acyloin from 4'-hydroxy-2-chloroacetophenone. He then protected the aromatic hydroxy group with Ac_2O, and glycosylated the acyloin in a standard Koenigs-Knorr reaction with silver carbonate in benzene with a yield of 53%, and then used an acid-mediated aldol condensation between the phenolic aldehyde and the glycosylated acetophenone to achieve a total yield of 22% his total synthesis of pelargonidin **5** (Scheme 3).



Scheme 3: Total synthesis of pelargonidin 3-glc (**5**) by Sir Robert Robinson in 1928[65].

Dangeles' synthesis of anthocyanins

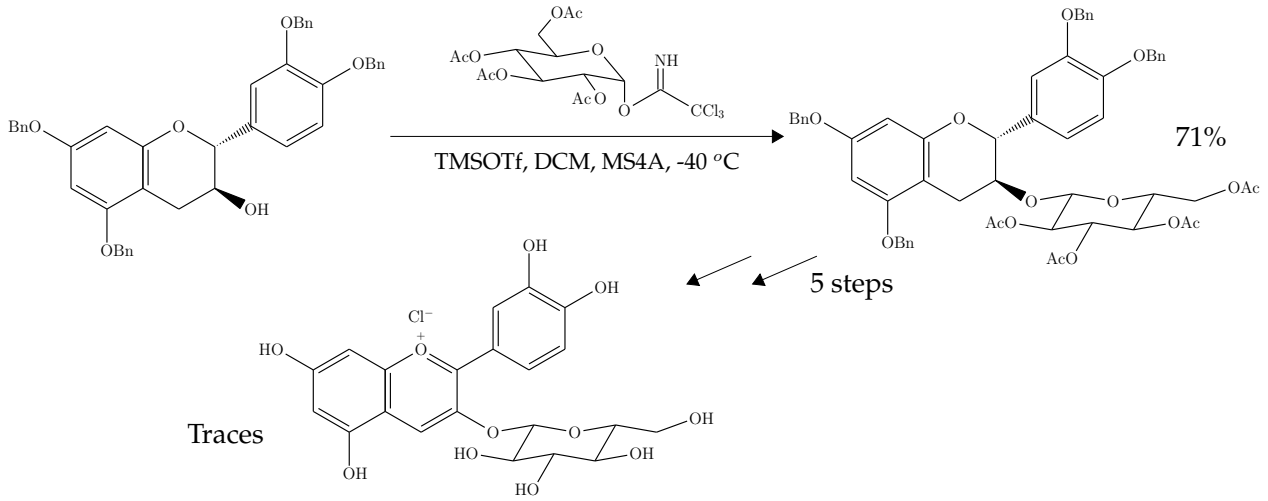
The second synthesis of anthocyanins was accomplished by Dangeles *et al.* in 1994[71]. Dangeles made the acetylated acyloin in 3 steps from 4-hydroxyacetophenone. He then used a modified version of the Koenigs-Knorr reaction with $Hg(CN)_2$ in toluene where he achieved a yield of 40%, and then used an acid-mediated aldol condensation between the acetyl protected phenolic aldehyde and the glycosylated acetophenone to achieve a total yield of 16% in his synthesis of pelargonidin 3-glc (**5**) (Scheme 4).



Scheme 4: Total synthesis of pelargonidin 3-glc (**5**) by Dangeles[71].

Kondo's synthesis of anthocyanins

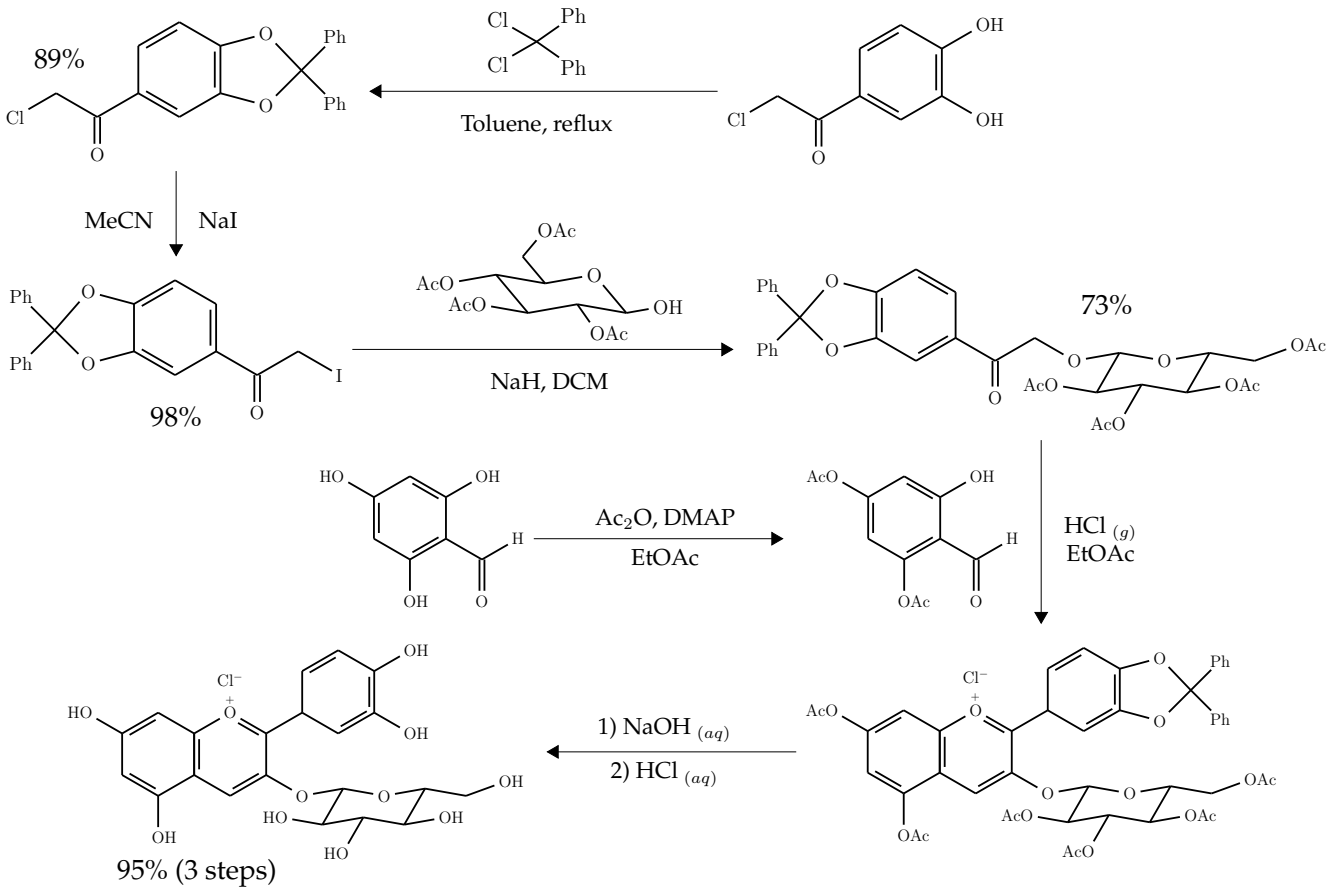
Kondo published a synthesis of anthocyanins in 2006, where he started with epicatechin[72]. He was able to glycosylate epicatechin with the Schmidt glycosylation, where he reported an impressive yield of 71%. After this he needed 5 steps from epicatechin-3-glc to cyanidin 3-glc (**7**), and only observed traces of it after these steps (Scheme 5). His method is however interesting since it follows a very different pathway compared to the other published methods to synthesize anthocyanins.



Scheme 5: Total synthesis of cyanidin 3-glc (**7**) by Kondo[72].

Biosynth's total synthesis of anthocyanins

In 2003, Bakstad's research group started with the project of synthesizing anthocyanins. Their main objective was to synthesize cyanidin 3-glc (**7**), although they also worked on the synthesis of delphinidin 3-glc (**10**). After getting poor yields from Koenigs-Knorr and Schmidt glycosylation, they instead settled on using β-tetraacetate **104** as a nucleophile (Scheme 6). With this approach, they achieved a yield of 73% in glycosylation and a total yield of 60% in the total synthesis of cyanidin 3-glc (**7**). Biosynth AS filed for a patent for the total synthesis of cyanidin 3-glc (**7**) and delphinidin 3-glc (**10**) in 2006[1]. In 2008 Ida T. Urdal (M.Sc.) synthesized peonidin 3-glc **6** and peonidin 3-GlcA[73]. In 2013 a total synthesis of cyanidin 4'-O-methyl-3-glc was published in tetrahedron letters, where they used the same approach as Biosynth AS had published in their patent several years earlier. There was however no reference to the patent[74]. After Biosynth AS had contacted the authors of the article regarding this, they published a corrigendum in 2014[75].



Scheme 6: Total synthesis of cyanidin 3-glc (**7**) developed by Bakstad's research group from 2003 to 2006.

In order to increase the overall yield and economic feasibility of the anthocyanin synthesis developed by Bakstad's research group, the focus of several master projects and this Ph.D. project have been to investigate the most challenging step in this total synthesis of anthocyanins, which has been the β-glycosylation of α-haloacetophenones.

4 Medicinal glycosides

The synthesis of anthocyanins was the primary reason for investigating anomeric *O*-alkylation. However, there is nothing inherent with anomeric *O*-alkylation, which prevents it from being used to prepare other glycosides. It has also been shown to be capable of producing α-glycosides by using different solvents and different bases (Scheme 72), and to be able to glycosylate α-haloketones, α-haloesters, and some other strong electrophiles (Table 6 and Table 7). To give the reader a broader context of what anomeric *O*-alkylation could be used for, several medicinal glycosides are presented in this chapter.

4.1 Chemical glycodiversification

Glycorandomization refers to the process of using enzymes to attach various sugars to an aglycon in order to get a vast diversity of glycosides[76]. If it is a medicinal aglycon, one of the new variants with a different sugar might work better than the previous one[77]. Microorganisms might also develop immunity against a medicinal glycoside with a specific sugar. The microorganism might, however, not have immunity against the same medicinal aglycon with a different sugar[78]. There is a large variety of monosaccharides and disaccharides with known bioactivity and toxicology that can be used. Not all aglycons are necessarily suitable for enzymatic glycosylation and might be more suitable for chemical glycodiversification. With anomeric *O*-alkylation, aglycons can be glycosylated either axial and equatorial (Figure 11) to give rise to an even broader diversity of medicinal glycosides.

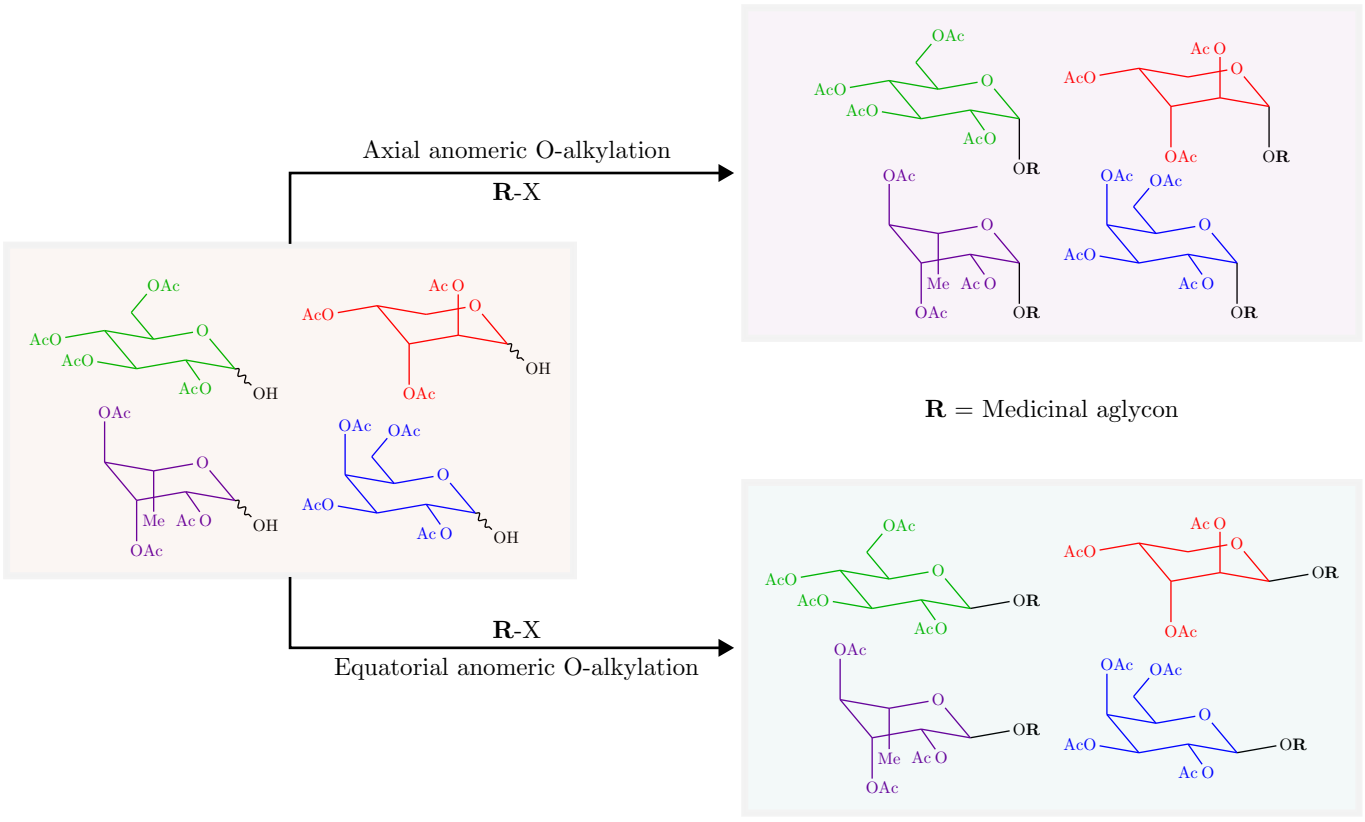


Figure 11: A few different monosaccharides glycosylated axial and equatorial with a medicinal aglycon.

Each of the medicinal glycosides that are presented in this chapter might be glycosylated with a different sugar, or with a sugar glycosylated perpendicularly at the anomeric center.

4.2 Traditional herbal glycosides

Paeoniflorin (**11**) (Figure 12) was first extracted from the flower *Paeonia lactiflora*, which has been used as a herbal medicine in Asia[79]. It has been investigated as an anti-inflammatory agent, cognitive enhancer, and neuroprotective agent[80]. The anti-inflammatory effects of paeoniflorin (**11**) may be a consequence of inhibiting the Nf-κB pathway. It has anti-androgenic properties, which makes it suitable for treatment of hypersexual disorder in men. It was synthesized by E. J. Corey and Yong-Jin Wu in 1993[81], where they used a glycosyl phosphite with a yield of 18% (more about glycosyl phosphites in chapter 5.13).

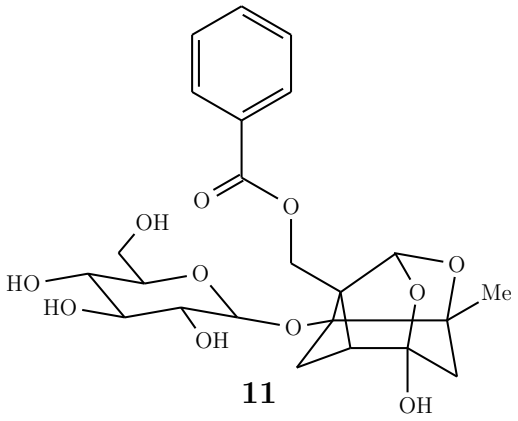


Figure 12: The molecule paeoniflorin.

4.3 Chemotherapeutic glycosides

Eleutherobin

Marine organisms have developed an exceptional repertoire of chemicals utilized for protection, communication, and reproduction. The environment has turned out to be a prolific supply of compounds with promising therapeutic action[82],. A molecule in a rare sort of coral may also wind up being a medication for individuals in the struggle against cancer. In nature, the soft coral *Eleutherobia* produces eleutherobin (**12**) (Figure 13)[83]. It is a cytotoxic molecule that induces tubulin polymerization, similarly to Paclitaxel (Taxol)[84]. K. C. Nicolaou's research group synthesized the molecule in 1997[85], where they used the Schmidt glycosylation method with a yield of 28% (more about the Schmidt glycosylation in chapter 5.9). Danishefsky's research group synthesized it in 1998[86], where they used Garegg's glycosylation with thioglycosides with a yield of 47% (more about thioglycosides in chapter 5.7).

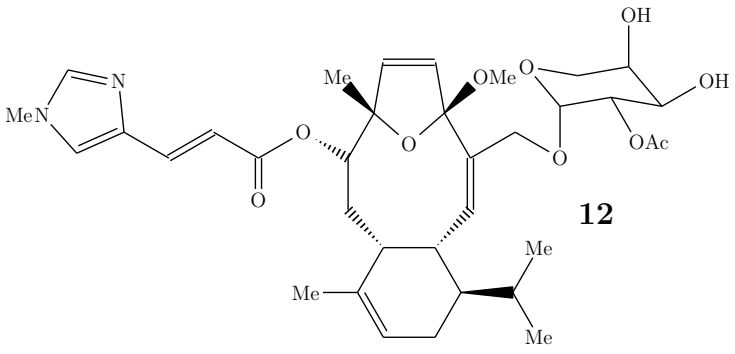


Figure 13: The molecular structure of eleutherobin (**12**).

Bleomycin

Bleomycin (**13**) (Figure 14) was first isolated from *Streptomyces verticillus*[87]. It is cytotoxic and acts by inducing DNA strand breaks[88]. It is currently used to treat a wide variety of cancer types, such as cervical cancer, ovarian cancer, testicular cancer, and lymphoma[89]. The World Health Organization regarded it as one of the most important medications in 2013[90]. A total synthesis was completed by Hecht's research group in 1982[91], where they used the Koenigs-Knorr method with 20-25% yield (more about the Koenigs-Knorr reaction in chapter 5.1). Boger's research group later synthesized it in 1994, where they used diphenyl phosphite as a leaving group on the glycoside, with 93% yield in the formation

of the disaccharide, and 54-63% yield in the attachment of the disaccharide to the aglycon.[92] (more about glycosyl phosphites in chapter 5.13).

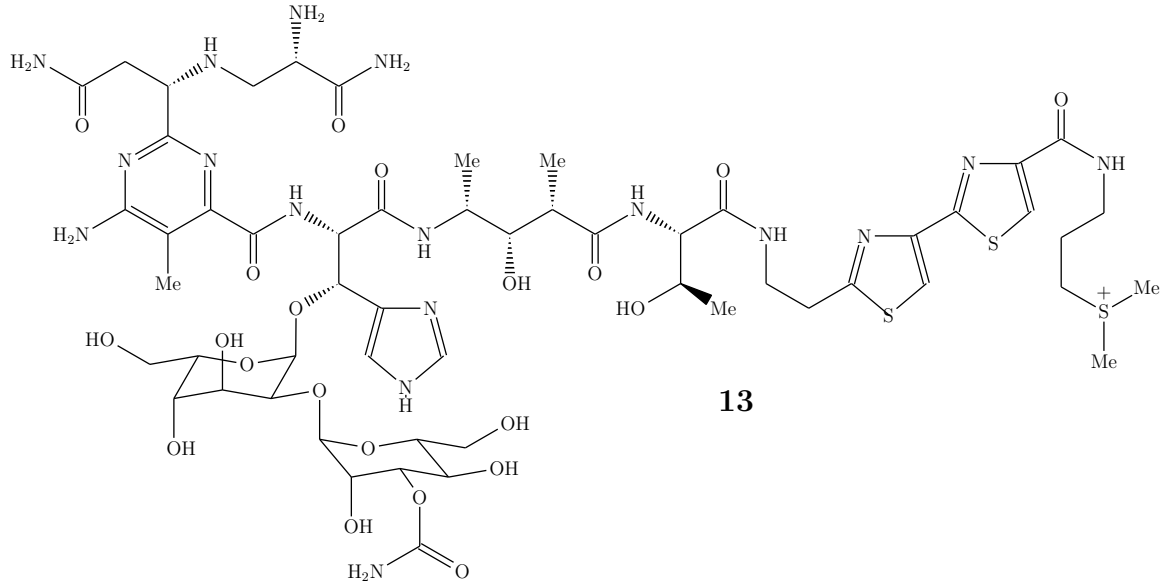
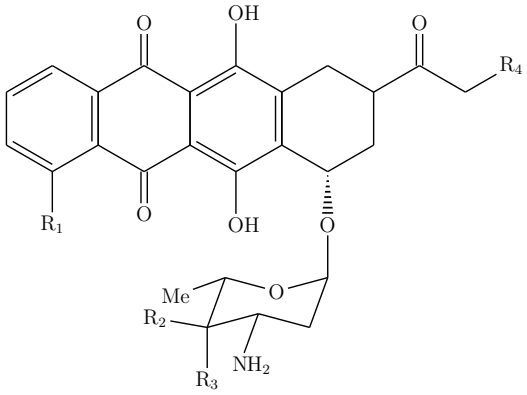


Figure 14: Molecular structure of bleomycin (**13**).

Anthracyclines

Anthracyclines (Figure 15) are a type of drugs used to treat a multitude of cancer types[93]. They work by intercalating DNA strands, which inhibit DNA/RNA synthesis, and triggers topoisomerase II to cleave it, eventually resulting in cell death[94]. Some of the most effective medicines against cancer used today are anthracyclines, and they are used to treat several different types of cancers. The first anthracycline, daunorubicin, was extracted from *Streptomyces peucetius*. The anthracycline doxorubicin (also called adriamycin) was developed shortly after[95]. Doxorubicin (**14**) has been widely used in cancer treatment of small animals. It is one of the most active chemotherapies against many types of sarcomas. It is also used to treat Hodgkin's disease and certain types of leukemia. Doxorubicin (**14**) might be used alone or together with other anticarcinogenic medicines. It is removed from the body via a system controlled by *p*-glycoprotein.



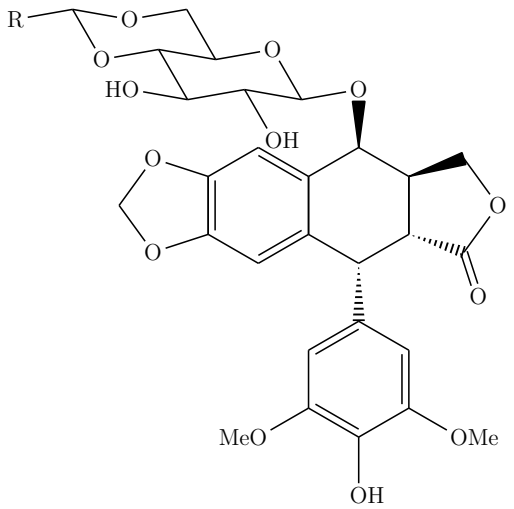
Name	R^1	R^2	R^3	R^4
Doxorubicin (**14**)	OMe	H	OH	OH
Daunorubicin (**15**)	OMe	H	OH	H
Epirubicin (**16**)	OMe	OH	H	OH
Idarubicin (**17**)	H	H	OH	H

Figure 15: Molecular structure of anthracyclines.

Epirubicin (**16**) is another anthracycline which has fewer side-effects than doxorubicin (**14**)[96]. It is marketed by Pfizer and used to treat breast cancer after surgical removal of the tumor[97]. It is frequently used as part of chemoradiation to deal with esophageal cancer. It can be used when treating adenocarcinoma of the esophagus. Idarubicin (**17**) is another anthracyclin utilized to treat some forms of cancer, including leukemia[98]. Considering it acts well alone, patients frequently do not need other adjuvant cancer treatments. As with most anthracyclines, idarubicin hydrochloride injection can cause myocardial toxicity resulting in congestive heart failure. The security and effectiveness of idarubicin (**17**) in children have not been established, and therefore it is not advisable for use in children.

Podophyllotoxin derivates

Etoposide (**18**) and teniposide (**19**) (Figure 16) are anticarcinogenic drugs which are derivated from Podophyllotoxin[99]. They work by inhibiting the enzyme topoisomerase II, which averts re-ligation of DNA strands, and induces DNA strands to break[100]. Cancer cells often rely more on topoisomerase II than healthy cells, given that they split rapidly. They are used to treat lung cancer, testicular cancer, lymphatic cancer, leukemia, and several other types of cancer[101]. To increase efficiency, they are often given in combination with other anticarcinogenic drugs. Etoposide (**18**), marketed under the brand name Etopophos amongst others, is a chemotherapy medicine utilized for the remedies of multiple types of cancer, including testicular cancer, lung cancer, lymphoma, leukemia, neuroblastoma, and ovarian cancer. It functions by averting re-ligation of DNA strands by inhibiting topoisomerase. Cancer cells rely more upon this enzyme than normal cells. Etoposide (**18**) has been approved for use in the United States and is listed on the World Health Organization List of Essential Medicines[90]. Teniposide (**19**) (trade name Vumon) is a chemotherapeutic medicine employed in treating youth acute lymphocytic leukemia (ALL), Hodgkin's lymphoma, certain brain tumors, and other types of cancer.



Name	R-group
Etoposide (**18**)	Me
Teniposide (**19**)	2-Thiophenyl

Figure 16: Molecular structure of Podophyllotoxin derivatives.

Side effects are common, and could consist of low blood cell counts, nausea, loss of appetite, hair loss, and fever. Other acute side effects include allergic reactions and low blood pressure. Use during pregnancy could hurt the infant.

Calicheamicin γ1 (20)

The calicheamicins are a group of antitumor antibiotics originally isolated in the mid-1980s from the actinobacterium *Micromonospora echinospora* found in chalky alkaline soils near Kerrville in Texas U.S.[102] Of the calicheamicins found in *Micromonospora echinospora*, calicheamicin γ1 (**20**) (Figure 17) is the most prevalent[103]. Calicheamicin γ1 (**20**) alters the expression of several genes[104] and causes cleavage of DNA[105]. It is incredibly toxic to all cells. An immunoconjugate of Calicheamicin γ1 (**20**) is currently marketed as targeted therapy against acute myeloid leukemia[106]. Another calicheamicin-linked monoclonal antibody has also been developed[107], and is currently being sold in the U.S. under the brand name Bespona to treat adults with lymphoblastic leukemia[108]. K. C. Nicolaou's research group synthesized the molecule in 1992[109], where he used the Schmidt glycosylation with glycosyl trichloroacetimidates with yields ranging from 72% to 95% (more about the Schmidt glycosylation in chapter 5.9) and Misunobu glycosylation with a yield of 53-56%.

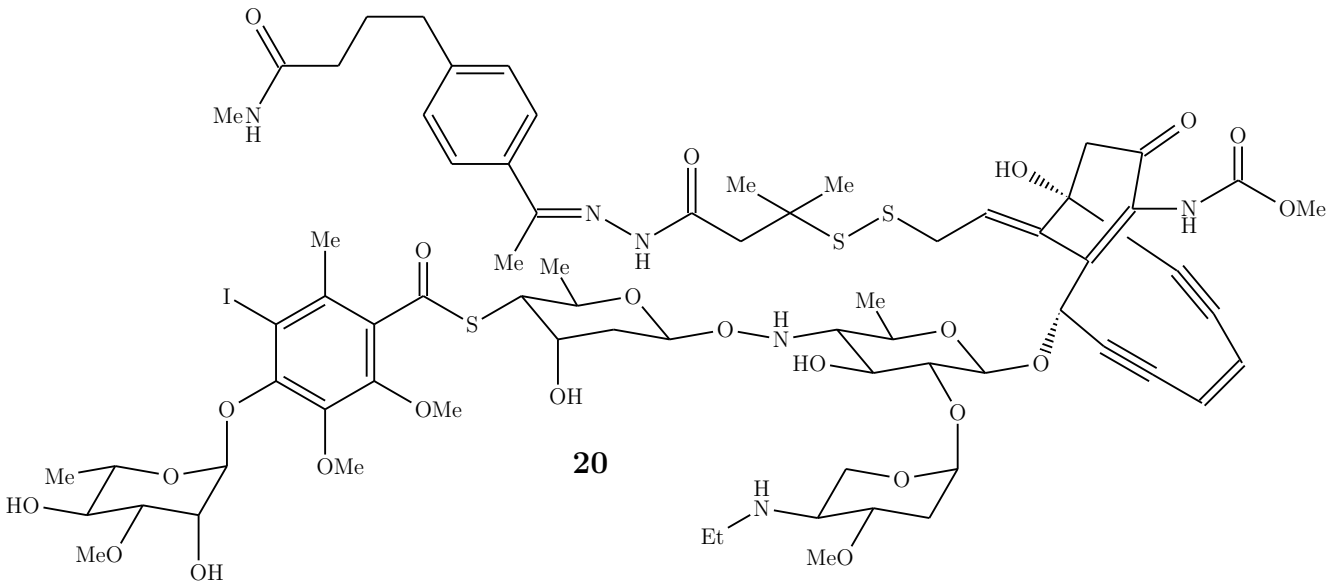


Figure 17: Molecular structure of calicheamicin γ1 (**20**).

Sugar coating on cancer cells

Glycosylation might have an application in the synthesis of molecules that can be used to detect cancer tumors. Sialic acid (Figure 19) has been found to be overrepresented in the sugar coating on cancerous cell surfaces[110]. It has also been found to deactivate immune cells[111], and therefore seems to play an important role in preventing the immune system from eradicating cancer cells.

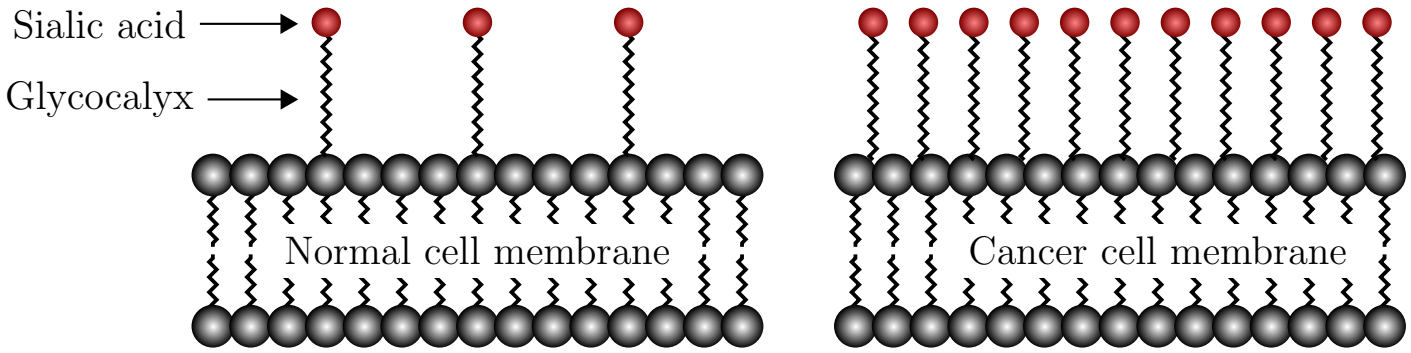
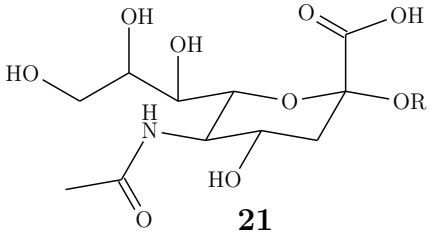


Figure 18: Comparison of a normal cell membrane and a cancer cell membrane with glycocalyx protruding out from the membrane[112]. Sialic acid is overrepresented on the tip of glycocalyx sticking out from cancer cells.

Radioligands binding the sialic acid could be used for cancer detection[113,114], and cleavage or blockage of sialic acid might make the cancer cells more susceptible to be attacked by the immune system[115,116]. Other anticarcinogenic drugs are often highly cytotoxic molecules, capable of destroying cancer cells. These molecules can in some instances be combined with antibodies from the immune system to create targeted cancer therapy.



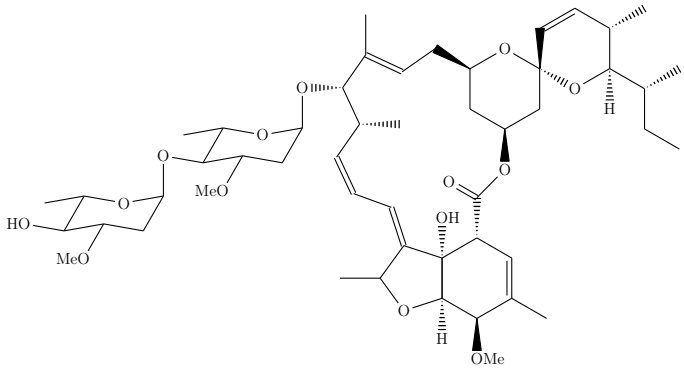
21

Figure 19: The molecular structure of sialic acid.

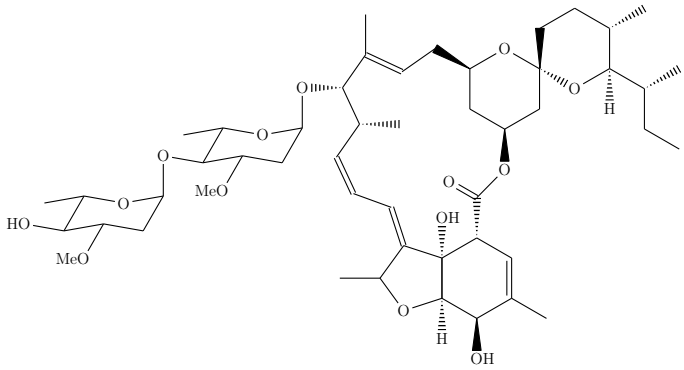
4.4 The antiparasitic avermectins

The avermectins (Figure 21) are a type of medicines and pesticides utilized in the treatment of parasitic fleas and insect pests[117]. These naturally occurring molecules are produced by the dirt actinomycete *Streptomyces avermitilis*. Eight different avermectins were first isolated from *Streptomyces avermitilis*. Some common anthelmintics produced from the avermectins include ivermectin (**23**), selamectin, doramectin, and abamectin. The avermectins obstruct the invertebrate-specific glutamate-gated chloride channel and cause an influx of chloride ions resulting in hyperpolarization and neuromuscular paralysis[118]. These channels are not found in mammals, and similar doses are therefore not hazardous to mammals[119]. Avermectins are used to treat a wide variety of parasitic infections, and the 2015 Nobel Prize in Physiology or Medicine was therefore awarded to William C. Campbell and Satoshi Ōmura for the discovery of avermectins[120].

Figure 20: Depiction of parasitic lice, which is commonly treated with ivermectin (**23**) (stock photo, used with license).



Avermectin A_{1a} **22**



Ivermectin **23**

Figure 21: Molecular structure of Avermectin A_{1a} (**22**) and Ivermectin (**23**).

Danishefsky's research group published a total synthesis of Avermectin A_{1a} (**22**) in 1989[121], where they used the glycal method for both glycosylations with a yield of 65% in both reactions (more about the glycal glycosylation in chapter 5.5). K. C. Nicolaou *et al.* coupled a disaccharide fluoride to the aglycon of Avermectin B_{1a} with a yield of 62%[122] (more about glycosyl fluorides in chapter 5.10). Synthetic avermectins, like Ivermectin, were later developed. Ivermectin (**23**) has greater potency and lower toxicity than the natural Avermectins, and The World Health Organization regarded it as one of the most important medications in 2015[90].

4.5 The antibacterial aminoglycosides, macrolides, and glycopeptides

Bacteria are quickly evolving to become immune to many of the antibiotics we are using today[123] (Figure 23). In 2016 a strain of carbapenem-resistant enterobacteriaceae (Figure 22) was isolated at Washoe County Health District in Reno from a 70 year old woman that had been hospitalized several times due to a bone infection in her femur while she had been in India. The strain was shown to be resistant to all the 26 different types of antibiotics that it was tested against at the Centers for Disease Control and Prevention in the United States[124]. In order to outcompete the evolution of multiresitant bacteria, we need to invent many new antibiotics. Such new antibiotics might include new aminoglycosides, macrolides, and glycopeptides with glycosidic bonds[125]. Just replacing the sugar molecules attached to old antibiotics could in some cases be enough to surpass the bacterial immunity[78].

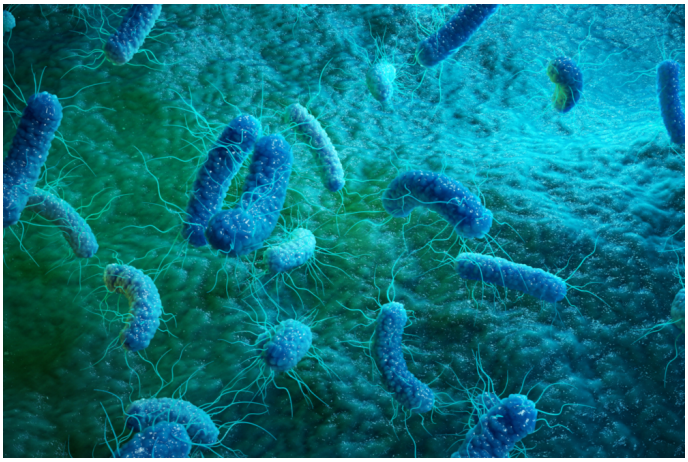


Figure 22: Depiction of multiresistant enterobacteriaceae (stock photo, used with license).

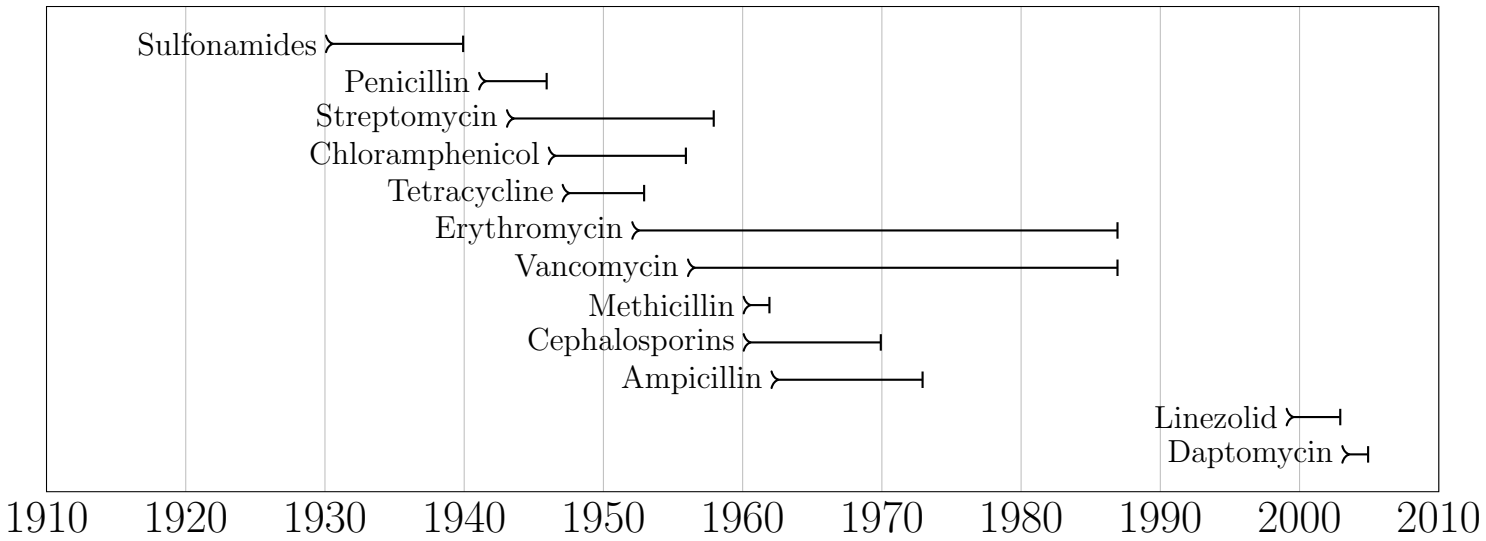
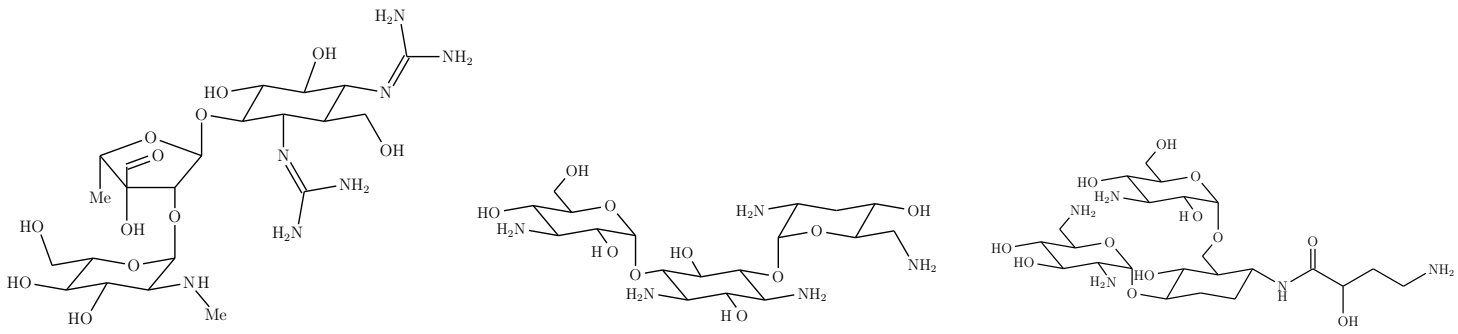


Figure 23: Intervals between when the antibiotics were deployed first and when the first bacterial resistances were observed.[126]

The aminoglycosides

Aminoglycosidic antibiotics (Figure 24) bind to the 30S subunit of the bacterial ribosome, and inhibit protein synthesis. Streptomycin (**24**) was first extracted from the bacteria *Streptomycin griseus*, while tobramycin (**25**) was first extracted from *Streptomyces tenebrarius*. Amikacin (**26**) was later developed based upon the structure of streptomycin (**24**) and tobramycin (**25**)[127]. These molecules contain both α and β-glycosidic bonds.



Streptomycin **24** Tobramycin **25** Amikacin **26**

Figure 24: Molecular structure of streptomycin (**24**), tobramycin (**25**) and amikacin (**26**).

The macrolides

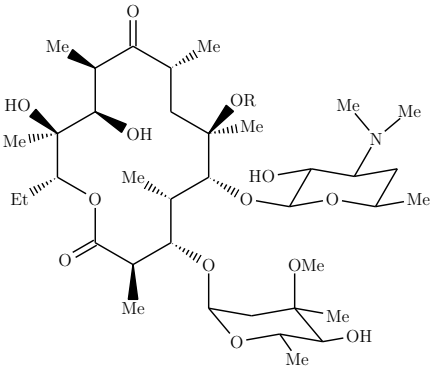
Macrolidic antibiotics (Figure 25) bind to the 50S ribosomal subunit of the bacterial ribosome, and inhibit protein synthesis[128]. Erythromycin (**27**) was first isolated in 1952 from the bacteria *Saccharopolyspora erythraea*[129], and was first synthesized by Robert B. Woodward's research group in 1981[130], where they glycosylated a thioglycoside with 20% yield for the α-glycosylation (more about thioglycoside donors in chapter 5.7), and 10% yield for the β-glycosylation (more about the

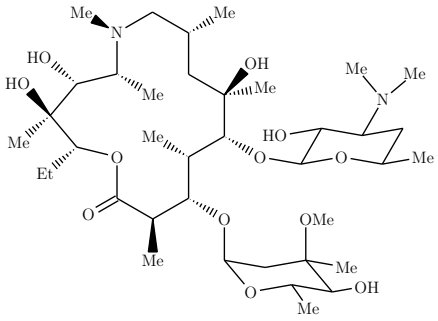
Koenigs-Knorr reaction in chapter 5.1).

Clarithromycin (**28**) was devised by researchers in the drug company Taisho Pharmaceutical in 1980[131]. It emerged through attempts to come up with a variant of erythromycin (**27**) which did not experience acid instability from the gastrointestinal tract, causing unwanted effects, like nausea and stomachache.

Azithromycin (**29**) is an antibiotic utilized for treating multiple bacterial infections, including middle ear ailments, strep throat, pneumonia, traveler's diarrhea, and also some other autoimmune diseases[131]. It may also be utilized against a few sexually transmitted diseases, such as chlamydia and gonorrhea[132]. Together with different drugs, it might also be utilized for malaria[133].

All these macrolides have one α, and one β-glycosidic bond.





Azithromycin **29**

Compound	Erythromycin **27**	Clarithromycin **28**
R-group	H	Me

Figure 25: Molecular structure of Erythromycin[130], Clarithromycin and Azithromycin.

Fidaxomicin (**30**) (Figure 26) is a small spectrum macrolide antibiotic which is utilized in treating diarrhea brought on by infection with *Clostridium difficile*[134]. Fidaxomicin (**30**) functions especially on *C. diff.* moreover, it has small influence on the other bacteria that are generally found in the gut. It was first extracted from the actinomycete *Dactylosporangium aurantiacum*, and was originally produced by Optimer Pharmaceuticals, which is a subsidiary of Merck & Co today.

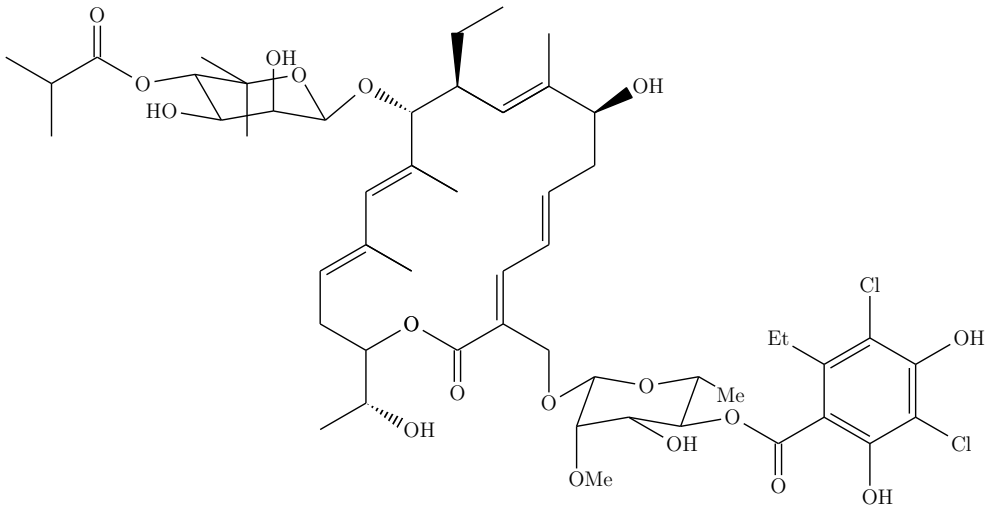
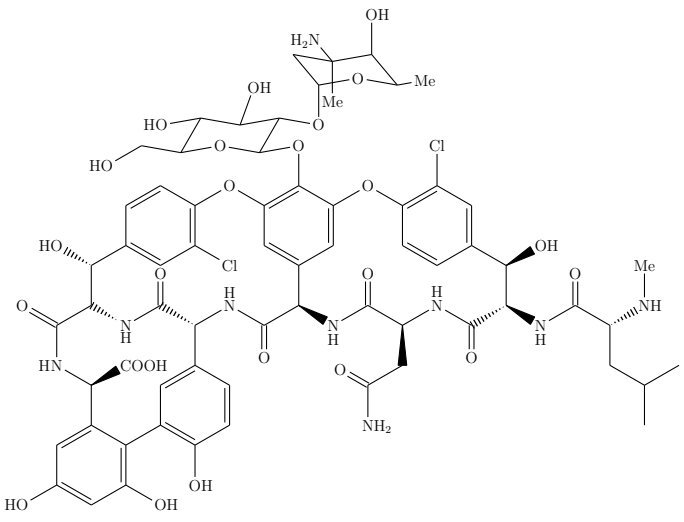


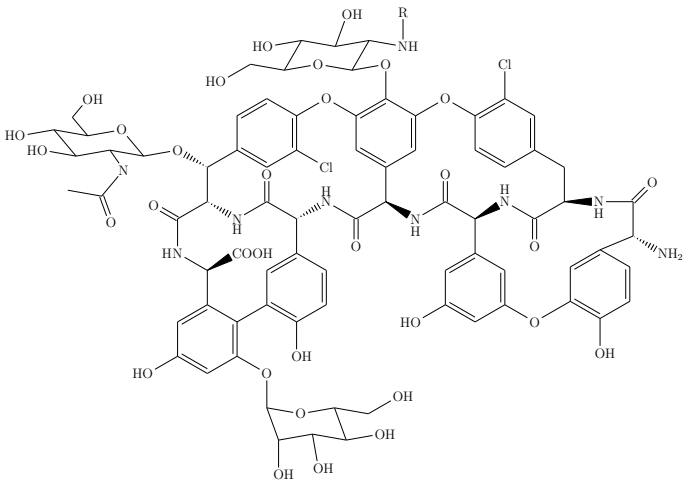
Figure 26: Molecular structure of fidaxomicin (**30**).

The glycopeptides

Glycopeptidic antibiotics inhibit cell wall synthesis in gram-positive bacteria, but are not useful against gram-negative bacteria. Most of them have both α and β-glycosidic bonds. Vancomycin (**31**) (Figure 27) was isolated from *Streptomyces orientalis* in 1953 by Eli Lilly and Company[135]. A total synthesis of the vancomycin aglycon was published by David Evan's research group in 1998[136], while a total synthesis of vancomycin (**31**) was published by K. C. Nicolaou's research group in 1999[137], where they used the Koenigs-Knorr reaction for the α-glycosylation with a yield of 84% (more about the Koenigs-Knorr reaction in chapter 5.1) and Schmidt's method with glycosyl trichloroacetimidates for the β-glycosylation with a yield of 82% (more about the Schmidt glycosylation in chapter 5.9). Teicoplanin (**32**) (Figure 27) was discovered in 1978 from *Actinoplanes teichomyceticus*. Boger's research group first synthesized the aglycon in 2000[138], while David A. Evan's research group came with another synthesis of the aglycon in 2001[139].



Vancomycin (**31**)



Teicoplanin (**32**)

Figure 27: Molecular structure of vancomycin (**31**) and teicoplanin (**32**).

4.6 The antifungal drug amphotericin B

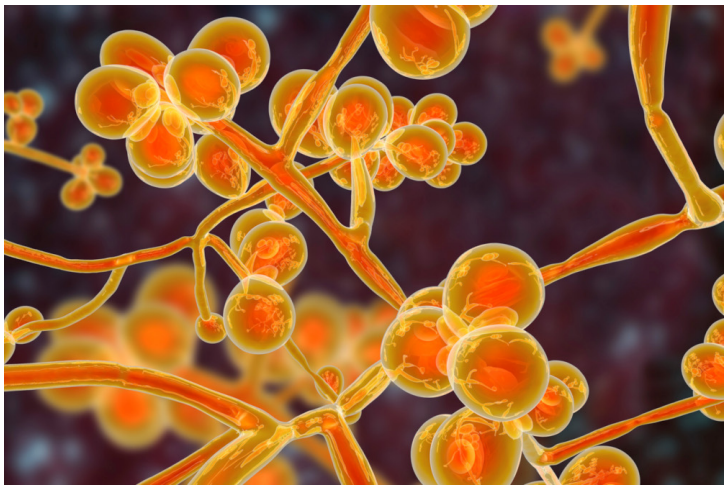


Figure 28: Depiction of the multiple drug resistant fungus *Candida auris* (stock photo, used with license).

Fungal infections have not been a priority in research, and there have not been developed as many drugs that are approved for treating fungal infections as there has been developed and approved for treating bacterial infections. *Candida auris* (Figure 28) is a fungus that initially was isolated in the ear canal of a woman in Japan in 2009[140], and has since spread across much of the world[141]. It has recently attracted attention due to its resistance to multiple antifungal drugs[142]. It also has the ability to survive for extended periods of time on surfaces, such as doorknobs, clothes, bed sheets, and the internal walls of buildings. It can grow on the skin of a person, but may also cause invasive candidiasis (fungemia) where the blood, the central nervous system, and inner organs are contaminated. For invasive candidiasis, a mortality rate of 30-60% has been reported[143]. Amphotericin-B (**33**) (Figure 29) is an antifungal drug which is reported to be effective against 65% of *C. auris* strains. It was first was isolated from the bacterium *Streptomyces nodosus* in 1955[144]. K. C. Nicolaou's research group synthesized it in 1993[145], where they used Schmidt glycosylation with a yield of 40% (more about the Schmidt glycosylation in chapter 5.9).

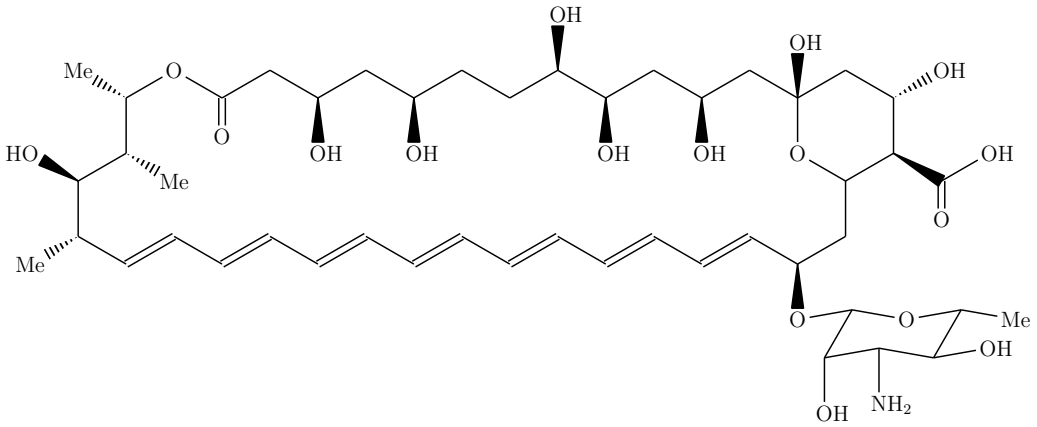


Figure 29: Molecular structure of amphotericin-B (**33**).

It is the only effective treatment against some severe cases of fungal infection[146]. For some infections, it is given with flucytosine. It is typically administered by intravenous injection. Its use is restricted due to severe side effects[147]. Common side effects include fever, chills, and headaches shortly after the drug is provided, in addition to kidney issues. Allergic symptoms, such as anaphylaxis might occur. Other adverse effects include low blood glucose and inflammation of the heart. It seems to be comparatively safe to be used during pregnancy despite its toxicity[148].

5 Glycosylation methods

Anomeric *O*-alkylation is the only glycosylation method that has been studied experimentally in this work. However, in order to give the reader more insight into how the performance and usefulness of anomeric *O*-alkylation fit into the broader context of other glycosylation methods, a short historical overview of glycosylation methods is presented in this chapter (Figure 30).

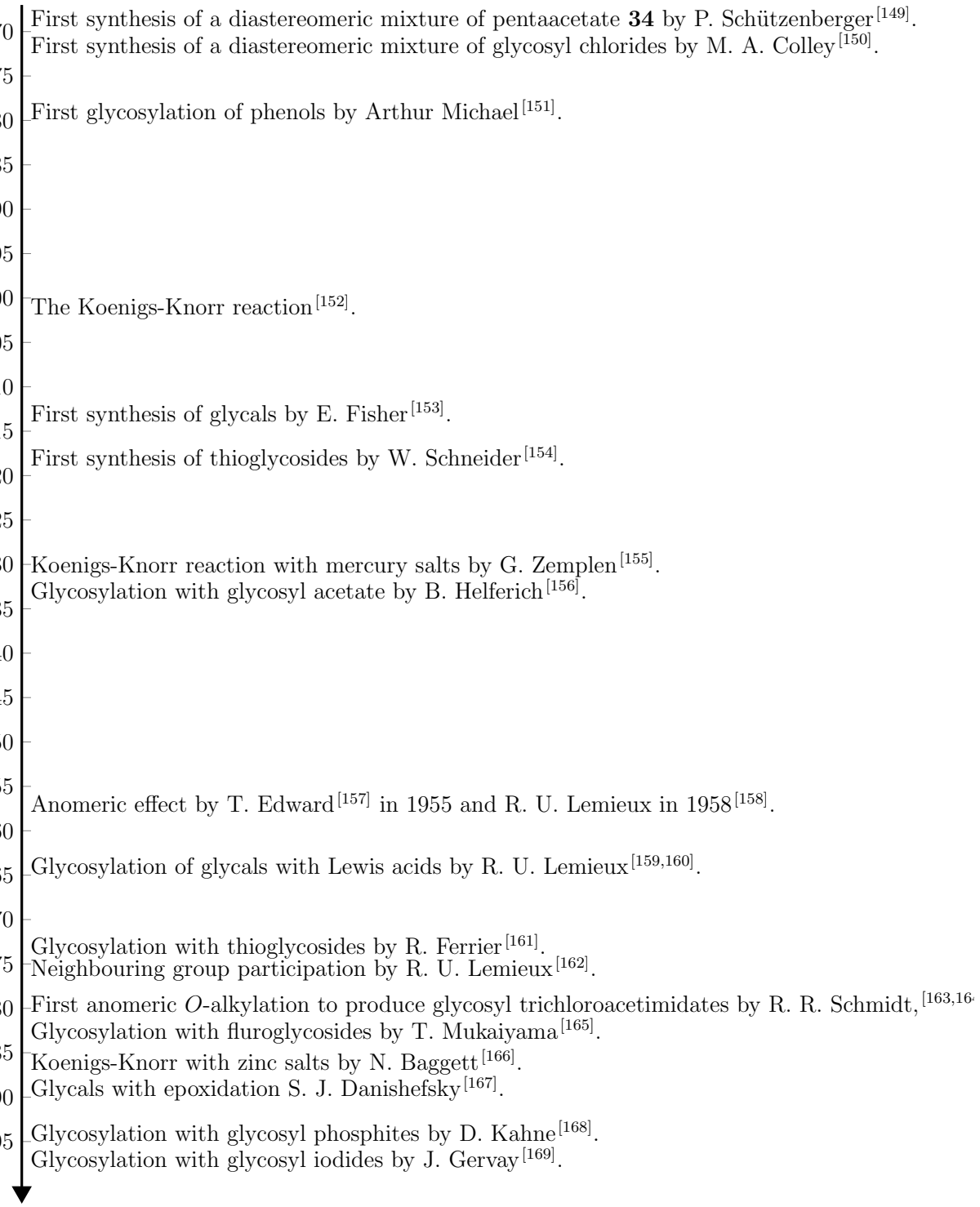
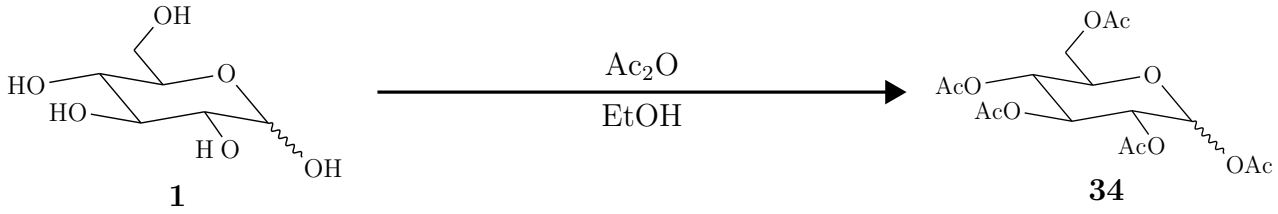


Figure 30: Timeline for some of the major milestones in the advancements of glycosylation.

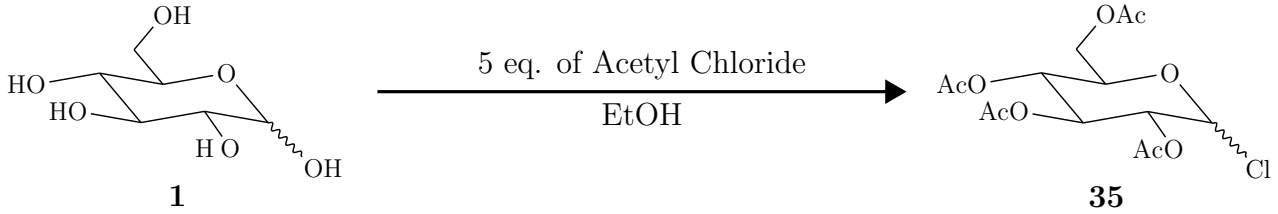
Glycosylation started in 1869-1870 (Figure 30) in France with publications from Paul Schützenberger[149].

Starting from D-glucose **1** he prepared a diastereomeric mixture of pentaacetate **34** with acetic anhydride in 1869[149].



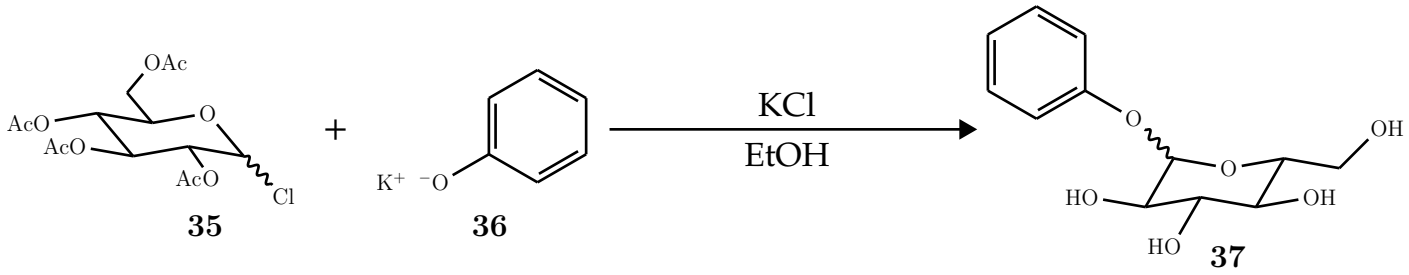
Scheme 7: First synthesis of pentaacetate **34** in 1869[149].

The first glycosyl chlorides **35** was made by M. A. Colley in 1870[150]. He reports having added 5 eq. of acetyl chloride to a solution of D-glucose **1** in ethanol. HCl was generated during the reaction, and elemental analysis showed the formation of a diastereomeric mixture of 2,3,4,6-tetra-O-D-glucopyranosyl chloride (**35**).



Scheme 8: First synthesis of chloroglucosides in 1870[150].

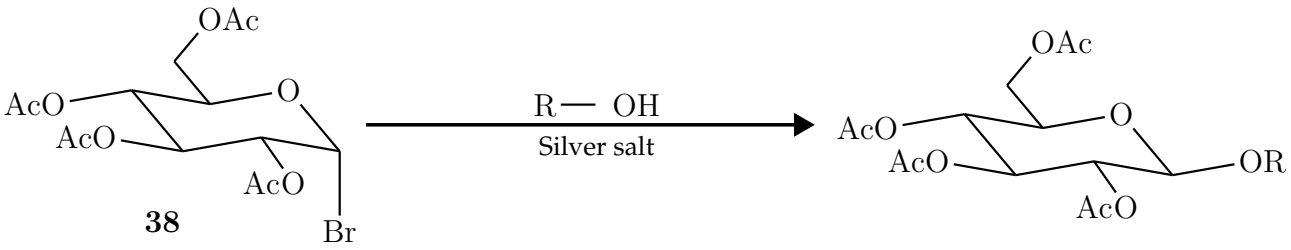
Arthur Michael used acetylated glycosyl chloride **35** together with potassium phenolate **36** in a solution of ethanol in 1879[151]. Elemental analysis showed that he had lost all his acetyl groups, and had formed a diastereomeric mixture og anomerically phenolated D-glucose **37**.



Scheme 9: First synthesis of phenolated D-glucose in 1879[151].

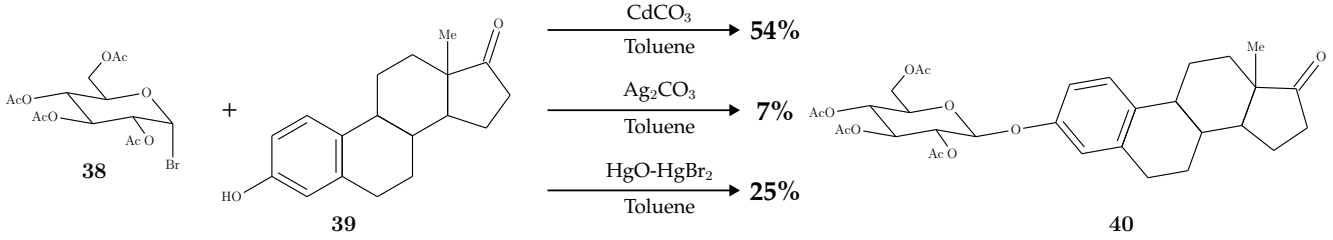
5.1 Koenigs-Knorr glycosylation

The first proper glycosylation method that involved nucleophilic substitution of halogens on the anomeric carbon is credited to Koenigs and Knorr in 1901[152]. They utilized silver salts to abstract chlorine or bromine from the anomeric carbon (Scheme 10), due to the low solubility of the resulting silver halides. This method is well suited for coupling to alcohols, phenols, or to some extent, other sugars and more complex aglycons.



Scheme 10: Generalized scheme of the Koenigs-Knorr reaction.

Although this method worked well for strong nucleophiles, it was less successful for poor nucleophiles, which occasionally was necessary for the synthesis of polysaccharides. In order to solve this problem, G. Zemplen[155] and B. Helferich[156] experimented with heavy metal catalysts, such as mercury and zinc salts. Using heavy metal salts in the Koenigs-Knorr glycosylation have been shown to be able to increase yields (Scheme 11). However, heavy metal salts, such as mercury and cadmium salts, are highly toxic, and also often gave more α-glycosylation[170].



Scheme 11: Comparison of glycosylation with standard Koenigs Knorr, Koenigs Knorr with a mercury salt, and Koenings Knorr with a cadmium salt[170].

Glycosyl bromides have traditionally been the most popular glycosides to use in the Koenigs-Knorr reaction, since glycosyl fluorides and glycosyl chlorides have been considered as not sufficiently reactive, while glycosyl iodides have been considered as too unstable for the Koenigs-Knorr reaction[171]. The stability and reactivity of the halogens is related to the different C-X bond dissociation energies of the halogens (Table 3).

Table 3: Covalent radius (r_{cov}), Pauling electronegativity (χ_r), C-X bond-dissociation energy (C-X BDE), and H-X bond-dissociation (H-X BDE) energy for halogens commonly used as leaving groups[172].

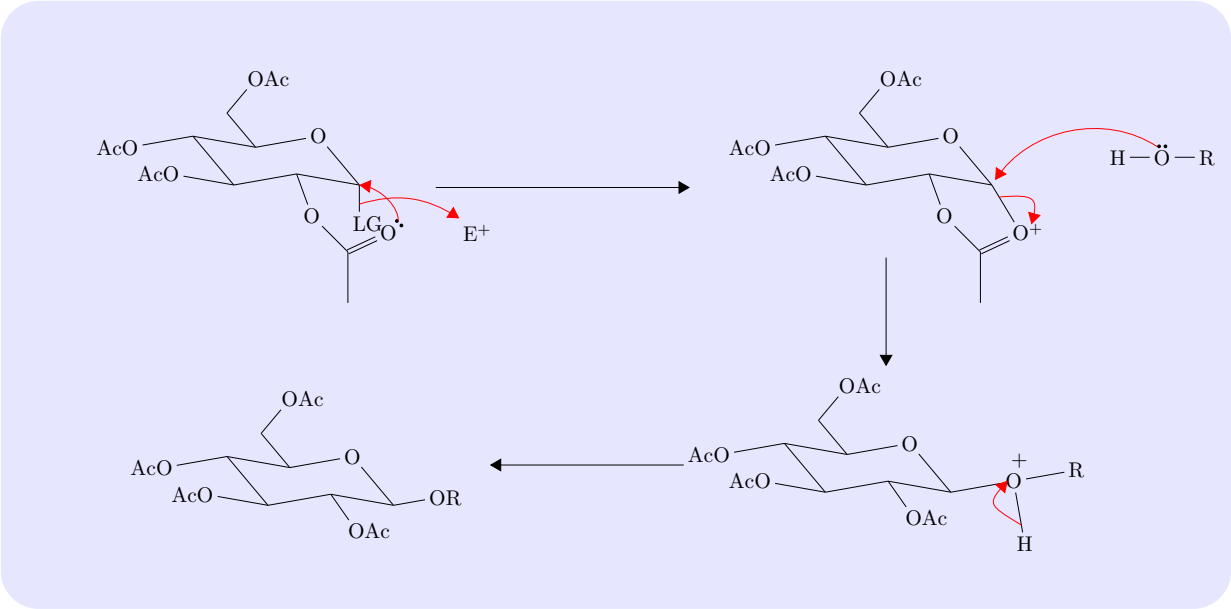
Stability ↑ / Reactivity ↓

Halogen	r_{cov} (Å)	χ_r	C-X BDE (kJ mol^{-1})	H-X BDE (kJ mol^{-1})
F	0.64	3.98	514	570
Cl	0.99	3.16	395	431
Br	1.21	2.96	318	366
I	1.40	2.66	253	298

However, during the last decades there has been an increase in the use of glycosyl fluorides (Scheme 31 and Scheme 32) and glycosyl iodides (Scheme 39). The Koenigs–Knorr reaction has been used in the synthesis of several complex medicinal molecules. R. B. Woodward used this method the synthesis of erythromycin [130] (**27**). It has also been used by Y. Aoyagi, S. M. Hecht *et al.* in the synthesis of bleomycin [91] (**13**) and by K. C. Nicolaou *et al.* in the synthesis of vancomycin (**31**).

5.2 Neighboring group participation

In 1975 R. U. Lemieux found that there is a direct correlation between the stereoselectivity and the protecting group at C2 [162]. Acetylated glycosides gave 1,2-*trans*-glycosides. For 1,2-*cis*-glycosylation, ether groups were used at C2, such as methoxy or benzyloxy. This is related to the carbonyl oxygen of the neighboring acetyl group helping to stabilize the anomeric cation which is developed after expulsion of the leaving group. In the stabilized configuration, the nucleophile can only attack equatorially (Scheme 12).



Scheme 12: Neighboring group participation of acetyl groups at C2 in glycosides.

5.3 Anomeric effect

The anomeric effect was first described in 1955 by T. Edward [157] and R.U. Lemieux in 1958 [158,173]. The effect relates to the preference of electron withdrawing substituents at the carbon next to the heteroatom of heterocyclohexanes to prefer the axial position even though the equatorial position should be most stable according to steric considerations. So for methoxy substituted cyclohexane, or for methyl substituted tetrahydropyran the β-configuration is most stable

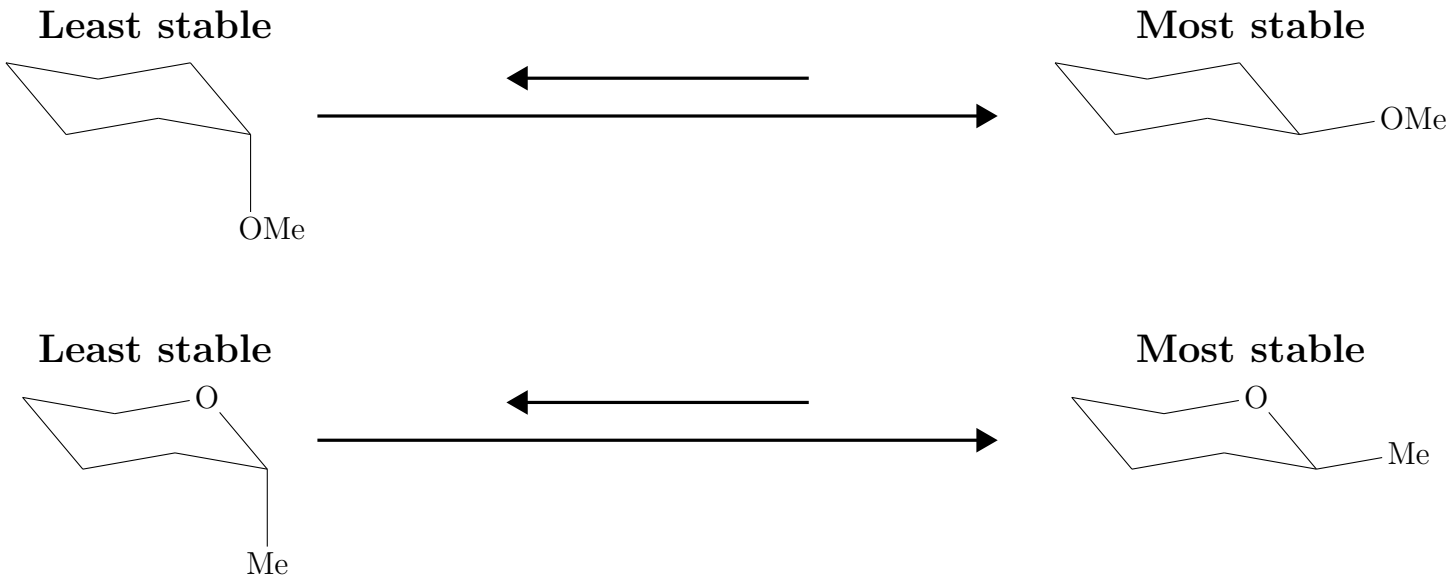
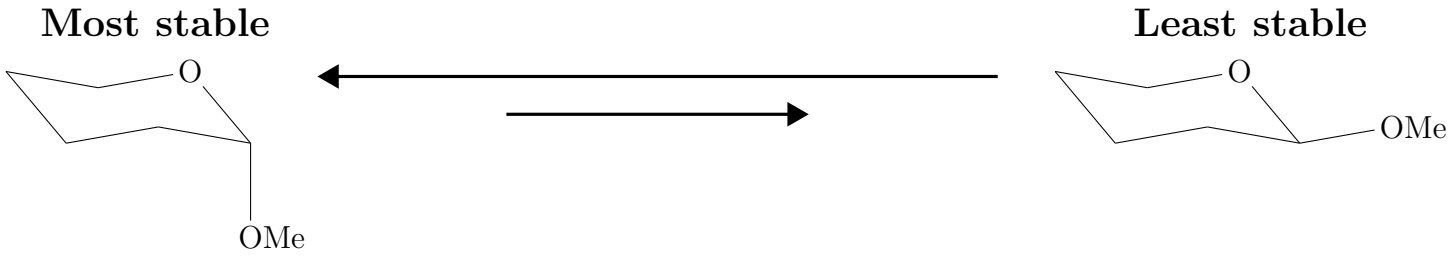


Figure 31: How there is no observed anomeric effect, unless there is both a heteroatom in the 6-membered ring and an electron rich substituent at the anomeric carbon.

However, when tetrahydropyran is substituted with a methoxy group at the anomeric center, the axial configuration becomes more significant. The prevalence of the α-anomer does however vary according to the solvent, with more of the β-anomer in more polar solvents (Figure 32).



Solvent	CCl_4	Benzene	$CHCl_3$	Acetone	MeOH	MeCN	H_2O
Solvent dipole	2.2	2.3	4.7	20.7	32.6	37.5	78.5
Axial (%)	83	82	71	72	69	68	52

Figure 32: How the equilibrium varies for α-MeO tetrahydropyran in different solvents.[174]

There is significant variation in the equilibrium for differently substituted tetrahydropyran rings. Generally, tetrahydropyran rings with more electron rich substituents at the anomeric carbon tend to have equilibriums that favor the α-anomer (Figure 33).

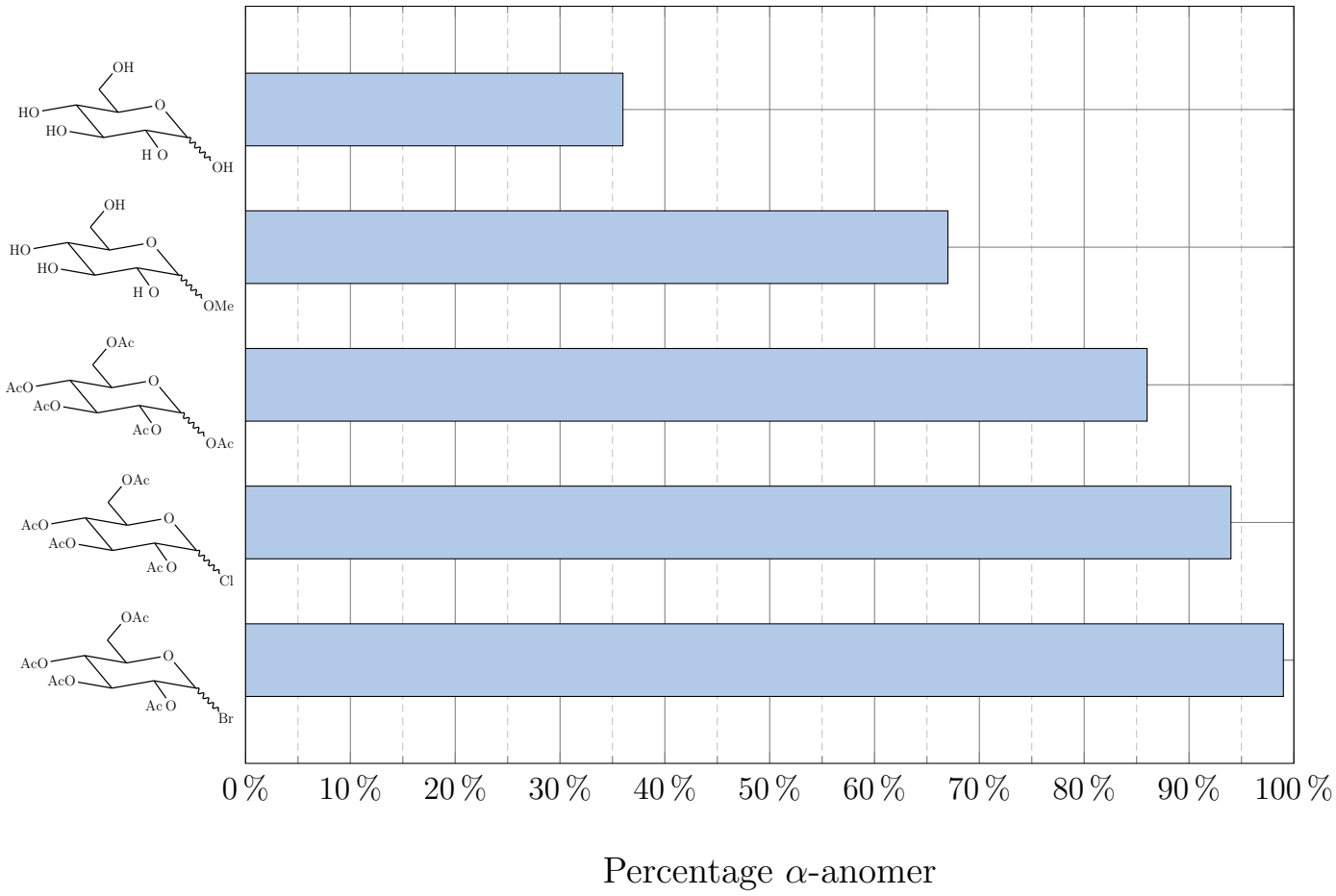


Figure 33: Amount of α-anomers for a few different glycosides.[175]

Even though the anomeric effect is most commonly discussed in regard to glucose derivatives, the trend is not restricted to oxygen substituents. The physical reason behind the anomeric effect is not entirely agreed upon, and several different theories have been proposed to explain the anomeric effect[176].

Dipole-Dipole interactions

The first proposed explanation for the anomeric effect was published by Edward in 1955[157] and focuses on the alignment of the dipoles between the heteroatoms in the equatorial state, while the dipoles are opposed in the axial state.

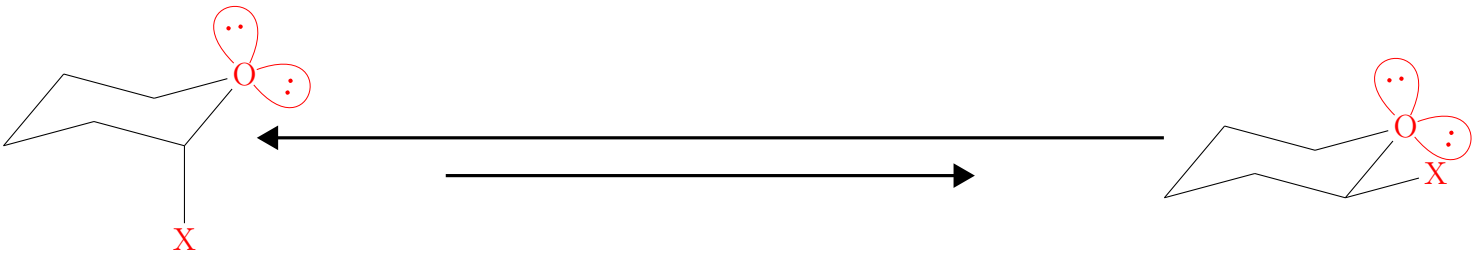


Figure 34: The dipoles are farther away from each other in the α-configuration than in the β-configuration.

Hyperconjugation

Another explanation was proposed in 1959[177], and focuses on hyperconjugation, or a stabilizing interaction between the unshared electron pair on the heteroatom and the σ^* orbital of the axial position. However, a study published by K. B. Wiberg *et al.* in 2018 claims that hyperconjugation is only a minor contributor to the anomeric effect[178].

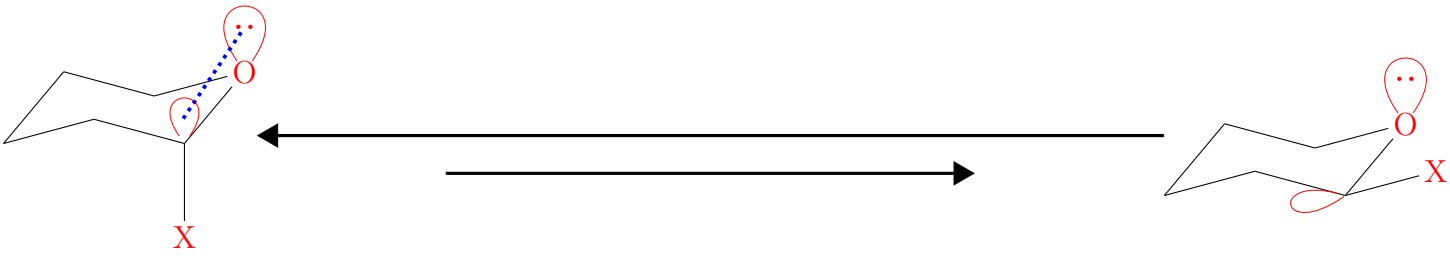


Figure 35: The empty orbital at the anomeric center is aligned with the electron pair on the oxygen in the α-configuration, but not in the β-configuration.

Non-classical CH-X hydrogen bond

More recently non-classical CH-X hydrogen bonds have also been proposed as an explanation for the anomeric effect[179].

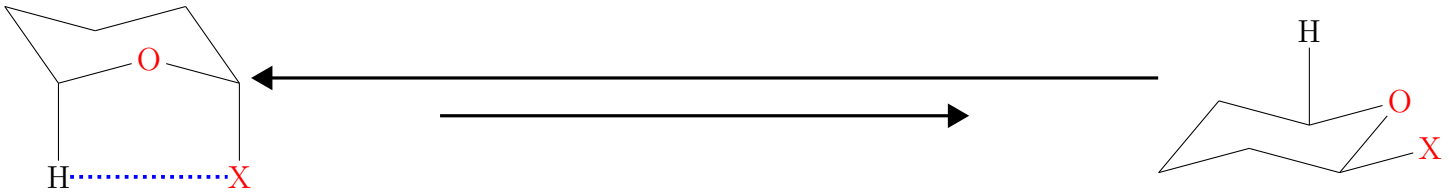
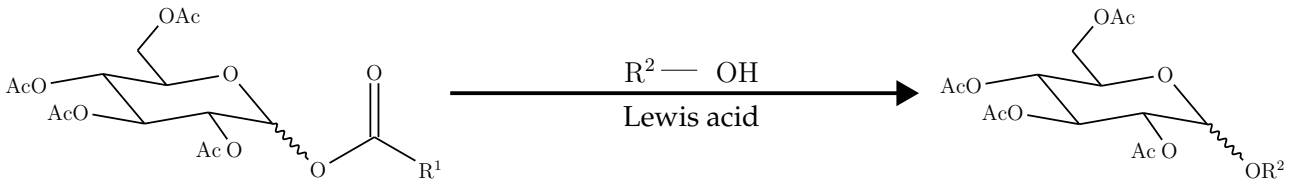


Figure 36: There is a possibility for a non-classical hydrogen bond in the α-configuration, but not in the β-configuration.

5.4 Glycosyl acetates

Glycosylation using anomeric ester donors (Scheme 13) presents a sensible and convenient alternative when choosing a way to facilitate glycosidic bond formation. 1,2-*Trans* anomeric esters are frequently utilized in glycosylations, and their high reactivity is credited to neighboring group participation from the C2 participatory group. Some of the benefits of utilizing glycosyl ester donors comprise their simple preparation and chemical equilibrium, which are attributes that typically enable these chemicals to be made in substantial quantities and managed with relative ease.

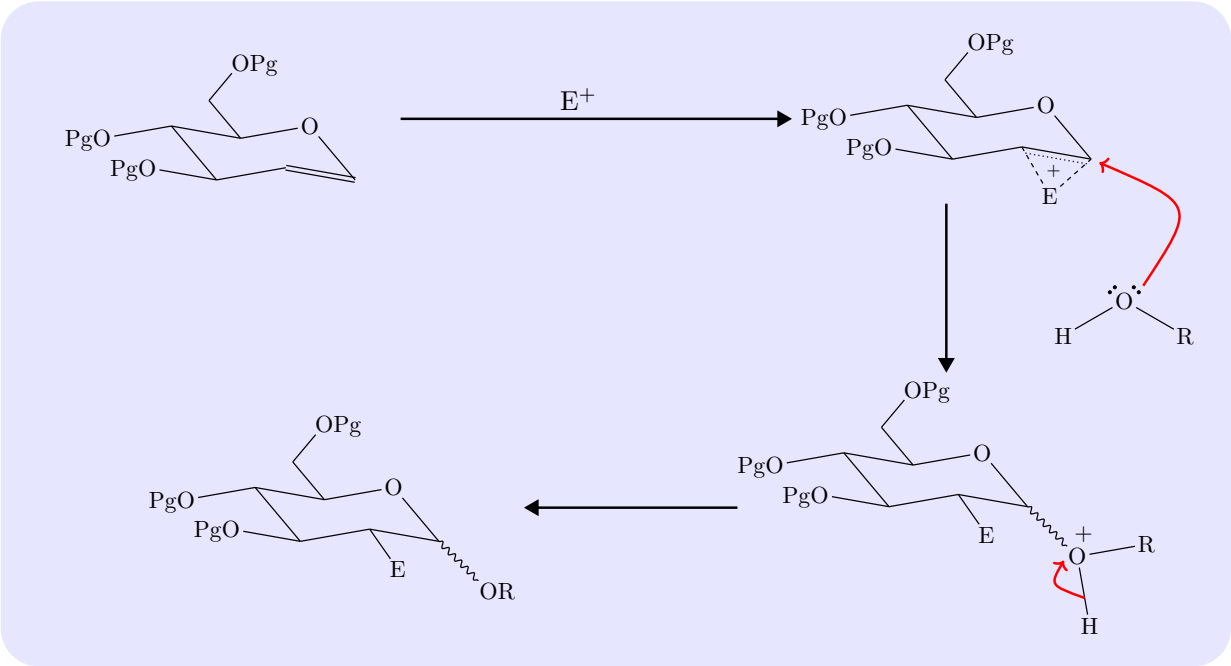


Scheme 13: Glycosylation of nucleophiles with glycosyl acetals.

In 1933 B. Helferich *et al.*, experimented with glycosylation of anomerically acetylated glycosides, using $ZnCl_2$ and catalytic amounts of TsOH[156]. The discovery of anomeric O-carbonyl donors has paved the way for brand new reactivity within this discipline. Specifically, the distant activation approach permits for moderate, chemoselective advertising of different glycosyl donors. S. Hanessian *et al.* experimented with Tin(IV) chloride as a promoter[180]. Glycosyl acetate donors are employed to complex molecular syntheses, even though their usage in this circumstance has been comparatively limited in amount.

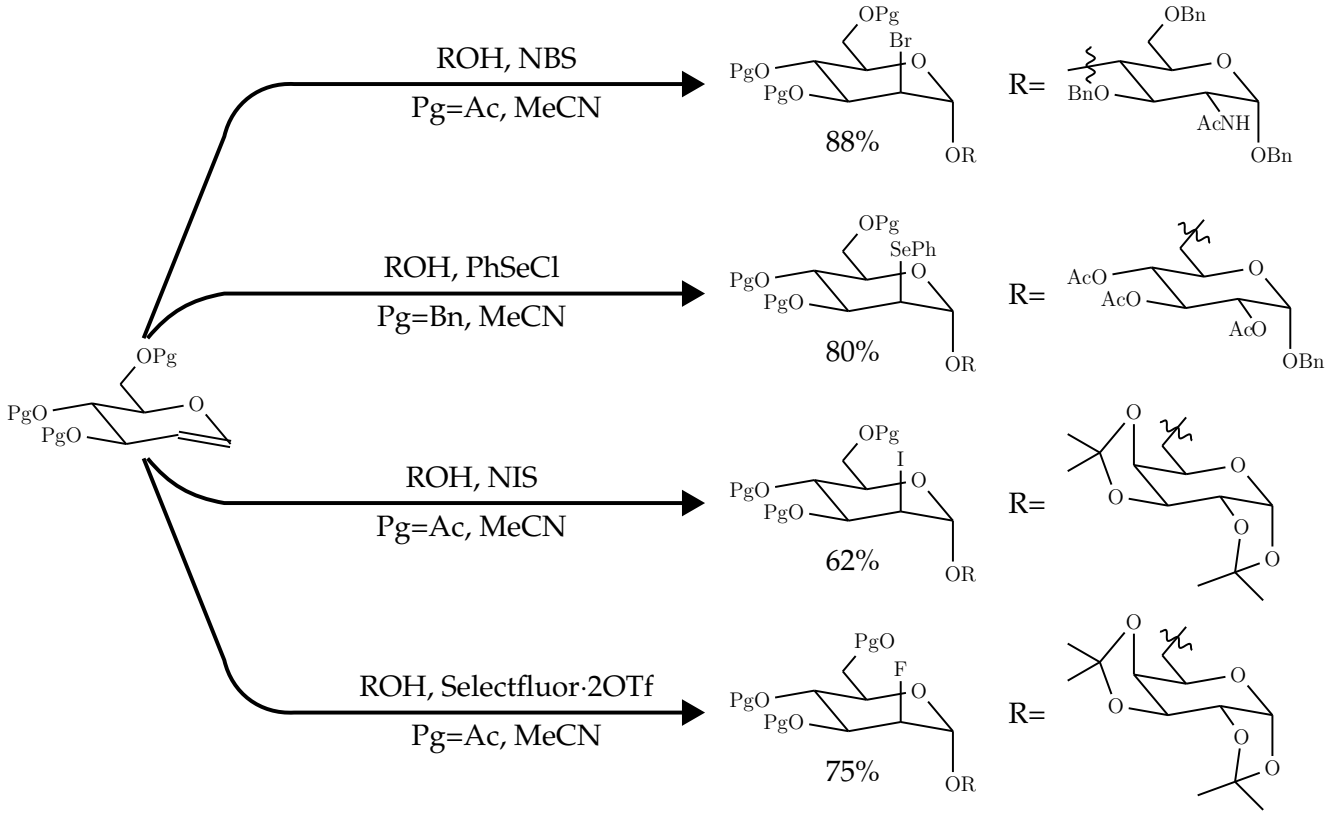
5.5 Glycosylation with glycals

Fisher made the first glycals in 1913[153], but were mistaken for aldehydes, and therefore they have the al-ending common to aldehydes. It was not before the 60's R.U. Lemieux started to glycosylate glycals[159,160]. With glycals, there is a possibility not just of a nucleophilic attack at the anomeric carbon, but also at the C2 carbon. The double bond in glycals will donate electrons to several Lewis acids. The complex of the glycal and the Lewis acid will have a highly reactive anomeric carbon, which readily will react with nucleophiles (Scheme 14).



Scheme 14: Propsed reaction mechanism for the glycosylation with glycals.

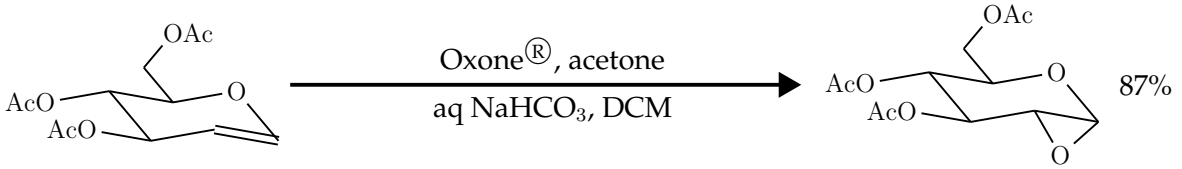
Several methods have been developed, depending on the desired addition to the C2 carbon: addition of alcohols with *N*-bromosuccinimide (NBS) in acetonitrile (MeCN) by K. Tatsuta in 1977[181], *N*-iodosuccinimide (NIS) by J. Thiem in 1978[182], Selectfluor by S. P. Vincent in 1999[183], and glycosyloxyselenation by G. Jaurand[184] (Scheme 15). Glycals are a promising and useful addition to glycosylation methods. Several protected glycals can be bought commercially, such as 3,4,6-tri-O-acetyl-D-glycal and 3,4,6-tri-O-acetyl-D-galactal. The value of acetylated glycals was enriched with access to one-pot approaches such as the transformation of acetylated sugars to glycals. The range of this process has been extended with the evolution of effective aprotic, non-acidic conditions. They are glycosyl donors themselves, but also precursors for several glycosyl donors functioning as building blocks to the formation of O-, N-, S- and - C-glycosides.



Scheme 15: A few different ways to glycosylate nucleophiles with glycals.

5.6 Glycosylation with epoxidized glycals

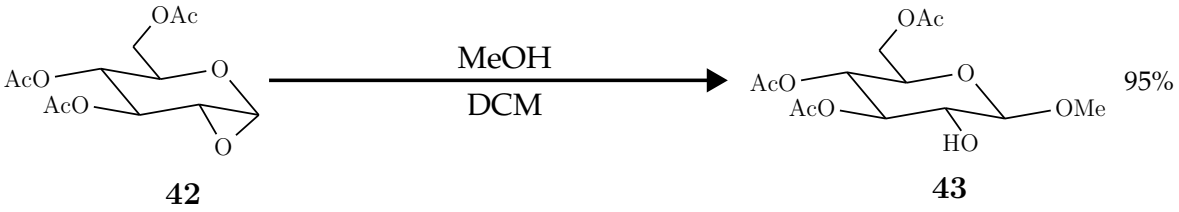
The usage of 1,2-anhydroglycoside donors was introduced in the late 1980s and early 1990s after S. Danishefsky introduced a set of effective methods for the creating them from glycals by using Murray's reagent dimethyldioxirane (DMDO)[167]. The 1,2-anhydrosugars are commonly known as 'glycal epoxides'. Danishefsky used 'glycal epoxides' in the synthesis of Avermectin A_{1a}[121]. DMDO can be generated *in situ* by using Oxone/acetone in two-phase system with DCM and aq. $NaHCO_3$[185] (Scheme 16).



41 **42**

Scheme 16: Preparation of epoxidized glycals[185].

The glycal epoxides will readily react with most nucleophiles and often give high yields and β-stereoselectivity (Scheme 17).

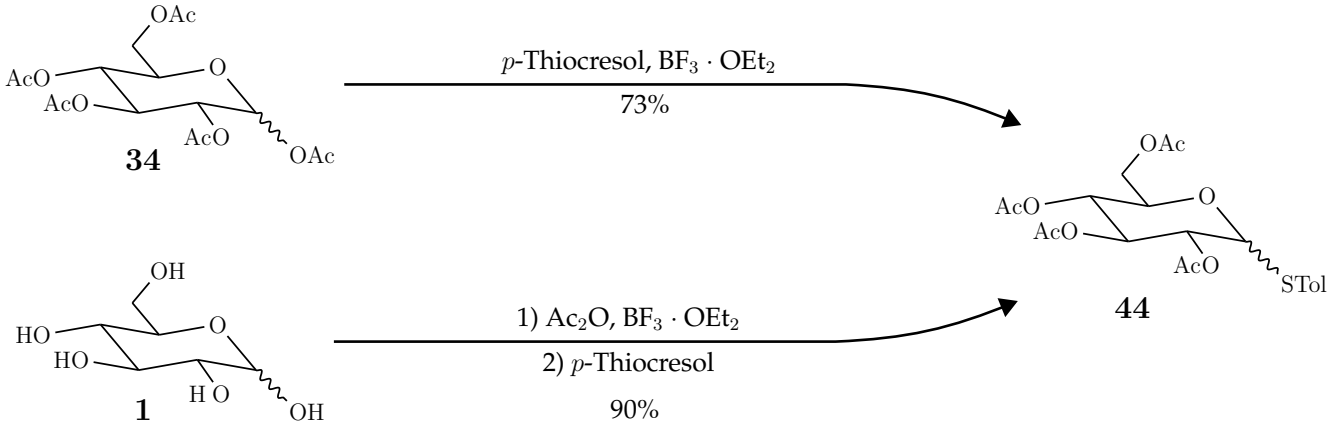


42 **43**

Scheme 17: Glycosylation of nucleophiles with epoxidized glycals[185].

5.7 Glycosylation with thioglycosides

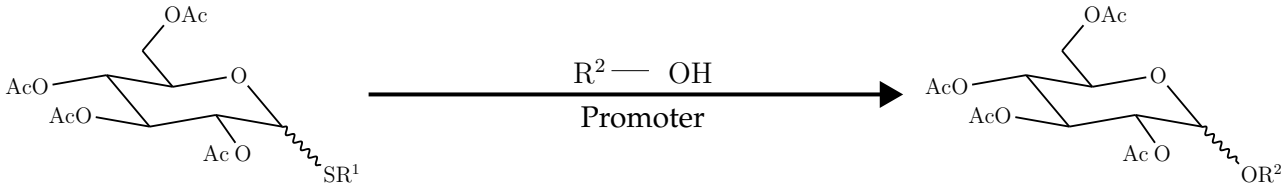
Carbohydrate derivatives, where the oxygen atom bonded to the anomeric center have been substituted by sulfur, are termed thiosugars. The flexibility of thiosugars in carbohydrate chemistry derives from the simple fact that the sulfur atom is a soft nucleophile and is consequently able to respond with soft Lewis acids, such as heavy-metal cations, halogens, alkylating reagents, and carbonium ions. W. Schneider *et al.* prepared thioglycosides from glycosyl halides in 1918[154]. Cheng-An Tai prepared thioglycosides in one step from pentaacetate **34** under solvent-free conditions in 2002[186], while G. Agnihotri found a way to prepare thioglycosides directly from unprotected glucose **1** in one step in 2005[187] (Scheme 18).



34 **44** **1**

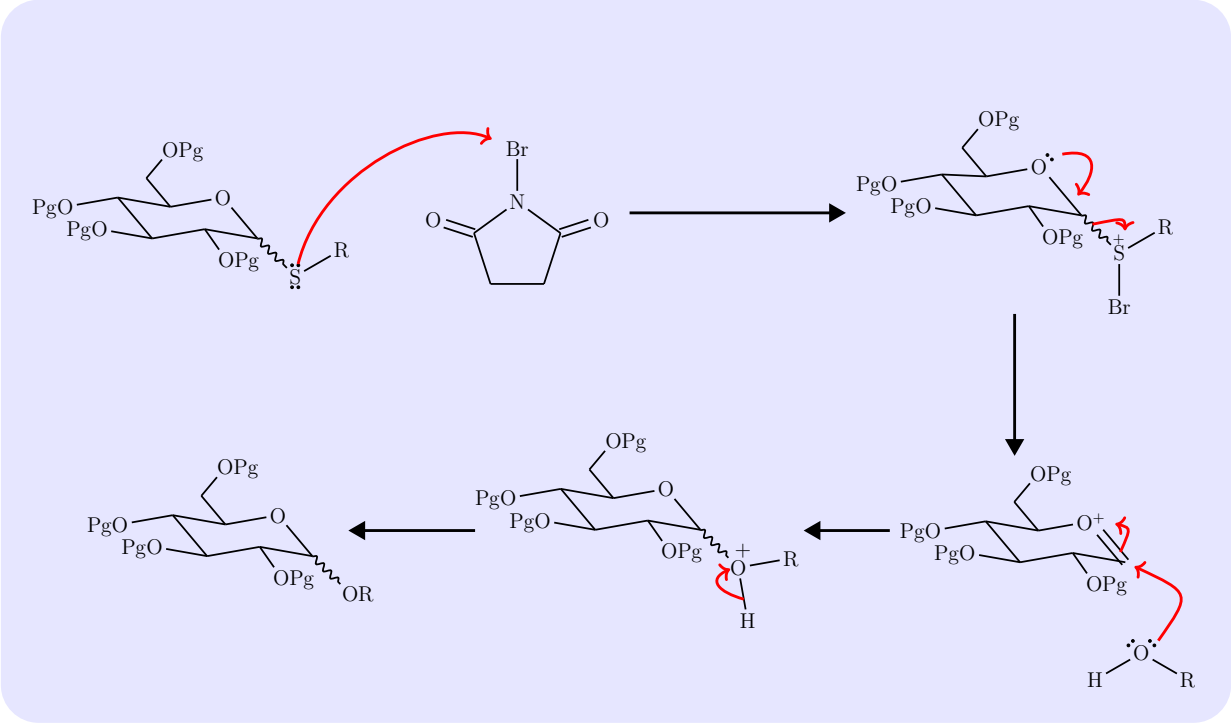
Scheme 18: Preparation of thioglycosides.

Thioglycosides were first used in glycosylation by R. J. Ferrier's research group in 1973[161]. Thioglycosides are one of the most adaptable glycosyl contributors to oligosaccharide synthesis. Thioglycosides are stable and provide protection of the anomeric center. The thio group can be activated by mild conditions with soft electrophiles, but is also stable against many different protecting group manipulations. This makes thioglycosides very suitable as glycosyl donors in a large variety of oligosaccharide glycosylations. They can act as glycosyl acceptors, but can also be transformed into many other glycosyl donors.



Scheme 19: Glycosylation with thioglycosides.

In order to transform the thio group into a good leaving group, the presence of a Lewis acid that the sulfur atom can donate electrons to is necessary. The more electropositive anomeric carbon will then become susceptible to attack from the nucleophile (Scheme 20).

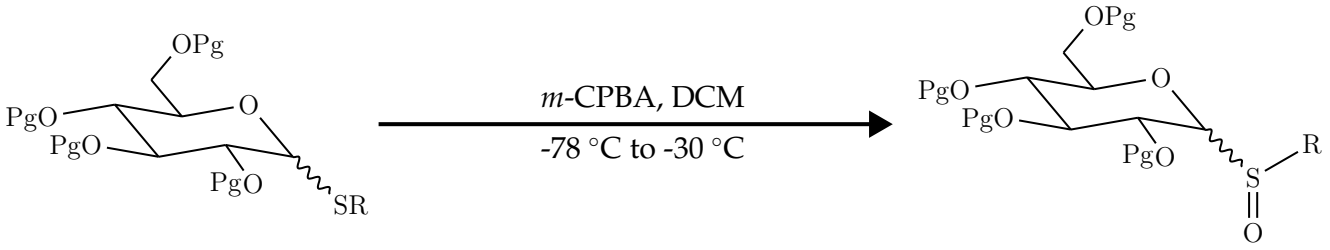


Scheme 20: Proposed reaction mechanism for the glycosylation of thioglycosides.

Several heavy metal salts have later been developed, such as mercuric (II) nitrate in 1980[188]. They have more recently been substituted with more mild halogen promoters; such as NBS by K. C. Nicolaou in 1983.[189], dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) explored by P. J. Garegg in 1986[190], NIS by G. H. Veeneman in 1990[191]. Recently, thiophilic activators for thioglycosides of low reactivity at low temperature: thiophilic promoter systems, such as diphenylsulfoxide in 2004[192], *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT) in 2000[193], benzenesulfinyl morpholine (BSM) in 2006[194] or 1-benzenesulfinyl piperidine/2,4,6-tri-*tert*-butylpyrimidine (BSP/TTBP)[195] in 2001, in combination with triflic anhydride (Tf_2O). Thioglycosides has been used in the synthesis of several complex medicinal molecules. R. B. Woodward *et al.* used $Pd(ClO_4)_2$, in the synthesis of erythromycin A[130] (**27**). It was also used in the preparation of avermectin (**22**) by P. G. M. Wuts and S. S. Bigelow[196].

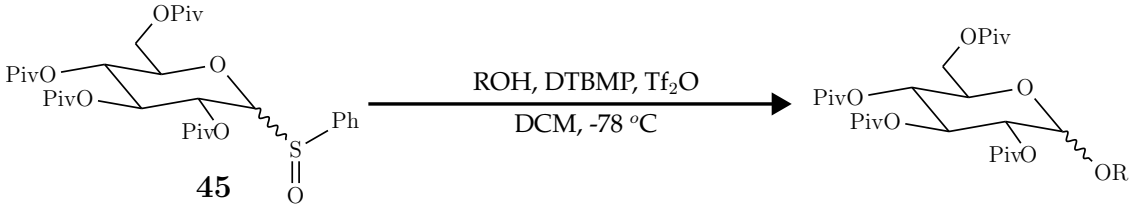
5.8 Glycosylation with glycosyl sulfoxides

Glycosyl sulfoxides can be prepared by oxidizing thioglycosides using *m*-CPBA[197].

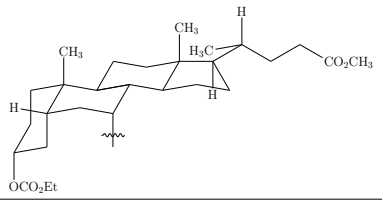


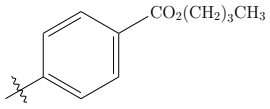
Scheme 21: Preparation of glycosyl sulfoxides.

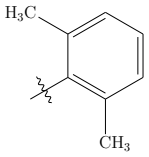
According to a publication by Daniel Kahne's in 1989, glycosyl sulfoxides are well suited for glycosylation of unreactive compounds, such as sterically hindered alcohols[168], and it often gave high yields even for sterically hindered nucleophiles. They investigated DCM as solvents and pivaloyl (Piv) as a protective group for β-glycosylation and achieved yields ranging from 60-80% (Scheme 22).



R-groups



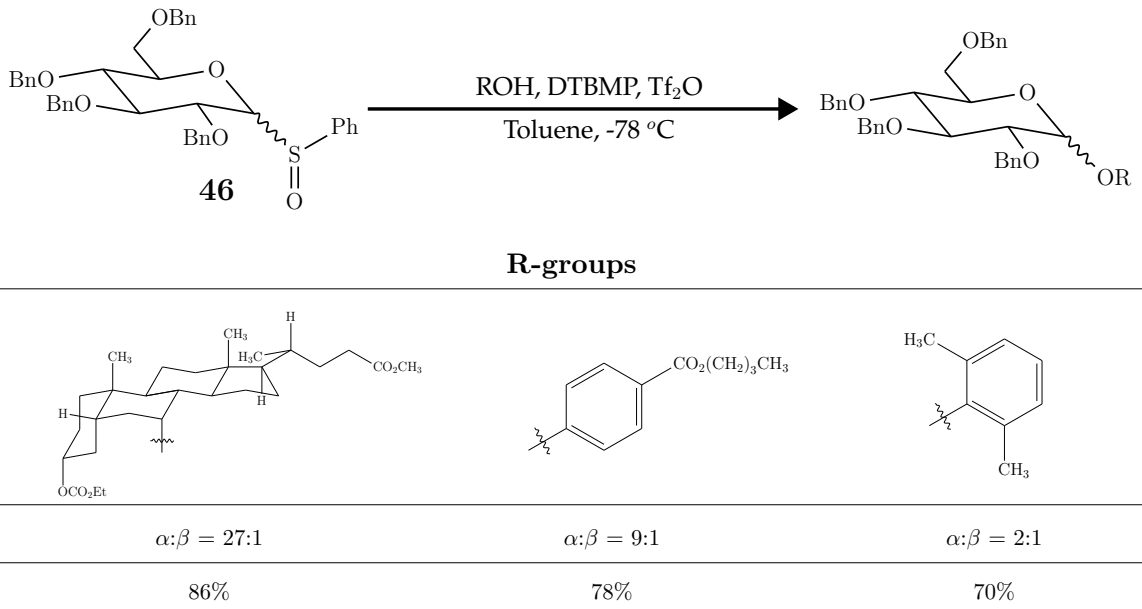




α:β = 1:3	α:β = 0:1	α:β = 0:1
(80%)	(60%)	(80%)

Scheme 22: β-Favored glycosylation with glycosyl sulfoxides[168].

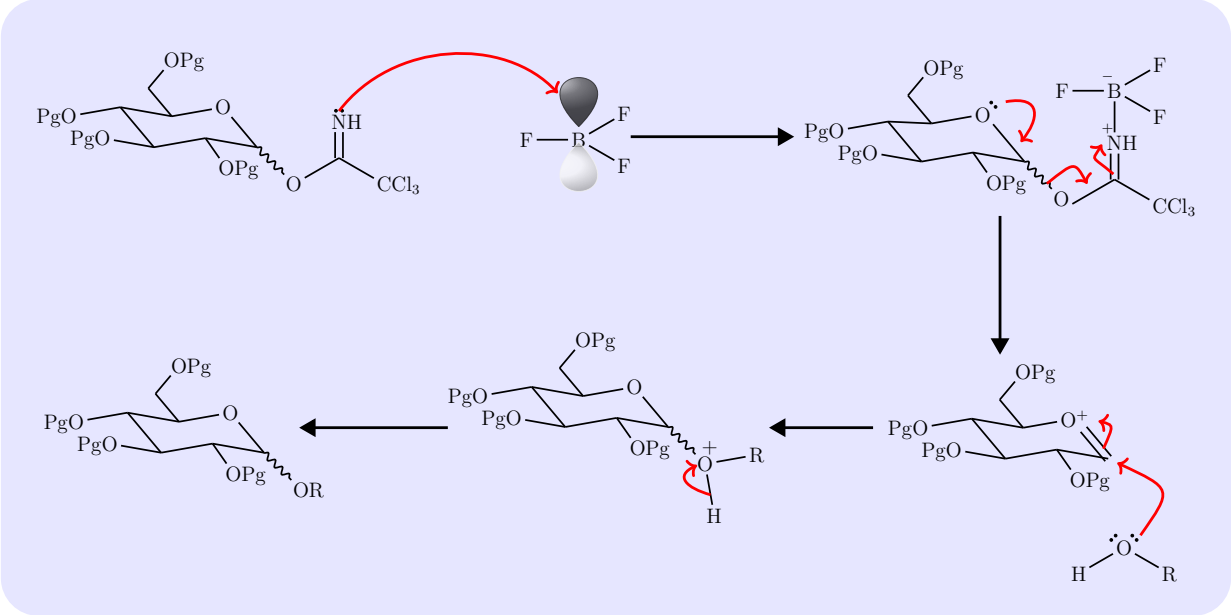
They also investigated toluene as a solvent and benzyl (Bn) as a protective group for α-glycosylation. The same nucleophiles were investigated with yields ranging from 70-86% (Scheme 23).



Scheme 23: α-Favored glycosylation with glycosyl sulfoxides[168].

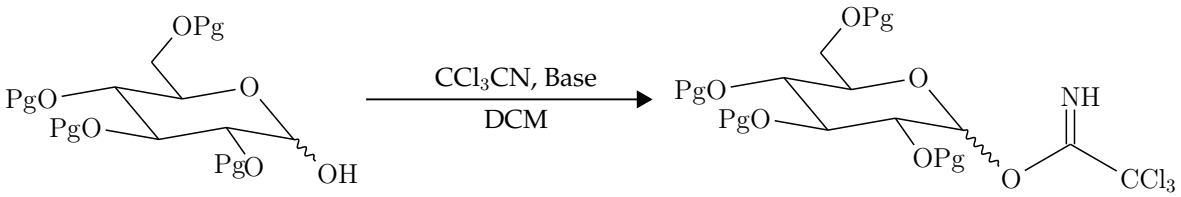
5.9 Schmidt glycosylation

Some of the most commonly employed glycosylation methods today were developed in the early 80's by Prof. Dr. Richard Schmidt and Teruaki Mukaiyama. The advancement in the growth of new coupling methods and effective approaches for oligosaccharide synthesis has given efficient and rapid access to complex oligosaccharides. Glycosylation with trifluoroacetimidates was published by R. Schmidt in 1980[198]. Since then, several different *N*-substituted glycosyl acetimidates have been prepared. Initial experiments revealed that glycosylations using glycosyl trifluoroacetimidates were significantly less efficient compared to glycosyl trichloroacetimidates. The tricholoroacetamide becomes an excellent leaving group, if there is a Lewis acid that the nitrogen can donate electrons to, and then a nucleophile can attack the electropositive anomeric carbon (Scheme 24). The stereoselectivity is derived from the anomeric arrangement of glycosylchloroacetimidates, neighboring group participation, the influence of solvents or thermodynamic or kinetic effects.



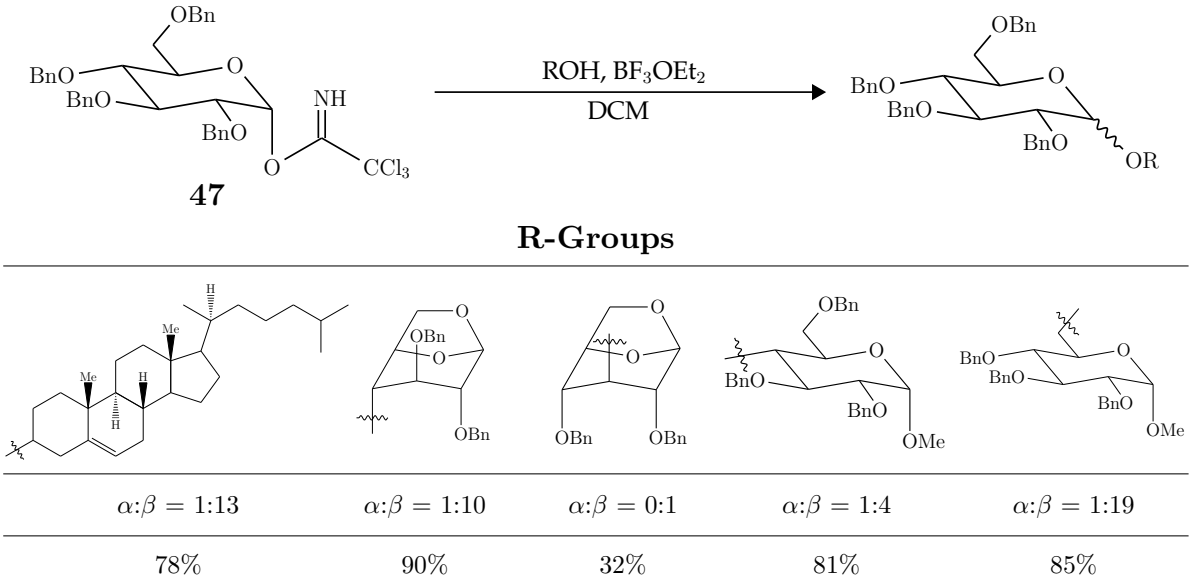
Scheme 24: Proposed reaction mechanism for Schmidt glycosylation.

Glycosyl trichloroacetimidates can be prepared from protected hemiacetals with trichloroacetonitrile under basic conditions, with bases such as NaH, K_2CO_3, Cs_2CO_3, and DBU.



Scheme 25: Preparation of trichlroacetimidates.

In the glycosylation of glycosyl trichloroacetimidates, Lewis acids such as BF_3[199], $ZnBr_2$[200], TMSOTf[201], AgOTf[202] can be used. Schmidt showed a high β-selectivity for the glycosylation of various of nucleophiles (Scheme 26).

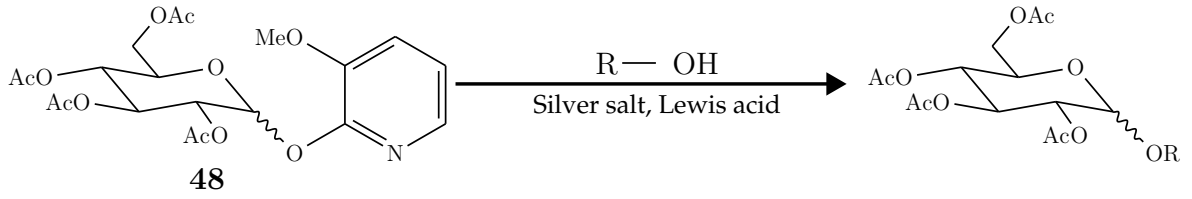


Scheme 26: β-Favored glycosylation with glycosyl trichloroacetimidates[203].

Schmidt glycosylation has been used several times by K. C. Nicolaou *et al.*. He has used it in the total synthesis of many complex medicinal molecules, such as amphotericin-B[145] (**33**), vancomycin[137] (**31**), calicheamicin $\gamma 1$[109] (**20**), and eleutherobin[85] (**12**).

Heterocyclic imidates

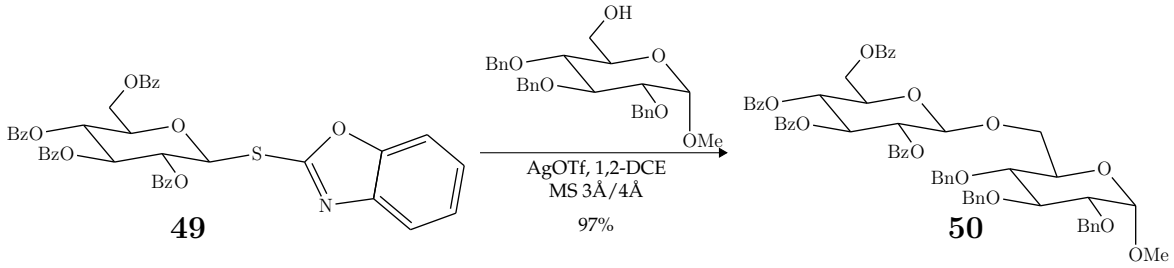
In 1994, the Hanessian research group investigated several heterocyclic imidates as potential anomeric leaving groups[204], and settled on 3-methoxy-2-pyridyloxy (MOP) as the best of these leaving groups. For this leaving group they reported high α-selectivity and short reaction times. For the glycosylation of 2-propanol with 1 equivalent of MeOTf in a mixture of nitromethane and 2-propanol, a yield of 79% was obtained. They also report similar reactivity with DMF. Catalytic amounts of MeOTf was used to activate the MOP glucosides in DMF or CH_3NO_2. A yield of 88%, with 8:1 α:β selectivity was reported with an unprotected MOP glucoside 2-propanol glucosylated in a 1:1 mixture of 2-propanol and CH_3NO_2 with stoichiometric amounts of MeOTf.



Scheme 27: Glycosylation reported by Hanessian in 1994.

Heterocyclic thioimidates

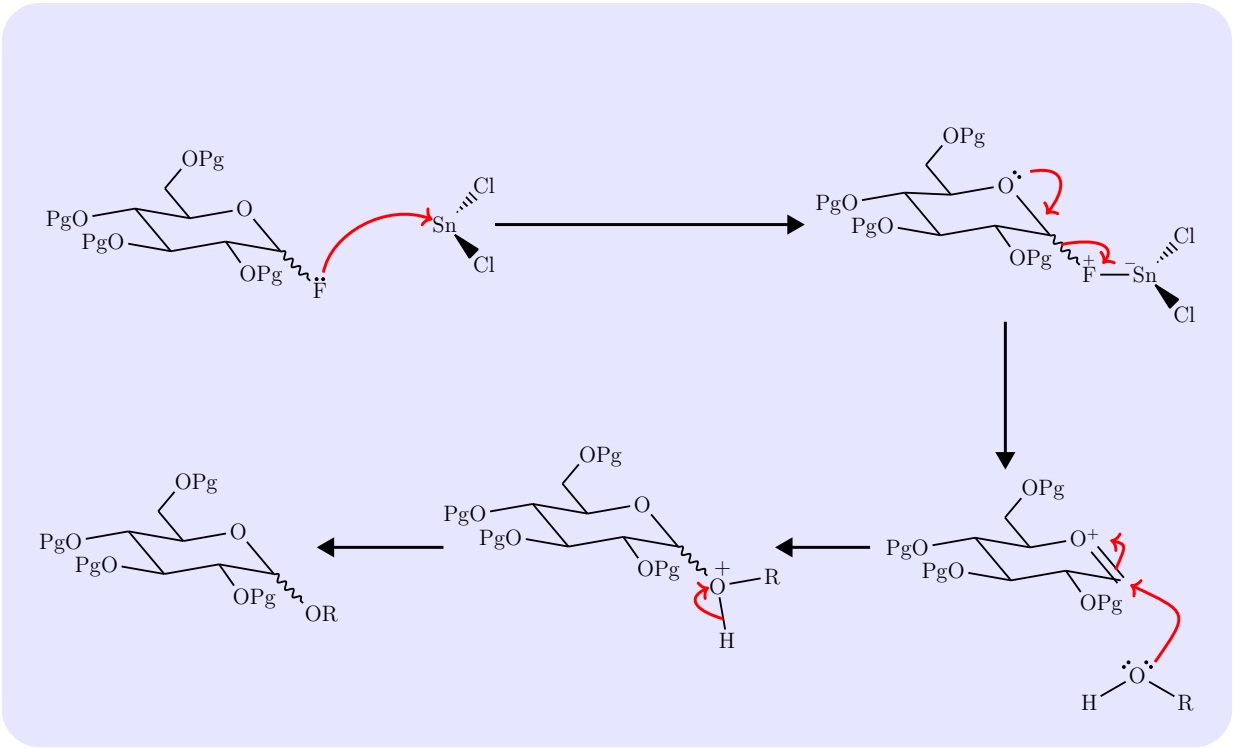
Glycosylation with thioimidates has also been explored[205]. The reactivity of thioimidates seems to give better yields with cyclic thioimidates, and with oxygen as an endocyclic heteroatom in the five-membered ring. The best yields were observed while using AgOTf and $Bi(OTf)_3$ as promoters (97%), while slightly lower yields were observed when using MeOTf (95%), $Cu(OTf)_2$ (85%), and TMSOTf (67%).



Scheme 28: Glycosylation with thioimidates[205].

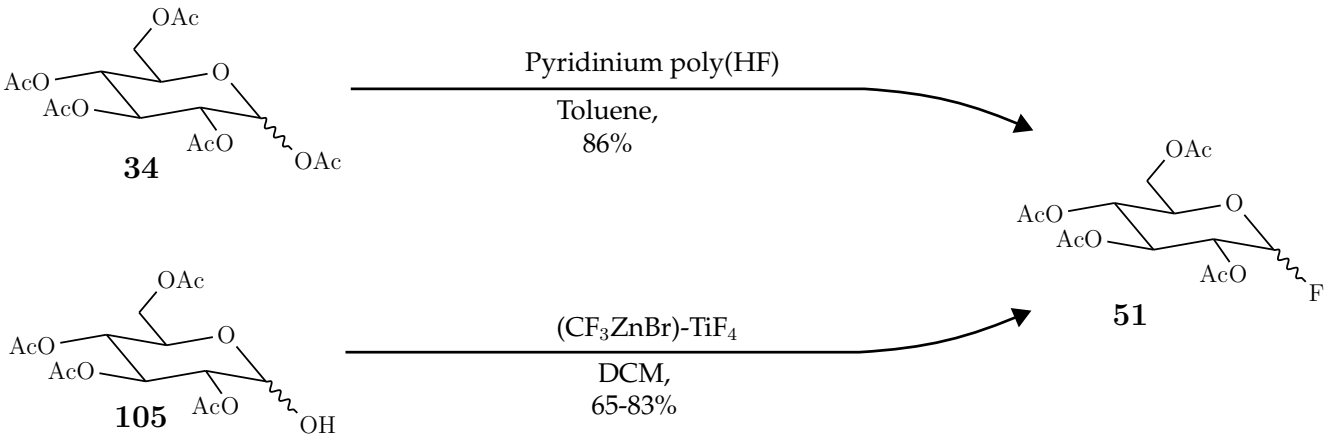
5.10 Mukaiyama-Suzuki glycosylation

Because of the massive bond-dissociation energy of the F-C bond (514 kJ mol^{-1})[172], chemists originally believed that glycosyl fluorides were too stable and therefore not sufficiently reactive for glycosidic bond formations[171]. These beliefs impacted chemists until the discovery of suitable promoters appeared since 1981 ($SnCl_2$, $AlClO_4$[165], $CpHfCl_2$-$AgCO_4$[206] and Cp_2ZrCl_2-$AgC1O_4$[207]). In order to transform the fluoride into a good leaving group, it needs to donate electrons to a Lewis acid, such as $SnCl_2$. It will then easily leave the anomeric carbon so that a nucleophile can attack the electropositive anomeric carbon (Scheme 29).



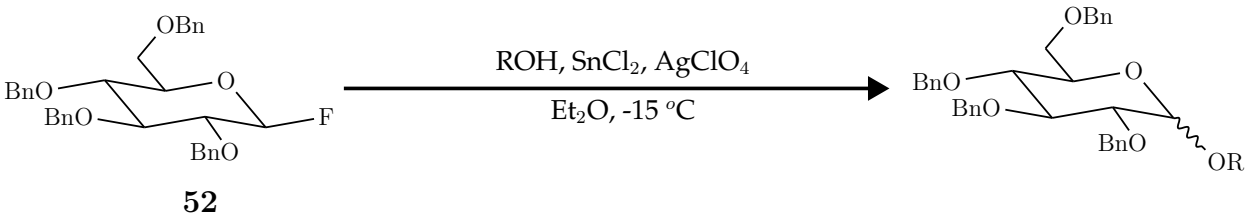
Scheme 29: Proposed reaction mechanism for glycosylation of glycosyl fluorides.

Glycosyl fluorides can be prepared at a low cost from pentaacetate **34** sugars[208], and tetraacetates[209] (Scheme 30).

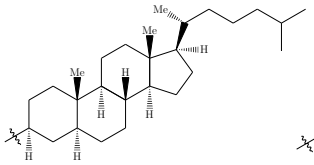
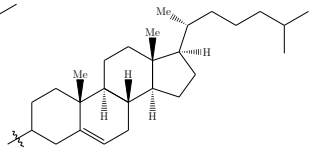
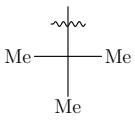
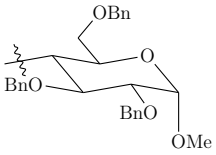
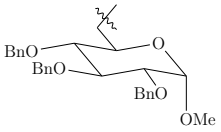


Scheme 30: Preparation of glycosyl fluorides.

Some advantages include high stability, tolerance for different reaction conditions than many less stable glycosides, application for armed-disarmed convergent synthesis, and the possibility for use in enzymatic reactions. Glycosyl fluorides can be used to produce α-glycosides, as shown by T. Mukaiyama in 1981 [165] (Scheme 31).

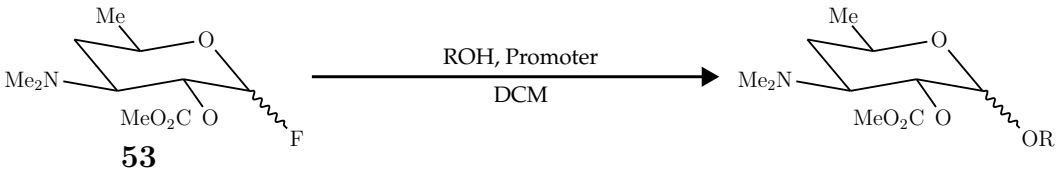


R-groups

				
α:β = 92:8	α:β = 89:11	α:β = 81:19	α:β = 80:20	α:β = 84:16
96%	76%	87%	91%	84%

Scheme 31: α-Favored glycosylation with glycosyl fluorides. Published by T. Mukaiyama in 1981 [165].

K. Suzuki later published how to prepare β-glycosides in high yields from glycosyl fluorides (Scheme 32).



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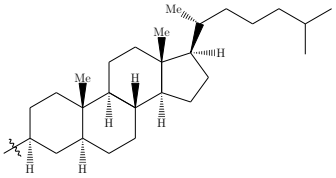
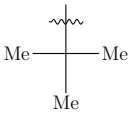
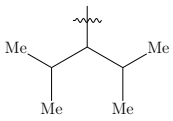
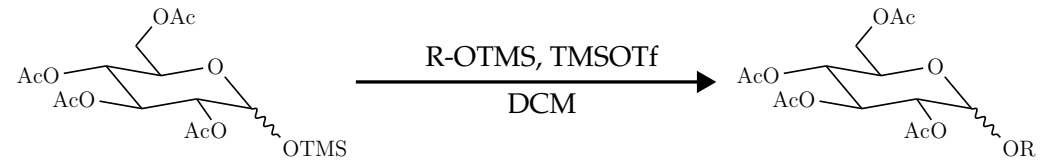
R-Group	Promoter	Ratio and yield
	$CpHfCl_2$-$AgClO_4$	α:β = 0:1 (92%)
	$SnCl_2$-$AlClO_4$	α:β = 0:1 (97%)
	$CpHfCl_2$-$AgClO_4$	α:β = 1:26 (93%)
	$SnCl_2$-$AlClO_4$	α:β = 0:1 (16%)
	$CpHfCl_2$-$AgClO_4$	α:β = 1:50 (91%)
	$SnCl_2$-$AlClO_4$	α:β = 0:1 (64%)
	$CpHfCl_2$-$AgClO_4$	α:β = 0:1 (91%)
	$SnCl_2$-$AlClO_4$	α:β = 0:1 (95%)

Scheme 32: β-Favored glycosylation with glycosyl fluorides. Published by K. Suzuki in 1988[206] .

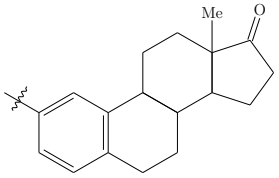
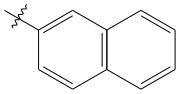
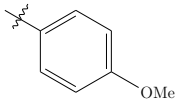
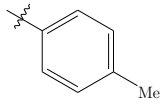
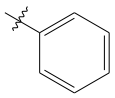
K. C. Nicolaou has used glycosyl fluorides in the glycosylation of several complex molecule. In 1984 he used it in the synthesis of avermectin[122] (**22**).

5.11 Glycosyl silyl ether

Glycosylation with trimethylsilyl ethers was explored by F. Tietze *et al.* in 1982[210]. They found that the acetylated glycoside gave almost exclusively β-glycosylation, with yields ranging from 64 to 90% (Scheme 33).

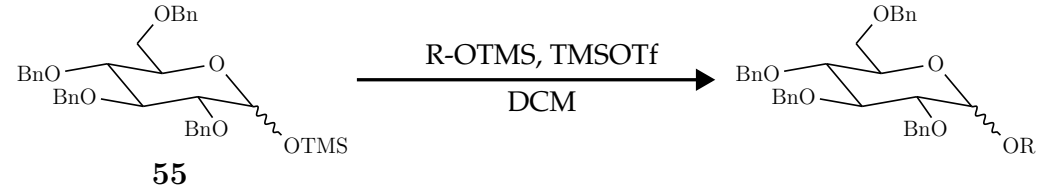


54

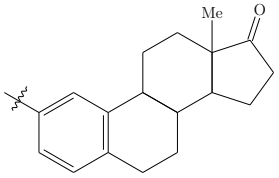
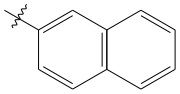
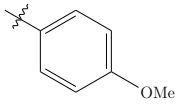
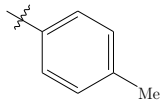
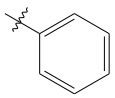
R-groups				
				
α:β = 3:97	α:β = 1:12	α:β = 3:97	α:β = 1:16	α:β = 1:10
64%	77%	86%	79%	90%

Scheme 33: β-Favored glycosylation with acetylated glycosyl silyl ethers[210].

While the benzylated glycosides gave mainly α-glycosylation, with yields ranging from 53 to 90% (Scheme 34).



55

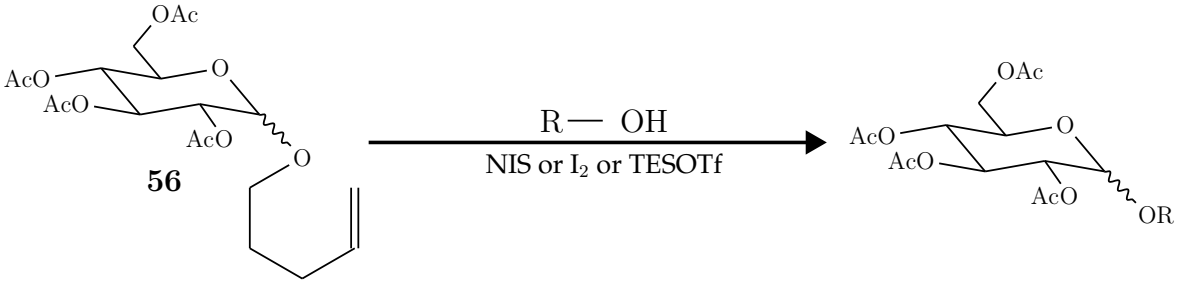
R-groups				
				
α:β = 3:1	α:β = 3:2	α:β = 3.5:1	α:β = 3.5:1	α:β = 3.5:1
69%	53%	80%	90%	75%

Scheme 34: α-Favored glycosylation with benzylated glycosyl silyl ethers[210].

5.12 Fraser-Reid glycosylation

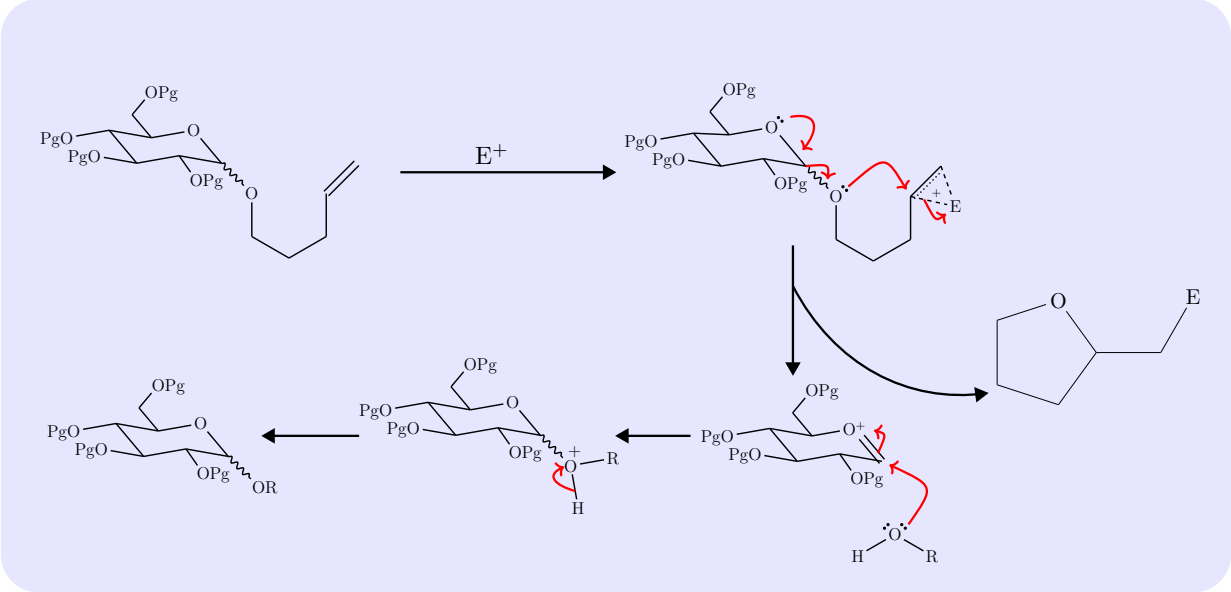
Fraser-Reid *et al.* in 1988 attracted awareness to a novel anomeric leaving group[211]. *n*-Pentenyl glycosides (NPGs) had been introduced as new derivatives that eased the chemospecific liberation of their anomeric center under non-acidic conditions. The latter undergo stereoelectronically driven rearrangements favoring oriented esters on cyclohexyl scaffolds. They are suited for complex oligosaccharide synthesis, and are often used as active forms in the active-latent strategy. There are numerous ways that the *n*-pentenyl group can be added to the anomeric position of a glycoside, such as

by standard Fischer glycosylation of the unprotected sugar with *n*-pentenyl under acidic condition[212] or by Koenigs–Knorr glycosylation[213].



Scheme 35: Fraser-Reid glycosylation[213,214].

In the Fraser-Reid glycosylation, electrons from the double bond on the *n*-pentyl chain will attract a Lewis acid, which will make the most substituted carbon in the double bond much more electropositive, so that the anomeric oxygen will donate electrons to it, and leave the anomeric carbon (Scheme 36).



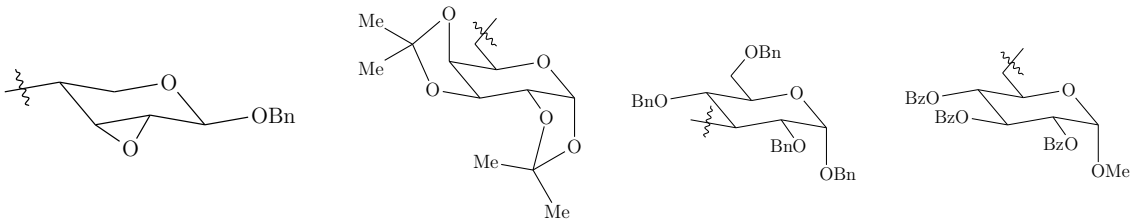
Scheme 36: Proposed reaction mechanism for Fraser-Reid glycosylation.

When Fraser-Reid's research group was working with the glycosylation of *n*-pentenyl glycosides, they discovered that acetylated sugars would prefer to react with similar benzyloxylated sugars, rather than with acetylated sugars[211].

5.13 Glycosylation with glycosyl phosphites

Glycosylation with glycosyl phosphites was explored by D. Kahne *et al.* in 1989[168]. This method presents a compelling alternative to earlier methods. Stereoselectivity can be achieved, and yields are often high. S. Hashimoto developed a highly β-stereoselective method for glycosylation of glycopyranosyl diethyl phosphites using boron trifluoride etherate as a promoter in DCM (Scheme 38).

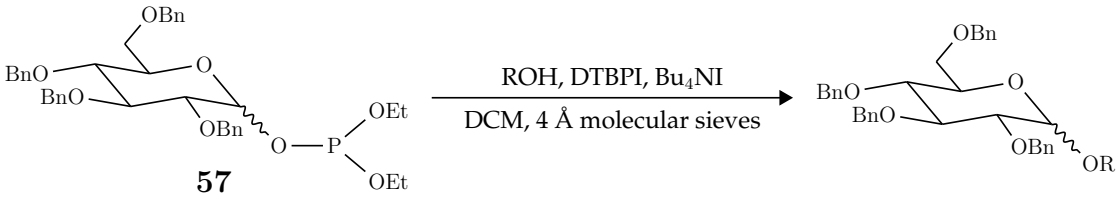
R-Groups



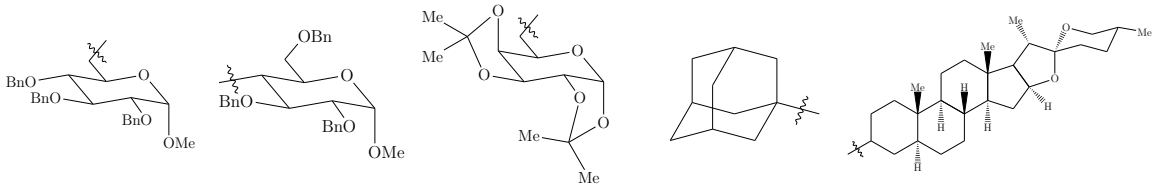
α:β = 1:99	α:β = 1:99	α:β = 2:98	α:β = 2:98
96%	92%	71%	91%

Scheme 37: β-Favored glycosylation with glycosyl phosphites[215].

S. Hashimoto later developed a mild and highly stereoselective method for α-glycosylation with glycopyranosyl diethyl phosphites using 2,6-di-*tert*-butylpyridinium iodide and tetrabutylammonium iodide (Scheme 38).



R-Groups



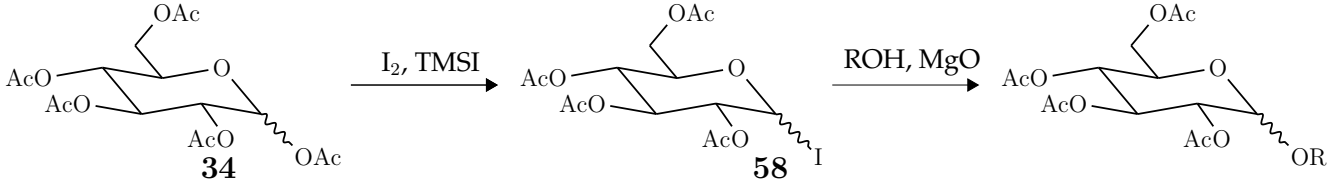
α:β = 98:2	α:β = 95:5	α:β = 94:6	α:β = 91:9	α:β = 92:8
85%	59%	91%	88%	92%

Scheme 38: α-Favored glycosylation with glycosyl phosphites[216].

Glycosyl phosphites have been used in the synthesis of complex medicinal molecules. Boger *et al.* used this method It was used in the synthesis of bleomycin A2[92] (**13**), while E. J. Corey *et al.* used glycosyl phosphites in his synthesis of paeoniflorin[81] (**11**).

5.14 Glycosyl iodides

Glycosyl iodides have traditionally been considered as too unstable for glycosylation[171], and they were not widely used before 1997 when J. Gervay's research group started using them[169]. In 2004, Field's research group documented the synthesis of glycosyl iodides from unprotected sugars and pentaacetate **34**. Over the last decade, glycosyl iodides have been used in several syntheses, their reactivity and stability may be rearranged by altering the protecting-group design. per-O-Silylated glycosyl iodides, that are usually generated *in situ*, are on the extreme side of this reactivity scale. While per-O-benzylated glycosyl iodides possess intermediate reactivity and can be stored for extended intervals in subzero temperatures, whereas per-O-acylated glycosyl iodides are secure crystalline solids with extended shelf life.

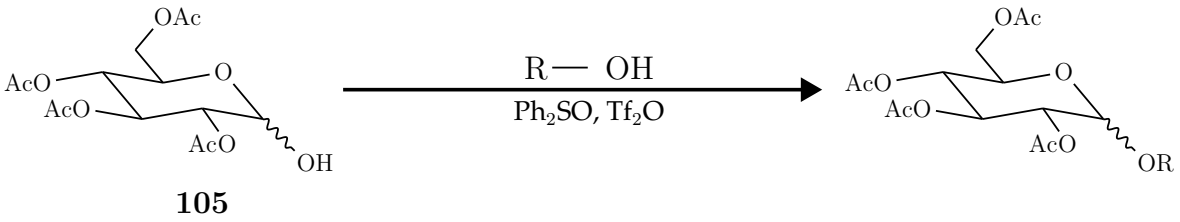


Scheme 39: Preparation of glycosyl iodides and subsequent glycosylation of glycosyl iodides.

Many research groups have shown that iodide donors exhibit unique properties in glycosylation reactions and frequently offer benefits over glycosyl chlorides and glycosyl bromides concerning response time, efficacy, and also the stereochemical outcome. The distinctive reactivity account of glycosyl iodides may be exploited for S_N2 glycosylations and solvolysis.

5.15 Glycosyl hydroxides

In 1997 David Y. Gin's research groups published a method for direct substitution of anomeric hydroxy groups of tetraacetates[217]. Glycosylation with tetraacetates is a noteworthy exception from most other glycosylation methods as it makes glycosylation to a one-pot treatment. This might be a more efficient strategy for the synthesis of oligosaccharides and glycoconjugates since traditional methods often included multiple steps. It averts the demand for isolation of both donors that are intermediate, which is sometimes desired in cases where the donor is not sufficiently stable for purification and/or isolation.



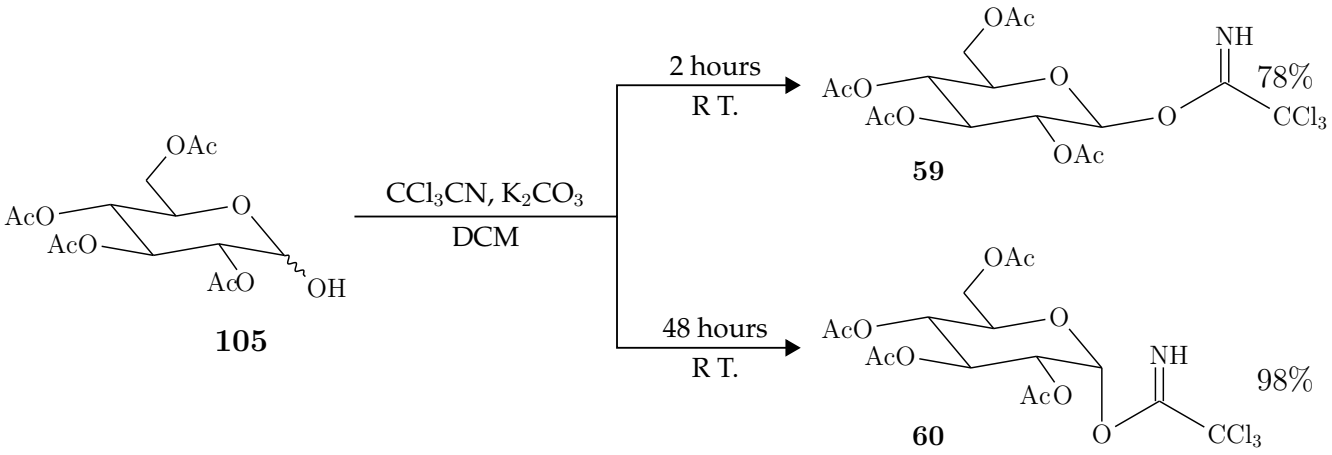
Scheme 40: Glycosyl hydroxide as a leaving group.

Unless tetraacetates are activated by acids they are not vulnerable to electrophilic reagents. Activation commonly utilizes trifluoromethanesulfonic anhydride and diphenyl sulfoxide. This method works with a wide range of acceptors, such as; sulfur, carbon, and nitrogen nucleophiles. Nevertheless, this method is still not widely used due to obstacles posed by donors, since the tetraacetate may also act as an acceptor. As a consequence, almost any procedure that creates an actuated tetraacetate intermediate is at a risk of self-condensation to build the corresponding glycoside-dimer.

6 Anomeric *O*-alkylation

Preparation of glycosyl trichloroacetimidates

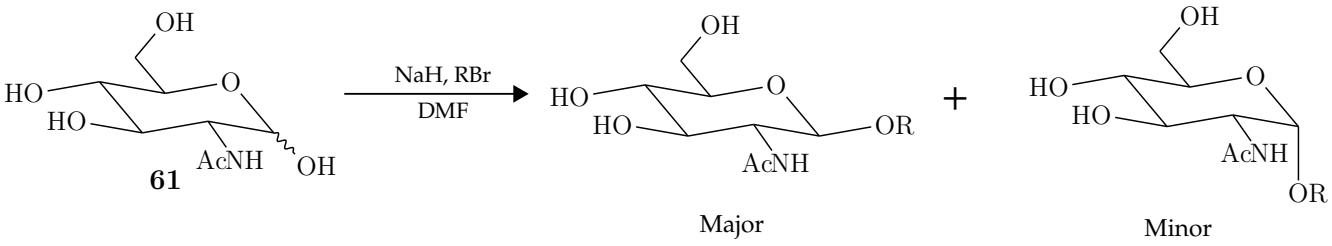
One of the most common applications for anomeric *O*-alkylation is to make glycosyl trichloroacetimidates, which are used as electrophiles in the Schmidt reaction. Schmidt introduced this method in 1980[198]. In the production of acetylated glycosyl trichloroacetimidates Schmidt used K_2CO_3 in DCM. He discovered that after 2 hours at R.T. mostly β-glycosylated trichloroacetimidates had been formed, while after leaving the reaction for 48 hours mostly α-glycosylated trichloroacetimidates[203] had been formed (Scheme 41).



Scheme 41: Stereoselective preparation of α and β glycosyl trichloroacetimidates[203].

Glycosylation of *N*-acetyl D-glucosamine

In 2001, Jean-Marie Beau *et al.* experimented with anomeric *O*-alkylation of *N*-acetyl D-glucosamine in DMF (Scheme 42)[218]. They produced mainly β-glycosides, but from 7-14% α-glycosides in the various electrophiles they tested.



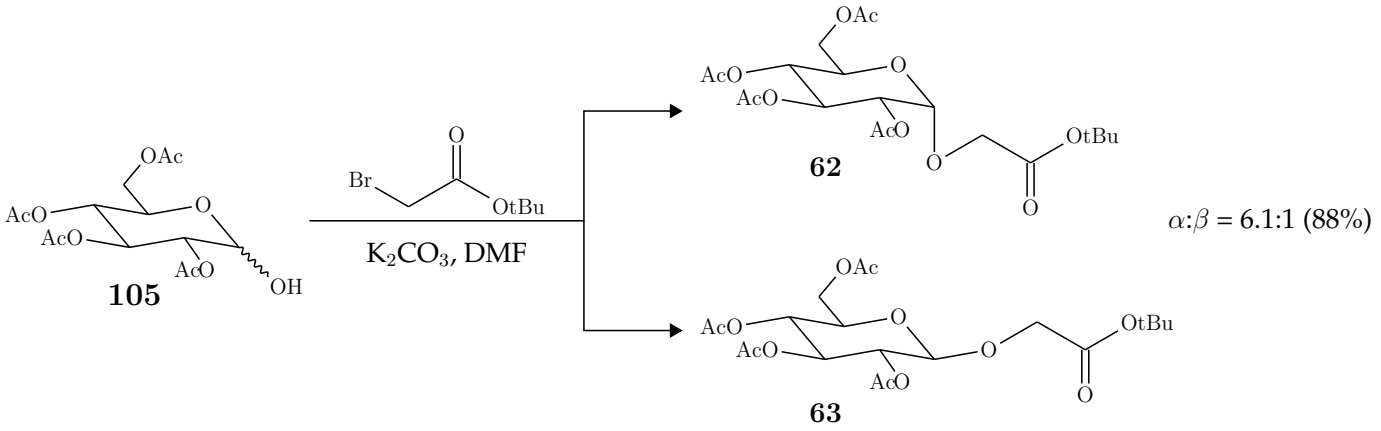
Electrophile	Allyl bromide	Benzyl bromide	Propagyl bromide	*p*-Nitrobenzyl bromide
β-yield	82%	75%	65%	58%
α-yield	12%	14%	9%	7%

Scheme 42: Anomeric *O*-alkylation of *N*-acetyl D-glucosamine[218].

They also investigated DMPU and DMSO as solvents, and reported similar results with DMSO, and much less stereoselectivity with DMPU. They also investigated adding LiBr as a salt, and found increased β-selectivity[218].

Glycosylation of α-haloesters

Glycosylation of α-haloesters was explored by R. Cheaib *et. al.* in 2008 with K_2CO_3 as a base and DMF as a solvent.[219]

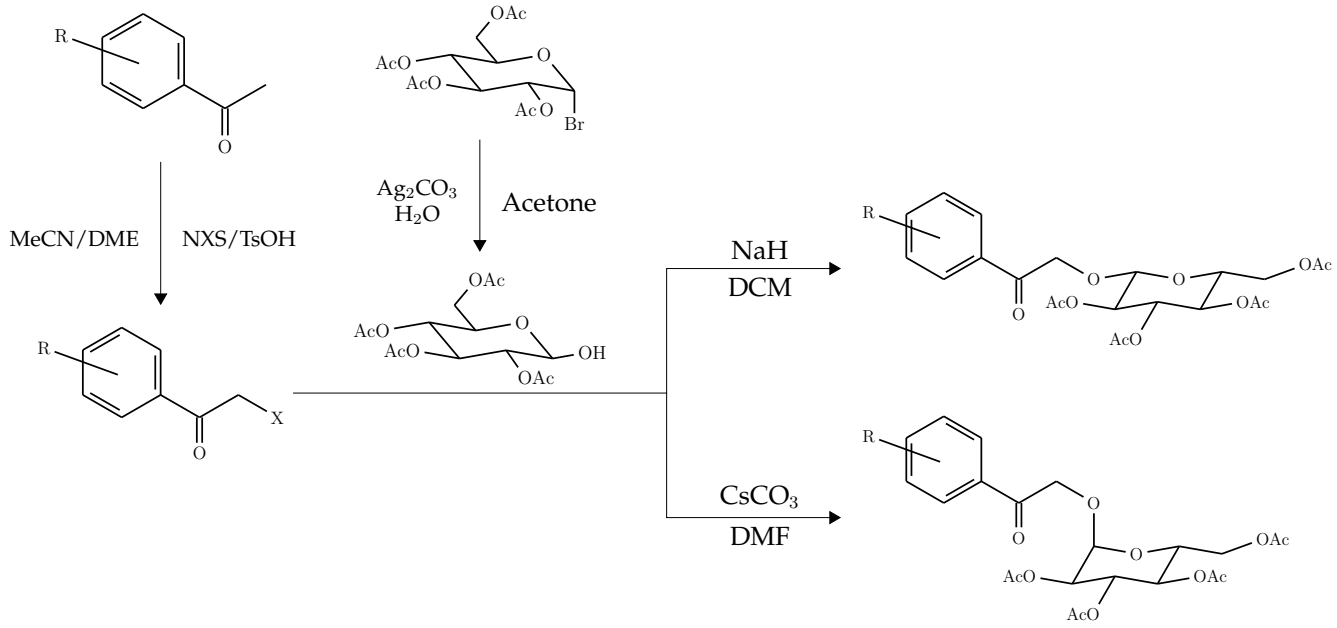


Scheme 43: Anomeric *O*-alkylation of α-haloesters[219].

They also experimented with glycosylated of unprotected sugars, but found K_2CO_3 to be an insufficient base for this purpose, and achieved much better yields with NaH. They also found that NaH favored more β-glycosylation.

Glycosylation of acetophenones

Bakstad's research group (Biosynth AS) filed for a patent that used anomeric *O*-alkylation to synthesize anthocyanins in 2006[1]. Since then, anomeric *O*-alkylation has been investigated with more electrophiles and to produce α-glycosides (Scheme 44 and Figure 37).



Scheme 44: Glycosylation of α-haloacetophenones developed by Bakstad's research group.

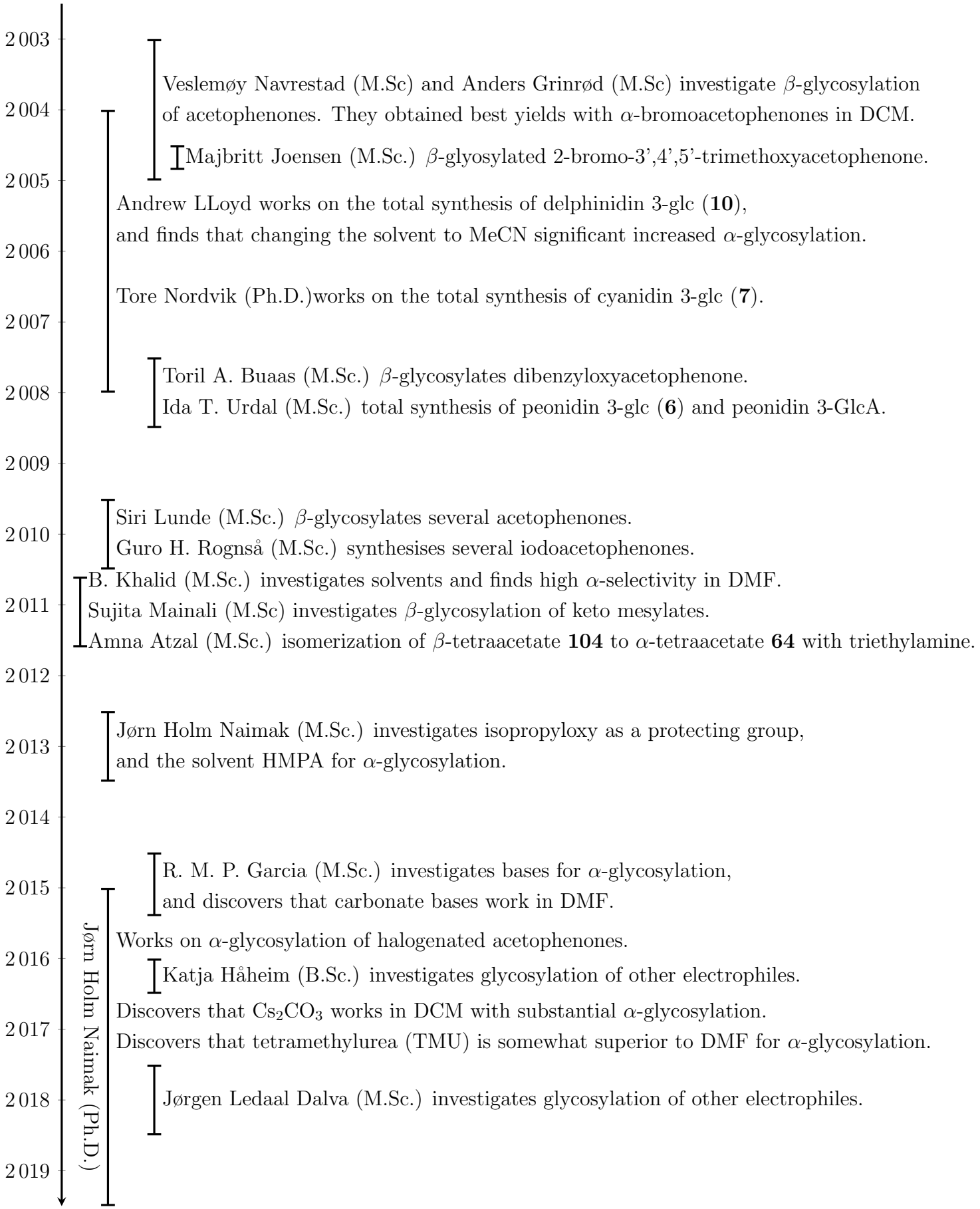
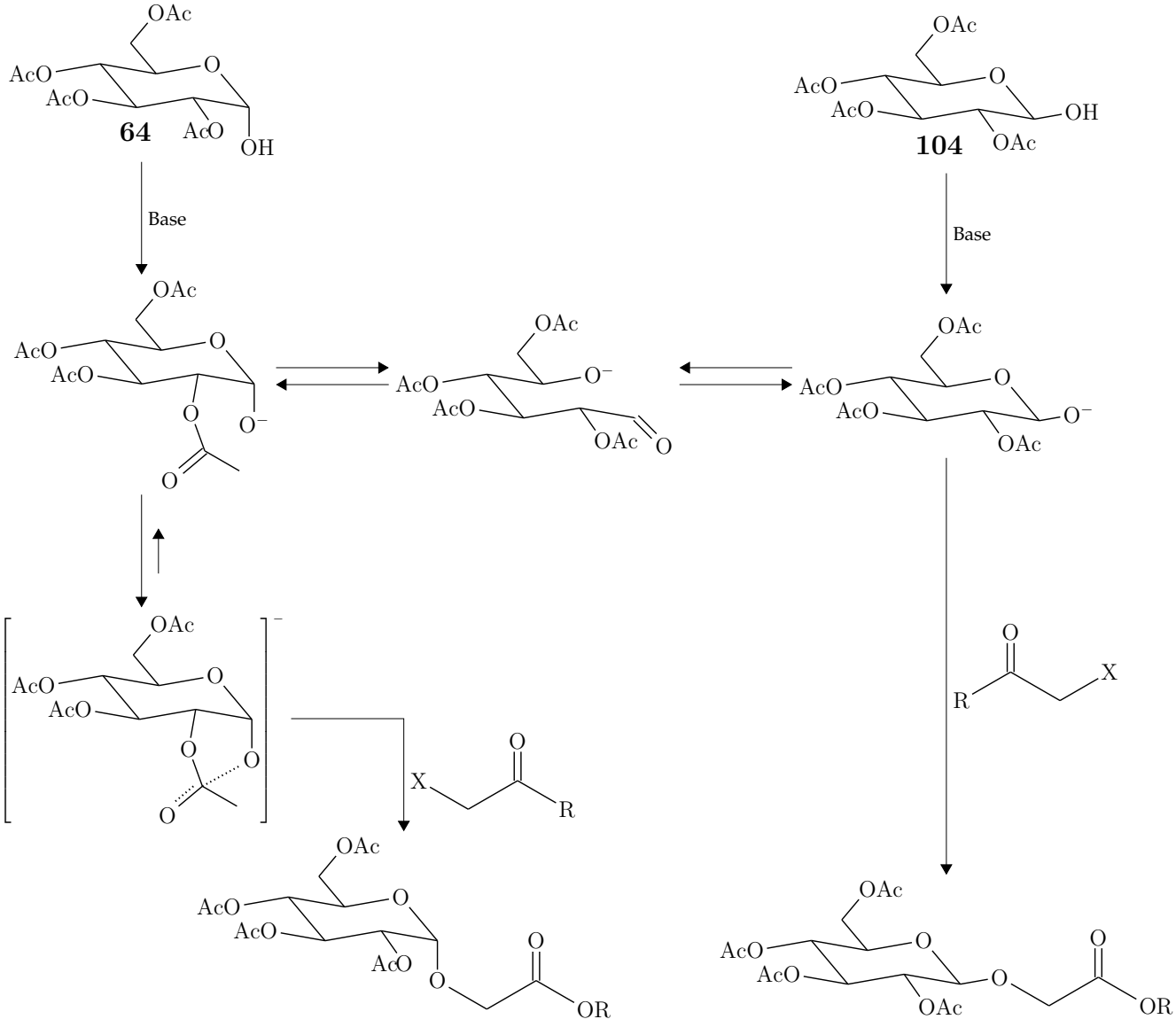


Figure 37: Timeline of development in Bakstad's research laboratory.

Proposed mechanism for anomeric *O*-alkylation

It is hypothesized that α-tetraacetate **64** has lower pKa than β-tetraacetate **104**. This could be an explanation for why there has been observed higher yields when starting with α-tetraacetate **64**. The deprotonated form of α-tetraacetate **64** is believed to be more thermodynamically stable, but less reactive than the deprotonated form β-tetraacetate **104** due to the stabilizing effect from the neighboring acetyl group attached to the oxygen at C2. This would explain why mainly β-glycosylated products are observed when reacting a mixture of the two isomers containing mostly α-tetraacetate **64** with an electrophile in less polar solvents such as DCM and toluene. The deprotonated form of α-tetraacetate **64** is possibly not sufficiently reactive to form products in these less polar solvents.



Scheme 45: Proposed glycosylation mechanism. The neighboring acetyl group can stabilize the anion of the α-glycoside, which makes it less likely to ring open and change into the anion of the β-glycoside, but it could also make it less reactive than the anion of the β-glycoside.

Influence of cation

Cations that are more shielded from the anion, or cations that have a more ionic and less covalent interaction with the anion, are expected to facilitate ring-opening and isomerization between the deprotonated form of α-D-glucose tetraacetate and β-D-glucose tetraacetate. The crystal energies of different alkali hydrides, show that LiH has the highest crystal energy, while CsH has the lowest crystal energy (Table 4).

Table 4: Crystal energies of different alkali hydrides[220].

Compound	LiH	NaH	KH	RbH	CsH
Crystal Energy (kcal mol^{-1})	217.18	192.45	171.04	164.37	156.84

The minimum amount of energy required to remove the valence electron of an alkali metal decreases with the size of the alkali metal (Figure 38).

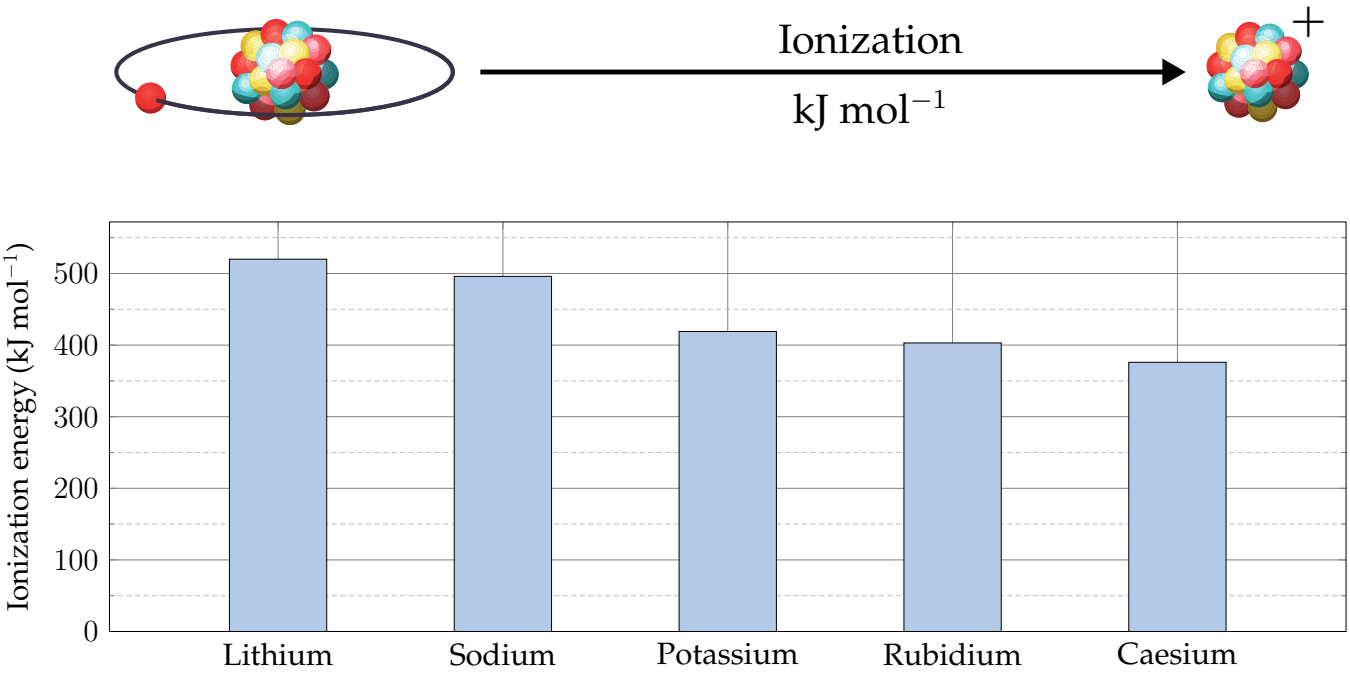


Figure 38: First ionization energy for the alkali metals[221].

Examining the difference in electron negativity between lithium and oxygen, and comparing it to the difference between caesium and oxygen, it is clear that there is less difference in electron negativity between lithium and oxygen (2.46) than between caesium and oxygen (2.65). Hence, the interaction between an oxygen anion and lithium cation can be considered to have a more polar covalent character than the interaction between an oxygen anion and a caesium cation. This may also be part of the explanation for why caesium bases are so much more reactive compared to structurally identical bases with smaller cations[222].

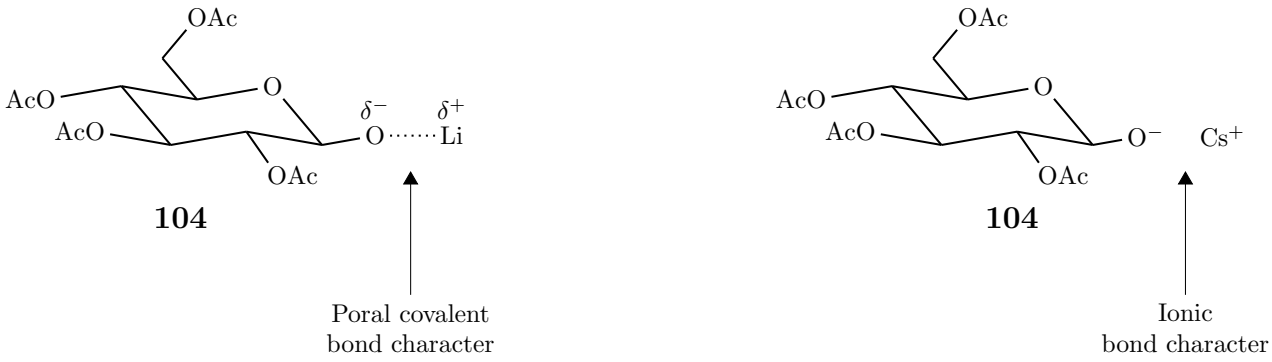


Figure 39: Difference in bond character between deprotonated β-tetraacetate **104** with lithium as a counterion and with caesium as a counterion.

Crown ethers can further help to stabilize alkali cations and weaken the interaction between cation and the anion of D-glucose tetraacetate. 12-Crown-4 can be used to capsulate lithium cations, 15-crown-5 can be used to capsulate sodium cations, 18-crown-6 can be used to capsulate potassium cations[223], and dibenzo-30-crown-10-ether can be used to capsulate caesium cations[224]. Other cation scavengers, such as triisopropylsilane (TIPS), might also be useful in this manner.

Influence of solvent

Solvents can also be used to either strengthen or weaken the interaction between the anion of D-glucose tetraacetate **105** and its counterion. Polar solvents are better at stabilizing ions and weaken the interaction between the anion of D-glucose tetraacetate **105** and its counterion, while less polar solvents are worse at stabilizing the ions and force them to be closer together or prevent them from being further apart. Some polar aprotic solvents are *N,N*-dimethylformamide (DMF), *N,N,N',N'*-tetramethylurea (TMU), and hexamethylphosphoric triamide (HMPA).

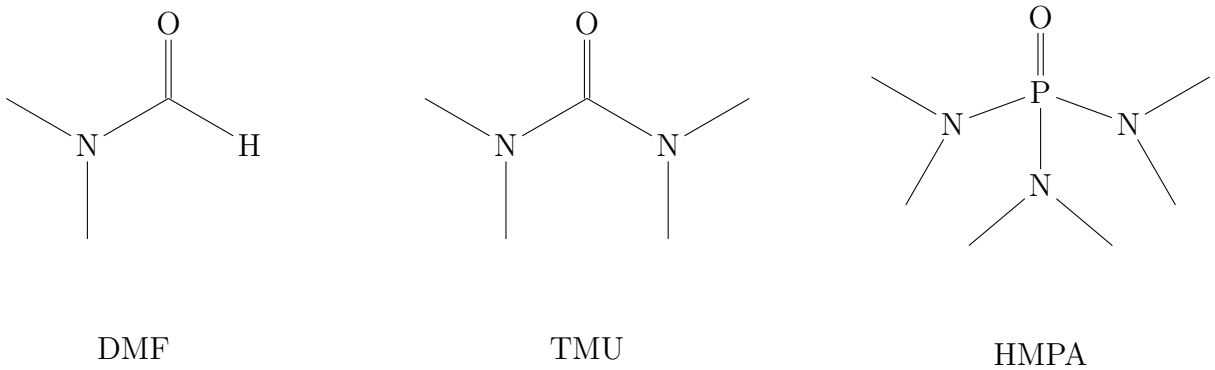
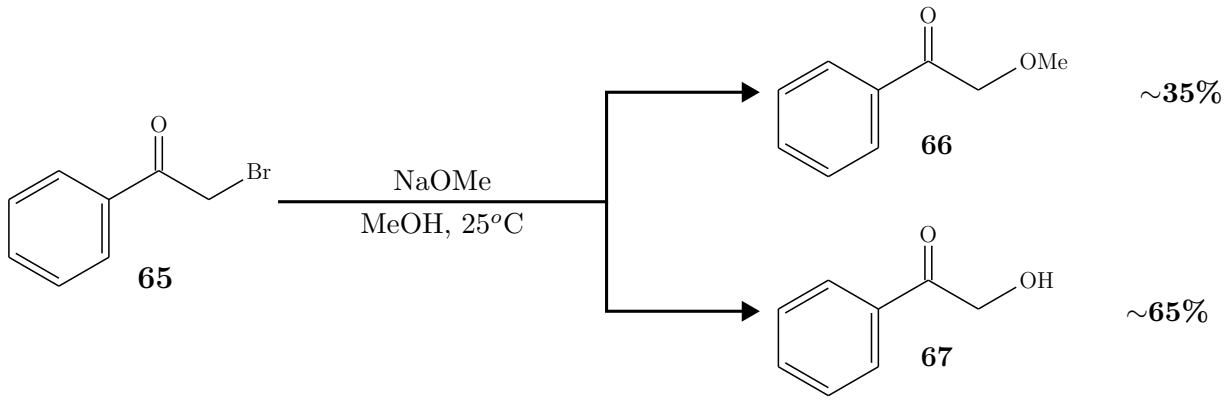


Figure 40: Structural similarities between DMF, TMU, and HMPA.

These solvents have ionic resonance forms which can stabilize anions of α-D-glucose tetraacetate **64** and β-D-glucose tetraacetate **104**. Less polar solvents, such as hydrocarbons or alkyl halides will be less able to stabilize the anion of D-glucose tetraacetate **105**.

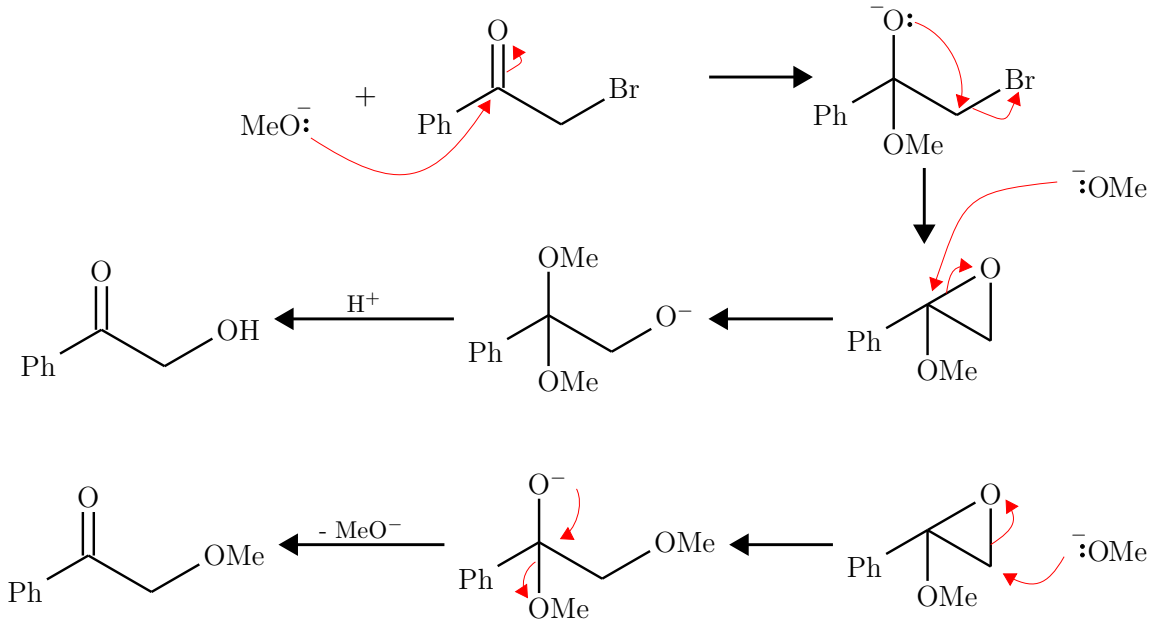
Nucleophilic substitution of α-haloketones

Nucleophilic substitution of α-haloketones has been extensively studied, and when methanol attacks a α-haloacetophenone as a nucleophile, both an acyloin **67** and an ether **66** is observed as the product (Scheme 46).



Scheme 46: How both acyloins and ethers are observed as products when MeO^- attack an α-haloacetophenone[225].

There has been proposed two competing mechanistic pathways to explain why both these products are observed[225]. The ether **66** might be produced in a standard S_N2 reaction with a nucleophilic attack on the α-carbon. The acyloin **67** might however be produced by a nucleophilic attack on the carbonyl carbon (Scheme 47). This is an exception to the tendency nucleophiles generally have to attack the least substituted carbon of epoxides. However, it depends more precisely upon which carbon of the epoxide is least electron rich.



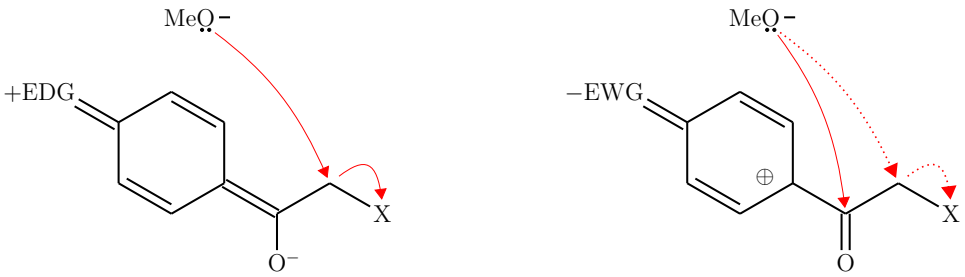
Scheme 47: Proposed mechanism for bifurcation during nucleophilic attack of α-haloacetophenones..

α-Haloacetophenones with electron withdrawing groups were found to produce more acyloins than α-haloacetophenones with electron donating groups (Table 5).

Table 5: Tendency for different substituents in the bifurcation mechanism of acetophenones[225].

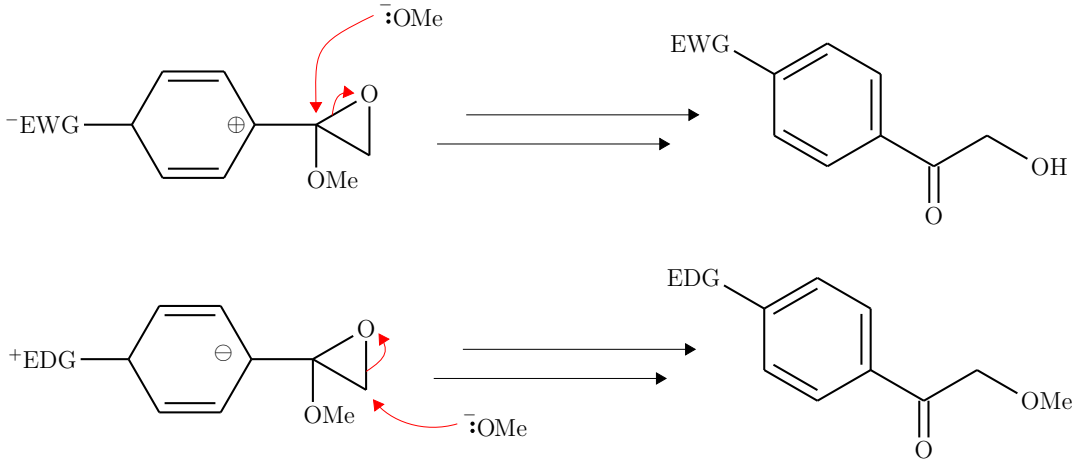
Substituent	*p*-MeO	*p*-Me	H	*p*-F	*p*-Cl	m-Cl	*p*-CF_3	*p*-NO_2
% Acyloin formation	31.3	55.9	65.8	74.3	81.5	90.5	92.2	100
% Ether formation	69.3	49	35.8	30.4	20.4	13	8.2	0

This can be explained by that electron donating groups in the *para* position of the aromatic ring donate electrons all the way to the carbonyl oxygen (Scheme 48), which at that time prevents nucleophiles from attacking the carbonyl carbon, and makes only the α-carbon available for a nucleophilic attack. Electron withdrawing groups put a positive charge at C1', one carbon away from the carbonyl carbon, but two carbons away from the α-carbon. This positive charge has the largest influence on the carbonyl carbon, and therefore increases the likelihood of a nucleophilic attack at the carbonyl carbon more than it increases the likelihood of a nucleophilic attack at the α-carbon.



Scheme 48: How EDGs and EWGs might influence the carbonyl carbon more than the α-carbon.

It is also likely that electron donating groups help to facilitate the ether forming pathway while electron withdrawing groups help to facilitate the acyloin pathway in Scheme 47 (Scheme 49).



Scheme 49: How EDGs and EWGs might influence which pathway is taken in Scheme 47.

Increasing the reactivity of electron-poor acetophenones

One way to increase the reactivity of an electrophile is by having a better leaving group. For example, fluorine is generally considered an inferior leaving group compared to chlorine; chlorine is generally considered an inferior leaving group compared to bromine; and bromine is generally considered an inferior leaving group compared to iodine. Other leaving groups, such as mesylates and tosylates might be better than iodine in some circumstances, while triflates are even better[226].

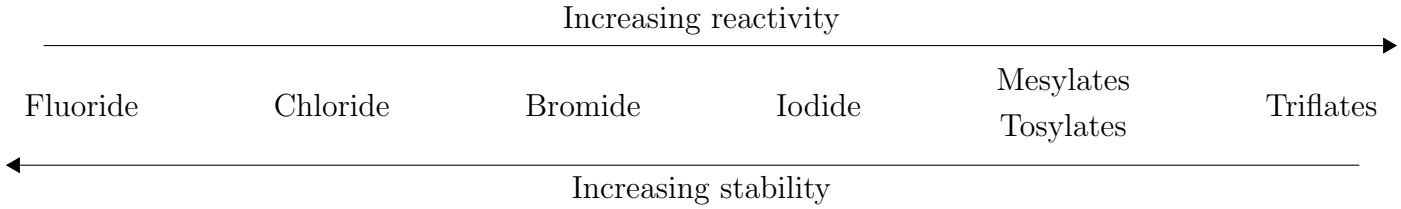


Figure 41: Reactivity and stability of some common leaving groups.

However, compounds with better leaving groups are generally also less stable. Poor leaving groups may also be activated by promoters *in situ*, such as with glycosyl fluorides in the widely used Mukaiyama-Suzuki glycosylation. This is however not necessarily applicable to anomeric *O*-alkylation under basic conditions.

There might also another way to increase the reactivity of electron-poor acetophenones.π-π-Interactions, known as stacking, is a type of interaction between two aromatic rings, where an electron-rich aromatic ring donates electron density to the electron-poor aromatic ring[227]. Adding an inert electron-rich aromatic ring to a solution with an electron-poor acetophenone might contribute to make an electron-poor acetophenone slightly electron-rich, and thereby more reactive in anomeric *O*-alkylation.

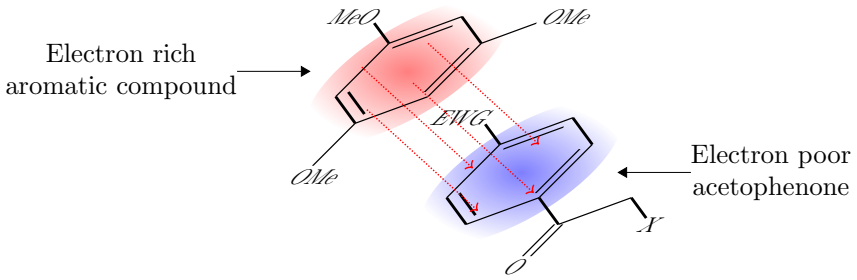


Figure 42: How an electron-rich aromatic ring can donate electron density to an electron-poor aromatic ring.

Sonochemistry

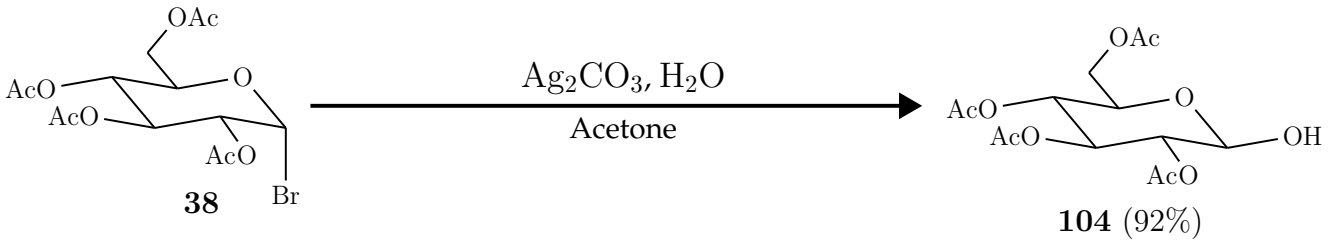
The use of ultrasound in chemical synthesis has been shown to reduce reaction time, increase yields, and decrease the formation of byproducts. It works by creating short-lived microcavities, which implode and generate high pressures ($\sim$ 500 atmospheres) and high temperatures ($\sim$5000 °C)[228]. Sonochemistry has successfully been applied to *O*-alkylation[229], and might be suitable for anomeric *O*-alkylation of α-haloacetophenones[230].

7 Results and discussion

7.1 Preparation of tetraacetate

The Koenigs–Knorr reaction

The least cumbersome way to obtain the pure β-tetraacetate **104** was under standard Koenigs Knorr conditions with acetobromo-α-D-glucose **38** and water in acetone (Scheme 50). The solvent (acetone) was cooled to 0 °C before adding the reagents to maximize the amount of β-stereoselectivity.

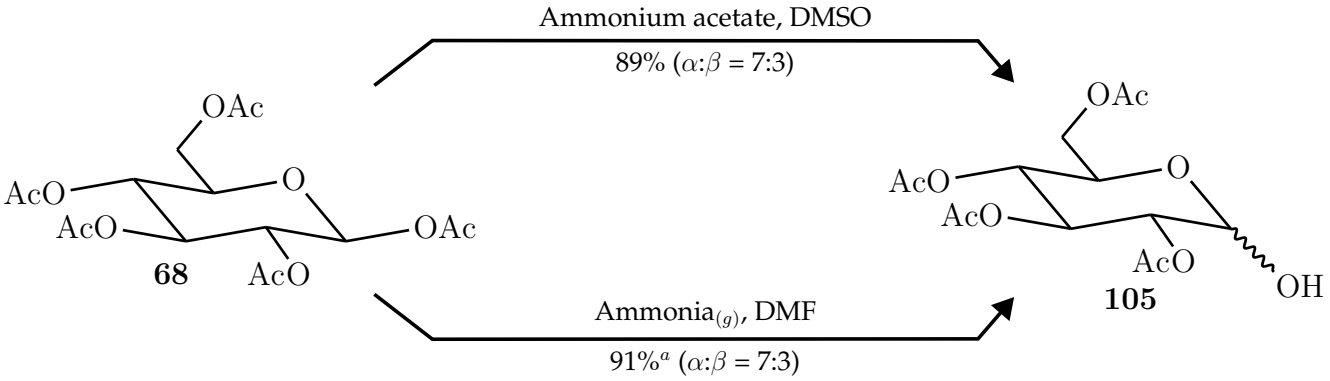


Scheme 50: How β-D-glucose tetraacetate was produced in a standard Koenigs-Knorr reaction.[152,231]

The reaction was performed innumerable times, and consistently gave yields of more than 90% of β-D-glucose tetraacetate. Traces of α-D-glucose tetraacetate was also frequently produced, especially when the reaction was performed at larger scales, such as with more than 100 mmol acetobromo-α-D-glucose. Traces of the α-anomer **64** were readily removed by recrystallization in methylcyclohexane.

Deacetylation of β-pentaacetate 68

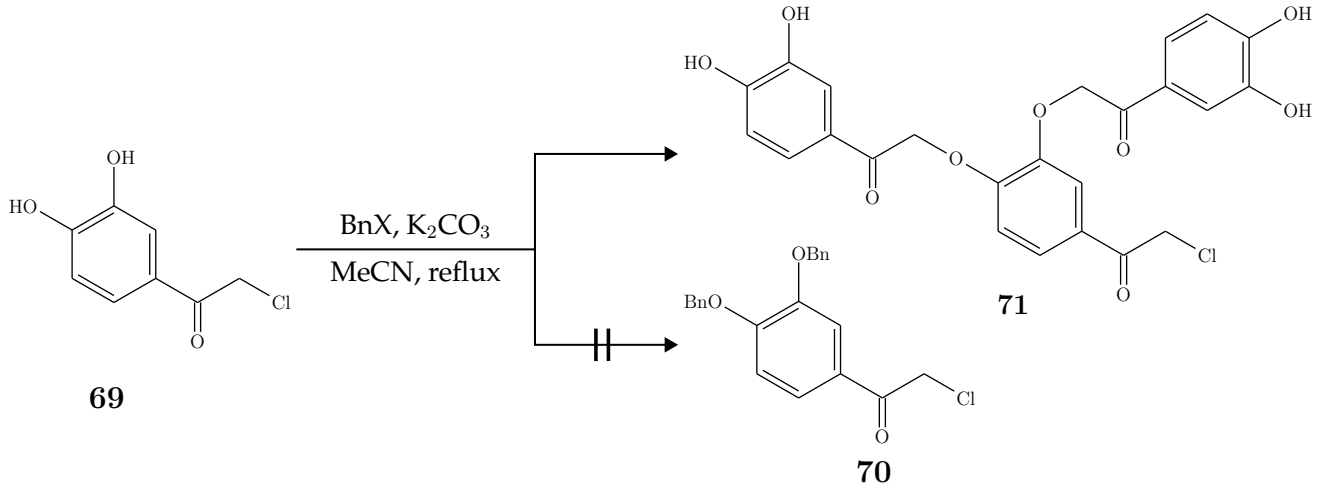
Since the Koenigs-Knorr reaction is somewhat costly on a large scale, deacetylation of pentaacetate **68** was investigated to find a more economically feasible way to produce D-glucose tetraacetate, and to produce more α-tetraacetate **64**. Several different methods were investigated. One of the most successful methods that were discovered (Scheme 51), utilized ammonium acetate[232] in a solution of DMF or DMSO at R.T. or in THF or MeCN at reflux. J. L. Dalva[233] also investigated a method that utilized ammonia$_{(g)}$[234] in DMF and MeCN at 0 ^{o}C to R.T. The yields were generally highest in DMF and DMSO.



Scheme 51: Deacetylation of β-pentaacetate **68** with ammonium acetate in DMSO, and ammonia in DMF. The yield with the notation "a" was reported by J. L. Dalva[233].

7.2 Preparation of α-haloketones

During the first attempts at a total synthesis of cyanidin 3-glc (**7**) in 2003-2004, Bakstad's research group attempted to protect 2-chloro-3',4'-dihydroxyacetophone (**69**) with BnCl. This was chosen as a starting material due to the low price from commercial vendors. Unfortunately a black syrup was obtained instead of 2-chloro-3',4'-dibenzyloxyacetophone (**70**). It is hypothesized that this is due to it reacting with itself (Scheme 52). It was shown by the author and M.Sc. R. M. P. Garcia[235] that α-chloroacetophenones can be glycosylated in DMF (Scheme 70). However, as has been shown later by the work of Katja Håheim[236], Jørgen Ledaal Dalva[233], and in this work; BnCl, BnBr are not sufficiently strong electrophiles to be glycosylated in DMF (Scheme 76), while BnI only gives traces.



Scheme 52: Proposal for how 2-chloro-3',4'-dihydroxyacetophone reacts with itself under attempts to protect it with BnX. This is a hypothesis. The predicted product was never isolated and analyzed by the author.

Bakstad's research group were however able to use diphenyldichloromethane as a protective group, and settled for this as their protective group in the total synthesis of cyanidin 3-glc (**7**) in the 2006 patent (Scheme 6)[1]. The benzylic protective group has however continued to be of interest. Perhaps the tendency to react with itself can be minimized by gradually adding 2-chloro-3',4'-dibenzyloxyacetophone over a long period of time to a solution of BnX in MeCN.

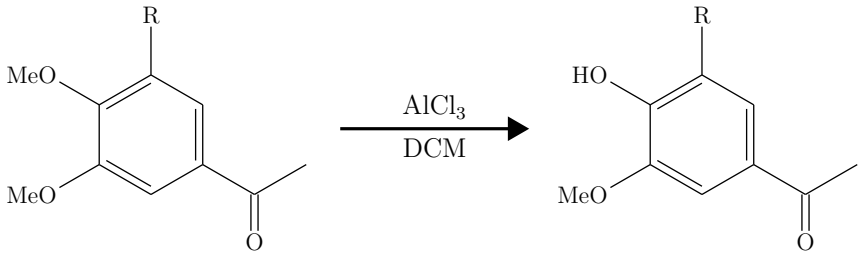
Friedel-Crafts acylation

Another possible starting material for synthesizing cyanidin 3-glc (**7**) is 3,4-dihydroxyacetophenone (**106**). It has however been costly to obtain this compound from commercial vendors. Friedel-Crafts acylation of catechol with chloroacetyl chloride has been reported in the literature with good yields in the preparation of 2-chloro-3',4'-dihydroxyacetophenone (**69**)[237]. In the master project of M.Sc. Toril Andresen Buass she attempted to synthesize 3,4-dihydroxyacetophenone (**106**) by Friedel-Crafts acylation of catechol with acetyl chloride[230]. However, she only reports a yield of 16%. Bakstad's research group attempted several times to improve the yield, but with little success.

Demethylation

3,4,5-Trihydroxyacetophenone is a compound that can be used as a starting material for producing delphinidin 3-glc (**10**), but this compound is also costly to obtain from commercial vendors. 3,4-Dimethoxyacetophenone and 3,4,5-trimethoxyacetophenone are however available at much lower prices. Anisol, *m*-cresol, and 3,5-dimethylphenol were demethylated by $AlCl_3$ in 1944[238]. Based upon similar work in the master project of by Adj. Prof. Dr. Einar Bakstad[239], he theorized that methoxy groups of acetophenones could be deprotonated in a similar fashion. During the work of master student K. S. Fagerstrand[240] methoxy groups at the *para* position of the acetyl group of acetophenones were readily demethylated with 3 equivalents of $AlCl_3$ (Scheme 53). However, methoxy groups at *meta* positions of the aromatic ring could not be cleaved with $AlCl_3$. Both 3,4-dimethoxyacetophenone and 3,4,5-trimethoxyacetophenone only cleaved the methoxy group in the *para* position.

R	Product	Yield
H	**72**	75%
MeO	**107**	92%

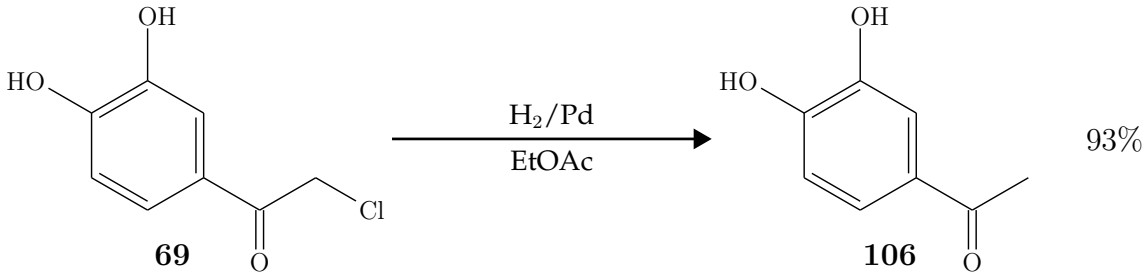


Scheme 53: Acetophenones that were demethylated by $AlCl_3$ in DCM.

This could be related to that the acetyl group helps to stabilize the intermediate in the *para* position when the ether bond is cleaved. Methoxy groups in the *meta* positions do not have this advantage. It is possible to cleave all three ether bonds by using a stronger Lewis acid (BBr_3), but this Lewis acid is toxic and difficult to work with. Perhaps tweaking the reaction conditions or using a compound capable of increasing the potency of $AlCl_3$ would help to facilitate cleavage of the *meta* positions. *N,N*-Dimethylaniline has been reported to increase the potency of $AlCl_3$ in ether cleavage[241].

Hydrogenation

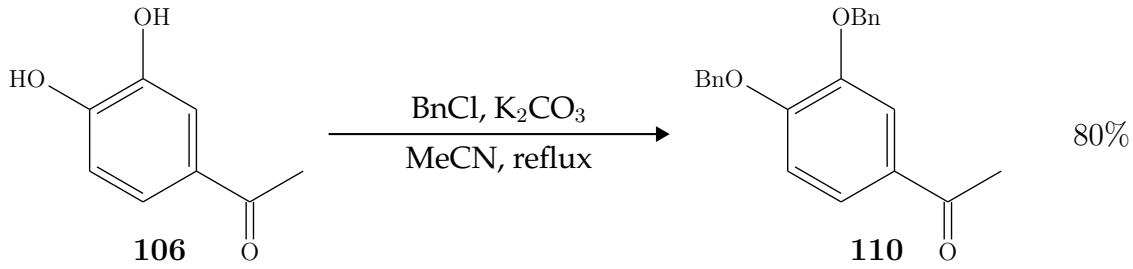
Due to the challenges with protecting 2-chloro-3',4'-dihydroxyacetophone (**69**) (Scheme 52) and the challanges with obtaining 3,4-dihydroxyacetophenone (**106**) from Friedel-Crafts acylation and from demethylation of 3,4-dimethoxyacetophenone, it was prepared by palladium-catalyzed hydrogenation of 2-chloro-3',4'-dihydroxyacetophone (**69**) on charcoal in EtOAc (Scheme 54). The hydrogenation afforded an excellent yield of 93%.



Scheme 54: Hydrogenation of 2-chloro-3',4'-dihydroxyacetophone (**69**).

Protection with benzyl chloride

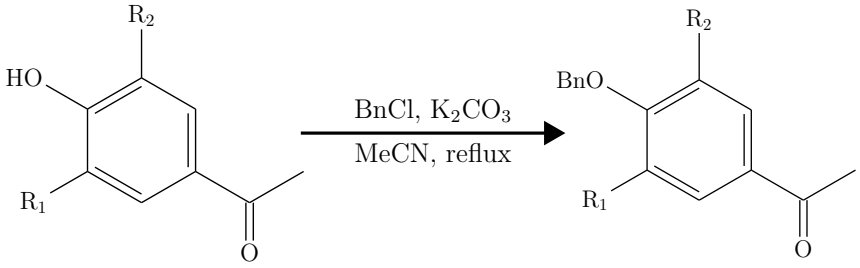
3,4-Dihydroxyacetophenone (**106**) was readily benzylated with BnCl to give 3,4-dibenzyloxyacetophenone (**110**) with a yield of 80% (Scheme 55).



Scheme 55: Benzylation of 3,4-dihydroxyacetophenone.

The 4-hydroxy group was protected with benzyl chloride (BnCl) for several other acetophenones (Scheme 56). The reaction afforded yields of more than 80% of the benzylated compounds.

R_1	R_2	Product	Yield
H	H	**108**	92%
H	MeO	**109**	94%
MeO	MeO	**111**	85%

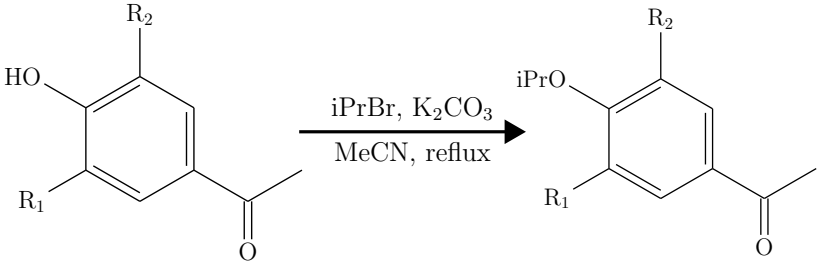


Scheme 56: Acetophenones protected by BnCl at the 4-hydroxy group.

Protection with isopropyl bromide

Isopropyl groups were also investigated as a potential protective group for hydroxy groups in acetophenones. The 4-hydroxy group was protected with iPrBr for several acetophenones (Scheme 57). The reaction afforded yields of more than 80% of the isopropylated compounds.

R_1	R_2	Product	Yield
H	H	**112**	86%
H	MeO	**113**	78%
MeO	MeO	**114**	87%

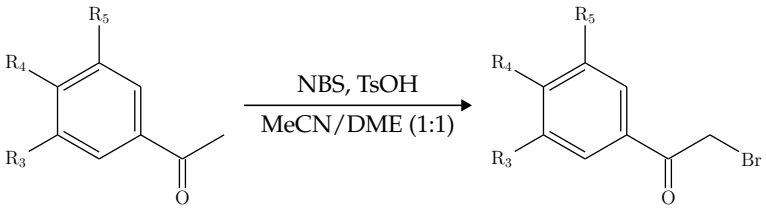


Scheme 57: Acetophenones protected by iPrBr at the 4-hydroxy group.

Bromination

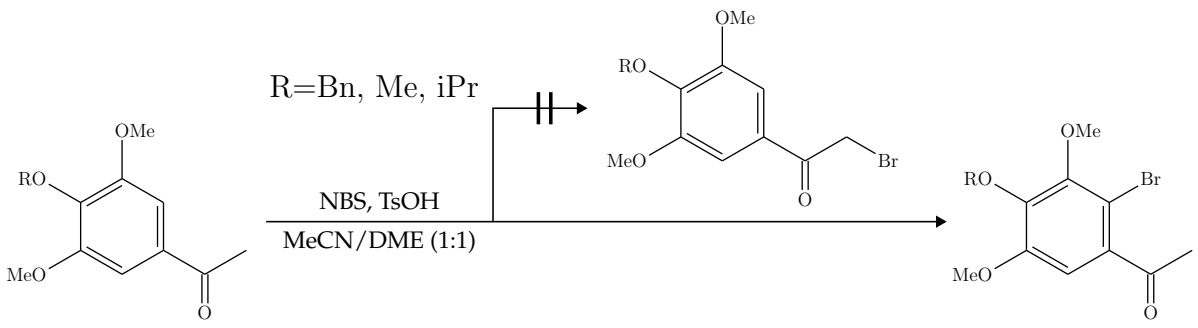
A modified version of the method for α-halogenation described by Lee, et al.[242] were used to brominate acetophenones. Acetophenones were brominated in a mixture of DME and MeCN, where MeCN with TsOH was added dropwise to a solution with DME with acetophenone and NBS. Acetophenones were usually brominated in high yields (Scheme 58).

R_3	R_4	R_5	Product	Yield
H	NO_2	H	**120**	57%
H	F	H	**122**	94%
H	Cl	H	**123**	54%
H	Br	H	**124**	74%
H	I	H	**125**	72%
H	Me	H	**121**	91%
H	MeO	H	**126**	91%
H	iPrO	H	**127**	96%
H	BnO	H	**128**	76%
MeO	BnO	H	**131**	79%
BnO	BnO	H	**132**	86%
MeO	MeO	H	**129**	93%
MeO	iPrO	H	**130**	85%



Scheme 58: Acetophenones that were brominated.

This bromination method worked well for mono and disubstituted acetophenones, but when trisubstituted acetophenones were brominated in this way, the aromatic ring was brominated instead of the α carbon (Scheme 59).



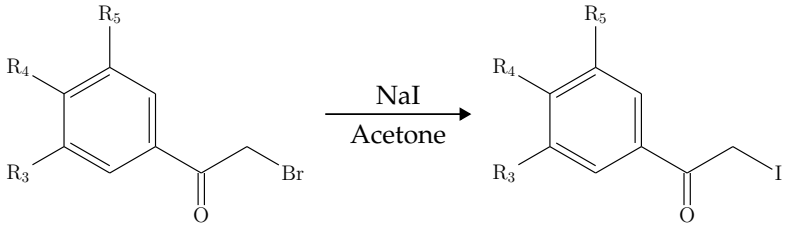
Scheme 59: How trisubstituted acetophenones were brominated on the ring instead of on the α carbon.

This did however not occur in the standard way that was used to iodinate acetophenones (Scheme 61), and the other methods that were found to brominate acetophenones either did the same, or were more toxic or expensive to perform. So the trisubstituted acetophenones that were glycosylated were α-iodoacetophenones.

The Finkelstein reaction

Iodine is a better leaving group than bromine. It was hypothesized that glycosylation yields would be higher with α-iodoacetophenones, so the Finkelstein reaction was used to produce several iodoacetophenones from α-bromoacetophenones (Scheme 60). However, for many acetophenones the yields from reactions with α-iodoacetophenones were found not to be considerably better than the yields from α-bromoacetophenones, so due to the higher stability of α-bromoacetophenones they were still often the preferred choice in glycosylations.

R_3	R_4	R_5	Product	Yield
H	iPrO	H	**136**	96%
H	MeO	H	**135**	79%
MeO	MeO	H	**138**	86%
MeO	iPrO	H	**139**	37%

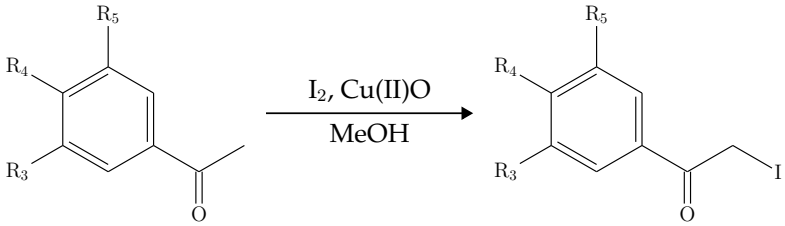


Scheme 60: Iodoacetophenones that were produced from α-bromoacetophenones by the Finkelstein reaction.

Iodination with I_2 and Cu(II)O in MeOH

The master students S. Lunde[243] and G. H. Rognsås[244] started using another low-priced method for producing α-iodoacetophenones[245]. Iodination of acetophenones was performed with elemental iodine (I_2) and Cu(II)O in MeOH. The author used this method to prepare several α-iodoacetophenones and the reaction generally afforded good yields (Scheme 61).

R_3	R_4	R_5	Product	Yield
H	Cl	H	**133**	80%
H	Br	H	**134**	71%
H	BnO	H	**137**	65%
H	MeO	H	**135**	76%
BnO	BnO	H	**140**	81%
MeO	BnO	H	**141**	81%
MeO	MeO	H	**138**	78 %
iPrO	MeO	H	**139**	78%
MeO	MeO	MeO	**143**	59 %
MeO	BnO	MeO	**142**	60 %
MeO	iPrO	MeO	**144**	24 %

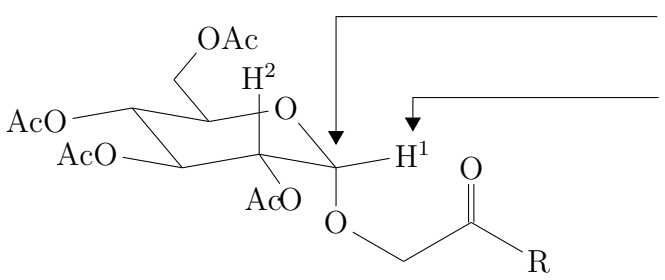


Scheme 61: Iodoacetophenones that were produced from acetophenones with I_2 in MeOH.

The α-bromoacetophenones and α-iodoacetophenones were subsequently used both in β-favored glycosylation (Scheme 62) and in α-favored glycosylation (Scheme 72).

7.3 Diastereoselective anomeric *O*-alkylation

The diastereomeric glycosides prepared by Bakstad's research group can be identified as distinct by ^{13}C NMR according to the chemical shift of the anomeric carbon, and more rigorously by ^{1}H NMR according to the size of the coupling constant between protons H^1 and H^2 (Figure 43). The diastereomeric glycosides can also be identified as distinct by optical rotation. The α-glycosides were found to have a positive optical rotation, while the β-glycosides were found to have a negative optical rotation.



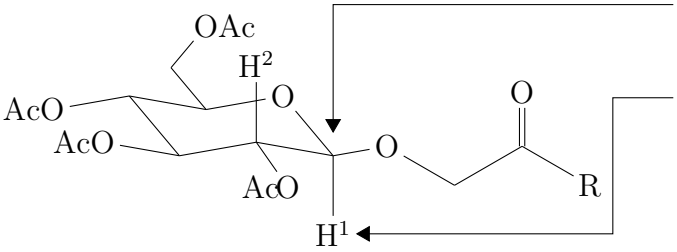
95.9-96.0 ppm (Lit. 95.7 ppm for compound **62**[219]).

5.16-5.22 ppm (Lit. 5.17 ppm for compound **62**).

$J_{1,2}$ = 3.5-3.7 Hz (Lit. 3.8 Hz for compound **62**[219]).

$[\alpha]_D^{24-29}$ = 135 to 39 (c. 0.5-4.3, DCM).

Lit. $[\alpha]_D$ = 129 (c. 1.0, DCM) for compound **62**[219].



100.0-100.2 ppm (Lit. 100.1 ppm for compound **63**[219]).

4.61-4.69 ppm (Lit. 4.68 ppm for compound **63**[219]).

$J_{1,2}$ = 7.8-8.0 Hz (Lit. 7.8 ppm for compound **63**[219]).

$[\alpha]_D^{25-28}$ = -34 to -3 (c. 1.5-5.3, DCM).

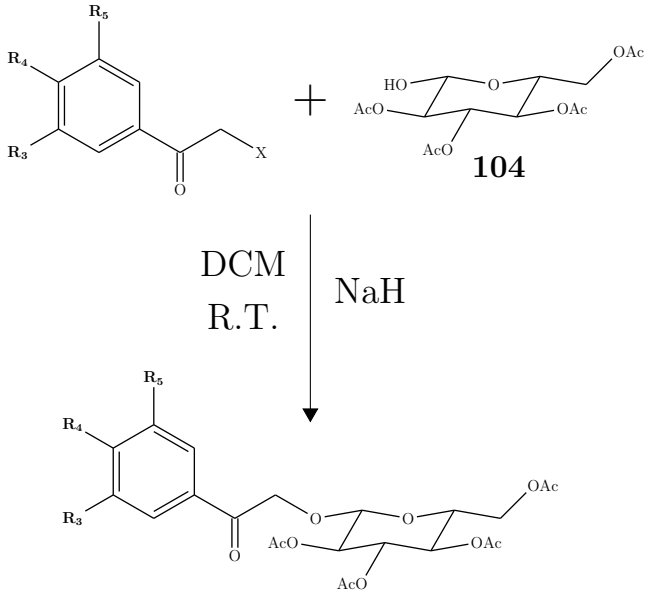
Lit. $[\alpha]_D$ = -29 (c. 1.0, DCM) for compound **63**[219].

Figure 43: How NMR and optical rotation differs between the α and β glycosides prepared by Bakstad's research group. In the reference compounds **62** and **63** R = tBuO.

β-Glycosylation of acetophenones in DCM

The first β-glycosylation of α-haloacetophenones with anomeric *O*-alkylation was performed by Veslemøy Narvestad (M.Sc.) and Anders Grinrød (C.Sc.) in 2003-2005[246]. After attempting to glycosylate acyloins several times by different methods, they attempted anomeric *O*-alkylation and obtained better yields. They glycosylate 2-bromoacetophenone (**65**), 2-bromo-4'-methoxyacetophenone (**126**), 2-bromo-3',4'-dimethoxyacetophenone (**129**), and 2-bromo-3',4'-*gem*-diphenylacetophenone. Andrew LLoyd and Tore Todvik (Ph.D.) subsequently worked on glycosylation of 2-iodo-3',4'-*gem*-diphenylacetophenone and 2-iodo-3',4',5'-tribenzyloxyacetophenon as steps in the total syntheses of cyanidin 3-glc **7** and delphinidin 3-glc **10**. The guest research scientist Josenne Mae Sanchez provided them with most of the starting materials. From 2007 until 2015, several master students worked on exploring β-glycosylation of acetophenones in DCM. The author also synthesized several β-glycosylated acetophenones (Scheme 62). During this period, it was discovered that electron-rich acetophenones were inclined to give higher yields than electron-poor acetophenones.

R_3	R_4	R_5	X	Product	Yield (%)
H	CF_3	H	Br	Not isolated	Traces
H	NO_2	H	Br	Not isolated	Traces
H	Br	H	Br	Not isolated	Traces
BnO	BnO	H	Br	**168**[b]	27
MeO	MeO	MeO	I	**164**[a]	47
H	iPrO	H	Br	**162**	50
H	Me	H	Br	**161**[d]	55
MeO	BnO	H	Br	**167**[c]	60
H	MeO	H	Br	**169**[e]	64
H	F	H	Br	**165**	65
MeO	MeO	H	Br	**166**[e]	69
iPrO	MeO	H	Br	**163**	77



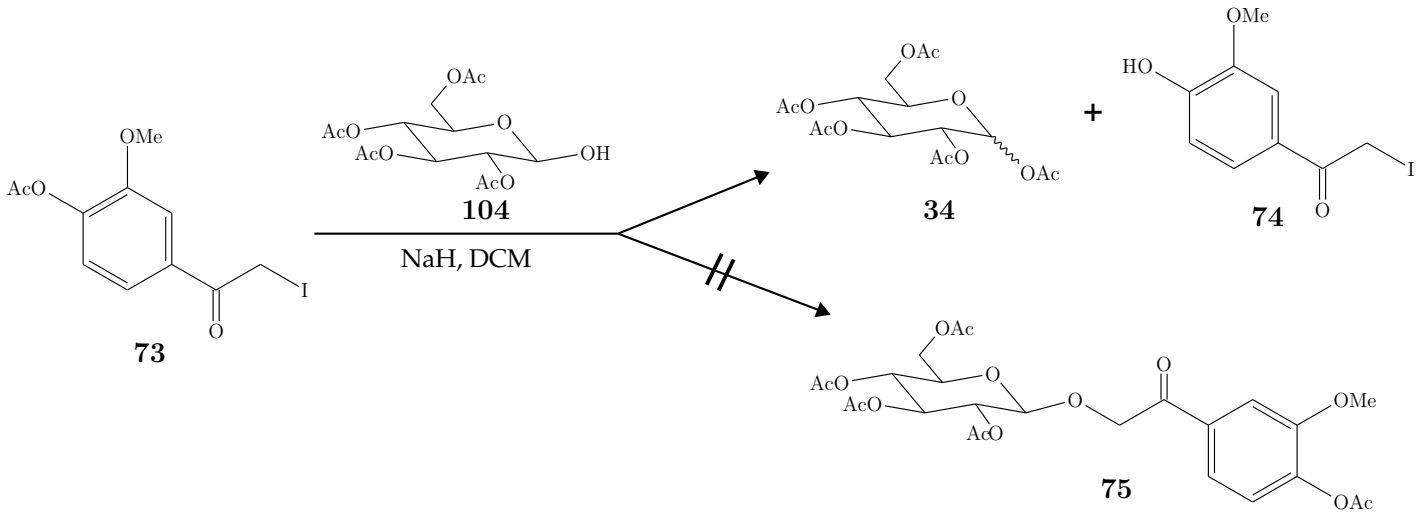
Scheme 62: β-Glycosylated α-haloacetophenones. Compounds with the notation "a" were first made by M. Joensen[247], compounds with notation "b" where made by T. A. Buass[230], compounds with the notation "c" were first made by I. T. Urdal[73], compounds with the notation "d" were first made by B. Khalid[248], and compounds with the notation "e" were first made by Veslemøy Narvestad and Anders Grinrød.

2-Bromo-4'-fluoroacetophenone reacted remarkably better than the α-haloacetophenones that were substituted in the *para* position with other halogens. Siri Lunde reported a yield of 15% when she first glycosylated 4'-chloro-2-iodoacetophenone[243], while Sujita Mainali was only able to see traces of the glycosylated product when she glycosylated 4'-bromo-2-iodoacetophenone[243]. These experiments were repeated multiple times to affirm this abnormality, which seems particularly strange since fluorine is the most electronegative halogen. It is also the preferred halogen to be used as a leaving group in nucleophilic aromatic substitution[249], which clearly indicates that more electronegativity is located on the aromatic carbon next to fluoro compared to aromatic compounds with other halogens. Fluorobenzene has however also been found to react much better than other halobenzenes in electrophilic aromatic substitution[250], and the reactivity of 2-bromo-4'-fluoroacetophenone might be related to the more overlapping orbitals between fluorine and carbon, compared to the less well overlapping orbitals of the other halogens and carbon. It might also be related to the larger HOMO-LUMO gap of fluorine, compared to the smaller HOMO-LUMO gaps for the other halogens[251].

The generation of pentaacetate 34 as a byproduct

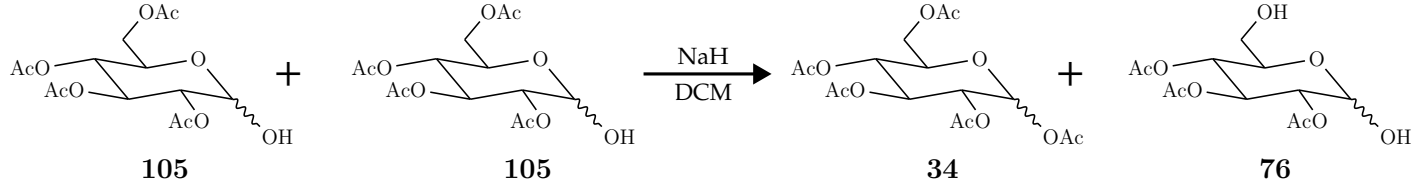
Varying amounts of pentaacetate **34** was formed as a side product in practically all the glycosylation reactions. More pentaacetate **34** was generally observed with less reactive electrophiles, while less pentaacetate **34** was generally observed with more reactive electrophiles. For acetophenones, this correlated with electron donating and electron withdrawing groups on the acetophenones (Scheme 62). Acetophenones with more electron donating groups usually produce less **34**, while acetophenones with more electron withdrawing groups usually produce more pentaacetate **34**. During the master project of I. T. Urdal, she attempted to glycosylate 4'-acetyloxy-3'-methoxy-2-iodoacetophene (**73**), but instead of the glycosylated product, she lost the acetyl group from the *para* position of the acetophenone and ended up

with pentaacetate **34** (Scheme 63)[73].



Scheme 63: When 4'-hydroxy-3'-methoxy-2-iodoacetophene was protected with an acetyl group, pentaacetate **34** was formed instead of the glycosylated acetophenone.[73]

It is suspected that tetraacetate **104** can take acetyl groups from other tetraacetate **104** molecules under basic conditions in a similar manner and generate pentaacetate **34**. A solution with tetraacetate **104** and NaH will produce pentaacetate **34**, and several other highly polar deacetylated glucosides that were difficult to isolate with flash chromatography. A dark brown oil which seemed to contain several deacetylated glucosides was however obtained when extracting the remaining compounds in a flash column with MeOH.



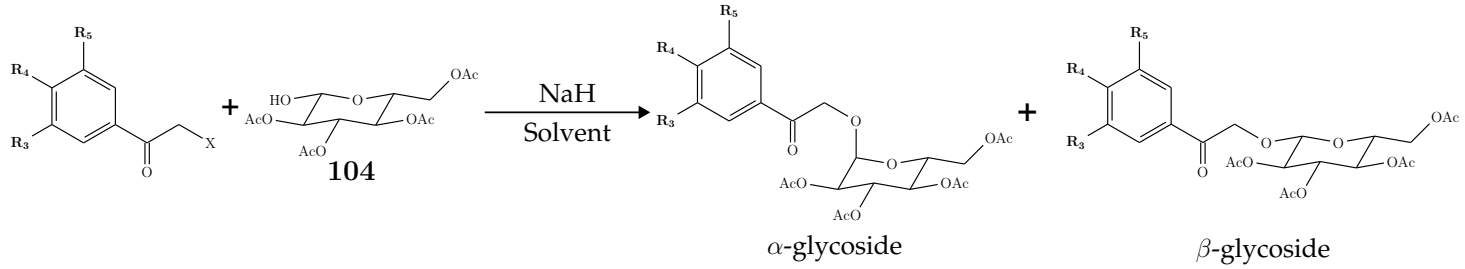
Scheme 64: The generation of pentaacetate as a side product. The acetate group presumably comes from the least sterically hindred acetate group of another tetraacetate.

J. L. Dalva reports that using more than 1.15 equivalents of NaH gave an increase in the amount of pentaacetate **34** as byproduct[233], while R. M. P. Garcia reports that heating the reaction produces more pentaacetate **34**[235]. J. L. Dalva also claims to have produced less pentaacetate **34** when starting reactions at 0 ^{o}C, and let them gradually warm to room temperature[233].

Investigation of solvents

Bakstad's research group had already uncovered that DCM and the ether solvents THF and DME facilitate β-glycosylation when they filed for their patent in 2006[1]. A. Loyd discovered in 2006 that performing the glycosylation with NaH in MeCN, rather than in DCM, had significantly increased the amount of α-glycosylation. To investigate this further, the master student B. Khalid started to experiment with different solvents in 2011[248]. It was discovered that DMSO, NMP, DMPU, and DMF produced mainly α-glycosides (Scheme 65). Later, in 2012-2013, it was discovered that HMPA also produces mainly α-glycosides. Of the

solvents that favored α-glycosylation, DMF seemed to give the largest amount of α-glycosides, and was therefore used as the standard solvent for α-glycosylation subsequently.

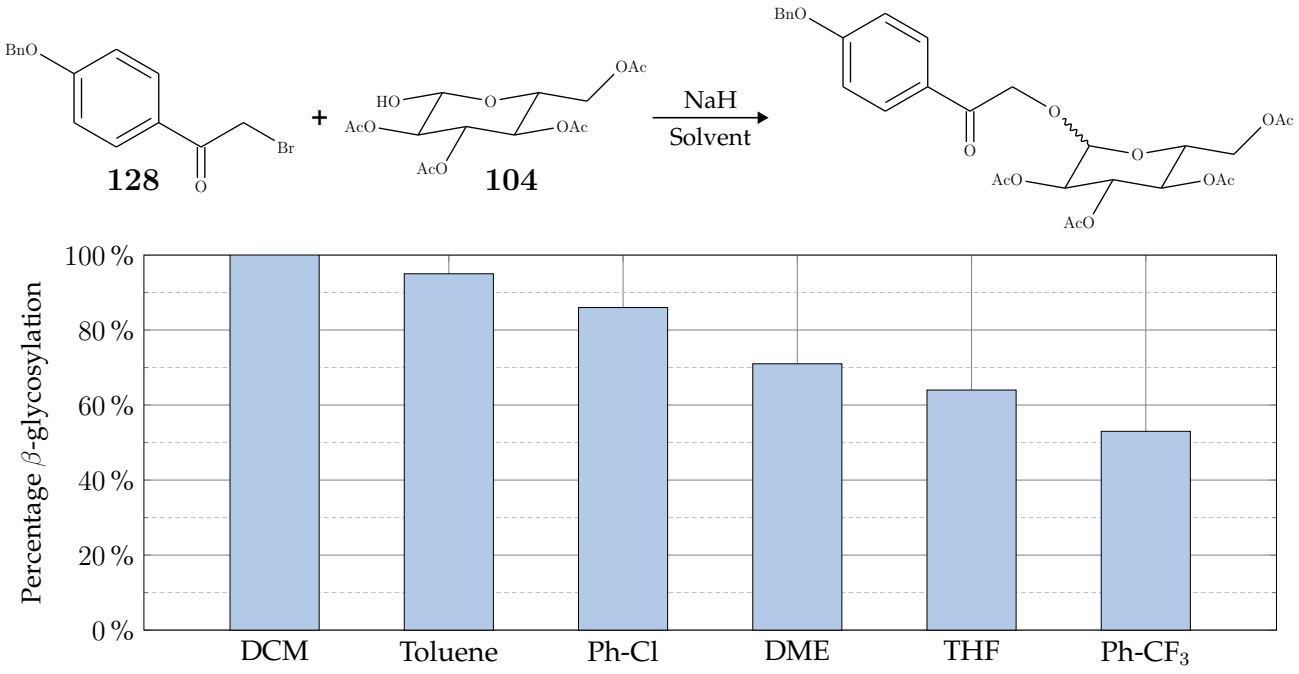


Solvent	DCM	THF	DME	MeCN	DMSO	NMP	DMPU	DMF	HMPA
Major product	β-glc	β-glc	β-glc	α-glc	α-glc	α-glc	α-glc	α-glc	α-glc

Scheme 65: Comparable stereoselectivity of some solvents that were tested. The exact amount of stereoselectivity was not investigated in these experiments[248,252].

R. M. P. Garcia also investigated some additional solvents. He found that TBME produces mainly β-glycosides. However, due to low yields or large amounts of impurities, none of these solvents were of much interest. As it was presumed that more polar solvents would give more α-glycosylation he also investigated the ionic solvent trihexyltetradecylphosphonium chloride (THTDPCI). However, there was no observable glycosylation when utilizing this solvent, possibly due to the high viscosity which lead to poor solubility of the substrates.

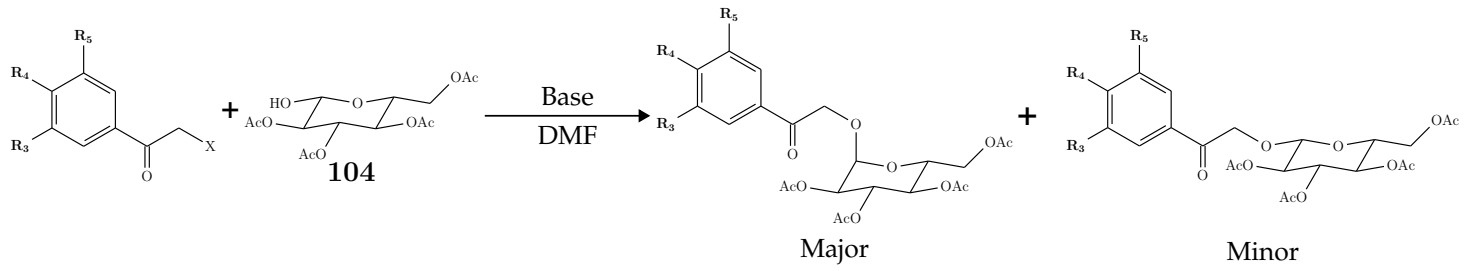
The author also investigated several solvents for β-glycosylation (Scheme 66). Bakstad's research group had already uncovered that DCM and the ether solvents THF and DME facilitate β-glycosylation when they filed for their patent in 2006[1]. However, THF and DME give considerably more α-glycosides as a byproduct than DCM. Other solvents, such as chlorobenzene and α,α,α-trifluorotoluene (TFT) give less α-glycosides as a byproduct, but still more than DCM. The only solvent that was found to nearly match the high β-stereoselectivity of DCM was toluene. However, DCM was still preferred for β-glycosylation in laboratory experiments, since it has a lower boiling point than toluene and is easier to remove under reduced pressure before flash chromatography.



Scheme 66: Stereoselectivity of different solvents that mainly favored β-glycosylation. All the reactions were performed at room temperature with 3 mmol tetraacetate **104**, 3 mmol 2-bromo-4'-benzyloxyacetophenone (**128**), and 3.5 mmol NaH. The percentage of β-glycosylation was determined by ^{1}H NMR integrals from an isolated mix of the anomers.

Investigation of bases

R. M. P. Garcia started to investigate the effect of bases in DMF in 2014 [235]. He discovered that the bases Et_3N and Li_2CO_3 were insufficient for glycosylation of α-haloacetophenones in DMF. Glycosylation was, however, observed with 5 equivalents of Na_2CO_3. This reaction did, however, take several days. With 5 equivalents of K_2CO_3 the glycosylation reaction generally completed overnight, but was still relatively slow compared to NaH. The reaction time started to match NaH with Cs_2CO_3 and DBU, and was typically completed within a few hours (Scheme 67).



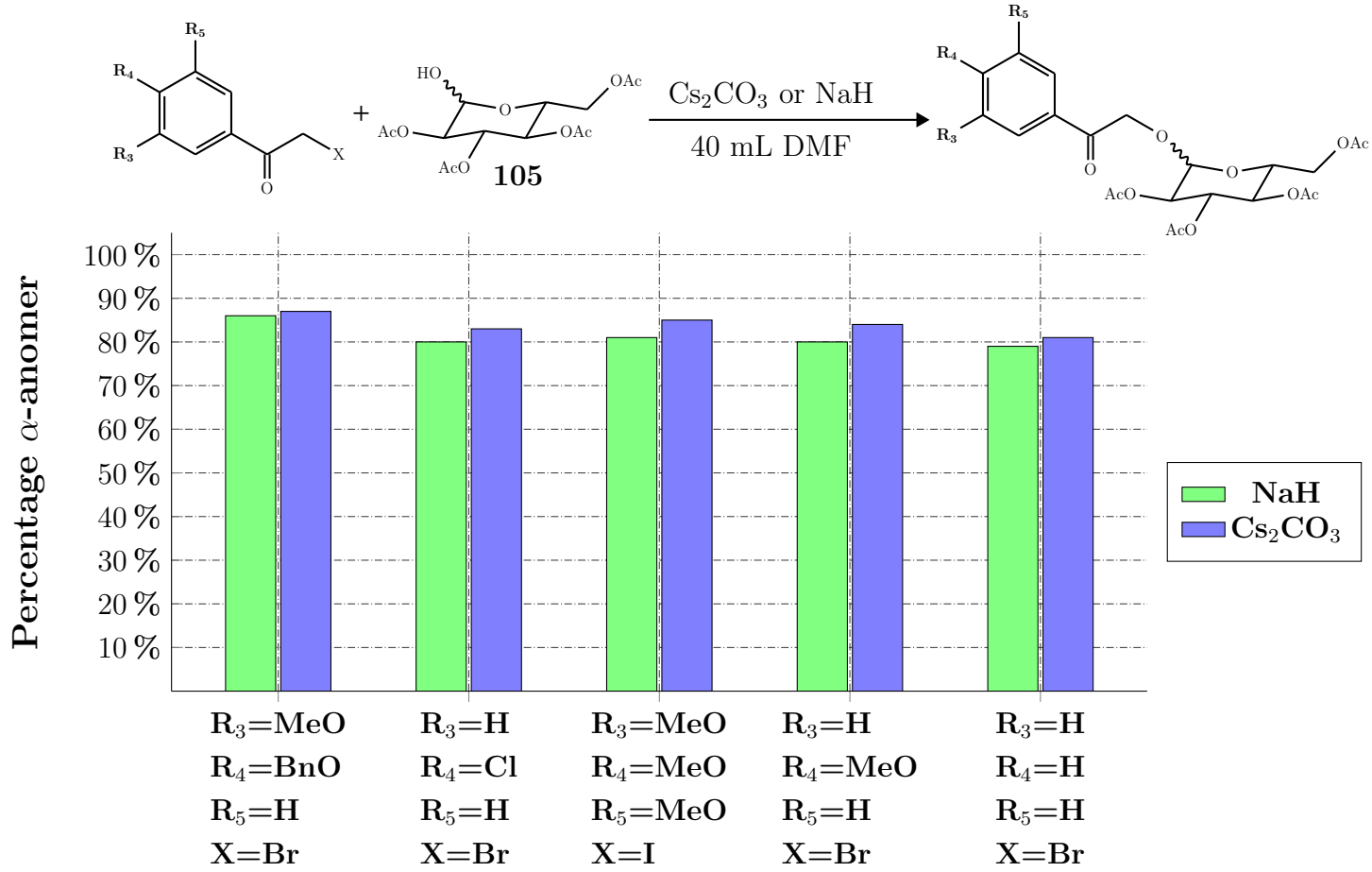
Base	Et_3N	Li_2CO_3	Na_2CO_3	K_2CO_3	Cs_2CO_3	DBU	NaH
Reaction time	Not applicable		Very slow	Slow	Fast		

Scheme 67: Comparisons of time needed to run glycosylation reactions in DMF to completion using different bases.

Bases such as KH, KtBuO, and potassium bis(trimethylsilyl)amide (KHMDS) were also tested. All these

bases were able to facilitate glycosylation, but were not investigated further due to poor α-stereoselectivity compared to DBU and Cs_2CO_3.

After discovering that carbonate bases are sufficiently strong to facilitate glycosylation in DMF, the author performed experiments to compare the stereoselectivity with Cs_2CO_3 compared to NaH (Scheme 68). It was found that Cs_2CO_3 facilitate marginally more α-stereoselectivity in DMF. This is most likely due to the larger ionic radius of Cs^+ from Cs_2CO_3 as compared to Na^+ from NaH. High stereoselectivity by using caesium bases has also been shown in other reactions[253].



Scheme 68: How Cs_2CO_3 seemed to give marginally more α-glycosylation in DMF. All the reactions were performed at room temperature with 3 mmol tetraacetate **105**, 4 mmol electrophile, and 4.5 mmol Cs_2CO_3 or 4 mmol NaH. The percentage of α-anomer was determined by ^{1}H NMR integrals from an isolated mix of the anomers.

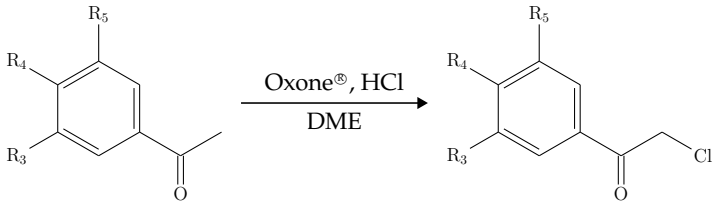
Since Cs_2CO_3 produced better yields with faster reaction times, this base was used as the standard for α-glycosylation in DMF going forward.

Investigation of α-chloroacetophenones

Since less reactive α-haloacetophenones should give β-tetraacetate **104** more time to convert into α-tetraacetate **64**, several α-chloroacetophenones were prepared by the author and R. M. P. Garcia (M.Sc.)[235]. Chlorination with NCS in the presence of TsOH was first explored[242], but generated considerable amounts of α,α-dichloroacetophenones. Another method utilizing 2 equivalents of NH_4Cl and 1.2 equivalents of Oxone® in MeOH[254] did not produce any dichlorinated acetophenones, but did

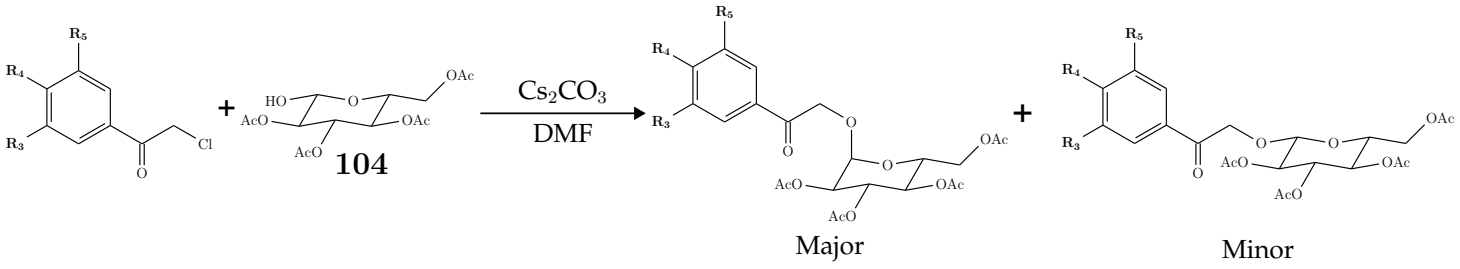
not always produce high yields. The reaction conditions were modified by changing NH_4Cl into HCl (12 M), and MeOH into DME, in order to improve yields.

R_1	R_2	R_3	Product	Yield
H	Cl	H	**115**	55%
H	Br	H	**116**	43%
H	Me	H	**117**	35%
H	MeO	H	**118**	82%
MeO	MeO	MeO	**119**	46%



Scheme 69: General reaction for the chlorination of acetophenones.

After several α-chloroacetophenones had been prepared, the α-stereoselectivity of α-chloroacetophenones was investigated with Cs_2CO_3 in DMF by the author, and with K_2CO_3 in DMF by R. M. P. Garcia (M.Sc.)[235].

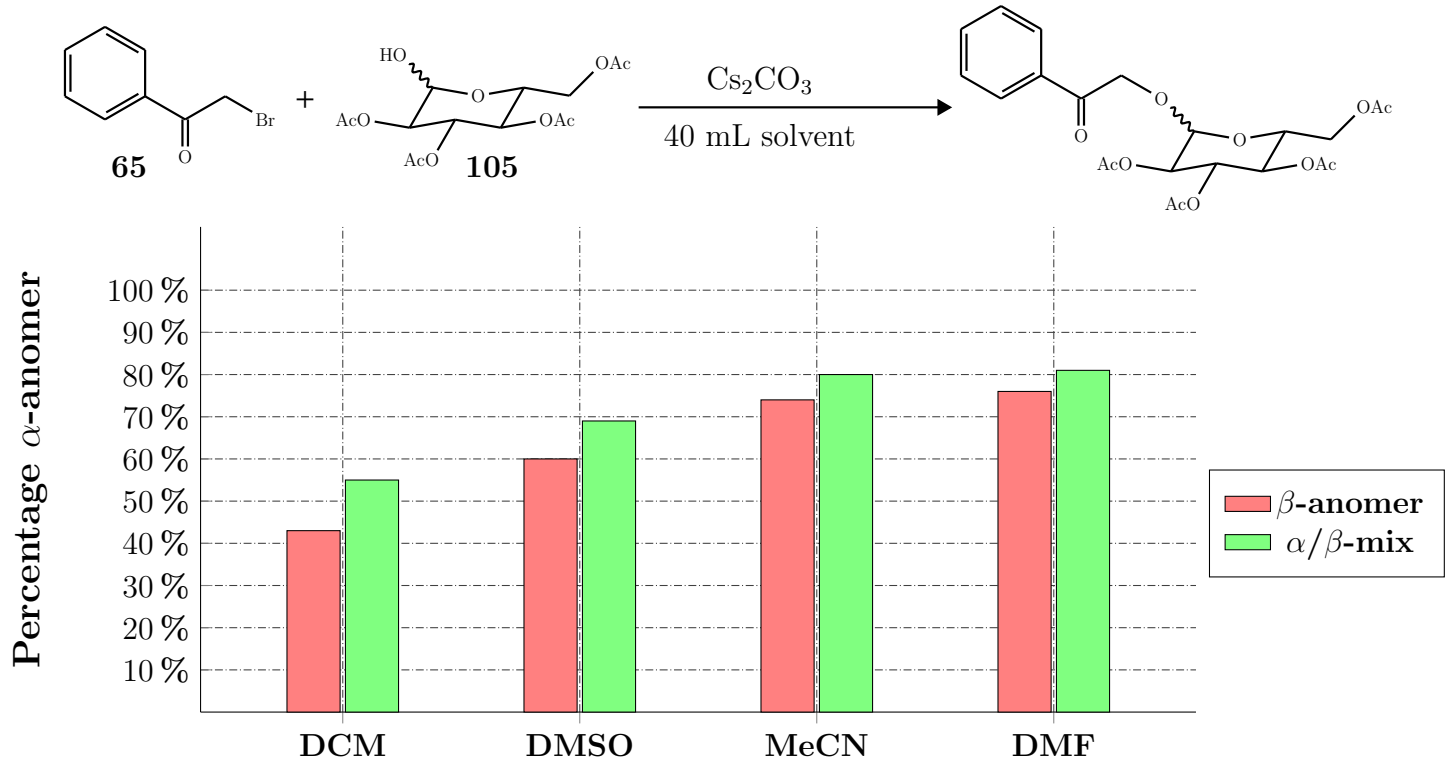


Scheme 70: General procedure for glycosylation of α-chloroacetophenones.

However, no perceivable difference was found in the α-stereoselectivity compared to using α-bromoacetophenones, and the reactions did not run to completion owing to the lower reactivity of α-chloroacetophenones when compared with their respective reactivity of α-bromoacetophenones and α-iodoacetophenones. After a few glycosylation experiments the investigation was discontinued.

Investigation of α-D-glucose tetraacetate in glycosylation

Several attempts were performed to synthesize the pure α-anomer of the tetraacetate. However, this proved to be extremely difficult. Although small amounts of the pure compound could be obtained by flash chromatography, it was challenging to get sufficient amounts to perform several experiments. A mixture of approximately 75% of the α-anomer and 25% of the β-anomer was however readily obtained by deacetylation of pentaacetate (Scheme 51). This mixture was used by the author in several experiments to see how it affected the stereoselectivity of the glycosylation (Scheme 71). As expected, somewhat more α-glycosylation was observed when starting with more of the α-anomer of the tetraacetate. The effect was largest in the least polar solvent investigated (DCM), while the effect was smallest in the most polar solvent that was investigated (DMF). This could be due to less isomerization in less polar solvents.



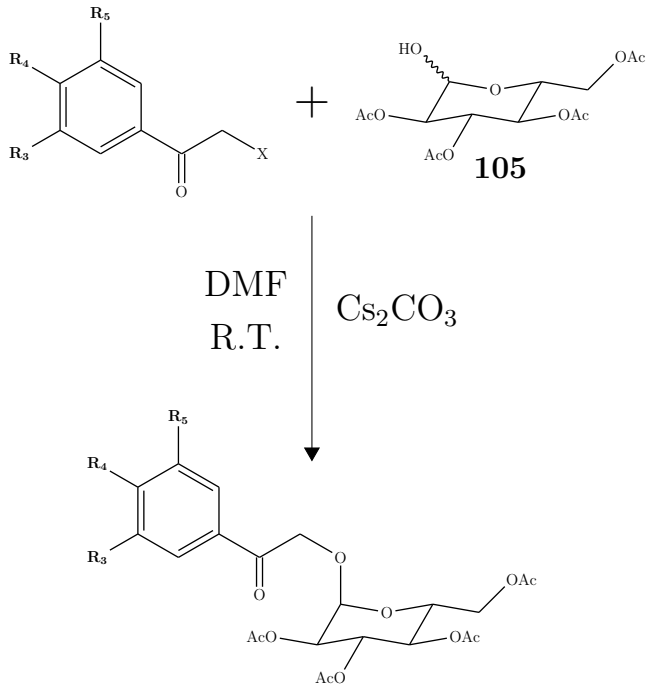
Scheme 71: How the stereoselectivity varied according to α-tetraacetete **64** and β-tetraacetete **104**. All the reactions were performed at room temperature with 3 mmol D-glucose tetraacetate, 4 mmol 2-bromoacetophenone (**65**), and 4.5 mmol Cs_2CO_3. The percentage of α-anomer was determined by ^{1}H NMR integrals from an isolated mix of the anomers.

Since more α-glycosylation was observed when using the mixture of approximately 75% of the α-anomer and 25% of the β-anomer, it was used in most of the experiments where the goal was to maximize α-glycosylation.

α-Glycosylation of acetophenones

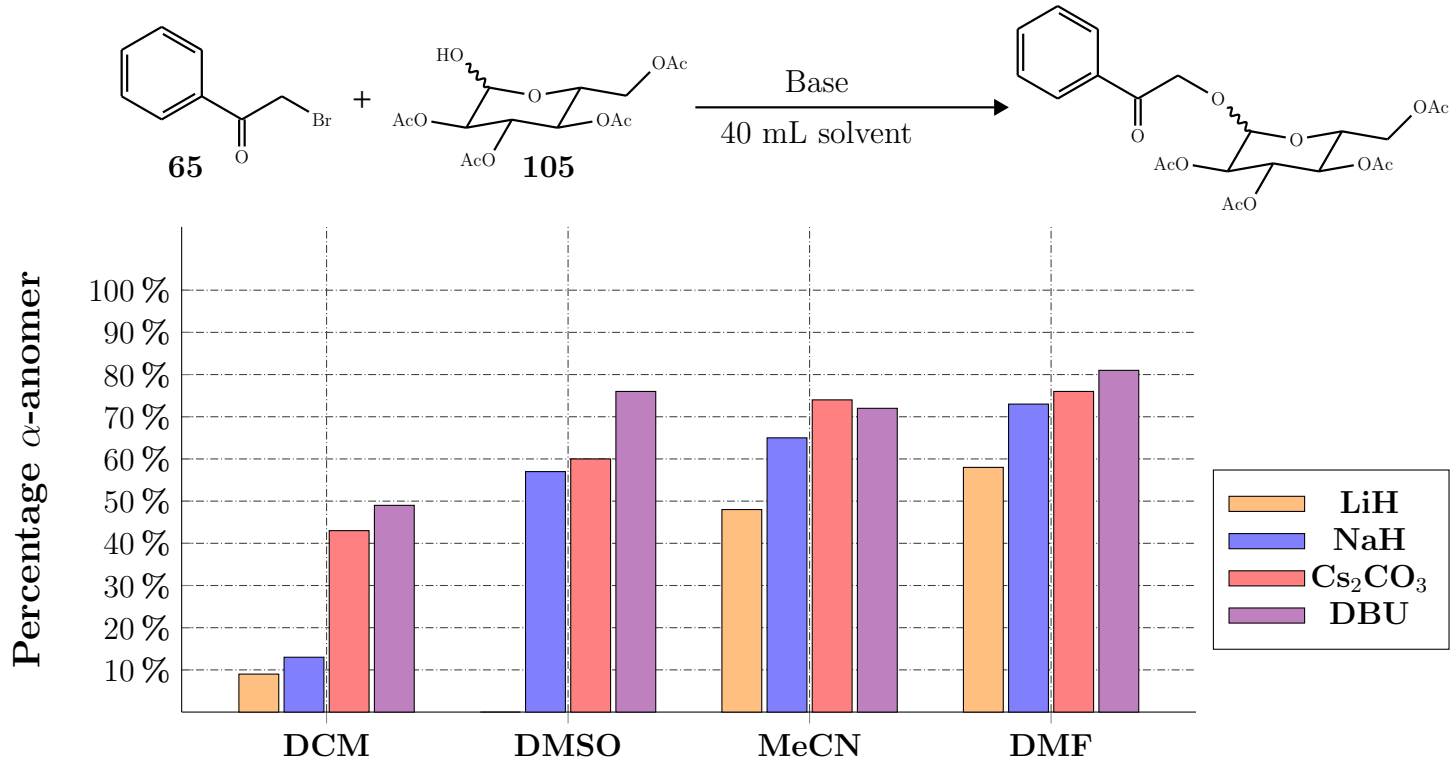
Several α-bromo and α-iodoacetophenones were glycosylated in DMF to give mostly α-glycosylated products (Scheme 72). The stereoselectivity was inferior to the stereoselectivity in β-glycosylation, but the conversion was generally higher. Due to challenges with isolating pure α-glycosides from the β-glycosylated residues and pentaacetate **34** impurities that were generated in the reaction, B. Khalid and R. M. P. Garcia only obtained analytical samples from preparative HPLC. However, by slight modifications of the techniques used for TLC and flash chromatography, the author was able to remove these residues with flash chromatography, to obtain yields in the rage from 39% to 76% (Scheme 72).

R_3	R_4	R_5	X	Product	Yield (%)
H	Cl	H	Br	**148**	39%[b]
MeO	BnO	MeO	I	**158**	40%
H	Br	H	Br	**149**	43%[b]
MeO	MeO	H	Br	**150**	55%[a]
MeO	MeO	MeO	I	**157**	55%
H	F	H	Br	**147**	57%[b]
BnO	BnO	H	I	**152**	64%
Gem-diphenyl		H	I	**153**	60%
H	Me	H	Br	**146**	61%[a]
H	iPrO	H	Br	**154**	62%
H	BnO	H	Br	**155**	64%
MeO	iPrO	MeO	I	**159**	66%
H	MeO	H	Br	**151**	67%[a]
H	H	H	Br	**145**	68%[a]
MeO	iPrO	H	Br	**156**	76%



Scheme 72: α-Glycosylated α-haloacetophenones. Compounds with the notation "a" were first prepared by B. Khalid[248], while compounds with the notation "b" were first made by R. M. P. Garcia[235].

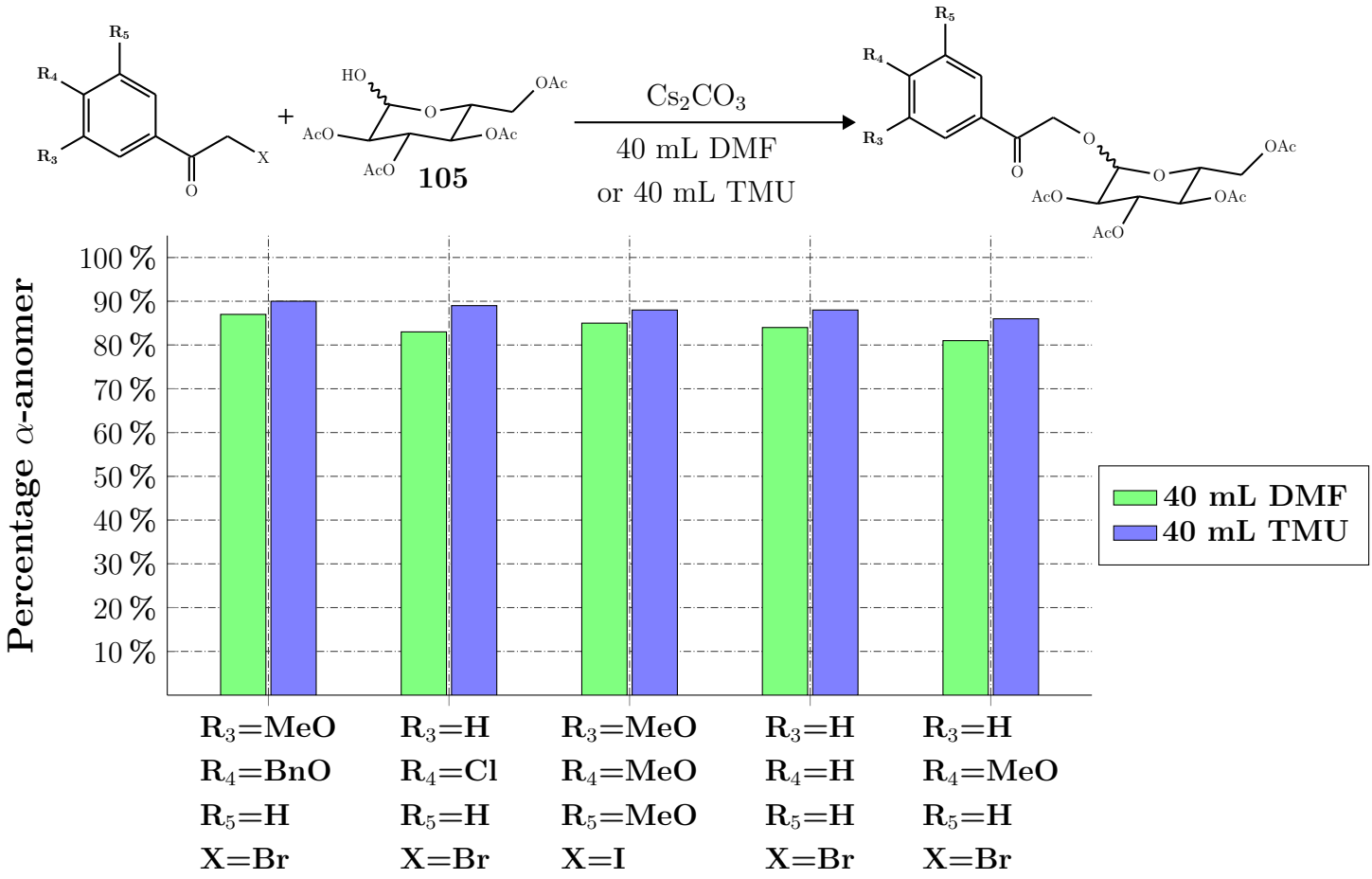
Subsequent experiments by the author compared different bases in different solvents (Scheme 73). It was found that significantly more α-glycosylation occurred in DCM when using Cs_2CO_3 or DBU compared to when using LiH and NaH. It was also found that considerably less α-glycosylation occurred in DMF and MeCN with LiH than when the other bases were used. Strangely, there was observed no glycosylation at all when using LiH in DMSO, and significantly more α-glycosylation with DBU compared to Cs_2CO_3. Generally, DBU seemed to facilitate more α-glycosylation than Cs_2CO_3 and should therefore be used as the standard base for α-glycosylation.



Scheme 73: Stereoselectivity of different bases in different solvents. All the reactions were performed at room temperature with 3 mmol tetraacetate **105** , 4 mmol 2-bromoacetophenone (**65**), and 4.5 mmol Cs_2CO_3 or 4 mmol NaH or 15 mmol LiH or 3.6 mmol DBU. The percentage of α-anomer was determined by ^{1}H NMR integrals from an isolated mix of the anomers.

α-Glycosylation of acetophenones in tetramethylurea (TMU)

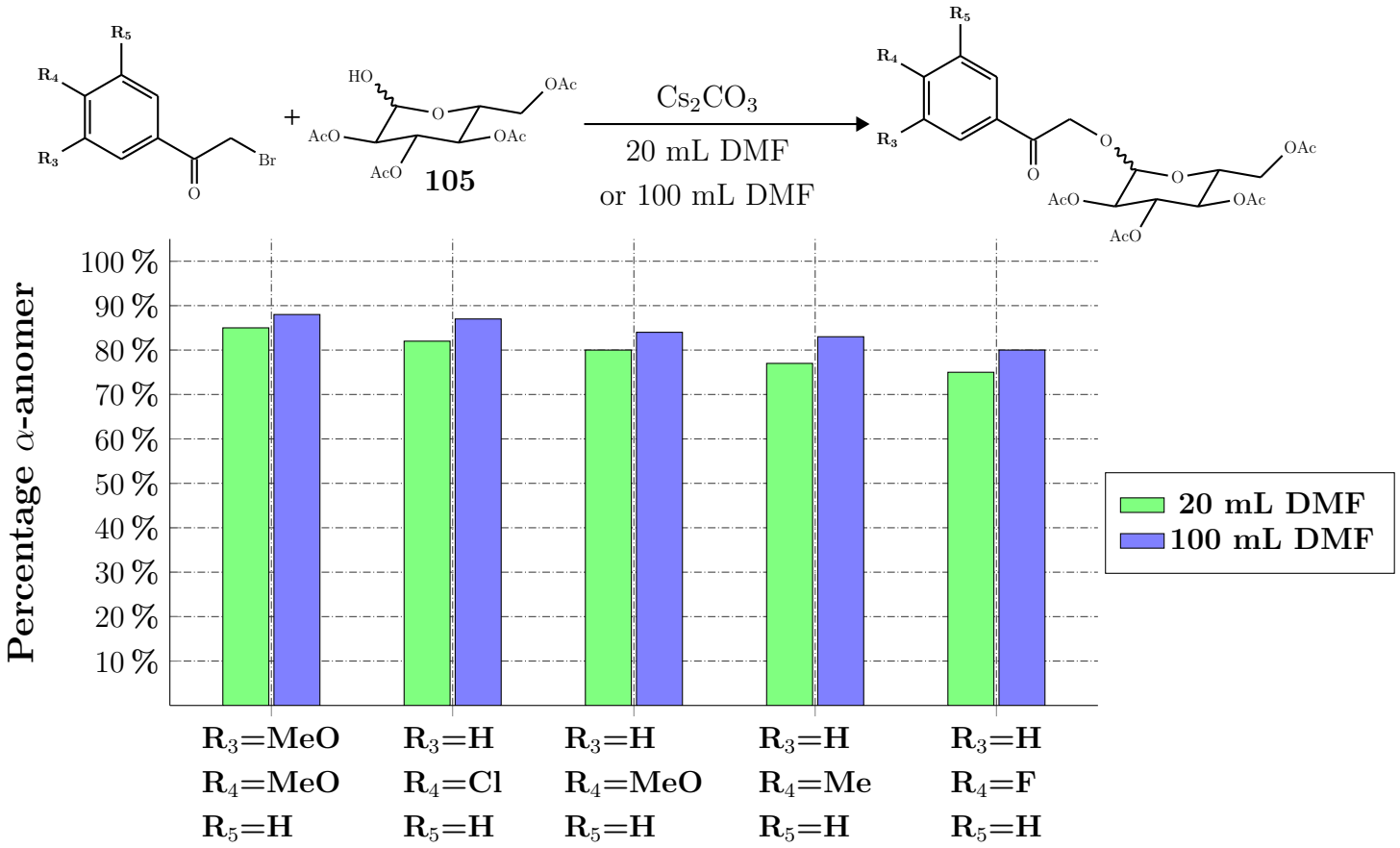
Since the highest amount of α-glycosylation had been achieved with DMF, the author performed experiments with structurally similar solvents. TMU is a solvent that has been described in the literature[255], but has not been as widely used as DMF. A small increase in α-glycosylation was achieved by using 40 mL of the solvent TMU with 3 mmol D-glucose tetraacetate (Scheme 74). However, the difference was negligible when 3 mmol D-glucose tetraacetate was alkylated in 100 mL TMU and 100 ml DMF.



Scheme 74: Comparison of the of α-glycosylation in 40 mL DMF and 40 mL TMU. All the reactions were performed at room temperature with 3 mmol tetraacetate **105**, 4 mmol electrophile, and 4.5 mmol Cs_2CO_3. The percentage of α-anomer was determined by ^{1}H NMR integrals from an isolated mix of the anomers.

α-Glycosylation of acetophenones in DMF 20 mL vs 100 mL

Subsequent experiments by the author with different concentrations of reactants in DMF found that the amount of α-glycosylation was higher when 3 mmol D-glucose tetraacetate was alkylated in 100 mL DMF as compared to 20 mL DMF (Scheme 75). However, increasing the amount of solvent only seemed to increase the amount of α-glycosylation up to a certain point. When 3 mmol D-glucose tetraacetate was alkylated in more than 100 mL DMF, the stereoselectivity seemed to be about the same as with 100 mL DMF.



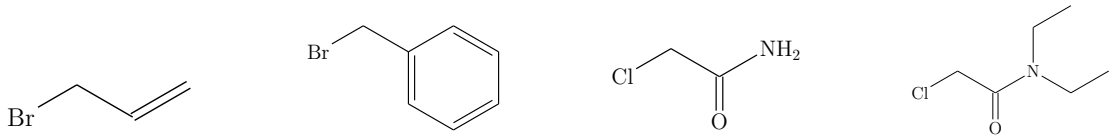
Scheme 75: Comparison of the of α-glycosylation in 20 mL DMF and 100 mL DMF. All the reactions were performed at room temperature with 3 mmol tetraacetate **105**, 4 mmol electrophile, and 4.5 mmol Cs_2CO_3. The percentage of α-anomer was determined by ^{1}H NMR integrals from an isolated mix of the anomers.

Temperature

R. M. P. Garcia reports increased β-glycosylation when he cooled down glycosylation reactions in DMF to 0 ^{o}C and 5 ^{o}C degrees, but with much lower yields[235]. He reported no significant change in the α:β stereoselectivity when he heated the glycosylation reactions in DMF to 30 ^{o}C, 50 ^{o}C and 70 ^{o}C, but an increased amount of pentaacetate **34** as a byproduct[235]. When glycosylation reactions in DCM were cooled down to 0 ^{o}C, very little product was formed. J. L. Dalva reported higher purity and less formation of pentaacetate **34** when he cooled the reactions in DCM down to 0 ^{o}C before adding the NaH, but afterwards let the reaction mixture warm to room temperature[233]. This might have gradually increased the solubility of NaH, and thereby produced a slower start for the reaction.

Investigation of other electrophiles

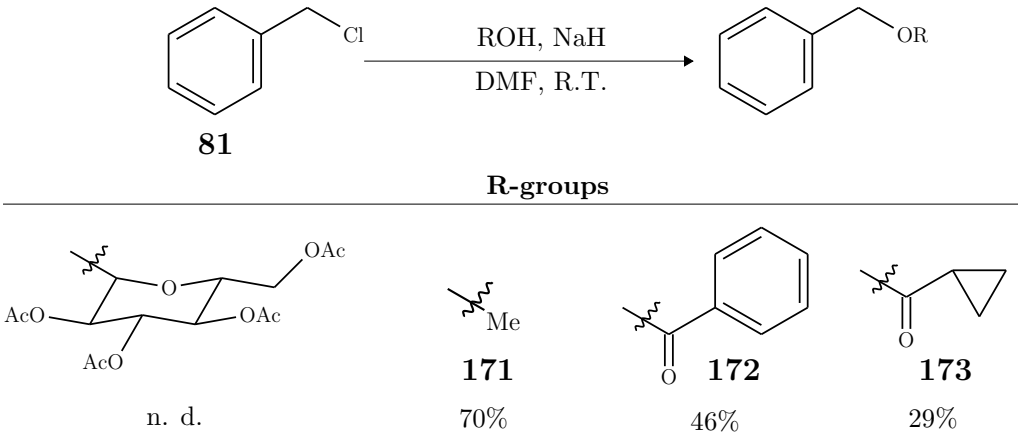
The glycosylation of other electrophiles was also investigated by bachelor student Katja Håheim in 2016 [236] and master student Jørgen Ledaal Dalva in 2017-2018 [233] (Table 6, Table 7). K. Håheim used α-haloketones and α-haloesters in anomeric *O*-alkylation. Since benzylation of phenoles with benzyl chloride (BnCl) is well established in the literature, and since the author protected several hydroxy substituted acetophenones with BnCl (Scheme 56) in this work, it was assumed that tetraacetate **105** also would react with BnCl. However, K. Håheim discovered to our surprise that benzyl chloride and benzyl bromide (**78**) did not react with tetraacetate **105**. Other electrophiles, such as 2-chloroacetamide (**79**), allyl bromide (**77**), and chloro diethylacetamine (**80**) also did not give any glycosylation neither in DMF or DCM.



77 **78** **79** **80**

Scheme 76: Some of the electrophiles that unexpectedly did not produce any glycosylated product.

These results made us aware of how reactive α-haloacetophenones, α-haloketones and α-haloesters are. To establish a better idea of the nucleophilicity of tetraacete **105** compared to other nucleophiles, the author benzylated several other nucleophiles under the same conditions (Scheme 77). Methanol, benzylic acid, and cyclopropanecarboxylic acid were all benzylated successfully under the same reaction conditions.

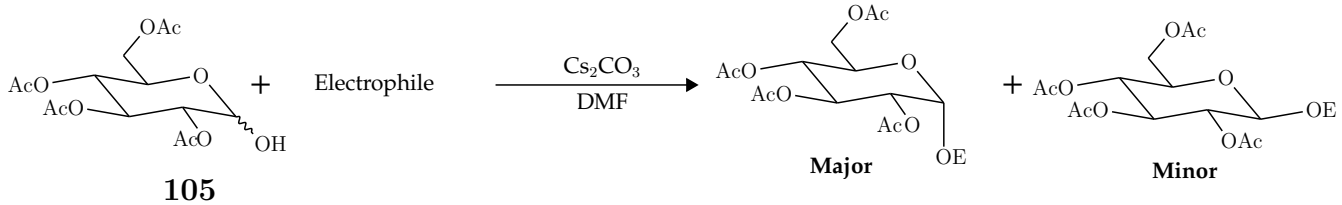


n. d. **171** 70% **172** 46% **173** 29%

Scheme 77: Reactions with benzyl chloride.

J. L. Dalva discovered several additional cyclic ketones that could be glycosylated, and found in addition that bromotriphenylmethane and iodoacetonitrile also were sufficiently good electrophiles to be glycosylated. Some of the cycloketones J. L. Dalva worked with (except for α-bromocyclohexanone) eliminated in DMF, and were only glycosylated in DCM.

Table 6: Comparison of electrophiles glycosylated in DMF. Compounds with the notation "a" were first made by K. Håheim[236], while the compounds with notion "b" were first made by J. L. Dalva[233]. The compound with the notation "c" was prepared by K. Håheim with a 17% yield when using NaH as a base and MeCN as a solvent[236]. The author made some of the compounds again in an attempt to improve the yields.



105

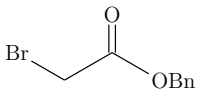
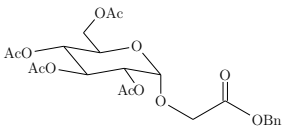
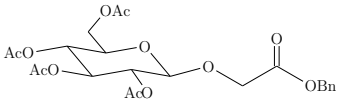
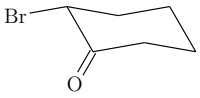
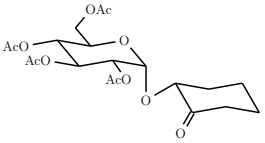
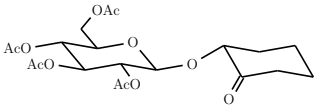
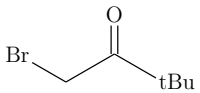
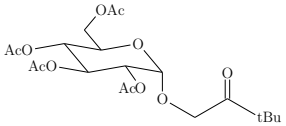
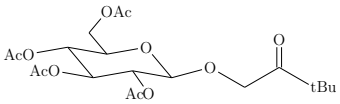
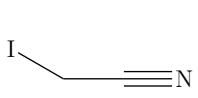
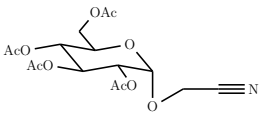
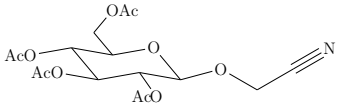
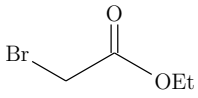
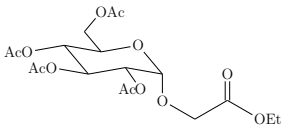
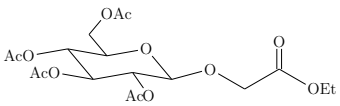
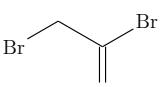
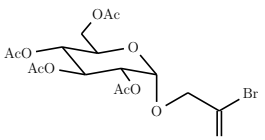
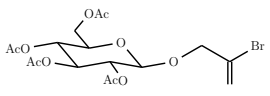
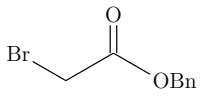
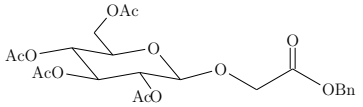
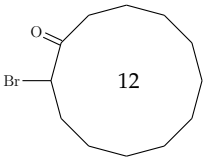
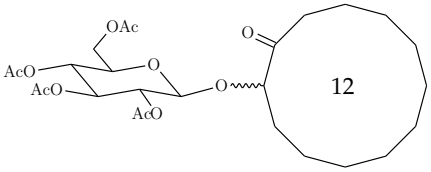
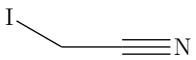
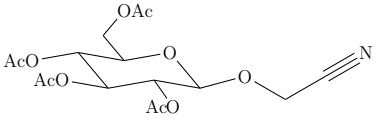
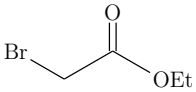
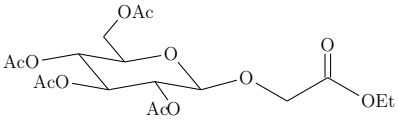
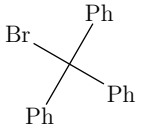
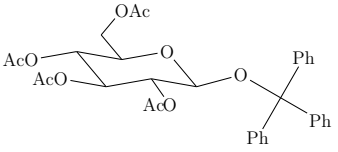
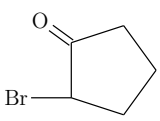
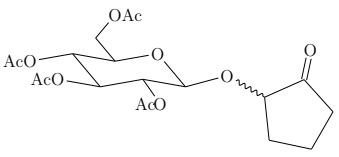
Electrophile	Major product	Minor product
		
82	**160** 59%[a]	**170** Traces
		
83	**84** 35%[b]	**85** Not observed
		
86	**87** 55%[a]	**88** Not observed[c]
		
89	**90** 24%[b]	**91** Traces
		
92	**93** 22%[a]	**94** Traces
		
95	**96** 9%[b]	**97** Traces

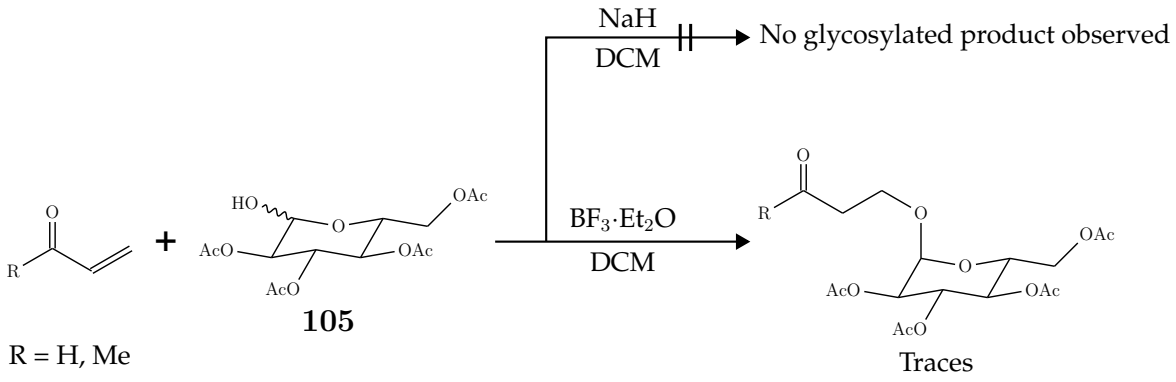
Table 7: Comparison of electrophiles glycosylated in DCM. Compounds with the notation "a" were first made by K. Håheim[236], while the compounds with notion "b" were first made by J. L. Dalva[233]. Some of the compounds were made again in an attempt to improve the yields.

105

Electrophile	Product
	
82	**170** 29%[a]
	
98	**99** 50%[b]
	
89	**91** 31%[b]
	
92	**94** 30%[a]
	
100	**101** 30%[b]
	
102	**103** 29%[b]

Michael addition

J. L. Dalva also investigated if Michael acceptors could be glycosylated[233]. He did not observe any glycosylation with Michael acceptors under basic conditions, however, he was able to see traces of some glycosylated Michael acceptors (acrolein and methylvinylketone) when he instead used a Lewis acid (Scheme 78).



Scheme 78: Glycosylation with Michael acceptors.

He further tried to glycosylate crotononitrile under the same conditions, but did not see any traces of any glycosylated product. Different solvents and different Lewis acids should be investigated to see if the yields can be improved.

Yield optimization with π-interactions

Since the yields were higher with more electron-rich acetophenones, ways of increasing the electron density of the aromatic rings in the acetophenones was explored[227]. Specifically, 1,3,6-trimethoxybenzene was added to see if it could donate electron density through aromatic π-π interactions (Figure 42).

When α-bromoacetophenone, 4-chloro-α-bromoacetophenone **123** and 4,α-dibromoacetophenone **124** were glycosylated with NaH in DCM, the reactions looked slightly cleaner on TLC and showed less formation of pentaacetate **34**. However the yields did not improve significantly. It is possible that a more electron-rich aromatic ring than 1,3,6-trimethoxybenzene would be more potent to donate electron density to electron-poor acetophenones.

8 Concluding remarks

Several other methods have been developed for β-favored glycosylation. R. Schmidt *et al.* achieved a β-stereoselectivity ranging from 80-100% and yields ranging from 32-90% using glycosyl trichloroacetimidates protected with benzyl groups (Scheme 26); S. Hashimoto *et al.* achieved a β-stereoselectivity of 98-99% and yields ranging from 71-96% using glycosyl phosphites protected with benzyl groups (Scheme 37); D. Kahne *et al.* achieved a β-stereoselectivity of 75-100% and yields ranging from 60-80% using glycosyl sulfoxides protected with propionitrile (Scheme 22); and F. Tietzce *et al.* achieved a β-stereoselectivity of 91-97% and yields ranging from 64-90% using TMS glycosides protected with acetyl groups (Scheme 33). Anomeric *O*-alkylation with NaH in DCM can easily compete with the β-stereoselectivity in these methods, but not necessarily with the yields. Anomeric *O*-alkylation seems to require strong electrophiles in order to afford high yields when reacting with β-tetraacetate **104** or **64**. Electrophiles such as BnCl and even BnBr does not seem to produce any glycosylated products, while BnI only seems to be able to produce traces with the reaction conditions used in Bakstad's research laboratory. This might pose a problem in the glycosylation of several medicinal compounds, where the aglycon is not a sufficiently strong electrophile for anomeric *O*-alkylation. In anthocyanin synthesis, many α-bromo and α-iodoacetophenones are however sufficiently strong electrophiles to afford reasonably good yields in β-selective anomeric *O*-alkylation. In 2008, Siri Lunde did one experiment with ultrasonication during a β-selective glycosylation[243] applied to a solution with NaH in DCM. She reports significantly reduced reaction time, and less formation of pentaacetate **34**. Only one experiment was performed, due to safety concerns with ultrasonication on a solution of DCM with NaH. Toluene is a solvent which seems to induce as much β-glycosylation as DCM, and there would be no safety concerns with applying ultrasound to a solution of toluene with NaH. The tetraacetate used in anomeric *O*-alkylation can affordably be produced from pentaacetate **34**, and therefore competes economically favorably with many of the other glycosyl donors which are more costly to produce. Ultrasound could potentially also allow the use of less reactive electrophiles that were unable to react without ultrasound.

It is uncertain if α-favored glycosylation in DMF or TMU with Cs_2CO_3 or DBU can be improved to much more than 80-90% stereoselectivity for most electrophiles. A few electrophiles, such as compounds **83** and **86** were glycosylated without any observable traces of β-glycosides. Some acetophenones, such as 4-benzyloxy-3-methoxy-2-bromoacetophenone (**131**) has been glycosylated with about 90% α-stereoselectivity when glycosylated with Cs_2CO_3 in TMU (Scheme 74). Small amounts of β-glycosides can readily be removed by flash chromatography or recrystallization. Several other methods have been developed for preparing α-glycosides. T. Mukaiyama *et al.* achieved an α-stereoselectivity of 80-92% and yields ranging from 76-96% with glycosyl fluorides (Scheme 31); S. Hashimoto achieved an α-stereoselectivity of 91-98% and yields ranging from 59-92% with glycosyl phosphites protected with benzyl groups (Scheme 38); D. Kahne *et al.* achieved an α-stereoselectivity of 60-78% and yields ranging from 70-86% with glycosyl sulfoxides protected with benzyl groups (Scheme 23); and F. Tietze *et al.* achieved an α-stereoselectivity of 67-96% and yields ranging from 53-90% with TMS-glycosides protected with benzyl groups (Scheme 34). It is uncertain whether anomeric *O*-alkylation in DMF can compete with the yields and stereoselectivity in these methods. All of these methods have however used glycosyl donors protected with benzyl groups, while all of the experiments performed with anomeric *O*-alkylation in DMF have used glycosyl donors protected with acetyl groups.

Anomeric *O*-alkylation is also different from all the other glycosylation methods, since the glycosides react with electrophiles rather than with nucleophiles. Under certain circumstances it might be favorable to make the aglycon into an electrophile, rather than into a nucleophile.

9 Experimental

9.1 General

Nuclear magnetic resonance 300 MHz ^{1}H NMR spectra and 75 MHz ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer. Nuclear magnetic resonance 400 MHz ^{1}H NMR spectra and 100 MHz ^{13}C spectra were recorded on bruker AvIII HD 400 MHz spectrometer. Nuclear magnetic resonance 500 MHz ^{1}H NMR spectra and 125 MHz ^{13}C spectra were recorded on a Bruker Advance series 500 MHz AvII 500 spectrometer. Chemical shift of ^{1}H NMR spectra were reported in relative to tetramethylsilane (TMS) (δ 0.0 ppm) or dimethyl sulfoxide-d_6 (DMSO-d_6) (δ 2.50 ppm). ^{13}C NMR spectra are referenced in ppm to deuterochloroform (δ 77.0 ppm) or dimethyl sulfoxide-d_6 (DMSO-d_6) (δ 39.51 ppm).

IR spectra were recorded on a Agilent Cary 630 FTIR spectrophotometer.

Optical rotation was recorded on a ADP440+ Polarimeter.

Low resolution mass spectra were obtained on an Advion expressions CMS mass spectrometer operating at 3.5 kV in electrospray ionization (ESI) mode. The low resolution mass spectrometer (LRMS) was routinely used to monitor reactions and identify the various components of reaction mixtures.

Dry flash chromatography (DFC) was carried out with silica gel (Sigma-Aldrich: Silica gel 60, particle size 0.040-0.063 mm (230-400 mesh)). Vacuum was created by a water aspirator.

Flash chromatography (FC) was carried out with silica gel (Sigma-Aldrich: Silica gel 60, particle size 0.040-0.063 mm (230-400 mesh). Pressure was created using pressurized nitrogen.

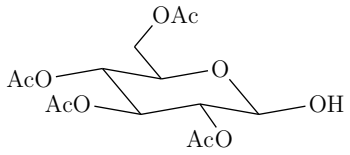
Thin-layer chromatography (TLC) was carried out using silica gel plates from Sigma-Aldrich (silica gel/dc-alufolienkieselgel with fluorescent indicator, production number 60778). The spots were detected with UV (extinction at λ = 254 nm or fluorescent at λ = 366 nm) in a UVP-UV cabinet and/or by staining with MOP (molybdate phosphoric acid (14 g) in ethanol (125 mL)), CER-MOP (molybdate phosphoric acid (5 g), cerium(IV)sulfate (2 g) and 98% sulfuric acid (16 mL) in water (180 ml)) or Anisaldehyde (5% 4-methoxybenzaldehyde in methanol (90 mL), 100% acetic acid (5 mL)) and developed by heating with a heat gun until spots appeared.

Melting points were determined on a Stuart scientific SMP3 melting point apparatus and are uncorrected.

Nitrogen was used in reactions that required dry conditions.

Commercially available chemicals were purchased from Fluka, Sigma-Aldrich, VWR, Acros, Merck, Lancaster and Chiron, standard purification was applied if necessary. Dry dichloromethane, ethyl acetate and acetone were purchased from VWR and Sigma-Aldrich.

2,3,4,6-Tetra-O-acetyl-β-D-glucose (104)

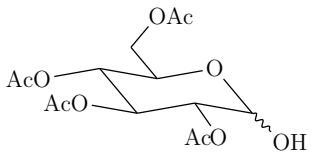


2,3,4,6-Tetra-O-α-D-glucopyranosyl bromide (8.22 g, 20.0 mmol) was dissolved in dry acetone (200 mL). After the solution had cooled in an ice bath, Ag_2CO_3 (5.22 g, 20.0 mmol) and water (0.36 g, 20.0 mmol) was added to the reaction mixture. The reaction mixture was stirred and monitored by TLC until all the starting materials had been consumed. The solvent was then filtrated and removed under reduced pressure to give the titled compound as a white powder.

Yield: 6.40 g (92%).
M.P.: 128-129 ^{o}C (Lit. 132-134 ^{o}C[231]).
IR (neat): ν 3451, 2968, 1935, 1745, 1698, 1605, 1229, 1162, 1037, 988, 823, 814, 722 cm $^{-1}$.
^{1}H NMR (400 MHz, $CDCl_3$) : δ 5.30-5.21 (m, 1H), 5.13-5.05 (m, 1H), 4.93-4.88 (m, 1H), 4.80-4.72 (m, 1H), 4.26 (dd, J = 12.3, 4.6 Hz, 1H), 4.16 (dd, J = 12.3, 2.4 Hz, 1H), 4.06-4.04 (m, 1H), 3.74 (ddd, J = 10.0, 4.6, 2.4 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) : δ 170.8, 170.7, 170.1, 169.5, 95.4, 73.1, 72.2, 72.0, 68.4, 61.9, 20.7, 20.5.

Spectroscopic data was in agreement with literature[256,257].

2,3,4,6-Tetra-O-acetyl-D-glucose (105)



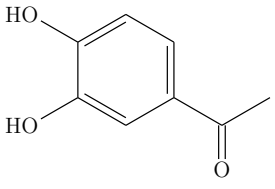
β-D-Glucose-1,2,3,4,6-D-glucose pentaacetate (19.52 g, 50 mmol) and ammonium acetate (NH_4OAc) (7.71 g, 100 mmol) was added to a solution of dimethylsulfoxide (DMSO) (200 mL). The mixture was stirred at R.T. overnight. Water (500 mL) was added and extraction was performed with *tert*-butyl methyl ether (TBME) (5 $\times$ 50 mL), the combined organic phases were washed with water (4 $\times$ 20 mL) and dried (Na_2SO_4). Solvent was removed under reduced pressure to give the titled compound as a faintly orange viscous oil which contained approximately 70% of the α-anomer and 30% of the β anomer.

Yield: 15.61 g (89% both anomers).
^{13}C NMR (100 MHz, $CDCl_3$) : δ 170.9, 170.8, 170.7, 170.2, 170.1, 169.7, 169.5, 95.4, 90.0, 73.1, 72.2, 72.0, 71.1, 69.8, 68.4, 68.3, 67.0, 61.9, 20.7, 20.6, 20.5.

Spectroscopic data was in agreement with literature[258,259].

9.2 Hydrogenation

3',4'-Dihydroxyacetophenone (106)

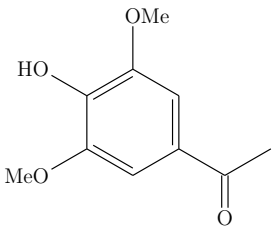


Pd/C (10%) (1.00 g) was added to a stirred solution of 2-chloro-3',4'.dihydroxyacetophenone (18.67 g, 100.0 mmol) in dry ethyl acetate (EtOAc) (500 mL). The atmosphere was changed to H_2 and hydrogenation took place until TLC indicated that the starting material had been consumed. The catalyst was removed by filtration and the solvent was removed under reduced pressure. Recrystallization from methylcyclohexane and ethyl acetate provided the titled compound as pale brown crystals.
Yield: 14.20 g (93%).
M.P.: 119-120 ^{o}C. (Lit. 117-119 ^{o}C[260]).

IR (neat): ν 3245, 1696, 1655, 1594, 1521, 1451, 1365, 1295, 1228, 1128, 1069, 1020, 986, 966, 927, 908, 887, 816, 789, 688, 638, 569 cm^{-1}.
^{1}H NMR (400 MHz, DMSO-d_6) : δ 7.38-7.36 (m, 2H), 6.84 (d, J = 8.6 Hz, 1H), 2.45 (s, 3H).
^{13}C NMR (100 MHz, DMSO-d_6) : δ 196.3, 150.7, 145.2, 129.1, 121.8, 115.2, 115.0, 26.3.
Spectroscopic data was in agreement with literature[261,262].

9.3 Demethylation with $AlCl_3$

3',5'-Dimethoxy-4-hydroxyacetophenone (107)

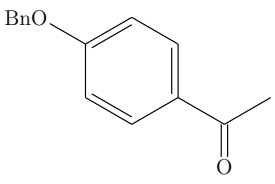


$AlCl_3$ (60.00 g, 0.45 mol) was slowly added to a solution of 3,4,5-trimethoxyacetophenone (31.53 g, 0.15 mol) in a solution of DCM (500 mL). The reaction mixture was monitored by TLC and left stirring overnight. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (4 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, andt he titled compound was obtained as light gray needle crystals.

Yield: 27.10 g (92%).
M.P.: 124-125 ^{o}C (Lit. 123-124 ^{o}C[263]).
IR (neat): ν 3157, 1653, 1605, 1574, 1516, 1466, 1424, 1364, 1330, 1269, 1201, 1116, 859, 833, 729 cm^-1.
^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.25 (s, 2H), 6.30 (s, 1H), 3.94 (s, 2H), 2.58 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) : δ 196.6, 146.6, 139.7, 128.5, 105.6, 56.3, 26.1.
Spectroscopic data was in agreement with literature[264,265], and previous work in Bakstad's research group[240]. The compound is commercially available (*e.g.* Sigma-Aldrich).

9.4 Protection with benzyl chloride

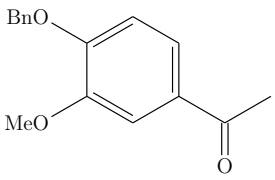
4-Benzyloxyacetophenone (108)



4-Hydroxyacetophenone (13.62 g, 100.0 mmol), K_2CO_3 (13.82 g, 100.0 mmol), benzyl chloride (12.66 g, 100.0 mmol) and a catalytic amount of NaI were dissolved in MeCN (250 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as white crystals.

Yield: 20.80 g (92%).
M.P.: 90-92 ^{o}C (Lit. 93 ^{o}C[266]).
IR (neat): ν 1739 , 1386, 1229, 1217, 1003, 827, 758, 709 cm^{-1}.
^{1}H NMR (400 MHz, $CDC1_3$): δ 7.93 (d, J = 8.0 Hz, 2H), 7.39-7.34 (m, 5H), 7.00 (d, J = 8.0 Hz, 2H), 5.12 (s, 2H), 2.54 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 162.6, 136.2, 130.6, 130.5, 128.7, 128.3, 127.5, 114.6, 70.1, 26.4
Spectroscopic data was in agreement with literature[267].

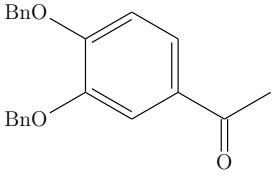
4-Benzyloxy-3-methoxyacetophenone (109)



4-Hydroxy-3-methoxyacetophenone (16.62 g, 100.0 mmol), K_2CO_3 (13.82 g, 100.0 mmol), benzyl chloride (12.66 g, 100.0 mmol) and a catalytic amount of NaI were dissolved in MeCN (250 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as light gray needle crystals.

Yield: 24.20 g (94%).
M.P.: 86-88 ^{o}C (Lit. 86-88[268]).
^{1}**H NMR** (400 MHz, CDC1$_3$): δ 7.55-7.48 (m, 7H), 6.89 (d, J = 8.0 Hz, 1H), 5.23 (s, 2H), 3.94 (s, 3H), 2.55 (s, 3H),
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 196.8, 152.4, 149.5, 136.3, 128.7, 127.2, 123.1, 112.1, 110.5, 79.8, 56.1, 26.2.
Spectroscopic data was in agreement with literature[267,268].

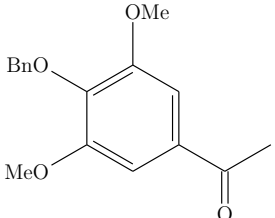
3,4-Dibenzyloxyacetophenone (110)



3,4-Dihydroxyacetophenone (7.61 g, 50.0 mmol), K_2CO_3 (13.82 g, 100.0 mmol), benzyl chloride (12.60 g, 100.0 mmol) and a catalytic amount of NaI were dissolved in MeCN (150 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as brown crystals.

Yield: 13.29 g (80%).
M.P.: 86-87 ^{o}C (Lit. 87-88^{o}C[269]).
IR (neat): ν 1674, 1595, 1507, 1455, 1427, 1381, 1356, 1268, 1205, 1147, 1135, 1081, 1020, 897, 873, 852, 807, 739, 699, 666, 642, 600, 563 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.25-7.60 (m, 12H), 6.89 (d, J = 8.1 Hz, 1H), 5.21 (s, 2H), 5.17 (s, 2H), 2.49 (s, 3H).
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 196.8, 153.2, 148.6, 136.8, 136.5, 130.8, 128.6, 128.5, 128.1, 128.0, 127.4, 127.1, 123.5, 113.7, 112.9, 71.2, 70.8, 26.3.
Spectroscopic data was in agreement with literature[270].

4-Benzyloxy-3,4-dimethoxyacetophenone (111)



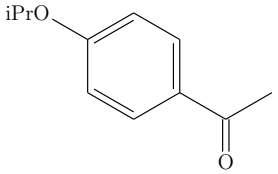
4-Hydroxy-3,5-dimethoxyacetophenone (7.84 g, 40.0 mmol), K_2CO_3 (5.52 g, 40.0 mmol), benzyl chloride (5.04 g, 40.0 mmol) and a catalytic amount of NaI were dissolved in MeCN (150 mL). The reaction mixture was refluxed overnight

and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as light brown crystals.

Yield: 9.70 g (85%).
M.P.: 59-60 ^{o}C (60-61 ^{o}C[271]).
IR (neat): ν 1738, 1673, 1582, 1455, 1412, 1365, 1221, 1201, 1122, 980, 850, 735, 700 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 7.47-7.19 (m, 7H), 5.10 (s, 2H), 3.88 (s, 6H), 2.58 (s, 3H).
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 197.0, 153.3, 141.4, 137.3, 132.6, 128.4, 128.2, 128.0, 105.8, 56.3, 26.5
Spectroscopic data was in agreement with literature[267,272].

9.5 Protection with isopropylbromide

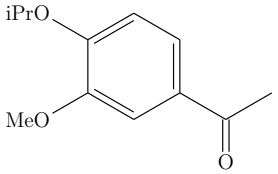
4-Isopropyloxyacetophenone (112)



4-Hydroxyacetophenone (6.81 g, 50.0 mmol), K_2CO_3 (6.91 g, 50.0 mmol), isopropylbromide (9.22 g, 75.0 mmol) and a catalytic amount of NaI were dissolved in MeCN (100 mL). The reaction mixture was refluxed and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as white crystals.

Yield: 7.65 g (86%).
M.P.: 39-41 ^{o}C (Lit. 38-39 ^{o}C[273]).
IR (neat): ν 1670, 1596, 1419, 1358, 1258, 1166, 947, 830 cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$) : δ 7.91 (d, J = 9.0 Hz, 2H) , 6.89 (d, J = 9.0 Hz, 2H) , 4.64 (h, J = 6.3 Hz, 1H), 2.53 (s, 3H), 1.36 (d, J = 6.3 Hz, 6H).
^{13}**C NMR** (75 MHz, $CDCl_3$) : δ 196.5, 161.8, 130.4, 129.7, 114.8, 69.8, 26.1, 21.7.
Spectroscopic data was in agreement with literature[274].

4-Isopropyloxy-3-methoxyacetophenone (113)

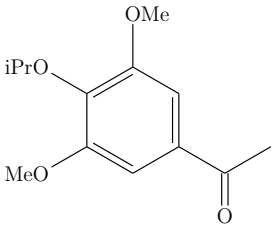


4-Hydroxy-3-methoxyacetophenone (8.31 g, 50.0 mmol), K_2CO_3 (6.91 g, 50.0 mmol), isopropylbromide (9.22 g, 75.0 mmol) and a catalytic amount of NaI were dissolved in MeCN (100 mL). The reaction mixture was refluxed and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as white crystals.

Yield: 8.09 g (78%).

M.P.: 40-42 ^{o}C (Lit. NA).
IR (neat): ν 1671, 1586, 1509, 1271, 1151, 1034, 954, 875, 805, 642, 571.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 7.56-7.52 (m, 2H), 6.89 (d, J = 8.4 Hz, 1H) , 4.66 (h, J = 5.7 Hz, 1H), 3.90 (s, 3H), 2.55 (s, 3H), 1.41 (d, J = 5.7 Hz, 6H).
^{13}**C NMR** (100 MHz, $CDCl_3$) : δ 196.5, 151.6, 149.6, 129.9, 122.9, 112.5, 110.4, 70.9, 55.7, 25.9, 21.7.

3,5-Dimethoxy-4-isopropyloxyacetophenone (114)

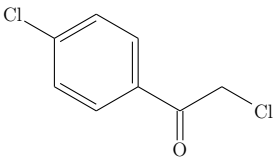


4-Hydroxy-3,5-dimethoxyacetophenone (3.41 g, 25.0 mmol), K_2CO_3 (3.46 g, 25.0 mmol), isopropylbromide (4.61 g, 37.5 mmol) and a catalytic amount of NaI were dissolved in MeCN (100 mL). The reaction mixture was refluxed and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4).The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as gray crystals.

Yield: 5.10 g (87%).
M.P.: 49-50 ^{o}C (Lit. NA).
IR (neat): ν 1675, 1583, 1410, 1321, 1214, 1184, 1121, 937, 831, 650 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 7.21 (s, 2H), 4.50 (h, J = 6.0 Hz, 1H), 3.90 (s, 6H), 2.59 (s, 3H), 1.31 (d, J = 6.0 Hz, 6H).
^{13}**C NMR** (100 MHz, $CDCl_3$) : δ 197.0, 153.7, 140.9, 132.2, 105.8, 75.8, 56.2, 26.4, 22.5.

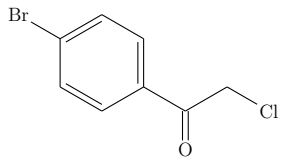
9.6 α-Chlorination

2,4'-Dichloroacetophenone (115)



4-Chloroacetophenone (7.73 g, 50.0 mmol) and HCl (12 M) (9.85 g, 100.0 mmol) were dissolved in DME (250 mL). Oxone®(33.81 g, 110 mmol) was added in portions. The mixture was stirred overnight and monitored by TLC. Water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as white crystals.
Yield 5.20 g (55%).
M.P.: 102-103^{o}C. (Lit. 101^{o}C[275]).
IR (neat): ν 1683, 1587, 1488, 1394, 1297, 1209, 1092, 997, 817, 779, 693 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 7.91 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 4.67 (s, 2H).
^{13}**C NMR** (100 MHz, $CDCl_3$) : δ 190.0, 140.6, 132.5, 130.0, 129.5, 129.3, 45.7.
Spectroscopic data was in agreement with literature[276].

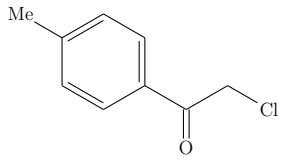
4'-Bromo-2-chloroacetophenone (116)



4-Bromoacetophenone (9.95 g, 50.0 mmol) and HCl (12 M) (9.85 g, 100.0 mmol) were dissolved in DME (250 mL). Oxone®(33.81 g, 110 mmol) was added in portions. The mixture was stirred overnight and monitored by TLC. Water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as white needle crystals.

Yield: 5.02 g (43%).
M.P.: 122-123^{o}C (Lit. 116^{o}C[275]).
IR (neat): ν 1685, 1582, 1484, 1394, 1296, 1208 1073, 995, 812, 774 cm^{-1}.
^{1}**H NMR** (400 MHz, CDC1$_3$): δ 7.83 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 4.68 (s, 2H).
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 190.2, 132.9, 132.2, 130.0, 129.3, 45.7.
Spectroscopic data was in agreement with literature[276].

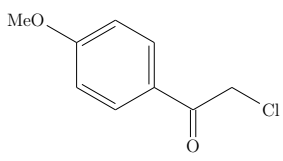
2-Chloro-4'-methylacetophenone (117)



4-Methylacetophenone (6.71 g, 50.0 mmol) and HCl (12 M) (9.85 g, 100.0 mmol) were dissolved in DME (250 mL). Oxone®(33.81 g, 110 mmol) was added in portions. The mixture was stirred overnight and monitored by TLC. Water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as gray crystals.

Yield: 8.17 g (97%).
M.P.: 53-55 ^{o}C (Lit. 56 ^{o}C[277]).
IR (neat): ν 1694, 1605, 1573, 1401, 1320, 1204, 1182, 1120, 1000, 801, 743 cm^{-1}.
^{1}**H NMR** (400 MHz, CDC1$_3$): δ 7.89 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.6 (s, 2H), 2.4 (s, 3H).
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 190.5, 144.9, 131.6, 129.4, 128.4 45.9, 21.6.
Spectroscopic data was in agreement with literature[277].

2-Chloro-4'-methoxyacetophenone (118)

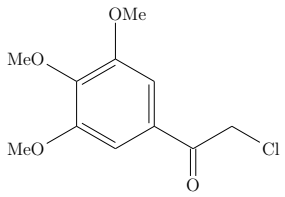


4-Methoxyacetophenone (0.75 g, 5.0 mmol) and HCl (12 M) (0.99 g, 10.0 mmol) were dissolved in DME (50 mL). Oxone®(3.38 g, 11.0 mmol) was added in portions. The mixture was stirred overnight and monitored by TLC. Water (100 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as light brown crystals.

Yield: 0.76 g (82%).
M.P.: 90-92 ^{o}C (Lit. 95-96 ^{o}C[278]).
IR (neat): ν 1688, 1595, 1509, 1340, 1396, 1307, 1260, 1217, 1170, 1119, 1020, 841, 815, 778, 734 cm^{-1}.

^{1}H NMR (400 MHz, $CDC1_3$): δ 7.93 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 4.6 (s, 2H), 3.8 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 164.1, 130.8, 127.1, 114.0, 55.5, 45.6.
Spectroscopic data was in agreement with literature[277].

2-Chloro-3',4',5'-trimethoxyacetophenone (119)

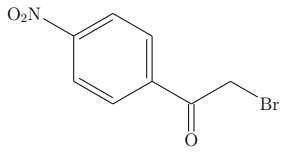


3,4,5-Trimethoxyacetophenone (3.15 g, 15 mmol) and HCl (12 M) (2.96 g, 30 mmol) were dissolved in DME (100 mL). Oxone®(10.14 g, 33 mmol) was added in portions. The mixture was stirred overnight and monitored by TLC. Water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as brown crystals.

Yield: 1.74 g (47%).
M.P.: 88-89 ^{o}C (Lit. 86-87 ^{o}C[279]).
IR (neat): ν 1686, 1580, 1505, 1463, 1411, 1332, 1211, 1155, 1114, 997, 820, 688, 660 cm^{-1}.
^{1}H NMR (400 MHz, $CDC1_3$): δ 7.21 (s, 2H), 4.69 (s, 2H), 3.93-3.92 (m, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) : δ 190.1, 153.2, 143.4, 129.3, 106.1, 61.0, 56.4, 45.7.

9.7 α-Bromination

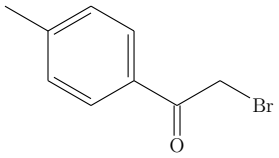
2-Bromo-4'-nitroacetophenone (120)



TsOH (9.47 g, 55.0 mmol) in MeCN (50 mL) was added dropwise to a solution of 4-nitroacetophenone (8.26, 100.0 mmol) and NBS (9.80 g, 55.0 mmol) in DME (50 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as gray crystals.

Yield: 6.95 g (57%).
M.P.: 92-93 ^{o}C (Lit. 98 ^{o}C[280]).
IR (neat): ν 1701, 1598, 1514, 1342, 1318, 1189, 996, 843, 743, 716, 683 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) : δ 8.34 (d, J = 8.4 Hz, 2H) 8.17 (d, J = 8.4 Hz, 2H) 4.47 (s, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) : δ 189.9, 150.6, 138.3, 130.0, 124.0, 30.2.
Spectroscopic data was in agreement with literature[281,282].

2-Bromo-4'-methylacetophenone (121)

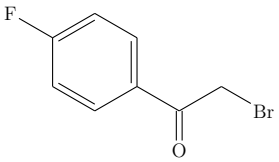


TsOH (9.47 g, 55.0 mmol) in MeCN (50 mL) was added dropwise to a solution of 4-methylacetophenone (6.71 g, 50.0 mmol) and NBS (9.80 g, 55.0 mmol) in DME (50 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as light gray crystals.

Yield: 9.66 g (91%).
M.P.: 45-48 ^oC (51-53 ^oC[283]).
IR (neat): ν 1739, 1678, 1605, 1573, 1429, 1357, 1268, 1182, 1111, 1014, 875, 814, 748 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): 7.89 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0, 2H), 4.4 (s, 2H), 2.4 (s, 3H).
^{13}**C NMR** (100 MHz, $CDCl_3$) : 190.9, 144.9, 131.3, 129.4, 128.9, 31.0, 21.6.

Spectroscopic data was in agreement with literature[282].

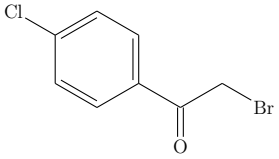
2-Bromo-4'-fluoroacetophenone (122)



TsOH (9.47 g, 55.0 mmol) in MeCN (50 mL) was added dropwise to a solution of 4-fluoroacetophenone (6.91 g, 50.0 mmol) and NBS (9.80 g, 55.0 mmol) in DME (50 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as brown crystals.

Yield: 10.20 g (94%).
M.P.: 47-49 ^oC (48-49 ^oC[284]).
IR (neat): ν 1676, 1594, 1507, 1406, 1276, 1237, 1194, 1157, 828 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 8.00 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 4.68-4.42 (m, 2H).
^{13}**C NMR** (100 MHz, $CDCl_3$) : δ 189.7, 167.5, 167.4, 164.9, 131.9, 131.7, 131.4, 131.3, 130.6, 130.6, 130.4, 130.3, 116.3, 116.1, 45.7, 30.5.
Spectroscopic data was in agreement with literature[285].

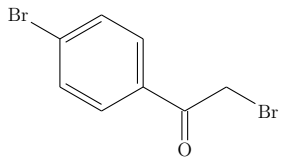
2-Bromo-4'-chloroacetophenone (123)



TsOH (18.94 g, 110.0 mmol) in MeCN (100 mL) was added dropwise to a solution of 4-chloroacetophenone (15.46 g, 100.0 mmol) and NBS (19.58 g, 110.0 mmol) in DME (100 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as white crystals.

Yield: 12.50 g (54%).
M.P.: 97-98 (Lit 95-96 ^{o}C[283]).
IR (neat): ν 1692, 1585, 1485, 1400, 1282, 1196, 1091, 992, 809, 756, 723, 663 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 7.93 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 4.41 (s, 2H).
^{13}**C NMR** (100 MHz, $CDCl_3$) : δ 190.2, 132.2, 130.4, 130.0, 129.3, 30.5.
Spectroscopic data was in agreement with literature[282].

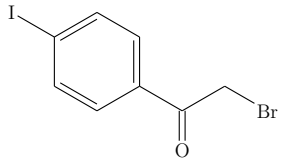
2,4'-Dibromoacetophenone (124)



TsOH (4.38 g, 27.5 mmol) in MeCN (50 mL) was added dropwise to a solution of 4-bromoacetophenone (4.98 g, 25.0 mmol) and NBS (4.90 g, 27.5 mmol) in DME (50 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as light gray crystals.

Yield: 5.10 g (74%).
M.P.: 109-110 ^{o}C (Lit. 108–109 ^{o}C[286]).
IR (neat): ν 1692, 1579, 1481, 1395, 1289, 1193, 1069, 988, 804, 714 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 4.41 (s, 2H).
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 190.4, 132.6 132.2, 130.4, 129.3, 30.4.
Spectroscopic data was in agreement with literature[282].

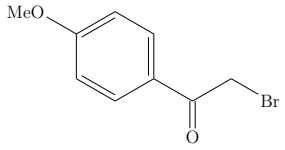
2-Bromo-4'-iodoacetophenone (125)



TsOH (4.38 g, 27.5 mmol) in MeCN (50 mL) was added dropwise to a solution of 4-iodoacetophenone (6.15 g, 25 mmol) and NBS (4.90 g, 27.5 mmol) in DME (50 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as brown crystals.

Yield: 5.86 g (72%).
M.P.: 105-106 ^{o}C (Lit. 102-106^{o}C[287]).
IR (neat): ν 1683, 1576, 1478, 1390, 1265, 1191, 1058, 985, 805, 710 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 4.39 (s, 2H).
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 190.7, 138.2, 133.2, 130.2, 102.2, 30.3.
Spectroscopic data was in agreement with literature[288].

2-Bromo-4'-methoxyacetophenone (126)

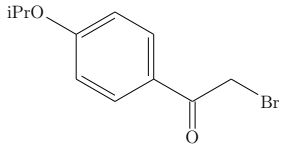


TsOH (18.94 g, 110.0 mmol) in MeCN (100 mL) was added dropwise to a solution of 4-methoxyacetophenone (15.02 g, 100.0 mmol) and NBS (19.58 g, 110.0 mmol) in DME (100 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as pale gray crystals.

Yield: 20.84 (91%).
M.P.: 76-79 ^oC (Lit. 76-78 ^oC[289]).
IR (neat): ν 1689, 1600, 1513, 1264, 1208, 1168, 1022, 841, 817, 580. cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.96 (d, J = 9.0 Hz, 2H) , 6.95 (d, J = 9.0 Hz, 2H), 4.40 (s, 2H), 3.88 (s, 2H).
^{13}**C NMR** (75 MHz, $CDCl_3$): δ 189.8, 165.0, 131.2, 126.7, 113.949, 55.5, 30.8.

Spectroscopic data was in agreement with literature[282].

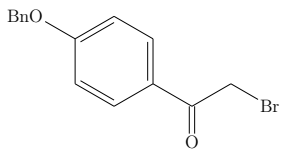
2-Bromo-4'-isopropyloxyacetophenone (127)



TsOH (18.94 g, 110.0 mmol) in MeCN (100 mL) was added dropwise to a solution of 4-isopropyloxyacetophenone (17.82 g, 100.0 mmol) and NBS (19.58 g, 110.0 mmol) in DME (100 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) an1d dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the titled compound was obtained as a black oil.

Yield: 23.91 g (93%).
IR (neat): ν 1672, 1602, 1507, 1602, 1507, 1363, 1260, 1169, 951, 831, 594 cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.96 (d, J = 9.0 Hz, 2H) , 6.93 (d, J = 9.0 Hz, 2H) , 4.68 (d, J = 6.0 Hz, 1H), 4.414 (s, 2H), 1.39 (d, J = 6.0 Hz, 6H).
^{13}**C NMR** (75 MHz, $CDCl_3$): δ 189.7, 162.2, 131.3, 126.3, 115.2, 70.2, 30.8, 21.8.

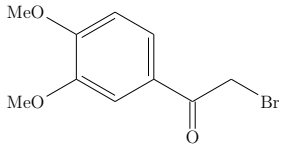
2-Bromo-4'-benzyloxyacetophenone (128)



TsOH (18.94 g, 110.0 mmol) in MeCN (100 mL) was added dropwise to a solution of 4-benzyloxyacetophenone (22.63 g, 100.0 mmol) and NBS (19.58 g, 110.0 mmol) in DME (100 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as pale gray crystals.

Yield: 23.19 g (76%).
M.P.: 76-78 ^{o}C (Lit. 82-84 ^{o}C[290]).
IR (neat): ν 1738, 1690, 1596, 1509, 1455, 1387, 1257, 1201, 920, 828, 708, 627 cm^{-1}.
^{1}**H NMR** (300 MHz, CDC1$_3$): δ 7.91 (d, J = 8.9 Hz, 2H), 7.41-7.33 (m, 5H), 6.99 (d, J = 8.9 Hz, 2H), 5.22 (s, 2H), 4.40 (s, 2H).
^{13}**C NMR** (75 MHz, CDC1$_3$): δ 190.1, 163.4, 135.6, 131.2, 128.8, 128.4, 127.2, 126.4, 114.8, 70.1, 30.3.
Spectroscopic data was in agreement with literature[288].

2-Bromo-3',4'-dimethoxyacetophenone (129)

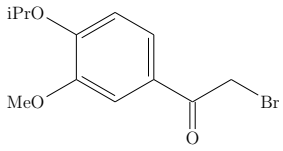


TsOH (18.94 g, 110.0 mmol) in MeCN (100 mL) was added dropwise to a solution of 3,4-dimethoxycetophenone (18.02 g, 100.0 mmol) and NBS (19.58 g, 110.0 mmol) in DME (100 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as pale pink crystals.

Yield: 26.51 g (93%).
M.P.: 73-74 ^{o}C (Lit. 81^{o}C[291]).
IR (neat): ν 1682, 1586, 1515, 1421, 1283, 1244, 1156, 1022, 868, 798, 684 cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$) : δ 7.62-7.54 (m, 2H), 6.91 (d, J = 8.1 Hz, 1H) , 4.42 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H).
^{13}**C NMR** (75 MHz, $CDCl_3$): δ 190.0, 153.9, 149.2, 126.9, 123.8, 110.7, 110.0, 55.9, 55.0, 30.4.

Spectroscopic data was in agreement with literature[292].

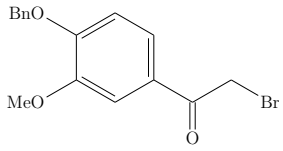
2-Bromo-3'-methoxy-4'-isopropyloxyacetophenone (130)



TsOH (18.94 g, 110.0 mmol) in MeCN (100 mL) was added dropwise to a solution of 4-isopropyloxy-3-methoxyacetophenone (20.83 g, 100.0 mmol) and NBS (19.58 g, 110.0 mmol) in DME (100 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as pale pink crystals.

Yield: 26.84 g (85%).
M.P.: 71-72^{o}C (Lit. NA).
IR (neat): ν 1676, 1580, 1507, 1417, 1255, 1155, 1019, 946, 881, 797, 687, 617 cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.56-7.51 (m, 2H), 6.89 (d, J = 8.4 Hz, 1H) , 4.66 (d, J = 6.0 Hz, 1H), 4.42 (s, 2H), 3.90 (s, 3H), 1.42 (d, J = 6.0 Hz, 6H).
^{13}**C NMR** (75 MHz, $CDCl_3$) : δ 189.9, 152.58, 149.9, 126.5, 123.7, 112.5, 111.3, 71.2, 56.0, 30.4, 21.8.

2-Bromo-4'-benzyloxy-3'-methoxyacetophenone (131)

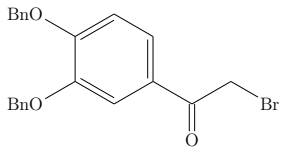


TsOH (8.76 g, 55.0 mmol) in MeCN (50 mL) was added dropwise to a solution of 4-benzyloxy-3-methoxyacetophenone (12.82 g, 50.0 mmol) and NBS (9.80 g, 55.0 mmol) in DME (50 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as white crystals.

Yield: 13.24 g (79%).
M.P.: 101-104 ^{o}C (Lit. 106-108 ^{o}C[268]).
IR (neat): ν 1682, 1582, 1512, 1418, 1283, 1153, 1021, 990, 803, 753, 686, 635 cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$) : δ 7.55-7.32 (m, 7H), 6.90 (d, J = 8.4 Hz, 1H), 5.24 (s, 2H), 4.38 (s, 2H), 3.94 (s, 3H).
^{13}**C NMR** (75 MHz, $CDCl_3$): δ 190.0, 153.1, 149.7, 135.9, 128.7, 128.2, 127.2, 123.6, 112.1, 111.2, 70.8, 56.1, 30.4.

Spectroscopic data was in agreement with literature[268].

2-Bromo-3',4'-dibenzyloxyacetophenone (132)

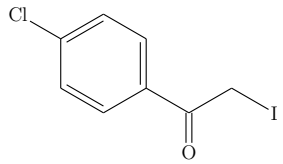


TsOH (4.38 g, 27.5 mmol) in MeCN (50 mL) was added dropwise to a solution of 3,4-dibenzyloxyacetophenone (8.31 g, 25.0 mmol) and NBS (4.90 g, 27.5 mmol) in DME (50 mL). The mixture was stirred overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as brown crystals.

Yield: 8.89 g (86%).
M.P.: 87-88 ^{o}C (Lit. 92-93 ^{o}C[293]).
IR (neat): ν 1665, 1579, 1513, 1434, 1266, 1222, 1147, 1107, 1077, 1018, 890, 847, 809, 730, 692 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.61-7.34 (m, 12H), 6.92 (d, J = 8.3 Hz, 1H), 5.22 (s, 2H), 5.17 (s, 2H), 4.31 (s, 2H).
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 189.9, 153.8, 148.7, 136.5, 136.2, 128.6, 128.5, 128.1, 127.9, 127.4, 127.2, 127.0, 124.0, 114.3, 112.8, 71.1, 70.8, 30.5

9.8 α-Iodination

4'-Chloro-2-iodoacetophenone (133)

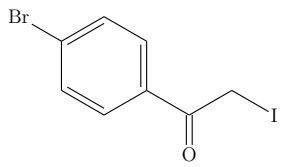


4-Chloroacetophenone (7.73 g, 50.0 mmol), Cu(II)O (3.98 g, 50.0 mmol) and I_2 (12.69 g, 50.0 mmol) were dissolved in MeOH (200 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was

then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as light brown crystals.

Yield: 11.26 g (80%).
M.P.: 75-76 ^{o}C (Lit. 72-74^{o}C[294]).
IR (neat): ν 1686, 1588, 1483, 1263, 1182, 1088, 977, 801, 760, 710 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDCl_3$) : δ 7.93 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 4.33 (s, 2H).
^{13}**C NMR** (100 MHz, $CDCl_3$) : δ 191.5, 140.2, 131.7, 130.4, 129.1, 1.2.
Spectroscopic data was in agreement with literature[276].

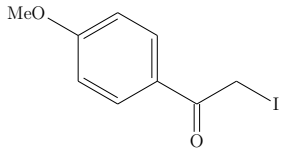
2-Iodo-4'-bromoacetophenone (134)



4-Bromoacetophenone (3.98 g, 20.0 mmol), Cu(II)O (1.59 g, 20.0 mmol) and I_2 (5.07 g, 20.0 mmol) were dissolved in MeOH (100 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as yellow crystals.

Yield: 4.50 g (71%).
M.P.: 94-95^{o}C (Lit. 97-99^{o}C[295]).
IR (neat): ν 1686, 1580, 1378, 1255, 1170, 1070, 980, 795, 612 cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.84 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.6 Hz, 2H), 4.33 (s, 2H).
^{13}**C NMR** (75 MHz,CDC13): δ 191.8, 132.4, 132.3, 130.3, 129.4, 1.2.
Spectroscopic data was in agreement with literature[276].

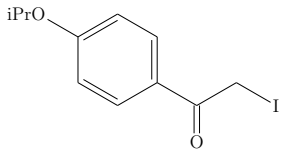
2-Iodo-4'-methoxyacetophenone (135)



4-Methoxyacetophenone (3.00 g, 20.0 mmol), Cu(II)O (1.59 g, 20.0 mmol) and I_2 (5.07 g, 20.0 mmol) were dissolved in MeOH (100 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as yellow crystals.

Yield: 4.20 g (76%).
M.P.: 62-64 (Lit. 59-61 ^{o}C[296]).
IR (neat): ν 1659, 1594, 1570, 1506, 1455, 1287, 1251, 1155, 1101, 1020, 845, 811, 758 cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.96 (d, J = 9.0 Hz, 2H) , 6.94 (d, J = 9.0 Hz, 2H) , 4.32 (s, 2H), 3.87 (s, 3H).
^{13}**C NMR** (75 MHz, $CDCl_3$): δ 191.5, 163.9, 131.3, 126.2, 113.9, 55.6, 1.8.
Spectroscopic data was in agreement with literature[276].

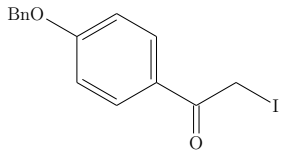
2-Iodo-4'-isopropoxyacetophenone (136)



2-Bromo-4'-isopropoxyacetophenone (3.86 g, 15.0 mmol) and NaI (3.37 g, 22.5 mmol) was dissolved in MeCN (100 mL). The reaction mixture was stirred at R.T. overnight and monitored by TLC. When all the starting materials had been consumed, the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure to give the titled compound as a black oil

Yield: 4.45 g (96%).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, J = 9.0 Hz, 2H) , 6.90 (d, J = 9.0 Hz, 2H) , 4.66 (h, J = 6.3 Hz, 1H), 4.30 (s, 2H), 1.34 (d, J = 6.3 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 191.3, 162.3, 131.4, 125.7, 115.1, 70.1, 21.8, 1.8.

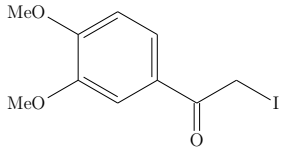
2-Iodo-4'-benzyloxyacetophenone (137)



4-Benzyloxyacetophenone (5.32 g, 50.0 mmol), Cu(II)O (1.59 g, 20.0 mmol) and I_2 (5.07 g, 20.0 mmol) were dissolved in MeOH (100 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as light pink crystals.

Yield: 4.61 g (65%).
M.P.: 32-33 (Lit. NA).
IR (neat): ν 1738, 1655, 1599, 1573, 1425, 1371, 1279, 1231, 992, 839, 760, 712 cm^{-1}.
^{1}H NMR (400 MHz, $CDC1_3$): δ 7.97 (d, J = 9.1 Hz, 2H), 7.43-7.35 (m, 5H), 7.02 (d, J = 9.1 Hz, 2H), 5.14 (s, 2H), 4.30 (s, 2H).
^{13}C NMR (100 MHz, $CDC1_3$): δ 191.4, 163.1, 135.9, 131.4, 128.7, 128.3, 127.5, 114.8, 70.2, 1.6.

3',4'-Dimethoxy-2-iodoacetophenone (138)

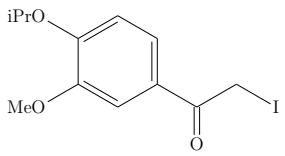


3,4-Dimethoxyacetophenone (9.01 g, 50.0 mmol), Cu(II)O (3.98 g, 50.0 mmol) and I_2 (12.69 g, 50.0 mmol) were dissolved in MeOH (200 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as brown crystals.

Yield: 13.16 g (86%).
M.P.: 61-62 ^{o}C (Lit. 65-66 ^{o}C[245]).
IR (neat): ν 1664, 1583, 1515, 1428, 1269, 1231, 1096, 1017, 769, 752, 618 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.64-7.54 (m, 2H), 6.90 (d, J = 9.0 Hz, 1H) , 4.33 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 191.5, 153.7, 149.1, 126.3, 123.8, 110.7, 109.9, 56.0, 55.9, 1.2.
Spectroscopic data was in agreement with literature[245].

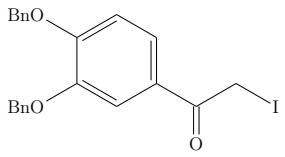
2-Iodo-4'-isopropyloxy-3'-methoxyacetophenone (139)



3-Methoxy-4-isopropyloxyacetophenone (10.41 g, 50.0 mmol), Cu(II)O (3.98 g, 50.0 mmol) and I_2 (12.69 g, 50.0 mmol) were dissolved in MeOH (200 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4).The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as yellow crystals.

Yield: 13.03 g (78%).
M.P.: 81-82 ^{o}C (Lit. NA).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.54 (m, 2H), (d, J = 8.4 Hz, 1H) , 4.69 (h, J = 6.0 Hz, 1H), 4.32 (s, 2H), 3.91 (s, 3H), 1.43 (d, J = 6.0 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 191.5, 152.5, 150.0, 126.0, 123.7, 112.4, 111.5, 71.2, 56.0, 21.8, 1.3.

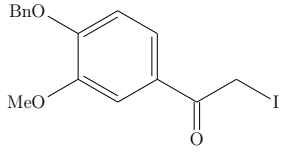
3',4'-Dibenzyloxy-2-iodoacetophenone (140)



3,4-Dibenzyloxyacetophenone (11.63 g, 35.0 mmol), Cu(II)O (2.79 g, 35.0 mmol) and I_2 (8.77 g, 35.0 mmol) were dissolved in MeOH (150 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (200 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as pale yellow crystals.

Yield: 12.99 g (81%).
M.P.: 85-86 ^{o}C.
IR (neat): ν 1663, 1594, 1584, 1513, 1454, 1426, 1383, 1341, 1274, 1221, 1180, 1146, 1099, 1021, 880, 854, 809, 793, 771, 745, 632, 566 cm^{-1}.
^{1}H NMR (400 MHz, $CDC1_3$): δ 7.62-7.25 (m, 12H), 6.94 (d, J = 8.3 Hz, 1H), 5.25 (s, 2H), 5.21 (s, 2H), 4.25 (s, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 191.4, 153.7, 148.8, 136.6, 136.2, 128.7, 128.6, 128.1, 128.0, 127.4, 127.1, 126.7, 124.1, 114.5, 112.8, 71.2, 70.8, 1.3.

4'-Benzyloxy-3'-methoxy-2-iodoacetophenone (141)

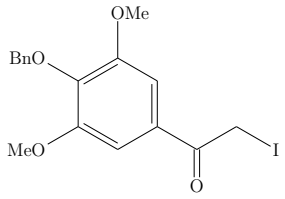


4-Benzyloxy-3-methoxyacetophenone (5.13 g, 20.0 mmol), Cu(II)O (1.59 g, 20.0 mmol) and I_2 (5.07 g, 20.0 mmol) were dissolved in MeOH (100 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound

was recrystallized in methylcyclohexane to give the titled compound as brown crystals.

Yield: 6.20 g (81%).
M.P.: 103-104 ^{o}C (Lit 104-105 ^{o}C).
IR (neat): ν: 1652, 1594, 1570, 1509, 1456, 1425, 1287, 1285, 1274, 1156, 1099, 1021, 880, 847, 812, 793, 771, 757, 632, 566 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 7.56-7.53 (m, 2H), 7.45-7.31 (m, 5H), 6.90 (d, J = 8.6 Hz, 1H), 5.24 (s, 2H), 4.30 (s, 2H), 3.94 (s, 3H).
^{13}**C NMR** (100 MHz, $CDC1_3$): δ 191.6, 153.0, 149.7, 136.1, 128.7, 128.2, 127.2, 126.7, 123.7, 112.0, 111.4, 70.8, 56.1, 1.2.
Spectroscopic data was in agreement with previous work in Bakstad's research group[248].

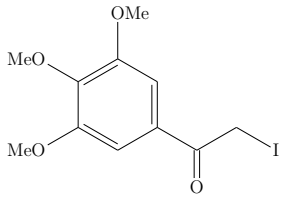
4'-Benzyloxy-3',5'-dimethoxy-2-iodoacetophenone (142)



4-Benzyloxy-3,5-dimethoxyacetophenone (5.73 g, 20.0 mmol), Cu(II)O (1.59 g, 20.0 mmol) and I_2 (5.07 g, 20.0 mmol) were dissolved in MeOH (100 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as yellow crystals.

Yield: 5.00 g (60%).
M.P.: 76 ^{o}C (Lit. NA).
IR (neat): ν 1739, 1656, 1579, 1500, 1457, 1409, 1371, 1334, 1233, 1206, 1182, 1128, 962, 744, 701, 612 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 7.48-7.23 (m, 7H), 5.12 (s, 2H), 4.33 (s, 2H), 3.89 (s, 6H).
^{13}**C NMR** (100 MHz, $CDC1_3$) : δ 191.8, 153.5, 142.1, 137.2, 128.7, 128.4, 128.2, 128.1, 106.6, 75.1, 56.3, 1.3.

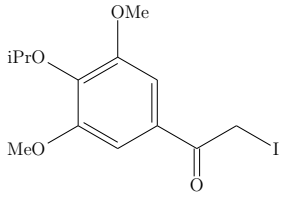
2-Iodo-3',4',5'-trimethoxyacetophenone (143)



3,4,5-Trimethoxyacetophenone (10.51 g, 50.0 mmol), Cu(II)O (3.98 g, 50.0 mmol) and I_2 (12.69 g, 50.0 mmol) were dissolved in MeOH (200 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (250 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as fluffy brown crystals.

Yield: 10.00 g (59%).
M.P.: 73-74 ^{o}C (Lit. 86-87 ^{o}C[245]).
IR (neat): ν 1668, 1588, 1508, 1454, 1409, 1333, 1236, 1130, 989 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDC1_3$): δ 7.25 (s, 2H), 4.34 (s, 2H), 3.94 (s, 3H), 3.93 (s, 6H).
^{13}**C NMR** (125 MHz, $CDC1_3$): δ 191.8, 153.1, 143.2, 128.5, 106.6, 61.0, 56.4, 1.2.
Spectroscopic data was in agreement with literature[245].

3',5'-Dimethoxy-2-iodo-4'-isopropyloxyacetophenone (144)

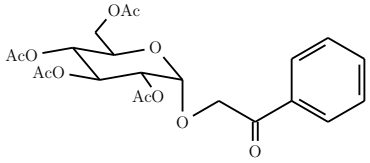


3,5-Dimethoxy-4-isopropyloxyacetophenone (3.57 g, 15.0 mmol), Cu(II)O (1.19 g, 15.0 mmol) and I_2 (3.81 g, 50.0 mmol) were dissolved in MeOH (100 mL). The reaction mixture was refluxed overnight and monitored by TLC. When all the starting materials had been consumed, water (150 mL) was added and the aqueous phase was extracted with TBME (3 x 50 mL). The combined organic phases were then washed with water (3 x 25 mL) and dried (Na_2SO_4). The organic solvent was then removed under reduced pressure, and the compound was recrystallized in methylcyclohexane to give the titled compound as light yellow fluffy crystals.

Yield: 1.29 g (24%).
M.P.: 92-93 ^{o}C (Lit. NA).
IR (neat): ν 1669, 1582, 1497, 1455, 1407, 1327, 1217, 1188, 1125, 1095, 1043, 918, 892, 860, 830, 740 cm^{-1}.
^{1}**H NMR** (400 MHz, $CDC1_3$): δ 7.25 (s, 2H), 4.53 (h, J = 6.0 Hz, 1H), 3.90 (s, 6H), 1.32 (d, J = 6.0 Hz, 6H).
^{13}**C NMR** (100 MHz, $CDC1_3$): δ 196.8, 191.9, 153.8, 141.7, 128.3, 106.6, 56.3, 22.6, 1.3.

9.9 α-Glycosylated compounds

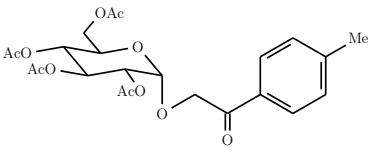
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-acetophenone (145)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-bromoacetophenone (0.60 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 0.95 g (68%).
IR (neat): ν 1744, 1703, 1598, 1449, 1367, 1217, 817, 971, 915, 808.4, 731, 690, 659 cm^{-1}.
^{1}**H NMR** (500 MHz: $CDC1_3$): δ 7.88-7.86 (m, 2H), 7.59-7.56 (m, 1H), 7.47-7.44 (m, 2H), 5.59-5.55 (m, 1H), 5.21 (d, J = 3.7 Hz, 1H), 5.09-5.06 (m, 1H), 4.92 (d, J = 17.0 Hz, 1H), 4.93-4.88 (m, 1H), 4.85 (d, J = 16.8 Hz, 1H), 4.25-4.19 (m, 2H), 4.08-4.05 (m, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H).
^{13}**C NMR** (125 MHz, $CDC1_3$): δ 194.3, 170.5, 170.3, 169.9, 1695, 1345, 133.7, 128.8, 127.7, 95.9, 70.4, 69.7, 69.6, 68.3, 67.8, 61.7, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{22}H_{26}O_{11}$ [M + Na^+] 489.1, found 489.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 43.72 (c 4.3, DCM).

2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-4'-methylacetophenon (146)

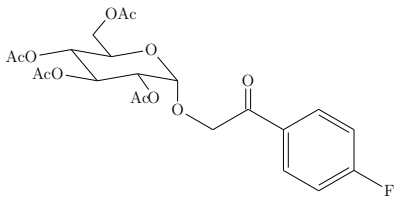


Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-bromo-4'-methylacetophenone (0.64 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight.

Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 0.88 g (61%).
IR (neat): ν 1744, 1600, 1513. 1367, 1216, 1169, 1032.974, 731, 6164 cm^{-1}.
^{1}H NMR (500 MHz: $CDC1_3$): δ 7.78-7.76 (m, 2H), 7.27-7.25 (m, 2H), 5.60-5.57 (m, 1H), 5.20 (d, J = 3.6 Hz, 1H), 5.10-5.07 (m, 1H), 4.92 (dd, J = 10.2, 3.8 Hz, 1H), 4.91 (d, J = 16.8 Hz, 1H), 4.85 (d, J = 16.7 Hz, 1H), 4.26-4.20 (m, 2H), 4.09-4.07 (m, 1H), 2.40 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 2.03 (5, 3H), 2.02 (s, 3H).
^{13}C NMR (125 MHz, $CDC1_3$): δ 193.9, 170.5, 170.4, 169.9, 169.5, 145.0, 131.91. 79.4, 127.7, 96.0, 77 .2, 77.0, 76.7, 70.4, 69.7, 69.5, 68.3, 67.7, 61.7, 21.6, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{23}H_{28}O_{11}$ [M + Na^+] 503.2, found 503.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 38.81 (c 2.4, DCM).

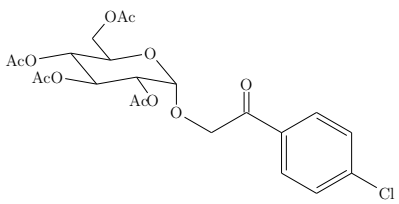
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-4'-fluoroacetophenone (147)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-bromo-4'-fluoroacetophenone (0.65 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 0.83 g, (57%).
IR (neat): ν 1751, 1598, 1425, 1256, 1043, 897, 721 cm^{-1}.
^{1}H NMR (500 MHz: $CDC1_3$): δ 7.92-7.89 (m, 2H), 7.15-7.11 (m, 2H), 5.58-5.54 (m, 1H), 5.19 (d, J = 3.7 Hz, 1H), 5.10-5.06 (m, 1H), 4.90 (dd, J = 10.4, 3.7 Hz, 1H), 4.86-4.80 (m, 2H), 4.23 (dd, J = 12.3, 4.1 Hz, 1H), 4.19-4.17 (m, 1H), 4.07 (dd, J = 12.3, 2.0 Hz, 1H), 2.11 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H).
^{13}C NMR (125 MHz, $CDC1_3$): δ 192.8, 170.6, 170.4, 170.0, 169.5, 166.1 (d, J_{CF} = 25.9 Hz), 131.0 (d, J_{CF} = 3.1 Hz), 130.5 (d, J_{CF} = 9.8 HZ), 116.0 (d, J_{CF} = 22.3 Hz), 96.0, 70.5, 69.7, 69.5, 68.3, 67.9, 61.7, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{22}H_{25}FO_{11}$ [M + Na^+] 507.1, found 507.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 125.33 (c 0.75, DCM).

2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-4'-chloroacetophenone (148)

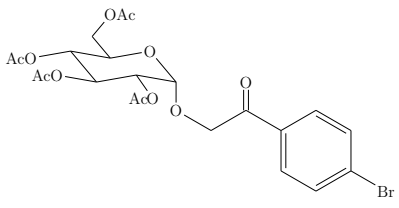


Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-bromo-4'-chloroacetophenone (0.70 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight.

Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a brown wax.

Yield: 0.58 g (39%).
IR (neat): ν 1742, 1703, 1590, 1366, 1211, 1090, 1031, 973, 925, 902, 823 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDC1_3$): δ 7.82-7.80 (m, 2H), 7.45-7.43 (m, 2H), 5.58-5.54 (m, 1H), 5.18 (d, J = 3.7 Hz, 1H), 5.10-5.06 (m, 1H), 4.90 (dd, J = 10.6, 3.7 Hz, 1H), 4.85-4.80 (m, 2H), 4.23 (dd, J = 12.3, 4.1 Hz, 1H), 4.19-4.16 (m, 1H), 4.07 (dd, J = 12.3, 2.0 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 193.3, 170.6, 170.5, 170.0, 169.6, 140.3, 132.7, 129.2, 96.0, 70.6, 69.7, 69.6, 68.3, 67.9, 61.7, 20.7.
LRMS (ESI): Calcd for $C_{22}H_{25}ClO_{11}$ [M + Na^+] 523.1, found 523.1.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 130.00 (c 0.5, DCM).

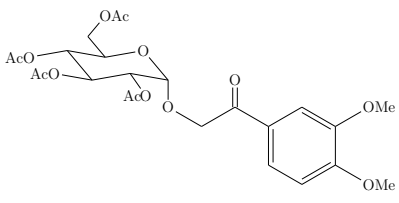
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-4'-bromoacetophenone (149)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2,4'-dibromoacetophenone (0.83 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 0.70 g (43%)
IR (neat): ν 1742, 1586, 1365, 1208, 1031, 972, 902, 818 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCI_3$): δ 7.74-7.72 (m, 2H), 7.62-7.60 (m, 2H), 5.58-5.54 (m, 1H), 5.18 (d, J =3.7, 1H), 5.10-5.07 (m, 1H), 4.90 (dd, J = 10.4, 3.7 Hz, 1H), 4.85-4.79 (m, 2H), 4.24 (dd, J = 12.3, 4.2 Hz, 1H), 4.19-4.16 (m, 1H), 4.07 (dd, J = 12.3, 2.0 Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H).
^{13}**C NMR** (125 MHz, $CDCI_3$): δ 193.5, 170.6, 170.5, 170.0, 169.6, 133.1, 132.2, 129.3, 129.1, 96.0, 70.5, 69.7, 69.6, 68.3, 67.9, 61.7, 20.7.
LRMS (ESI): Calcd for $C_{22}H_{25}BrO_{11}$ [M + Na^+] 567.0, found 567.1.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = 39.43 (c 2.79, DCM).

2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-3',4'-dimethoxyacetophenone (150)

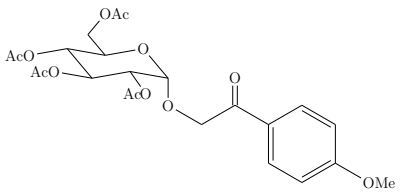


Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-bromo-3',4'-dimethoxyacetophenone (0.77 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight.

Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 0.87 g (55%).
IR (neat): ν 1744, 1690, 1595, 1516, 1420, 1367, 1218, 1166, 1135, 1035, 767, 729 cm^{-1}.
^{1}H NMR (500 MHz, $CDC1_3$): δ 7.44-7.42 (m, 2H), 6.86 (d, J = 8.3 Hz, 1H), 5.60-5.56 (m, 1H), 5.21 (d, J = 3.5 Hz, 1H), 5.10-5.06 (m, 1H), 4.91 (dd, J = 10.3, 3.6 Hz, 1H), 4.88 (d, J = 16.5 Hz, 1H), 4.82 (d, J = 16.4 Hz, 1H), 4.25-4.20 (m, 2H), 4.09-4.07 (m, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H).
^{13}C NMR (125MHz, $CDC1_3$): δ 192.8, 170.6, 170.4, 170.0, 169.6, 153.8, 149.3, 127.7, 122.2, 110.1, 110.0, 95.9, 70.5, 69.8, 69.3, 68.4, 67.8, 61.7, 56.1, 56.0, 20.8, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{24}H_{30}O_{13}$ [M + Na^+] 549.2, found 549.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = 42.34 (c 1.78, DCM).

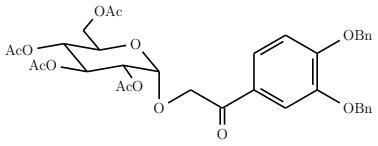
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-4'-methoxyacetophenone (151)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-bromo-4'-methoxyacetophenone (0.69 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a orange wax.

Yield: 1.00 g (67%).
IR (neat): ν 1745, 1695, 1600, 1513, 1368, 1223, 975, 913, 740 cm^{-1}.
^{1}H NMR (500 MHz, $CDC1_3$): δ 7.87-7.85 (m, 2H), 6.94-6.92 (m, 2H), 5.60-5.56 (m,1H), 5.21 (d, J = 3.7 Hz, 1H), 5.10-5.06 (m, 1H), 4.92 (dd, J = 10.4, 3.7 Hz, 1H), 4.87 (d, J = 16.8 Hz, 1H), 4.80 (d, J =16.5 Hz, 1H), 4.27-4.23 (m, 2H), 4.09-4.06 (m, 1H), 3.78 (s, 3H), 2.13 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H).
^{13}C NMR (125MHz, $CDC1_3$): δ 192.8, 170.6, 170.4, 170.0, 169.6, 163.9, 130.1, 127.5, 114.0, 95.9, 70.5, 69.8, 69.4, 68.4, 67.8, 61.8, 55.5, 20.8, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{23}H_{28}O_{12}$ [M + Na^+] 519.1, found 519.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = 59.68 (c 1.6, DCM).

2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-3',4'-dibenzyloxyacetophenone (152)

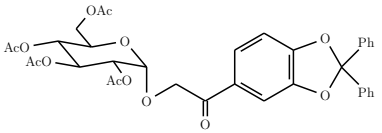


Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 3',4'-dibenzyloxy-2-iodoacetophenone (1.37 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl

(6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 1.18 g (58%).
IR (neat): ν 1752, 1422, 1259, 1153, 1040, 896, 773, 713 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 1.9 Hz, 1H), 7.48–7.30 (m, 11 H), 6.92 (d, J = 8.6 Hz, 1H), 5.61-5.56 (m, 1H), 5.24 (s, 2H), 5.19 (s, 2H), 5.12–5.07 (m, 1H), 4.92 (dd, J = 10.3, 3.7 Hz, 1H), 4.84 (d, J = 16.5 Hz, 1H), 4.77 (d, J = 16.5 Hz, 1H), 4.28–4.19 (m, 1H), 4.09–4.06 (m, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 170.6, 170.4, 169.9, 169.6, 153.6, 148.8, 136.5, 136.2, 128.6, 128.5, 128.0, 127.9, 127.8, 127.4, 127.0, 122.5, 113.4, 112.9, 95.9, 71.3, 70.7, 70.4, 69.8, 69.3, 68.4, 67.7, 61.7, 20.7, 20.6.
LRMS (ESI): Calcd for $C_{36}H_{38}O_{13}$ [M + Na^+] 701.2, found 701.3.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{29}}$ = 41.40 (c 4.3, DCM).

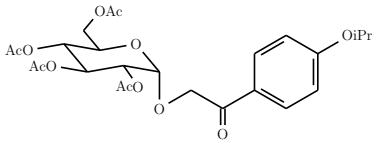
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-3',4'-diphenylmethylenedioxyacetophenone (153)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-iodo-3',4'-diphenylmethylenedioxyacetophenone (1.33 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 1.20 g (60%).
IR (neat): ν 1743, 1705, 1493, 1448, 1366, 1206, 1034, 848, 774, 746, 698 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.35 (m, 12 H), 6.89 (d, J = 8.2 Hz, 1H), 5.58- 5.54 (m, 1H), 5.16 (d, J = 3.7 Hz, 1H), 5.09–5.05 (m, 1H), 4.90 (dd, J = 10.4, 3.7 Hz, 1H), 4.81 (d, J = 16.5 Hz, 1H), 4.76 (d, J = 16.5 Hz, 1H), 4.25–4.16 (m, 1H), 4.07–4.04 (m, 1H), 2.07 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 192.2, 170.5, 170.4, 169.9, 169.5, 151.7, 147.8, 139.3 139.2, 129.3, 129.2, 128.2, 126.1, 124.0, 118.3, 108.2, 107.9, 95.9, 70.4, 69.7, 69.4, 68.3, 67.7, 61.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{35}H_{34}O_{13}$ [M + Na^+] 685.2, found 685.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = 78.67 (c 1.5, DCM).

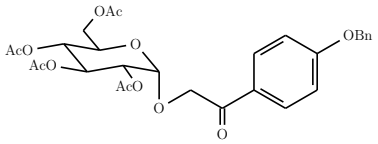
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-4'-isopropoxyacetophenone (154)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-bromo-4'-isopropyloxyacetophenone (0.77 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 0.98 g (62%).
IR (neat): ν 1750, 1693, 1600, 1509, 1425, 1369, 1225, 1169, 1040, 977, 950, 839 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.82–7.80 (m, 2H), 6.88–6.86 (m, 2H), 5.18 (d, J = 3.7 Hz, 1H), 5.58-5.54 (m, 1H), 5.08–5.04 (m, 1H), 4.89 (dd, J = 10.4, 3.7 Hz, 1H), 4.85 (d, J = 16.5 Hz, 1H), 4.79 (d, J = 16.5 Hz, 1H), 4.62 (h, J = 6.1 Hz, 1H), 4.24–4.20 (m, 1H), 4.06–4.03 (m, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.33 (d, J = 6.0 Hz, 6H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 192.7, 170.5, 170.4, 169.9, 169.5, 162.4, 130.0, 127.0, 115.2, 95.9, 70.4, 70.1, 69.7, 69.4, 68.4, 67.7, 61.7, 21.8, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{25}H_{32}O_{12}$ [M + Na^+] 547.2, found 547.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{29}}$ = 53.33 (c 3.0, DCM).

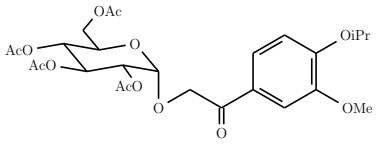
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-4'-benzyloxyacetophenone (155)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-bromo-4'-benzyloxyacetophenone (0.92 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a orange wax.

Yield: 1.10 g (64%).
IR (neat): ν 1753, 1510, 1422, 1268, 1229, 1170, 1041, 896, 724 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.85–7.83 (m, 2H), 7.40–7.30 (m, 5H), 6.99–6.97 (m, 2H), 5.59-5.55 (m, 1H), 5.18 (d, J = 3.7 Hz, 1H), 5.11 (s, 2H), 5.11–5.05 (m, 1H), 4.90 (dd, J = 10.4, 3.7 Hz, 1H), 4.85 (d, J = 16.5 Hz, 1H), 4.79 (d, J = 16.5 Hz, 1H), 4.25–4.17 (m, 1H), 4.07–4.04 (m, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 192.7, 170.6, 170.4, 169.9, 169.5, 163.0, 135.9, 130.0, 128.6, 128.2, 127.7, 127.4, 114.8, 95.9, 70.4, 70.1, 69.8, 69.4, 68.4, 67.7, 61.7, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{29}H_{32}O_{12}$ [M + Na^+] 595.2, found 595.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 134.67 (c 1.5, DCM).

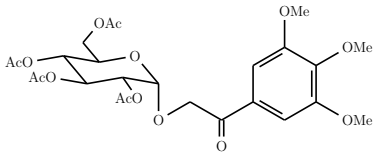
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-4'-isopropoxy-3'-methoxyacetophenone (156)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-bromo-3'-methoxy,4'-isopropyloxyacetophenone (0.86 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 1.26 g (76%).
IR (neat): ν 1743, 1691, 1593, 1510, 1420, 1367, 1212, 1031 , 950, 772 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.46–7.42 (m, 2H), 6.86 (d, J = 8.5 Hz, 1H), 5.21 (d, J = 3.7 Hz, 1H), 5.61-5.57 (m, 1H), 5.11–5.07 (m, 1H), 4.91 (dd, J = 10.4, 3.7 Hz, 1H), 4.88 (d, J = 16.5 Hz, 1H), 4.82 (d, J = 16.5 Hz, 1H), 4.65 (h, J = 6.1 Hz, 1H), 4.25–4.23 (m, 1H), 4.09–4.07 (m, 1H), 3.90 (s, 3H), 2.13 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 1.40 (d, J = 6.0 Hz, 6H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 192.8, 170.6, 170.5, 170.0, 169.6, 152.4, 150.1, 127.3, 122.1, 112.7, 110.6, 95.9, 71.3, 70.5, 69.8, 69.3, 68.4, 67.8, 61.7, 56.1, 21.8, 20.7, 20.7, 20.6.
LRMS (ESI): Calcd for $C_{26}H_{34}O_{13}$ [M + Na^+] 577.2, found 577.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = 45.81 (c 1.55, DCM).

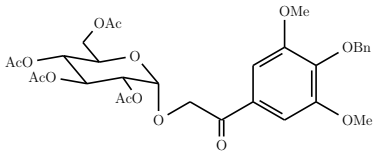
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-3',4',5'-trimethoxyacetophenone (157)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 2-iodo-3',4',5'-trimethoxyacetophenone (1.01 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a yellow oil.

Yield: 0.92 g, (55%).
IR (neat): ν 1750, 1677, 1584, 1501, 1451, 1408, 1355, 1327, 1216, 1122, 992, 887, 856, 825 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.13 (s, 2H), 5.60-5.56 (m, 1H), 5.19 (d, J = 3.7 Hz, 1H), 5.11–5.07 (m, 1H), 4.90 (dd, J = 10.4, 3.7 Hz, 1H), 4.86 (d, J = 16.5 Hz, 1H), 4.81 (d, J = 16.5 Hz, 1H), 4.26–4.18 (m, 1H), 4.11–4.08 (m, 1H), 3.90 (s, 6H), 2.10 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 193.2, 170.6, 170.5, 170.0, 169.6, 153.2, 143.2, 129.6, 105.4, 96.0, 70.5, 69.7, 68.4, 67.9, 61.7, 61.0, 56.2, 20.7, 20.6.
LRMS (ESI): Calcd for $C_{25}H_{32}O_{14}$ [M + Na^+] 579.2, found 579.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$ = 56.36 (c 1.1, DCM).

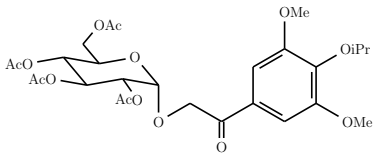
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-4'-benzyloxy-3',5'-dimethoxyacetophenone (158)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 4'-benzyloxy-3',5'-dimethoxy-2-iodoacetophenone (1.24 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 0.75 g (40%).
IR (neat): ν 1743, 1697, 1584, 1415, 1368, 1215, 1125, 1034, 738, 697 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.46–7.45 (m, 2H), 7.35–7.28 (m, 3H), 7.12 (s, 2H), 5.63 - 5.59 (m, 1H), 5.22 (d, J = 3.7 Hz, 1H), 5.13–5.10 (m, 1H), 5.10 (s, 2H), 4.92 (dd, J = 10.4, 3.7 Hz, 1H), 4.89 (d, J = 16.5 Hz, 1H), 4.84 (d, J = 16.5 Hz, 1H), 4.28–4.21 (m, 1H), 4.13–4.11 (m, 1H), 3.88 (s, 6H), 2.12 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 193.2, 170.6, 170.4, 169.9, 169.5, 153.5, 141.9, 137.1, 129.7, 128.3, 128.2, 128.0, 105.3, 96.0, 74.9, 70.5, 69.7, 68.3, 67.8, 61.6, 56.3, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{30}H_{34}O_{14}$ [M + Na^+] 655.2, found 655.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = 81.33 (c 1.5, DCM).

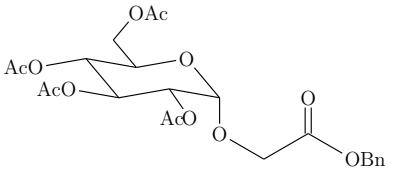
2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)-3',5'-dimethoxy-4'-isopropyloxyacetophenone
(159)



Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of 3',5'-dimethoxy-2-iodo-4'-isopropyloxyacetophenone (1.09 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a pale yellow wax.

Yield: 1.16 g (66%).
IR (neat): ν 1754, 1422, 1254, 1043, 896, 716 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.15 (s, 2H), 5.63-5.59 (m, 1H), 5.22 (d, J = 3.7 Hz, 1H), 5.13–5.09 (m, 1H), 4.92 (dd, J = 10.4, 3.7 Hz, 1H), 4.90 (d, J = 16.6 Hz, 1H), 4.84 (d, J = 16.6 Hz, 1H), 4.51 (h, J = 6.2 Hz, 1H), 4.28–4.21 (m, 1H), 4.12–4.09 (m, 1H), 3.89 (s, 6H), 2.12 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.30 (d, J = 6.2 Hz, 6H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 193.2, 170.6, 170.4, 170.0, 169.5, 153.9, 141.6, 129.4, 105.3, 96.0, 75.8, 70.5, 69.7, 68.3, 67.8, 61.7, 56.3, 22.4, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{27}H_{36}O_{14}$ [M + Na^+] 607.2, found 607.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 70.67 (c 1.5, DCM).

2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyloxy)acetic acid benzyloxy ester (160)

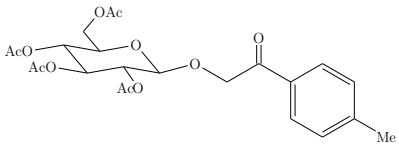


Cs_2CO_3 (1.47 g, 4.5 mmol) was added to a stirred solution of benzyl bromoacetate (0.69 g, 3.0 mmol) and β-D-glucose-2,3,4,6-tetraacetate (1.04 g, 3.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess Cs_2CO_3 was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a yellow oil.

Yield: 0.88 g (59%).
IR (neat): ν 1752, 1425, 1371, 1046, 899 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.30 (m, 5H), 5.52-5.48 (m, 1H), 5.17 (d, J = 3.7 Hz, 1H), 5.14 (s, 2H), 5.07-5.03 (m, 1H), 4.87 (dd, J = 10.4, 3.7 Hz, 1H), 4.20 (dd, J = 12.3, 4.3 Hz, 1H), 4.18-4.16 (m, 2H), 4.15-4.12 (m, 1H), 4.02 (dd, J = 12.3, 1.9 Hz, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 170.6, 170.3, 169.9, 169.5, 168.9, 135.0, 128.6, 128.5, 128,4 95.9, 70.3, 69.6, 68.2, 67.9, 66.9, 64.4, 61.6, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{23}H_{28}O_{11}$ [M + Na^+] 519.1, found 519.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = 104.2 (c 2.2, DCM).

9.10 β-Glycosylated compounds

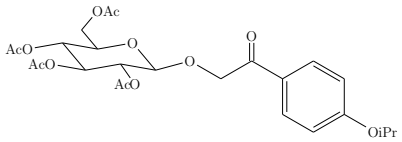
2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4'-methylacetophenone (161)



A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of 2-bromo-4'-methylacetophenone (0.64 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 0.79 g (55%).
IR (neat): ν 1744, 1600, 1513, 1367, 1216, 1169, 1032, 974, 731 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.81-7.80 (m, 2H), 7.27-7.26 (m, 2H), 5.25-5.21 (m, 1H), 5.12-5.07 (m, 2H), 4.93 (d, J = 16.2 Hz, 1H), 4.84 (d, J = 16.2, 1H), 4.69 (d, J = 7.9 Hz, 1H), 4.24 (dd, J = 12.5, 4.5 Hz, 1H), 4.13 (dd, J = 12.1, 2.1 Hz, 1H), 3.69 (ddd, J = 9.9, 4.3, 2.1 Hz, 1H), 2.41 (s, 3H) 2.07 (s, 3H), 2.02 (s. 3H), 2.00 (s, 3H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 194.4, 170.6, 170.1, 169.6, 169.4, 144.6, 132.2, 129.4, 128.2, 100.2, 72.5, 71.8, 71.0, 70.4, 68.3, 61.7, 21.6, 20.6, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{23}H_{28}O_{11}$ [M + Na^+] 503.2, found 503.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = -18.30 (c 4.7, DCM).

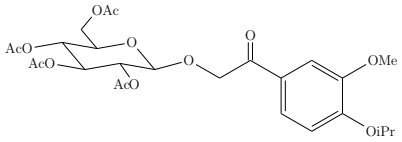
2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4'-isopropoxyacetophenone (162)



A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of 2-bromo-4'-isopropyloxyacetophenone (0.77 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 0.79 g (50%).
IR (neat): ν 1749, 1600, 1370, 1218, 1037, 912, 731 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.82-7.80 (m, 2H), 6.85-6.83 (m, 2H) 5.19-5.15 (m, 1H), 5.05-5.00 (m, 2H), 4.85 (d, J = 16.0 Hz, 1H), 4.74 (d, J = 16.0 Hz, 1H), 4.64 (d, J = 7.8 Hz, 1H), 4.59 (h, J = 6.1 Hz, 1H), 4.18 (dd, J = 12.4, 4.7 Hz, 1H), 4.07 (dd, J = 12.4, 2.3 Hz, 1H), 3.64 (ddd, J = 10.0, 4.6, 2.3 Hz, 1H), 2.01 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.30 (d, J = 6.1 Hz, 6H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 193.2, 170.5, 170.0, 169.6, 169.3, 162.3, 130.4, 127.2, 115.1, 100.1, 72.5, 71.8, 70.9, 70.3, 70.1, 68.2, 61.7, 21.8, 20.6, 20.5, 20.4.
LRMS (ESI): Calcd for $C_{25}H_{32}O_{12}$ [M + Na^+] 547.2, found 547.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$ = -33.71 (c 3.5, DCM).
Spectroscopic data was in agreement with previous work in Bakstad's research group[252].

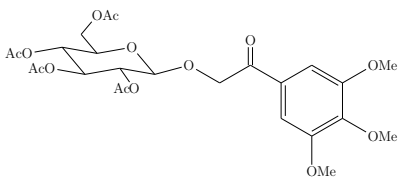
2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4'-isopropoxy-3'-methoxyacetophenone (163)



A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of 2-bromo-3'-methoxy,4'-isopropyloxyacetophenone (0.86 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 1.28 g (77%).
IR (neat): ν 1752, 1691, 1593, 1512, 1371, 1222, 1039, 913, 739 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.45-7.43 (m, 2H), 6.83 (d, J = 8.2 Hz, 1H), 5.19-5.16 (m, 1H), 5.06-5.01 (m, 2H), 4.87 (d, J = 16.0 Hz, 1H), 4.76 (d, J = 16.0 Hz, 1H), 4.63 (d, J = 8.0 Hz, 1H), 4.61 (h, J = 6.1 Hz, 1H), 4.19 (dd, J = 12.4, 4.6 Hz, 1H), 4.08 (dd, J = 12.4, 2.3 Hz, 1H), 3.85 (s, 3H), 3.64 (ddd, J = 10.0, 4.7, 2.4 Hz, 1H), 2.02 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.36 (d, J = 6.1 Hz, 6H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 193.3, 170.5, 170.0, 169.6, 169.3, 152.3, 149.9, 127.4, 122.6, 112.7, 110.8, 100.1, 72.5, 71.8, 71.2, 70.9, 70.3, 68.2, 61.7, 55.9, 21.8, 20.6, 20.5, 20.4.
LRMS (ESI): Calcd for $C_{26}H_{34}O_{13}$ [M + Na^+] 577.2, found 577.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$ = -14.67 (c 1.5, DCM).

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-3',4',5'-trimethoxyacetophenone (164)

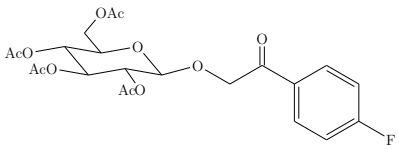


A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of 2-iodo-3',4',5'-trimethoxyacetophenone (1.01 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl

(6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 0.78 g (47%).
IR (neat): ν 1783, 1692, 1583, 1469, 1417, 1367, 1323, 1227, 1157, 1130, 1049, 984, 876, 729, 597 cm^{-1}.
^{1}H NMR(500 MHz, $CDCl_3$): δ 7.15 (s, 2H), 5.21-5.17 (m, 1H), 5.08-5.03 (m, 2H), 4.88 (d, J = 15.9 Hz, 1H), 4.76 (d, J = 15.9 Hz, 1H), 4.63 (d, J = 8.0 Hz, 1H), 4.21 (dd, J = 12.4, 4.6 Hz, 1H), 4.10 (dd, J = 12.4, 2.2 Hz, 1H), 3.67 (ddd, J = 10.0, 4.5, 2.3 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 6H), 2.04 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.7, 170.5, 170.0, 169.5, 169.3, 153.1, 143.0, 129.6, 105.7, 100.2, 72.4, 71.8, 70.9, 70.8, 68.2, 61.6, 60.8, 56.2, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{25}H_{32}O_{14}$ [M + Na^+] 579.2, found 579.2.
$[\alpha]_D^{26}$ = -31.43 (c 3.5, DCM).

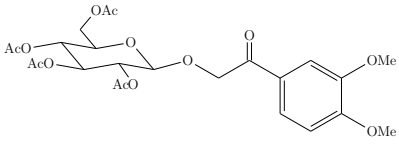
2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4'-flouroacetophenone (165)



A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of 2-bromo-4'-fluoroacetophenone (0.65 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 0.94 g (65%).
IR (neat): ν 1747, 1599, 1369, 1215, 1035, 912, 737 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89-7.86 (m, 2H), 7.08-7.05 (m, 2H), 5.17-5.13 (m, 1H), 5.02-4.98 (m, 2H), 4.82 (d, J = 16.2 Hz, 1H), 4.75 (d, J = 16.2 Hz, 1H) 4.61 (d, J = 8.0 Hz, 1H), 4.15 (dd, J = 12.3, 4.7 Hz, 1H), 4.13 (dd, J = 12.3, 2.3 Hz, 1H), 3.67 (ddd, J = 10.0, 4.6, 2.3 Hz, 1H), 1.99 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.92 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3, 170.4, 170.0, 169.4, 169.2, 165.8 (d, J_{CF} = 255.7 Hz), 131.0 (d, J_{CF} = 3.2 Hz), 130.8 (d, J_{CF} = 9.2 Hz), 115.7 (d, J_{CF} = 21.9 Hz), 100.1, 72.4, 71.8, 70.8, 70.6, 68.1, 61.6, 20.5, 20.4, 20.3.
LRMS (ESI): Calcd for $C_{22}H_{25}FO_{11}$ [M + Na^+] 507.1, found 507.2.
$[\alpha]_D^{28}$ = -2.67 (c 1.5, DCM).

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-3',4'-dimethoxyacetophenone (166)

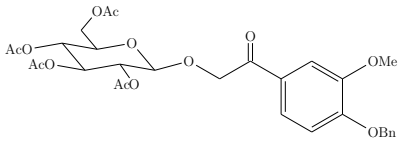


A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of 2-bromo-3',4'-dimethoxyacetophenone (0.77 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 1.09 g (69%).
IR (neat): ν 1746, 1688, 1594, 1516, 1420, 1366, 1215, 1129, 1034, 949, 809, 765, 729, 633 cm^{-1}.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.44 (m, 2H), 6.85 (d, J = 8.5 Hz, 1H), 5.21-5.17 (m, 1H),

5.07-5.03 (m, 2H), 4.88 (d, J = 16.0 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 7.9 Hz, 1H), 4.20 (dd, J = 12.4, 4.6 Hz, 1H), 4.09 (dd, J = 12.4, 2.3 Hz, 1H), 3.65 (ddd, J = 10.0, 4.6, 2.3 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.4, 170.5, 170.1, 169.6, 169.4, 153.7, 149.1, 127.8, 110.2, 110.1, 100.2, 72.5, 71.8, 71.0, 70.4, 68.3, 61.7, 56.1, 55.9, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{24}H_{30}O_{13}$ [M + Na^+] 549.2, found 549.2
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$ = -24 (c 1.5, DCM).

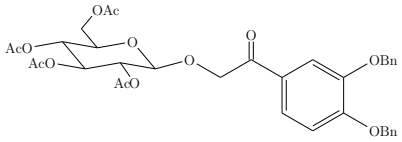
2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4'-benzyloxy-3'-methoxyacetophenone (167)



A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of 2-bromo-4'-benzyloxy-3'-methoxyacetophenone (1.01 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 1.08 g (60%).
IR (neat): ν 1744, 1703, 1672, 1592, 1515, 1373, 1212, 1036, 904, 848, 807, 742, 698 cm^{-1}.
^{1}H NMR (500 MHz, $CDC1_3$): δ 7.47–7.24 (m, 7H), 6.85 (d, J = 8.5 Hz, 1H), 5.21-5.19 (m, 1H), 5.08–5.02 (m, 2H), 4.87 (d, J = 16.0 Hz, 1H), 4.76 (d, J = 16.0 Hz, 1H), 4.64 (d, J = 7.9 Hz, 1H), 4.20 (dd, J = 12.4, 4.6 Hz, 1H), 4.09 (dd, J = 12.4, 2.3 Hz, 1H), 3.65 (ddd, J = 10.0, 4.6, 2.3 Hz, 1H), 3.90 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.4, 170.6, 170.1, 169.6, 169.4, 152.8, 149.6, 136.1, 128.7, 128.1, 128.0, 127.1, 122.6, 112.2, 110.6, 100.2, 72.5, 71.8, 71.0, 70.7, 70.3, 68.3, 61.7, 56.0, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{30}H_{34}O_{13}$ [M + Na^+] 625.2, found 625.2.
$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -14.68 (c 1.77, DCM).
Spectroscopic data was in agreement with previous work in Bakstad's research group[297].

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-3',4'-dibenzyloxyacetophenone (168)

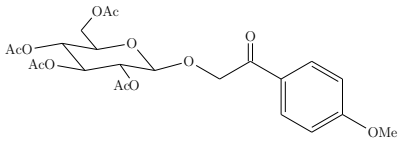


A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of 2-bromo-3',4'-dibenzyloxyacetophenone (1.23 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 0.55 g (27%).
IR (neat): ν 1755, 1690, 1594, 1514, 1454, 1429, 1375, 1226, 1170, 1149, 1128, 1041, 907, 807, 736, 698, 666 cm^{-1}.
^{1}H NMR (500 MHz, $CDC1_3$): δ 7.56 (d, J = 2.0 Hz, 1H), 7.48-7.30 (m, 11H), 6.92 (d, J = 8.5 Hz, 1H), 5.24 (s, 2H), 5.23-5.20 (m, 1H), 5.20 (s, 2H), 5.10-5.05 (m, 2H), 4.86 (d, J = 16.0 Hz, 1H), 4.75 (d, J = 16.0 Hz, 1H), 4.66 (d, J = 7.9 Hz, 1H), 4.23 (dd, J = 12.3, 4.7 Hz, 1H), 4.12 (dd, J = 12.1, 2.3 Hz, 1H), 3.67 (ddd, J = 10.0, 4.6, 2.2 Hz, 1H), 2.06 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H).
^{13}C NMR (125 MHz, $CDC1_3$): δ 193.2, 170.6, 170.1, 169.6, 169.4, 153.6, 148.7, 136.6, 136.3, 128.6,

128.5, 128.1, 128.0, 127.9, 127.4, 127.0, 123.1, 113.7, 113.0, 100.2, 72.6, 71.9, 71.1, 71.0, 70.8, 70.3, 68.3, 61.7, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{36}H_{38}O_{13}$ [M + Na^+] 701.2, found 701.3.
$[\alpha]_D^{25}$ = -16.57 (c 1.75, DCM).

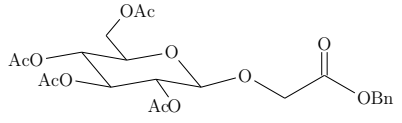
2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-4'-methoxyacetophenone (169)



A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of 2-bromo-4'-methoxyacetophenone (0.40 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 0.95 g (64%).
IR (neat): ν 1752, 1685, 1602, 1574, 1514, 1438, 1423, 1376, 1315, 1231, 1169, 1132, 1094, 1043, 986, 963, 904, 835, 777, 736, 696 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDC1_3$): δ 7.85 (m, 2H), 6.90 (m, 2H), 5.21-5.17 (m, 1H), 5.07-5.02 (m, 2H), 4.87 (d, J = 16.0, 1H), 4.77 (d, J = 16.0, 1H), 4.66 (d, J = 7.9 Hz, 1H), 4.20 (dd, J = 12.2, 4.6 1H), 4.09 (dd, J = 12.2, 2.0, 1H), 3.84 (s, 3H), 3.66 (ddd, J = 10.0, 4.6, 2.1, 1H) 2.03 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 196 (s, 3H).
^{13}**C NMR** (125 MHz, $CDC1_3$): δ 193.2, 170.5, 169.5, 169.2, 163.7, 130.3, 130.0, 127.6, 113.8, 100.0, 72.5, 71.7, 70.9, 70.3, 68.2, 61.6, 55.4, 20.6, 20.5, 20.4.
LRMS (ESI): Calcd for $C_{23}H_{28}O_{12}$ [M + Na^+] 519.1, found 519.2.
$[\alpha]_D^{28}$ = -9.43 (c 5.3, DCM).

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)acetic acid benzyloxy ester (170)

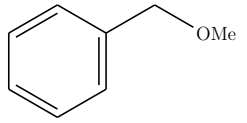


A 50% NaH suspension in oil (0.17 g, 3.5 mmol) was added in portions to a stirred solution of benzyl bromoacetate (0.69 g, 3.0 mmol) and 2,3,4,6-tetra-O-β-D-glucose (1.04 g, 3.0 mmol) in anhydrous DCM (40 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). The crude product was purified with FC (silica gel, 30% EtOAc in methylcyclohexane), to give the titled compound as a yellow wax.

Yield: 0.43 g (29%).
IR (neat): ν 1759, 1422, 1270, 1043, 896 cm^{-1}.
^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.32 (m, 5H), 5.23-5.19 (m, 1H), 5.16 (s, 2H), 5.08-5.01 (m, 2H), 4.65 (d, J = 7.9 Hz, 1H), 4.30 (s, 2H), 4.22 (dd, J = 12.4, 4.7 Hz, 1H), 4.10 (dd, J = 12.4, 2.3 Hz, 1H), 3.66 (ddd, J = 9.9, 4.7, 2.3 Hz, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H).
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 170.6, 170.2, 169.6, 169.4, 169.0, 135.1, 128.6, 128.5, 128,4 100.1, 72.5, 72.0, 71.9, 70.9, 68.3, 66.8, 65.0, 61.7, 20.7, 20.6, 20.5.
LRMS (ESI): Calcd for $C_{23}H_{28}O_{12}$ [M + Na^+] 519.1, found 519.2.
$[\alpha]_D^{25}$ = -22.6 (c 3.0, DCM). (-22.4 (c 1.7, $CHCl_3$))[298].

9.11 Reactions with benzyl chloride

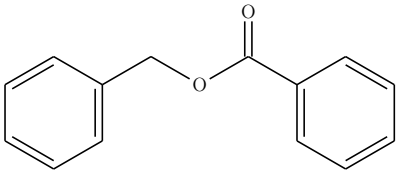
Benzyl methyl ether (171)



A 50% NaH suspension in oil (0.55 g, 11.5 mmol) was added in portions to a stirred solution of benzyl chloride (1.27 g, 3.0 mmol) in anhydrous MeOH (30 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a liquid.

Yield: 0.85 g (70%).
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.23-7.31 (m, 5H), 4.50 (s, 2H), 3.30 (s, 3H)
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 137.4, 128.7, 128.3, 127.6, 74.6, 58.0.
The compound is commercially available (*e.g.* Sigma-Aldrich), and spectroscopic data was in agreement with literature[299].

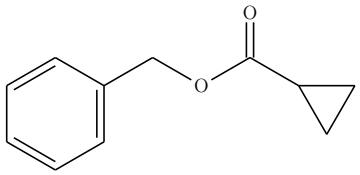
Benzyl benzoate (172)



A 50% NaH suspension in oil (0.55 g, 11.5 mmol) was added in portions to a stirred solution of benzyl chloride (1.27 g, 10.0 mmol) and benzoic acid (1.00 g, 10.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a liquid.

Yield: 0.98 g (46%).
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.06-8.08 (M, 2H),7.52-7.57 (m, 1H), 7.33-7.44 (m, 7H), 5.36 (s, 2H),
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 166.3, 137.0, 133.0, 130.1, 129.6, 128.6, 128.5, 128.3, 128.1, 66.6
The compound is commercially available (*e.g.* Sigma-Aldrich),), and spectroscopic data was in agreement with literature[300]

Benzyl cyclopropanecarboxylate (173)



A 50% NaH suspension in oil (0.55 g, 11.5 mmol) was added in portions to a stirred solution of benzyl chloride (1.27 g, 10.0 mmol) and cyclopropane carboxylic acid (1.00 g, 10.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred at room temperature overnight. Excess NaH was decomposed by addition of suitable amounts of HCl (6 M). Water (150 mL) was added and the mixture was extracted by Et_2O (3 x 50 mL). The combined organic phases were washed with water (5 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by FC (silica gel, 25 % MeOAc in methylcyclohexane), to give the titled compound as a liquid.

Yield: 0.51 g (29%).
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.38 (m, 5H), 5.12 (s, 2H), 1.63-1.69 (m, 1H), 1.02-1.04 (m, 2H),

0.87-0.92 (m, 2H).
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 174.2, 136.5, 128.3, 128.2, 127.7, 65.8, 13.8, 8.1.
The compound is commercially available (*e.g.* Ambinter),), and spectroscopic data was in agreement with literature[300]

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