KJE-3900

Master's Thesis

in Organic Chemistry

On the synthesis of pyrylium salts

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May, 2009

Faculty of Science
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Abstract

The present work is on the synthesis of a pyrylium salt, 8-hydroxy-2,4-diphenyl-5,6,7,8-tetrahydrochromenylium tetrafluoroborate, a precursor for interesting transition metal ligands. Different routes are presented with the aim of making an affordable precursor for the variety of syntheses possible from these versatile pyrylium salts. New findings include a preparative non optimized 2-hydroxy – cyclohexanone synthesis. It includes high resolution measurements not found in literature for several substrates.

Keywords

Triphenylpyrilium, 8-oxo-2,4-diphenyl-5,6,7,8- tetrahydrobenzopyrylium tetrafluoroborate, Ichiis reagent, CBS reductions, oxygen insertions, DIBAL reductions, singlet oxygen, Magtrieve™ oxidation, Oxone™ oxidations, manganese oxidation, Oppenauer and Meerwein Schmidt Ponndorf Verley transfer hydrogenations.

Aim of master thesis

Bidentate ligands with nitrogen and phosphorous functionalities that coordinate the transition metal iridium are employed in hydrogenating alkenes and imines. *N,P* ligands are utilized in an important class of catalysts that are able to hydrogenate tertiary alkenes and imines without adjacent functionality. The first *N,P* catalyst was developed by the French graduate student George Morris and Robert Crabtree in the 1970s. Since then, Pfaltzs group in Switzerland among many others has tweaked the properties and geometry of these *N,P* ligands[1]. In 2006 Christian Mũller[2] made a hydroxy-functionalized pyrylium salt that was converted into phosphine. This salt was coordinated with rhodium, and was found to be a highly selective hydrogenating catalyst[2]. The goal of my master work is the total synthesis of a pyrylium salt (fig 1) that is a precursor for a variety of hydrogenating catalysts. Transformation of this molecule into phosphinine (fig 2) gives the molecule that holds the active seats in the right configuration. The pyrylium alcohol (fig 1) can also be a precursor to the pyridine analogue (fig 3) such a molecule has successfully hydrogenated unfunctionalized alkenes[3]. Our group wants to explore functionalized phosphinines, instead of the pyridine analogue that is explored by other groups for iridium catalysed hydrogenations. In this context the ligand shown on figure 2 is of interest. The phosphorous is bigger, and electron withdrawing in comparison with the aromatic nitrogen. This is expected to bring different properties to the catalyst and might make it work better on imine reductions. The properties of each intermediate in the synthesis have to be studied to choose pathways and compatible reagents. We want to find a simple route to the molecule on figure one and characterize its properties to aid further work on this molecule.

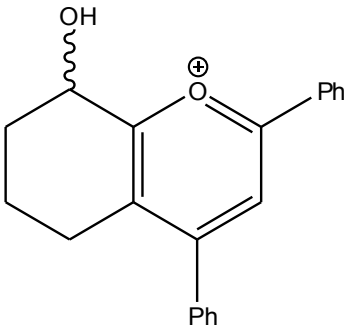


Figure 1.1 pyrylium alcohol

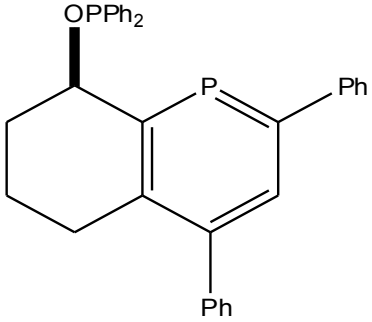


Figure 1.2 phosphinine isomer

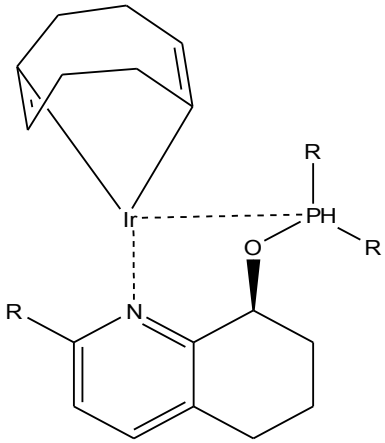


Figure 1.3 pyridine analogue

1 Andeas Pfaltz_Acc. Chem. Res.(2007)p1402
2 C Muller_Tetrahedron Lett.(2006)p2017
3 Stefan Kaiser_ Angew. Chem. Int. Ed(2006)p5194

Abbreviations and definitions

9-BBN 9-borabicyclo [3,3,1] nonane
Proline pyrrolidine-2-carboxylic acid,
CBS 2-methyl-CBS-oxazaborolidine, the Corey-Bakshi-Shibata catalyst
MSPV Meerwein Schmidt Ponndorf Verley, follows a reversed Oppenauer mechanism
NMR nuclear magnetic resonance, used as denotation of the instrument
LAH $LiAlH_4$, lithium aluminium hydride
THF tetrahydrofuran
MTBE methyl tert butyl ether
EtOAc ethyl acetate
DMSO dimethyl sulfoxide
DIBAL diisobutylaluminium hydride
DEANB N,N diethyl aniline borane complex
Bach-EI *N*-ethyl-*N*-isopropylaniline borane complex
Oxone potassium peroxymonosulfate
aq aqueous
eq equivalents
ee enantiomeric excess
m.p. melting point
b.p. boiling point
RT room temperature
UIT University of Tromsø

Stereoisomer
Stereoisomers are molecules with chiral centers, they differ in the way the substituents are arranged in space.

Enantiomer
An enantiomer is one of the two stereoisomers possible with one chiral center. An enantiomer refer to a substance with only one configuration. An enantiomer might have the capability to rotate light. A pair of enantiomers are mirror images of each-other and rotate light in opposite directions.

Enantiomeric excess (ee)
The ee is a value that represent the percentage of one enantiomer, dominating over the other, from the whole fraction of both.

Stereoselective
A stereoselective mechanism creates or maintain stereocenters with unequal proportions of stereoisomers.

Stereospecific
Stereospecific reagents on one particular orientation of substituents, gives a configuration of its substituents, that would had been different if the orientation had been opposite.

Asymmetric induction
Induced formation of one enantiomer, or diastereomer, over the other.

Enantioselective reaction
In an enantioselective reaction an asymmetric induction of prochiral center occurs. These mechanism depends upon chiral reagents or catalysts.

Prochiral center
A prochiral center has the ability to become a chiral center. One example is by reduction of an unsymmetrical carbonyl. With a stereoselective reagent might yield a chiral center and a pure enantiomer.

Bũrgi-Dunitz angle
The Bũrgi-Dunitz angle is the 107 degrees angle favoured for nucleophilic attack on carbonyl groups.

Denticity
Denticity designates number of atoms that coordinate to one metal. Examples of ligands includes EDTA, which is hexadentate. The PHOX ligand has one phosphorous and one nitrogen atom coordinated to iridium, two coordinating centers makes it bidentate.

Chemoselective
Chemoselective reagents reacts with one specific group and leaves other functional groups alone.

Bathochromic / fluorescence shift / effect
Bathochromic effect is the classical term describing some molecules ability to absorb light and transmit the energy with a longer wavelength. More common today is the term fluorescence. The effect depends upon polarity of the solvent and is in that aspect called solvatochromism. The difference of incoming and outgoing radiation energy is released as molecular rotation, vibration or emitted as heat.

Polymorph
A polymorph substance have the capability to be grown into different crystal structures. The physical properties might differ significantly between differently packed but otherwise equal substances.

Pyrophoric
Pyrophoric substances spontaneously ignites at room temperature. To avoid combustion oxygen need to be kept away. Pyrophoric substances like boranes are kept in solvents like THF or toluene solutions to ease handling and avoid exposure to air and water. Inert gases are often used in conjugation, to avoid that oxygen is absorbed into the solvent.

Hydrogenation
Hydrogenation is an addition of molecular hydrogen. Metals are useful to lower the energy needed to weaken the bond between the hydrogens.

Transfer hydrogenation
Transfer hydrogenation is a term for adding hydrogen from other sources than gaseous hydrogen.

Solvolysis and hydrolysis
Solvolysis is a term for the incorporation of the solvent molecules to substrates. Hydrolysis refers to water as solvent, the water molecule is divided into hydrogen and hydroxide ions.
These ions ruptures the substrate while connecting to one or more bond in the reacting substrate. A condensation is the opposite of a hydrolysation.[4]

Convergent syntheses
Convergent synthesis is an alternative approach to a linear synthesis, where the starting material goes through all consecutive steps. Separate parts of the molecule are made alone and condensated in a late step. This often give a higher total yield compared to linear synthesis.[5]

Flash column
A flash column is a pressurized packed column, pressure is applied to eluate faster, dry nitrogen is commonly used.

Telescoped reactions
In a telescoped reaction the content in transferred to the next reaction without laborious work-up.

FT - IR - ATR
Fourier transformation - infra red - attenuated total reflection,
It is a recent technique that can measure the infra red spectra of solid compounds. The dry sample is compressed towards a crystal. The reflected radiation is recorded directly. Classic sample cells are made of quarts, or salt, that requires the sample to be dissolved.

Oxonium ions
Oxonium ions have positively charged oxygen, for example a protonated ketone, has three bonds on its oxygen. Any compound with three bonds to oxygen fall into this category.

4 "The gold book" IUPAC recommendations, doi : 10.1351/goldbook.S05762 , read 18 february 2009
5 "Chemical development & scale-up" Dr. Will Watson & Dr Derek Robinson Course manual from course given 3-5 of march 2009

Pyrylium salts
The pyrylium salts consists of six membered heteroaromatic ring systems with oxygen incorporated into their ring. The positively charged oxygen require a counter anion, hence pyrylium is only found as salts.

Pyridines
The pyridine group consists of six membered heteroaromatic ring systems with nitrogen incorporated. Nitrogen is the only heteroatom found in greater number than one, in aromatic systems.

Phosphinine
Phosphinines are six membered phosphorous containing aromatic ring systems.

Pyrrole
Pyrroles are five membered nitrogen containing aromatic systems. The lone pairs from nitrogen are spread in the aromatic system. Generally less reactive than pyridines.

Contents:

Contents

Contents

Synthetic pathways

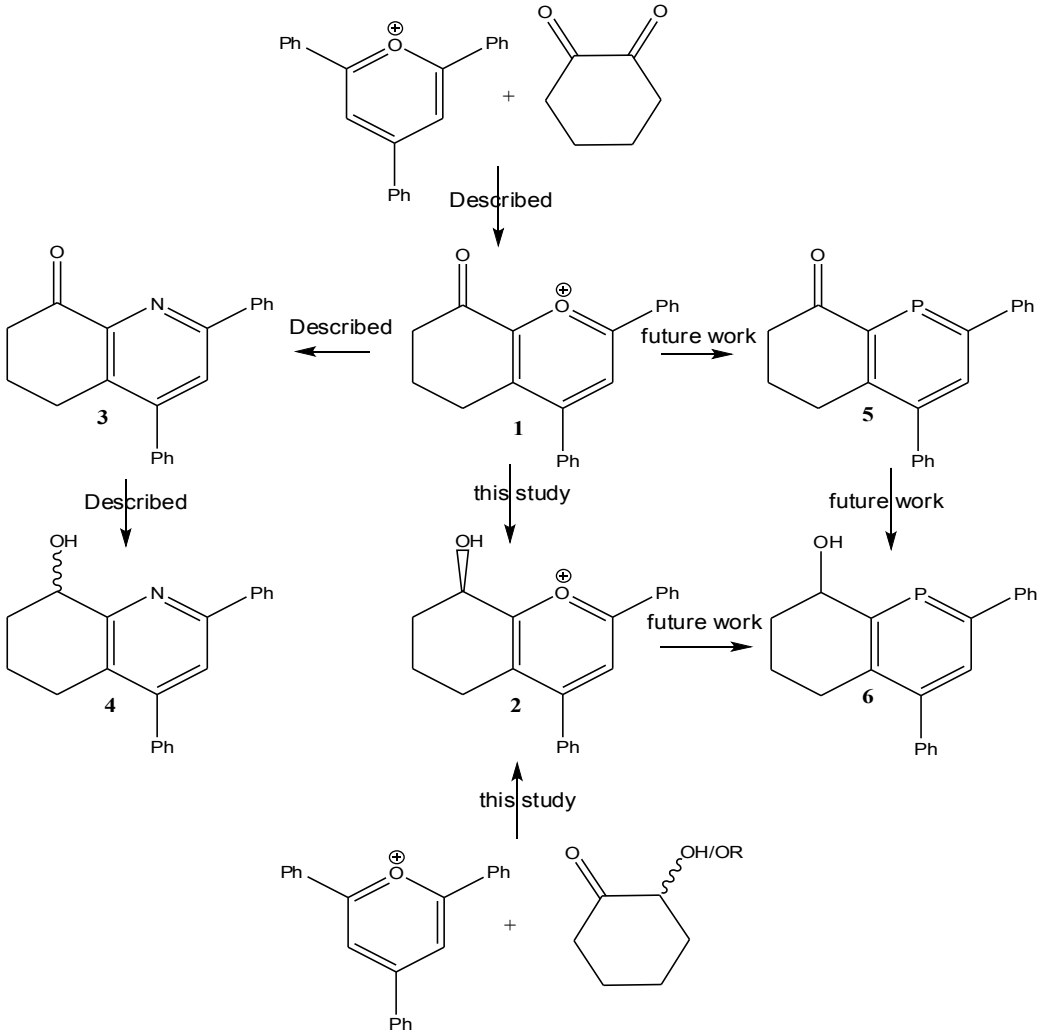


Figure 1.4 representation of pathways to obtain the phosphinine ligand **6**

Three pathways can be chosen for the synthesis of compound **6**, a ligand that is a precursor for the catalyst in fig 1.2.

Synthetic route 1: pyrylium salt **1** transformed to phosphinine **5** before asymmetric reduction to **6**. The phosphinines are known to be unstable in water, and this functionality probably better introduced as a last step. Due to the sensitivity of phosphinines this assignment was not given as master thesis work.

Synthetic route 2: pyrylium salt **1** is reduced to **2**, preferably asymmetrically, then transformed to the phosphinine **6**. To obtain alcohol **2** from ketone **1**, careful consideration has to be put into the choice of reducing agent. A strong nucleophilic hydride donor would attack and break its pyrylium ring. Electrophile reducing agents are needed, there are available several for asymmetric reduction. A hydroboration mechanism, appears to be a plausible route for reducing the pyrylium salts. The free electrons from the carbonyl group of oxygen, coordinates the borane towards itself. The boranes hydride is then transferred to the positively charged carbon. The borane has to be held by a ligand directing it towards only one of the pyryliums sides, to make it asymmetrically. If the reducing agent is chemoselective enough, it will distinguish the

different sites of the pyrylium, and if it is stereospecific enough it will distinguish the sides to produce a pure enantiomer. There are several electrophile reagents that asymmetrically reduces ketones.

Synthetic route 3: A third approach is to introduce one alcohol functionality replacing one of the ketones on the cyclohexan-1,2 dione, before the condensation. Vicinal diketones are the only reagents found described condensated to the 2,3 positions of pyrylium. Since the mechanism is though to occur without participation of the second ketone moiety this reagent needs to be synthesised for testing. Several procedures are available in the literature but, not in preparative scale. The alcohol moiety may also be protected before the condensation, e.g. if the conditions for the condensation is shown to damage the alcohol. To assess the ability to condensate other functionalities to pyrylium rings, derivatives of 2-hydroxycyclohexanone with a variety of substituents in the α position to the ketone have to be prepared. Five or seven membered rings are reported to not condensate under the same conditions, so our primary focus for this study is six membered rings

Synthetic route 2 and 3 will be explored in this work. A general problem when working with pyrylium salts is the limited solubility in a number of solvents. Therefore the reagents have to be compatible with solvents found to dissolve each substrate.

2 Background

2.1.1 General homogeneous catalysis

The addition of a catalyst to a reaction lowers the energy needed for a certain reaction pathway. The energy difference between the pathways should be so high that the alternative reaction do not occur. The requirement for a molecule to be called a catalyst is that it remains unchanged when the reaction is completed and hence might be employed in a sub molar ratio of the substrate. A homogeneous catalyst has the advantage of having a greater reaction surface than a heterogeneous, as it has no metallic or polymer surface that serves as a support. A disadvantage of homogeneous catalysis is separation of the catalyst, from the reaction media, when the reaction is completed. Examples of natural catalysts are enzymes, bacteria, and yeast.

2.1.2 Catalyst life

It is important to understand the nature of the catalyst during the reaction. Some are deactivated when they meet another catalyst molecule as they polymerize. This occurs at low substrate conditions, such as at the end of the reaction when the catalyst meet other catalyst molecules more often than substrate molecules. Some are unstable in water or in other catalyst specific pollutants. Reagents need to be chosen carefully to avoid producing any of these as long as the catalyst is present. The life of the catalyst might be thought of as how many substrate molecules it can convert, under the conditions in the reaction, before an alternative reaction pathway deactivates it or an unwanted reaction occurs. The Si unit is Katal, that is the measurement of how many catalyst molecules are needed to convert one mole of substrate molecules per second, hence the units are mol/sec. The turn over number (TON) is the amount of substrate molecules one catalyst can convert before it is deactivated. The turn over frequency (TOF) is the speed of conversion and as for TON, TOF is also highly dependent on the reaction conditions.

2.1.3 Metal ligand complexes as asymmetric catalysts

An organic framework / skeleton is used as a ligand to hold metal atoms in a certain configuration. The metal is chosen by the geometry of its higher order orbitals.
Depending upon the purpose of the catalyst, the framework sterically allows the metal to interact with certain reaction sites. A catalyst for asymmetric catalysis needs to be both chemoselective and stereoselective. The framework might contain other coordinating atoms making it custom designed both with respect to their positions and reactivity towards a specific substrate. The ligand helps to coordinate the metal to the substrate positioning the metal in the right position on the functionality undergoing reaction. A prochiral ketone, might for example be hydrated selectively on only one of its sides. This is called asymmetric induction. The other side has a transition phase of higher energy and hence the molecule is produced in lesser amounts or not at all.

2.1.4 Chiral molecules

The easiest way of understanding chiral molecules is as a pair of identical left and right hands; they are the same and have the same properties, but are mirror images of each other. If you stack them, neither will hide the hand underneath. A pile of right hands of the same shape and size will look different from a pile of both left and right hands. A pile of left sided hands would in chemistry be single enantiomers. They have more surface that fits together, this makes their melting and boiling points higher. The R and S designation is based upon weight of different substituents. To designate configuration the lightest atom is imagined moved backwards with the three different substituents pointing forwards. Then they are counted from lightest to heaviest and the clockwise direction is defined as the R configuration. If a mixture of enantiomers are in exact proportion to each other, it is called a racemic mixture. A racemic mixture of a drug might have fatal consequences. For example, the drug Thalidomide is in its R configuration a sedative but, its S configuration causes birth defects[6].

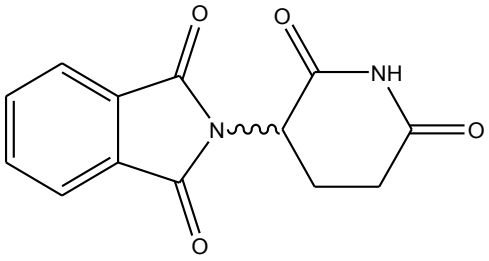


Figure 2.1 Thalidomide

Substrates derived from nature often come in a enantiopure form. Small amounts of an undesired enantiomer can be removed by recrystallization of the crude product. As single enantiomers will stack or pack better in carefully grown crystal allowing the by-product to remain in the solution. A racemate mixture is harder to resolve; a chiral chromatography column might be utilized for gram scale productions. A counterion that only binds to one configuration of a racemic mixture of molecules is another way of separation. This generates a diastereomer that is easier to separate from the mixture. The unwanted diastereomer could be either discarded or racemized to generate more of the wanted enantiomer.

2.2 Pyrylium salts

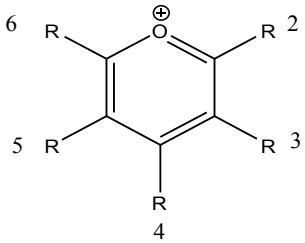


Figure 2.2 pyrylium nomenclature

2.2.1 Nomenclature and structure

Pyrylium salts are six membered aromatic rings that lack a carbon in favour of a positively charged oxygen. The IUPAC nomenclature dictates the oxygen to be the 1 position while the ortho carbons are 2 and 6 positions. In older literature the C-2 and C-6 are called α positions. The structure core ring is a flat pyrylium. If the 2,4,6 positions

6 Pharmacogenics knowledge base, http://www.pharmgkb.org/views/index.jsp?objId=PA451644#tabview=tab1, read 11 march 2009

have phenyl substituents, the one in the 4 position tends to bend slightly more than the 2 and 6 positioned but all in the range of 20° relative to the pyrylium plane[7]. Nucleophiles are known to react with the 2, 6 or 4 positioned carbons on pyrylium. These are the positions that are prone to hydrolysis. The electrophilic character of these carbons is visualized clearly by their ^{13}C NMR shifts values.
For example, the shifts for methyl substituted C-2 and C-6 show a resonance around 180 ppm and the C-4 has a slightly lower shift at 177 ppm [7]. These NMR shift values differ significantly from aromatic carbons (around 130 ppm) and are more related to shift values expected for ketones (around 200 ppm). The properties of the C-3 and C-5 position are related to benzene, both with respect to chemical inertness and in resonance frequency. These NMR shifts were recorded in a mixture of fluoroacetic acid and DCM at methyl substituted positions. Traditionally these were the solvents of choice for pyrylium NMR. Recent publications describe pyrylium NMR shifts recorded in acetonitrile, DMSO and chloroform.

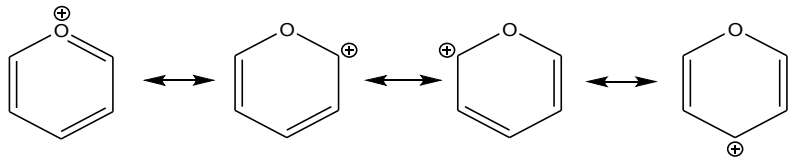


Figure 2.3 pyrylium resonance structures

2.2.2 Reactivity

The reactivity of the pyrylium ring is much higher than for benzene that hardly is attacked by nucleophiles.[7] Pyrylium is less reactive than other oxonium ions. Its increased stability is influenced by the aromaticity of the ring but also depends upon the stabilizing effect of the anion. The aromatic properties of these compounds can be fine tuned by phenyls that has the right electron contribution. Upon hydrolysis, the 2 or 6 positions are almost exclusively attacked. Roy et al[8]. states that the energy difference is less than 4,2 kJ mol^{-1} for attacking equally substituted 2 / 6 positions versus the 4 position, but the tendency is drawn towards reversible addition in the 2 / 6 position. The reversible cleavage occurs where the best leaving group is situated next to the oxygen. Hydrolysing pyryliums generates an acidic solution, 2,4,6-triphenylpyrylium perchlorate has a p*K*a = 5.0 in 0,1M solution[8]. That occurs because the one hydroxide from the water is used for cleavage, while the proton remains in solution. Triphenylpyrylium salts in aqueous media are in an equilibrium between a cyclic and an open chain structure. The equilibrium depends on the pH and temperature. To obtain the 2,4,6-triphenylpyrylium as an open chain, a stoichiometric amount of sodium acetate in a solution with the substrate is reduced in vacuum.

2.2.3 The salt effect of the counterion

All pyryliums have a counter ion that balances the positive charge developed in the aromatic system. In the past little attention had been paid to the counterion of pyryliums. They were merely thought of as inactive electron donors, that contributed little to the chemical properties. Pyrylium salts have different colour depending on the interaction between the pyrylium ring and its ion. Smaller and more polarizeable anions, shows this effect more than the polyatomic[7]. This effect is seen by dissolving pyrylium in solvents with different polarity. Triphenylpyrylium has absorption maxima at 408 nm for the x

7 Pyrylium salts: Science of synthesis T. Balaban (2003)p11-200
8 Roy Beddoes_J. Chem. Soc. Perkin Trans.(1995)p307

band and 361 nm for the y band. The absorbed wavelengths in the x band are connected to the properties of the phenyls in C-2 and C-4 position. Balaban[7] reports that the x band absorbs at higher wavelengths if electron donating substituents occur at the 2 and 6 positioned phenyls. The Y band, at 361 nm, moves to higher wavelengths if electron donating substituents are put onto the phenyl on the C-4 of the pyrylium. The intensity of the emissions is thought to depend upon the charge transfer, from the cation to the anion, occurring in the excited state. In 2007 Milov et al. [9] did a thorough study of pyryliums with different counterions. Their study indicated that the polyatomic BF_4 and ClO_4 anions are located directly in the middle above the pyryliums aromatic system. In gas phase and non polar solvents these systems ionic bonds have the characteristics of σ bonds that decrease with increasing ionic character of the solvent. The difference in coordination pattern for polyatomic counterions is less affected by solvent than for simple halides. The counterion positioned as shown on the figure underneath might provide shelter against nucleophile attacks, further improving the stability of the system. The reactivity might become a problem, if the counterion permanently prefers one of the sides, and blocks reagents.

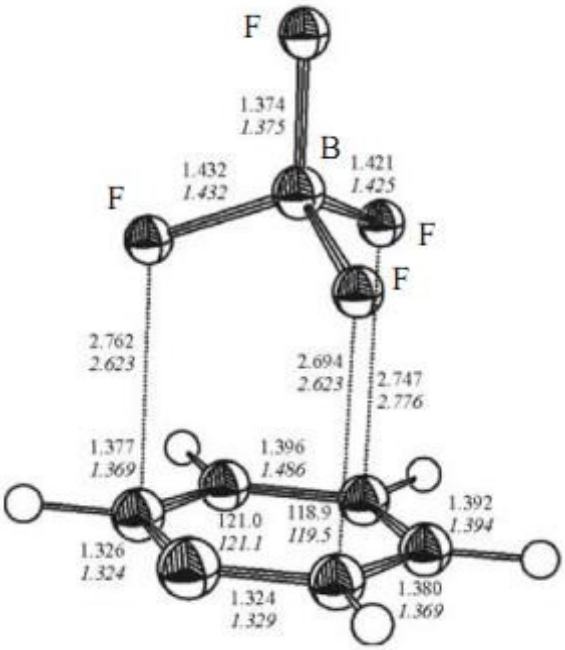


Figure 2.4 methyl substituted pyrylium, the BF_4 counterion is in the position corresponding to lowest free energy[9]

2.2.4 Synthesis

In general, pyrylium salts precipitate out in organic solvents. In some cases it is also an advantage, like that it is easy to remove them from product mixtures, leaving unreacted synthons in the mother liqueur. Symmetrical pyrylium salts are preferentially prepared by a one pot procedure with two or three different pieces contributing to the carbon skeleton. The reactivity of these pieces has to be carefully chosen to avoid a product mixture

9 A Milov_Russian Journal of General Chem.(2007)p1294

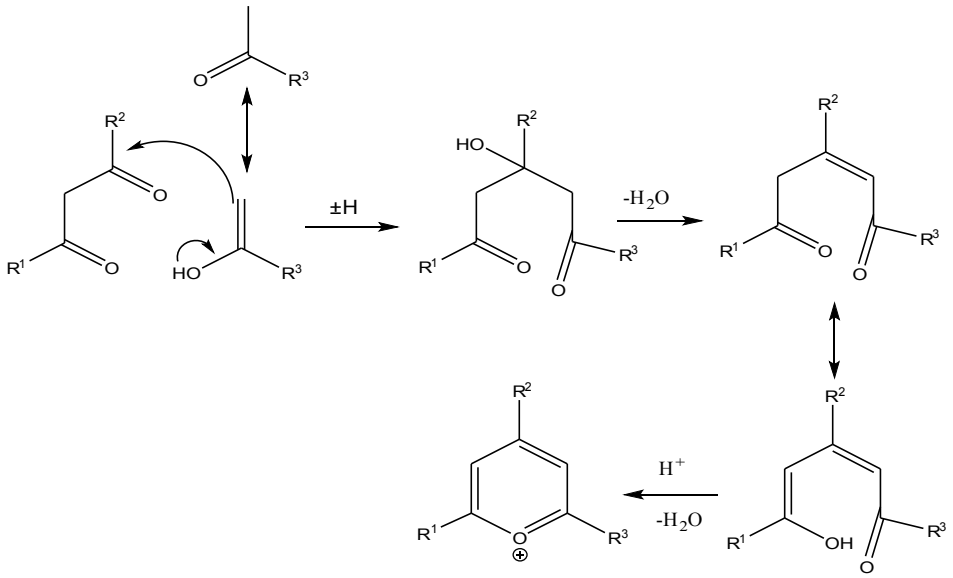


Figure 2.5 2 different synthons contributing to the pyrylium skeleton

Balaban advice to try to synthesise pyrylium from two or three synthons as they in general give higher yields than by condensating an 1,5-dione[7]. Its terminal carbonyl groups condensates together, with the help of a brønstedt acid that conveniently turn into the necessary counter ion. There are several good books that describes the details for each kind of synthesis depending on the desired target pyrylium. A thorough discussion and detailed reaction parameters, that might be useful while planning a pyrylium synthesis is found from reference 7 and to some degree 10[10].

A 2 component pyrylium synthesis[11], developed by Vogel, Dimroth and Reichardt in the sixties, has been cited in numerous articles. Their synthesis uses 2 1,3-diphenyl-2-propenone molecules together with one acetophenone. The first 1,3-diphenyl-2-propenone provides two phenyl substituents and three carbons for the skeleton. Acetophenone provides the second synthon a phenyl group and two carbons. The last 1,3-diphenyl-2-propenone serves as a hydride acceptor as sketched in figure 2.6.

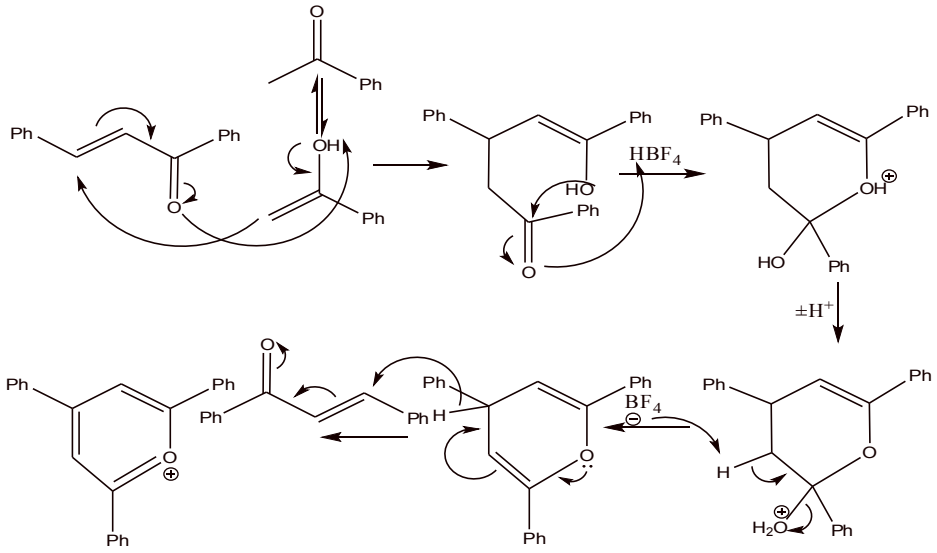


Figure 2.6 2 synthon, pyrylium condensation

10 A Katritzky_ Academic press(1982) Supplement 2 pyrylium salts: syntheses, reactions and physical properties
11 K Dimroth_Org.Syntheses Coll.(1969)p1135

2.2.5 Applications

The major direct application of pyrylium salts is related to their colours. They are used in dye lasers and serve as photosensitizers in electron transfer reactions.
Single ring pyryliums have not yet been isolated from nature, hence the synthesized ones serve as convenient, versatile building blocks for a wide range of syntheses. Balaban has described several ways to exploit the equilibrium that is developed in solutions. The equilibrium developed between open chain and cyclic structures could be used to replace the oxygen with other heteroatoms[12]. For example, by replacing the oxygen with a nitrogen, a pyridine analogue is generated. Phosphorous converts the pyrylium ring into a phosphinine.

2.3 Reduction

In chemistry, a reduction is most often thought of as addition of electrons. In organic chemistry it is more often an addition of hydrogen or removal of oxygen, on carbon at the substrate molecule[13]. An oxidation is the opposite, of reduction, either loosing hydrogen or addition of oxygen. Figure drawn underneath demonstrates carbon from the lowest at the left in the figure as pentane. The highest oxidation state with 4 electron withdrawing substituents is to the very right of the figure. In general, a carbon in the lowest oxidation state is surrounded only by atoms that donate electron density. Reducing agents becomes oxidized, while oxidizing agents becomes reduced during the conversion and need to be used in stoichiometric amounts or regenerated.

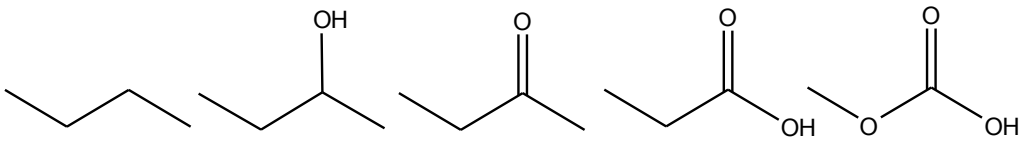


Figure 2.7 oxidation states

2.3.1 Nucleophilic and electrophilic reducing agents

Nucleophilic reducing agents like LAH (lithiumaluminiumhydride) have a metal that is highly electropositive, rendering their hydrogens electronegative, allowing them to leave with the electron density. LAH is not very chemoselective as it attacks almost any site that can be reduced. These nucleophilic reducing agents donate hydrides to the substrate in a concerted manner. Electrophile reducing agents works by a less direct mechanism. They are themselves low on electron density and attract electron density from the substrate. Then in a concerted way donate a hydrogen or hydride to the substrate. The oxygen of a ketone attracts the electrophile reducing agent. In a concerted manner a hydride is then transferred to the ketones carbon. This carbon simultaneously donates electron density, to the positive oxygen, as the hydride is attached.

12 2,6-Di-tert-butyl-4-methylpyrylium trifluoromethanesulfonate _Organic Syntheses_(1981)p34
13 T J Donohoe_Oxidation and reduction in organic syntheses_Oxford chemistry primers(2003)p3

2.3.2 Reducing agents and pyrylium salts

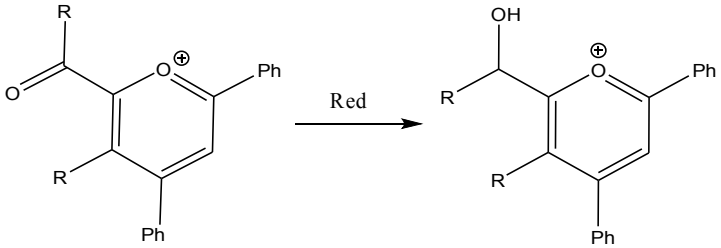


Figure 2.8 reduction of side chain of pyrylium

When these syntheses of pyrylium was initiated, in 2007, no reports of selective reduction of functional groups on side chain of pyrylium salts could be found. Nucleophilic reducing agents will attack pyrylium ring positions with low electron density. The aromatic oxygen does in a way act like a ketone, withdrawing electron density from carbon to oxygen, making the carbons next to the oxygen vulnerable for nucleophilic attacks. These C-2, C-4 and C-6 positions does in NMR spectra appear around 170 ppm. Literature search did reveal examples where pyrylium salts had been reduced with reagents like sodium borohydride, even at 0°C[14] [15]. This unwanted mechanism is shown on figure 2.9 underneath where either ortho or para addition breaks up the ring. The proportion of para attacks decreases as the size or the R groups are increased according to Balaban.

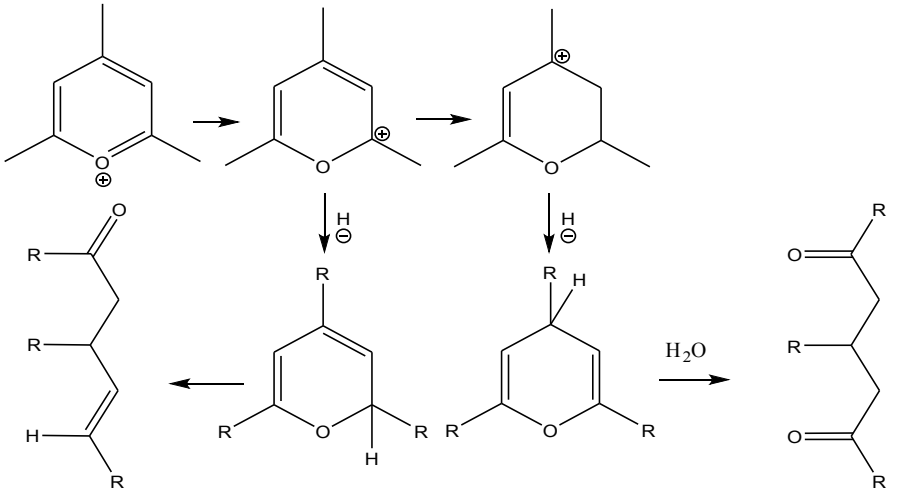


Figure 2.9 hydride reduction upon pyrylium salt, reproduced from reference 14

A transformation, done on a side chain of a pyrylium, need to be so chemoselective that it wont change the somewhat fragile pyrylium system. A reduction done on a side chain ketone need to leave the 2, 4 and 6 positioned electrophile pyrylium carbons untouched. A side chain ketone will have oxygen with more available electrons compared to the pyrylium oxygen. Despite the ketone like character found in pyrylium, its oxygen has only one lone pair. This lone pair is tightly held to the oxygen in the electron poor aromatic system. The availability of electrons might be helpful if they can be used to direct a reagent towards the ketone. The more different the reactive sites are, the easier it is to find a reagent that is chemoselective enough to distinguish between them.

14 A T Balaban_Adv. Heterocyclic Chem.(1969)p241
15 A T Balaban_Tetrahedron(1961)p257

2.3.3 Hydroboration of carbonyl groups

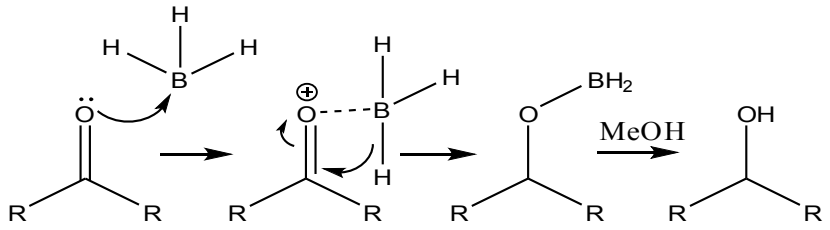


Figure 2.10 hydroboration of carbonyle group

The mechanism for hydroboration consists of several steps. The first step is when the electrophile reducing agent, borane, is attracted by the electron density from the oxygen of the ketone. The hydride transfer is pushed by the surplus of electrons around the small boron. In the last step methanol or a peroxide gives the alcohol on the substrate, with retention of stereo configuration. Borane in its pure form is a dimeric, highly toxic and reactive gas. A convenient source for the electrophile reducing agent BH_3 is THF*BH_3. The THF is used as a ligand that coordinates the slightly positive borane to the slightly negative oxygen. There are several coordinating ligands available, the advantage of one over the other depends upon usage. The reagent is usually shipped in a solvent like toluene, that makes the borane easier to handle. The borane is available with 1-3 hydrides, with a wide range of chelating / coordinating ligands. Herbert Browns laboratories have done extensive studies exploring the mechanisms behind hydroboration[16]. The stereoselective hydroboration reagent 9-BBN was tested on a series of 1,2 unsaturated ketones. In 1976 they proved that the oxygens lonepairs on carbonyl groups draw the borane towards itself. The 9-BBN donates its one hydrogen to the carbonyl, that lost electron density making the bond to the borane. This mechanism was particularly interesting as adjacent double bonds were essentially left unchanged. In a competitive reaction Brown got 1:37 reduction in favour of the ketone in six membered α, β unsaturated rings[16]. There are ligands readily available that catalytically pick up BH_3 from BH_3 donors to favour attachment on one side over the other on pro chiral ketones. One is the famous CBS catalyst discussed below.

2.3.4 CBS hydroboration

The CBS ligand was developed in the late eighties by Corey, Bakshi and Shibata. The CBS ligand is derived from proline and is the most utilized catalyst in chiral reductions[17].

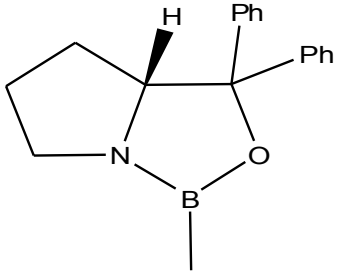


Figure 2.11 CBS ligand

The CBS ligand picks up a BH_3 molecule from a donor in the reaction mixture.
CBS has a structure that makes the different approaches towards the substrate energetically different, since it sterically blocks approaches from the more hindered side of the substrates ketone. The unfavourable approach is illustrated on figure 2.12 on the next page.

16 S Krishnamurthy_J. Org. Chem(1977)p1197
17 Biao Jiang_Tetrahedron Lett.(2000)p10281

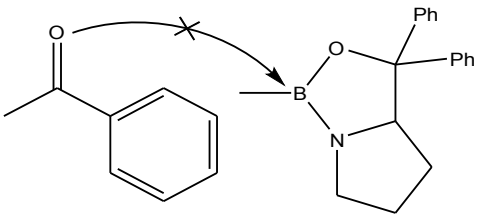


Figure 2.12 unfavourable CBS approach on acetophenone, illustrates why the phenyl group coordinates away from the big bulky groups on the CBS molecule

As evident from the sketch (fig 2.13), the CBS mechanism consists of many steps. CBS picks up a BH_3 molecule in the first step that is seen occurring between state 1 and 2 in the scheme. Between state 2 and 4, the CBS coordinates to the substrate. The hydride from the boron is then transferred to the substrates carbonyl carbon while the oxygen coordinates electron density to the boron of CBS. After the ligand has coordinated the BH_3 molecule to a substrate, it is released and picks up a new BH_3 molecule. This continues until the catalyst is deactivated, or has depleted the borane donors available.

In synthesis, the CBS might be kept as low as at 5 mol%, while the hydroboration reagent losing its hydride in the reduction is needed in stoichiometric amounts. Ashok[18] found that if they used the CBS catalyst without a methyl group on the borane, it dimerized into a less reactive form. Byung et. al. did an extensive study of 8 different catalysts and 10 different borane reagents to find CBS to be the superior catalyst and BACH-EI to be a slightly better borane donor compared to DEANB in the reduction of 2,2- diethoxy-1-phenylethanone[19]. BACH-EI and CBS gave 97% yield and 94% ee on that substrate in room temperature. In their study, BH_3-THF and DEANB as borane donors gave satisfactory results (more than 90% yield and ee). Byung also varied the temperature and used different solvents. They concluded that room temperature is the optimal temperature, and that THF and to some degree toluene were the better solvents. Byung tested their setup on more hindered substrates to find that the ee decreased with on more sterically crowded substrates. The reasoning for this was that the borane donor itself reduced the ketone or liberated BH_3 molecules. The liberated borane has no preference for either side of ketones. Byung quenched the reaction mixtures into methanol and purified it in a silica loaded flash column.

18 Ashok M. Salunkhe_Tetrahedron Lett.(1997)p1523
19 Byung Tae Cho_J. Chem. Soc. Perkin Trans.(1999)p2095

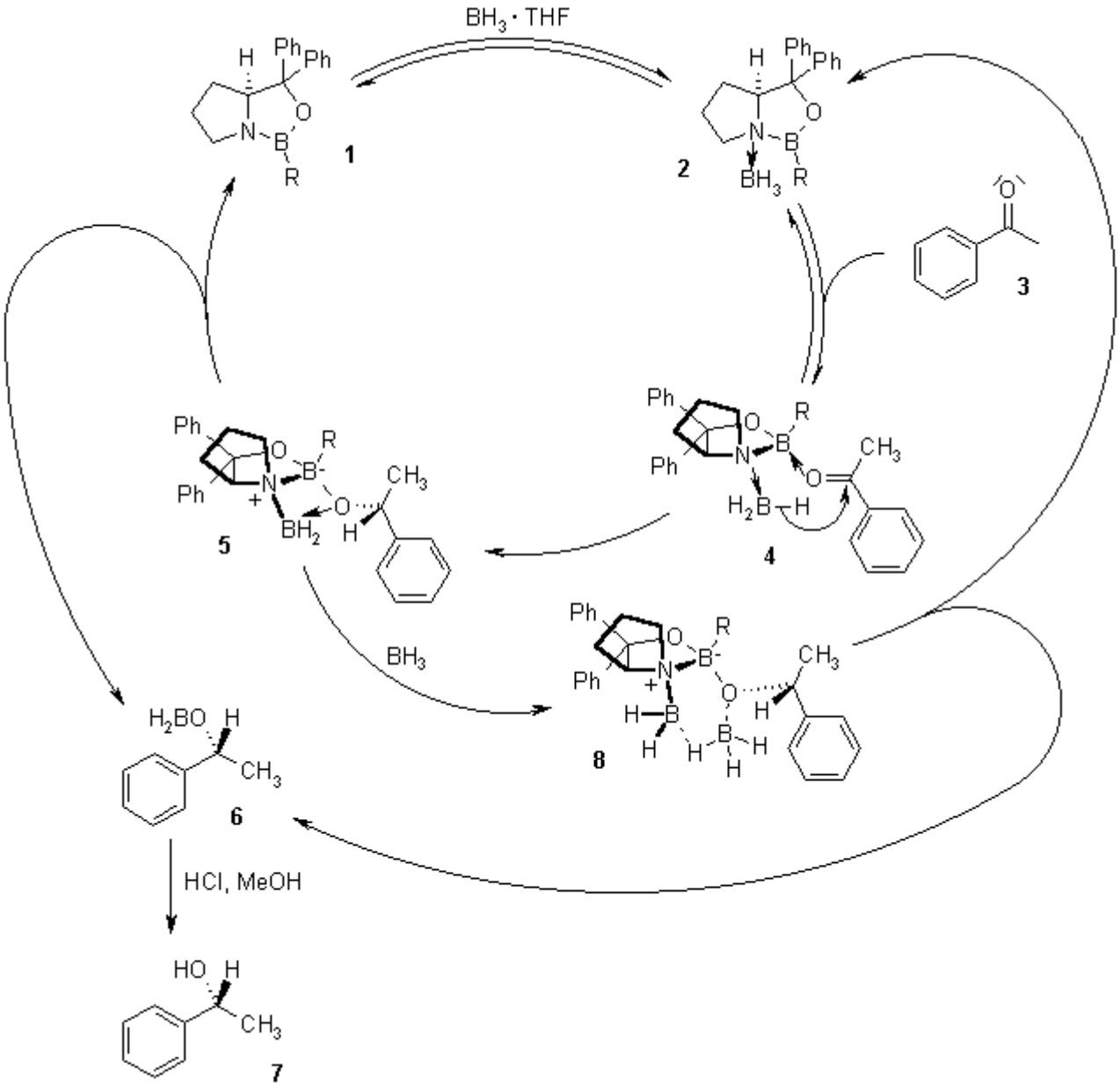


Figure 2.13 CBS reduction of acetophenone[20]

2.3.5 DIBAL reduction

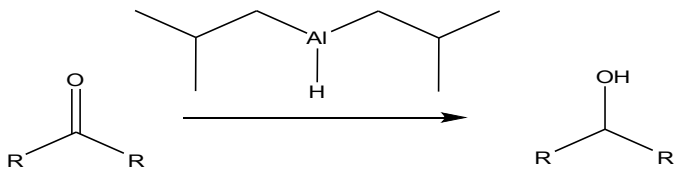


Figure 2.14 DIBAL sterically hindered hydride donor

Other metals, that also are electro positive compared to carbon, share borons capability of donating hydrides. One example is the aluminium in the reagent DIBAL (Diisobutylaluminium hydride), aluminium is more electro positive than both boron and silicon. The aluminium equivalent of borane is the highly unstable AlH_3, produced from LAH ($LiAlH_4$). Its reactivity is very high, being quite close to LAH. The DIBAL is more selective and only reacts slowly with electron poor compounds. If used in stoichiometric

20 Mechanism reproduced from http://www.organic-chemistry.org/namedreactions/corey-bakshi-shibata-reduction.shtm read 4 february 2009

amounts where there are two ketone moieties, it will favour the ketone with the most available electrons. The second electron poor moiety, if different enough compared to the rich one, will not be reduced. The hydride held by the aluminium in DIBAL is sterically hindered by the two isobutyl groups. In its pure form it is a highly pyrophoric liquid that is miscible with most organic non protic solvents[21]. Akiko et. al. reduced octalone with dibal in quantitative yields at temperatures as low as -78°C in 5 minutes[22]. They utilized dibal, solvated in hexane to a solvent consisting of DME / THF to generate the molecule in 100% yield with 96% d.e In a stereoselective study with DIBAL, 39% of trifluoro acetophenone got reduced in favour of the acetophenone (1:1 competing for 1 eq dibal)[23]. DIBAL displays attractive features as a slightly electrophile hydride donor.

2.3.6 Hydrosilylation

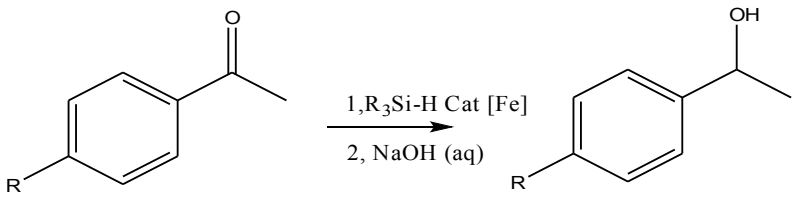


Figure 2.15 silylation

The silicon atom is bigger than borane, allows more bonds, and is slightly more electro-positive. The lone pairs from the ketone, similar to what they do in hydroborations, binds to the electron deficient silicone. Then the hydride is transferred to the ketone. The greater size of silicon does not hinder the transfer of the hydride as the bond between the oxygen and the silicon is long[24]. Addition of trimethyl silyl chloride(TMS-chloride) makes the reducing agent favour ketones. This is because the ketone loses electron density to the TMS, favouring a hydride attack at this position. This makes other more electronegative positions on the molecule less attractive, like aromatic systems or double bonds. Ojima silylated a wide variety of conjugated ketones to further reduce them to alcohols[25]. Ojima did stereoselective studies with silylation reagents on Pulegone (figure2.16). He achieved 100% conversion on the ketone and neither of the double bonds were touched. The more accessible double bonds in Pulegones regioisomer Piperitone gave the same results, under mild conditions. The reaction was worked up with potassium carbonate in methanol to afford the alcohol.

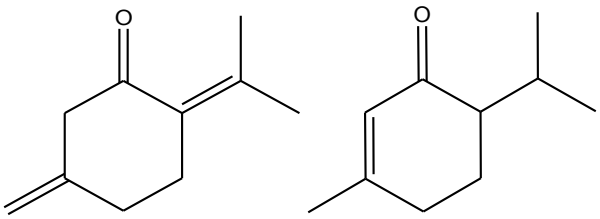


Figure 2.16 Pulegone (left), Piperitone (right) both reduced100% on the ketone moiety

21 Dibal characteristics http://mrw.interscience.wiley.com/eros/articles/rd245/frame.html, read desember 2007
22 Mark Midland_Org. Syntheses Coll.(1985)p57
23 Andre Gemal_J. Am. Chem. Soc.(1981)p5454
24 Clayden et al._Organic Chemistry_Oxford university press(2007)p1297
25 Iwao Ojima_Organometallics(1982)p1390

2.3.7 $CeCl_3$ / $NaBH_4$

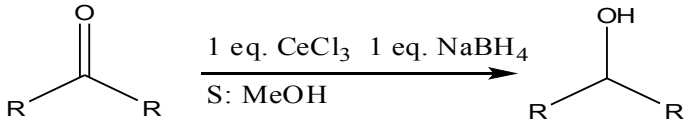


Figure 2.17 $CeCl_3$ as hydride director with a strong hydride donor

This cerium chloride mediated reduction favours electron rich carbonyls, that have readily available lone pairs. In aqueous methanol, the ketones lone pairs draws the cerium salt towards itself[26]. The salt withdraws electron density from the carbonyl, which makes the carbonyl more accessible for the hydride, as a result the selectivity towards ketone reduction is increased. Andre did a study, of different coordinating metallic salts influence on regioselectivity[23]. Cerium were found superior, to other metals, in making hydrides favour ketones instead of double bonds. The hydride donor, $NaBH_4$ were found to be needed stochiometrically, rendering a 4 fold excess, of hydrides to the substrate. In a different study from the same laboratories they made 1 equivalent of acetophenone compete with 1 equivalent of trifluoro-acetophenone for one equivalent of reducing agent[27]. The acetophenone was converted at 95% yield with only traces of the fluorine isomer reduced. The carbonyl NMR shift was found to be 197 ppm in acetophenone and 182 ppm for its fluorine isomer. The reagent favoured reducing the electron rich acetophenone. The mechanism being chemoselective for electron rich ketones is very interesting as the calculated NMR shift is 197,6 ppm for the ketone moiety in ketone [54].

Hydrogenation catalysts

The addition of a H_2 molecule to a carbonyl group reduces it into an alcohol. The strong bond between the hydrogens has to be weakened by absorption onto a metal. For example; platinum is used as a heterogeneous catalysts. When the right kind of rare earth metal is utilized or “poisoned” to gain the right activity, very selective catalysis may be achieved. PHOX is a ligand used for asymmetric catalytic hydrogenation.

2.3.8 Transfer hydrogenation

Meerwein Schmidt Ponndorf Verley (MSPV) reduction

This is a kind of hydrogenation that occurs by aluminium containing bases. The aluminium is connected in a framework that direct, or hinders, certaint approaches. The aluminium coordinates to an alcohol that becomes capable of donating a hydride in a six membered ring as seen sketched on figure 2.18 on the next page.

26 Andre Gemal_J. Org. Chem(1979)p418
23 Andre Gemal_J. Am. Chem. Soc.(1981)p5454
27 Shigeru Sasaki_Tetrahedron Lett.(2005)p1497
54 Calculated with Chem Bio Draw Ultra edition, version 11.0

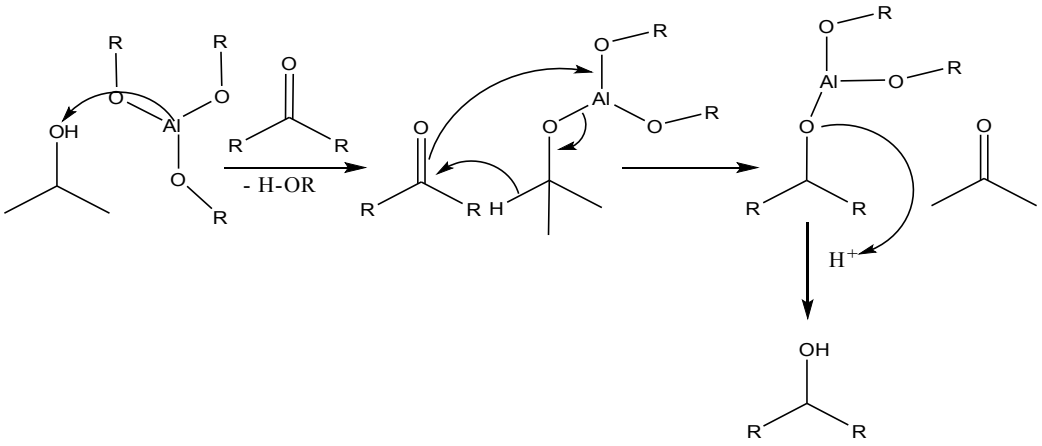


Figure 2.18 MSPV transfer hydrogenation

The shape of the ligand dictates in what places the hydride reaches on substrates e.g. only from one of the sides. By utilizing an asymmetric alumina base, Doering described in the early fifties one of the first asymmetric reductions ever done[29]. Doering figured that the approach from one of the non identical sides had a lower energy barrier. This reaction follows a reversed Oppenauer mechanism, described in chapter 2.5.3, there an excess of acetone in combination with an alumina base oxidised ketones. Instead of acetone, isopropanol or a more electron rich alcohol is used in great excess together with an alumina base to reduce ketones into the corresponding alcohols. Doering did some mechanistic studies in the same paper[29]. He used deuterized solvents to rule out that the proton or hydride came from the solvent. Hence this was proven to be a concerted reaction. The reaction is referred to as a gentle reaction. The reactants are not strong enough for substrates having a high reduction potential compared to the alcohol that is getting oxidized into a ketone. The same difference in potential as in the Oppenauer oxidation applies here. A difference of 100 mV between substrate ketone and alcohol gives 98% conversion with equal amounts of reagents. In organic terminology this means that the less electron density the ketone carbon has, the faster the carbonyl is reduced. The alcohol that is oxidized has to be geometrically accessible for the 6 membered transition state and has to have substituents that donate electron density. Acetones carbon NMR shift is at 206,7 ppm[30], so a considerable difference would be achieved by replacing the alcohols substituents with ones donating more electron density. This will increase the difference in oxidation potential between these reactants. A major advantage utilizing aluminium isopropoxide as base is that it binds water, hence if the base is used in 2-3 fold excess, it removes any traces of water present in the system. The work-up should be easy since acidification in the later step turns the base into aluminium and isopropanol. The generated acetone is also easily removed as lower boiling solvent.

29 W Doering_J. Am. Chem. Soc.(1950)p631

30 UCLA webpage http://www.chem.ucla.edu/~webspectra/NotesOnSolvents.html, read november 2007

2.4 Condensation with 2-hydroxycyclohexanone

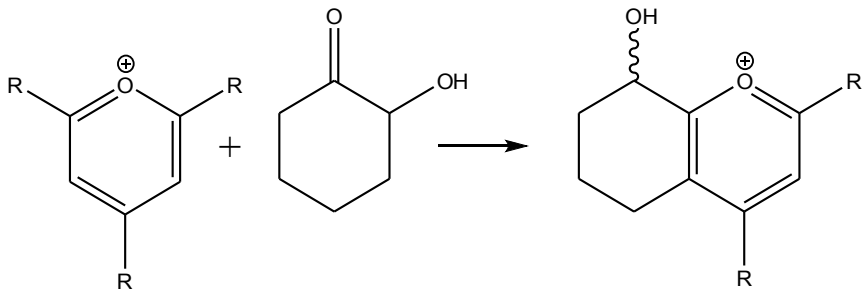


Figure 2.19 Pyrylium condensation

The mechanism that connects the diketone to the triphenyl pyrylium, described in chapter 2.24, may not include participation of the second ketone moiety. Hence a ring with the second ketone replaced by an alcohol or a protected alcohol could eliminate the necessity to reduce the ketone after is has been condensed with pyrylium. No reports where found were pyrylium had been condensated with this reagent. Diketones seem to be the only reagents condensated in the 2,3 positions of pyrylium. The most obvious reason to test the possibility to condensate the alcohol directly onto the molecule is that it might be the only way. It is possible that the ketone can not be reduced with the pyrylium present. Reduction of the ketone moiety on the whole molecule might break up the sensitive pyrylium ring system or give a low conversion rate, that will require further clean-up. The unconverted molecules might be recycled and reduced again but this will again only reduce the same ratio as the first reduction. From a chemical economic point of view, it is also smarter to do the transformations with the lowest yields as early in the row of syntheses as possible. Then valuable chemicals will not be used unnecessarily on molecules that will not make it through the synthesis. The relatively harsh conditions involving both reflux and a mixture of acetic acid and triethylamine as base can render a enantiomerically pure, but unstable,
2-hydroxycyclohexanon into a racemic mixture. Hence, the first priority is to try the condensation on a racemic mixture of the alcohol, that is expected to be easier to synthesize, to avoid unnecessary use of resources on a potentially dead end synthesis. If an enantiomerically pure or enriched route is discovered but found not to produce the required enantiomeric excess, a resolution could be done before condensation. This may be cleaner, faster and cheaper than to resolve the pyrylium salt.

Preparation of 2-hydroxycyclohexanone
The hydroxy ketone is known to dimerize into adipoin. The possibility of conservating the monomer or to break up the dimer before condensation needs to be explored. If it is made in a suitable solvent and no interfering by-products are generated, its reactivity may be tamed. A plausible route is to telescope the reaction immediately into the condensation stage. If the concentration is kept low, dimerization should be minimized.

2.4.1 Synthesis: Ishiis reagent on cyclohexane-1,2-diol

By oxidizing one of the alcohol moieties on various diols, Matthias discovered that Ishiis reagents; sodium bromate and sodium bisulfite in aqueous media, prefer axial ring positions. $NaHSO_3$ is by itself a mild reductant while $NaBrO_3$ is an oxidating reagent. The mixture generates a mild oxidant, applied in stoichiometric amounts relative to each

other. The mechanism is under dispute. Matthias[31] states that Br^+ is the actual oxidizing agent while Ichii thought HOBr was the actual reagent. The reagent oxidises electron poor alcohols and is used in excess over the substrate. Terminal aldehydes are reported to over oxidise into their acidic form[32]. The authors of this article ran the reaction at room temperature providing isolated yields up to 99% for conversion from the alcohol form of acetophenone in one hour. Studies has been done varying the proportions of the reagents, the selectivity was not changed, only reactivity[31]. Both chemicals are readily available and the method has reduced cyclohexan-1,2-diol to 95% yield in 2 hours at room temperature[31]. They got less than 5% over oxidation that generated the diketone. 5% is acceptable, the diketone has a lower boiling point and can be removed by a simple distillation. In this study, the products was not isolated, but was verified with NMR and GC.

2.4.2 Synthesis: nitrosobenzene oxidative insertion cyclohexanone

This mechanism inserts a oxygen asymmetrically via an intricate mechanism on cyclo-hexanone. The method utilizes nitrosobenzene and proline as directing catalyst that will give a choice of enantiomer configuration by utilizing L or R proline.
The mechanism is reproduced in fig 2.20 on the next page, the sketch is based upon a mechanistic study by Dhevalapally[33]. The nitrogens lone pairs, on proline attack the carbonyl carbon of the substrate that in turn ads the nitrosobenzene. The six membered transition state transfers the oxygen in alpha position. Armando Corvova et al. describe an insertion where they utilized proline as directing catalyst[34]. The nitrosobenzene they used to insert the oxygen into the ortho position of the ketone was only 0,1 equivalents to the substrate, making it the limiting reagent. Dhevalapally that did the mechanistic study, did use an excess of 3 equivalents of the nitrosobenzene.

31 Matthias Bierenstiel_Tetrahedron(2005)p4911
32 C Lee_Bull Korean Chem. Soc.(2002)p1667
33 D Ramachary_Org. Lett.(2005)p1577
34 Armando Cordova_Eur. Chem. Jour.(2004)p3673

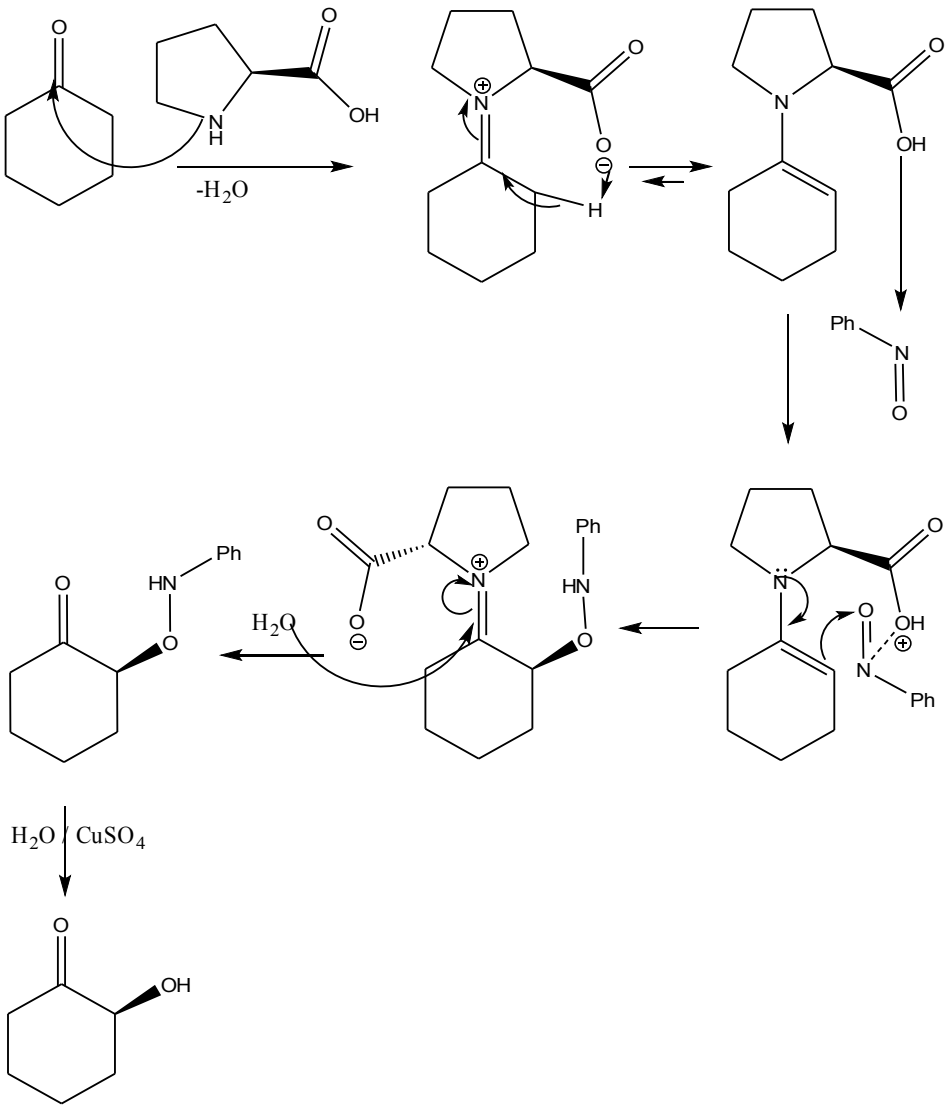


Figure 2.20 proline mediated oxidative insertion

2.4.3 Synthesis: activated zinc on cyclohexane-1,2 dione

Zinc is usually a strong reducing agent, but both the metallic form and zinc oxide have low solubility in water or alcohols. Rahim describes how an aqueous ammonium chloride solution charged with plain zinc dust, together with THF, reduces 1,2- diketones into 2-hydroxy ketones[35]. Rahim utilized 2 equivalents of the metal for each diketone. The zinc powder is reported to disappear during the reaction. With 1,2-cyclohexanone as substrate it was reported to take 45 minutes to get an yield of 92%.

35 Rahim Hekmatshoar_Monatshefte Fũr Chemie(2002)p195

2.4.4 Synthesis: singlet oxygen insertion

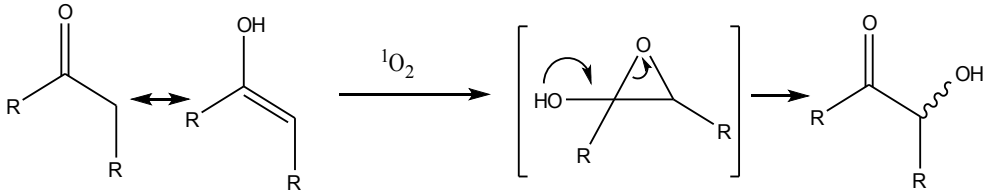


Figure 2.21 addition of an alcohol moiety by epoxide opening

Singlet oxygen can be generated *in situ*, from oxygen by radiation at 1270 nm, that corresponds to the energy needed (94,3 kJ mol^{-1}) to excite the oxygen molecule from its lower triplet state. Excited singlet oxygen acts as an electrophile that generates epoxides from the enol form of ketones. Since the solvent absorbs the radiation emitted in the heat range, a photosensitizer is required to transfer the energy. The photosensitizer absorbs radiation in the visible radiation range. This energy is in turn transferred as frequency that is suitable to excite the oxygen. These sensitisers are required to avoid making singlet oxygen in gas phase. A swede, Henrik Sunden, used tetraphenylporphine (TPP) as photo activator, and alanine as an asymmetric catalyst to insert oxygen in the ortho position of cyclohexanone[36]. They achieved 93% yield and an enantiomeric excess of 56%. This was not an isolated yield, they did *in situ* reductions with sodium borohydride to generate the diol.

2.4.5 Synthesis: functionalized silica, bromination of cyclohexanone

A sulfonic acid functionalized silica did together with NBS afford a variety of mono brominated ketones. Cyclohexanone was brominated with 95% isolated yield, CCl_4 was found to be the solvent of choice but, also the greener solvent diethyl ether afforded the product. The catalyst was recovered and utilized in three consecutive brominations without loss of activity, making the reaction attractive for scaled up procedures as well. The functionalized silica was prepared by immobilization of propyl thiol groups on silica using 3-mercaptopropyl trimethoxy silane. These groups were then oxidized to achieve sulfonic acid moieties with hydrogen peroxide. They only ran their synthesis in 1mmol scale, but at room temperature and with a procedure that seems applicable to larger scale synthesis. The next step, replacing the bromine, is a classical Sn_2 reaction with water in alkali conditions.

2.5 Condensation with 2-methoxycyclohexanone and derivatives

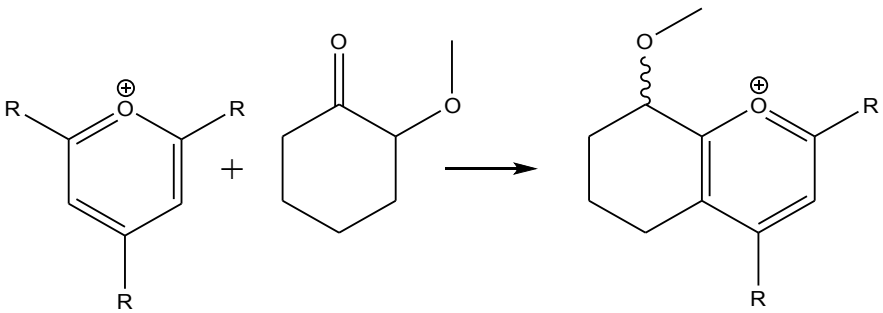


Figure 2.22 Pyrylium condensation with protected hydroxy functions

36 Henrik Sunden_Angew. Chem.(2004)p6532

Preparation of 2-methoxycyclohexanone

This molecule is more stable than 2-hydroxycyclohexanone since its alcohol is protected as a methoxy group, that makes it unable to dimerize.
The methoxy cyclohexanone is reported to have an IR peak at 1720 cm^{-1} and is a colourless or pale yellow oil with a boiling point at 78°C[37]. The NMR spectra recorded in chloroform: proton δ 3,67 (2H,m) 3,36 (3H,s) 2,45 (1H, m) 2,21 (2H,m) 1,89 (2H, m) 1,64 (3H,m) Carbon δ 209,9 84,1 57,5 40,4 34,1 27,5 23,0[38].

2.5.1 Synthesis: 2-methoxycyclohexanol the substrate to oxidize to ketone

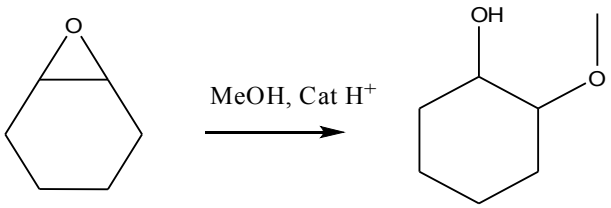


Figure 2.23 acid catalyzed epoxide opening

An approach to synthesise 2-methoxycyclohexanone is by preparation of 2-methoxy cyclohexanol to further oxidise its alcohol moiety. The alcohol is synthesized by epoxide cleavage on cyclohexene oxide. The nucleophile is the methanol. The catalytic amount of a strong acid like sulphuric acid, makes the epoxide ring opening occur easier. Given the methanol is dry, as water might compete as nucleophile to generate the diol, this method could hardly generate any by-products. A 100 % conversion should be achieved when a sufficient amount of methanol is utilized and the reaction is allowed to stand until completion. Afterwards the excess methanol, having a much lower boiling point, is evaporated off. The acid and, if present, water can be removed by simple washing of the evaporated residue. Dissolved e.g. in ether and brine, followed by drying of the organic phase with a hygroscopic salt like $MgSO_4$.

2.5.2 Synthesis: manganese dioxide

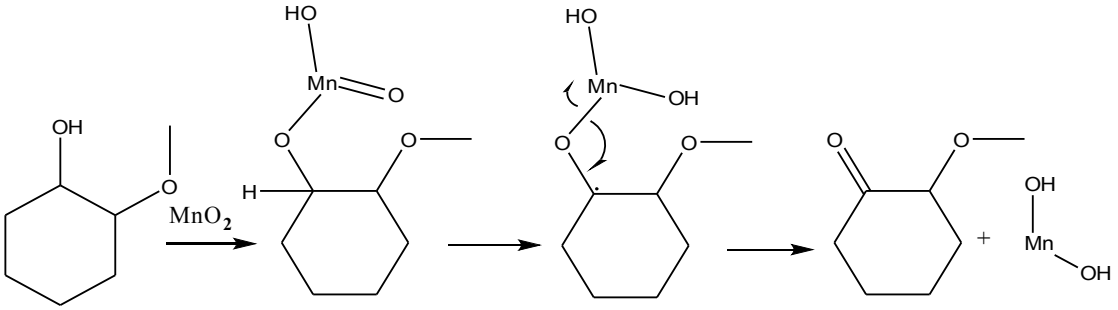


Figure 2.24 one of possible mechanisms in room temperature

MnO_2 is a common reagent for gentle oxidization of primary and secondary alcohols into carbonyls. The oxidation is most often done in room temperature in solvents that interact as little as possible with the surface of the particles. The lesser solvent the better, saturated solvents like straight and cycled alkanes are excellent choices. Compatible solvents less good but, able to dissolve more substrates are the more polar e.g. EtOAc, DMSO,THF but not alcohol as it will reduce the MnO_2 surface. If the

37 Kandasamy Jeyakumar_Synthesis(2007)p807
38 Gerhard Lauktien_Tetrahedron As.(1997)p3457

reaction is run in a very polar solvent, the solvent might block or compete with the substrate for the metallic surface. The mechanism for the oxidation in room temperature has been of great dispute, but is thought to occur as sketched in figure 2.24. The manganese oxidant has to be employed in great excess. Manganese that has not been thoroughly cleansed is reported to be chemically more active than pure[39]. Gritter suggests that the real oxidising reagent are small amounts of impurities present in various amounts depending on the production procedure of the manganese. Manganese with a little water gives better results than dry[40]. At elevated reaction temperatures, the origin of the manganese is reported to be of lesser importance. Then the active surface area of the metal is the limiting factor. The chemoselectivity of manganese is better at low temperatures, allylic alcohols are oxidized in favour of saturated alcohols. Elevated temperatures make the manganese behave as a strong oxidant, able to react with alkenes and saturated alcohols. The active manganese dioxide can easily be recovered by heating at 110 degrees for 24 hours[41]. A collection of oxidations with mechanisms and discussions has been collected by Tojo[64]. This is a good book where a vast amount of authors has contributed. In this book the authors that recommended elevated temperatures, for recovering the manganese surface, also recommended to let it equilibrate with atmospheric moisture for several days. To avoid deactivating the manganese during reaction, released water might be trapped with molecular sieves or magnesium sulphate.

2.5.3 Synthesis: Oppenauer oxidation

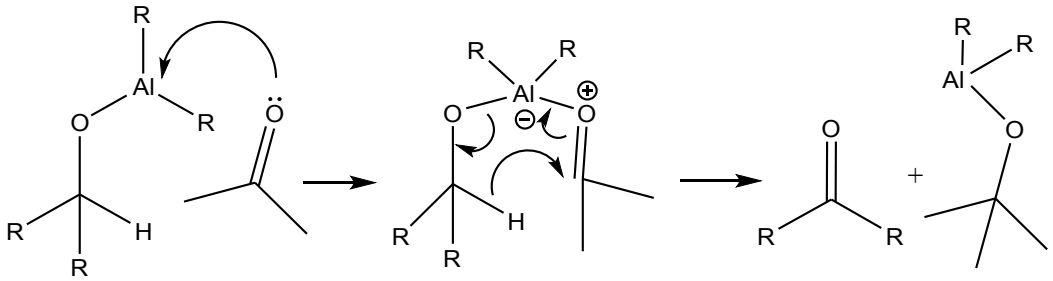


Figure 2.25 Oppenauer mechanism

This Oppenauer oxidation follows the Meerwein Schmidt Ponndorf Verley (MSPV) mechanism (described in chapter 2.3.8) except that is goes the opposite way. The Oppenauer mechanism in figure 2.25 shows how the six membered transition state is formed between the ketone, the substrate alcohol and aluminium tert-butoxide[41]. The conversion rate depends on the potential difference between the alcohol and the ketone. For cyclohexanone and acetone the difference is about 33 mV. Gabriel states that an 98% conversion could only be achieved with a difference greater than 100 mV. Le Chatliers principle does in this reversible reaction dictate that the conversion is higher with higher excess of "lower worthy" ketone. The most selective oxidations occur at temperatures around 20°C. Cristopher oxidated many different substrate alcohols, with three equivalents of 3-nitrobenzaldehyde and 0,1 equivalent of $AlMe_3$ as the catalytic base[42]. One of the substrates were 1-methyl cyclohexanol were he achieved a 99% conversion within one hour. The supporting paper following that publication[42] described successful up-scaling to 10 gram substrate. Their substrate is 10 times cheaper than MnO_2 easy and cheap to dispose afterwards compared to heavy metal oxidizing agents.

39 Gritter_Nature(1964)p179
40 Patent: Evans R.M _Quat.Rev.(1959)
41 Vogel's Textbook of practival organic chemistry_Longman scientific and technical(1989)p445 p520 p524 p611
64 Gabriel Tojo; Marcos Fernández_Springer(2002)
42 C Graves_J. Am. Chem. Soc.(2006p)p12596

2.5.4 Synthesis: Magtrieve(TM) oxidation

Magtrieve is a trademark for Dupoints tetravalent chromium dioxide oxidant. It has been manufactured in such a way that in can be retrieved with a magnet. Regular commercial CrO_2 goes through a reductive surface treatment, due to its common application on magnetic tape[43]. It has been reported that it can be recycled many times with low loss of oxidating power, extracted simply by holding a strong magnet underneath the beaker when removing the liquid reaction contents[44]. Wan reported 92% activity the fifth run after the metal is washed with ether and regenerated in hot air. It is reported to work well in microwave[45]. Heterogeneous reactants that are easy to recycle is specially attractive if the procedure is to be scaled up.

2.5.5 Synthesis: sodium hypochlorite

This reaction is done with an laboratory equivalent of the household bleach Chlorine. In fact several papers are written where Chlorine gave great yields[46] [47]. The concentration of active chlorine decreases upon storage. Stored reagents require a titration to obtain the true concentration. Production of chlorine is done by passing chlorine gas through a solution of sodium hydroxide, producing a relatively stable mixture containing between 3-6% active chlorine. As seen from the equation salt is a by-product that can be seen precipitating in the bottles of commercial quality.

$$3\ Cl_2 + 6\ NaOH \rightarrow 5\ NaCl + NaClO_3 + 3\ H_2O$$

Gholam[47] utilized “Clorox Fresh scent Bleach™ “ to convert various alcohols in good isolated yields at room temperature with short reaction times. None of the starting material was left unoxidized, making the clean-up easy. The stronger solutions are made by electrolysis, generating about 14% active chlorine, and need to be kept cold and used relatively fast. The mechanism for this reaction favour oxidation of secondary vs primary alcohols. A common procedure is to slowly add an excess of about 3 equivalents of aqueous sodium. This is added over the substrate dissolved in acetic acid. This is then quenched with $NaHCO_3$ in an aqueous solution. Followed by extraction into an organic solvent, washed, dried and concentrated. The reaction is highly exothermic, the temperature needs to be controlled. Increased temperature increases the oxidation power.

2.5.6 Synthesis: molybdenum mediated epoxide opening

43 Ross A. Lee_Tetrahedron Lett.(1997)p3857
44 Marcin Lukasiewicz_MDPI(2002)
45 H Wan_Monatshefte Fũr Chemie(2008)p909
46 Czech Pat. No 265359/19901990
47 G Mirafzal_Tetrahedron Lett.(1998)p7263

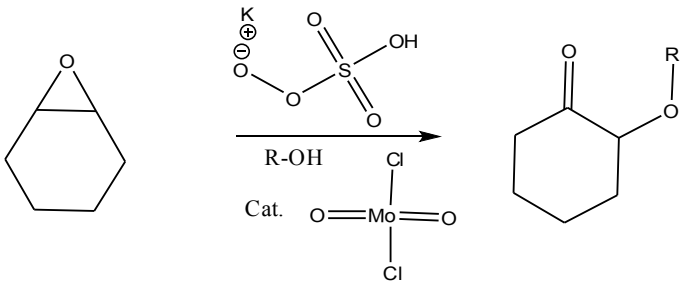


Figure 2.25 Oxone as oxidant on epoxide opening

Molybdenum in the form of dichlorodioxomolybdenum MoO_2Cl_2 is employed in catalytic amount of the substrate with an alcohol serving as solvent and reagent. Oxone(TM) (Potassium peroxymonosulfate) is added to oxidise the intermediate alcohol *in situ*. This strong oxidant is a Du Pont de Nemours & Co trademark. It is a mixture of K_2SO_4,$KHSO_4$ and KHSO5, the latter the strong oxidant[48]. Kandasami converted cyclohexene oxide to get 91% 2-methoxycyclohexanol in one hour with the metal in methanol[37]. In this reaction they used dried solvents under inert conditions. They ran the same reaction open vessel with 1,2 equivalents of Oxone and isolated 72% of the corresponding ketone after 2 hours. Tu-Cai and David made an another procedure that in one pot converts 45% of cyclohexanol into ketone with one equivalent of Oxone in water[49]. They found the reaction to be optimum in the pH range between 6 and 8.

48 From dupoints webpage www2.dupont.com/Oxone/en_US/assets/downloads/K20108%20Oxone®%20Safety%20and%20Handling.pdf , read 17 may 2009

49 T Zheng_Tetrahedron Lett.(1995)p833

3 Results and discussion

3.1 Preparation of the 5,6,7,8-tetrahydro-8-oxo-1-benzopyrylium salt

3.1.1 Synthesis 2,4,6-triphenylpyrylium tetrafluoroborate

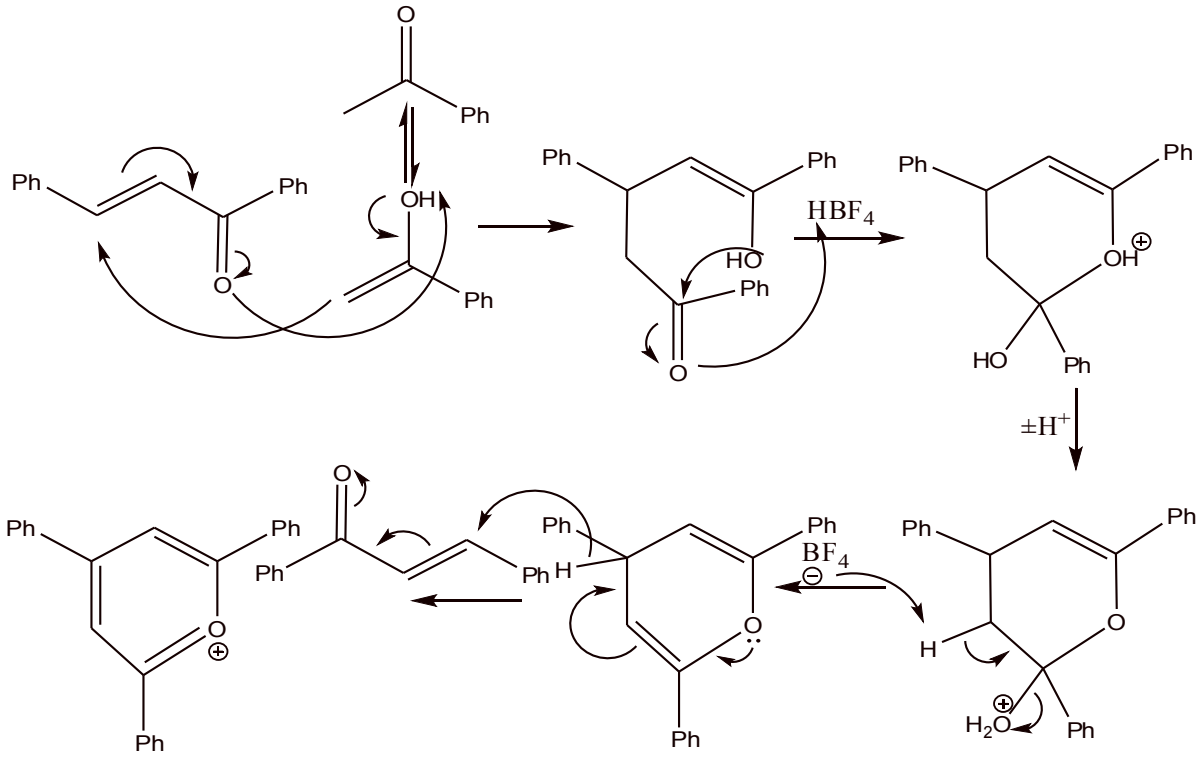


Figure 3.1 mechanism triphenylpyrilium synthesis

A procedure for preparation of this symmetrical pyrylium ring was described by Vogel, Dimroth and Reichardt in the late sixties[11]. The synthesis was done with acetophenone that donated 2 carbons to the pyrylium skeleton. One of the two 1,3-diphenyl-2-propenone molecules contributed with the additional 3 carbons and the oxygen. In the last step of the mechanism, the intermediate pyran gains aromaticity by transferring the hydride from its 4 position to 1,3-Diphenyl-2-propenone, as seen in figure 3.1.The second equivalent of 1,3-diphenyl-2-propenone served only as a hydride acceptor to remain in the solution. Cheap and readily available starting materials was utilized in the reaction. In an industrial sized reaction it could be recycled.

Vogel and co-workers reported 52-54% yield after recrystallization from 1,2 dichloroethane. In our hands we achieved 35% crude, after recrystallization from acetone and pentane the yield was 28%. The lower yield may be explained by change of two factors. The scale of our synthesis (20,8g 1,3-Diphenyl-2-propenone) was only 10% of the reported procedure (208 g 1,3-Diphenyl-2-propenone). In addition, the different solvent system we used for the recrystallization may explain some of our lesser yield. On the other hand recrystallization from acetone and pentane was advantageous because the product became less static and appeared more dense. Also, acetone and pentane are more environmentally friendly and cheaper than 1,2 dichloroethane. The

11 K Dimroth_Org. Syntheses Coll.(1969)p1135

difference in physical properties might be because the structure is a polymorph, capable of packing different crystals. The compound has a strong deep yellow colour, and is fluorescent dissolved in solution. The proton NMR spectrum, recorded in acetone, shows peaks corresponding to nine protons in the phenyl region between 7,99- 7,74 ppm. There are four protons at resonating at 8,66 ppm and two at 8,85 ppm these are the residual aromatic protons affected by the electron withdrawing pyrylium ring. There are two protons resonating as a singlet at 9,17 ppm, corresponding to the two protons on the pyrylium ring, that is electron deficient compared to benzene. The reported proton specter is in agreement with our findings.
The carbon spectrum shows nine peaks. The signal at 171 ppm corresponds to the 2 and 6 positioned carbons of the pyrylium ring that are in equivalent environments. The weaker signal at 167 ppm fit to the quaternary carbon in 4 position on the pyrylium ring .The expected number of different carbon shifts was eleven, the observed deviation may be due to overlap of signals in the aromatic region. HRMS analysis was in agreement with the calculated mass of the pyrylium cation. The mass is exact, since the compound is a cation. The NMR spectra can be found in appendix A.

^{1}H (400 MHz,acetone) δ 9,17 (2H,s) 8,66 (4H,m) 8,58 (2H,m) 7,99- 7,74 (9H,m) ppm.
^{13}C (100 MHz,acetone) δ171,4 166,7 135,5 133,3 130,3 130,2 129,6 129,2 115,7 ppm.
m.p beyond 240°C (limited by instrumentation, lit: 251-257°C)
I.R (solid ATR) 1621 cm^{-1}
Ms: m/z 309,12743 (100% base peak) [M+] calc 309,12739

3.1.2 Synthesis and investigation of condensation, ketone 1 intermediate

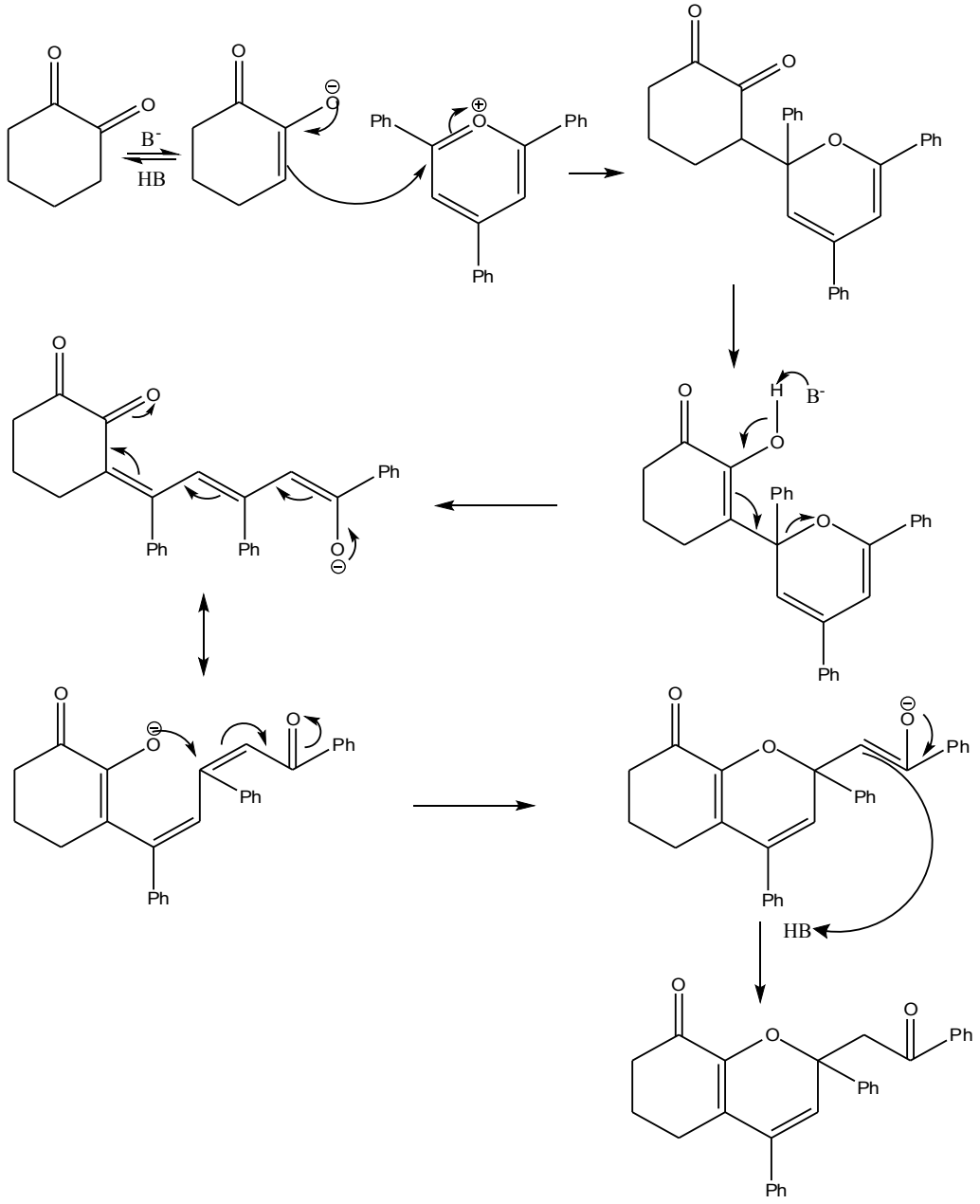


Figure 3.2 condensation on triphenylpyrilium

This procedure was slightly modified from one found were the counterion was perchlorate. It is the condensation between pyrylium and the diketone. The triphenylpyrilium from the previous synthesis (1 eq 4,8 g 0,0121 mol) was dissolved in 25 ml dry methanol followed by addition of five equivalents of cyclohexan-1,2 dion. Two equivalents of triethylamine was mixed with two equivalents of the acetic acid and added to the mixture. The mixture was allowed to condensate on reflux for five hours. The enol form of the diketone is nucleophilic, hence it is able to attach to the electrophile positions on the pyrylium ring. This attachment expels the counterion and interrupts the aromatic ring system, resulting in ring opening. The original pyrylium oxygen did help to rebuild the ring since it worked as an electron accepting side chain ketone. The reaction mixture was measured to be slightly basic. The whole reaction was done in one pot and was reported to yield 76% with triphenylpyrilium perchlorate after recrystallization. We achieved 89% as crude material. Recrystallization was not found necessary, the crude product was found clean after treatment with cold ethanol and ether. The IR peak for the perchlorate analogue, measured in perchloromethane, had

an IR peak at 1680 cm^{-1} [50]. Our product measured neat was at 1671 cm^{-1}. The proton NMR spectrum, recorded in chloroform, shows two protons at 7,9 ppm and two at 7,6 ppm. These have the same coupling constant J = 7,3 and corresponds to splitting of the ortho positions in the phenyl rings. There are nine protons that resonates around 7,3 ppm as a multiplet from the phenyl rings The proton on the C-3 on the pyran ring resonates as a singlet at 6,57 ppm. An AB coupling system J=15,7 shown at 3,89 ppm and 3,65 ppm, it corresponds to the two CH_2 protons on the ketone side chain. The remaining 6 aliphatic signals corresponds to the side chain protons. A proton NMR spectra of this product was found reported[50] but, with few details, nevertheless they do not contradict our results. The two ketone carbons resonates at 197 and 193 ppm in the carbon specter. The aromatic area is as expected crowded, and multiple overlap occurs. The peak at 80 ppm is the phenyl substituted quaternary carbon next to the oxygen in the main ring. The three saturated carbons on the pyran side chain appear as peaks at lower shifts. The perchlorate analogue of this molecule was reported to have IR carbonyl peaks between 1680 – 1682 cm^{-1} in perchloromethane. The NMR spectra can be found in appendix A.

^{1}H (400 MHz,chloroform) δ 7,90 (2H,d,J=7,3) 7,61 (2H,d,J=7,3) 7,44 - 7,28 (9H,m) 6,57 (1H,s) 3,89 (1H,d,J=15,7) 3,65 (1H,d,J=15,7) 2,45 - 2,27 (4H,m) 1,73 (2H,m) ppm.
^{13}C (100 MHz,chloroform) δ 197 193 144 143 137,7 137,5 137,2 133,4 130,5 129,5 128,8 128,7 128,6 128,5 128,3 128,2 128,0 125,8 79,5 50,5 38,5 26,2 22,2 ppm.
I.R (solid ATR) 1671 cm^{-1}
m.p 225°C slight brown 240°C melts.

Investigating the condensation

The motivation for starting this investigation was to get an impression of what factors did play in on this condensation, and later on use them to make procedures to connect hydroxycyclohexanone and other substituted cyclohexanones to the pyrylium salt.
The goal was also to actually consume the expensive substrate on producing the product and find the settings to optimize its usage. The study was done in a 4,1% scale compared too our original synthesis. 0,0005 mol of the substrate triphenylpyrilium was used in comparison with the 0,0121 mol of substrate consumed in our original synthesis. The reaction temperature was originally around 72°C when the solvent refluxed. These reagents were moved into sealed vessels and heated in microwave at 100°C. The concentration was slightly increased, 80% of solvent was used compared to the original procedure. After 1 hour this gave 43,6% yield. Increasing the time to two hours gave 42,6% and is not a significant difference. The original paper did state to use dry alcohol as solvent, this lead to the assumption that the reaction would work better in dry and inert conditions. A drop of water was added to the solvent, this resulted in 44,2% yield, the extra yield might be contributed by the weight of the water left in the salt.

The limitation of only 2,5 equivalents instead of 5 diketone, resulted in 35% yield. This is a 20% increase in the utilization of the expensive diketone. Further experiments should be done to establish more material to calculate the best parameters regarding the scale and cost factor. All samples were found pure with NMR with the exception of traces of water left from the condensation in wet solvent The individual samples were otherwise treated as similar to each other as possible.

50 T Zimmermann_J. Fũr Prak. Chemie(1988)p306

3.1.3 Alternative approach to reduction on ketone 1

The ability to condensate with the methyl, methoxy and silyl analogue of the diketone from the synthesis described on the previous page were investigated. A success to condensate them depends on their ability to enolize and act as nucleophiles. There has not been identified any work with alternative nucleophile rings, to condensate to the pyrylium ring. Adipoin, 2-hydroxycyclohexanone, 2-methoxycyclohexanone,2-(tert-butyldimethylsilyloxy) cyclohexanone and 2-methylcyclohexanone were tested.
When neither of the 4 substrates attempted, did condensate in the original reaction conditions. The temperature and time was increased but no condensation did still occur. More attempts were done by exchanging the base with a more sterically hindered; morpholine. This base was advised in the publication for condensations were there was bromine and chlorine present on the substrate[50]. The idea was that the base would maintain a certaint amount on the substrate in its enol form. Adipoin and 2-hydroxycyclohexanone did neither condensate to the substrate. The reasoning for the first adipoin failure was thought to be that is did not cleave into its monomeric form. The monomer did neither condensate to the ring, but this was first tested after the adipoin condensations. The problems with condensating other nucleophile rings to the pyrylium ring was mentioned in the paper we found for this synthesis[50]. They had also failed with five and seven membered rings.

3.1.4 8-oxo-2,4-diphenyl-5,6,7,8- tetrahydrobenzopyrylium tetrafluoroborate

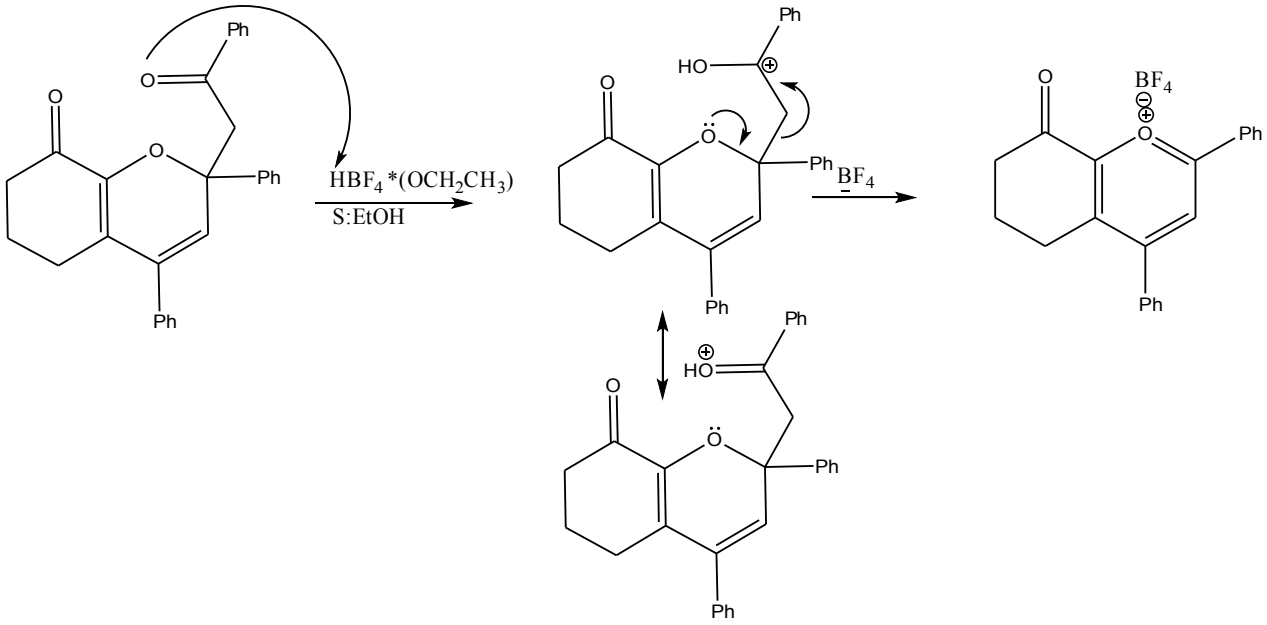


Figure 3.3 synthesis of ketone **1**

The last step, achieving the pyrylium moiety back on the molecule, was done with fluoroboric acid that not only consists of the counterion to the pyrylium salt but its also a strong acid (pKa -0,4). The product from the previous synthesis 2-(2-oxo-2-phenylethyl)-2,4-diphenyl-6,7-dihydro-2H-chromen-8(5H)-one (1 eq 2,52 g 0,003 mol) was mixed with 60 ml dry ethanol that was heated to 50°C before adding the acid HBF_4 (about 6 eq 6,5 ml 52% in ether) dropvice, the authors utilizing perchlorate added it in one hit[50]. The reaction was fast, the ability to use ethanol both as reaction solvent and for washing was ideal. It gave 71,3% yield after only 30 minutes on reflux. Slightly less, but cleaner, product was achieved by washing the filtrate with THF in addition to ethanol. The product was found insoluble in ethanol, but the starting material dissolves slightly under reflux. Addition of fluoroboric acid to this solution did achieve some precipitation but,

50 T Zimmermann_J. Fũr Prak. Chemie(1988)p306

only gave one percent more yield. In the reaction the acid protonates the ketone side chain, this makes it into a better leaving group. At the same time the, counterion of the acid gets attracted by the positive charge developed in the ring as it lowers its energy by gaining aromaticity. This salt effect made the compound precipitate out from the reaction mixture as it was generated. Precipitation removes the product from the reactants and makes it easy work-up.

The original procedure utilizes perchlorate as counterion that in its pure form has a decomposition energy of 5020 Jg^{-1} (higher than the energy of TNT that has4295 Jg^{-1}). The tetrafluoroborate is safer with a decomposition energy of 260 Jg^{-1} [51]. The utilization of perchlorate requires that the product is kept wet, and not crushed or induced energy uncarefully, or it might explode. The disadvantage of BF^{4-} compared to ClO^{4-} or PF^{6-} is that it is less stable in water and requires more polar organic solvents. The yield we achieved was 71% while the people that synthesized it with perchlorate anion achieved 80% with the same 0,003 mol starting material as in our synthesis. A patent was discovered[52], where they achieved 99% with minor modifications of this synthesis. Instead of the HBF_4 ether complex we used, they used BF_3 complexed with methanol. Upon acidification this does *in situ* generate BF_4 but if there is water present it might generate reactive HF.

Our procedure was slightly modified from the literature, more ethanol was needed to dissolve the substrate. The addition of the acid was done over a period of 30 minutes while the authors mixed all chemicals together. A cleaner but also lesser amounts of product was achieved when THF was used to wash the filtrate. This is due to the fact that the product dissolves slightly in THF. The increased yield we obtained by adding HBF_4 and reduce it in vacuum, is not worth the increased time and costs. The proton NMR of the perchlorate analogue of this molecule had been recorded in trifluoroacetic acid, the results are in agreement with ours. Our proton NMR specter was recorded in acetonitrile and did show the only proton on the main ring as a singlet at 8,76 ppm, significantly less shielded than before it became aromatic having a shift at 6,57 ppm. The aromatic area of the specter is rather chaotic but, the amount of protons corresponds to the structure. The carbon specter has 17 distinct peaks, among them characteristic pyrylium shifts at 172 ppm corresponding to C-2 and C-6, also the three saturated carbons is seen at lower shift. The aromatic area around 130 ppm is expected to contain overlap that corresponds to the 4 lacking carbon shifts. The sample dissolved badly, the solvent was saturated but, still the solvent signal was much stronger than the samples signals. The mass is in agreement with the calculations. Total conversion appears possible with further investigations of solvent systems, temperature, time, and maybe different counter ions.

^{1}H (400 MHz,CD_3CN) δ 8,76 (1H,s) 8,43 (2H,d) 7,94 (1H,t) 7,79 (7H,m) 3,21 (2H,t) 3,10 – 2,90 (2H,t) 2,36 – 2,10 (2H,m) ppm.
^{13}C (100 MHz,CD_3CN) δ188,9 172,0 172,0 155,4 139,5 137,4 133,9 133,5 130,7 130,0 129,9 129,7 128,5 124,2 38,2 26,7 21,7 ppm.
I.R (solid ATR) 1714,59 cm^{-1} (lit 1716 cm^{-1})[50].
m.p [183, 185]°C.
Ms: m/z [M+Na^+] 341,1153 (100% base peak) 301,1229 [M^+] calculated 301,1223.

51 "Chemical development & scale-up" Dr. Will Watson & Dr Derek Robinson Course manual from course given 3-5 of march 2009 Rome
52 patent: DE 102007012794

Total yield

The total yield of our 3 step procedure towards ketone **1** is 17,8%. That is 28% generating the pyrylium, a 89% yield in attaching the diketone and 71% giving back the aromaticity of the ring in the last step.
The reaction intermediates, might not, have needed to be washed and dried but, could had been telescoped into the next reaction. This would give higher yields but to the expense of the possibility of starting unwanted side reactions.

Figure 3.4 2,4,6- triphenylpyrilium tetrafluoroborate dissolved in different solvents under long wave UV radiation. Studies on this fluorescent effect of pyrylium salts show that it is highly dependent upon how the counterion interacts with the pyrylium.

3.2 Attempted regioselective reduction of ketone 1

3.2.1 Analysing the product mixtures

We were not able to measure conversions with the more classical methods, like chromatography. An injection of the reaction mixture directly into GC that is a convenient was of measuring reaction mixtures directly, but is does not work with salts.
TLC could to some degree be used but, was found to have limited usage when many components did not dissolve or moved little on the plates. Salts generally has low solvability in apolar solvents. Carbon and proton NMR has been used to identify and measure product mixtures, but precipitation or limited solvability did prove to be a considerable problem. Tables like the one in figure 3.5 is helpful when you want to understand what properties the solvent need to have to dissolve the substrate.

	triphenyl pyrylium	Ketone **1**
H_2O	2	2
MeOH	5	5
EtOH	3	2
THF	2	2
MTBE	4	2
Ether	2	1
Acetone	5	5
Acetonitrile	5	5
Toluene	2	3
1,2 dichlorethane	5	4
DCM	4	3
Chloroform	3	3

1 = undissolved 5 = completely dissolved at 20°C

Figure 3.5 table from a relative study of the solubility of tetrafluoroborate pyrylium

3.2.2 The CBS mediated hydroboration reduction

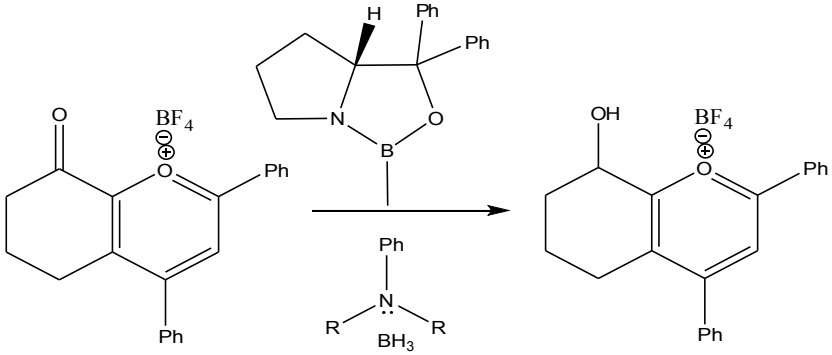


Figure 3.6 ketone **1** and its reduced form, CBS and borane reagent

Literature:[18] [19] [17] [52]

The substrate ketone **1** 0,0035 mol and the CBS catalyst (0,1 eq) were mixed in dry THF under inert atmosphere. Before careful stoichiometric addition of the respective borane reagents in room temperature. CBS mediated reactions with borane has proven to be one of the most versatile systems for asymmetric induction, covering a wide range of substrates. As all borane reagents are sensitive to water, we acquired the two we tried as solutions.

We tested DEANB and BACH-EI, two structurally similar, tertiary amine borinating reagents. They differ where DEANB has two ethyl groups, BACH-EI has one ethyl and one isopropyl group. Their chemical properties are thought to differ only slightly. Byung has earlier tested these borane donors with great yields and enantiomeric excess on a series of alkenes with aromatic substituents[56]. These two reagents borane reagents different configuration gave negligible difference in enantioselectivity, in their study. Ketone **1** did not appear to dissolve properly in any of these reagent mixtures. THF was on our substrate already discovered to be a bad solvent. This can be seen from the study we did on solvability on ketone **1** in the table on figure 3.5. The reactions were still allowed to commence as a small ratio of the substrate was still thought to be dissolved.

18 Ashok M. Salunkhe_Tetrahedron Lett.(1997)p1523
19 Byung Tae Cho_J. Chem. Soc. Perkin Trans.(1999)p2095
17 Biao Jiang_Tetrahedron Lett.(2000)p10281
52 H C Brown_Acc. Chem. Res.(1991)p16
56 Byung Tae Cho_Tetrahedron Ass.(1999)p1843

Ketone **1** was once heated in THF at 50°C and much effort was put in adding it as a solution during addition to the reactants, but in vain. We began to separate the product mixture on flash column to identify the components. This was abandoned when triphenylpyrilium also gave a mixture of products under the same reaction conditions. The pyrylium ring was tested to see if it remained unchanged. The pyrylium part of the ketone **1** should essentially have the same reactivity as triphenylpyrilium. When this was discovered we began to focus our efforts on a different strategy. The same conditions as applied on ketone **1** did successfully reduce acetophenone with BACH-EI as borane agent.

3.2.3 DIBAL reductions

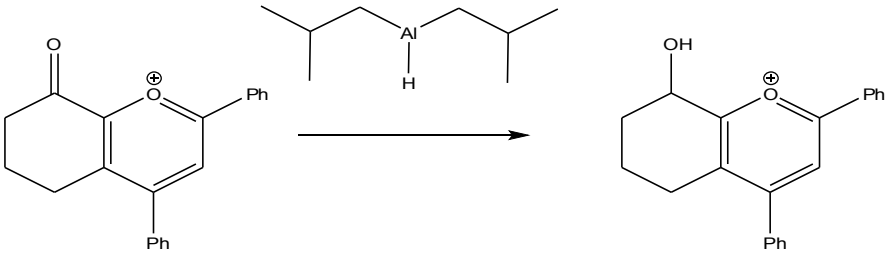


Figure 3.7 sketch of dibal, ketone **1** and its reduced form

Literature[21 22 23]

The first reduction was done inert, with 0,00144 mol of the substrate ketone **1** with 1,3 equivalents of DIBAL in toluene as solvent at -78°C. After 10 minutes the substrate was recovered, this encouraged use of higher temperatures and longer reaction times. 7 reactions were conducted varying temperature between -78 to 0°C, DIBAL between 1,3 to 2,6 eq and time between 6 to 40 minutes. Also the solvent was varied as pure and mixtures of toluene, DCM and THF. Either the starting material, along with some by-products, was recovered as long as the temperature was kept low or the pyrylium aromatic system was destroyed when the reaction was done at 0°C in DCM. In toluene and THF the substrate is thought to not have been properly dissolved. THF had previously been found to dissolve the product during wash of the compound during work-up but, that was at room temperature. Moving the substrate under inert atmosphere did prove hard, as it dissolved badly. Hence the idea to drop the substrate into dibal instead of the other way around became impossible. Gave back starting material and some by-products, as long as the temperature was kept low and the pyrylium ring survived the conditions. When the reaction was done in 0°C in DCM the substrate appeared dissolved, and its pyrylium aromatic system was destroyed.

3.2.4 Transfer hydrogenation, Meerwein Schmidt Ponndorf Verley reduction

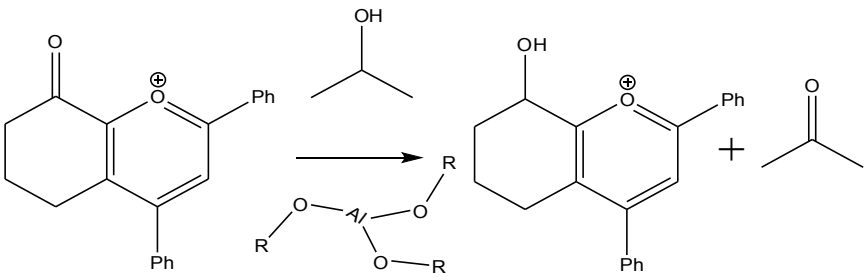


Figure 3.8 ketone **1**, with the MSPV reactants and its reduced form

Literature[53]

53 J Yin_J. Org. Chem.(2006)p840

Aluminium isopropoxide (3 eq) and isopropanol (240 eq) had been stirred for a few minutes and heated until reflux under nitrogen atmosphere before ketone **1** (1 eq 0,20 g 0,00055 mol) was added dry. The aluminium isopropoxide being highly hygroscopic would had bounded any water present in the reaction mixture before the ketone was added. The basic conditions could have pushed the equilibrium between open chain and cycle towards open chain. But no water was present, and the base seem unlikely to attack the pyrylium as a nucleophile, and the acidic work-up would had pushed any equilibrium of reversible ring openings towards an aromatic pyrylium ring again. The NMR spectra from the reaction mixtures did not contain the pyrylium signals. The configuration of the substrate, ketone **1**, might indicate a relatively electron rich carbonyl that had a calculated shift at 197 ppm[54]. Later it was measured till 189 ppm this low value indicates an even more electron rich ketone. That makes it even less attractive for the hydride. The equilibrium between ketone and alcohol was nevertheless 1 : 240 and such an excess should had pushed even an really unfavourable equilibrium towards product. To completely rule out this as a plausible pathway the $AlMe_3$ base should be tested. This base is also recommended by the author for the Oppenauer oxidation.

3.2.5 $CeCl_3$ / $NaBH_4$

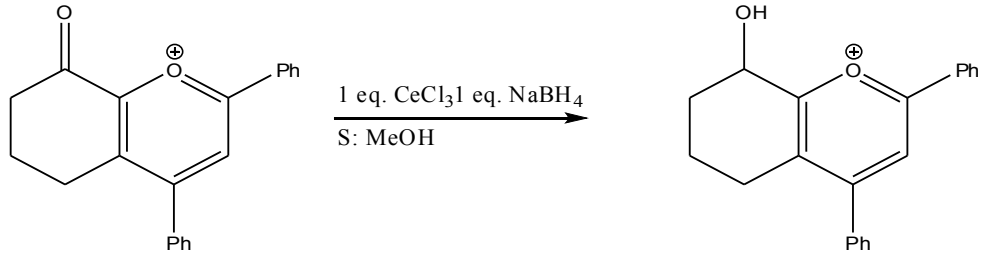


Figure 3.9 The reducing agent and the directing salt

Literature[26] [23] [27]

This reaction was done on 0,00051 mol of ketone **1** as substrate. First the cerium salt was added to the substrate in methanol, before the reducing agent was added. The addition of the sodium borohydride was tested in RT and at 0°C both reduced the pyrylium ring. We added in a consecutive reaction reducing agent just until we observed that no more bobbles occurred. About half the amount, was added, compared to the first attempts but neither this gave the product. One addition was attempted at - 70°C on the precursor of the ketone **1**, when the pyrylium ring was a pyrane. The idea was to see if we could reduce the ketone on the ring and build the pyrylium in a consecutive step. Neither of its two ketone functionalities became reduced, the substrate was untouched. Andre's study[27], that is discussed in chapter 2.3.7, had shown that it reduced electron rich ketones. A ^{13}C-NMR measurement on the substrate ketone **1** did prove that its side chain ketone has a shift at 189 ppm. The value calculated had predicted 198 ppm[54], but 189 ppm indicates that it is electronically quite close to the pyryliums nucleophilic centers at C-2 and C-4 having shifts at 172 ppm. This reagent did not show the chemoselectivity required for the substrate. In retrospective the strong nucleophilic acid HCl used to acidify the reaction after quenching may had been replaced by a weaker acid.

54 Calculated with Chem Bio Draw Ultra edition, version 11.0
26 Andre L Gemal_J. Org. Chem(1979)p418
23 Andre Gemal_J. Am. Chem. Soc.(1981)p5454
27 Shigeru Sasaki_Tetrahedron Lett.(2005)p1497

3.3 Conversion of ketone 1, into its pyridine analogue

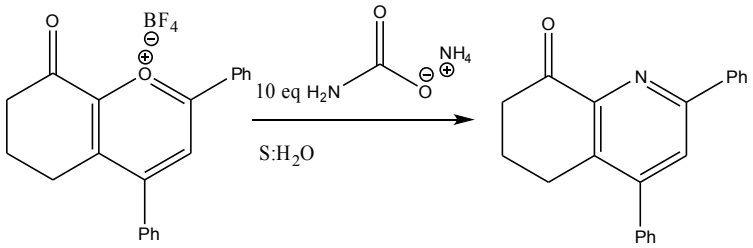


Figure 3.10 conversion of heteroatom

Literature: [52]
The conversion of the heteroatom from oxygen to nitrogen in the aromatic system.
Ketone **1** (0,0028 mol) was mixed with water gaining a suspension, 10 equivalents of ammoniumcarbamate was added followed by strong stirring for 24 hours in room temperature. The precipitate was washed with water followed by diethyl ether yielding 82% as a slight brownish white powder with traces of water present. In the patent[52] the authors had heated the product at 50°C during drying. This was found necessary in our labs as well to achieve the salt without water. We had tried drying it in a rotavapor for 1 hour at 50 mbar in room temperature but, could not remove all the water. They achieved a slightly higher yield, 87,5% compared to our 82%. This motivates to run this reaction 10 times scaled-up to their 0,03 mol substrate, or beyond. The melting point was measured 5°C higher than theirs, that might be a indicator of impurities in their product, our NMR spectra was nevertheless very similar to theirs. The IR measurements found in the paper had a carbonyle peak at 1700 cm^{-1} .They do not say in what form they measured it in. But if they were measured the same way the difference from ours at 1715 cm^{-1} is quite big. Nevertheless the NMR and mass is in agreement with its structure.

^{1}H (400 MHz,chloroform) δ 8,10 (2H,d,J=7,1) 7,79 (1H,s) 7,59 – 7,35 (8H,m) 2,95 (2H,t,*J*=6,0) 2,86 (2H,t,J=6,0) 2,13 (2H,m) ppm.
^{13}C (100 MHz,chloroform) δ197,0 156,5 151,6 148,7 138,7 138,5 137,1 129,5 129,0 128,9 128,8 128,7 127,4 124,6 40,0 27,7 23,0 ppm (17 carbons, 4 carbons overlapping).
I.R 1714,59 cm^{-1} .
m.p [183, 185] °C (reported in 52 as 177-178 °C).
Ms: m/z [$M+H^{+}$] 300,1387 (100% base peak) calc 299,1310.

52 patent: DE 102007012794

3.4 Synthesis of 2-hydroxycyclohexanone

3.4.1 Analysis of 2-hydroxycyclohexanone

The hydroxycyclohexanone is to reactive to be shipped, hence it can only be bought as a dimer. The NMR spectra SIGMA-ALDRICH ™ supplied for the dimer in DMSO (appendix C) appeared to be the spectrum of the monomeric compound. The monomer is reported to have a carbonyl shift at 203 ppm. SIGMA-ALDRICH ™ reports the dimer to have a carbonyle peak as well, at 212 ppm, despite that there is no ketone in the dimeric structure. We wanted to cleave the dimer into its monomeric form. One paper was found that described how the relation-ship was between the monomeric and dimeric state of this molecule[55]. Unfortunately it was only discussed with water as a solvent, but they stated that it broke apart to become the monomer in water.

3.4.2 Physical data:

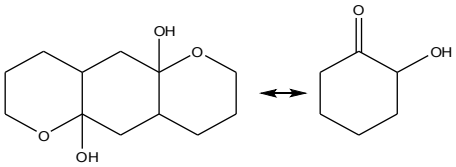


Figure 3.11 2-hydroxycyclohexanone and its dimer

Monomer:
The NMR spectra was found reported as:
^{13}C(100 MHz,chloroform) δ 203 63 39 37 27 23 ppm.
^{1}H(400 MHz,chloroform) δ 4,35 (1H,dd) 2,82-2,75 (1H,OH) 2,4 (2H,m) 2,1-1,7 (6H,m) ppm[57].
The neat FTIR specter reported in the same publication[57]:
3146 2969 1790 1716 1383 1097 cm^{-1}.
Own IR measurement [58]
3421 2936 2863 1713 1449 1386 1352 1109 cm^{-1}.

Dimer:
^{13}C (100 MHz,DMSO) δ 95, 73, 36, 28, 25, 23 ppm[59].
^{1}H (400 MHz,DMSO) δ 3,87 (2H,m) 1,48 - 1,11 (16H,m) ppm[59].
IR spectra from SIGMA-ALDRICH: 3375 2950 2850 1450 1120 cm^{-1}.
Own IR measurement (neat): 3335 2943 2857 1449 1085 cm^{-1}.

3.4.3 Equilibrium dimer - monomer

The dimer that was bought from SIGMA-ALDRICH did not dissolve in chloroform, while the synthesised monomer did dissolve to some degree. A study done on the dimer concluded from IR spectra recorded in water that only the monomeric form was present[57]. This they also verified by NMR with deuterized water as solvent. An idea came to mind; if it broke apart in water it could be washed out into a chloroform phase, where the dimer did not dissolve.

55 H F Shurvell_J. Mol.Structure(1982)p11
57 Arab K_J. Org. Chem(2002)p50
58 IR sample, product from "ICHIIs reagent" chapter 5.5.1
59 Sample ran in DMSO as solvent as the compound purchased from Sigma Aldrich did not to dissolve in chloroform

First about 50 mg dimer was dissolved in 0,5 ml water, this was added 1 ml deuterized chloroform, that after a few minutes of stirring was analysed on NMR but no compound was found in that phase. Water seemed not to be able to break apart the dimer, a contradiction of what was found reported[57], in reference 57. The monomer could also had dissolved so much better in the water phase, that nothing moved into the chloroform phase. In a second attempt the dimer was tried dissolved in D_2O. At first it seemed to float in the upper layer, after a few minutes of stirring the solution was clear. Upon analysis in NMR no hydrocarbons were detected. It is reasoned from this that more extreme conditions are required to cleave the dimer.

NMR samples from the reactions we have tested to make 2-hydroxycyclohexanone often became cloudy upon standing. And some did not dissolve completely in any solvent. Some NMR tubes did look like completely different layers upon standing. This problem was not recognized until late in the work. Some methods might have been rejected as the product might had been in the tube but as undissolved dimer. Another obstacle was that the composition of some of the samples changed during NMR proton acquisition, that has a time frame of less than a couple of minutes.

3.4.4 Synthesis: Ishiis reagent on cyclohexane-1,2-diol

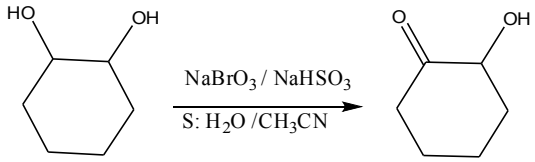


Figure 3.12 ichiis reagents

60 ml water was mixed with 80 ml acetonitrile before trans-cyclohexandiol (1 eq 4,64 g 0,04 mol). The reagent consisted of $NaBrO_3$ (1,2 eq 7,2 g 0,048 mol) that was added first followed by $NaHSO_3$ dissolved in water (1,2 eq 40% 0,048 mol). The reaction mixture was stirred at room temperature for 16 hours. GC measurements did show 88% conversion and the reaction was quenched and worked up into diethyl ether. The GC does not distinguish between the mono and dimeric form. After work-up, the yield was 61%, it appears as a sticky transparent strong smelling liquid. The product was found stable over a period of days, as long as it was kept as an diethyl ether solution in the freezer and concentrated in vacuum just before utilization. The diol in cis configuration was reported to be oxidated faster than our substrate that had trans configuration. Both were nevertheless reported oxidized, and the trans isomer is only 10% of the price of the cis isomer[60]. The trans isomer has both OH groups in its energetically favourable equatorial positions. The protons that the oxidant need to reach is then in the more sterically hindered axial positions. Hugo Gottlieb et al. had found that after 24 hours they achieved complete conversion under the same conditions[31]. One of the reasons why we would not allow our reactions to stand for to long was that we were afraid of over oxidation and dimerization. But a paper was found where they elevated the temperature to 60°C on the same substrate and achieved completion within two hours, without over oxidation or by-products[31]. They state that order of addition of the reagents were irrelevant and that over oxidation of the product never exceeded 5%. Our reaction was stirred for 16 hours and gave 61% total yield (both monomer and dimer). Our crude carbon NMR specter recorded in chloroform did only show the monomer. The specter recorded in DMSO specter (page 73) shows significant contribution of peaks belonging to the dimer. The sample dissolved in chloroform did precipitate out a white layer on top. This layer is reasoned to be the dimer since it also had proved insoluble in chloroform.

57 Arab K_J. Org. Chem(2002)p50
60 Price compared from Sigma Aldrich webpagehttp://www.sigmaaldrich.com/catalog , 26 april 2009
31 Matthias Bierenstiel_Tetrahedron(2005)p4911

The NMR spectra are reproduced in appendix C, they show the compound as a monomer with some shifts from the dimer. The spectra looks somewhat simpler recorded in chloroform as it misses the peaks from the dimer that is apparent in the DMSO spectra.
^{13}C NMR (100 MHz,chloroform) δ 209 94,3 94,1 93,8 74,3 73,9 73,5 71,3 70,2 37,6 35 34,8 31,1 30,9 28,4 27,8 25,7 22,5 22,45 22,4 22,2 21,5 20,8 20,4 19,9 ppm.
IR (neat ATR) 3421 broad 2936 2863 1713,49 1449 1386 1352 cm^{-1}.

3.4.5 Oxidative insertion from nitrosobenzene mediated by proline

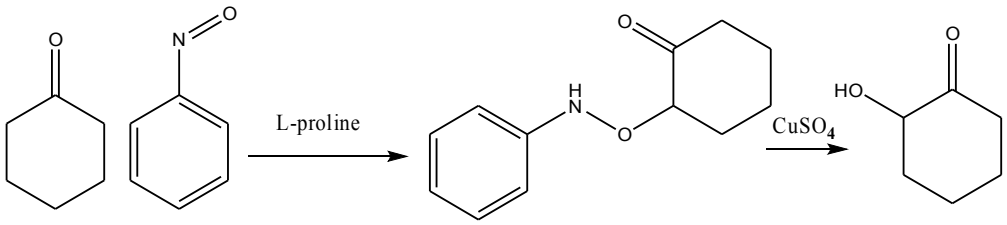


Figure 3.13 oxidative insertion from nitrosobenzene

Literature:[31] [32]
The reaction parameters were varied over the experiments. The one that gave the NMR in appendix C was done with 9,5 g cyclohexanone (1 eq 0,097 mol) as substrate. This was mixed with 30 ml DMSO together with the proline catalyst (0,01 eq 0,106 g 0,0092 mol). In an open flask the nitrosobenzene (0,1 eq 1,03 g 0,0096 mol) dissolved in 5 ml DMSO was added to the substrate over a period of 3 hours. After 2 days at room temperature the reaction was quenched, washed into EtOAc, concentrated, dissolved in methanol and stirred with $CuSO_4$ (10% aqueous). Added aqueous NH_4Cl and washed into EtOAc and concentrated. The raw mixture were cleansed on flash column and afforded the product in small yield and with the nitrosobenzene still attached. The addition was verified from the aromatic signals corresponding to the nitrosobenzene on the NMR specter. The carbon and proton NMR spectra before and after cleavage can be found in appendix C. The continuous treatment with aqueous $CuSO_4$ for 12 hours followed by another flash column, did as seen in the specter only remove some of the nitrosobenzene. From the 9,5 grams of substrate the yield was just enough for a NMR sample. A reagent like nitrosobenzene, utilized in stoichiometric amounts can only be done in a small scale or for special occasions. The method was not found useful at a preparative scale, after seven experiments it was abandoned.

31Matthias Bierenstiel_Tetrahedron(2005)p4911
32 C Lee_Bull Korean Chem. Soc.(2002)p1667

3.4.6 Synthesis: Activated zinc reduction on cyclohexane-1,2 dione

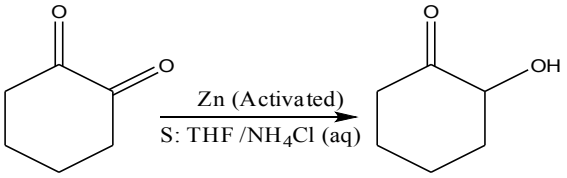


Figure 3.14 zinc reduction

Literature:[35]
The diketone (1 eq 0,23 g 0,002 mol) was dissolved in the solvent mixture (10 ml 1:1 THF:NH_4Cl (sat aq)) before zinc dust (2 eq) was added neat. First old zinc dust was utilized directly from the shelf, when that reaction gave no conversion, activated zinc[61] was tested. The paper used two equivalents of zinc, and their reaction reaction was complete when the zinc had disappeared. It did seem strange that the 2 equivalents could be used up with only one equivalent of substrate to reduce. This reduction did not work at all, the substrate was recovered, and the zinc remained in the reaction mixture.

3.4.7 Singlet oxygen on cyclohexanone

Cyclohexanone (1 eq 0,098 g 0,001 mol), the TPP photosensitizer (0,01 eq), and the alanine catalyst (0,2 eq) were all dissolved in DMSO in a reagent tube. An old mercury lamp, with water cooling, was placed 7 cm away from the reagent tube. Oxygen was bobbled through the reaction that was allowed to stir for 90 minutes. The oxygen gets excited into singlet state, with radiation at 1270 nm. That wavelength is the wave length corresponding to the energy difference between singlet and triplet state. But that it unlikely to have occurred, at least to a significant degree since the light had to travel 7 cm, passing cooling water and several layers of glass. The photosensitizer,on the other hand, has an absorptions maxima around 400 nm, and this wavelength should pass unhindered through these materials. This photosensitizer was the same at the one the authors of the paper used. The same paper that inspired us to try to make a synthetic route from these reagents. The reaction did not provide the ketone, but as there was so many parameters to adjust also trying out different equipment is rather expensive. Both the substrate and oxygen is really cheap and further work to make a synthetic procedure with these reagents is encouraged by the author.

35 Rahim Hekmatshoar_Monatshefte Fũr Chemie(2002)p195
61 Vogel's Textbook of practival organic chemistry_Longman scientific and technical(1989)p467

3.5 Synthesis of 2-methoxycyclohexanone

3.5.1 Analysis of 2-methoxycyclohexanone

The methoxy cyclohexanone has a IR peak at 1720 and is a colourless viscous oil[37]. The same article reported this proton specter from chloroform δ 3,67 (1H,m) 3,36 (3H,s) 2,45 (1H,m) 2,21 (2H,m) 1,89 (2 H,m) 1,64 (3H,m) ppm. The carbon shifts are found in figure 3.15.

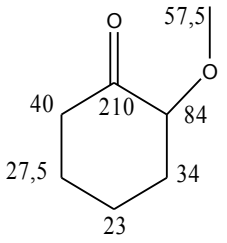


Figure 3.15 2-methoxycyclohexanone with ^{13}C NMR shifts recorded in chloroform, reproduced from reference[38]

3.5.2 Synthesis: 2-methoxycyclohexanol

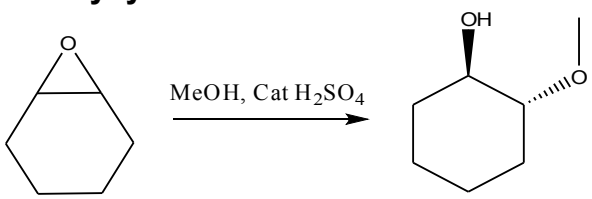


Figure 3.16 acid catalysed epoxide cleavage

The 2-methoxycyclohexanol were synthesized both in 1 and 10 gram scale with 100% conversion. The methanol attacked the cyclohexene oxides epoxide ring in a Sn^2 manner hence this reaction generates the trans (R,R) isomer. 100% conversion was achieved after 5 days at room temperature. The catalytic amount of acid should truly be catalytic, the reaction mixture became really exothermic by a single drop of pure acid.

NMR spectra of trans methoxycyclohexanol recorded in chloroform was found reported as 3,3 (3H,s,OCH_3) 3,0 – 2,8 (1H,OH) 2,4 -1,0 (10H,m) ppm[62].
The IR spectrum is reported to have an OH peak centred on 3360 cm^{-1} [62].

Our spectra is in agreement with its structure and with their somewhat simpler spectrum.
^1H (400 MHz,chloroform) δ 3,35 (3H,s) 2,89 (1H,m) 2,13 – 2,02 (1H,m) 1,97 – 1,90 (2H,m) 1,70 – 1,58 (2H,m) 1,27 – 1,09 (3H,m) 1,05 (2H,m) ppm.
^{13}C (400 MHz,chloroform) 85,1 73,9 56,5 50,4 32,4 28,6 24,2 ppm.

37 Kandasamy Jeyakumar_Synthesis(2007)p807
38 Gerhard Lauktien_Tetrahedron As.(1997)p3457
62 K Ravikumar_Tetrahedron (1997)p2973

3.5.3 Synthesis: manganese dioxide on 2-methoxycyclohexanol

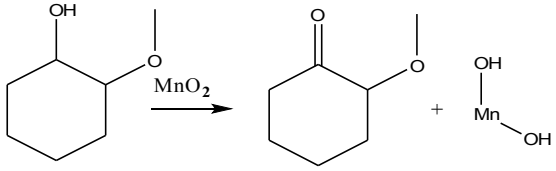


Figure 3.17 oxidation of 2-methoxycyclohexanol

Literature:[39] [40] [41] [42]
This reaction was first done neat, then acetone, chloroform, DCM, and pentane was tested as solvents. They made the reaction easier to move and stir by decreasing the viscosity. The 2-methoxycyclohexanol (1 eq 0,25 g 0,0019 mol) was dissolved in the solvent before 15 equivalents of manganese dioxide was added. One was heated at 60°C for 30 minutes while another one was stirred at room temperature for three weeks. The literature does not agree upon how the mechanism occurs, some think that there is some impurity that is the actual oxidizing agent[39]. The first MnO_2 we tried was old and had been exposed to air for a long time, and the second was new. The reagent were found to weak, the only measurable conversion occurred after three weeks in room temperature.

3.5.4 Synthesis: Oppenauer oxidation, on 2-methoxycyclohexanol

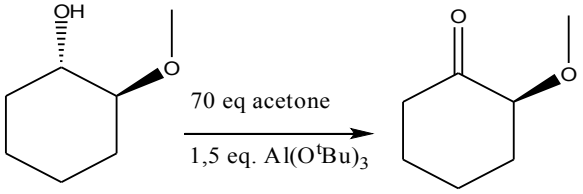


Figure 3.18 Oppenauer oxidation

This is the same mechanism going the opposite direction as the Meerwein Schmidt Ponndorf Verley reduction that we tested on ketone **1**. The methoxycyclohexanol (1 eq 1,3 g 0,01 mol) were dissolved in 70 equivalents of the acetone that acts as hydride acceptor. The aluminium tertbutoxide was employed in 1,5 eq generating an excess that also removes water from the reaction. The reaction were done in microwave at 90°C for 30 minutes and also with conventional refluxing at 87°C oilbath for 10 hours. Neither did oxidise the substrate. The difference in oxidation potential between acetone and the alcohol substrate would by equimolar ratio probably not produce more than a few percent, but the huge excess of one of the starting substrates (70 eq acetone) should had pushed the equilibrium towards product side. In retrospective a ketone with less electron density should had been tested as well. In the collection of these reactions found in a book by Tojo[63], Cristopher et al. used a nitro substituted benzaldehyde in 3 eq of the substrate alcohol. With this reagent they got 99% conversion on a whole variety of secondary alcohols, including 2-methylcyclohexanol. Cristopher used $AlMe_3$ as base, but did also test aluminium isopropyl, which is the classical reagent for the oppenauer oxidation, and also the reagent we tried in this investigation. They achieved 65% conversion within one hour.

39 Gritter_Nature(1964)p179
40 Patent: Evans R.M _Quat.Rev.(1959)
41 Vogel's Textbook of practival organic chemistry_Longman scientific and technical(1989)p445 p520 p524 p611
42 C Graves_J. Am. Chem. Soc.(2006p)p12596
63 Gabriel Tojo; Marcos Fernández_Springer(2002)

3.5.5 Synthesis: Magtrieve(TM) on 2-methoxycyclohexanol

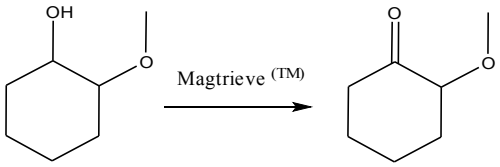


Figure 3.19 Magtrieve oxidation

Literature:[43] [44] [45]
Despite several attempts with 1,2 dichloroethane, acetone and toluene as solvents with reaction temperatures as high as 90°C in microwave. Not a trace of product was identified after work-up. The reagent is to weak to oxidise this substrate.

3.5.6 Synthesis: sodium hypochlorite

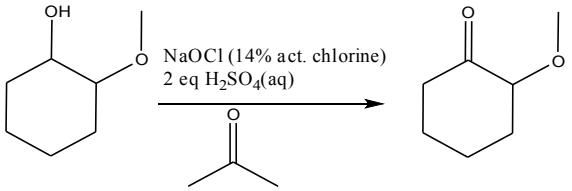


Figure 3.20 oxidation with sodium hypochlorite (chlorine)

Literature:[46] [47]
2-methoxycyclohexanol (1 eq 0,48 g 0,0037 mol) was dissolved in acetone (80 eq 17 g 0,297 mol), aqueous sulphuric acid (2 eq ~22% (w/w) 0,0075 mol) was added by syringe. Sodium hypochlorite (~14 % active chlorine 2,00 ml) was then added as the last component before it was heated at 50°C in microwave for one hour. All samples were worked up into MTBE, washed with water and brine before they were reduced in vacuum. These settings gave a reddish residue with a smell like acrolein. Calculated conversion from NMR spectra after work-up 18%. The work-up made the relative proportions of product, by-products and starting material difficult to assess.

The first attempts on this reaction was done by adding acid to the substrate then sodium hypochlorite dropvice at room temperature. After some investigation; addition of the oxidating reagent in one shot appeared to give the highest conversions. Fast hypochlorite addition give higher concentration of active chlorine since the reagent is unstable. The reactivity was concluded to be to low to oxidise the substrate under low chlorine concentrations. The reaction that worked the best was when all the reagents were mixed and ran in microwave as described above.

43 Ross A. Lee_Tetrahedron Lett.(1997)p3857
44 Marcin Lukasiewicz_MDPI(2002)
45 H Wan_Monatshefte Fũr Chemie(2008)p909
46 Czech Pat. No 265359/19901990
47 G Mirafzal_Tetrahedron Lett.(1998)p7263

3.6.1 Synthesis: molybdenum mediated epoxide opening with Oxone reduction

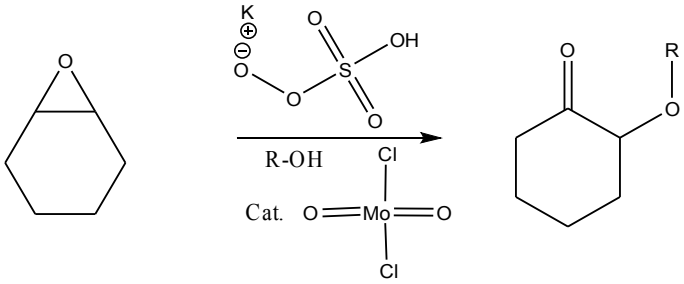
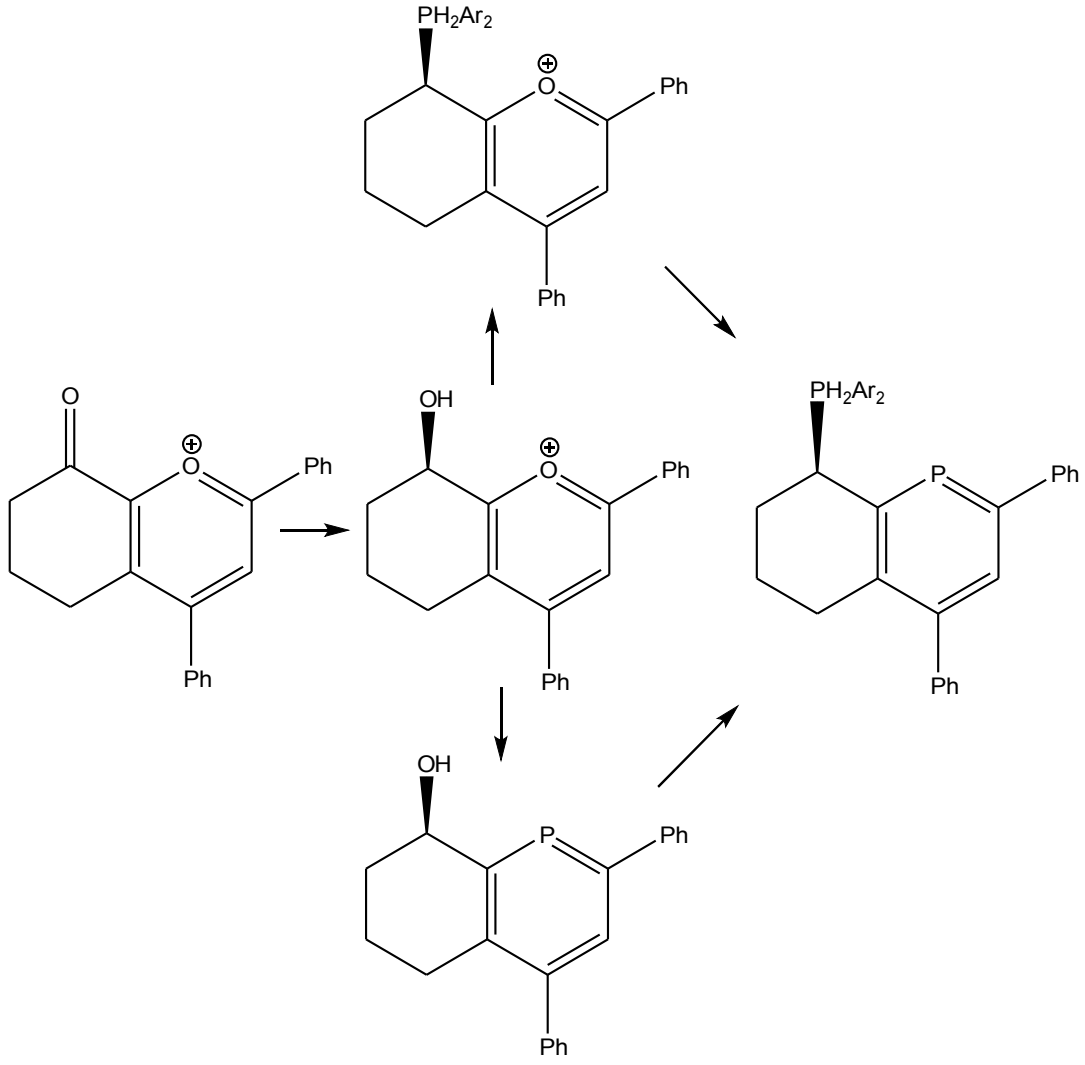


Figure 3.21 reagents epoxide opening with in situ oxidation

Literature:[37]
Experiment done as in publication with 0,001 mol cyclohexen epoxide as substrate. After reaction, the epoxide ring opening had occurred by an Sn_2 attack of the alcohol but no oxidation was observed. The Oxone seem to fail to oxidise the intermediate 2-methoxycyclohexanol. Omitting Oxone from the reaction mixture yielded 2-methoxycyclohexanol as was the isolated product with Oxone. The only reason we have identified for Oxones failure to oxidise is the age of the reagent. On Du Ponts web page[48], they state reduced activity during storage, specially if not protected against moisture.

37 Kandasamy Jeyakumar_Synthesis(2007)p807
48 From dupoints webpage www2.dupont.com/Oxone/en_US/assets/downloads/K20108%20Oxone®%20Safety%20and%20Handling.pdf , read 17 may 2009

4 Conclusion - outlook



The long term plan of my group with this project is to develop a variety of phosphinine catalysts, ketone **1** was the precursor for the alcohol in the middle. The route were the reduction of ketone **1** was replaced by condensating the ring with the alcohol moiety already present . The only condensation we have been able to do was the one that already was described with the diketone. These authors wrote that several other attempts failed to condensate. Nevertheless many routes and pathways has been sought to achieve this alcohol, and as a result of constrains both in time and equipment many pathways has been left unexplored. The search to make the compound by our group continues when this work is completed. Ideas, on both plausible reducing agents to reduce ketone **1**, and protected alcohols to condensate onto the triphenylpyrylium has been tested, but several has not been tested yet. Hydrosilylation from chapter 2.3.6 is still to be tested on ketone **1** as well as functionalized silica to put a bromine onto cyclohexanone.

The reduction to achieve the alcohol from ketone **1** would not be necessary if we had succeed to condensate the pyrylium with the 2-hydroxycyclohexanone
The preparation of 2-hydroxycyclohexanone was challenging and time consuming but we were determined not to give up. This route might had proven to give better yields, be cheaper or more practical. To say that a synthetic route is good a thorough investigation of all plausible routes should be attempted. A lot of practical knowledge was gained working with these tricky compounds, despite that it has been tedious with all the limitations, they dimerize, are pyrophoric, or are just unstable. The ability to produce and maintain the 2-hydroxycyclohexanone as a monomer, in freezer dissolved in ether was encouraging as no work-up of this compound had been found.

5 Experimental

5.1 Equipment

5.1.1 Materials

All glassware that was utilized for air or water sensitive experiments had been oven dried at 150 degrees for a minimum of one hour. Also flushed with dry nitrogen, and joints heated with air gun, depending on the sensitivity to moisture. Molecular sieves had been activated at 500 degrees for a minimum of 5 hours before equilibrated with room temperature in an empty glass desiccator equipped with a bubbler for outgoing pressure equilibration.

5.1.2 Solvents

Solvents were purchased from VWR and Sigma-Aldrich and used without further purification, the dry solvents were delivered from a drying rack.
Acetone, methanol, ethanol, and isopropanol were dried with magnesium sulphate and stored with activated molecular sieves or magnesium sulphate. Their water content was not measured but assumed acceptable for the reactions described. THF was dried with sodium / benzophenone under reflux in nitrogen atmosphere, moved with freshly opened disposable syringes and utilized directly from distillation apparatus.

5.1.3 Reagents

Reagents were purchased from Sigma-Aldrich and VWR.
Distilled reagents were distilled with a short condenser, connected to water aspirator or vacuum pump, depending on the volatility and toxicity of the reagent cold traps were used. They were used fresh from the apparatus or stored with drying agent. Unstable reagents or reagents of unknown quality were analysed with NMR.

5.1.4 Instruments

NMR Nuclear Magnetic Resonance

Mercury- Varian Plus instrument with an Oxford magnet providing 400 MHz proton and 100MHz carbon. Chemical shifts are reported as ppm, reference peaks picked from the deuterized solvents.

GC Gas Chromatography

Varian 3300 instruments with columns of different polarity and length, during the work of this master they were changed from time to time by our technicians. The detectors operate on the flame ionization principle, connected to Integrators delivering the results directly on paper.

I.R instrument used to measure infra red spectra

FT- IR from Varian model 7000e with ATR sample cell from Pike model MIRacle, capable of measuring the infra red region spectra neat of solid compounds.

Microwave

Delivered by Initiator EXP EU, used with capped vials equipped with stirring bone, reactions could be done with elevated pressure, maximum vial fill volume 20 mL.

5.2 Synthesis of pyrylium salt

5.2.1 2,4,6- triphenylpyrilium tetrafluoroborate

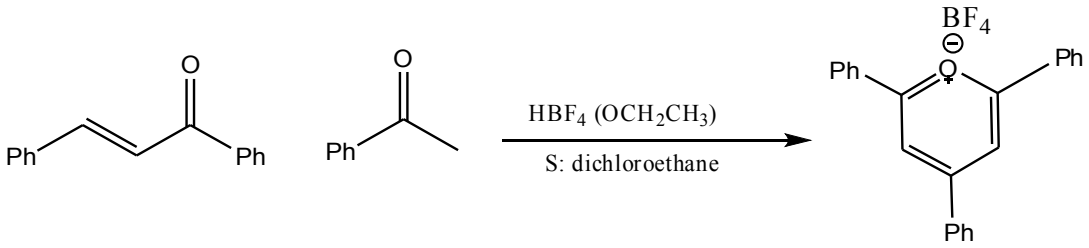


Figure 5.1 scheme for synthesis of triphenylpyrylium and its synthons

Literature:[11]

A 250 mL 3 necked flask equipped with strong neodymium stirring bone and a reflux condenser were added 1,3-Diphenyl-2-propenone, (1 eq 20,8 g 0,1 mol), freshly distilled acetophenone (0,5 eq 6,0 g 0,05 mol) and 1,2-dichloroethane 35 mL, this was heated in oil bath at 72°C. A schlenk addition funnel were charged with HBF_4 (16 mL of 52% in diethyl ether) that was added over a period of 40 minutes, care was taken as the addition is highly exothermic. After addition the oilbath was heated until reflux occurred at 105°C and kept refluxing, for one hour. The gas evolved was vented through a water trap to capture excess trifluoroborane. Precipitation occurs while the mixture slowly is chilled to room temperature. The residue gave the product in 35% yield. A recrystallization of this residue with acetone and pentane gave the product in 28% Yield.

Comments:

The procedure was changed little from the one suggested in the publication, it is 10% of the original scale, but stochiometrically the same proportions. The recrystallization was done with different solvents.

Analytical data:

^{1}H (400 MHz,acetone) δ 9,17 (2H,s) 8,66 (4H,m) 8,58 (2H,m) 7,99- 7,74 (9H,m) ppm.
^{13}C (100 MHz,acetone) δ171,4 166,7 135,5 133,3 130,3 130,2 129,6 129,2 115,7 ppm.
m.p beyond 240 °C (as high as instrumentation at UIT allows, lit: 251-257 °C).
I.R (solid ATR) 1621 cm^{-1}.
Ms: m/z 309,12743 (100% base peak) [M^{+}] calc 309,12739.

11 K Dimroth_Org. Syntheses Coll.(1969)p1135

5.2.2 2-(2-oxo-2-phenylethyl)-2,4-diphenyl-6,7-dihydro-2H-chromen-8(5H)-one

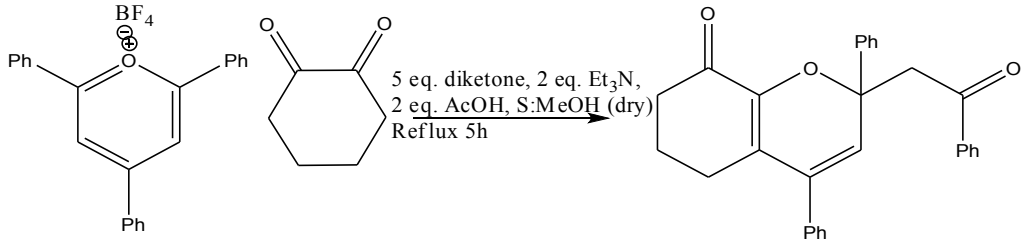


Figure 5.2 scheme for condensation of diketone on triphenylpyrilium

Literature:[50]
2,4,6 triphenylpyrylium tetrafluoroborate (1 eq 4,8 g 0,0121 mol) was mixed with 25 ml dry methanol in a 3 neck flask. Followed by addition of cyclohexan-1,2-dion (5 eq 6,78 g 0,0606 mol) triethylamine (2 eq 2,45 g 0,0242 mol) and acetic acid (2 eq 1,45 g 0,0242 mol). The reaction was stirred under nitrogen atmosphere at reflux for 5 hours with an oilbath temperature at 72°C, then chilled slowly to room temperature. After 1 hour, or more, on ice, the precipitate were filtered on a sinter 4 funnel, washed with cold ethanol followed by cold ether. Yield: 89%.

Comments:
This procedure was slightly adapted from a german paper[50], our synthesis was done with 2,5 times their substrate amount, we also used substrate with BF_4 instead of the ClO_4 counterion, neither did we recrystallize the crude product .

Analytical data:
^{1}H (400 MHz,chloroform) δ 7,90 (2H,d,J=7,3) 7,61 (2H,d,J=7,3) 7,44 - 7,28 (9H,m) 6,57 (1H,s) 3,89 (1H,d,J=15,7) 3,65 (1H,d,J=15,7) 2,45 - 2,27 (4H,m) 1,73 (2H,m) ppm.
^{13}C (100 MHz,chloroform) δ 197 193 144 143 137,7 137,5 137,2 133,4 130,5 129,5 128,8 128,7 128,6 128,5 128,3 128,2 128,0 125,8 79,5 50,5 38,5 26,2 22,2 ppm.
I.R (solid ATR) 1671 cm^{-1}.
m.p 225°C slight brown, 240°C melts.

5.2.3 Optimization of the diketone condensation
The 2,4,6 triphenylpyrylium tetrafluoroborate (1 eq 0,198 g 0,0005 mol) was mixed with diketone, a buffer solution corresponding to 2 eq triethylamine together with 2 eq acetic acid was premixed with 0,80 ml methanol before it was added to the reactants. The dry reaction mixtures was premixed in sealed vials before the buffer solution was introduced through a septum right before the sample was heated in microwave. The samples were heated for one hour, with stirring at 100°C. Samples were allowed to stand for a minimum of one hour at 5°C, before filtering on sinter 3 funnels and consecutive washing with copious amounts of cold EtOH. The filtrate was dried on the sinter funnel under suction until dry, weighted and verified on NMR. Care was taken to treat the samples equally. The table, in figure 5.3 on the next page, describes the experiments. The wet solvent was made by simply adding a drop of water.

50 T Zimmermann_J. Fũr Prak. Chemie(1988)p306

triphenyl - pyrylium	cyclohexane - 1,2-dione	notes	yield (%)
0,0005 mol	0,00250 mol		43,6
0,0005 mol	0,00250 mol	reaction time 2h	42,6
0,0005 mol	0,00250 mol	wet	44,2
0,0005 mol	0,00125 mol	Only 2,5 eq diketone	35,0

Figure 5.3 table of reaction settings with diketone on triphenylpyrilium

5.2.4 Alternative condensations

Adipoin (2-hydroxycyclohexanone dimer) (2 eq dimer corresponding to 4 eq monomer 0,91 g). The reaction setup was otherwise similar to the original procedure (described in chapter 5.2.2). The condensation was in a consecutive reaction allowed to reflux for 24 hours. In the next reaction tested, some drops of water was added. In the next adipoin condensation the base was replaced with another base 1,1-cyclohexan-1-methylamine, and no acetic acid was used.

2-hydroxycyclohexanone synthesized with ichiis reagent described in chapter 5.5.1 were added in 5 equivalents to triphenylpyrilium (0,59 g 0,0015 mol) first as in the original procedure. A consecutive reaction was done at 100°C in microwave.

2-methylcyclohexanone monomer was tested in 3 eq to the substrate at 0,0015 mol scale but otherwise similar to the original procedure. The base from the original procedure was replaced with morpholine, in a consecutive reaction. The last attempt was heated in microwave at 100°C.

2-(tert-butyldimethylsilyloxy)cyclohexanone was tested in 3 eq to the substrate at 0,0015 mol scale but otherwise similar to the original procedure. Another was done at gentle reflux for 24 hours without any condensation occurring. Morpholine replaced triethylamine in the last condensation attempt.

5.2.5 8-oxo-2,4-diphenyl-5,6,7,8- tetrahydrobenzopyrylium tetrafluoroborate

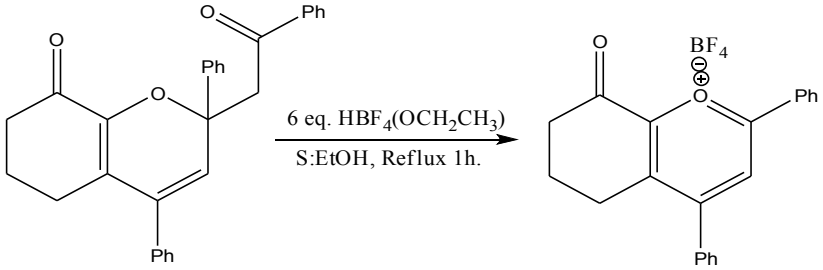


Figure 5.4 rebuilding the pyrylium system

Literature:[50]

2-(2-oxo-2-phenylethyl)-2,4-diphenyl-6,7-dihydro-2H-chromen-8(5H)-one (jhs-002) (1 eq 2,52 g 0,003 mol) was transferred into 60 ml ethanol (dissolved only partially) in a dry 3 neck flask. The mixture was heated to 50°C before adding HBF_4 (about 6 eq 6,5 ml 52% in ether) drop-vice through a schlenck funnel over a period of 30 minutes. To capture gaseous fluoroborane, a water trap was connected as vent from the system. The reaction bath was heated at 105°C, that generated a gentle reflux. After 30 minutes it was cooled slowly to room temperature. The sample was afterwards immersed in ice

50 T Zimmermann_J. Fũr Prak. Chemie(1988)p306

bath or put in fridge over night. Washed on sinter 3 with ethanol and or THF until the precipitates colour was clear. Recrystallized in acetonitrile it yielded 71,3% (1,66g) as brown powder.

Comments:

The procedure was slightly modified from the literature, more ethanol was needed to dissolve the substrate.

Analytical data:

^{1}H (400 MHz,CD_3CN) δ 8,76 (1H,s) 8,43 (2H,d) 7,94 (1H,t) 7,79 (7H,m) 3,21 (2H,t) 3,10 – 2,90 (2H,t) 2,36 – 2,10 (2H,m) ppm.
^{13}C (100 MHz,CD_3CN) δ188,9 172,0 172,0 155,4 139,5 137,4 133,9 133,5 130,7 130,0 129,9 129,7 128,5 124,2 38,2 26,7 21,7 ppm.
I.R (solid ATR) 1714,59 cm^{-1} (lit 1716 cm^{-1}).
m.p [183, 185] °C (lit: 244-246 with perchlorate as counterion).
Ms: m/z [M+Na^+] 341,1153 (100% base peak) 301,1229 [M^+] calc 301,1223.

5.3 Reduction attempts on pyrylium salt

5.3.1 CBS mediated hydroboration

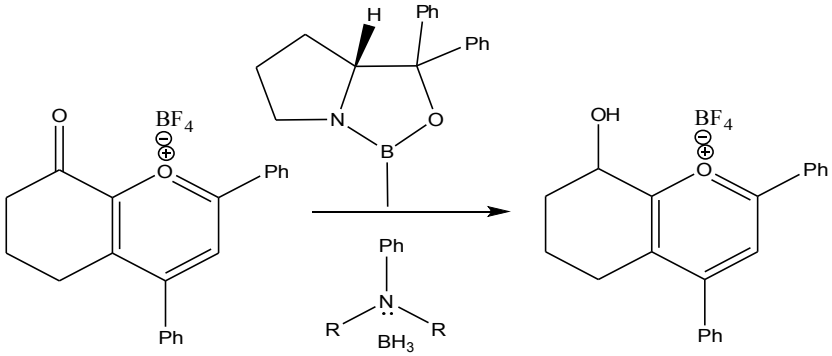


Figure 5.5 ketone **1** and its reduced form and the synthons for CBS reduction

Literature:[65] [18] [19]

Ketone **1** (1 eq 1,36 g 0,0035 mol) was mixed with dry THF in dry glassware under nitrogen atmosphere. CBS was first dissolved in dry THF (0,1 eq 0,035 mol 10ml) and added to the mixture. Then 1 equivalent of the borane reagent, either BACH-EI or DEANB, was added drop vice. The addition was chilled in a water bath at 25°C and took one hour. A few minutes after addition careful addition of methanol from a syringe tip immersed in the reaction mixture quenched the reaction, while stirring. Reduced in vacuum, no work-up, crude mixture analysed on NMR.

65 H C Brown_Acc. Chem. Res.(1991)p16
18 Ashok M. Salunkhe_Tetrahedron Lett.(1997)p1523
19 Byung Tae Cho_J. Chem. Soc. Perkin Trans.(1999)p2095

5.3.2 DIBAL

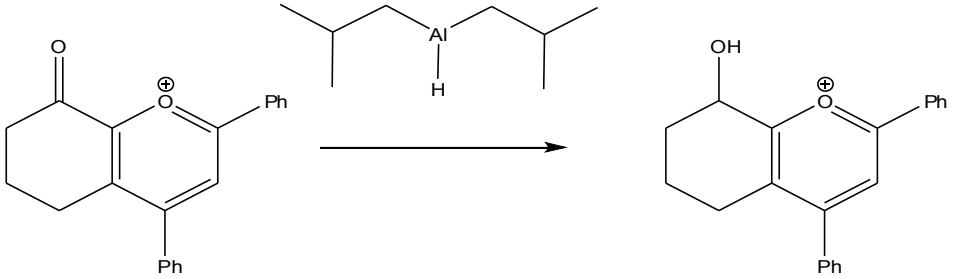


Figure 5.6 ketone **1** and its reduced form with dibal

Literature:[22]
Typical procedure: a dry flask was charged with ketone **1** (1 eq 0,56 g 0,00144 mol) added 30 ml dry solvent under nitrogen atmosphere. The reaction mixture was allowed to equilibrate with cooling medium before the addition of dibal (1,3 – 2,6 eq 20% solution). After a reaction period between 6 and 40 minutes the reaction was quenched with methanol until foam ceased to develop. 1 ml saturated sodium tartrate was added to the solution before it was washed with DCM. Organic phases washed with water and brine and reduced in vacuum.

Detailed conditions:

substrate ketone 1	**DIBAL**	**solvent**	**reaction time**	**reaction temp.**
0,00144 mol	1,3 eq	toluene	10 min	-78°C
0,00025 mol	2,6 eq	4%toluene / THF	6 min	-78°C
0,00025 mol	1,3 eq	23% toluene / 38% THF / 38% DCM	6 min	-78°C
0,00041 mol	1,3 eq	1% toluene / DCM	10 min	0°C
0,00041 mol	1,3 eq	1% toluene / DCM	40 min	-78°C
0,00026 mol	2,6 eq	DCM	6 min	0°C
0,00015 mol	2,6 eq	DCM	200 min	-78°C - 0°C

Figure 5.7 table with detailed DIBAL conditions

Toluene had to be present in the first samples since the first dibal was acquired as a 20% solution in this solvent. DIBAL was then bought as a solution in DCM.

5.3.3 $CeCl_3$ with $NaBH_4$ as hydride donor

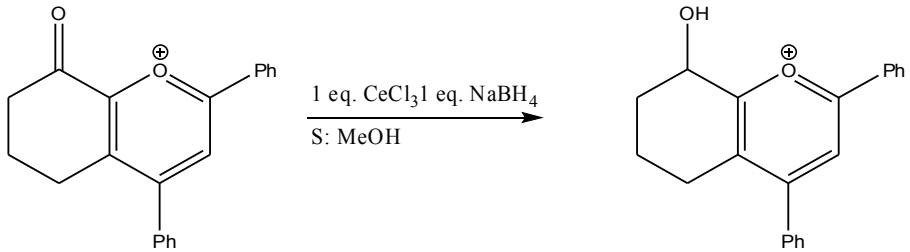


Figure 5.8 $CeCl_3$ mediated borohydride reduction on ketone **1**

Literature:[26] [23] [27]
Ketone **1** (1 eq 0,2 g 0,00051 mol) and $CeCl_3$ (1 eq 0,19 g 0,00052 mol) were dissolved in MeOH (15ml) followed by addition of $NaBH_4$ (1 eq 0,02 g 0,00053 mol). The mixture

22 Akiko Saito_Tetrahedron As.(1996)p2923
26 Andre L Gemal_J. Org. Chem(1979)p418
23 Andre Gemal_J. Am. Chem. Soc.(1981)p5454
27 Shigeru Sasaki_Tetrahedron Lett.(2005)p1497

was stirred for 5 minutes at room temperature before acidification with diluted HCl . Reduced under vacuum to yield a residue with tar like appearance. This was tried recrystallized with acetone / pentane but yielded no product.

5.3.4 Meerwein Schmidt Ponndorf Verley reduction (MSPV)

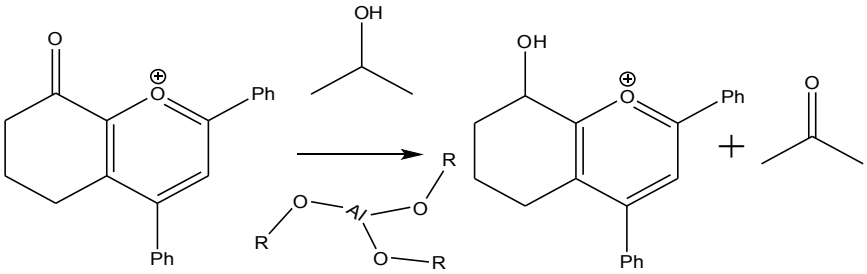


Figure 5.9 MSPV reagents and ketone **1** and the product sought for

Literature:[53]
Aluminium isopropoxide (3 eq 0,34 g 0,00155 mol) was added to a dry hot 2 neck flask that was immersed in oil bath and equipped with a condenser. Dry Isopropanol (240 eq 10 ml 7,86 g 0,131 mol) was added through the condenser under a steady N_2 flow. Heated until reflux before ketone **1** (1 eq 0,20 g 0,00055 mol) was added dry. After 45 min refluxing, the reaction mixtures pH was carefully adjusted with aqueous 10% H_2SO_4 until pH was about 4,then the colour changed from turbid brown / grey to clear brown. After a few minutes chloroform was added and the mixture washed with water followed by brine, Na_2SO_4 added to organic phase, filtered and concentrated.

5.4 Conversion of heteroatom

5.4.1 Ketone 1 transformed into its pyridine analogue

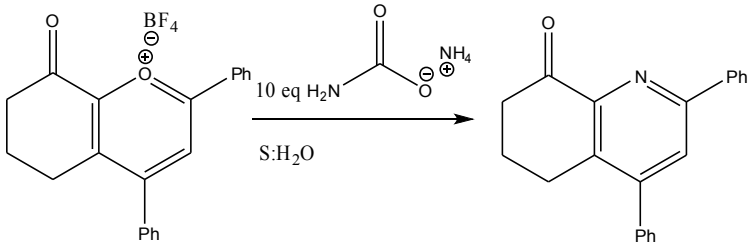


Figure 5.10 conversion of heteroatom on ketone **1**

Literature:[52]
Conversion from 8-oxo-2,4-diphenyl-5,6,7,8-tetrahydrochromenylium tetrafluoroborate into 2,4-diphenyl-6,7-dihydroquinolin-8(5H)-one. Ketone **1** (1eq 1,0g 0,0028mol) was mixed with 6,5 ml water to gain a suspension in an open flask. Ammonium carbamate (10 eq 2,19 g 0,028 mol) was mixed with 17,6 ml water to also make a suspension that were mixed into the reaction mixture. The reaction mixture was stirred by a strong neodymium magnet for 24 hours in room temperature. A sinter 3 funnel is utilized to capture the brown powder like crystals that afterwards was washed with water (150 ml) ether (50 ml) and MTBE (20 ml).Yield 82% weight 0,69 g after 1h in vacuum.

53 J Yin_J. Org. Chem.(2006)p840
52 patent: DE 102007012794

Analytical data:

^{1}H(400 MHz,chloroform) δ 8,10 (2H,d,J=7,1) 7,79 (1H,s) 7,59 – 7,35 (8H,m) 2,95 (2H,t,*J*=6,0) 2,86 (2H,t,J=6,0) 2,13 (2H,m) ppm.
^{13}C (100 Mhz,chloroform) δ197,0 156,5 151,6 148,7 138,7 138,5 137,1 129,5 129,0 128,9 128,8 128,7 127,4 124,6 40,0 27,7 23,0 ppm (17 carbons, 4 carbons overlapping).
I.R 1714,59 cm^{-1}.
m.p [183, 185]°C (reported to to 177-178°C)[52].
Ms: m/z [M+H] 300,1387 (100% base peak) calc 299,1310.

5.5 Synthesis 2-hydroxycyclohexanone

The main obstacle in the synthesis of this molecule is its ability to dimerize.
There are no gram scale methods found for the synthesis where work-up is described.

Analytical data:

2-hydroxycyclohexanone
^{13}C(100 MHz,chloroform) δ 203 63 39 37 27 23 ppm[57].
^{1}H (400 MHz,chloroform) δ 4,35 (1H,dd) 2,82-2,75 (1H,OH) 2,4 (2H,m) 2,1-1,7 (6H,m) ppm[57].
IR (neat): 3146 2969 1790 1716 1383 1097 cm^{-1} [57].

Adipoin (sample from Sigma Aldrich, dimer of 2-hydroxycyclohexanone)
^{13}C (100 MHz,DMSO) δ 95, 73, 36, 28, 25, 23 ppm.
^{1}H (400 MHz,DMSO) δ 3,87 (2H,m) 1,48 - 1,11 (16H,m)ppm.
^{13}C / ^{1}H (100 Mhz,chloroform) not able to record spectra in this solvent.
IR (neat): 3380 3350 2950 1470 1230 1100 cm^{-1}[66].
Own IR measurement commercial sample (neat):
3335 2943 2857 1449 1085 cm^{-1}

5.5.1 Ichiis reagent

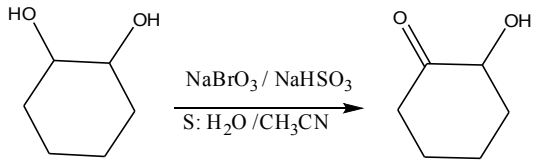


Figure 5.11 ichiis reagents on diol

Literature[31] [32]
In a open flask trans-cyclohexandiol (1 eq 4,64 g 0,04 mol) was mixed with 80 ml acetonitrile and 60 ml of distilled water, the mixture became cold. $NaBrO_3$ (1,2 eq 7,2 g 0,048 mol) was added dry, before a dropping funnel was charged with $NaHSO_3$ as a 40% solution in water (1,2 eq 0,048 mol) and dropped into the solution while stirring over a period of 10 minutes, a yellow-orange colour develops. The progress of the reaction was measured with GC, after 16 hours the colour was slightly more pale yellow, 88% conversion was measured. Water (50 ml) was added in the reaction mixture and dry $Na_2S_2O_3$ was added slowly until the colour faded, this quenching is exothermic when

57 Arab K_J. Org. Chem(2002)p50
66 Adipoin specter from sigma aldrichs webpage, http://www.sigmaaldrich.com/catalog , read 9 may 2009
31 Matthias Bierenstiel_Tetrahedron(2005)p4911
32 C Lee_Bull Korean Chem. Soc.(2002)p1667

to much thiosulphate is added (after the bromate is neutralized). 150 ml diethyl ether was added together with dry NaCl until precipitation occurred, in the water phase, and thoroughly stirred. The water phase was further extracted with 2 x 100 ml ether. All organic phases were combined and washed once with brine and dried with Na_2SO_4. A representative sample was reduced in vacuum for identification, yielding 61,4% as a sticky transparent liquid.
The remainder of the ether solution was kept in freezer to evaporate just before usage. The GC gave same ratio of starting compound (10%) and product (89%) after quenching. In the finished ether dilution, the ratio was: starting compound 13% product 85%.

Comments:

All solutions were neutralized with copious amounts of $Na_2S_2O_3$.
Cis cyclohexanediol is of higher energy, and the oxidant works faster with axial OH groups. Also 60°C reaction temperature is reported to achieve completion within 2 hours without by-product formation.

Analytical data (product mixture):

The spectra recorded in DMSO can be found in appendix C.
They show the monomer with some shifts from the dimer.
IR (ATR,neat) 3421 broad 2936 2863 1713,49 1449 1386 1352 cm^{-1}.

5.5.2 Oxidative insertion from nitrosobenzene mediated by proline

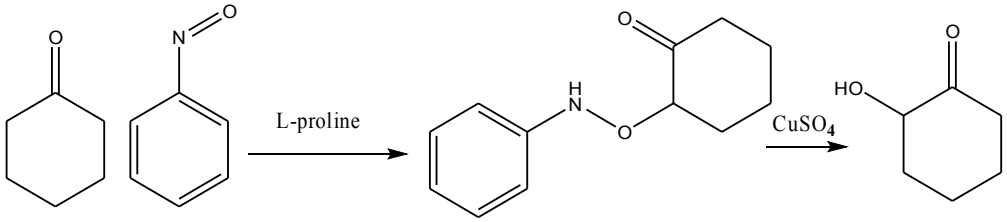


Figure 5.12 oxidative insertion, proline mediated

Literature:[31] [32] [66]
Typical procedure:
Cyclohexanone (1 eq 9,5 g 0,097 mol) L- proline (0,01 eq 0,106 g 0,00092 mol) was mixed with solvent (30 ml) in an open flask. Nitrosobenzene (0,1 eq 1,03 g 0,0096 mol) was mixed with solvent and added with syringe or syringe pump. Quenched with aqueous NH_4Cl brine (5 ml), washed with EtOAc (3 x 100 ml), and concentrated in vacuum. To remove the nitrosobenzene the intermediate product was dissolved in MeOH (50 ml) that was added $CuSO_4$ (30 ml 10% in water) and stirred for 50 minutes. NH_4Cl brine was added again, where the colour changed from yellow / brown to dark brown. Washed out into EtOAc, this was reduced in vacuum.

31Matthias Bierenstiel_Tetrahedron(2005)p4911
32 C Lee_Bull Korean Chem. Soc.(2002)p1667
66 Anders Bøgevig_Angew. Chem.(2004)p1109

Tested conditions:

substrate cyclohexanone	nitroso – benzene	reaction time	solvent	comments
0,097 mol	0,01 eq	4 hours	chloroform	substrate added through syringe into reactants
0,0097 mol	0,1 eq	16 hours	DMSO	nitrosobenzene added into other reactants
0,097 mol	0,1 eq	50 hours	DMSO	nitrosobenzene added into other reactants during3 h
0,0047 mol	0,2 eq	15 hours	DMSO	substrate added into other reactants with syringepump during 7 h
0,021 mol	0,5 eq	50 hours	DMSO	nitrosobenzene added into other reactants with syringepump during 5 h
0,097 mol	0,1 eq	45 hours	chloroform	nitrosobenzene added into other reactants during 20 h

Figure 5.13 table detailed conditions for the insertion attempt with nitrosobenzene

5.5.3 Zinc reduction on cyclohexane-1,2 dione

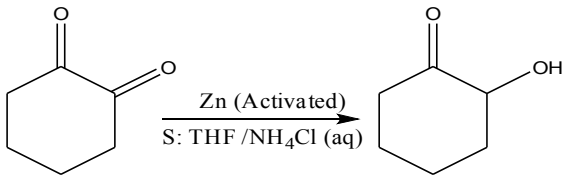


Figure 5.14 zinc reduction

Literature[35] [61]

Zinc (2 eq) in powder form was stirred with the substrate cyclohexane-1,2dione (1 eq 0,22g 0,002 mol) in THF / NH_4Cl brine. The reaction was stirred for 45 minutes. But no reduction had occurred. The deactivating surface oxide of the Zinc was thought to be the problem and was removed by thorough washing with 10% hydrochloric acid, followed by filtering with water and finally acetone sprinkled over the zinc dust. Neither this metal did oxidise anything, even in 4 equivalents of the substrate.

5.5.4 Singlet oxygen

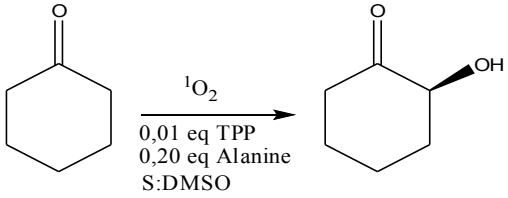


Figure 5.15 singlet oxygen insertion

Literature:[36]

Cyclohexanone (1 eq 0,1 g 0,001 mol), tetraphenylporphorine (0,01 eq 0,00615 g), and L-alanine (0,2 eq 0,0178 g) was mixed in DMSO (1,3 ml). A old mercury lamp that was surrounded by water for cooling was placed 7 cm away from the reaction tube. The reaction was allowed to continue for 90 minutes with gaseous oxygen bobbling through. It was worked up from the DMSO by adding NaCl until precipitation, followed by extraction into ethyl acetate that was dried and concentrated.

35 Rahim Hekmatshoar_Monatshefte Fũr Chemie(2002)p195

61 Vogel's Textbook of practival organic chemistry_Longman scientific and technical(1989)p467

36 Henrik Sunden_Angew. Chem.(2004)p6532

5.6 Synthesis 2-methoxycyclohexanone

The ratio of conversion from crude product mixtures underneath has been calculated from proton NMR spectra. This was done from the ratio of protons at 2,9 ppm (substrate) and 3,7 ppm (product).

Analytical data:

2-methoxycyclohexanone is reported to have an IR peak at 1720 cm^{-1} and appear as a colourless viscous oil[37]. The same article reported this proton spectrum from chloroform δ 3,67 (1H,m) 3,36 (3H,s) 2,45 (1H,m) 2,21 (2H,m) 1,89 (2H,m) 1,64 (3H,m) ppm. The carbon specter from Sigma Aldrich recorded in chloroform is reported as 210 85 41 34 28 24 ppm.

5.6.1 Epoxide opening to synthesize 2-methoxycyclohexanol

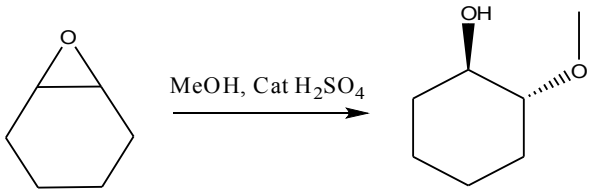


Figure 5.16 epoxide cleavage, methoxy insertion

The substrate cyclohexen oxide (1 eq 10 g 0,102 mol) was dissolved in methanol (24 eq 79,2 g 2,47 mol) with a catalytic amount of H_2SO_4 and stirred for three days. The reaction mixture is evaporated, dissolved in MTBE and washed with brine to remove the acid. The scale of this reaction was done from NMR scale to 10 gram of substrate with the same result;100% conversion.

Analytical data:

^{1}H (400 MHz,chloroform) δ 3,35 (3H,s) 2,89 (1H,m) 2,13 – 2,02 (1H,m) 1,97 – 1,90 (2H,m) 1,70 – 1,58 (2H,m) 1,27 – 1,09 (3H,m) 1,05 (2H,m) ppm.
^{13}C (400 Mhz,chloroform) 85,1 73,9 56,5 50,4 32,4 28,6 24,2 ppm.

37 Kandasamy Jeyakumar_Synthesis(2007)p807

5.6.2 MnO_2 oxidation

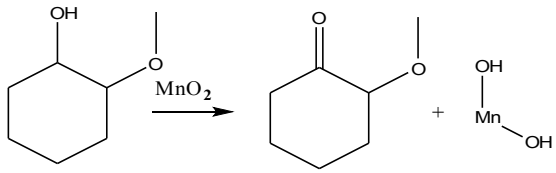


Figure 5.17 manganese oxidation

Literature:[39 40 41 42 64]

General procedure:

The substrate 2-methoxycyclohexanol was stirred with manganese dioxide, with or without solvent. To remove the manganese dioxide celite was stirred in the solvent and filled into a long sinter funnel. The filtration was found to be easier if a funnel equipped with a filter paper was put on top of the sinter funnel, to avoid manganese passing through the celite. The filtrate was concentrated. No isolated yield, conversion assessed from crude filtrate with NMR.

Detailed conditions:

2-methoxy - cyclohexanol	MnO_2	solvent	reaction time	reaction temp.
0,0019 mol	15 eq (not activated)	acetone	16 hours	RT
0,0037 mol	7,5 eq (not activated)	acetone	30 min	60°C micro wave
0,0013 mol	15 eq (not activated)	neat, pentane after 1 hour	24 hours	RT
0,0017 mol	31 eq (activated)	chloroform	24 hours	RT
0,0011 mol	56 eq (activated)	acetone (dry)	24 hours	RT
0,0077 mol	15 eq (activated)	acetone (dry)	3 weeks	RT
0,0038 mol	9 eq (activated)	DCM	16 hours	40°C reflux
0,0038 mol	9 eq (act. + 5% water)	DCM	16 hours	40°C reflux

Figure 5.18 table of detailed oxidation attempts with manganese

5.6.3 The Oppenauer oxidation

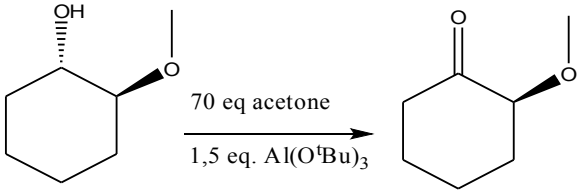


Figure 5.19 oxidation with the reversible Oppenauer oxidation

Literature:[42]

The reaction was tested with 2-methoxycyclohexanol (1 eq 1,3 g 0,01 mol), dry acetone (70 eq), aluminium isopropoxide (1,5 eq) and dry toluene (60 ml) as co-solvent. The base was introduced as the first reagent, if employed in excess it binds residual water from solvents. After 10 hours at reflux (87°C oilbath) the mixture was chilled to RT before H_2SO_4 (30 ml 7%) was added, 2 phases emerge the water phase turbid white and a clear top phase. No conversion had occurred and consecutive reactions done in microwave at 90°C gave back the starting material.

39 Gritter_Nature(1964)p179
40 Patent: Evans R.M _Quat.Rev.(1959)
41 Vogel's Textbook of practival organic chemistry_Longman scientific and technical(1989)p445 p520 p524 p611
42 C Graves_J. Am. Chem. Soc.(2006p)p12596
64 Gabriel Tojo; Marcos Fernández_Springer(2002)

5.6.4 Magtrieve (TM) oxidation

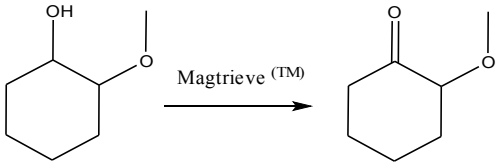


Figure 5.20 Magtrieve oxidation material tested on 2-methoxycyclohexanol

Literature:[43] [44] [45]
Typical procedure: Magtrieve(TM) was mixed with 2-methoxycyclohexanol, ratio by weight, added solvent and ran in microwave. To remove the magtrieve from the reaction medium hyflo super celite was mixed with solvent and moved into a long sinter funnel, a funnel equipped with a filter paper was put on top on the sinter funnel, where the reaction mixture carefully was applied. After filtration the residue was reduced in vacuum. No conversion occurred in any of these conditions.

Detailed conditions:

2-methoxy – cyclohexanol	Magtrieve eq (w/w)	solvent	reaction time	reaction temp.
0,1 g	1,8	1,2 dichloroethane	15 min	80°C Microwave
1,0 g	2,1	1,2 dichloroethane	30 min	90°C Microwave
0,2 g	2,5	acetone	15 min	60°C Microwave
2,5 g	1,8	acetone	40 min	60°C Microwave
0,5 g	4,1	acetone	20 min	60°C Microwave
0,65 g	3,1	toluene / acetone	18 hours	conventional reflux

Figure 5.21 table of detailed Magtrieve oxidation attempts

5.6.5 Sodium hypochlorite oxidation

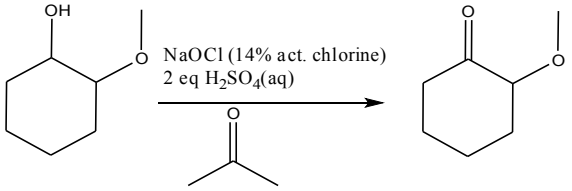


Figure 5.22 sodium hypochlorite (Chlorine) as oxidant

Literature:[46] [47]
2-methoxycyclohexanol (1 eq 0,48 g 0,0037 mol) was dissolved in acetone (80 eq 17 g 0,297 mol) in a microwave vial. The reaction mixture was immersed on a water bath before aqueous sulphuric acid (~22% (w/w) 2 eq 0,0075 mol) was added by syringe. Stirred for a few minutes in water bath before adding sodium hypochlorite (~14 % active chlorine 2,00 ml) also from syringe. The reaction was then heated at 50°C in microwave for one hour before it was quenched with $Na_2S_2O_5$ (2 – 3 times the substrates weight). Dissolved in MTBE that was washed thoroughly with water and brine, dried with Na_2SO_4. Reduced in vacuum, got a reddish residue with a smell like acrolein. Conversion after work-up 18%.

43 Ross A. Lee_Tetrahedron Lett.(1997)p3857
44 Marcin Lukasiewicz_MDPI(2002)
45 H Wan_Monatshefte Fũr Chemie(2008)p909
46 Czech Pat. No 265359/19901990
47 G Mirafzal_Tetrahedron Lett.(1998)p7263

Comments:

A few reactions were done at room temperature, also the sodium hypochlorite was added with syringe pump over 10 hours, the acid was exchanged with phosphoric acid, a reaction was done with acetic acid as solvent. All these had less than 10% conversion.

5.6.6 Molybdenum mediated epoxide opening

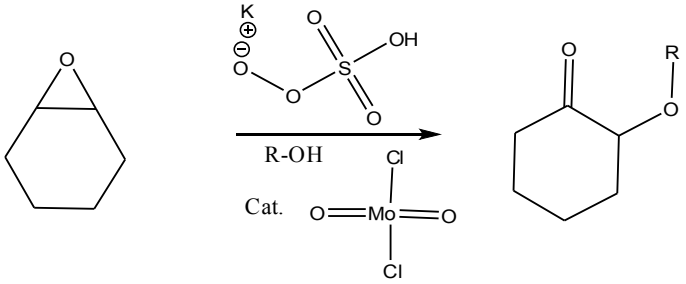


Figure 5.23 substrate epoxide, molybdenum chloride and oxidant Oxone

Literature:[37]

Cyclohexene oxide (1 eq 0,098 g 0,001 mol), oxone (1,2 eq 0,73 g 0,0012 mol) $MoCl_2O_2$ (0,15 eq 0,030 g 0,00015 mol) was mixed with MeOH (74 eq 3 ml 0,074 mol). The publication did the same experiment on the same substrate at room temperature. In our hands it failed to produce the ketone, even when heated at 80°C. The product achieved was 2-methoxycyclohexanol. A test reaction done without Oxone gave the same product.

37 Kandasamy Jeyakumar_Synthesis(2007)p807

1 Andeas Pfaltz_Acc. Chem. Res.(2007)p1402
2 C Muller_Tetrahedron Lett.(2006)p2017
3 Stefan Kaiser_ Angew. Chem. Int. Ed(2006)p5194
4 “The gold book” IUPAC recommendations, doi:10.1351/goldbook.S05762 read 18.02.09
5 “Chemical development & scale-up” Dr. Will Watson & Dr Derek Robinson Course material from course given 3-5 of march 2009
6 Pharmacogenics knowledge base, http://www.pharmgkb.org/views/index.jsp?objId=PA451644#tabview=tab1, read 11 march 20096
7 Pyrylium salts: Science of synthesis T. Balaban (2003)p11-200
8 Roy Beddoes_J. Chem. Soc. Perkin Trans.(1995)p307
9 A Milov_Russian Journal of General Chem.(2007)p1294
10 A Katritzky_ Academic press(1982) Supplement 2 pyrylium salts: syntheses, reactions and physical properties
11 K Dimroth_Org.Syntheses Coll.(1969)p1135
12 2,6-Di-tert-butyl-4-methylpyrylium trifluoromethanesulfonate _Organic Syntheses_(1981)p34
13 T J Donohoe_Oxidation and reduction in organic syntheses_Oxford chemistry primers(2003)p3
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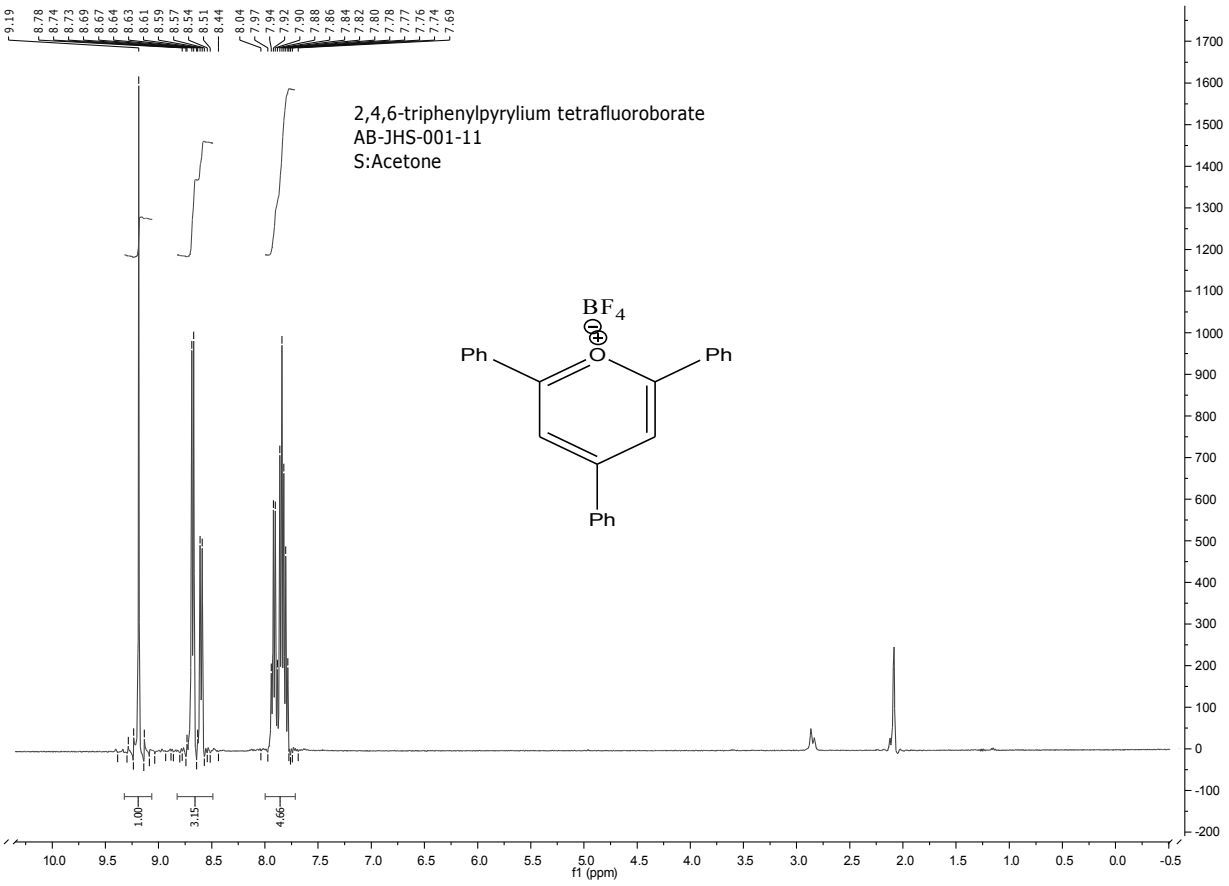
15 A T Balaban_Tetrahedron(1961)p257
16 S Krishnamurthy_J. Org. Chem(1977)p1197
17 Biao Jiang_Tetrahedron Lett.(2000)p10281
18 Ashok M. Salunkhe_Tetrahedron Lett.(1997)p1523
19 Byung Tae Cho_J. Chem. Soc. Perkin Trans.(1999)p2095
20 Mechanism reproduced from http://www.organic-chemistry.org/namedreactions/corey-bakshi-shibata-reduction.shtm, read 4 february 2009
21 Dibal characteristics http://mrw.interscience.wiley.com/eros/articles/rd245/frame.html, read desember 2007
22 Mark Midland_Org. Syntheses Coll.(1985)p57
23 Andre Gemal_J. Am. Chem. Soc.(1981)p5454
24 Clayden et al._Organic Chemistry_Oxford university press(2007)p1297
25 Iwao Ojima_Organometallics(1982)p1390
26 Andre Gemal_J. Org. Chem(1979)p418
27 Shigeru Sasaki_Tetrahedron Lett.(2005)p1497
28 NMR shifts from the webpage of SIGMA ALDRICH http://www.sigmaaldrich.com/catalog, read 30 march 2009
29 W Doering_J. Am. Chem. Soc.(1950)p631
30 UCLA webpage http://www.chem.ucla.edu/~webspectra/NotesOnSolvents.html, read november 2007
31 Matthias Bierenstiel_Tetrahedron(2005)p4911
32 C Lee_Bull Korean Chem. Soc.(2002)p1667
33 D Ramachary_Org. Lett.(2005)p1577
34 Armando Cordova_Eur. Chem. Jour.(2004)p3673
35 Rahim Hekmatshoar_Monatshefte Fur Chemie(2002)p195
36 Henrik Sunden_Angew. Chem.(2004)p6532
37 Kandasamy Jeyakumar_Synthesis(2007)p807
38 Gerhard Lauktien_Tetrahedron As.(1997)p3457
39 Gritter_Nature(1964)p179
40 Patent: Evans R.M _Quat.Rev.(1959)

41 Vogel's Textbook of practival organic chemistry_Longman scientific and

technical(1989)p445 p520 p524 p611
42 C Graves_J. Am. Chem. Soc.(2006p)p12596
43 Ross A. Lee_Tetrahedron Lett.(1997)p3857
44 Marcin Lukasiewicz_MDPI(2002)
45 H Wan_Monatshefte Fur Chemie(2008)p909
46 Czech Pat. No 265359/19901990
47 G Mirafzal_Tetrahedron Lett.(1998)p7263
48 From dupoints webpage www2.dupont.com/Oxone/en_US/assets/downloads/K20108%20Oxone®%20Safety%20and%20Handling.pdf , read 17 may 2009
49 T Zheng_Tetrahedron Lett.(1995)p833
50 T Zimmermann_J. Fur Prak. Chemie(1988)p306
51 “Chemical development & scale-up” Dr. Will Watson & Dr Derek Robinson Course manual from course given 3-5 of march 2009 Rome
52 H C Brown_Acc. Chem. Res.(1991)p16
53 J Yin_J. Org. Chem.(2006)p840
54 Calculated with Chem Bio Draw Ultra edition, version 11.0
55 H F Shurvell_J. Mol.Structure(1982)p11
56 Byung Tae Cho_Tetrahedron Ass.(1999)p1843
57 Arab K_J. Org. Chem(2002)p50
58 IR sample, product from “ICHIIs reagent” chapter 5.5.1
59 Sample ran in DMSO as solvent as the compound purchased from Sigma Aldrich did not to dissolve at all in chloroform
60 Price compared from Sigma Aldrich webpagehttp://www.sigmaaldrich.com/catalog , 26 april 2009
61 Vogel's Textbook of practival organic chemistry_Longman scientific and technical(1989)p467
62 K Ravikumar_Tetrahedron (1997)p2973
63 Gritter_Nature(1964)p179
64 Gabriel Tojo; Marcos Fernández_Springer(2002)
65 H C Brown_Acc. Chem. Res.(1991)p16
66 Anders Bøgevig_Angew. Chem.(2004)p1109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8.51
8.44
8.04
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7.94
7.92
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7.77
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7.74
7.69
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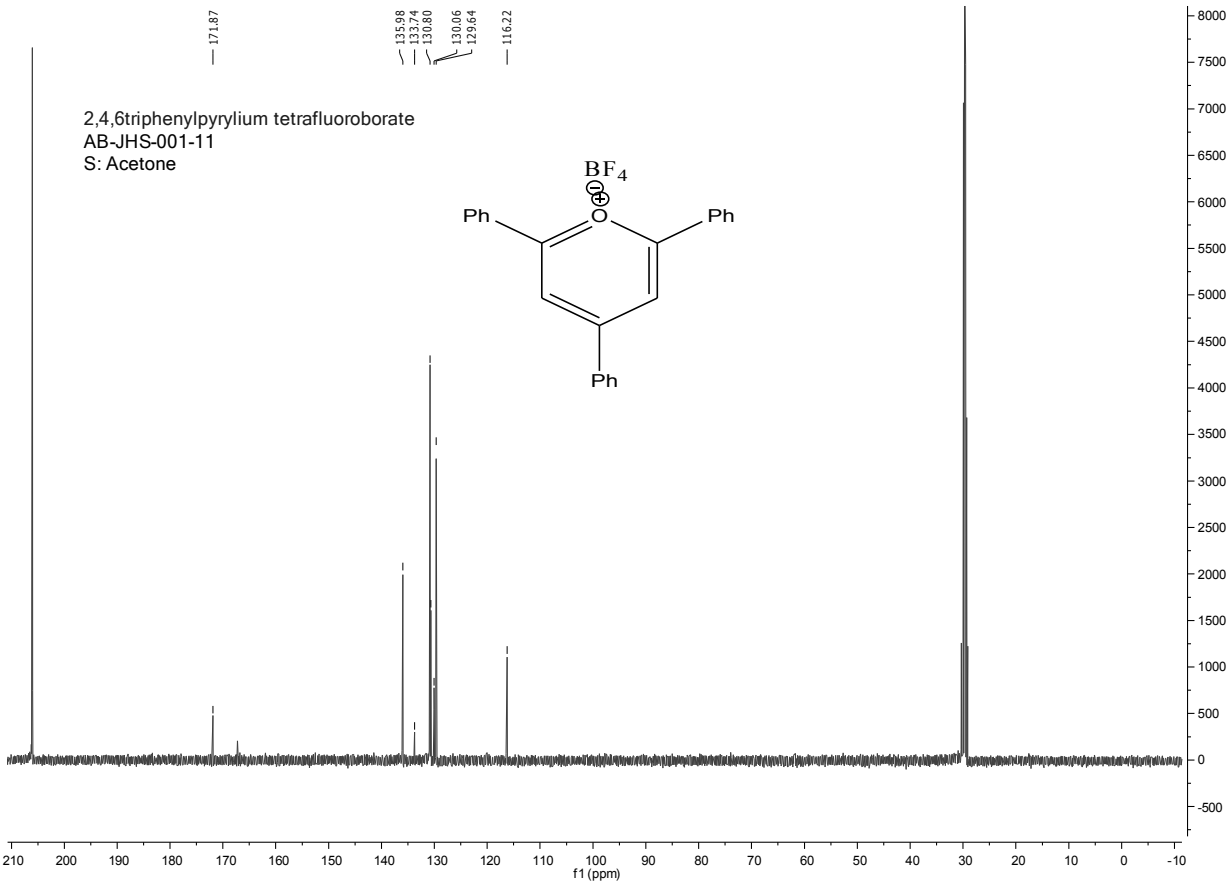
f1 (ppm)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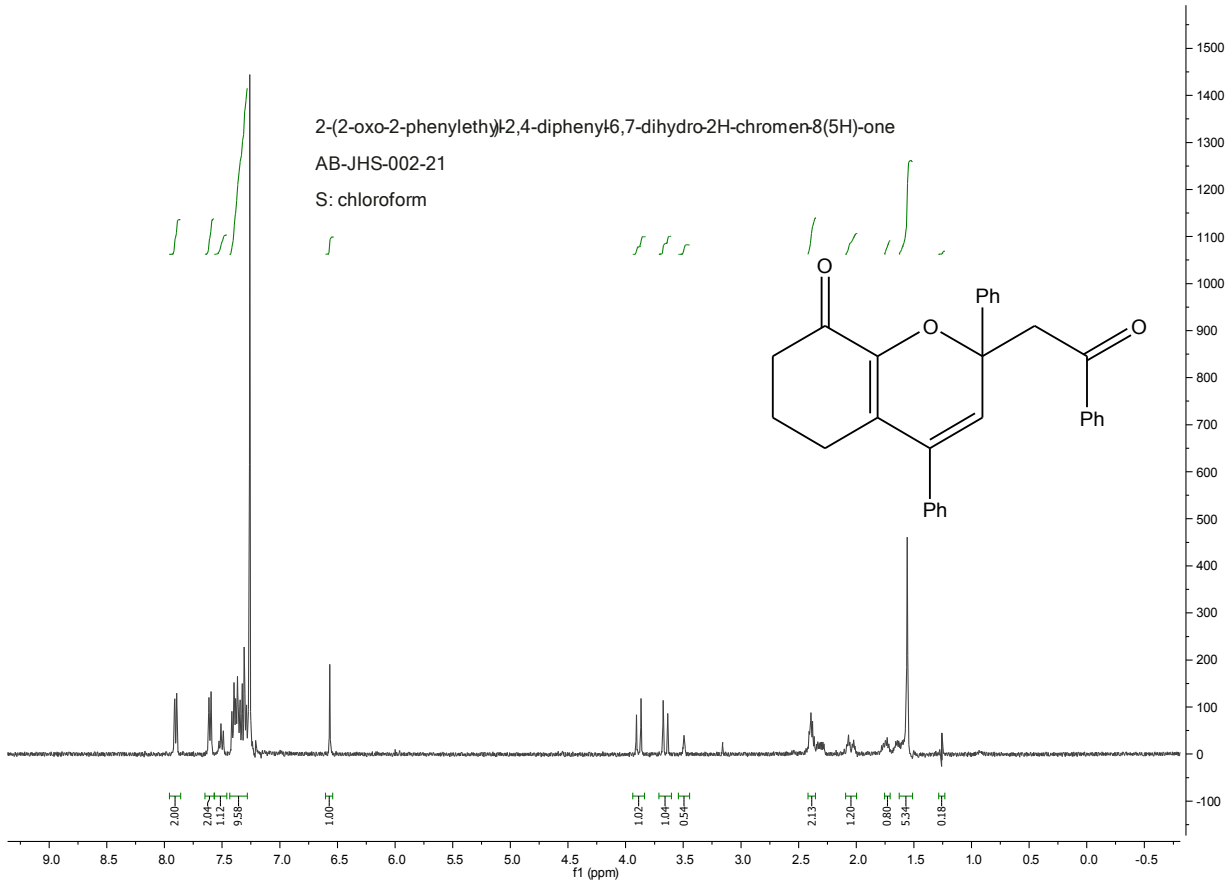
f1 (ppm)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O
O
Ph
Ph
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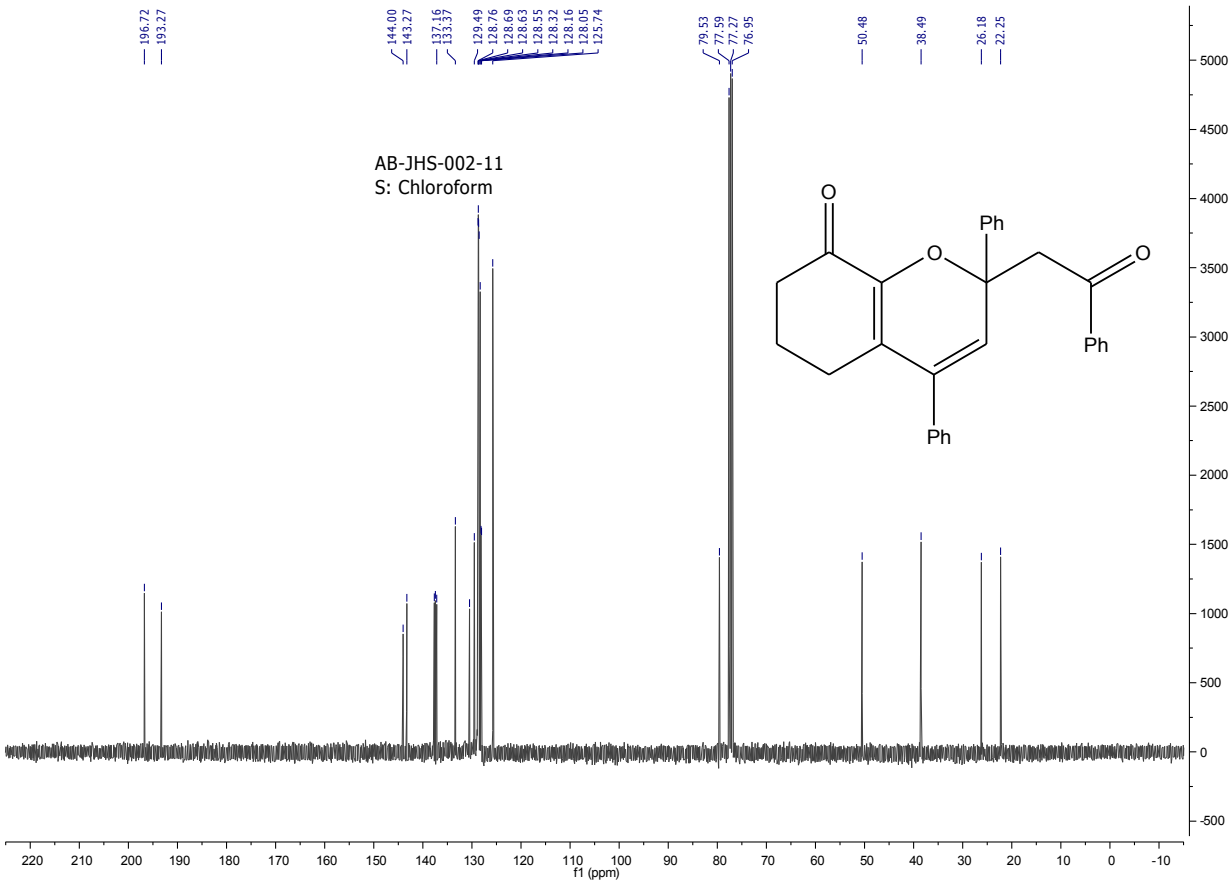
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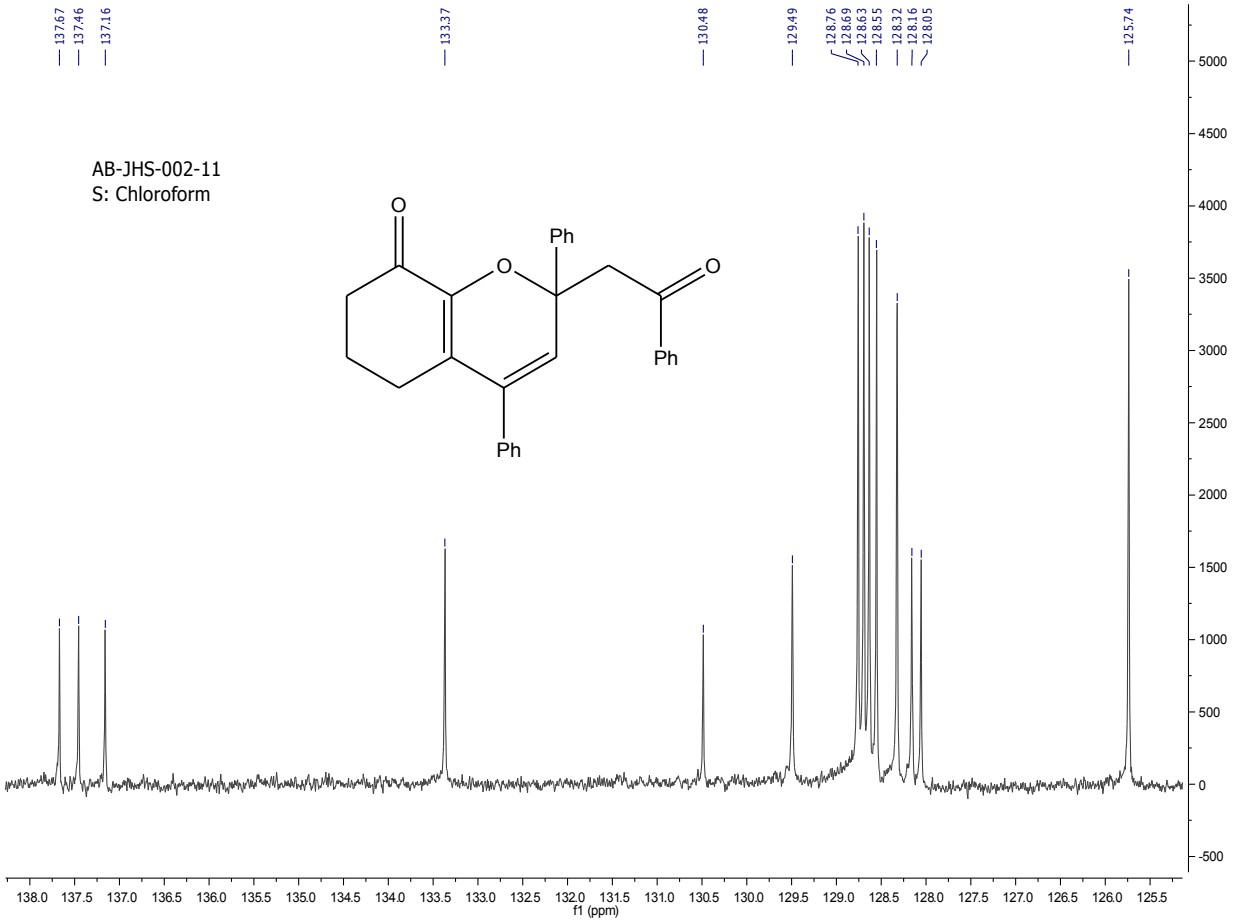
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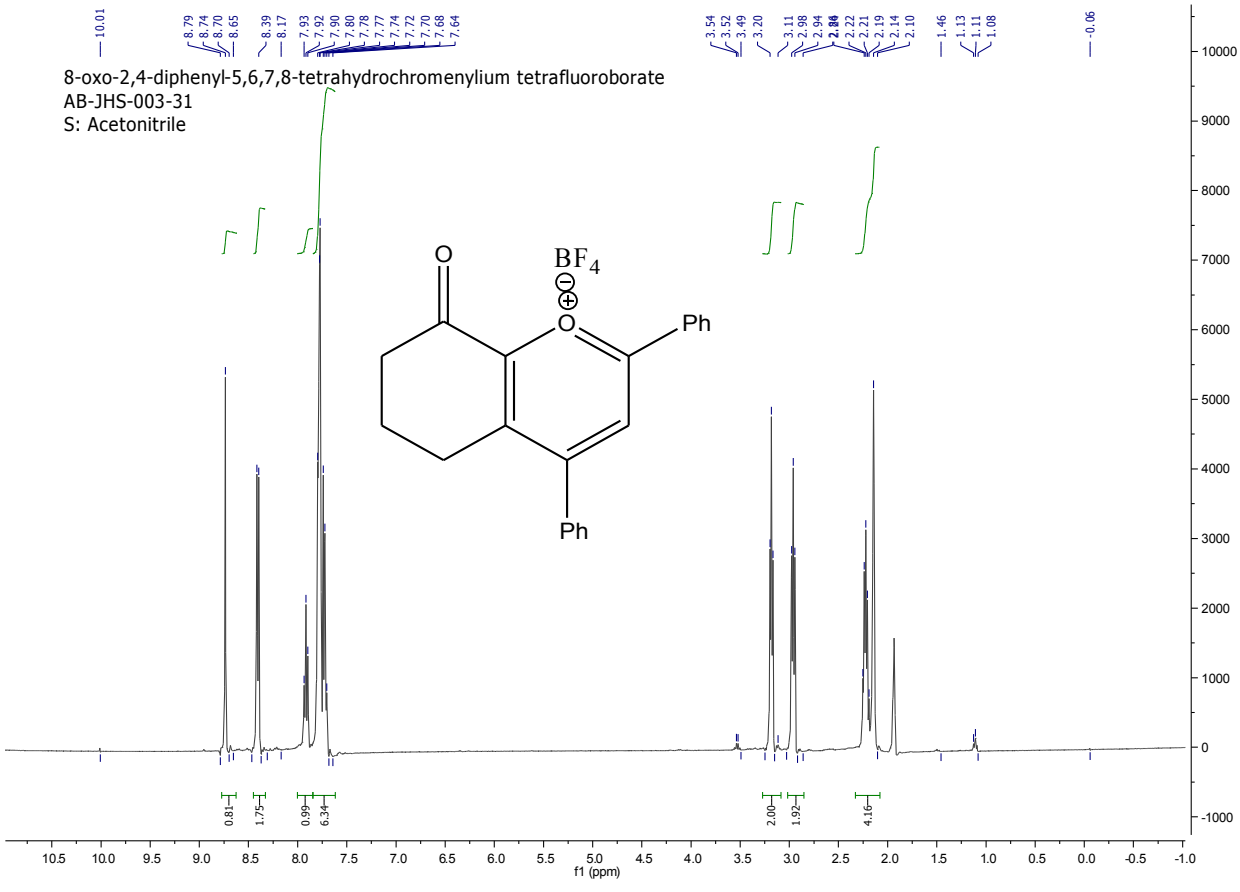
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3.52
3.49
3.20
3.11
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2.21
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1.46
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1.11
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AB-JHS-003-31
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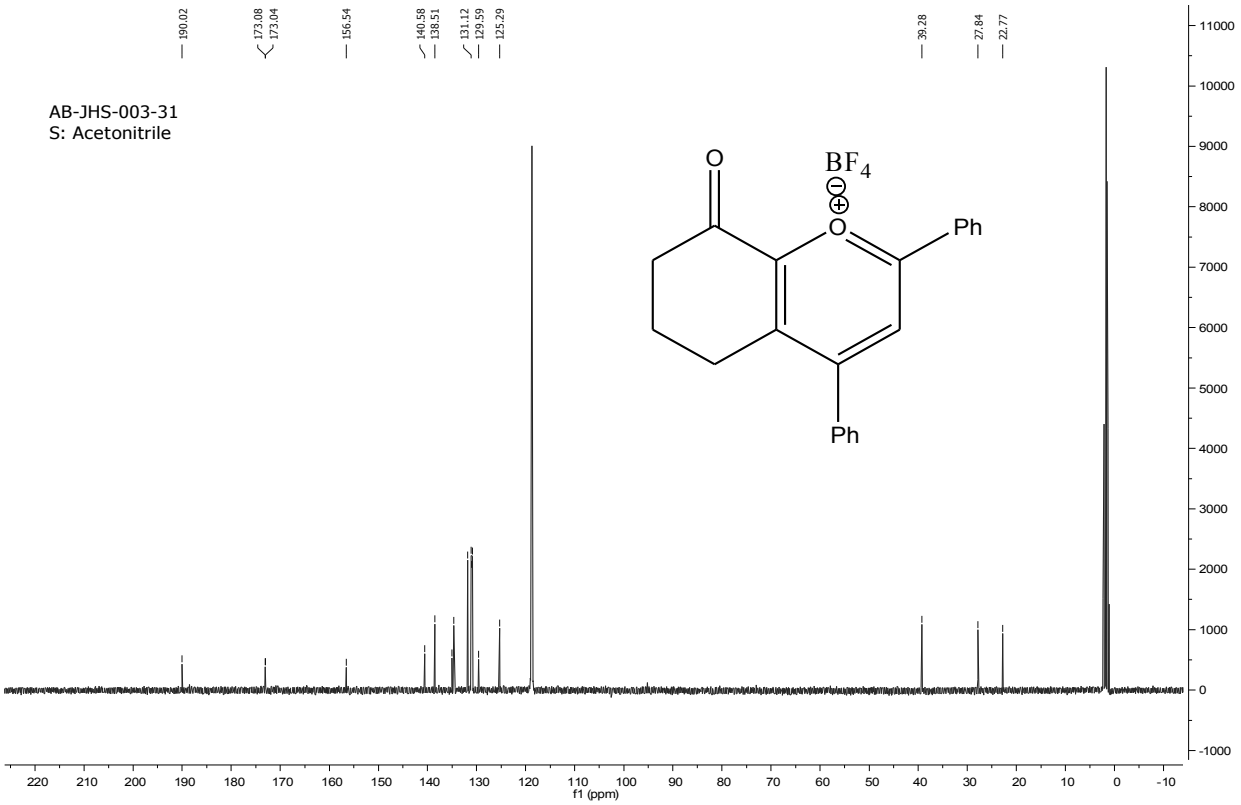
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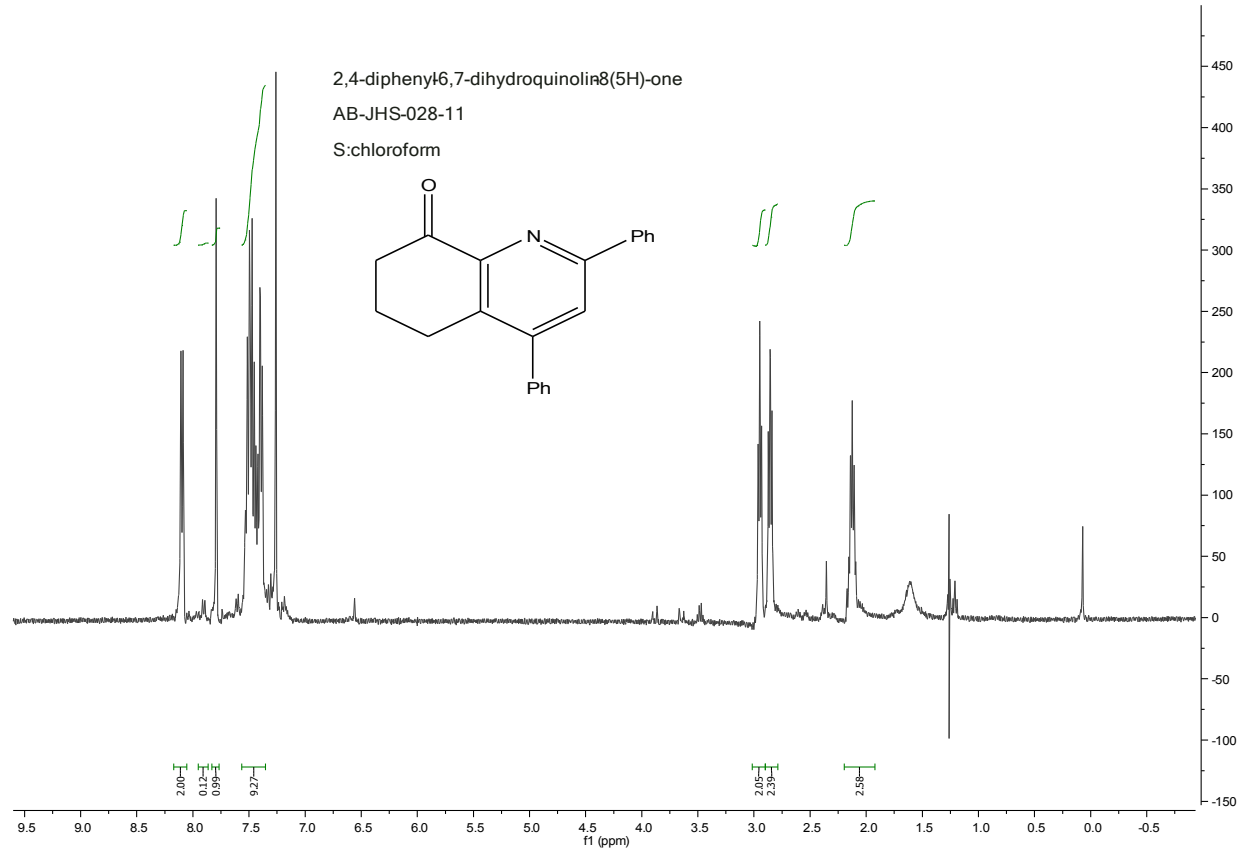
Ph
f1 (ppm)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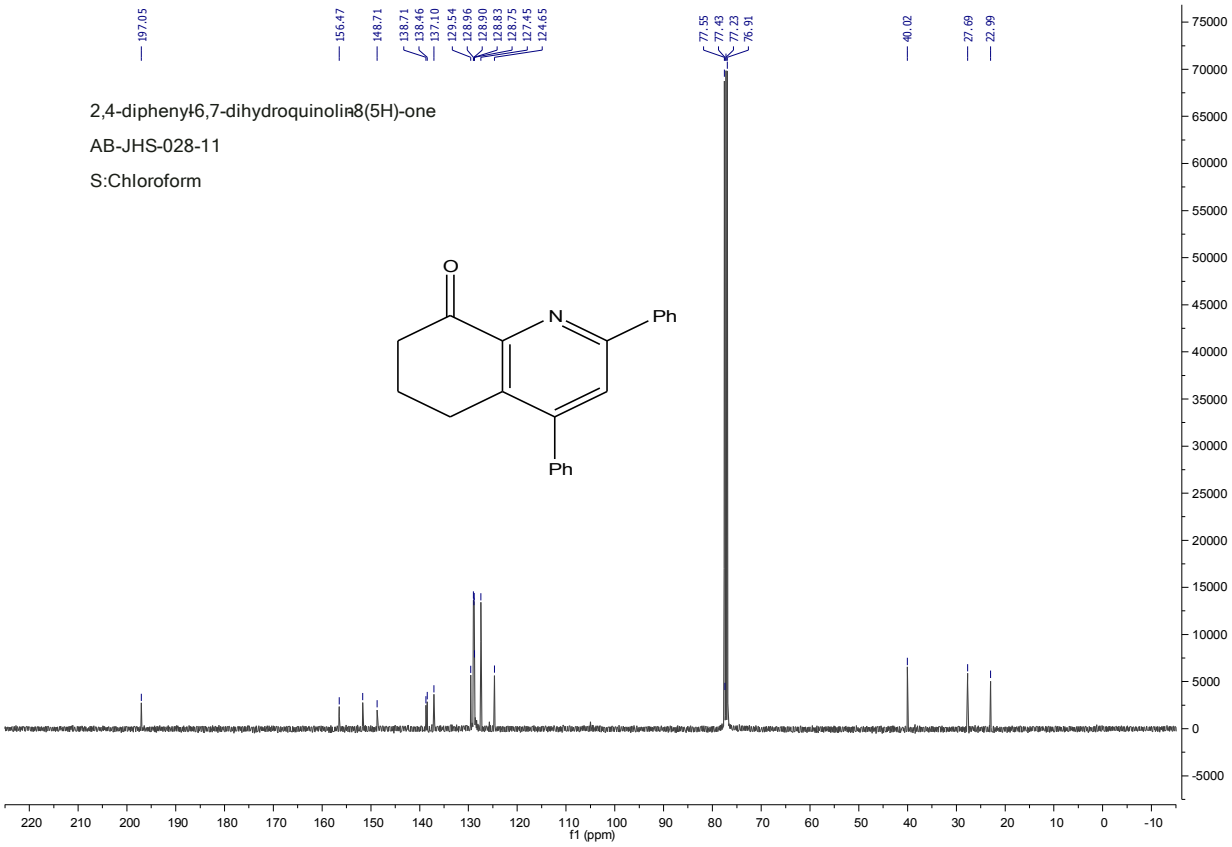
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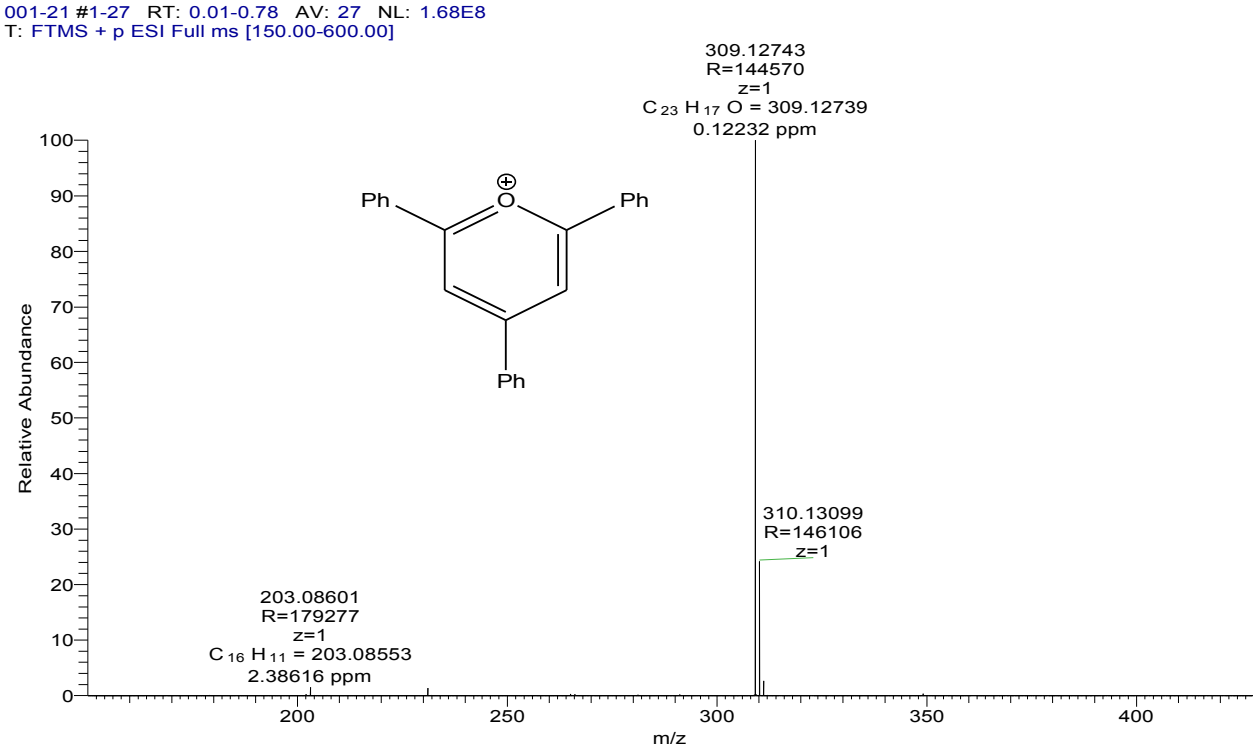
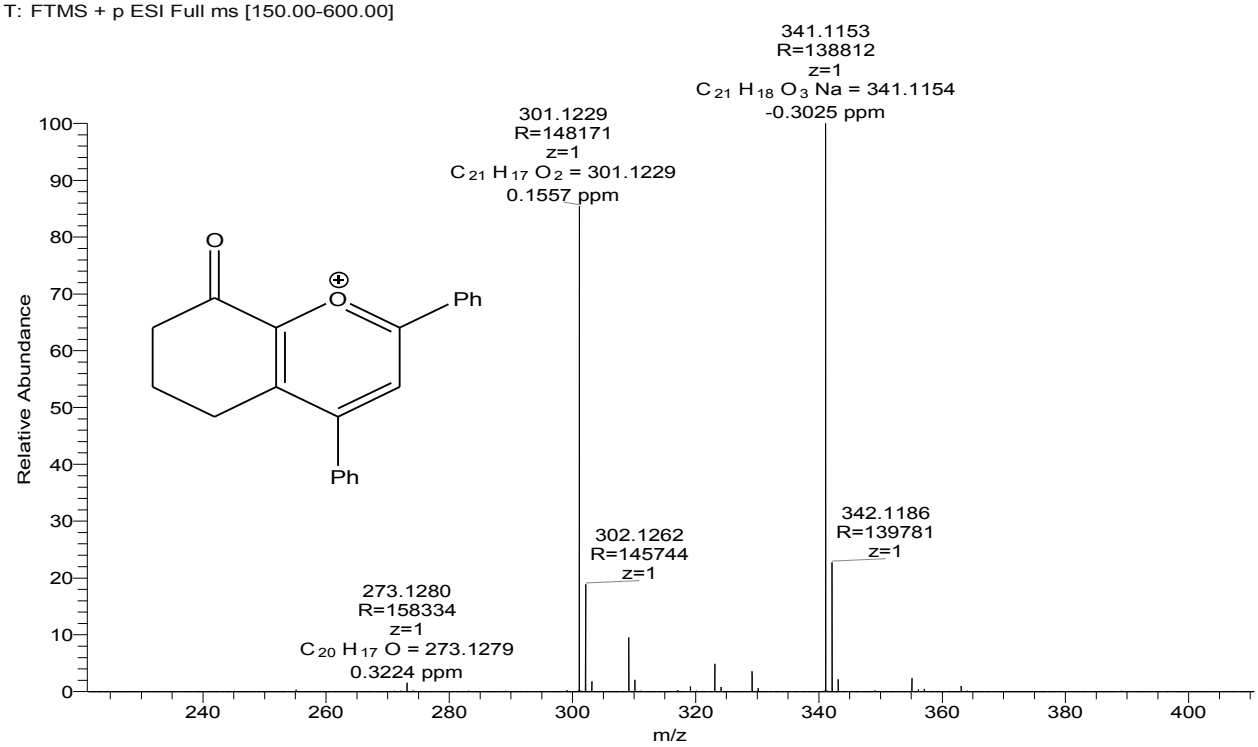
O
N
Ph
Ph
f1 (ppm)

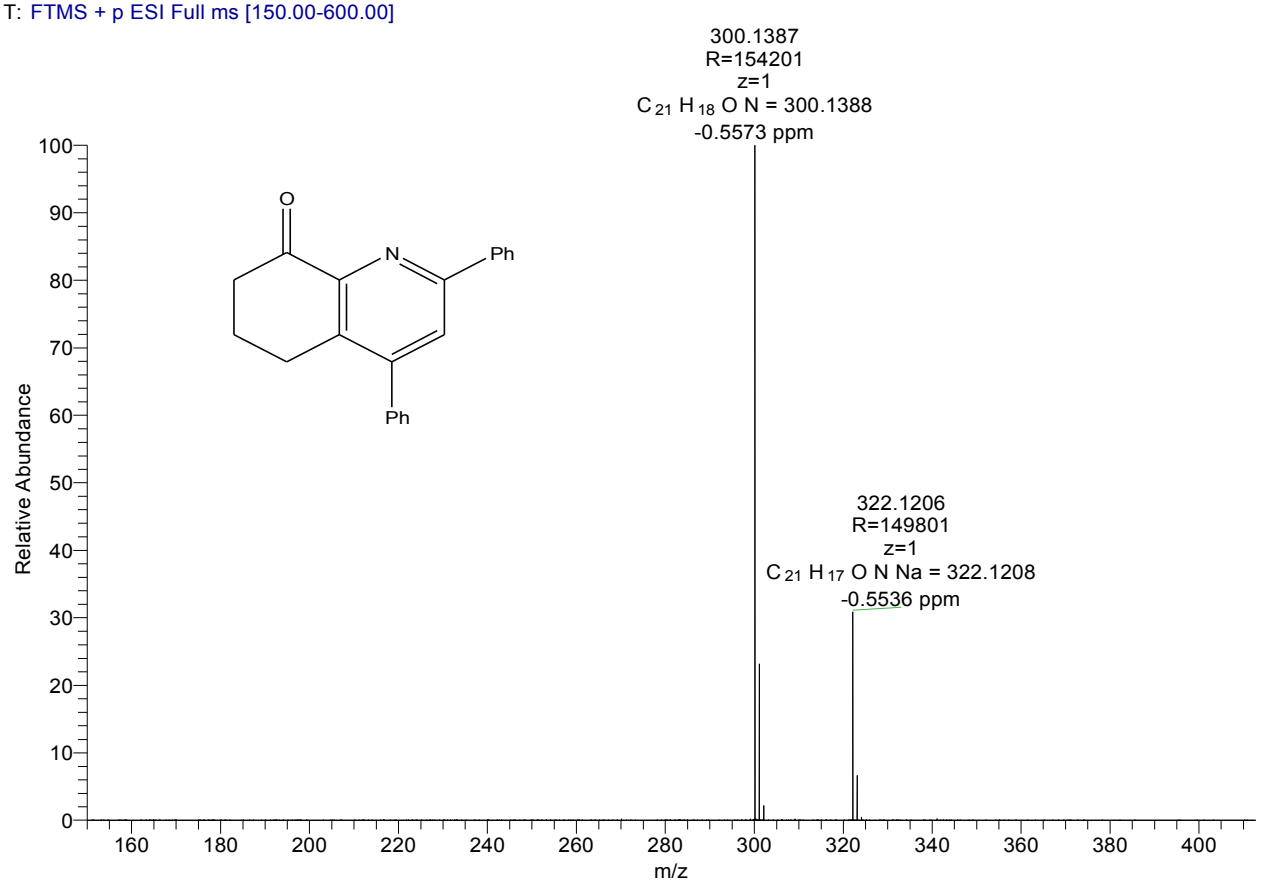
Triphenylpyrylium, calculated mass: 309,12739

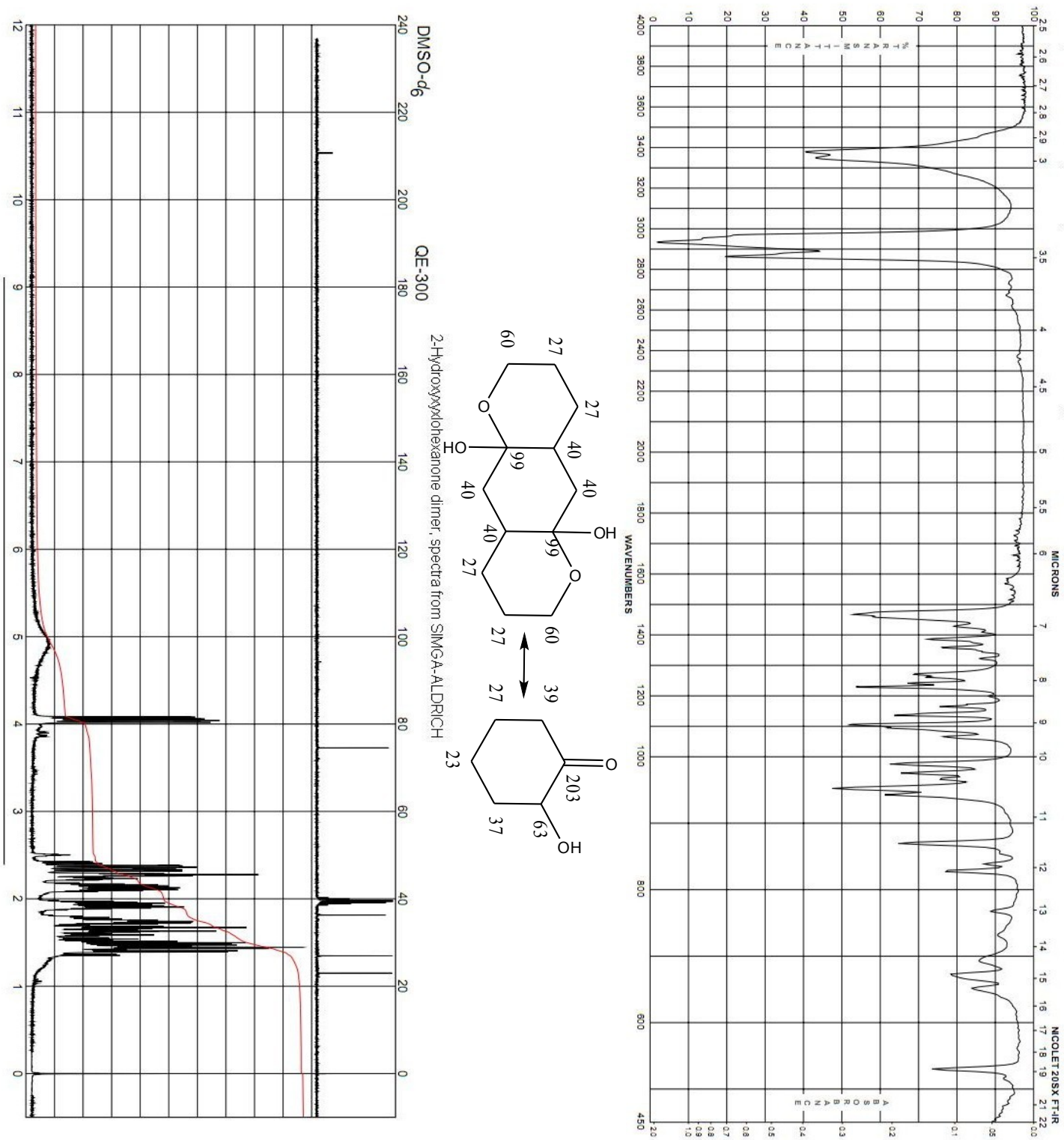


8-oxo-2,4-diphenyl-5,6,7,8-tetrahydrochromenylium tetrafluoroborate
calculated mass 301,12231



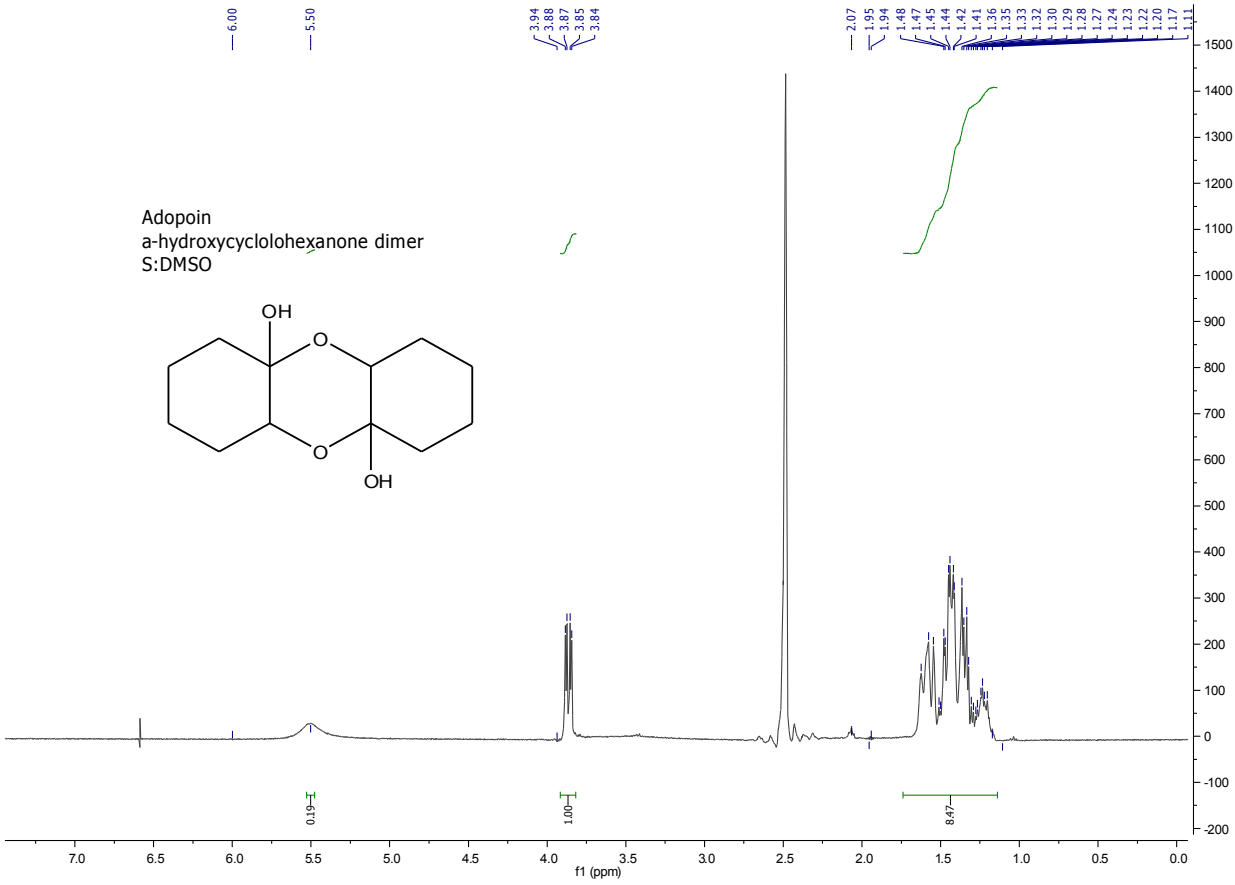
2,4-diphenyl-6,7-dihydroquinolin-8(5H)-one
calculated mass 299,13101 ($C_{21}H_{17}ON$) , spectrum shows protonated species

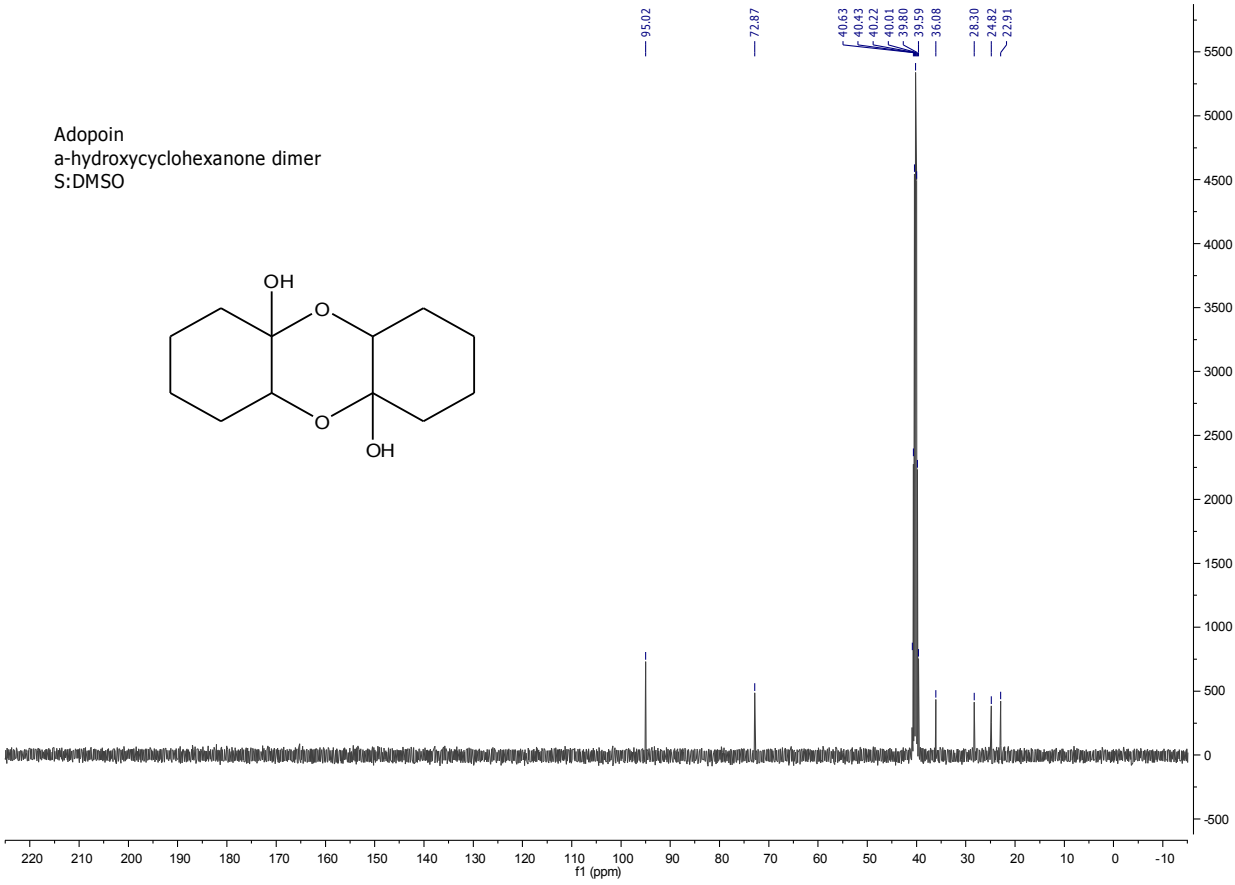




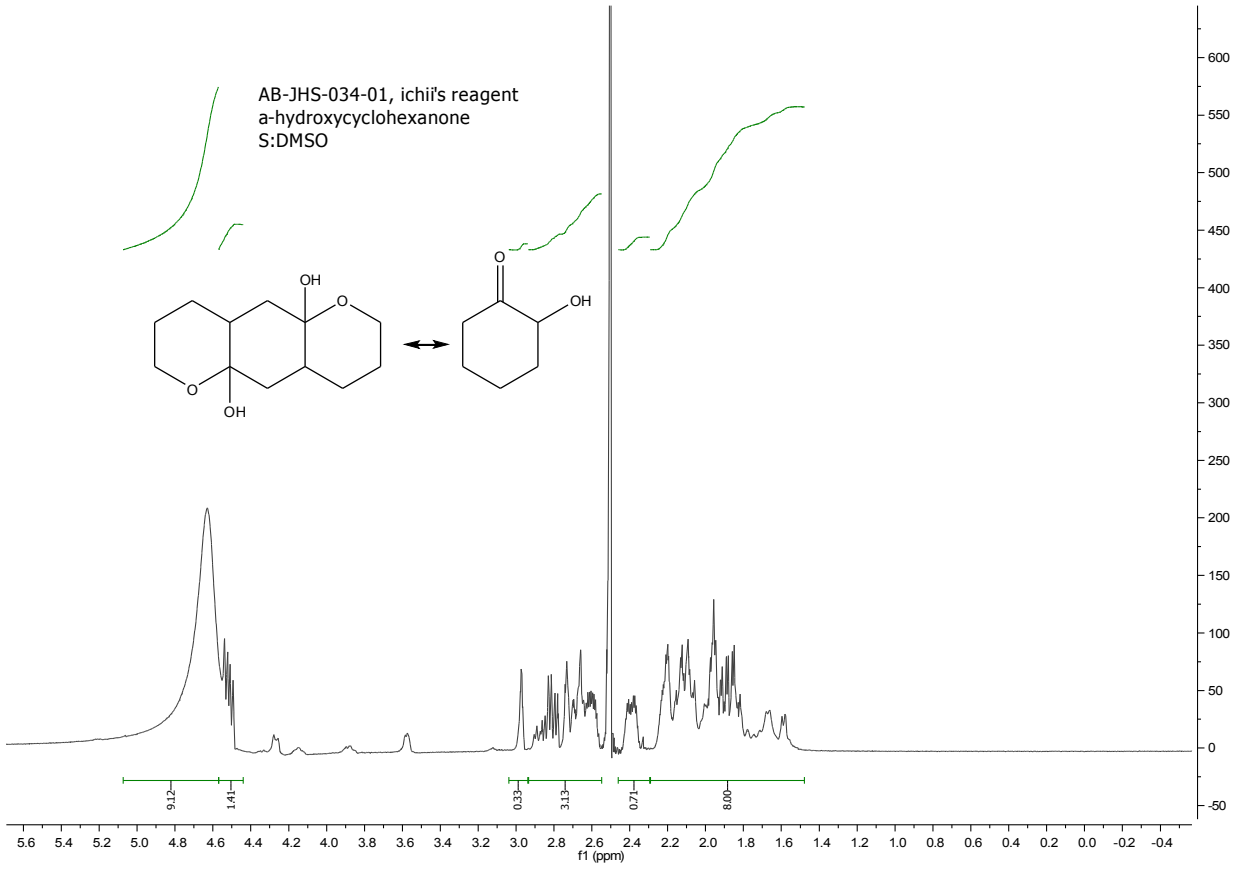
Dimeric values are calculated with MestReNova, monomer shifts recorded in chloroform from publication 57 Arab K_J. Org. Chem(2002)p50

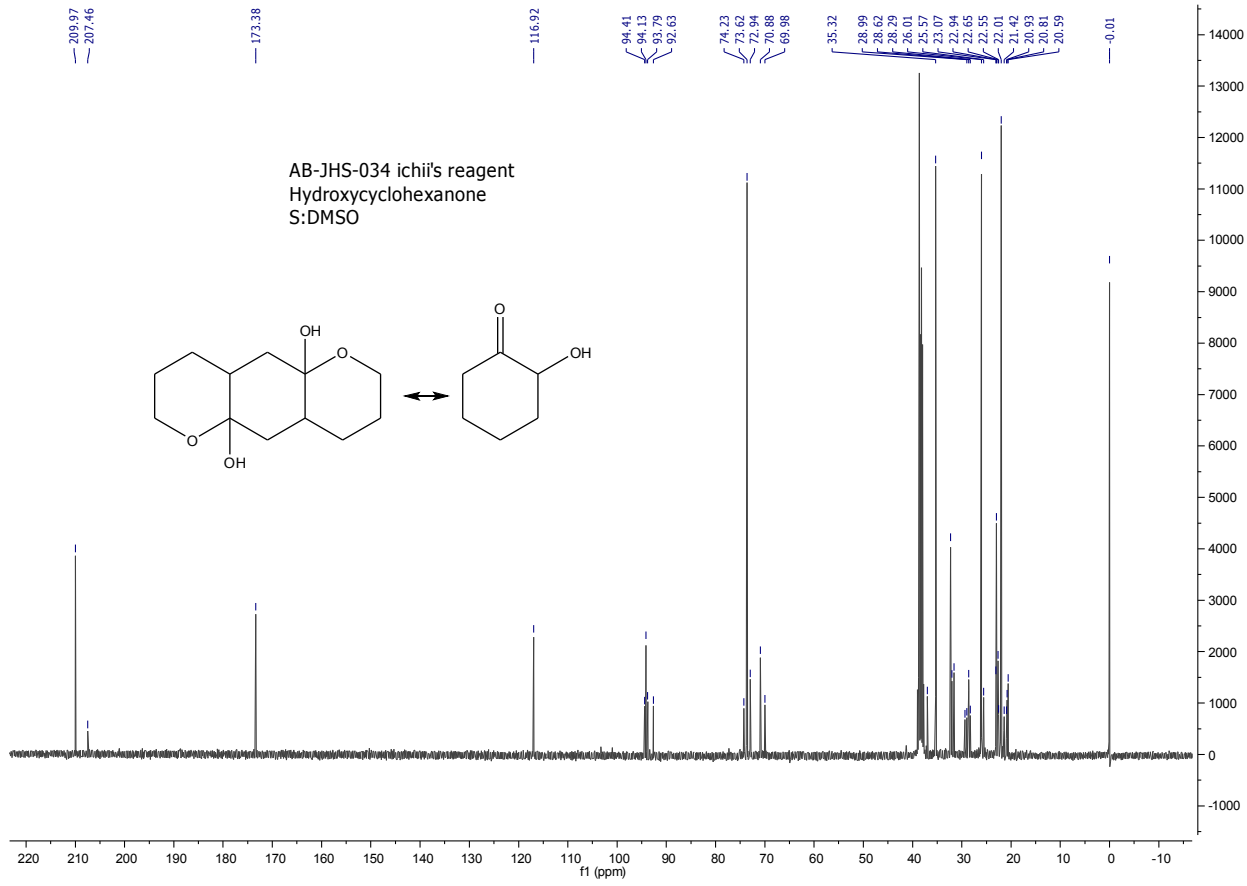
Adipoin commercial sample



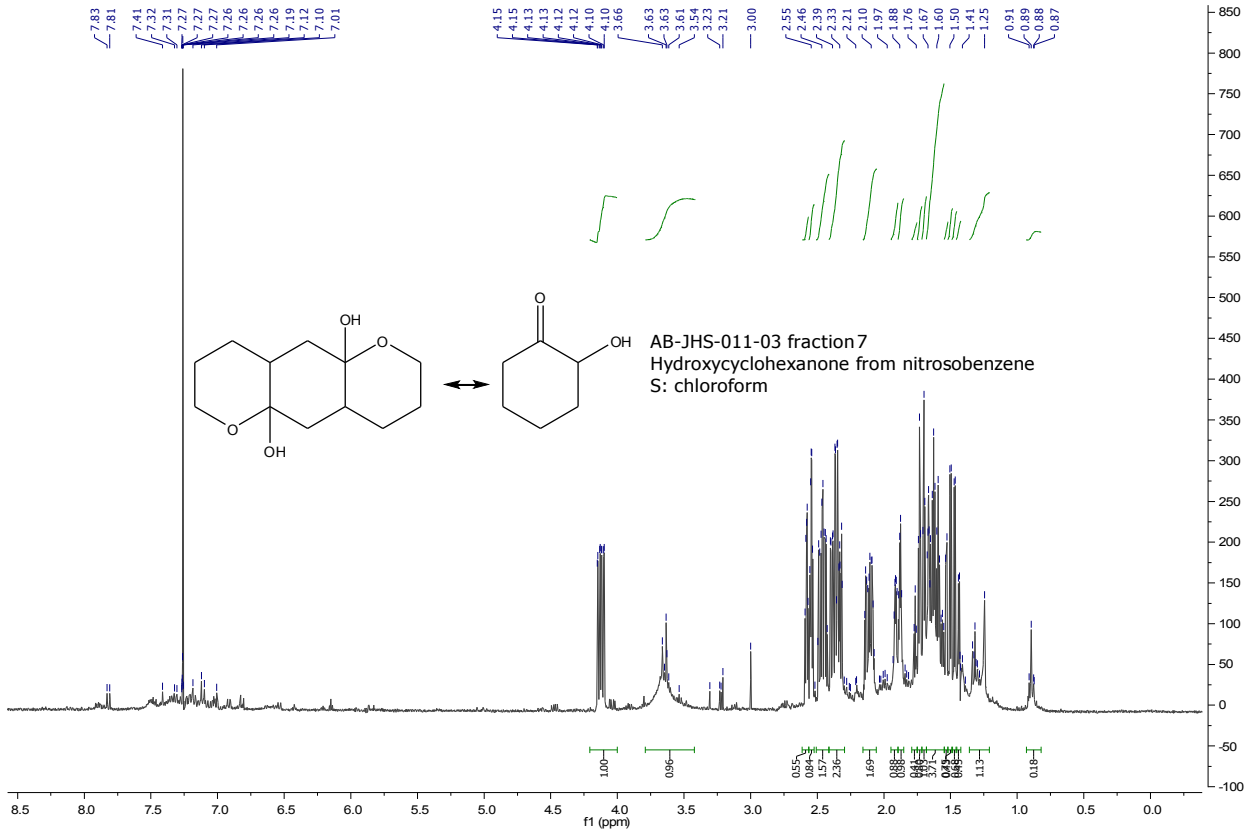


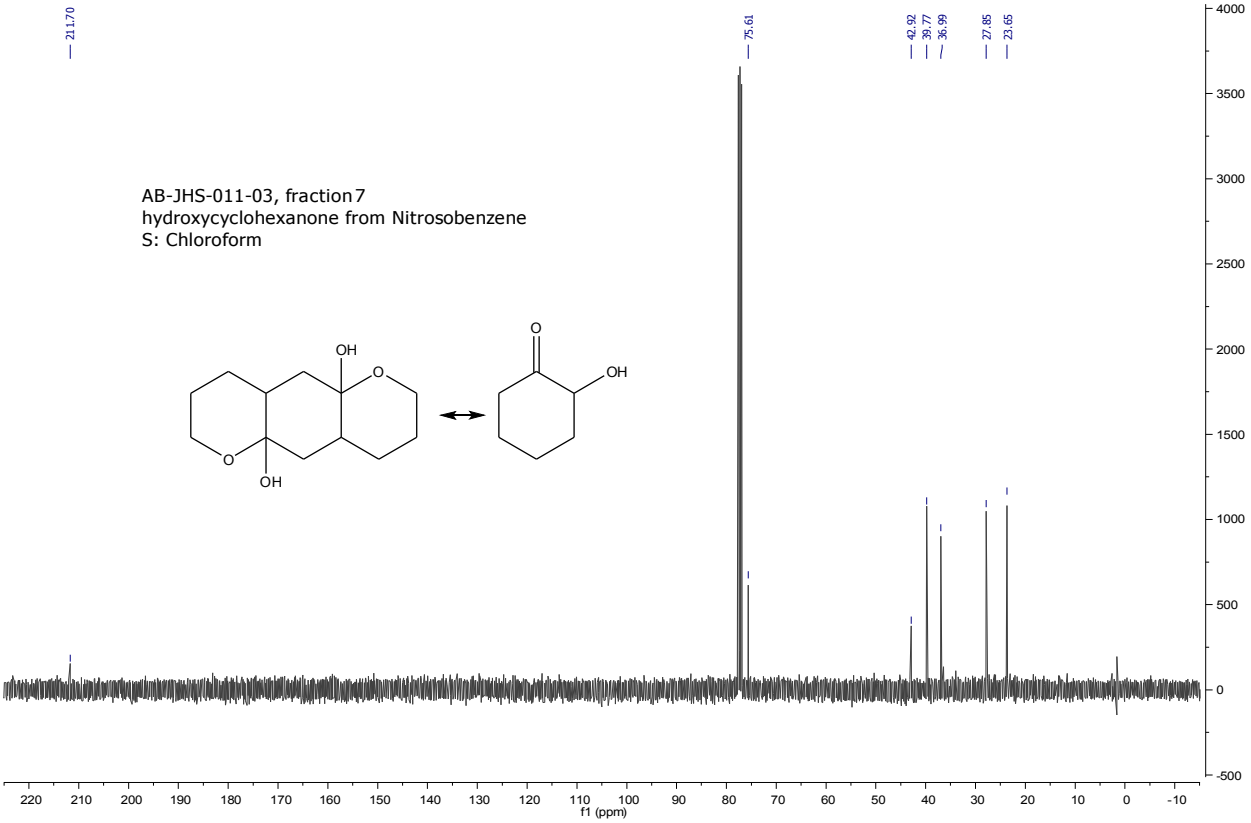
Ichiis reagent crude



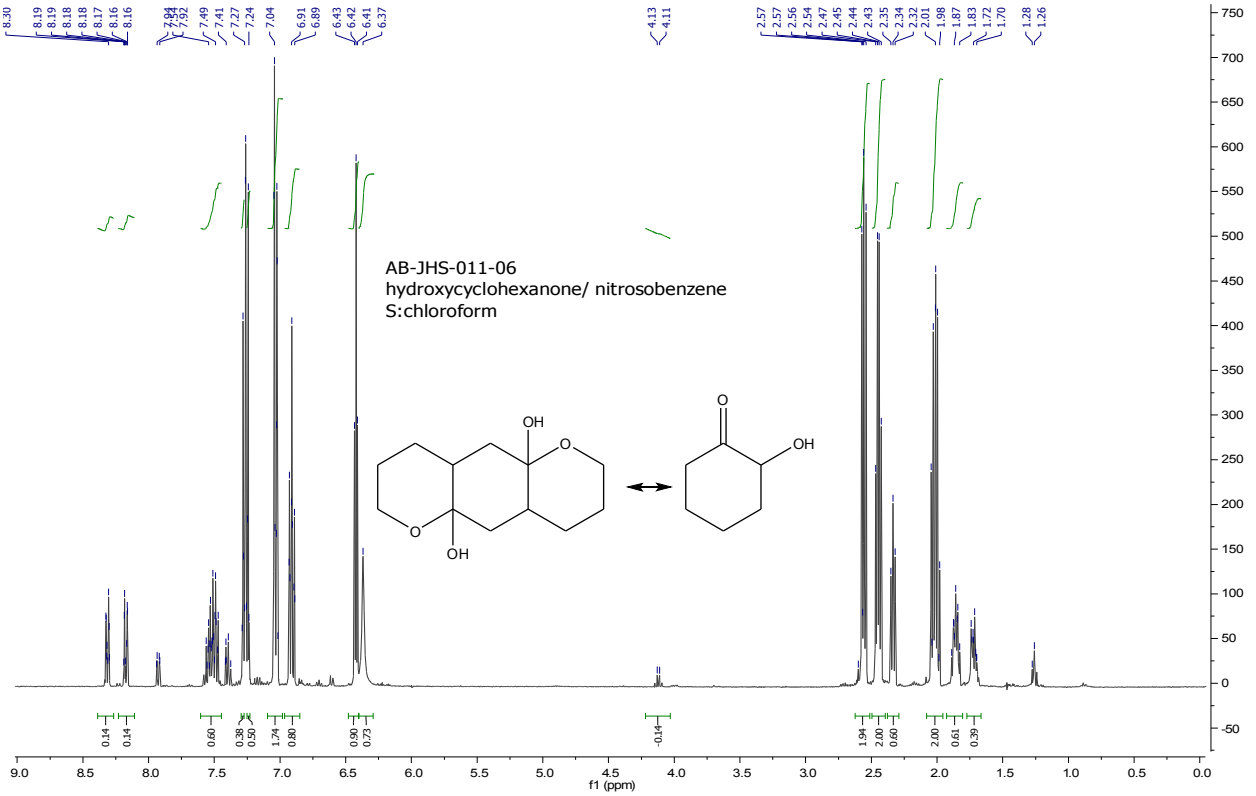


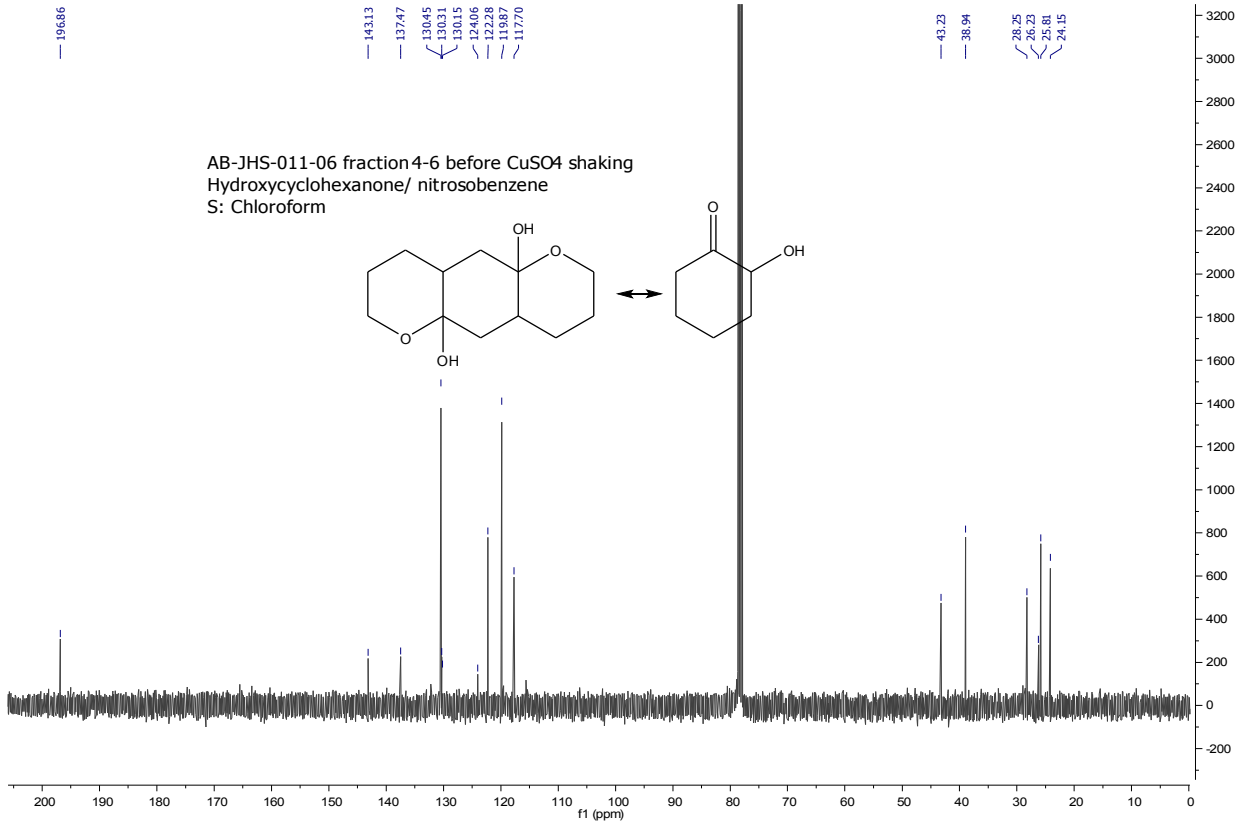
Nitrosobenzene reaction, crude mixture treated with $CuSO_4$,one fraction from silica column

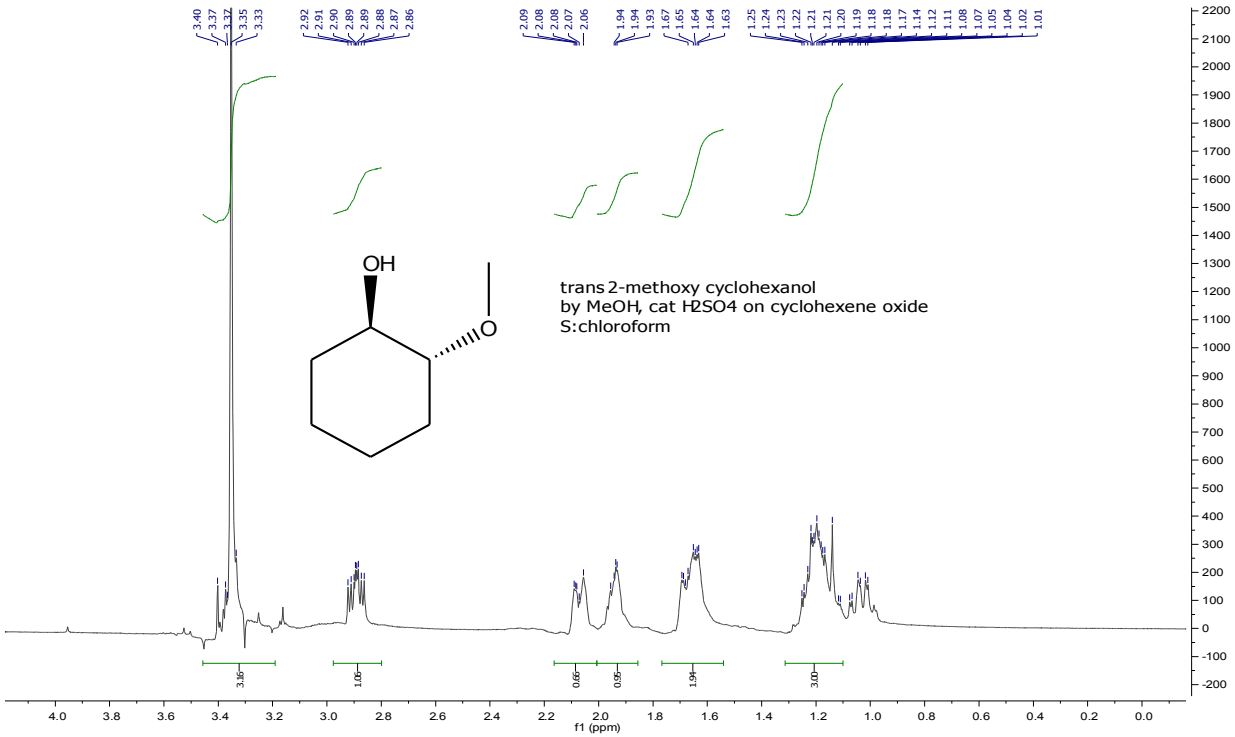




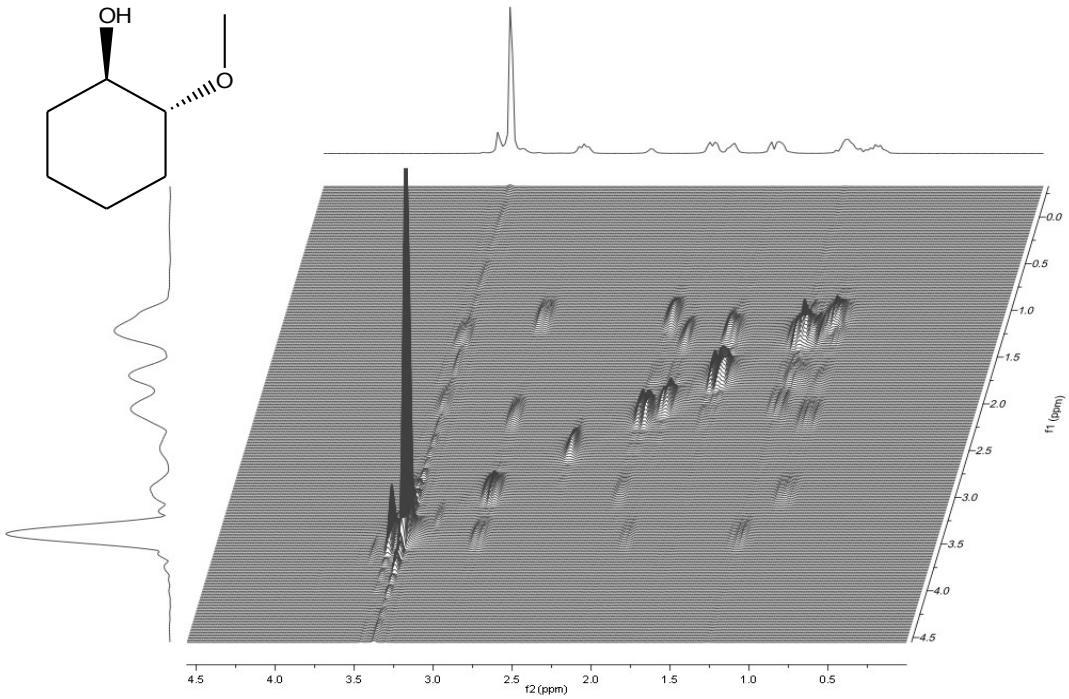
Nitrosobenzene reaction, cleansed in column, not attempted cleaved with $CuSO_4$







2-methoxycyclohexanol connected 1,1 2,2 *1,25 1,75 *3 1,1 2,1 3,4



Molybdenium mediated epoxide cleavage, with oxonium that failed to reduce the alcohol