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Abstract

Part A: Synthesis of acetophenones with possible applications in anthocyanin synthesis.

The preparations of 4 acetophenones were investigated: 4-Hydroxy-3,5-dimethoxyacetophenone, 3,4-dihydroxy-5-methoxyacetophenone, 3,4,5-trihydroxyacetophenone and 3,4-dihydroxyacetophenone. These acetophenones can be used to synthesize the natural occurring anthocyanins: Malvidin 3-*O*-β-D-glucopyranoside chloride, petunidin 3-*O*-β-D-glucopyranoside chloride, delphinidin 3-*O*-β-D-glucopyranoside chloride and cyanidin 3-*O*-β-D-glucopyranoside chloride, respectively.

3,4-Dihydroxyacetophenone with 2 different protection groups was prepared with 3,4-dihydroxybenzoic acid as starting material. The ketones were prepared from the corresponding acids by a reaction with methyllithium. This investigation showed that both benzyloxy- and diphenylmethylenedioxy protection are applicable for this reaction.

4-Hydroxy-3,5-dimethoxyacetophenone, 3,4-dihydroxy-5-methoxyacetophenone and 3,4,5-trihydroxyacetophenone were prepared by using an Ullmann-type coupling approach. One type of Ullmann-type coupling was able to replace bromine or iodine with a hydroxy group. This reaction was used to prepare 3,4-dihydroxy-5-methoxyacetophenone and 3,4,5-trihydroxyacetophenone. 4-Hydroxy-3,5-dimethoxyacetophenone was prepared by an Ullmann-type coupling which replaced iodine with a methoxy group. Except for the preparation of 4-hydroxy-3,5-dimethoxyacetophenone, Ullmann-type couplings were found to be too "messy" and work in too low yields to effectively prepare larger amounts of the target acetophenones.

3,4-Dihydroxy-5-methoxyacetophenone was also prepared from 3-amino-4-hydroxy-5-methoxyacetophenone by employing a diazonium reaction. The amine was prepared in 2 steps with acetovanillone as starting material. Unfortunately, the diazonium reaction worked in a very low yield and this strategy is therefore not usable to prepare sufficient amounts of 3,4-dihydroxy-5-methoxyacetophenone.

Formylation of acetovanillone followed by Dakin oxidation was another strategy attempted to prepare 3,4-dihydroxy-5-methoxyacetophenone. Despite several attempts, the formylation of acetovanillone could not be accomplished.

There was made an attempt to prepare 3,4,5-trimethoxyacetophenone by a Friedel-Crafts approach. Direct acylation of 1,2,3-trimethoxybenzene gives substitution at the wrong position. The undesired positions were therefore first blocked by bromine before acylation was attempted. Unfortunately, the brominated compound resisted all attempts at acylation.

Part B: Synthesis and ring opening of selected strained *gem*-dihalocyclopropyl ethers

Typically, *gem*-dihalocyclopropyl ethers can be ring opened by alkoxides to give vinylic acetals. For instance, 2,2-dichlorocyclopropyl ethyl ether undergoes ring opening with ethoxide in ethanol to give 2-chloro-3,3-diethoxy-1-propene. The *gem*-dihalocyclopropyl ethers investigated in this thesis were strained, fused ring systems. These compounds can be used to study how ring opening takes place under strained conditions, and if ring opening will

take place at all. This investigation is based on an earlier investigation by Prof. Lars Skattebøl and former M.Sc. student Bjørn Erik Jønsberg.

17,17-Dichloro-13,16-dioxa[10.4.1]propellane was prepared successfully from cyclododecanone in 3 steps.The dibromo analouge could not be isolated by the Skattebøl research group, but suffered ring opening during its preparation to give 6-bromo-1,4-dioxaspiro[4.12]heptadecan-7-one.

Ring opening with ethoxide in ethanol of 17,17-dichloro-13,16-dioxa[10.4.1]propellane was attempted. This resulted in an unstable compound which was difficult to purify, but ^{13}C NMR of the crude product indicated that the dichloro propellane had ring opened similarly to the ring opening described for 2,2-dichlorocyclopropyl ethyl ether. In a later attempt, the ring opened product was hydrolyzed with dilute hydrochloric acid to give 2-chlorocyclotridecane-1,3-dione. This result corresponds to the expected product from hydrolysis of the ring opened dichloropropellane.

13,13-Dibromo-9,12-dioxa[6.4.1]propellane was prepared successfully from cyclooctanone in 4 steps. Former M.Sc. student Bjørn Erik Jønsberg reported that this compound underwent a reaction with *t*-BuOK in tetrahydrofuran to give the corresponding monobromine, 13-bromo-9,12-dioxa[6.4.1]propellane. This reaction was attempted with the same conditions, but was unsuccessfull.

Acknowledgement

I would like to thank Adj. Prof. Dr. Einar Bakstad for all help and great supervision during the work of this master thesis.

I would like to thank Biosynth for the opportunity to work with organic synthesis and the use of their laboratories.

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Part A: Synthesis of acetophenones with possible applications in anthocyanin synthesis

1. Introduction

1.1 Background

Biolink Group was established in 1998 and is mainly involved in isolating anthocyanins from natural sources. MP865 (Medox®), a dietary supplement produced by the Biolink Group, consists of 17 different anthocyanins extracted from *vaccinium myrtillus* (common bilberry) and *ribes nigrum (*blackcurrant). Besides Medox, the company also isolates and provides pure anthocyanins as well as other flavonoids for research.

The daughter company Biosynth has since 2002 among other things been tasked with the total synthesis of selected anthocyanins. The main vision is to be able to synthesize anthocyanins on large scale and in this way be able to provide larger quantities of pure anthocyanins for research.

The total synthesis of 4 natural anthocyanins have been accomplished: Cyanidin 3-*O*-β-D-glucopyranoside chloride (Cy 3-glc), delphinidin 3-*O*-β-D-glucopyranoside chloride (Dp 3-glc), peonidin 3-*O*-β-D-glucopyranoside chloride (Pn 3-glc) and peonidin 3-*O*-β-D-glucuronide chloride (Pn 3-glue). Currently, the anthocyanins of interest which have yet to be synthesized are malvidin 3-*O*-β-D-glucopyranoside chloride (Mv 3-glc) and petunidin 3-*O*-β-D-glucopyranoside chloride (Pt 3-glc).

The work of this thesis focuses on the preparation of acetophenones required to synthesize some of the mentioned anthocyanins. This thesis is based on previous work by M.Sc. students Tom Arne Sola and Kristine Støvik Fagerstrand.

1.2 Anthocyanins

Anthocyanins belong to a class of molecules called flavonoids and are secondary metabolites found in plants. Anthocyanins are responsible for many colors observed in nature. For instance the color of flower petals as well as the red colors of autumn leaves. More than 400 different anthocyanins have so far been identified.[1] The structures of some of the most common anthocyanins are shown in figure 1 and table 1.

Anthocyanins contain 3 aromatic rings designated with the letters A, B and C. The C ring is heterocyclic and is fused with the A ring. The B ring contains between 1 and 3 hydroxy or methoxy groups depending on the specific anthocyanin. All anthocyanins are glycosylated, most commonly at the C-3 position as shown in figure 3. The unglycosylated counterparts are called anthocyanidins or aglycones. Anthocyanins are also positively charged. Together with the presence of glucose and several hydroxyl groups this makes them water soluble. [1]

The color of an anthocyanin is dependent on many factors. For instance the pH in aqueous solution largely regulates color. pH 1-3 gives a red colored flavylium cation, pH 5 a colorless carbinol pseudo base and pH 7-8 a blue purple quinoidal base. Color also depends on the substitution pattern on the B ring, solvent, temperature and the presence of co-pigments. [1]

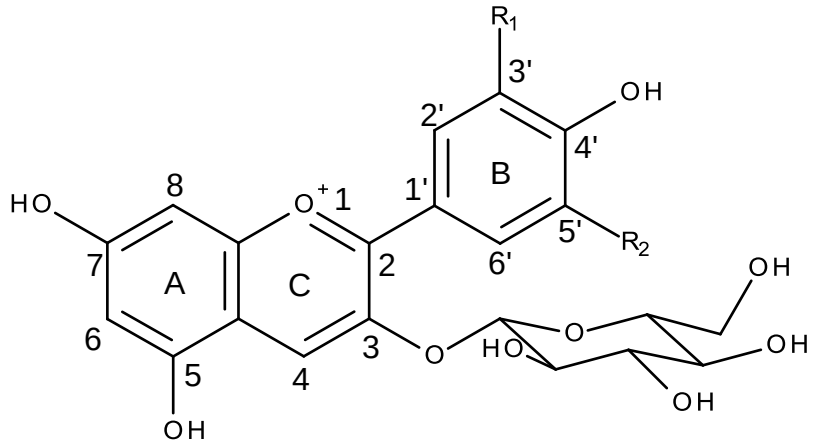


Figure 1 General structure for anthocyanins of interest

Table 1 List of some common anthocyanins.

Anthocyanin	Abreviation	R_1	R_2
Delphinidin 3-*O*-β-D-glucopyranoside chloride	Dp 3-glc	-OH	-OH
Petunidin 3-*O*-β-D-glucopyranoside chloride	Pt 3-glc	-OH	$-OCH_3$
Malvidin 3-*O*-β-D-glucopyranoside chloride	Mv 3-glc	$-OCH_3$	$-OCH_3$
Cyanidin 3-*O*-β-D-glucopyranoside chloride	Cy 3-glc	-H	-OH
Peonidin 3-*O*-β-D-glucopyranoside chloride	Pn 3-glc	-H	$-OCH_3$
Pelargonidin 3-*O*-β-D-glucopyranoside chloride	Pg 3-glc	-H	-H

1.2.1 Role in plants

The precise role anthocyanins play in plants is at this point still somewhat unclear. In fruit and berries their colors can help attract animals that help the plant disperse its seeds, while in flowers it can help attract pollinators. However, anthocyanin-function in other tissues, like leaves, is more puzzling.

It has been suspected that their ability to absorb yellow-green light can help protect the plant, since light can otherwise cause formation of reactive species. Anthocyanins have also been shown to absorb ultraviolet B (UV-B) radiation. Ultraviolet (UV) radiation harms the plant by inducing damage to deoxyribonucleic acid (DNA) and anthocyanins can function as a sunscreen to help prevent this.[2]

Anthocyanins have also proven to be effective scavengers of free radicals. Plant cells constantly generate reactive oxygen and nitrogen species because of ongoing photosynthesis and respiration and this can cause harm to DNA and other molecules. Anthocyanins have been proven to be exceptional at removing these species *in vitro*, compared to for instance ascorbate (vitamin C) and α-tocopherol (vitamin E).[2] There is also evidence that this

property is relevant *in vivo*. In *Arabidopsis* anthocyanin deficient mutants showed a higher degree of lipid peroxidation under strong light and low temperature. Also, when subjected to gamma radiation only plants that contained both anthocyanin and ascorbic acid were able to grow and flower normally.[2]

Anthocyanins also seem to increase the plants tolerance to other stress factors. Anthocyanins have for instance been associated with increased resistance to freezing, heavy metal contaminants and wounding. The exact mechanisms for these properties are still not known.[2]

1.2.2 Health effects

Anthocyanins have shown to have many beneficial health effects for humans. They seem to have important dietary applications, but also the potential for future therapeutic use.

Reactive oxygen species as a result from respiration are suspected to play a role in development of many diseases. The antioxidant effects seen *in vitro* and in plants can also be observed in humans after consumption of anthocyanins. For example, subjects have shown an increased antioxidant capacity in blood serum after consumption of 100 g blueberry supplement.[1] Only a limited amount of data is available on the antioxidant activity in humans. More studies are needed to see if the antioxidant effect of anthocyanins really is relevant. Even though concentration of anthocyanins in blood serum is too low to protect against reactive oxygen species, they can still interact with other molecules and in this way be beneficial.

1.2.2.1 Anthocyanins and cardiovascular disease

Cardiovascular disease (CVD) is a class of disease which includes diseases related to the heart and\or blood vessels. Atherosclerosis is perhaps the disease most often associated with CVD. It is characterized by chronic inflammation caused by erosion or rupture of plaques in blood vessels. This can lead to formation of clots and in most severe cases myocardial infarction (heart attack) or a cerebrovascular accident (stroke). Deaths related to (CVD) are increasing worldwide. The main cause for this increase is believed to be behavioral risk factors. Factors like lack of physical activity, poor diet and smoking are believed to be the cause of ~80% of CVD.[3]

Through epidemiological studies, anthocyanins have been associated with a reduced risk of developing CVD. This has for instance been observed for strawberries, blueberries and is also suspected to be part of the reason for the positive health effects of small amounts of red wine.[3]

Nitric oxide (NO) is an important biological signal molecule. Deficiencies in the production of NO have been associated with atherosclerosis and other cardiovascular diseases. NO help protect against initiation and progression of atherosclerosis by preventing adhesion and aggregation of blood cells and platelets along the endothelial cell lining. NO also inhibits proliferation of smooth muscle cells along the blood vessels which helps keep a good blood flow. NO can also help scavenge reactive oxygen species and in this way prevent oxidation of

low-density lipoprotein (LDL). Ignarro *et al.* showed that pomegranate juice, a rich source of anthocyanins, helped protect nitric oxide from destruction by reactive oxygen species and also increased its biological activity. This may be because of anthocyanins' antioxidant properties. By scavenging reactive oxygen species, NO is spared and can function better as a signal molecule.[4]

Low grade inflammation has been recognized as an independent risk factor for CVD. The degree of inflammation is measured by the amount of C-reactive protein (CRP). Elevated levels of CRP is associated with chronic inflammation and may be linked to atherosclerosis.[3] In a study by Anette Karlsen *et al.* the concentration of several pro-inflammatory mediators were measured in healthy adults before and after using the dietary supplement MP865 (Medox®) for 3 weeks. Even though no significant differences in CRP levels were observed, several pro-inflammatory mediators were found to be at decreased concentrations.[5] These mediators were all activated by a transcription factor, nuclear factor-κB (NF- κB). NF- κB can be activated by oxidative stress and many other pro-inflammatory stimuli. The decreased NF-κB activity might be due to anthocyanins ability to rapidly remove reactive oxygen species before they can activate NF- κB.[5]

1.2.2.2 Anthocyanins and cancer

Anthocyanins also show some promise as an anticarcinogen. Cells undergo a number of steps before they turn into malignant cancer cells. Benign tumors are caused by cells simply dividing in a somewhat uncontrolled manner. However, if these cells suffer further mutations, they may turn malignant. Malignant tumor cells invade neighboring tissue, and can spread through blood vessels to other parts of the body.[6] Anthocyanins have been showed to halt the development of cancer cells and even to kill them through programmed cell death, apoptosis. An *in vitro* study showed that cyanidin 3-glucoside was capable of inducing apoptosis in leukemic cell lines.[1] Cyanidn-3-glucoside was also shown to revert human melanoma cells from the proliferating to the less dangerous differentiated state.[1]

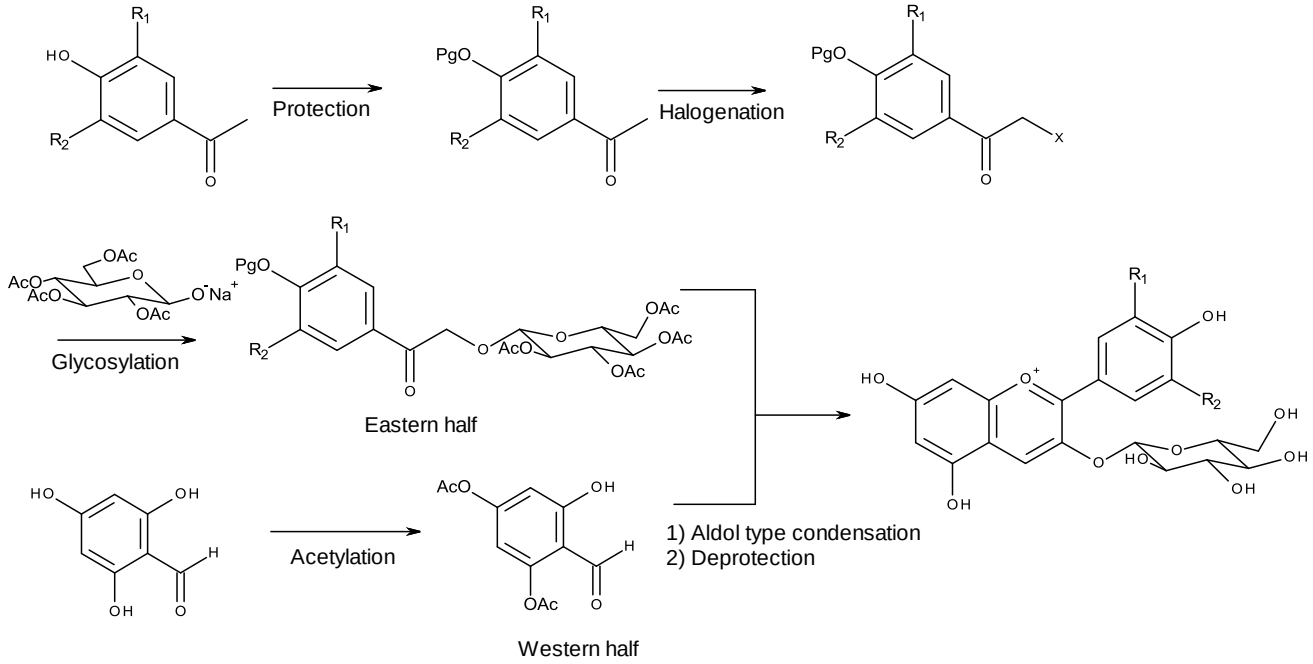
Anthocyanins have also been showed to have cancer preventive effects *in vivo* in a study with rats. Rats which had an anthocyanin-rich diet of extracts from chokeberry, bilberry, grapes and black raspberries showed a decreased number of abberant crypt foci when being exposed to a carcinogen. Abberant crypt foci are changes observed in the colon which may lead to cancer.[1]

More generally, the study of health patterns has associated a high intake of anthocyanins with a reduced chance of developing different types of cancer.[1] More research is required however, to identify the most active compounds and also the most effective routes of administration to treat or help prevent cancer.

2. Theory and synthetic strategies

2.1 Total synthesis of anthocyanins

The Bakstad research group has synthesized several anthocyanins. Scheme 1 shows the general outline of the strategy employed. An acetophenone with a substitution pattern corresponding to the B-ring of the wanted anthocyanin is first required. To avoid unwanted byproducts in the glycosylation reaction, any free hydroxyl groups in the acetophenone needs to be protected. The preferred protection has for a long time been benzyl. The main reason for this is that the benzyl group can be removed quite easily by using H_2 and Pd\C. After protection, a halogen is introduced at the α-position. The preferred halogen for the glycosylation reaction is iodine. Bromine has also been used, but has been shown to give some reduction in yield compared to iodine. The glycosylation, which has been developed by the research group, couples the sugar with the acetophenone through a nucleophilic substitution with iodine\bromine. Aldol type condensation between western and eastern half followed by removal of protection groups gives the anthocyanin. Protection of western half is required for the aldol type condensation to work.



Scheme 1 General strategy used by the Bakstad research group for synthesis of anthocyanins.

2.2 Target molecules

The acetophenones shown in figure 2 have for some time been of great interest to the research group. These acetophenones can be used to synthesize the anthocyanins: Mv 3-glc, pt 3-glc, dp 3-glc and cy 3-glc. 3,5-Dimethoxy-4-hydroxyacetophenone (**1**) is commercially available, but it is quite expensive. 3,4-Dihydroxyacetophenone (**4**) and 3,4-dihydroxy-5-methoxyacetophenone (**2**) became commercially available from Sigma-Aldrich during the work of this thesis, around February 2011. However, these two compounds are only available

in milligram quantities and are very expensive. An efficient synthesis of these acetophenones is therefore of great importance in order to synthesize the associated anthocyanins, especially on industrial scale.

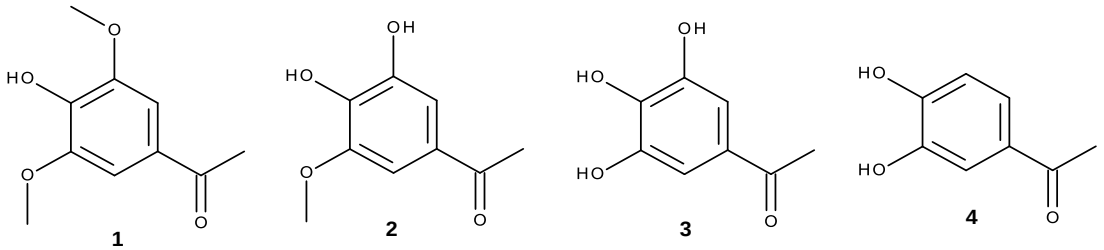
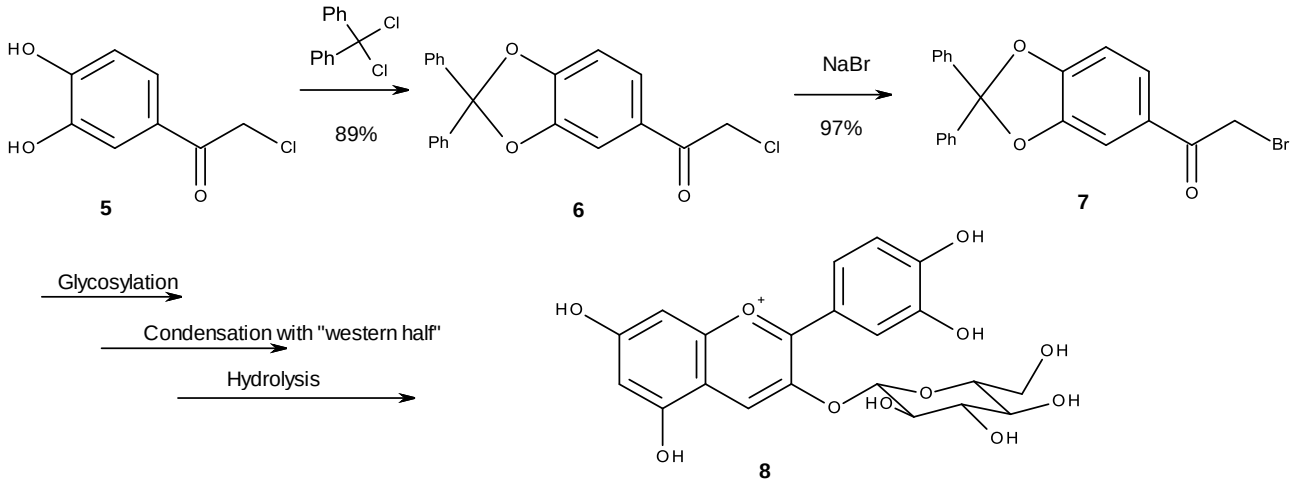


Figure 2 3,5-Dimethoxy-4-hydroxyacetophenone (**1**), 3,4-dihydroxy-5-methoxyacetophenone (**2**), 3,4,5-trihydroxyacetophenone (**3**) and 3,4-dihydroxyacetophenone (**4**). Can be used to synthesize malvidin 3-glc, petunidin 3-glc, delphinidin 3-glc and cyanidin 3-glc, respectively.

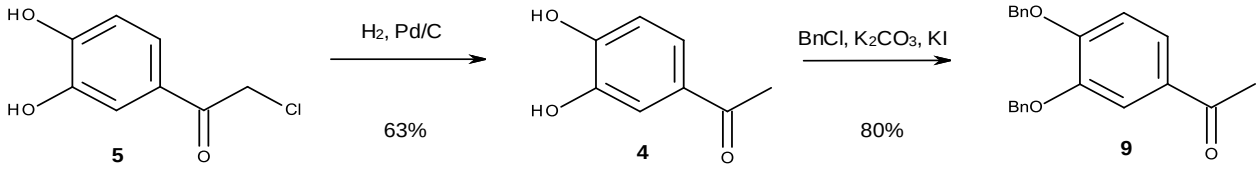
2.3 Previous synthesis of 3,4-dihydroxyacetophenone (4)

Even though **4** is difficult to obtain commercially, 2-chloro-3',4'-dihydroxyacetophenone (**5**) is not. Bakstads research group was able to use **5** directly in the total synthesis of cy 3-glc (scheme 2), which made **5** a nice starting material for anthocyanin synthesis.[7] [8]In this case however, the most advantageous protection of the hydroxy groups was the diphenyl protection. Benzylation of the chloroacetophenone (**5**) was attempted several times, but did not work out as expected. If this protection was to be used, the halogen had to be removed first (scheme 3). The diphenyl protection was preferred over other possible protections because it proved to be quite easy to remove. Methylenedioxy and *gem*-dimethyl methylenedioxy was also investigated as protection groups. These protections proved to be very difficult to remove and were not suitable for anthocyanin synthesis.



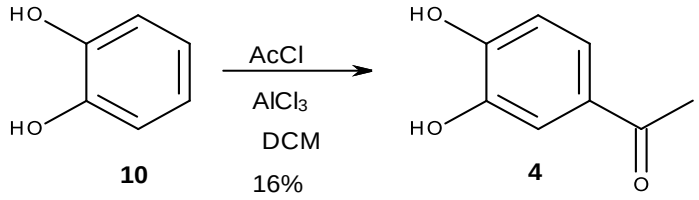
Scheme 2 Total synthesis of cyanidin 3-glc (**8**) by using 2-chloro-3',4'-dihydroxyacetophenone (**5**) as starting material.

3,4-Dibenzyloxyacetophenone (**9**) was synthesized by former M.Sc. student Torill Buaas from **5** first by removing the halogen with H_2 and Pd/C followed by standard benzylation conditions (scheme 3).[9]

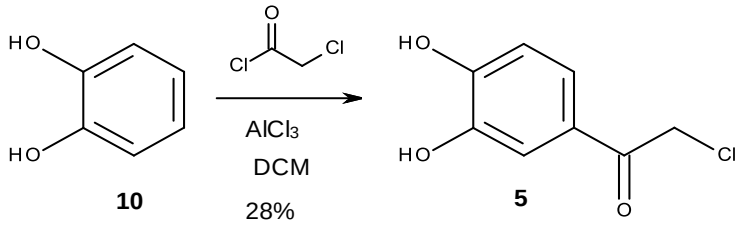


Scheme 3 Synthesis of 3,4-dibenzyloxyacetophenone (**9**).

Torill Buaas has also prepared **4** and **5** by a Friedel-Crafts approach. The yields for these reactions were somewhat poor however (scheme 4 and 5). [9]

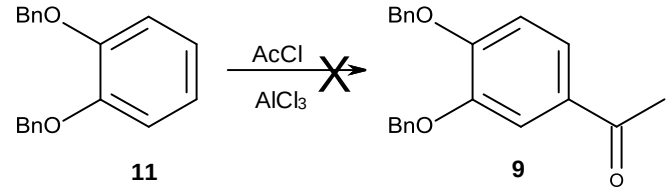


Scheme 4 Synthesis of 3,4-dihydroxyacetophenone (**4**) by a Friedel-Crafts reaction.

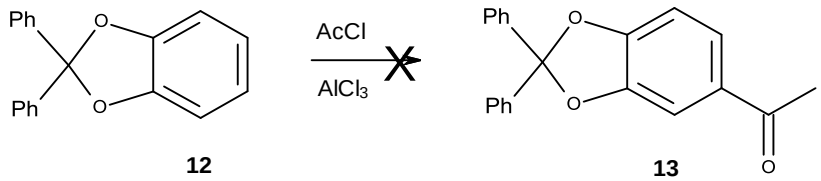


Scheme 5 Synthesis of 2-chloro-3',4'-dihydroxyacetophenone (**5**) by a Friedel-Crafts reaction.

There was also made an attempt to acylate 1,2-dibenzyloxyacetophenone (**11**) (scheme 6) and 1,2-diphenylmethylenedioxybenzene (**12**) (scheme 7). In these cases no reaction occurred.[10]



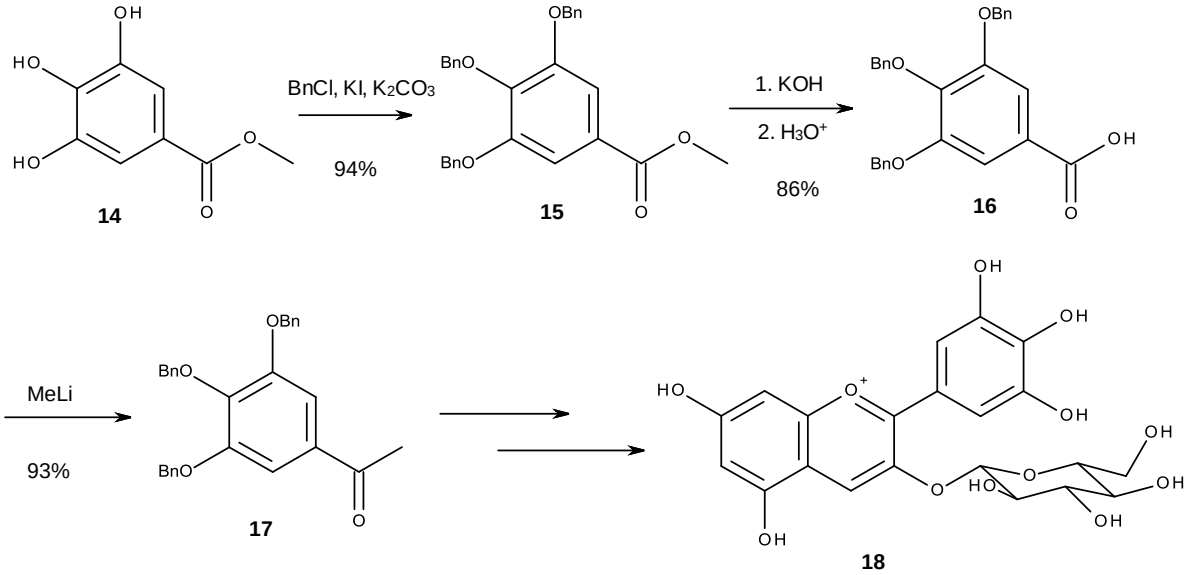
Scheme 6 Attempt at Friedel-Crafts acylation of 1,2-dibenzyloxyacetophenone (**11**)



Scheme 7 Attempt at Friedel-Crafts acylation of 1,2-diphenylmethylenedioxybenzene (**12**)

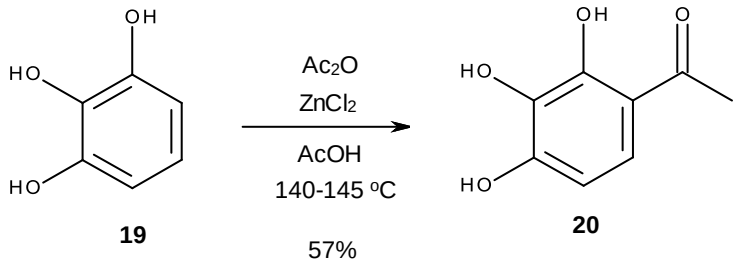
2.4 Previous synthesis of 3,4,5-trihydroxyacetophenone (3)

The research group has developed a synthesis for 3,4,5-tribenzyloxyacetophenone (**17**) and used this synthesis as part of the total synthesis of dp 3-glc (**18**).[7] [8] The starting material was methyl gallate and the protected acetophenone (**17**) was synthesized in high yields in 3 steps (scheme 8). The only challenge with this approach is the use of methyllithium (MeLi), which can be problematic on larger scales.



Scheme 8 Synthesis of 3,4,5-tribenzyloxyacetophenone and the corresponding anthocyanin

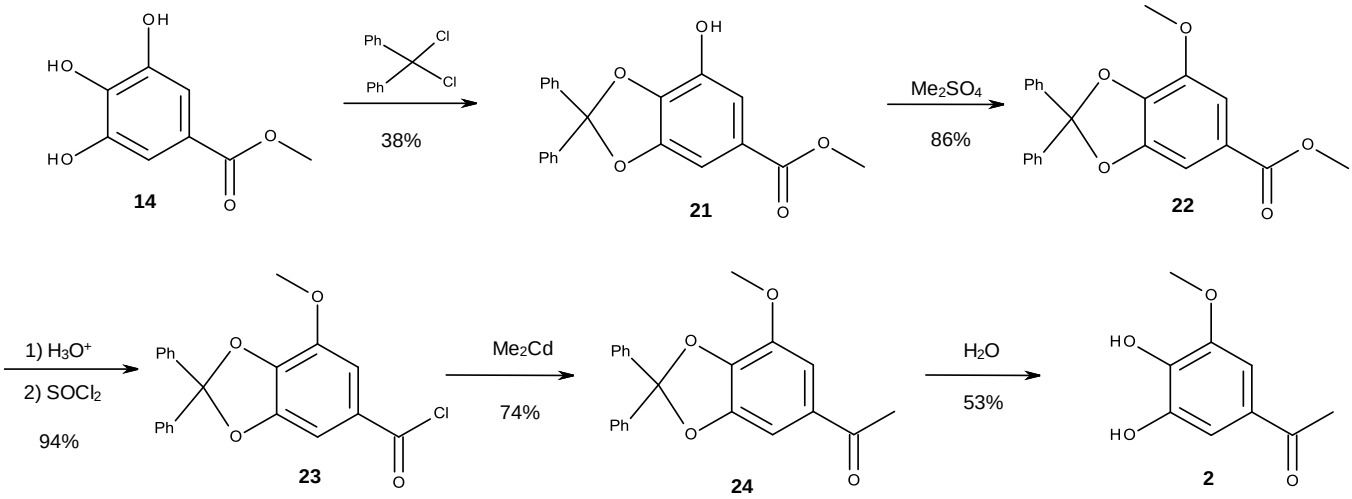
Currently there is no known method to synthesize **3** by a Friedel-Crafts approach. A Friedel-Crafts reaction using pyrogallol (**19**) as starting material gives acylation at the wrong position as shown by I.C. Badhwar *et al.* (scheme 9).[11]



Scheme 9 Acylation of pyrogallol (**19**) by I.C. Badhwar *et al.*

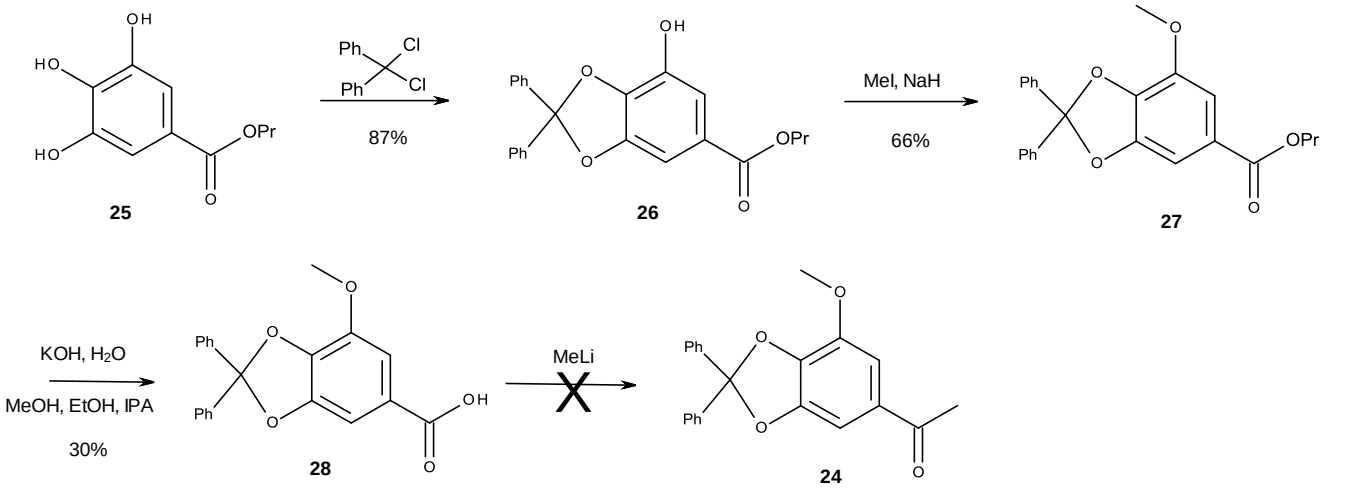
2.5 Previous synthesis of 3,4-dihydroxy-5-methoxyacetophenone (2)

3,4-Dihydroxy-5-methoxyacetophenone (**2**) has been synthesized before by several groups. One strategy by Ekkehard Geyer *et al.* involves 6 steps with gallic acid as starting material (Scheme 10).[12] This method however suffers from the use of some very toxic chemicals.



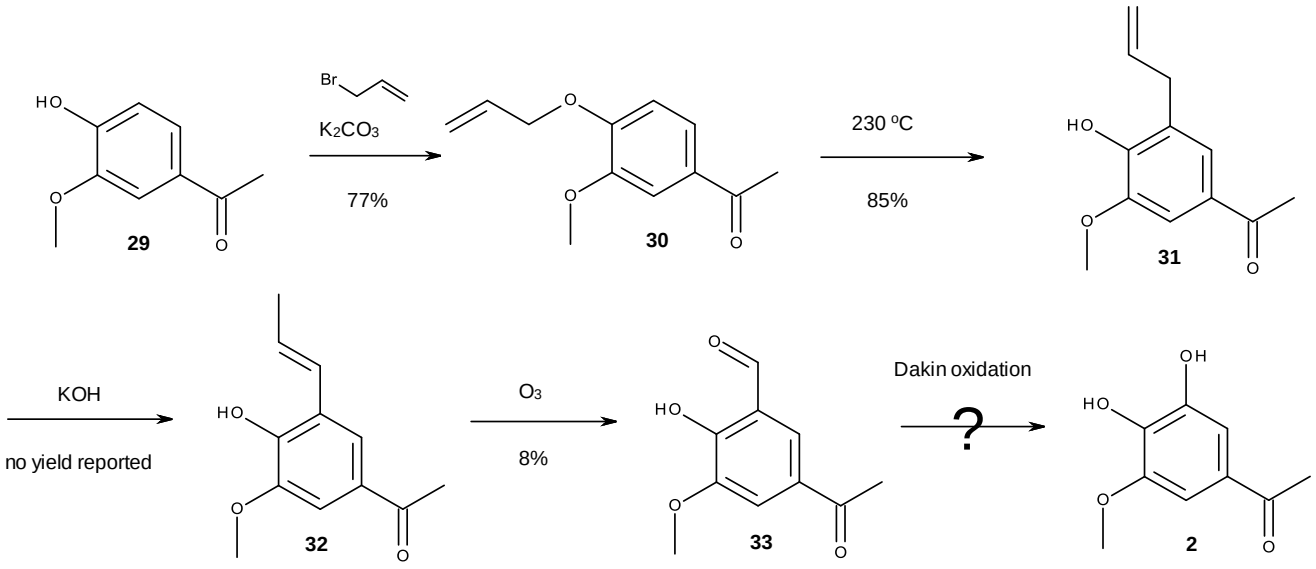
Scheme 10 Synthesis of 3,4-dihydroxy-5-methoxyacetophenone (**2**) by Ekkehard Geyer *et al*.[12]

A similar method was attempted by former M.Sc. student Kristine Fagerstrand, however in this case the protected acid would not undergo a reaction with methyllithium, even when heated (Scheme 11).[13]



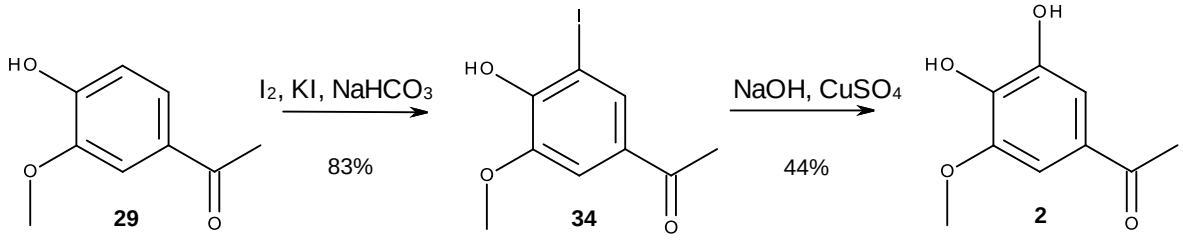
Scheme 11 Attempt at synthesis of 3,4-dihydroxy-5-methoxyacetophenone by Kristine Fagerstrand.[13] The protected acid, **28** refused to react with MeLi even when heated.

Another preparation of **2** which has been investigated by the former M. Sc. Students Tom Arne Sola and Kristine Støvik Fagerstrand is based on a method by Sin'iti Kawai *et al.* to prepare 5-acetyl-2-hydroxy-3-methoxybenzaldehyde (**33**)[14] followed by a Dakin oxidation to give **2** (scheme 12). The last step, the Dakin oxidation, has to the best of our knowledge never been attempted on this type of compound. A necessary but reasonable assumption in this case is that the oxidation occurs exclusively at the aldehyde position and not at the ketone. Aldehydes are in most cases much more reactive than ketones and it seems therefore likely that it should be possible to exclusively convert the aldehyde into a phenol.



Scheme 12 Synthesis of 5-acetyl-2-hydroxy-3-methoxybenzaldehyde (**33**) by Sin'iti Kawai *et al.*. The last step, the Dakin oxidation was never attempted. 3,4-dihydroxy-5-methoxyacetophenone (**2**) is the expected product from this reaction.

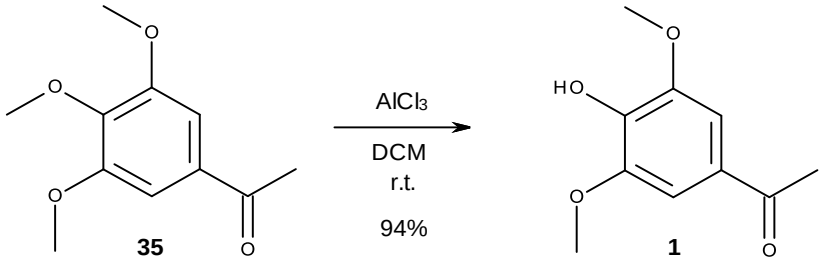
S. K. Banerjee *et al*. prepared **2** in two steps with reasonable yields using acetovanillone (**29**) as starting material (scheme 13).[15] The second step is an Ullmann-type coupling



Scheme 13 Synthesis of 3,4-dihydroxy-5-methoxyacetophenone (**2**) by S. K. Banerjee *et al*

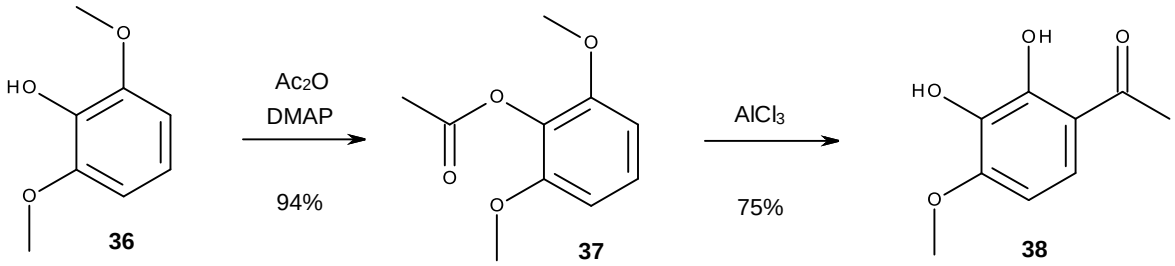
2.6 Previous synthesis of 3,5-dimethoxy-4-hydroxyacetophenone (1)

3,5-Dimethoxy-4-hydroxyacetophenone (**1**) was prepared by Kristine Fagerstrand from 3,4,5-trimethoxyacetophenone (**35**) simply by using $AlCl_3$ (scheme 14).[13]



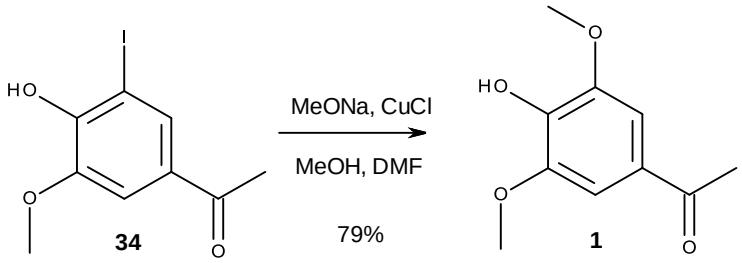
Scheme 14 Preparation of 4-hydroxy-3,5-dimethoxyacetophenone (**1**) by selective demethylation of 3,4,5-trimethoxyacetophenone (**35**).

Former M.Sc. student Guro Helgesdotter Rognså made another attempt to prepare **1** by using 2,6-dimethoxyphenol (**36**) as starting material (scheme15).[16] The second step, the Fries rearrangement, usually rearranges the acetyl group to the ortho or para position. In this case however, the acetyl group ended up in the meta position, which is rather unusual. The loss of a methyl was also unwanted.



Scheme 15 Acylation of 2,6-dimethoxyphenol (**36**) followed by Fries rearrangement to give 2,3-dihydroxy-4-methoxyacetophenone (**38**). 4-Dimethylaminopyridine (DMAP) was used as catalyst for the acylation.

Ri-ling Deng *et al.* synthesized **1** by a similar strategy as S. K. Banerjee *et al.* used for **2**. This was also carried out by an Ullmann-type coupling of 4-hydroxy-3-iodo-5-methoxyacetophenone (**34**), but in this case methoxy was inserted instead of a hydroxy group (scheme 16).[17]

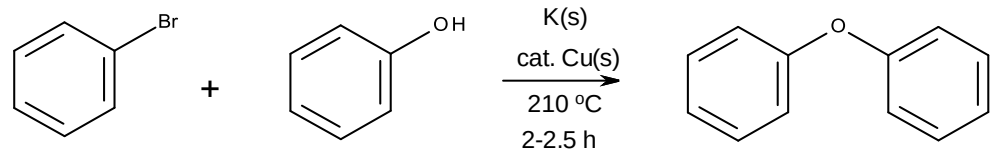


Scheme 16 Preparation of 4-hydroxy-3,5-dihydroxyacetophenone (**1**) by Ri-ling Deng *et al*.

2.7 Ullmann-type coupling

A type of reactions called Ullmann-type couplings was found to have potential for the synthesis of the target acetophenones. Strategies based on Ullmann-type couplings were also used by S. K. Banerjee *et al.* and Ri-ling Deng *et al.*to synthesize **2** and **1** respectively.[15] [17]

The "modern" Ullmann-type coupling is based on a reaction published by Fritz Ullmann in 1905. This is a coupling between a phenol and a bromo-aryl compound to give an aryl-aryl ether. Scheme 17 shows and example between bromobenzene and phenol. These reactions typically require quite harsh conditions in the form of high temperature and a strong base. Catalytic amounts of copper metal are also required. These reactions are named Ullmann condensation or Ullman's ether synthesis.[18]

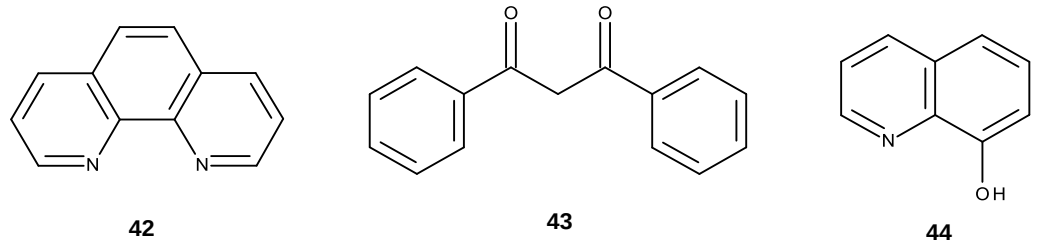


39 **40** **41**

Scheme 17 Ullmann's ether synthesis of diaryl ether (**41**) with bromobenzene (**39**) and phenol (**40**) as substrates

The modern Ullmann-type coupling is a more generalized reaction, where the phenol has been replaced with what in principle can be any nucleophile. Reactions are possible for alcohols as well as various nitrogen- and sulfur-containing compounds like amines, amides and thiols.

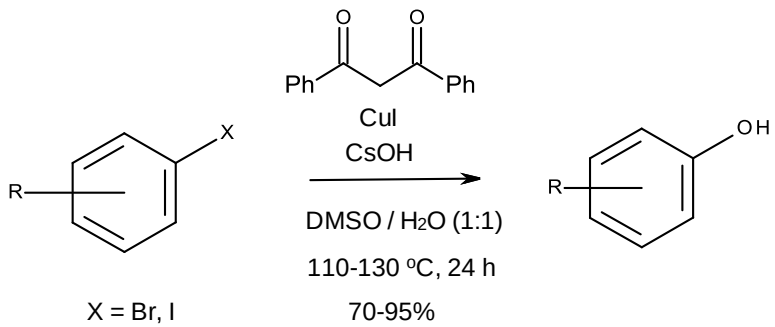
Ullmann-type couplings have turned out to not be very sensitive towards the copper source used. Metallic copper is a possible catalyst, but also various copper(I) salts like CuCl and CuI. The choice of solvent and base does however, seem to be more crucial. Commonly used solvents are toluene, dimethyl formamide (DMF) and *N*-Methyl-2-pyrrolidone (NMP). These solvents are preferred for their high boiling points. Temperature does not need to be as high as in the classical Ullmann ether synthesis, but usually needs to be in a range between 80 and 120 ^{o}C. Preferred bases are K_2CO_3, Cs_2CO_3 and alkoxides if alcohols are to be coupled. Various ligands have been found to increase the yield and rate of the Ullmann-type couplings. These ligands are mostly bidentate chelators, containing oxygen, nitrogen or both. Some examples are shown in figure 3.[18]



42 **43** **44**

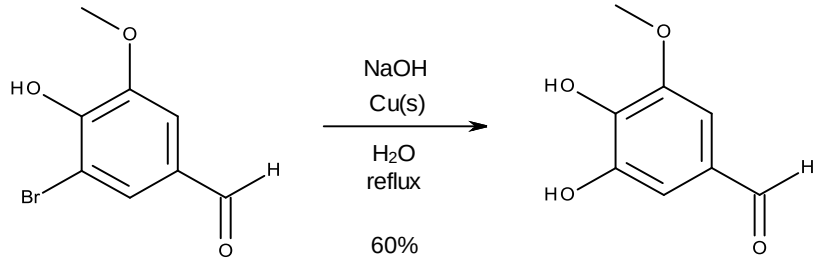
Figure 3 Some examples of ligands used in Ullmann-type couplings. 1,10-phenanthroline (**42**), 1,3-diphenylpropane-1,3-dione (**43**) and 8-hydroxyquinoline (**44**),

An Ullmann-type coupling of great interest for the synthesis of the target acetophenones is the addition of water. This coupling has been described in the literature. One example is the work of Anis Tlili *et al.*(scheme 18). They managed to couple water with a wide range of different aryl halides and studied the effects of different bases and ligands. The preferred ligand was **43** and the preferred base was CsOH. However, KOH was also reported to work, but in lower yields.[19]



Scheme 18 Synthesis of phenols from aryl halides by Anis Tlili *et al.*

James E. Ellis *et al.* reported another method of interest which they used in the preparation of 3,4-dihydroxy-5-methoxybenzaldehyde (**46**), a molecule very similar to target acetophenone **2**. For this coupling NaOH and copper powder were used (scheme 19).[20]



45 **46**

Scheme 19 Synthesis of 3,4-dihydroxy-5-methoxybenzaldehyde (**46**) by using an Ullmann-type coupling.

3. Results and discussion

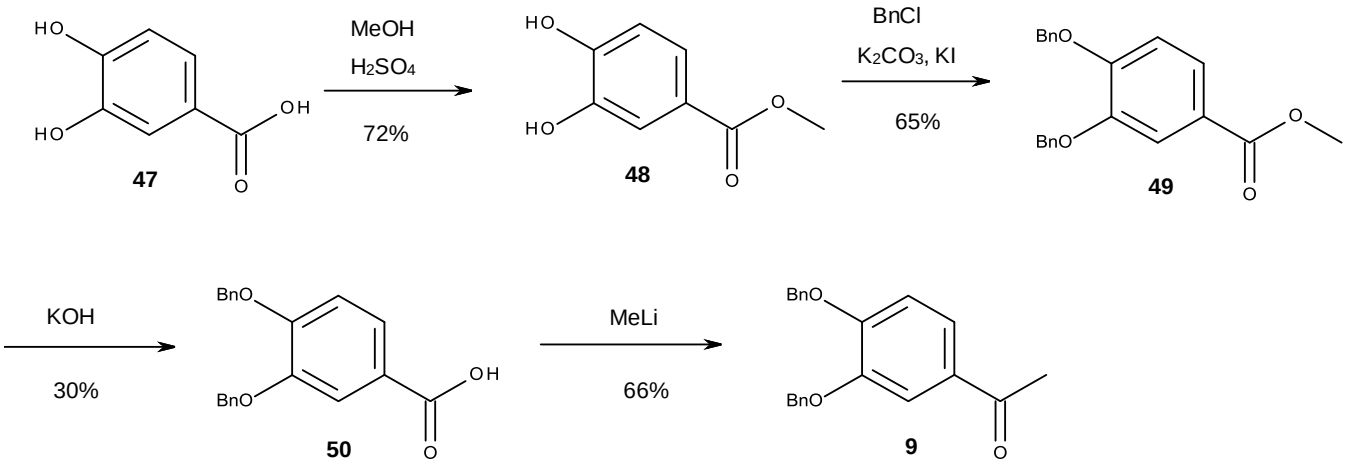
3.1 Synthesis of protected 3,4-dihydroxyacetophenone

Synthesis of protected 3,4-dihydroxyacetophenone was carried out by using 3,4-dihydroxybenzoic acid as starting material (scheme 20 and 21). Two different protections were tested: Dibenzyloxy and diphenylmethylenedioxy. This was partly to investigate the effect of the different protection groups on the methyllithium reaction. After M.Sc. student Kristine Fagerstrand showed that 4,5-diphenylmethylenedioxy-3-methoxybenzoic acid (**28**) would not undergo a reaction with methyllithium, it was suspected that the diphenyl protection might be the reason. It was therefore expected that 3,4-diphenylmethylenedioxybenzoic acid (**51**) also would be unwilling to react with methyllithium. This turned out not to be the case. The diphenyl protected acid, **51**, reacted readily with methyllithium, thereby excluding this protection as the sole reason **28** would not react with methyllithium.

Scheme 20 shows the synthesis of 3,4-dibenzyloxyacetophenone (**9**). The formation of the ester was carried out by two different methods. The preferred method was the use methanol and concentrated H_2SO_4. The other method, which used $BF_3 \cdot OEt_2$, worked most of the time, but sometimes gave crude products in the form of oil, which resisted all attempts of recrystallization. It was also disconcerting that the product from the $BF_3 \cdot OEt_2$ method had a significantly lower melting point than the one reported in literature. The reported melting point for this compound is 137-139 ^oC while the observed melting point was 95-100 ^oC. The big gap between these melting points led us to suspect that $BF_3 \cdot OEt_2$ might have contaminated the product in some way, maybe by being bound between the hydroxyl groups present in the molecule. Nuclear magnetic resonance (NMR) did not show any significant differences from the product obtained by the H_2SO_4 method though, and the contaminated product reacted readily in subsequent reactions.

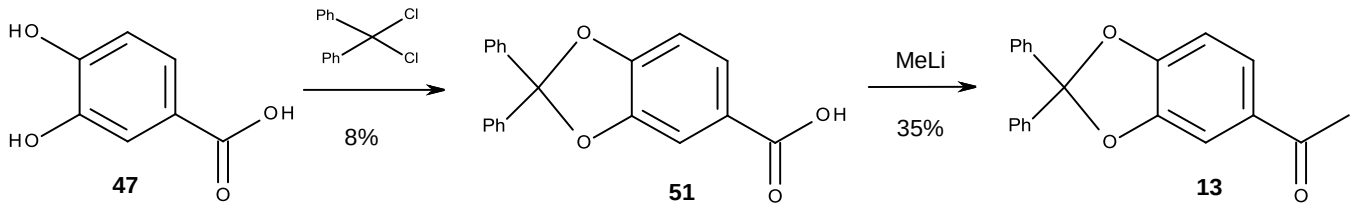
The benzylation was carried out with standard conditions and worked fairly well. The hydrolysis of the ester was carried out by the use of KOH. Heating and addition of extra KOH was required for complete conversion to the acid. The bad yield is probably mostly due to the

type of workup employed for this reaction. No attempts were made to improve this yield, since a sufficient amount of this compound had already been made. The MeLi reaction worked out as expected.



Scheme 20 Synthesis of 3,4.dibenzyloxyacetophenone (**9**) with 3,4-dihydroxybenzoic acid (**47**) as starting material.

Synthesis of 3,4-diphenylmethylenedioxyacetophenone (**13**) is shown in scheme 21. The protection of the acid, **47**, by using the diphenyl protection did not work out as well as expected. After vigorous reflux and stirring for many days, most of the starting material had still not been converted. Protection of the methyl ester with the diphenyl protection was also attempted but without any apparent improvement. The difficulties of protecting the acid and the ester with the diphenyl protection are surprising. The research group has previously used this protection several times to great success. For instance, protection of propyl gallate (**25**) (section 2.5, scheme 11) and 2-chloro-3',4'-dihydroxyacetophenone (**5**) (section 2.3, scheme 2) with the diphenyl protection has been carried out in good yields. The MeLi reaction worked out fairly well. There was made no attempt to improve this yield, since the main goal was to investigate if the reaction worked at all.



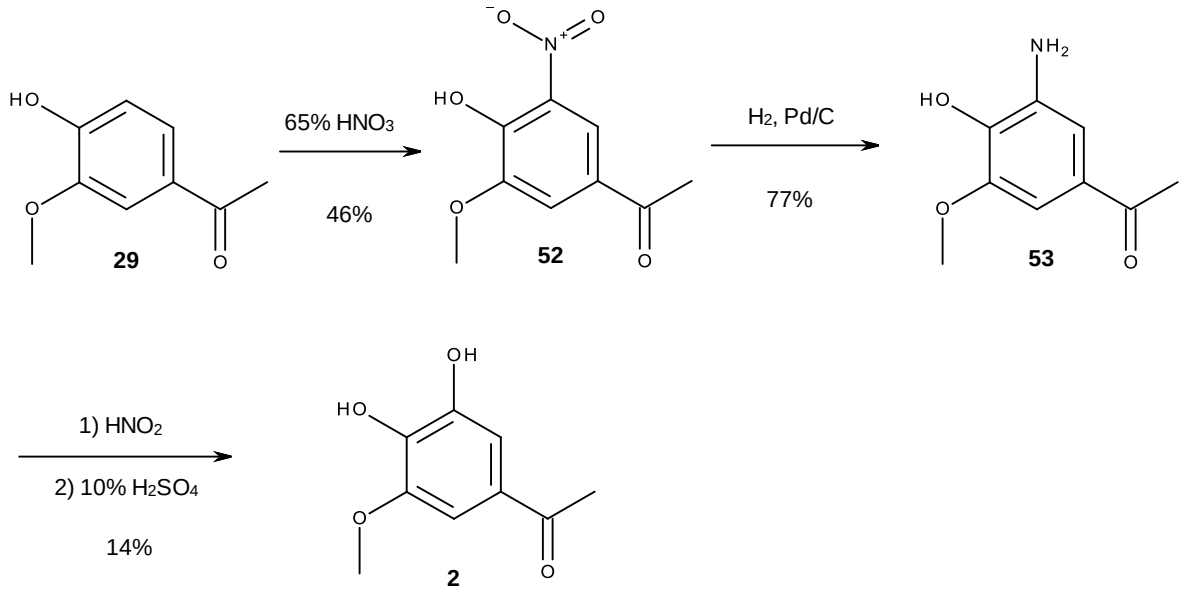
Scheme 21 Synthesis of 3,4-diphenylmethylenedioxyacetophenone (**13**) with 3,4-dihydroxybenzoic acid (**47**) as starting material.

Even though of some academic interest, the above strategies toward protected 3,4-dihydroxyacetophenone, is inferior to the one already established by the research group by using 2-chloro-3',4'-dihydroxy (**5**) as starting material. The use of MeLi in the above reactions limits its use in large scale production, not to mention that the established method is carried out in excellent yields and fewer steps.

3.2 Synthesis of 3,4-dihydroxy-5-methoxyacetophenone by diazonium pathway

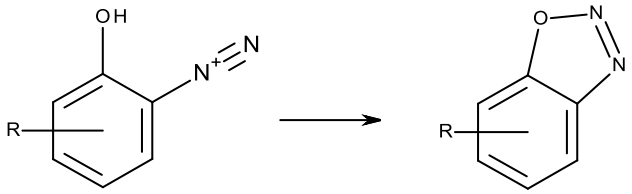
Despite its simple structure, the synthesis of 3,4-dihydroxy-5-methoxyacetophenone (**2**) has for some time been a challenge for the research group. One simple strategy employed here is the addition of a nitro group and subsequent conversion of this group to an amino group, then to a diazonium salt and finally to the target phenol (scheme 22).

The nitration was carried out by a procedure by Reijo Johannes Backstrom *et al.* and worked nicely in acceptable yields.[21] The reduction of the nitro group by H_2 and Pd/C was also a success. The step toward the diazonium salt and finally the phenol was however, unexpectedly challenging. Many different methods were attempted, but most did not work at all. The procedure finally employed, was a method by Masazum Watanabe *et al.* which used classical conditions, by heating the formed salt in 10% H_2SO_4.[22] A promising method by Theodore Cohen *et al.*, which used milder conditions to convert the salt to the phenol, was also attempted. This method used an aqueous solution of $CuNO_3$ and Cu_2O at room temperature to convert the salt into the phenol.[23] NMR showed that in this case the desired product had been formed but still in a poor yield and with unwanted side products. The use of very large amounts of $CuNO_3$ (100 equivalents) also made this procedure unattractive when scaling up the experiment.



Scheme 22 Synthesis of 3,4-dihydroxy-5-methoxyacetophenone (**2**) by using a diazonium approach.

A problem with diazonium reactions is the fact that they can undergo a lot of unwanted side reactions. Theodore Cohen *et al.* reported that challenges arise when the formed diazonium salt is in close proximity to other functional groups. For instance, the presence of a hydroxy group in the ortho position may lead to the formation of a 1,2,3-benzoxadiazole (scheme 23).[23]



Scheme 23 Potential byproduct from diazonium reactions with a hydroxy group in ortho position to the formed diazonium salt.

No attempt was made to investigate the byproducts formed during the preparation of **2**. It was however apparent that some factors severely disturbed the reaction. Short time after the addition of $NaNO_2$, the reaction mixture turned to a disconcerting black color.

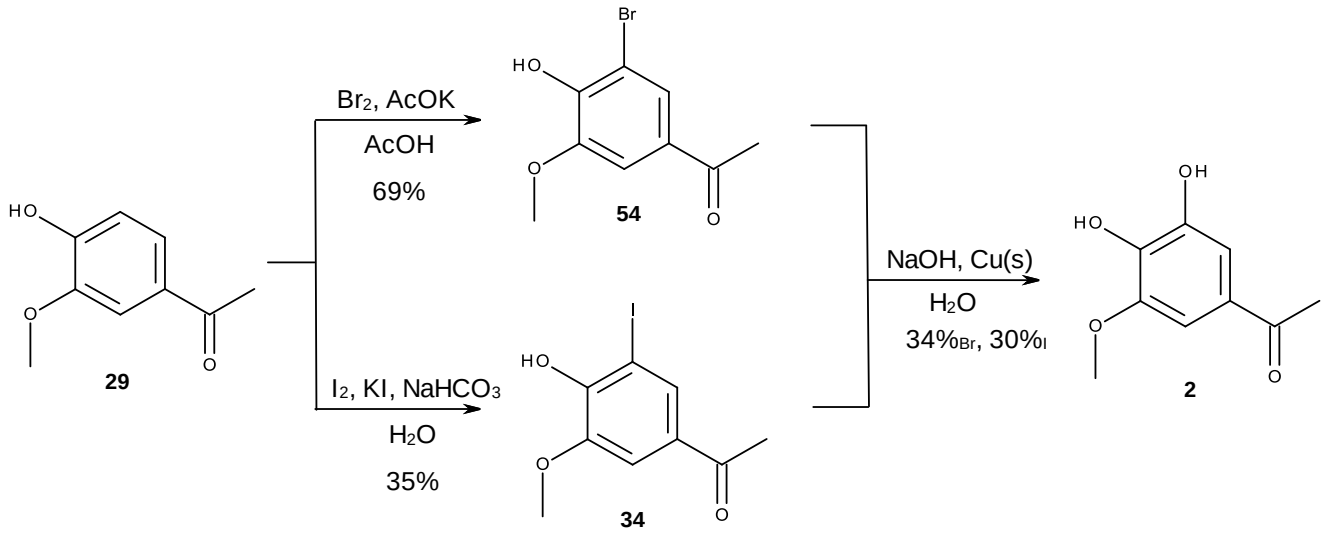
3.3 Synthesis of various acetophenones by Ullman-type coupling

Ri-ling Deng *et al.* and S. K. Banerjee *et al*. used Ullmann-type couplings to synthesize **1** and **2** respectively. A similar approach was used in the work of this thesis.

The synthesis of **2** by this approach was studied extensively (scheme 24).

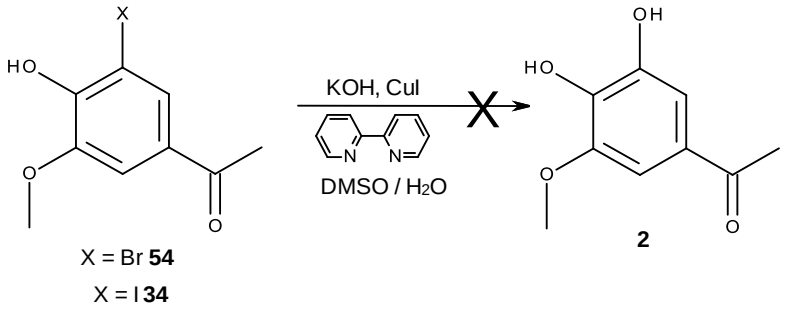
Addition of both bromine and iodine to the aromatic ring of acetovanillone was carried out successfully. The bromination was carried out by a method by Karl W. Rosenmund.[24] The addition was done by Br_2 in the presence of large amounts of potassium acetate and concentrated AcOH as solvent. The addition of potassium acetate is essential to avoid alpha bromination of the ketone. It is suspected that potassium acetate helps to capture HBr formed during the reaction conditions and thereby prevents formation of the enol and subsequent bromination next to the ketone. The addition of iodine was carried out by a method by L. W. Crawford *et al.* and worked out as expected.[25] The yield for this reaction was reported to be 83% in literature, while the achieved yield was 35% The decrease in yield is probably mostly due to addition of too much solvent during recrystallization.

Many different Ullmann-type coupling reactions were investigated for the conversion of the halogenated acetophenones into **2**. The method mentioned in section 2.7 developed by James E. Ellis *et al.* was the only one found usable for this application. This involved heating the halogenated compounds **54** or **34** with copper powder and NaOH in water. This method has many drawbacks however: Long reaction time, incomplete reaction, formation of byproducts and demanding workup. These reaction conditions were also sufficiently tough to corrode and destroy the standard pyrex round bottomed flasks. One side product identified from this reaction was acetovanillone. The type of halogen seemed to have little impact on the reaction, as the yield is about the same with both bromine and iodine.



Scheme 24 Synthesis of 3,4.dihydroxy-5-methoxyacetophenone (**2**) by the use of an Ullmann-type coupling on halogenated acetovanillone

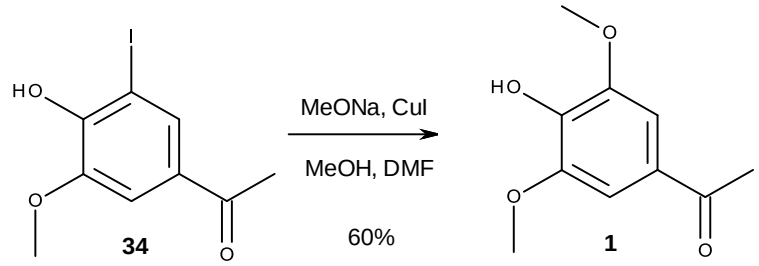
The reaction developed by Anis Tlili *et al.* (described in section 2.7) was also attempted for the preparation of **2** (scheme 25). The base used was KOH, the catalyst CuI and the ligand 2,2'-bipyridine. The solvent was a mixture of water and dimethyl sulfoxide (DMSO). The method was reported to work for a great range of different compounds, but the exact scope and limitations of the method were not very well described. This method did not work for the preparation of **2** from the brominated or iodinated analogue. In both cases, even after vigorous heating, no reaction had occurred at all and only starting material was present.



Scheme 25 A procedure based on the method developed by Anis Tlili *et al.* could not be used to prepare 3,4.dihydroxy-5-methoxyacetophenone (**2**).

4-Hydroxy-3,5-dimethoxyacetophenone (**1**) was prepared by an Ullmann type coupling. The method used was loosely based on the method by Ri-ling Deng *et al*. **1** was prepared by heating 4-hydroxy-3-iodo-5-methoxyacetophenone (**34**) with MeONa in a mixture of MeOH and DMF. CuI was used as catalyst (scheme 26).

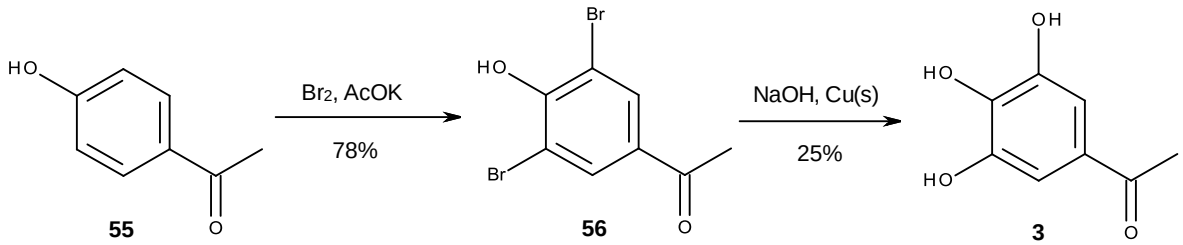
This reaction worked much better than the previous Ullmann-type coupling to make **2**. The yield was better and the reaction was much cleaner, which made workup and purification easier. Some unidentified byproducts were observed by NMR however. After this result was obtained, similar conditions were used in an attempt to make **2**. In this case H_2O and NaOH were used instead of MeOH and MeONa. Sadly, no reaction occurred at all.



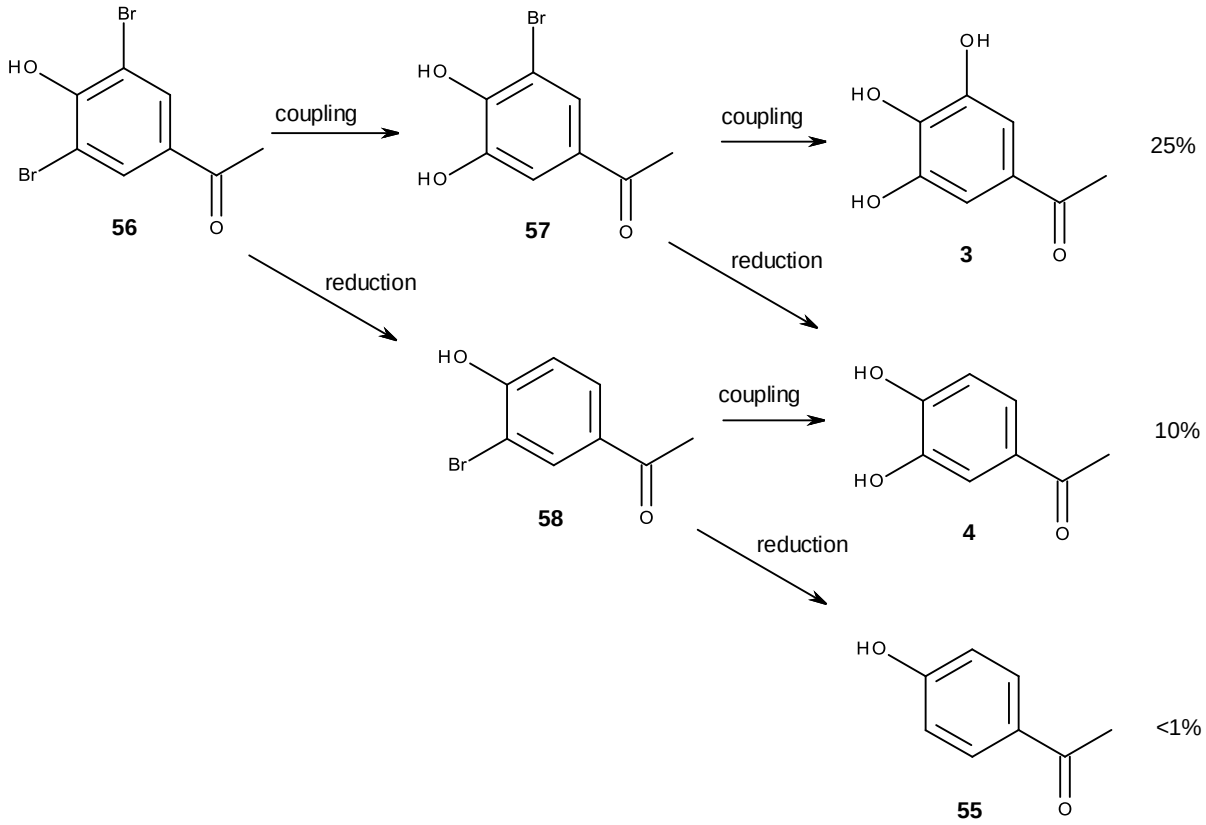
Scheme 26 Synthesis 4-hydroxy-3,5-dimethoxyacetophenone (**1**) by using an Ullmann-type coupling

Another compound prepared by an Ullmann-type coupling was **3**. In this case 4-hydroxyacetophenone was used as starting material (scheme 27).

The bromination was performed under similar conditions used to synthesize **54**. This was done by using 2 equivalent Br_2, AcOK and acetic acid. The following Ullmann-type coupling used the conditions developed by James E. Ellis *et al*.[20] The yield was not very good and several byproducts were isolated. It is believed that these byproducts are formed as a result of some kind of additional reductive reaction with copper where the halogen is simply exchanged for hydrogen. A list of byproducts isolated from this reaction and a proposal for how these are formed is shown in scheme 28.



Scheme 27 Synthesis of 3,4,5-trihydroxyacetophenone (**3**) by using an Ullmann-type coupling.

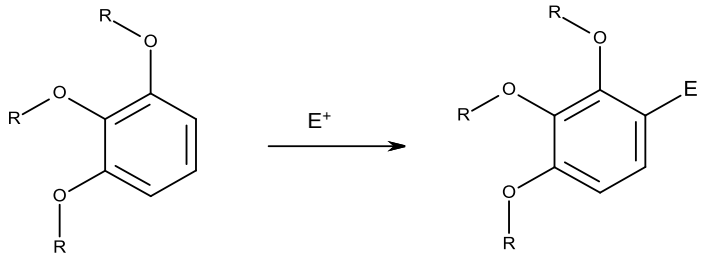


Scheme 28 Byproducts isolated form reaction used to prepare **3**.

Even though Ullmann-type couplings can be used to prepare a great range of substituted acetophenones, their use is somewhat limited because of their messy reactions and poor yields. With the exception of the Ullmann-type coupling used to prepare **1**, the other Ullmann-type couplings are not believed to be suitable for larger scale. However, if the method can be improved or other methods are found to work for these acetophenones, it has great promise as a way to prepare acetophenones which can otherwise be difficult to obtain.

3.4 Attempts at Friedel-Crafts approach

Friedel-Crafts acylation have been shown to be difficult to use for the synthesis of the wanted acetophenones. Problems arise because the acylation does not take place at the desired positions. One example is the acylation of pyrogallol (**19**) (section 2.4, scheme 9) which results in acylation of the C-4 position. Acylation of 1,2,3-trimethoxybenzene (**59**) also results in C-4 substitution as shown by Xin-Hua Liu *et al.*[26] More generally speaking, it seems as though electrophilic substitution might occur exclusively at this position for these types of compounds (scheme 29).



R = H **19**
R = Me **59**

Scheme 29 General scheme for electrophilic aromatic substitution of pyrogallol (**19**) and 1,2,3-trimethoxybenzene (**59**)

One strategy, briefly investigated, was to block the unwanted positions with bromine. Hopefully the ensuing acylation would then be forced to take place at the C-5 position. The removal of bromine after successful acylation could for instance be accomplished with butyllithium (BuLi). The compound investigated for this strategy was 1,2,3-trimethoxybenzene (**59**). Acylation of this compound at the desired position, C-5, should give **35**, which Kristine Fagerstrand showed could be used to synthesize **1** in good yields.

Bromination of **59** was carried out by *N*-Bromosuccinimide (NBS) in MeCN. The number of bromines added could be controlled by changing the temperature and the amount of NBS added (scheme 30). It is interesting to note that even when adding 2 bromines, absolutely no substitution was observed at the C-5 position.

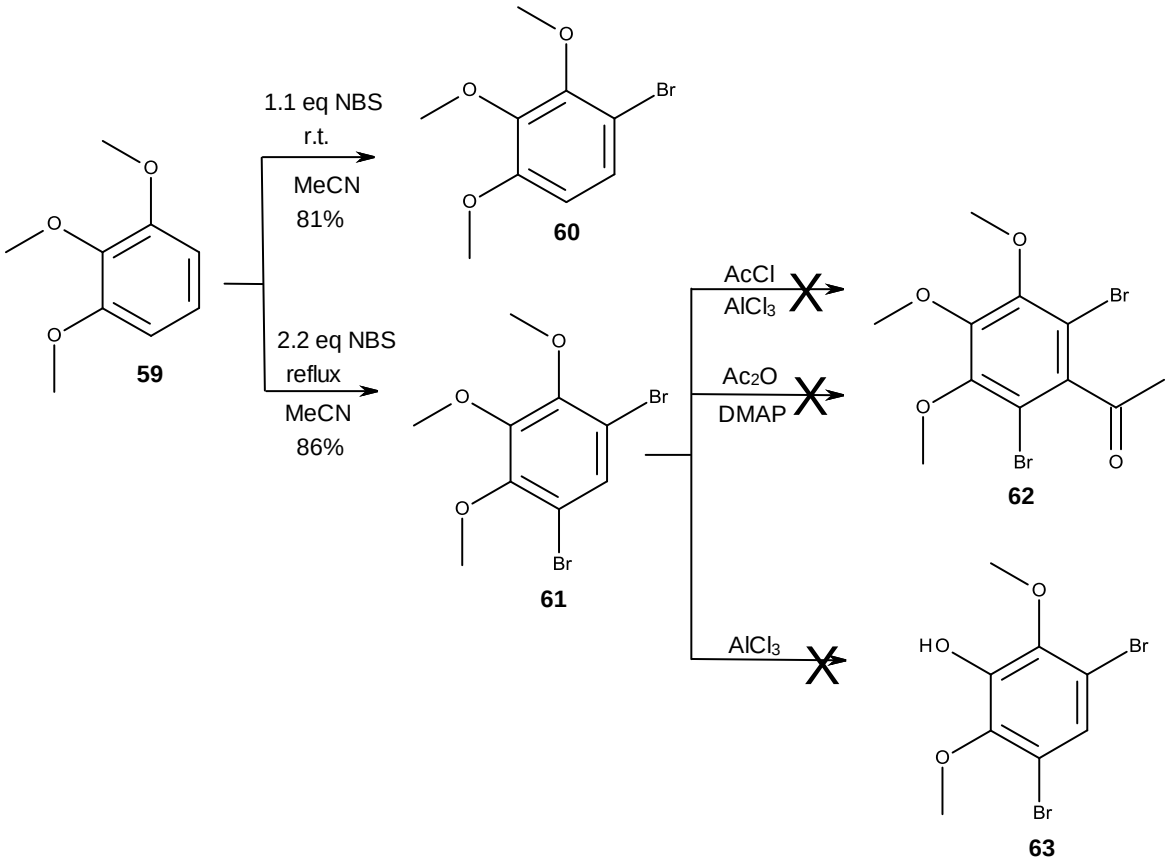
Acylation of 1-bromo-2,3,4-trimethoxybenzene (**60**) was of little value after the result of adding 2 bromines to the ring was discovered. The addition of any electrophile would probably have ended in unwanted substitution of the C-6 position.

Acylation was attempted on 1,5-dibromo-2,3,4-trimethoxybenzene (**61**). One attempt was made by using Ac_2O and DMAP. In this case no reaction occurred. Another attempt was made by using AcCl and $AlCl_3$. This gave a mixture of products, but no signals corresponding to a ketone was observed. It is suspected that $AlCl_3$ alone reacts with **61** under these conditions to give unwanted products. This was the case when an attempt was made at demethylating **61** by using $AlCl_3$. This gave a strange mix of products were none was the wanted compound, 3,5-dibromo-2,6-dimethoxyphenol (**63**).

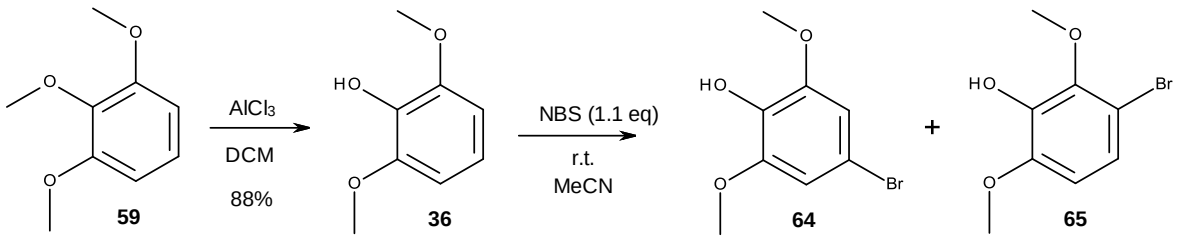
However, demthylation of the unbrominated analogue (**59**) was achieved in high yields (scheme 31). Bromination of 2,6-dimethoxyphenol by NBS seemed unfortunately to give a mixture of different substitutions and could not be used for a similar strategy. This was indicated by NMR of the crude product. No starting material was confirmed to be present. ^{1}H NMR showed two doublets with chemical shifts 7.01 and 6.56 ppm, both with coupling constants equal to 9 Hz. These doublets are believed to correspond to the compound 3-bromo-2,6-dimethoxyphenol (**65**). There was also observed a singlet at 6.72 ppm believed to correspond to 4-bromo-2,6-dimethoxyphenol (**64**). From the ratio between the integrals the ratio between **65** and **64** were roughly estimated to be 3:1.

It is noteworthy that removal of the “middle” methyl group activates the position (C-4) which was impossible to substitute for the trimethoxy ether, **59**. Addition of bromine exclusively to the C-4 position of 2,6-dimethoxyphenol (**62**) is documented in the literature. Among others,

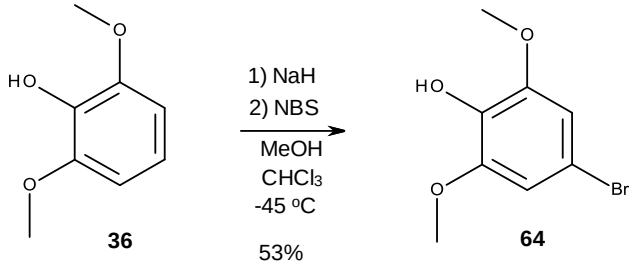
this has been done by Sabine Choppin *et al.* (scheme 32).This reaction requires addition of NaH prior to addition of NBS and low temperature (-45 ^{o}C). [27]



Scheme 30 Preparation of 1,5-dibromo-2,3,4-trimethoxybenzene (**61**) and 1-bromo-2,3,4-trimethoxybenzene (**60**). Acylation as well as demethylation of **61** was unsuccessful.



Scheme 31 Preparation and bromination of 2,6-dimethoxyphenol (**36**). Bromination gave a mixture of different compounds.



Scheme 32 Bromination of 2,6-dimethoxyphenol (**36**) at the C-4 position by Sabine Choppin *et al.*

3.5 Formylation

Formylation, followed by Dakin oxidation is an interesting approach to introduce a phenol to an aromatic ring. To the best of our knowledge this oxidation has never been attempted on a molecule containing both a formyl and an acetyl group. Formylation of acetovanillone (**29**) would give a molecule containing both these functional groups and the selectivity of the Dakin oxidation could be investigated.

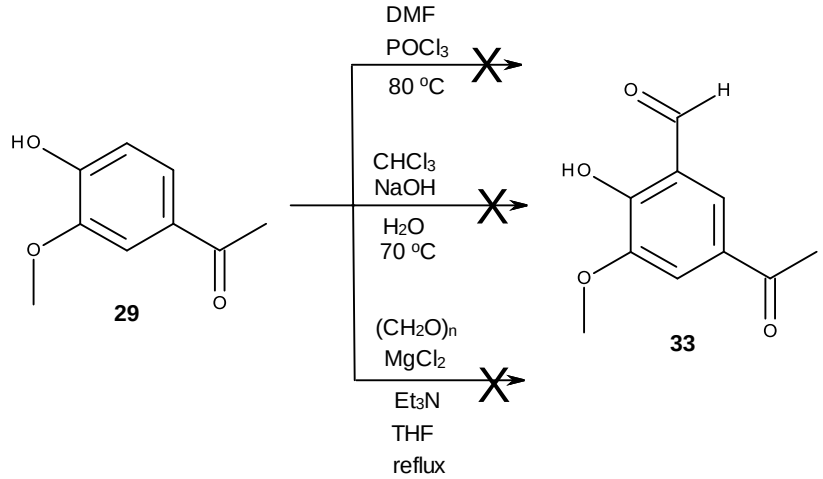
Formylation of acetovanillone (**29**) has however been unexpectedly difficult. The 4-step-formylation investigated by Tom Arne Sola and Kristine Støvik Fagerstrand (scheme 12, section 2.5) were found to be unattractive because of numerous steps and a poor overall yield.

Several one step formylations were investigated in the work of this thesis: Vilsmeier-Haack formylation, Reimer-Tiemann formylation and Skattebøl formylation (scheme 33).

Vilsmeier-Haack formylation of acetovanillone was performed by using a mixture of $POCl_3$ and DMF. The reaction was attempted both at room temperature and at 80 ^oC. In both cases a mixture of products were obtained, but no characteristic aldehyde signals were observed in ^1H NMR (9-11 ppm).

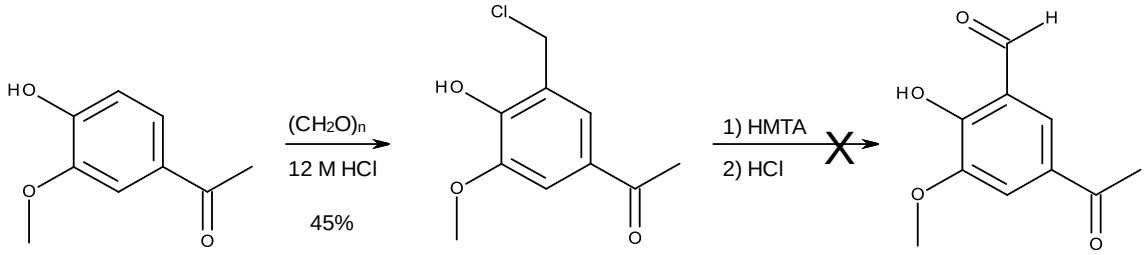
The Reimer-Tiemann formylation was attempted by heating acetovanillone with NaOH and small amounts of $CHCl_3$ in water. The next day, (thin layer chromatography) TLC indicated that no reaction had occurred.

The Skattebøl formylation was also attempted. This formylation requires $MgCl_2$, Et_3N and paraformaldehyde. It is important that all the reagents and solvents used in this reaction are free of water, as the presence of even tiny amounts of water prevents the formylation from occurring.[28] To make sure all reagents were sufficiently dry, the formylation was first tested on 4-methoxyphenol, a compound known to react readily in this reaction.[29] When this reaction was successful, identical conditions were attempted with acetovanillone. Unfortunately, no reaction occurred. Only starting material was present after 48 hours of reflux.



Scheme 33 Failed attempts at one-step formylation of acetovanillone

A 2-step formylation based on chloromethylation and Sommelet oxidation was also investigated (scheme 34). 3-Chloromethyl-4-hydroxy-5-methoxyacetophenone (**66**) was successfully prepared[1], but the following Sommelet oxidation did not work. The Sommelet oxidation was performed first by heating **66** with hexamethylenetetramine (HMTA) in AcOH and then acidified with HCl. The crude product exhibited some NMR signals characteristic for aldehydes, but only traces seemed to be present.



Scheme 34 Attempt at 2-step formylation of acetovanillone (**29**). The chloromethylation was successful, but the following Sommelet oxidation failed.

So far, formylation followed by Dakin oxidation does not seem like a useful strategy to prepare the target acetophenones. The main challenge so far is the formylation itself. One formylation not attempted in the work of this thesis which should be tried, is the Rieche formylation. This formylation was avoided mainly because of its use of the highly toxic dichloromethyl methyl ether.

4. Conclusion

Protected forms of 3,4-dihydroxyacetophenone was prepared successfully with 3,4-dihydroxybenzoic acid as starting material. A reaction with methyllithium was used to convert the acids to the corresponding ketones. Both benzyloxy- and diphenylmethylenedioxy protection was usable for the methyllithium reaction. This showed that the diphenyl protection alone was not the cause of 3,4-diphenylmethylenedioxy-5-methoxybenzoic acid's (**28**) unwillingness to react with methyllithium.

3,4-Dihydroxy-5-methoxyacetophenone (**2**) was successfully prepared by using a diazonium pathway with acetovanillone (**29**) as starting material. The nitration and the following reduction of the nitro group worked in acceptable yields, but the diazonium ion reaction was challenging. The low yield from this reaction made the approach unusable for preparation of larger amounts of **2**.

4-Hydroxy-3,5-dimethoxyacetophenone (**1**), 3,4-dihydroxy-5-methoxyacetophenone (**2**) and 3,4,5-trihydroxyacetophenone (**3**) were prepared successfully by using Ullmann-type couplings. The Ullmann-type coupling used to make **2** and **3** were quite "messy" and proceeded in low yields (34% and 25% respectively). This makes this method unattractive for preparation of larger amounts of these acetophenones. The preparation of **1** by an Ullmann-type coupling went much better (Yield: 60%). This approach is believed to be usable for preparing larger amounts of **1** if needed.

[1] Preparation of **65** was first accomplished by M.Sc. student Kristine Støvik Fagerstrand

Ullmann-type couplings show great synthetic potential since all reagents involved are cheap and they can be used to prepare acetophenones which can otherwise be difficult to obtain. Some future investigation could be performed to see if other variations of the Ullmann-type coupling can prepare **2** and **3** more effectively. Another interesting investigation would be to study the scope of these couplings for these types of compounds. In this thesis, methanol and water were coupled with halogenated acetophenones, but it is possible that other alcohols as well can be coupled by similar methods.

With the exception of 3,4-dihydroxyacetophenone (**4**), Friedel-Crafts acylation has not worked for the synthesis of the target acetophenones. This was also the case for the work in this thesis. The unwanted positions of 1,2,3-trimethoxybenzene (**59**) was blocked with bromine, but the following acylation did not work. This might be due to deactivation and steric hindrance caused by the presence of bromine.

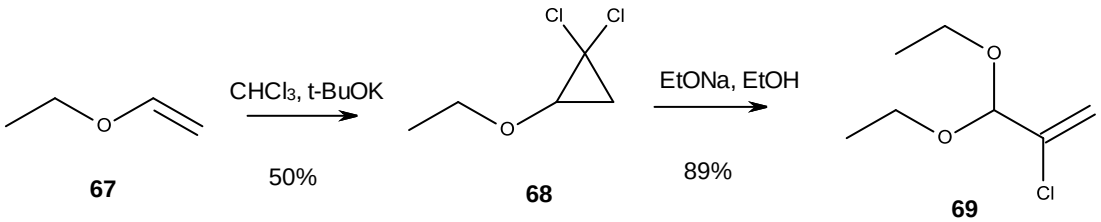
Formylation of acetovanillone (**29**) was unsuccessful and the planned Dakin oxidation of the resulting compound could not be investigated. Formylations attempt was Vilsmeier-Haack formylation, Reimer-Tiemann formylation, Skattebøl formylation and chloromethylation followed by Sommelet oxidation. So far, this does not seem like a promising strategy to prepare any of the target acetophenones.

Part B: Synthesis and ring opening of selected strained *gem*-dihalocyclopropyl ethers

5. Introduction

Synthesis and ring opening of *gem*-dihalocyclopropyl ethers can be used to synthesize a range of interesting compounds. These reactions can however be quite sensitive to functional groups present elsewhere in the molecule and can sometimes lead to unexpected products. The study of these ring openings can lead to better understanding regarding the underlying mechanisms and can also help map possible products from these types of ring openings. The unique nature of many of the products also makes them interesting as building blocks for synthesis of more complex compounds.

A useful example for these ring openings is the synthesis and ring opening of 2,2-dichlorocyclopropyl ethyl ether (**68**) studied among others by Prof. Lars Skattebøl (scheme 35).[30]

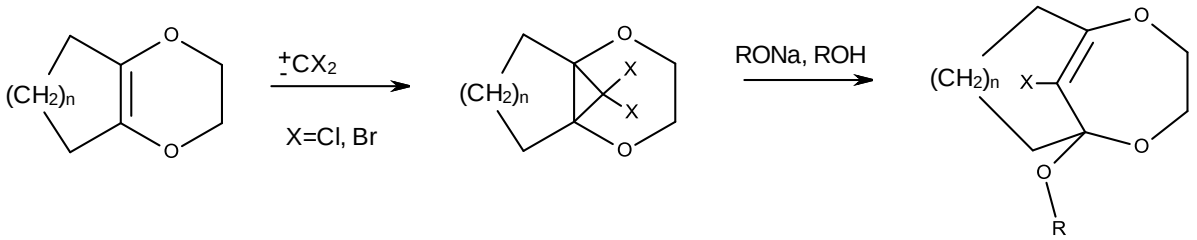


67 **68** **69**

Scheme 35 Synthesis and ring opening of 1,1-dichloro-2-ethoxycyclopropane performed by Lars Skattebøl.

The study in this thesis focuses on what happens if this ring opening is performed in a more strained system, where fused rings limits the options for how this ring opening can take place. The *gem*-dihalocyclopropanes shown in scheme 36 can be synthesized and used for this purpose.

This investigation is based on earlier work performed by Bjørn Erik Jønsberg, a former M.Sc. student of the Skattebøl research group.



Scheme 36 Proposed method and products for studying ring opening of *gem*-dihalocyclopropanes. The final product is not expected to form when n is sufficiently small.

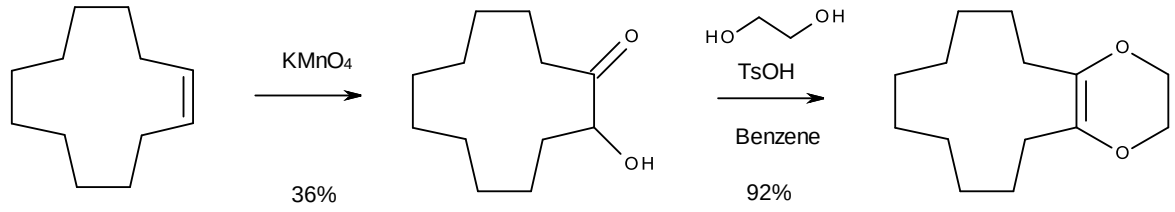
The ring opening product shown in scheme 36 is a proposed product based on the ring opening typical for *gem*-dihalocyclopropyl ethyl ether. This product is less likely to be formed when the ring gets smaller. The smallest ring which can sustain a trans double bond at room temperature is cyclooctene. When n gets smaller then 4, the proposed product cannot form or will immediately have to rearrange into something else. Because of the strained nature of these compounds it is also possible that entirely different products will form even when n is larger than 4.

6. Previous synthesis and investigation of ring-openings

6.1 Previous synthesis of bicyclic dihydrodioxins

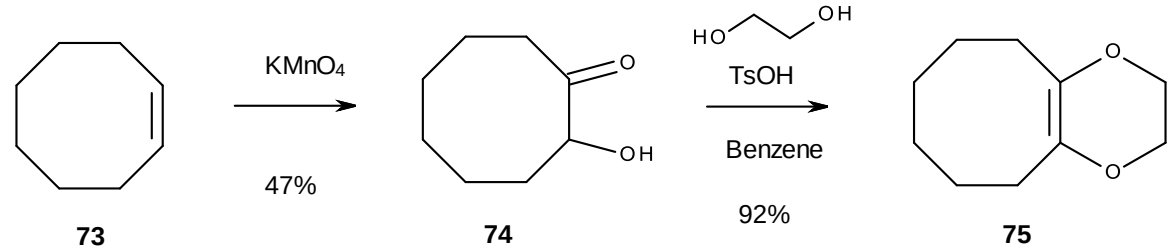
The synthesis of the dihydrodioxins of interest can be carried out by different methods.

Members of the Skattebøl research group, Inger Reidun Fjeldskaar *et al.*, prepared the dihydrodioxins **72** and **75** from their corresponding cyclic alkenes (scheme 37 and 38). This strategy worked in good yields. The biggest drawback was the first step, the $KMnO_4$ oxidation, which was reported to be simple experimentally, but only gave moderate yields of the required acyloins. The addition of ethylene glycol under acidic conditions worked in excellent yields. Water had to be removed azeotropically for this reaction.[31]



70 **71** **72**

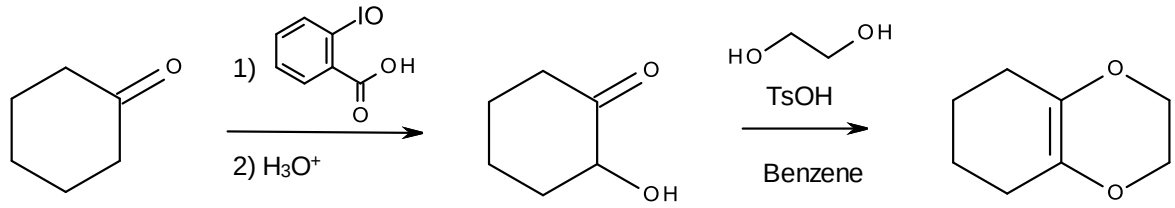
Scheme 37 Preparation of $\Delta^{1(12)}$-13,16-dioxabicyclo[10.4.0]hexadecene (**72**) from cyclododecene (**70**) by Inger Reidun Fjeldskaar *et al.*



73 **74** **75**

Scheme 38 Preparation of $\Delta^{1(8)}$-9,12-dioxabicyclo[6.4.0]dodecene (**75**) from cyclooctene (**73**) by Inger Reidun Fjeldskaar *et al.*

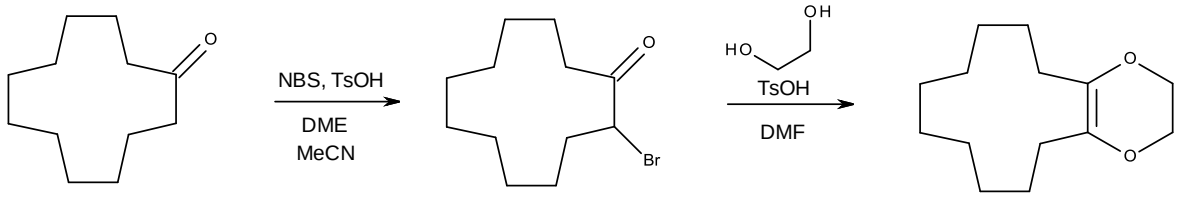
An alternative strategy was used for the preparation of dihydrodioxin **78** (scheme 39). The $KMnO_4$ oxidation was found to work in poor yields, so an oxidation with *O*-iodosylbenzoic acid of cyclohexanone (**76**) followed by hydrolysis was used instead.[31] The oxidation is originally a method developed by Robert M. Moriarty to make α-hydroxydimethyl ketals.[32]



76 74% **77** 90% **78**

Scheme 39 Preparation of $\Delta^{1(6)}$-2,5-Dioxabicyclo[4.4.0]decene (**78**) from cyclohexanone (**76**) by Inger Reidun Fjedlskaar *et al.*

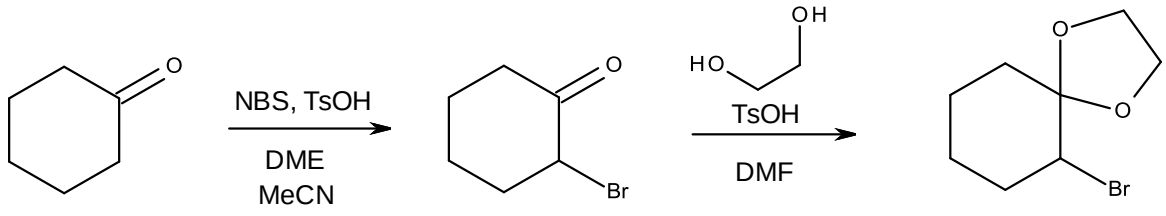
Guest research scientist of the Bakstad research group, Rosalie R. Sanchez, discovered an interesting approach which worked very well for the preparation of dihydrodioxin **72** (scheme 40). Cyclododecanone (**79**) was used as starting material. The bromination of cyclododecanone (**79**) was inspired by a general method by Jong Chan Lee *et al.*to make alpha-bromo ketones.[33] The addition of ethylene glycol is inspired by the similar reaction used in the Skattebøl research group's approach. In this case, bromide as well as water takes the role of leaving groups instead of only water, which is the case for the Skattebøl group's approach. This reaction did not require azeotropic removal of water.[34]



79 **80** **72**

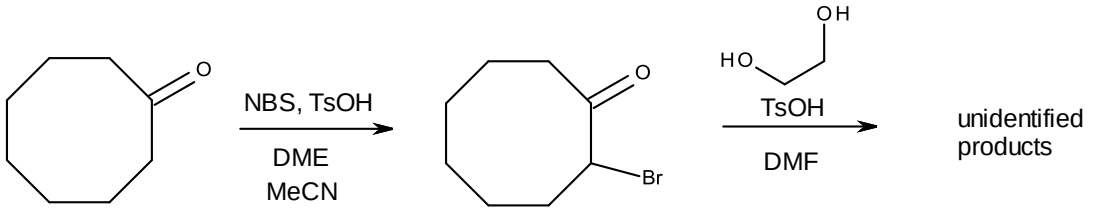
Scheme 40 Preparation of $\Delta^{1(12)}$-13,16-Dioxabicyclo[10.4.0]hexadecene (**72**) from cyclododecanone (**79**) by Rosalie R. Sanchez and Einar Bakstad.

The strategy used for the preparation of **72** did unfortunately not work for the preparation of the other dihydrodioxins of interest, **75** and **78**. The bromination worked, but the addition of ethylene glycol did not result in the desired products. For 2-bromocyclohexanone (**81**), the brominated ketal, **82**, was identified as the main product (scheme 41). 2-bromocyclooctanone (**84**) gave a mixture of products which was not further investigated (scheme 42).[34]



76 **81** **82**

Scheme 41 Failed attempt at preparation of $\Delta^{1(6)}$-2,5-dioxabicyclo[4.4.0]decene (**78**) by Rosalie R. Sanchez and Einar Bakstad. The brominated ketal was produced instead



83 **84**

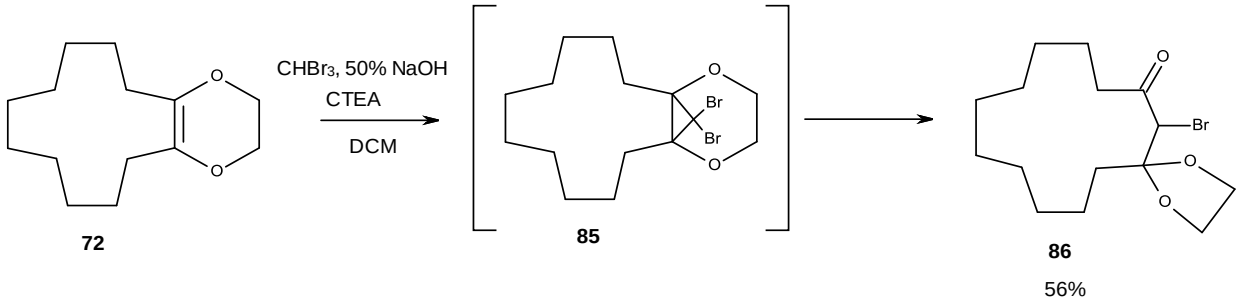
Scheme 42 Failed attempt at preparation of $\Delta^{1(8)}$-9,12-dioxabicyclo[6.4.0]dodecene (**75**) by Rosalie R. Sanchez and Einar Bakstad. The ethylene glycol reaction gave a mixture of products which were not identified.

6.2 Previous synthesis and ring opening of 17,17-dibromo-13,16-dioxa[10.4.1]propellane (85)

Many of the ring openings have already been studied by former M.Sc. student Bjørn Erik Jønsberg of the Skattebøl research group. After dihydrodioxin **72** was prepared, addition of dibromocarbene was attempted for this compound. During the addition of dibromocarbene an unexpected product was formed (scheme 43).[35]

Phase transfer conditions where used to generate dibromocarbene. Cetyltriethylammonium chloride (CTEA) was used as phase transfer catalyst. The dibromo propellane **85** could not be

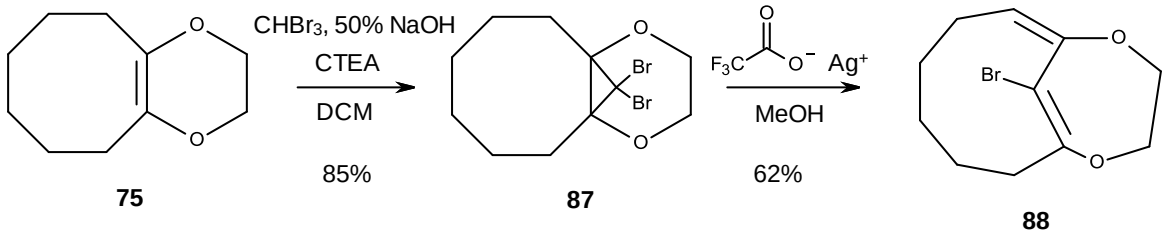
isolated during these reaction conditions, but apparently rearranged to form the product (**86**) shown in scheme 43.[35]



Scheme 43 Formation of an unexpected product after addition of dibromocarbene to $\Delta^{1(12)}$-13,16-dioxabicyclo[10.4.0]hexadecene (**86**).

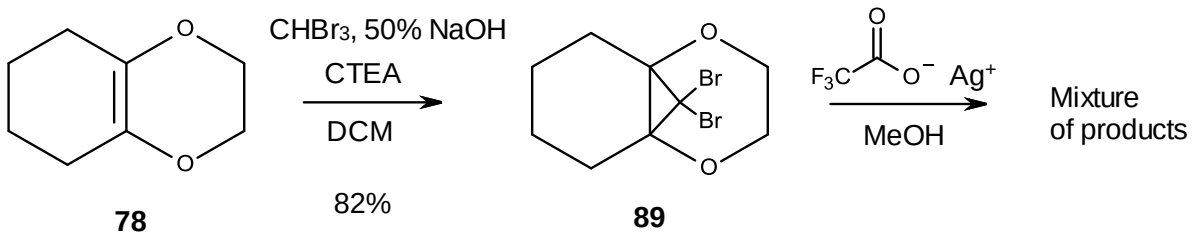
6.3 Previous synthesis and ring opening of 13,13-dibromo-9,12-dioxa[6.4.1]propellane (87) and 11,11-dibromo-2,5-dioxa[4.4.1]propellane (89)

After the dihydrodioxin **75** was synthesized successfully, this compound was reacted with dibromocarbene. The dibromo propellane **87** was prepared successfully. The classical conditions for ring opening of *gem*-dihalocyclopropyl ethers, with ethanol and EtONa, did not work for **87**. This is probably due to the strained nature of the system. The ring opening of **87** was achieved by using silver trifluoro acetate (scheme 44).[35]



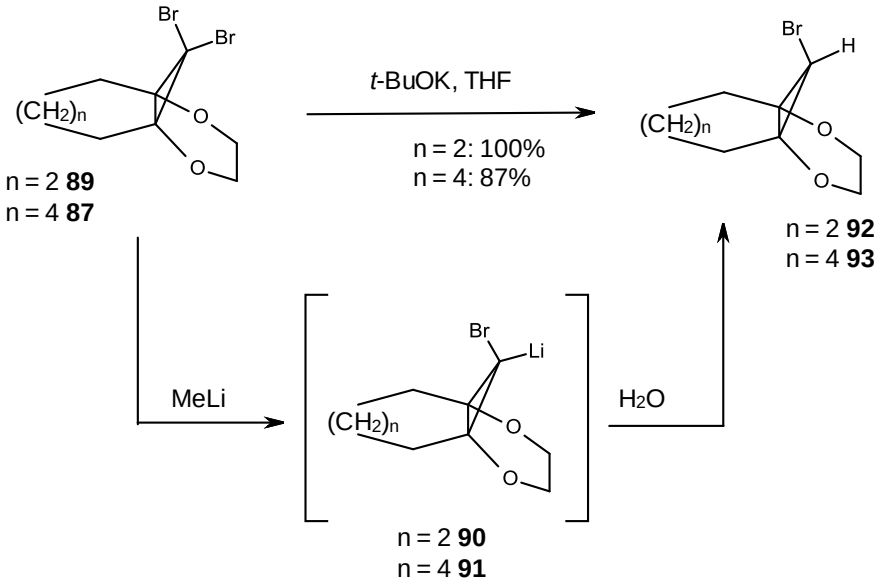
Scheme 44 Preparation and ring opening of 13,13-dibromo-9,12-dioxa[6.4.1]propellane (**87**) by Bjørn Erik Jønsberg. The ring opening required the use of silver trifluoro acetate.

The propellane **89** was synthesized from the dihydrodioxin **78** analogous to the synthesis of **87**.The reaction with silver trifluoroacetate gave a complex mixture of different products which was not further investigated (scheme 45).[35]



Scheme 45 Preparation of 11,11-dibromo-2,5-dioxa[4.4.1]propellane (**89**) by Bjørn Erik Jønsberg. The ring opening gave a mixture of products which were not further investigated.

The propellanes **87** and **89** were also reacted with t-BuOK in tetrahydrofuran (THF) to give high yields of the corresponding monobromines **93** and **92** respectively (scheme 46). This reaction is not described in the literature and is quite puzzling from a mechanistic point of view. The same product could be formed from the propellanes by a metal-halogen-exchange with MeLi and quenching with water, which is a method known in the literature. It is noteworthy that in both cases only the bromine closest to the oxygen atoms where exchanged with hydrogen. For the MeLi reaction this can be explained by a chelation effect from oxygen which stabilizes this specific lithium compound.[35]



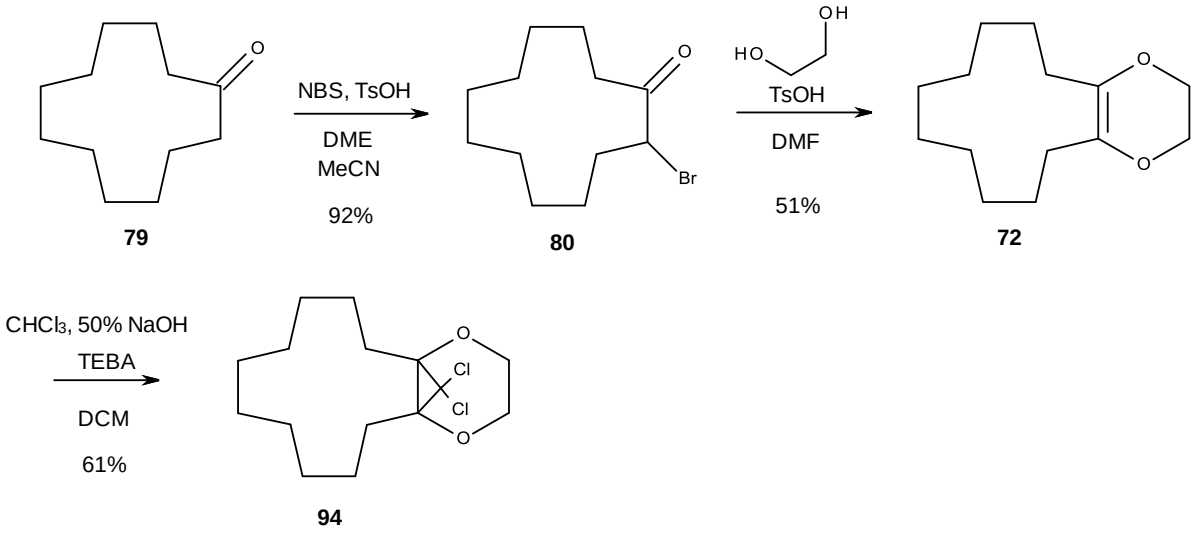
Scheme 46 Preparation of the monobromo propellanes **92** and **93** from the corresponding dibromo propellanes.

7. Results and discussion

7.1 Synthesis and ring opening of 17,17-dichloro-13,16-dioxa[10.4.1]propellane (94)

Dichloro propellane **94** was prepared with cyclododecanone as starting material (scheme 47) according to the strategy first used by Rosalie R. Sanchez. The addition of bromine was accomplished with a modified procedure based on a method by Jong Chan Lee *et al*.[33] The dihydrodioxin **72** was prepared in acceptable yields by acid catalyzed addition of ethylene glycol to the α-haloketone and subsequent elimination of water. Preparation of the dichloro cyclopropane was successful. The preferred method for this was phase transfer conditions with $CHCl_3$, NaOH and benzyltriethylammonium chloride (TEBA).[2] The Doering-Hoffmann method was also attempted, but gave a lower yield and a crude product containing more impurities.

[2] The preparation up to and including 17,17-dichloro-13,16-dioxa[10.4.1]propellane (**94**) was first performed in the Bakstad research group by guest research scientist Rosalie R. Sanchez



Scheme 47 Preparation of 17,17-dichloro-13,16-dioxa[10.4.1]propellane (**94**) in 3 steps by using cyclododecanone (**79**) as starting material.

Ring opening with EtONa in EtOH was attempted for the propellane, **94**. The product from this reaction proved to be quite unstable and purification was difficult. Both recrystallization and purification by silica gel destroyed the compound and storage for a few days in glass containers was also sufficient to cause decomposition. NMR of the crude product did however give a strong indication that **94** had reacted according to the typical ring opening for *gem*-dihalocyclopropyl ethers (section 5, scheme 35). The most intensive signals were in accordance with the predicted structure. Figure 4 shows the structure and some assigned ^{13}C NMR values of interest for this compound.

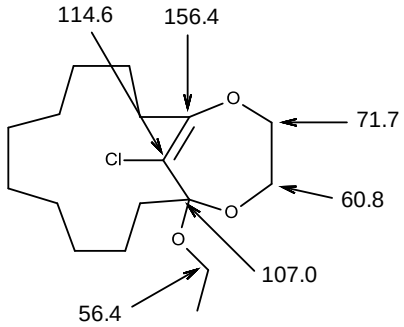
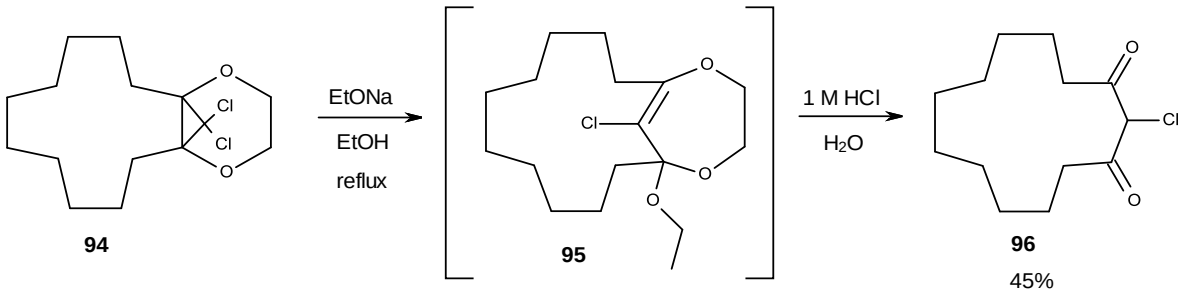


Figure 4 ^{13}C NMR signals observed after attempting ring opening of **94** with EtONa in EtOH. The values are assigned to the structure expected from a typical ring opening of *gem*-dihalocyclopropyl ethers. Values are listed in ppm

Since the product from the ring opening appeared to be difficult to purify, an alternative strategy was attempted. Instead of purification, diluted HCl was added after complete reaction. The acidic hydrolysis of the ring opened propellane was successful and resulted in the diketone **96** shown in scheme 48.

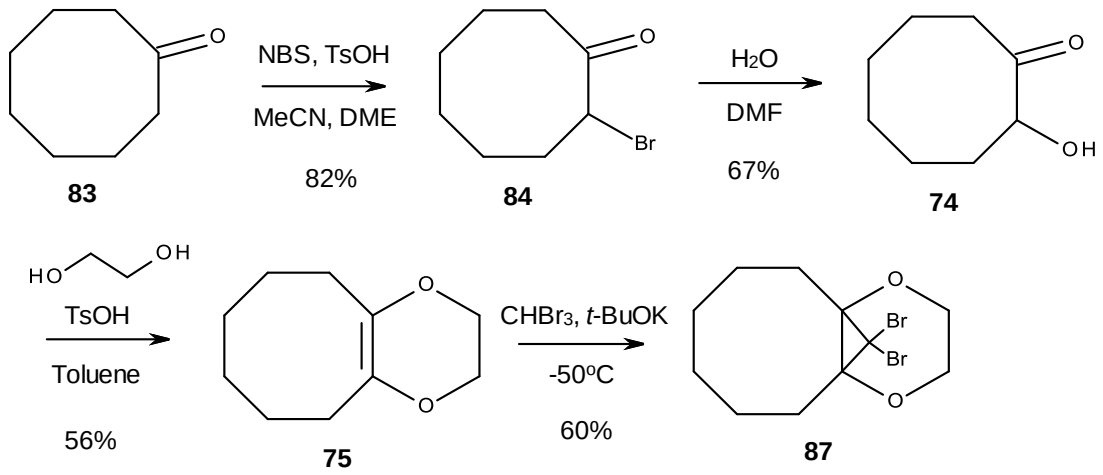


Scheme 48 Ring opening of 17,17-dichloro-13,16-dioxa[10.4.1]propellane (**94**) immediately followed by acidic hydrolysis to give 2-chlorocyclotridecane-1,3-dione (**96**).

There was also made an attempt to isolate the dibromo propellane **85**. This was done with $CHBr_3$ and potassium *tert*-butoxide (*t*-BuOK) in petroleum ether (PE) at -50^oC. This is a variation of the Doering-Hoffmann method. Normally this is done at -30^oC and not -50 ^oC. However, experiences in the Bakstad research group have shown that vinyl ethers react readily even at this significant lower temperature. This can be explained by the neighboring oxygen atoms making the double bond more electron rich and thereby more reactive. The crude product exhibited NMR signals characteristic for these type of compound, however the compound proved to be quite unstable and difficult to isolate. While trying to remove traces of $CHBr_3$ by vacuum distillation the mixture was gently heated. NMR of the residue indicated that the compound of interest had decomposed under this process.

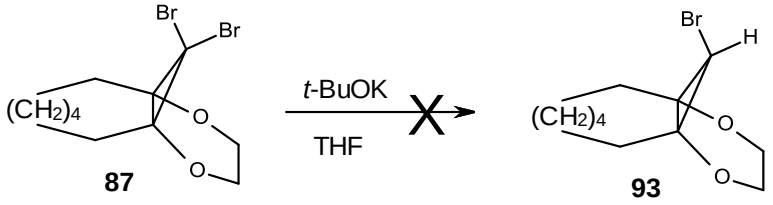
7.2 Synthesis of 13,13-dibromo-9,12-dioxa[6.4.1]propellane (87)

The dihydrodioxin **75** was prepared by a combination of the strategies used by Rosalie R. Sanchez and the Skattebøl research group. Cyclooctanone (**83**) was used as starting material (scheme 49). Bromine was added by the method by Jong Chan Lee *et al.*[33] and worked in good yields. Since the direct addition of ethylene glycol did not work (section 6.1), some variations had to be employed. Acyloin **74** was prepared in acceptable yields by heating the α-bromoketone, **84**, in a mixture of DMF and water. Dihydrodioxin **75** was prepared by heating the acyloin with ethylene glycol and *p*-toluenesulfonic acid (TsOH) in toluene. Water was removed from the reaction mixture by using a Dean-Stark apparatus. Toluene was used instead of benzene because of its lower toxicity, this might however have caused some reduction of the yield. The dibromo propellane **87** was prepared with $CHBr_3$ and *t*-BuOK with PE as solvent at -50 ^oC.



Scheme 49 Synthesis of 13,13-dibromo-9,12-dioxa[6.4.1]propellane (**87**) from cyclooctanone (**83**) in 4 steps

The reaction with *t*-BuOK in THF reported by Bjørn Erik Jønsberg (section 6.3) was attempted for propellane **87** in an attempt to make the corresponding monobromine. This reaction did not give the product reported by Bjørn Erik Jønsberg. Some signals from new compounds were observed on NMR, but none matched to the ones reported for the monobromine. A lot of unreacted starting material was also present.



Scheme 50 Failed attempt at preparing 13-bromo-9,12-dioxa[6.4.1]propellane (**93**) fom the corresponding dibromo compound **87** by *t*-BuOK in THF

8. Conclusion

Dichloro propellane **94** was prepared successfully in 3 steps from cyclododecanone. The Skattebøl research group showed that the dibromo analogue, **85**, ring opens during the phase transfer conditions used to prepare the propellane. Unlike **85**, **94** proved to be stable under similar phase transfer conditions and could be ring opened in a more controlled manner. Ring opening with EtONa in EtOH yielded an unstable compound, but ^{13}C NMR indicated that the propellane had underwent the ring opening typical for *gem*-dihalocyclopropyl ethers. In a later attempt, the ring opened propellane **94** was hydrolyzed with 1 M HCl to give the diketone **96**.

Dibromo propellane **87** was prepared successfully in 4 steps with cyclooctanone as starting material. This propellane has previously been prepared by the Skattebøl research group. Former M.Sc. student Bjørn Erik Jønsberg reported that this compound underwent a reaction with *t*-BuOK in THF to give the monobromine **93**. This reaction was repeated, but the product previously reported could not be identified. Some additional future attempts should be made to try and confirm if this reaction works or not.

Because of time restraints, several reactions and reaction pathways were not pursued. The dibromopropellane **89** was not prepared and possible ring opening or other reactions for this compound were not investigated. Several additional reactions for the propellane **87** should also be investigated. For instance, the reaction with MeLi to give the corresponding monobromine and the ring opening with silver trifluoroacetate should be investigated further.

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 500 MHz ^{1}H NMR spectra and 125 MHz ^{13}C NMR spectra were recorded on a Bruker Avance 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), DMSO-d_6 (δ 39.51 ppm).

Dry flash chromatography (DFC) was carried out with a silica gel (Fluka: 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 a silica gel (Fluka: silica gel 60, particle size 0.040-0.063 mm (230-400 mesh)).

Thin layer chromatography (TLC) was carried out using silica gel plates from Fluka (silica gel/dc-alufolien-kieselgel with fluorescent indicator, production number 60778). The spots were detected with UV (extinction at λ=254 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)) or CER-MOP (molybdate phosphoric acid (5 g), cerium(IV)sulfate (2 g) and 98% sulfuric acid (16 mL) in water (180 mL)) and developed by heating with a heat gun until spots appeared.

Thin layer chromatography was generally used to monitor reactions. Workup was normally carried out when TLC indicated that all starting material had been consumed or that only traces remained.

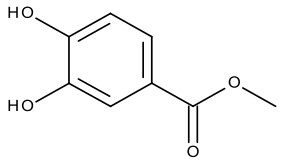
Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and were uncorrected. Infrared (IR) spectroscopy was performed on a Varian 1000 FT-IR spectrophotometer.

Nitrogen atmosphere was used in reactions that required dry conditions.

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

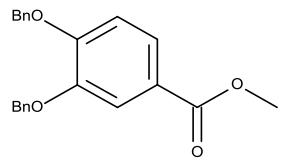
9.2 Synthesis of protected 3,4-dihydroxyacetophenone with 3,4-dihydroxybenzoic acid (47) as starting material

Methyl 3,4-dihydroxybenzoate (48); Method A: 3,4-Dihydroxybenzoic acid (**47**) (4.62 g, 30.0 mmol) was dissolved in methanol and conc. H_2SO_4 (1 mL) was added. The reaction mixture was refluxed overnight. Water (150 mL) was added. The aqueous phase was extracted with *tert*-butyl methyl ether (TBME) (3 x 50 mL). The combined organic phases were washed with water (3 x 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a white powder which was essentially pure. M.p.= 136-137 ^oC (137-139 ^oC).[36] Yield: 3.37 g (72%). R_f = 0.49 (ethyl acetate). IR (neat): ν 3466, 3261, 1686, 1609, 1522, 1448, 1411, 1292, 1268, 1239, 1185 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 9.62 (s br, 2 H), 7.41-7.34 (m, 2 H), 6.85 (d, *J* = 8.4 Hz, 1 H), *3*.79 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.3, 150.5, 145.2, 121.9, 120.6, 116.4, 115.4, 51.7.

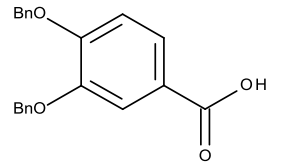


Method B: 3,4-Dihydroxybenzoic acid (**47**) (15.41 g, 100.0 mmol) was dissolved in methanol (150 mL) and $BF_3{\cdot}Et_2O$ (50 mL) was added drop wise to the mixture. The reaction mixture was refluxed overnight. The solvent was removed under vacuum to give pale brown powder. The crude product was recrystallized from chloroform to give a white powder. M.p.= 95-100 ^oC (137-139 ^oC)[36]. Yield: N.A.

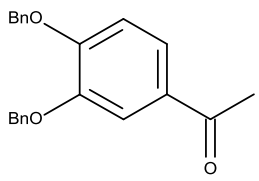
Methyl 3,4-dibenzyloxybenzoate (49); Methyl 3,4-dihydroxybenzoate (**48**) (2.52 g, 15.0 mmol) was dissolved in acetone (50 mL). Benzyl chloride (3.80 g, 3.45 mL, 30.0 mmol), K_2CO_3 (4.15 g, 30.0 mmol) and KI (catalytic amount) were added. The reaction mixture was refluxed overnight. When the mixture had cooled down, the suspended solid was filtered and washed with acetone. The filtrate was concentrated under reduced pressure to give yellow oil. The crude product was recrystallized from methylcyclohexane and ethyl acetate to give yellow crystals. M.p.= 61-62 ^oC (61-63 ^oC).[37] Yield: 3.40 g (65 %). R_f = 0.51 (30 % ethyl acetate in hexanes). IR (neat): ν 1713, 1595, 1510, 1460, 1436, 1420, 1385, 1337, 1294, 1263, 1206, 1139 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 7.64-7.31 (m, 12 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 5.18 (s, 2 H), 5.17 (s, 2 H), 3.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 152.8, 148.2, 136.7, 136.4, 128.5, 128.4, 127.9, 127.8, 127.3, 127.0, 123.9, 122.9, 115.3, 113.0, 71.0, 70.6, 51.9.



3,4-Dibenzyloxybenzoic acid (50); Methyl 3,4-dibenzyloxybenzoate (**49**) (4.18 g, 12.0 mmol) was dissolved in a mixture of methanol, ethanol and isopropanol (150 mL). Water (50 mL) and KOH (1.43 g, 21.7 mmol, 85%) were added. The reaction mixture was refluxed and monitored by TLC. After 24 hours, starting material was still present. Additional KOH (1.00 g, 15.2 mmol, 85%) was added. The reaction mixture continued refluxing until all starting material had been consumed (additional 24 hours). The reaction mixture was cooled and the pH was adjusted to 2 (6 M HCl). The precipitate formed during acidification was filtrated and washed with water. The crude product was recrystallized from methanol to give white crystals. M.p. = 186-188 ^oC (187-188 ^oC).[38] Yield: 1.2 g (30%). R_f = 0.29 (50 % ethyl acetate in hexanes). IR (neat): ν 1676, 1600, 1520, 1440, 1384, 1347, 1305, 1275, 1224, 1124 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 7.61-7.32 (m, 12 H), 7.16 (d, *J* = 7.8 Hz), 5.19 (s, 2 H), 5.22 (s, 2 H); ^{13}C NMR

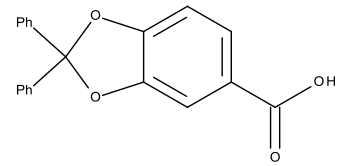


(75 MHz, DMSO-d_6): δ 167.1, 152.2, 147.7, 137.1, 136.8, 128.5, 128.5, 128.0, 127.9, 127.6, 127.5, 123.6, 123.4, 114.6, 113.1, 70.1, 69.9.

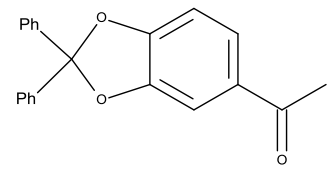


3,4-Dibenzyloxyacetophenone (9); 3,4-Dibenzyloxybenzoic acid (**50**) (1.00 g, 3.0 mmol) was dissolved in dry 1,2-dimethoxyethane (DME) (50 mL) under nitrogen atmosphere. Methyllithium (4.4 mL, 6.6 mmol, 1.5 M) was slowly added and the reaction mixture was stirred at room temperature. After 2 hours TLC indicated that all starting material had been consumed. Water (100 mL) was added and the solution was extracted with TBME (4 x 40 mL). The combined organic phases were washed with water (5 x 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a yellow solid. The crude product was recrystallized from methylcyclohexane to give yellow crystals. M.p. = 70-75 ^oC (89 ^oC).[39] Yield: 0.66 g (66 %). R_f = 0.59 (50 % ethyl acetate in hexanes) IR (neat): ν 1667, 1588, 1512, 1454, 1426, 1383, 1355, 1266, 1216, 1145 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 7.60-7.28 (m, 12 H), 6.91 (d, *J* = 8.10 Hz, 1 H), 5.21 (s, 2 H), 5.19 (s, 2 H), 2.49 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.6, 153.0, 148.5, 136.7, 136.4, 130.6, 128.5, 128.4, 127.9, 127.8, 127.3, 127.0, 123.4, 113.5, 112.7, 71.0, 70.7, 26.2.

3,4-Diphenylmethylenedioxybenzoic acid (51); 3,4-Dihydroxybenzoic acid (**47**) (7.71 g, 50.0 mmol) was dissolved in toluene (100 mL) and α,α-dichlorodiphenylmethane (11.86 g, 50.0 mmol) was added. The reaction mixture was refluxed and monitored by TLC. The next day, starting material was still present. The reaction was cooled and toluene (100 mL) was added to better dissolve the reagents. The reaction mixture was refluxed for an additional 48 hours. Starting material was still present. The solvent was removed under reduced pressure. The crude product was purified by DFC (Silica gel, 20-40 % ethyl acetate in hexanes) and recrystallized twice from methylcyclohexane and ethyl acetate to give white crystals. M.p. = 180-182 ^oC. Yield: 1.22 g (8 %). R_f = 0.40 (50 % ethyl acetate in hexanes) IR (neat): ν 1677, 1620, 1600, 1494, 1448, 1412, 1360, 1286, 1261, 1198 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 12.85 (s br, 1 H), 7.64 (d, *J* = 8.3 Hz, 1 H), 7.56-7.54 (m, 5 H), 7.44-7.38 (m, 6 H), 7.12 (d, *J* = 8.2 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.8, 150.4, 146.9, 139.5, 129.7, 128.8, 126.1, 125.6, 125.5, 117.6, 109.6, 108.8.

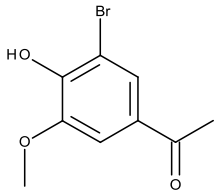


3,4-Diphenylmethylenedioxyacetophenone (13); 3,4-Diphenylmethylenedioxybenzoic acid (**51**) (0.96 g, 3.0 mmol) was dissolved in dry DME (50 mL) under nitrogen atmosphere. Methyllithium (4.4 mL, 6.6 mmol, 1.5 M) was added slowly and the reaction mixture was stirred at room temperature. After 2 hours TLC indicated that all the starting material had been consumed. Water (100 mL) was added and the solution was extracted with TBME (4 x 30 mL). The combined organic phases were washed with water (3 x 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give yellow oil. The crude product was purified by flash chromatography (Silica gel, 15 % ethyl acetate in hexanes) to give white crystals. M.p. = 87-89 ^oC. Yield: 0.33 g (35 %). R_f = 0.20 (15 % ethyl acetate in hexanes) IR (neat): ν 1681, 1616, 1492, 1433, 1363, 1259, 1215, 1181 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57-7.51 (m, 6 H), 7.37-7.34 (m, 6 H), 6.88 (d, *J* = 8.1 Hz, 1 H), 2.48 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.0, 151.1, 147.6, 139.5, 132.0, 129.2, 128.2, 126.1, 124.6, 118.0, 108.1, 107.9, 26.3.

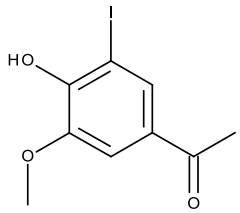


9.3 Synthesis of various acetophenones using the Ullmann-type coupling pathway

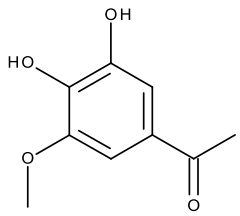
3-Bromo-4-hydroxy-5-methoxyacetophenone (54); Acetovanillone (**29**) (6.65 g, 40.0 mmol) was dissolved in 100% acetic acid (114 mL) and potassium acetate (20 g) was added. Br_2 (2.1 mL, 6.39 g, 40.0 mmol) was added slowly and the reaction mixture was stirred overnight. Water (200 mL) was added and the solution was extracted with ethyl acetate (3 x 75 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 to give a brown solid. The crude product was recrystallized from methylcyclohexane and ethyl acetate to give light brown crystals. M.p. = 156-157 ^oC (157-158 ^oC).[13] Yield: 6.78 g (69 %). R_f = 0.46 (50 % ethyl acetate in hexanes) IR (neat): ν 3269, 3005, 1740, 1668, 1562, 1504, 1466, 1414, 1365, 1299, 1213, 1130 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 10.42 (s, 1 H), 7.70 (s, 1 H), 7.40 (s, 1 H), 3.85 (s, 3 H), 2.48 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 195.5, 148.5, 148.0, 129.2, 126.1, 110.0, 108.9, 56.3, 26.4.



4-Hydroxy-3-iodo-5-methoxyacetophenone (34); Acetovanillone (**29**) (3.32 g, 20.0 mmol) was suspended in water (60 mL) and $NaHCO_3$ (1.06 g, 12.6 mmol) was added. The mixture was heated to 90 ^oC and a solution of I_2 (5.08 g, 20.0 mmol) and KI (5.68 g, 34.2 mmol) in water (60 mL) was added drop wise under vigorous stirring. The reaction mixture was stirred at 90 ^oC overnight. To the hot solution, a minimum amount of $Na_2S_2O_3$ (saturated solution) was added until the mixture was decolorized. The mixture was filtered while still hot and washed with water. The residue was recrystallized from methylcyclohexane and ethyl acetate to give brown crystals. M.p. = 174-176 ^oC (Lit. 172-174 ^oC).[25] Yield: 2.04 g (35 %). R_f = 0.45 (50 % ethyl acetate in hexanes) IR (neat): ν 3297, 3080 3009, 1663, 1565, 1496, 1463, 1410, 1362, 1292, 1251, 1210, 1185 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 10.49 (s, 1 H), 7.89 (s, 1 H), 7.44 (s, 1 H), 3.87 (s, 3 H), 2.50 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 195.3, 150.9, 146.7, 131.9, 130.2, 110.8, 84.0, 56.2, 26.4.

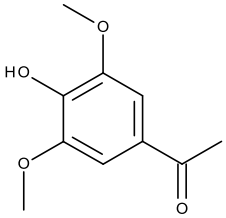


3,4-Dihydroxy-5-methoxyacetophenone (2); Method A: 3-Bromo-4-hydroxy-5-methoxyacetophenone (**54**) (1.47 g, 6.00 mmol) was suspended in water (40 mL). NaOH (2.24 g, 56.0 mmol) and copper powder (6 mg) were added. The reaction mixture was stirred at 140 ^oC overnight. TLC indicated unreacted starting material and additional copper powder (20 mg) was added. The reaction mixture was stirred at 140 ^oC for additional 24 hours. TLC then indicated that almost all starting material had been consumed. The pH was adjusted to 1 (6 M HCl). Ethyl acetate (50 mL) was added and the mixture was pulled through a layer of celite. The celite layer was washed with ethyl acetate (50 mL). The phases were separated and the water phase was extracted with ethyl acetate (3 x 40 mL). The combined organic phases were washed with water (2 x 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (Silica gel, 45 % ethyl acetate in hexanes) to give a white powder. M.p. = 159-160 ^oC (Lit. 159-160 ^oC).[12] Yield: 0.37 g (34 %). R_f = 0.31 (50 % ethyl acetate in hexanes) IR (neat): ν 3446, 3286, 2922, 2853, 1651, 1589, 1521, 1455, 1347, 1298, 1264, 1230, 1180 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 9.34 (s, 2 H), 7.17 (s, 1 H), 7.13 (s, 1 H), 3.88 (s, 3 H), 2.53 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.3, 148.0, 145.3, 139.7, 127.6, 110.1, 103.9, 56.0, 26.3.

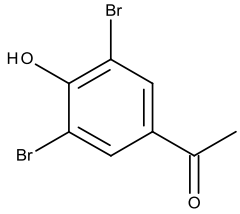


Method B: The same procedure as described in method A were used, except with 4-hydroxy-3-iodo-5-methoxyacetophenone (**34**) (1.75 g, 6.00 mmol) instead of 3-bromo-4-hydroxy-5-methoxyacetophenone (**54**). Yield: 0.33 g (30 %). Melting point, R_f value and spectroscopic values were in accordance with previous results.

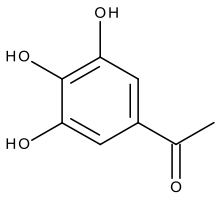
3,5-Dimethoxy-4-hydroxyacetophenone (1); 4-hydroxy-3-iodo-5-methoxyacetophenone (**34**) (1.02 g, 3.50 mmol) was dissolved in DMF (15 mL) and MeOH (15 mL). NaOMe (945 mg, 17.50 mmol) and CuI (catalytic amount) were added and the mixture was stirred at 110 ^oC overnight. TLC indicated unreacted starting material. Additional NaOMe (945 mg, 17.50 mmol) and CuI (catalytic amount) were added. The next day, all starting material had been consumed. The mixture was acidified (12 M HCl). Water (40 mL) was added and the solution was extracted with ethyl acetate (4 x 40 mL). The combined organic phases were washed with water (3 x 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (Silica gel, 45 % ethyl acetate in hexanes) to give a pale yellow powder. M.p. = 117-125 ^oC (Lit. 124-127 ^oC).[40] Yield: 0.41 g (60 %). R_f = 0.24 (50% ethyl acetate in hexanes) IR (neat): ν 3362, 1738, 1663, 1603, 1573, 1518, 1463, 1419, 1354, 1330, 1280, 1255, 1184 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 7.26 (s, 2 H), 3.86 (s, 6 H), 2.56 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.3, 147.5, 140.9, 127.4, 106.2, 56.1, 26.3.



3,5-Dibromo-4-hydroxyacetophenone (56); 4-Hydroxyacetophenone (**55**) (3.50 g, 25.71 mmol) was dissolved in acetic acid (86 mL, 100%) and potassium acetate (15 g) was added. Br_2 (2.65 mL, 8.22 g, 51.42 mmol) was carefully added and the mixture was stirred for 1 hour. Water (200 mL) was added and the solution was extracted with TBME (3 x 60 mL). The combined organic phases were washed with water (5 x 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give light brown crystals. M.p. = 183-185 ^oC (Lit. 181 ^oC).[24] Yield: 5.95 g (78 %). R_f = 0.53 (40 % ethyl acetate in hexanes) IR (neat): ν 3150, 1662, 1581, 1544, 1479, 1425, 1398, 1361, 1301, 1257, 1234, 1136 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.03 (s, 2 H), 2.50 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 194.6, 155.0, 132.6, 130.9, 111.5, 26.5.

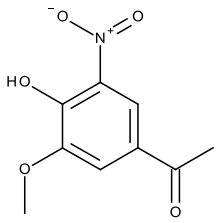


3,4,5-Trihydroxyacetophenone (3); 3,5-Dibromo-4-hydroxyacetophenone (**56**) (1,76 g, 6.00 mmol) was mixed with water (40 mL). NaOH (2.48 g, 62.0 mmol) and copper powder (200 mg) were added. The reaction mixture was stirred at 140 ^oC for 72 hours. The pH was adjusted to 3 (6 M HCl). Ethyl acetate (40 mL) was added and the mixture was pulled through a layer of celite. The celite layer was washed with ethyl acetate (40 mL). The phases were separated and the water phase was extracted with ethyl acetate (4 x 40 mL). The combined organic phases were washed with water (1 x 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (Silica gel, 50 % ethyl acetate in hexanes) to give yellow powder. M.p. = 183-184 ^oC. Yield: 0.26 g (25 %). R_f = 0.18 (50 % ethyl acetate in hexanes) IR (neat): ν 3370, 3132, 1738, 1639, 1593, 1552, 1471, 1330, 1258, 1219, 1079 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 9.22 (s, 3 H), 6.97 (s, 2 H), 2.42 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.4, 145.6, 138.8, 127.8, 107.9, 26.3.

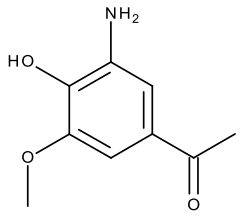


9.4 Synthesis of 3,4-dihydroxy-5-mehoxyacetophenone (2) from acetovanillone (29) using the diazonium ion pathway.

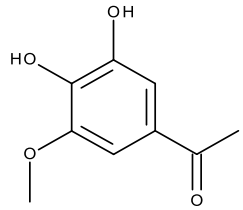
4-Hydroxy-3-methoxy-5-nitroacetophenone (52); Acetovanillone (**29**) (9.97 g, 60.0 mmol) was suspended in water (16 mL) and the mixture was cooled by an ice bath. 65% HNO_3 (16 mL, 233 mmol) was slowly added under vigorous stirring. The reaction mixture was kept in ice bath for 30 minutes. The suspended solid was filtered, washed with water and recrystallized from methanol and ethyl acetate to give yellow crystals. M.p. = 161-163 ^oC (163-164 ^oC).[41] Yield: 11.60 g (46 %). R_f = 0.27 (50 % ethyl acetate in hexanes) IR (neat): ν 3250, 3105, 1678, 1611, 1536, 1468, 1413, 1386, 1334, 1285, 1247, 1219, 1182 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 8.05 (m, 1 H), 7.64 (m, 1 H), 3.98 (s, 3 H), 2.59 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 195.2, 149.4, 146.5, 136.6, 127.1, 117.7, 113.5, 56.7, 26.2.



3-Amino-4-hydroxy-5-methoxyacetophenone (53); 4-Hydroxy-3-methoxy-5-nitroacetophenone (**52**) (2.11 g, 10.0 mmol) was dissolved in ethyl acetate (100 mL) and Pd/C (150 mg) was added under nitrogen atmosphere. The atmosphere was switched to hydrogen by the use of a balloon. The reaction mixture was stirred at room temperature under a mild hydrogen pressure overnight. The suspended Pd/C was filtrated and the filtrate was concentrated under reduced pressure to give a brown powder which was essentially pure. M.p. = 119-121 ^oC. Yield: 1.40 g (77 %). R_f = 0.28 (50 % ethyl acetate in hexanes) IR (neat): ν 3439, 3365, 3002, 2945, 1725, 1665, 1603, 1581, 1518, 1453, 1339, 1294, 1257, 1228, 1186 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6): δ 7.02 (s, 1 H), 6.89 (s, 1 H), 3.81 (s, 3 H), 2.45 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.7, 147.1, 137.6, 136.9, 128.3, 109.2, 101.1, 55.9, 26.3.

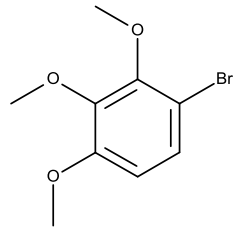


3,4-dihydroxy-5-methoxyacetophenone (2); 3-Amino-4-hydroxy-5-methoxyacetophenone (**53**) (1.09 g, 6.00 mmol) was dissolved in acetic acid (12 mL, 100%), HCl (2 mL, 12 M) and H_2O (6 mL). The mixture was placed in ice bath and an aqueous solution of $NaNO_2$ (6 mL, 9 mmol, 1.5 M) was added under vigorous stirring. The mixture was stirred in ice bath for 30 minutes. Urea (174 mg, 3 mmol) was added and the mixture was slowly added to a solution of 10% H_2SO_4 (20 mL) which had been preheated to 100 ^oC. The reaction mixture was stirred at 100 ^oC for 1 hour. Water (80 mL) was added and the solution was extracted with ethyl acetate (4 x 40 mL). The combined organic phases were washed with water (5 x 10 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (Silica gel, 40-50 % ethyl acetate in hexanes) to give a brown solid. Yield: 0.15 g (14 %). Melting point, R_f value and spectroscopic values were in accordance with previous results.

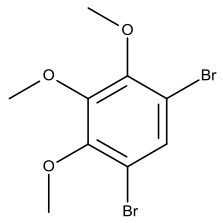


9.5 Compounds prepared in attempts to prepare acetophenones by a Friedel-Crafts approach

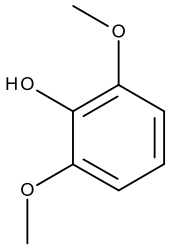
1-Bromo-2,3,4-trimethoxybenzene (60); 1,2,3-Trimethoxybenzene (**59**) (1.68 g, 10.0 mmol) was dissolved in MeCN (50 mL) and NBS (1.96 g, 11 mmol) was added. The reaction mixture was stirred at room temperature overnight. Water (150 mL) was added and the solution was extracted with TBME (3 x 50 mL). The combined organic phases were washed with HCl (1 M) (2 x 20 mL), water (2 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give pale brown oil. Yield: 2.00 g (81%). R_f = 0.31 (40% ethyl acetate in hexanes) IR (neat): ν 2938, 1575, 1477, 1460, 1430, 1409, 1294, 1269, 1236, 1218, 1174, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.7 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.84 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2, 150.8, 143.4, 126.6, 108.5, 108.2, 61.0, 60.9, 56.0.



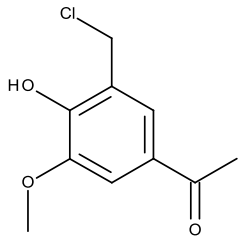
1,5-diBromo-2,3,4-trimethoxybenzene (61); 1,2,3-Trimethoxybenzene (**59**) (8.41 g, 50.0 mmol) was dissolved in MeCN (200 mL) and NBS (19.58 g, 110 mmol) was added. The reaction mixture was refluxed overnight. Water (150 mL) was added and the solution was extracted with TBME (3 x 75 mL). The combined organic phases were washed with HCl (1 M) (2 x 25 mL), water (4 x 25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give brown oil. Yield: 14.06 g (86%). R_f = 0.57 (30% ethyl acetate in hexanes) IR (neat): ν 2938, 1457, 1396, 1271, 1216, 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (s, 1 H), 3.93 (s, 3 H), 3.89 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.9, 148.3, 129.7, 112.3, 61.3, 61.0.



2,6-dimethoxyphenol (36); 1,2,3-Trimethoxybenzene (**59**) (8.41 g, 50.0 mmol) was dissolved in DCM (200 mL) and $AlCl_3$ (20.00 g, 150.0 mmol) was added. The reaction was stirred at room temperature overnight. The reaction mixture was cooled by an ice bath before careful addition of water (200 mL). The pH was adjusted to 0-1 (12 M HCl) and the phases were separated. The aqueous solution was extracted with DCM (3 x 75 mL). The combined organic phases were washed with water (3 x 25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give brown oil, which later solidified to give a brown solid. M.p. = 47-50 ^oC (50-57 ^oC).[40] Yield: 6.78 g (88%). R_f = 0.33 (40% ethyl acetate in hexanes) IR (neat): ν 3489, 3455, 2961, 2939, 2839, 1612, 1508, 1479, 1458, 1443, 1361, 1282, 1237, 1210, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.78 (t, *J* = 8.4 Hz, 1 H), 6.56 (d, *J* = 8.4 Hz, 1 H), 5.64 (s, 1 H), 3.85 (s, 6 H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.0, 134.6, 118.8, 104.7, 56.0.



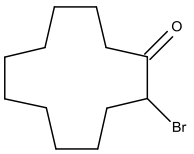
9.6 Compounds prepared in attempts at formylation of acetovanillone (29)



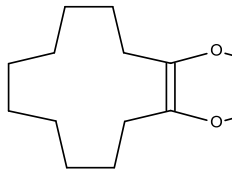
3-Chloromethyl-4-hydroxy-5-methoxyacetophenone (66); Acetovanillone (**29**) (4.99 g, 30.0 mmol) was dissolved in HCl (30 mL, 12 M) and paraformaldehyde (1.45 g, 45 mmol) was added. The mixture was stirred at room temperature for 72 hours. Water (200 mL) was added and the mixture was filtered. The residue was partly dissolved in Et_2O (100 mL), filtered and washed with additional Et_2O (100 mL). The filtrate was concentrated under reduced pressure to give a purple solid. The crude product was recrystallized from methylcyclohexane and ethyl acetate with charcoal to give pale pink crystals. M.p. = 111-115 ^oC (117-119 ^oC).[13] Yield: 2.90 g (45%). R_f = 0.27 (50% ethyl acetate in hexanes) IR (neat): ν 3311, 1664, 1595, 1506, 1424, 1353, 1306, 1281, 1222, 1185, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (s, 1 H), 7.30 (s, 1 H), 6.45 (s, 1 H), 4.51 (s, 2 H), 3.74 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.5, 148.4, 146.6, 129.5, 124.7, 109.6, 56.2, 40.4, 26.1.

9.7 Synthesis and ring opening of selected strained *gem*-dihalocyclopropyl ethers

2-Bromocyclododecanone (80); TsOH (19.02 g, 100.0 mmol) dissolved in MeCN (150 mL) was added drop wise to a stirred solution of cyclododecanone (**79**) (18.23 g, 100.0 mmol) and NBS (19.58 g, 110.0 mmol) in DME (150 mL). The mixture was stirred overnight. Water (200 mL) was added and the solution was extracted with PE (3 x 75 mL). The combined organic phases were washed with water (4 x 25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give pale brown oil which later solidified to give a white solid which was sufficiently pure for further synthetic use. Yield: 24.0 g (92 %). R_f = 0.60 (20% ethyl acetate in hexanes). Spectroscopic values were in accordance with previous results.[42] [43]



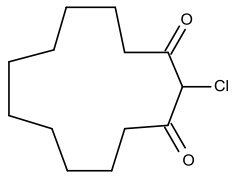
$\Delta^{1(12)}$-13,16-Dioxabicyclo[10.4.0]hexadecene (72); 2-Bromocyclododecanone (**80**) (13.06 g, 50.0 mmol) was dissolved in DMF (25 mL) and ethylene glycol (25 mL) and TsOH (catalatytical amount) was added. The mixture was stirred at 140 ^oC overnight. The next day a small amount of $NaHCO_3$ and water (200 mL) was added and the solution was extracted with PE (3 x 75 mL). The combined organic phases were washed with water (6 x 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by DFC (Silica gel, 5 % ethyl acetate in hexanes) to give yellow crystals. M.p. = 38-40 ^oC. Yield: 5.75 g (51%). R_f = 0.53 (10% ethyl acetate in hexanes) IR (neat): 2926, 2861, 1708, 1685, 1467, 1443, 1275, 1238, 1204, 1171, 1107, 1094 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 4 H), 2.12 (t, *J* = 6.9 Hz, 4 H), 1.60-1.52 (m, 4 H), 1.37-1.26 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.1, 64.2, 26.2, 24.7, 24.3, 24.2, 22.3.



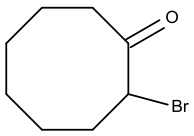
17,17-Dichloro-13,16-dioxa[10.4.1]propellane (94); 72 (2.40 g, 10.7 mmol) was dissolved in DCM (50 mL). $CHCl_3$ (2.6 mL, 32.1 mmol), ethanol (2 mL) and TEBA (catalytic amount) were added. The mixture was placed in an ice bath. The mixture was vigorously stirred by mechanical stirring and an

aqueous solution of NaOH (191 mmol, 10 mL, 19.1 M) was added drop wise. The mixture was stirred overnight. Water (100 mL) was added and the solution was extracted with Et_2O (4 x 50 mL). The combined organic phases were washed with water (3 x 15 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give orange oil. The crude product was recrystallized from methanol to give colorless crystals. M.p. = 59-62 ^oC. Yield: 1.99 g (61%). R_f = 0.46 (10% ethyl acetate in hexanes) IR (neat): ν 2928, 2859, 1469, 1442, 1176, 1152, 1138, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.02-3.93 (m, 2 H), 3.70-3.61 (m, 2 H), 1.99-1.79 (m, 4 H), 1.70-1.26 (m, 16 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.2, 65.0, 63.4, 29.0, 27.4, 27.3, 23.6, 22.0.

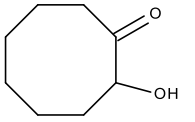
2-Chlorocyclotridecane-1,3-dione (96); Na(s) (70 mg, 3.0 mmol) was mixed with ethanol (25 mL, 100%) under nitrogen atmosphere. When all Na(s) had been consumed, propellane **94** (610 mg, 2.0 mmol) was added and the reaction mixture was refluxed overnight. TLC indicated that all starting material had been consumed. The reaction mixture was cooled with an ice bath and 1 M HCl (10 ml) was added. After 15 minutes the ice bath was removed. After additional 15 minutes, a white precipitate was formed. Water (10 mL) was added and the solution was filtered. The precipitate was washed with water. The crude product was recrystallized from methanol and water to give white crystals. M.p. = 55-57 ^oC. Yield: 220 mg (45%). R_f = 0.44 (5% ethyl acetate in hexanes) IR (neat): ν 2926, 2858, 1703, 1199, 1149, 1112, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.94 (s, 1 H), 2.88-78 (m, 2 H), 2.68-2.59 (m, 2 H), 1.75-1.67 (m, 4 H), 1.29-1.19 (m, 8 H), 1.05-1.00 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.3, 71.5, 37.3, 25.9, 25.2, 24.2, 21.1.



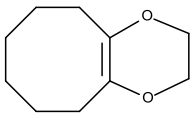
2-Bromocyclooctanone (84); TsOH (19.02 g, 100.0 mmol) dissolved in MeCN (150 mL) was added drop wise to a stirred solution of cyclooctanone (**83**) (12.62 g, 100.0 mmol) and NBS (19.58 g, 110.0 mmol) in DME (150 mL). The mixture was stirred overnight. Water (200 mL) was added and the solution was extracted with PE (3 x 75 mL). The combined organic phases were washed with water (4 x 20 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give orange oil which was sufficiently pure for further synthetic use. Yield: 16.76 g (82 %). R_f = 0.65 (25% ethyl acetate in hexanes). Spectroscopic values were in accordance with previous results.[44]



2-Hydroxycyclooctanone (74); 2-Bromocyclooctanone (**84**) (8.20 g, 40.0 mmol) was dissolved in DMF (100 mL) and H_2O (100 mL). The mixture was stirred at 140 ^oC for 72 hours. The solution was extracted with TBME (4 x 75 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 to give orange oil which was sufficiently pure for further synthetic use. Yield: 3.80 g (67%). R_f = 0.27 (25% ethyl acetate in hexanes). Spectroscopic values were in accordance with previous results.[45]

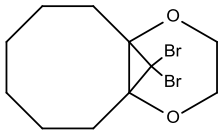


$\Delta^{1(8)}$-9,12-Dioxabicyclo[6.4.0]dodecene (75); 2-Hydroxyacetophenone (**74**) (7.04 g, 50.0 mmol) was dissolved in toluene (200 mL) and ethylene glycol (3.62 mL, 65 mmol) and TsOH (catalytic amount) were added. The mixture was refluxed in a Dean-Stark apparatus overnight. The solvent was removed under reduced pressure and the crude product was purified by DFC (Silica gel, 5 % ethyl acetate in hexanes) to give a pale orange oil. Yield: 4.71 g



(56%). R_f = 0.57 (25% ethyl acetate in hexanes) IR (neat): ν 2922, 2852, 1699, 1448, 1276, 1249, 1202, 1178, 1138, 1125, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.00 (s, 4 H), 2.17-2.13 (m, 4 H), 1.60-1.53 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.2, 64.5, 29.1, 29.0, 26.5.

13,13-Dibromo-9,12-dioxa[6.4.1]propellane (87); 75 was dissolved in PE (50 mL) and t-BuOK (13.46 g. 120.0 mmol) was added. The mixture was cooled to -50 ^oC by a dry-ice-methanol bath. A mixture of $CHBr_3$ (10.5 mL 120 mmol) and PE (10.5 mL) was carefully added under vigorous stirring over the course of 1 hour. The mixture was kept at -50 ^oC for an additional 2 hours and then allowed to come to room temperature while stirred overnight. The suspended solid was filtered and washed with PE. The filtrate was concentrated under reduced pressure and purified by flash chromatography (Silica gel, 10% ethyl acetate in hexanes) to give a brown oil which was sufficiently pure for further synthetic use. Yield: 2.44 g (60%). R_f = 0.37 (10% ethyl acetate in hexanes) Spectroscopic values were in accordance with previous results.[46]

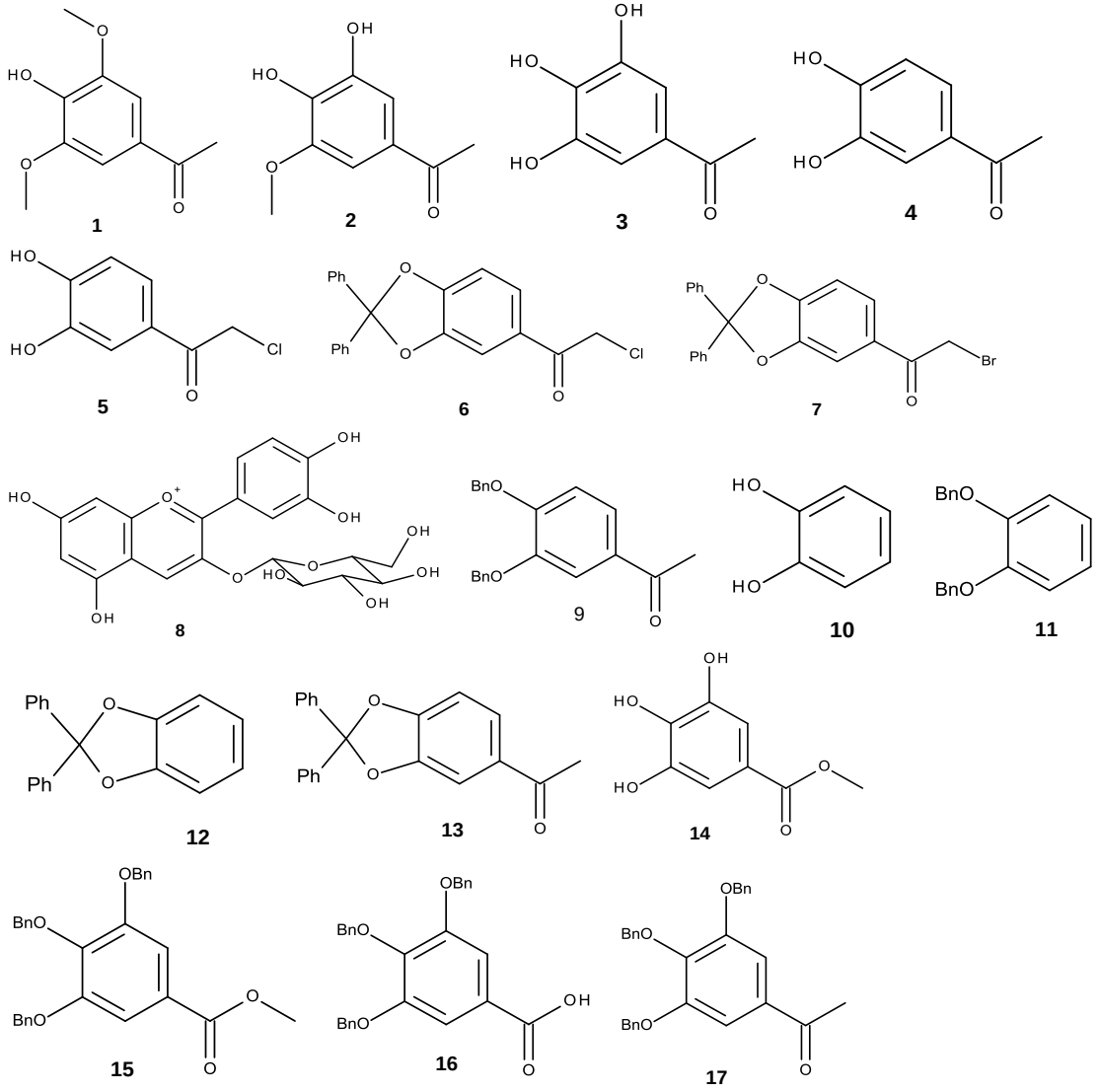


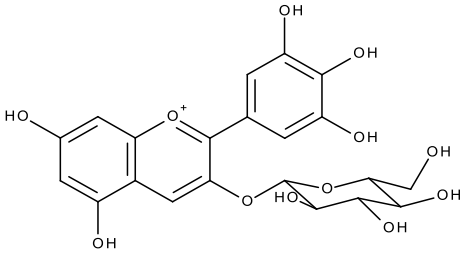
Abbreviations

Ac	Acetyl
Bn	Benzyl
Bu	Butyl
CRP	C-reactive protein
CTEA	Cetyltriethylammonium chloride
CVD	Cardiovascular disease
Cy 3-glc	Cyanidin 3-*O*-β-D-glucopyranoside chloride
DCM	Dichloromethane
DFC	Dry flash chromatography
DMAP	4-Dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	Dimethyl formamide
DMSO	dimethyl sulfoxide
DMSO-d_6	dimethyl sulfoxide-d_6
DNA	Deoxyribonucleic acid
Dp 3-glc	Delphinidin 3-*O*-β-D-glucopyranoside chloride
Et	Ethyl
FC	Flash chromatography
HMTA	Hexamethylenetetramine
IR	Infrared
Me	Methyl
MOP	Molybdate phosphoric acid
Mv 3-glc	Malvidin 3-*O*-β-D-glucopyranoside chloride
NBS	*N*-Bromosuccinimide
NF- κB	nuclear factor-κB
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
PE	Petroleum ether
Pg	Protecting group

Ph	Phenyl
Pn 3-glc	Peonidin 3-*O*-β-D-glucopyranoside chloride
Pg 3-glc	Pelargonidin 3-*O*-β-D-glucopyranoside chloride
Pt 3-glc	Petunidin 3-*O*-β-D-glucopyranoside chloride
t-Bu	*tert*-butyl
TBME	*tert*-butyl methyl ether
TEBA	benzyltriethylammonium chloride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	tetramethylsilane
TsOH	*p*-Toluenesulfonic acid
UV	Ultraviolet
UV-B	Ultraviolet B

Compounds





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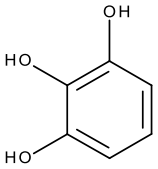

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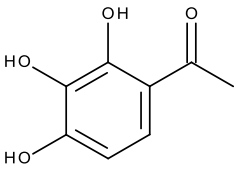

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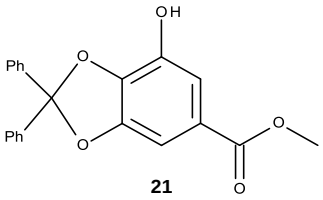

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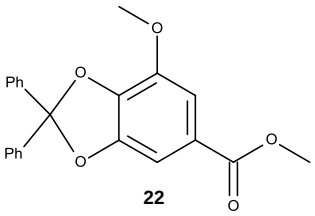

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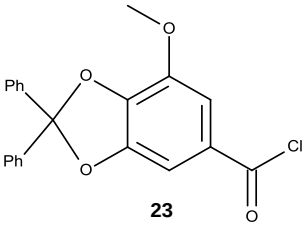

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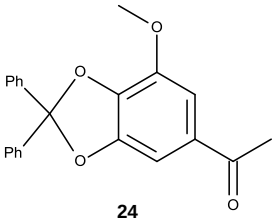

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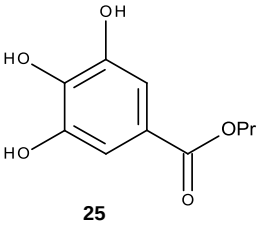

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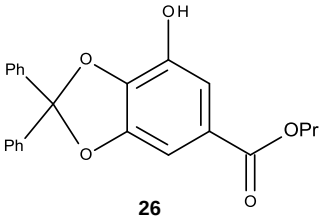

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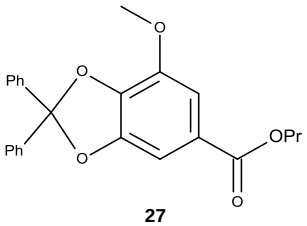

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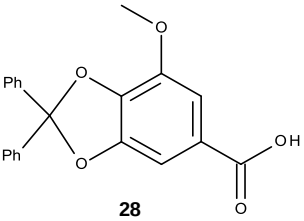

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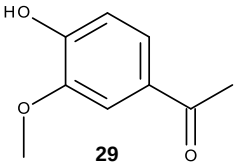

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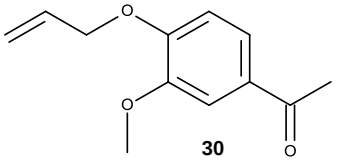

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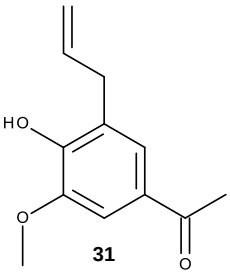

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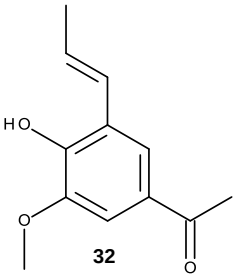

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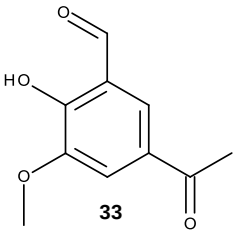

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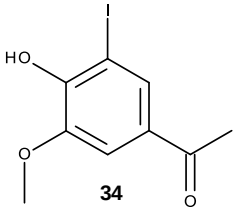

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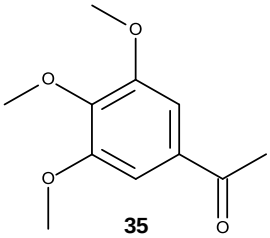

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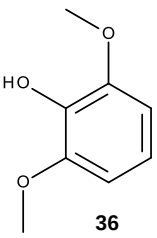

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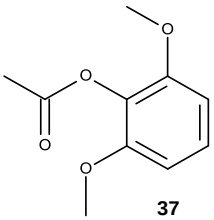

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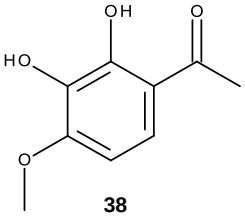

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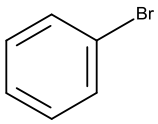

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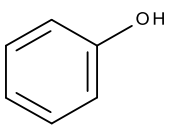

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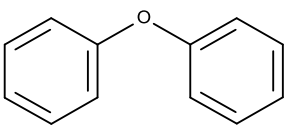

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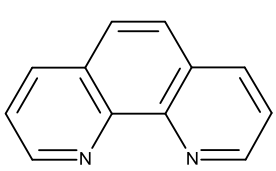

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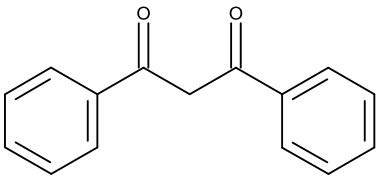

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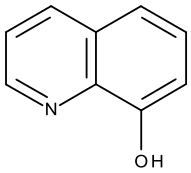

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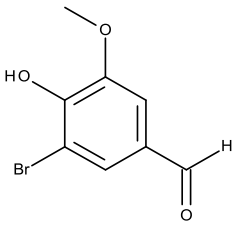

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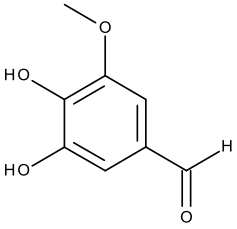

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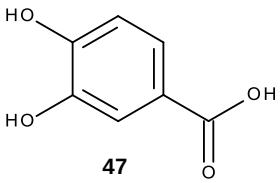

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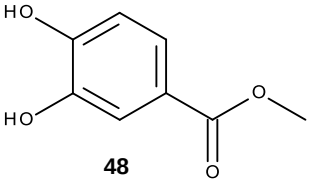

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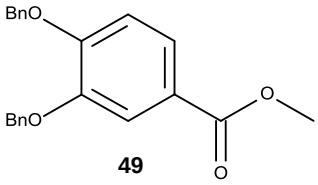

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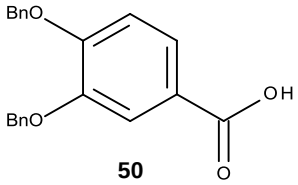

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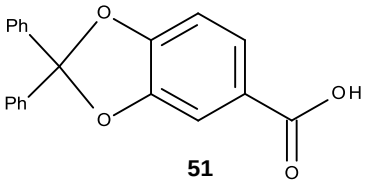

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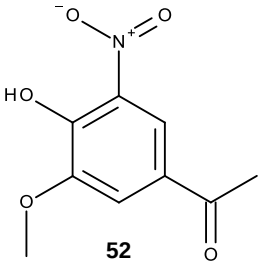

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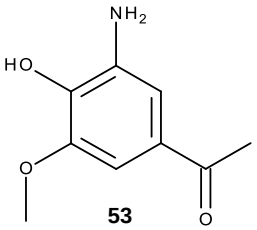

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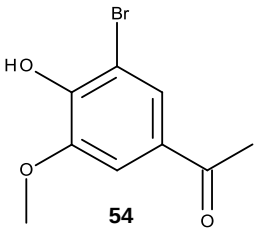

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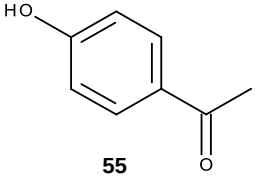

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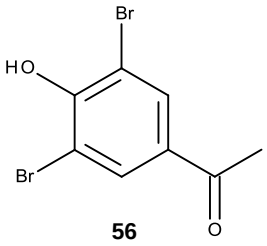

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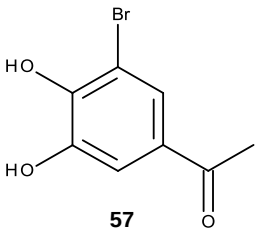

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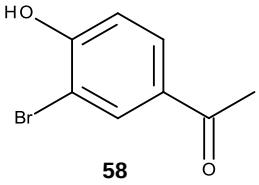

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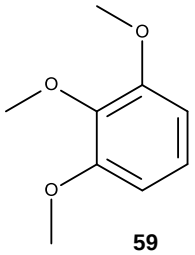

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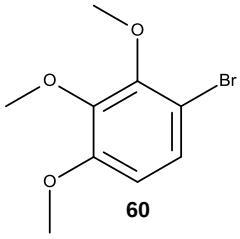

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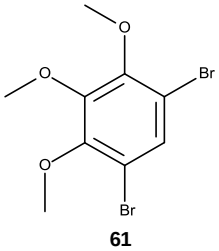

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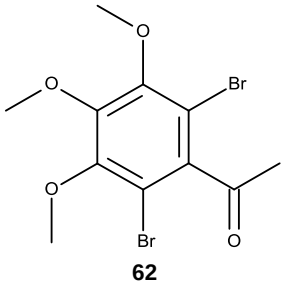

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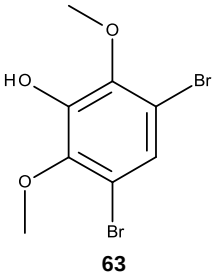

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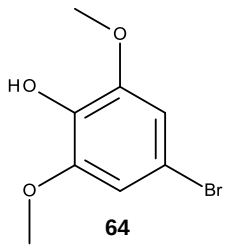

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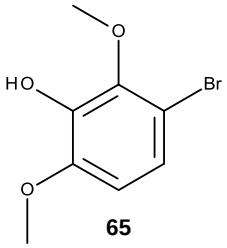

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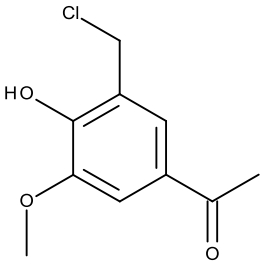

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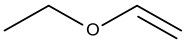

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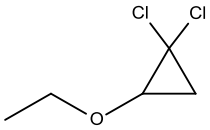

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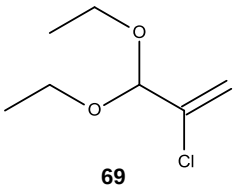

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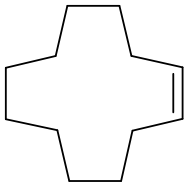

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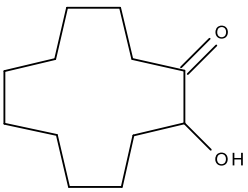

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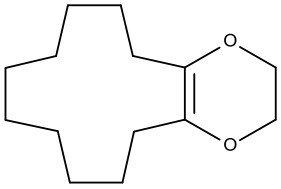

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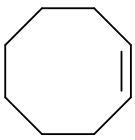

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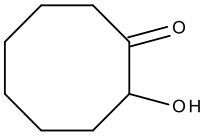

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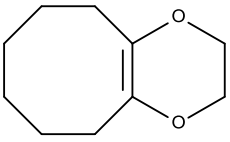

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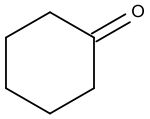

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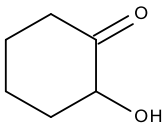

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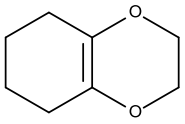

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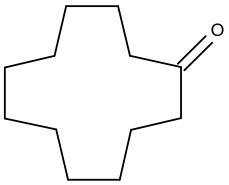

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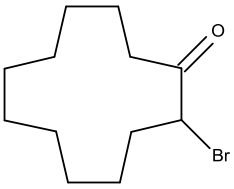

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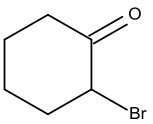

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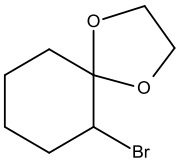

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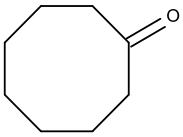

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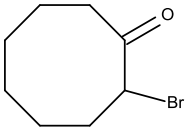

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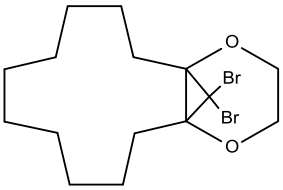

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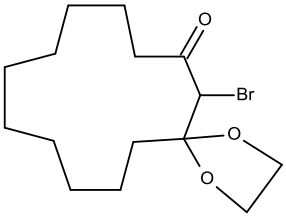

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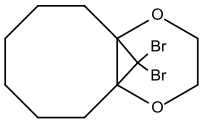

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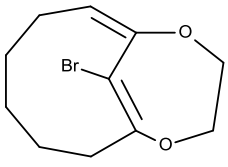

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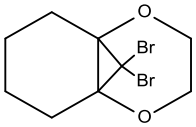

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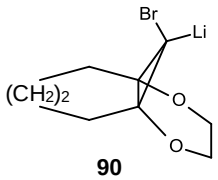

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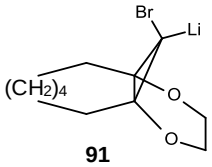

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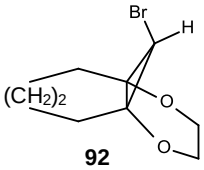

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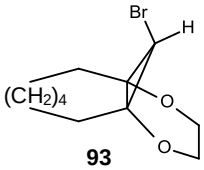

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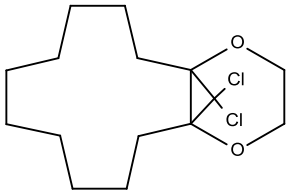

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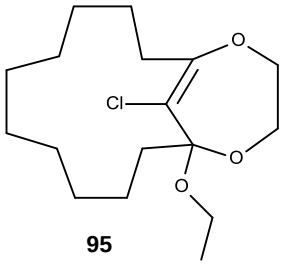

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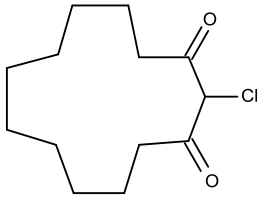

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