Stereoselective synthesis of polysubstituted bicyclo[4.4.0]decanes and bicyclo[3.3.1]nonanes

Rúmvendnar efnasmíðar fjölsetinna bicyclo[4.4.0]dekana og bicyclo[3.3.1]nónana

M.Sc. Thesis

January 2009

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Yfirlýsing

Hér með lýsi ég því yfir að ritgerð þessi er samin af mér og að hún hefur hvorki að hluta né í heild verið lögð fram áður til hærri prófgráðu.

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Andri Guðmundsson

Abstract

For the past decade or so, synthesis of polysubstituted bicyclo[3.3.1]nonanes and bicyclo[4.4.0]decanes and research on the biological activity of such compounds has been conducted at the University of Iceland Science Institute (SI). These novel compounds have been tested against various types of cancer and results indicate potential use as cytotoxic agents, especially those bicyclic compounds that possess an aromatic substituent.

The synthetic pathways implemented at SI towards these bicyclo[3.3.1]nonanes and bicyclo[4.4.0]decanes are relatively simple and remarkably stereoselective. In both cases, these compounds are formed by reaction of an α,β-unsaturated aldehyde and dimethyl 1,3-acetonedicarboxylate under basic condititions.

As precursors of bicyclo[4.4.0]decanes, various aromatic α,β-unsaturated aldehydes were synthesized in good yields using a Heck coupling reaction variant involving reactions of aryl iodides and acrolein. Chan-Lam coupling of arylboronic acid derivatives and 4-iodophenol was used to synthesize novel aryl iodides. The resulting aryl iodides were then reacted with acrolein under Heck reaction conditions, providing novel, ether-bonded, aromatic α,β-unsaturated aldehydes.

These novel aldehydes, as well as aromatic aldehydes that were obtained from commercial suppliers, were then used in synthesis of novel bicyclo[4.4.0]decanes which were obtained in moderate to excellent yields.

Extensive research on a viable synthetic pathway towards enantiomerically pure bicyclo[3.3.1]nonanes using asymmetric organocatalysis was also carried out showing some promise but has yet to be optimized.

Ágrip

Undanfarin ár hafa verið stundaðar nýsmíðar á fjölsetnum bicyclo[3.3.1]nónan og bicyclo[4.4.0]dekan efnasamböndum á Raunvísindastofnun Háskólans og lífvirkni þessara efnasambanda verið rannsökuð. Efnin hafa t.d. sýnt virkni gegn ýmsum tegundum krabbameins, sérstaklega þau bicycloefni sem hafa arómatíska sethópa. Aðferðirnar sem notaðar eru við nýsmíðar á þessum efnum eru fremur einfaldar og í eðli sínu mjög rúmvendnar. Bicyclo[3.3.1]nónan og bicyclo[4.4.0]dekan efnasamböndin eru mynduð með því að hvarfa saman α,β-ómettuð aldehýð og tríkarbónýlefnið dimetýl 1,3-asetóndíkarboxylat við basískar aðstæður.

Nokkur arómatísk α,β-ómettuð aldehýð voru nýmynduð í ágætum heimtum með Heck kúplunar hvarfi milli arýljoðíða og 2-própenals. Chan-Lam kúplun var einnig notuð til að arýla 4-joðófenól með arýlbórsýru afleiðum. Þau arýljoðíð sem fengust úr þeim hvörfum voru þá notuð til myndunar á nýstárlegum α,β-ómettuðum arómatískum aldehýðum sem innihalda díarýl eter tengi.

Öll nýmynduð aldehýð voru svo notuð ásamt nokkrum aðkeyptum aldehýðum til nýsmíða á nýstárlegum bicyclo[4.4.0]dekan afleiðum sem voru einangruð í meðalgóðum eða mjög góðum heimtum.

Umfangsmiklar rannsóknir voru einnig framkvæmdar til þess að þróa nothæfa aðferð fyrir nýsmíðar á handhverfuhreinum bicyclo[3.3.1]nónan afleiðum með lífrænum hvötum. Niðurstöður þeirra rannsókna lofa góðu en aðferðir hafa ekki verið fullmótaðar.

Acknowledgements

- Dr. Jón K. F. Geirsson for invaluable guidance, limitless patience and for providing a pleasant work environment.
- Dr. Sigríður Jónsdóttir for NMR measurements and help with HPLC analysis.
- Gunnur Jónsdóttir for proofreading and for being supportive.
- Svana H. Stefánsdóttir for providing various chemicals at crucial junctures during the course of this project.
- Sverrir Guðmundsson for providing glassware and other laboratory equipment when needed.
- Óskar R. Kettler for stimulating conversations, good company and for being helpful.
- The University of Iceland Research fund and the Icelandic Center for Research for financial support.

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1 Introduction

Research on the nature and treatment of neoplastic cancer is conducted by scientists all over the world. This class of diseases affects people of all ages and causes almost 13% of all deaths according the World Health Organisation [1].

In the year 1994, researchers at the University of Iceland Science Institute (SI) discovered by chance a synthetic pathway towards polysubstituted bicyclo[3.3.1]nonanes (type **2** compounds) by reaction of 1-aza-1,3-butadienes and dimethyl 1,3-acetonedicarboxylate [2,3]. Since then the reaction conditions have been refined and instead of using enimines, the bicyclo[3.3.1]nonanes are now formed by reaction of an α,β-unsaturated aldehyde and dimethyl 1,3-acetonedicarboxylate under basic condititions (**Figure 1.1**) [4-6].

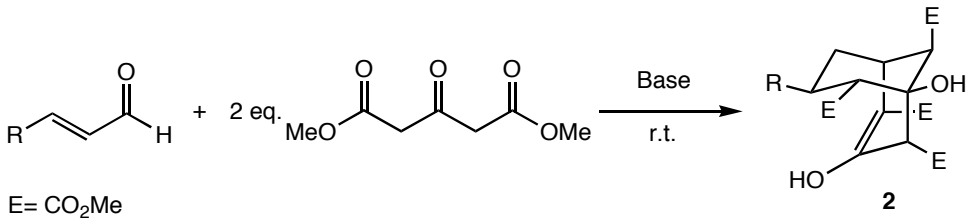


Figure 1.1. Synthetic route towards polysubstituted bicyclo[3.3.1]nonanes discovered at SI.

These compounds awoke interest because the bicyclo[3.3.1]nonane framework occurs in many biologically active compounds such as hyperforin, a compound that has been shown to inhibit cancer growth. The bicyclo[3.3.1]nonane skeleton is also present in many terpenoids and alkaloids [4]. As a result, some of these novel compounds were sent to the National Cancer Institute (NCI) for *in vitro* cytotoxicity testing. The results implied cytotoxic potential, especially those compounds bearing an aromatic R-substituent [4-6]. These findings gave grounds and inspiration for further research.

Furthermore, bicyclo[3.3.1]nonane derivatives have been used as a precursor in the synthesis of a taxane skeleton which intrigued researchers further. Taxanes have been known to be highly effective in the treatment of various types of cancer for many years. One of the best known and most widely used taxane is paclitaxel (**Figure 1.2**) [6]. Geirsson and co-workers at SI tried to develop a synthetic strategy using these bicyclo[3.3.1]nonanes towards the taxane skeleton.

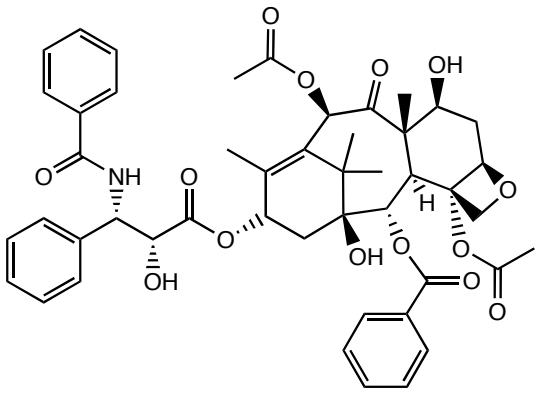


Figure 1.2. Chemical structure of paclitaxel.

The idea was to bring about a photochemical [2+2] cycloaddition reaction between a bicyclo[3.3.1]nonane derivative and cyclohexene. This was envisioned to result in the formation of a strained cyclobutane ring which then would be opened in a retro-aldol reaction, thus producing an eight-membered ring (**Figure 1.3**) [7].

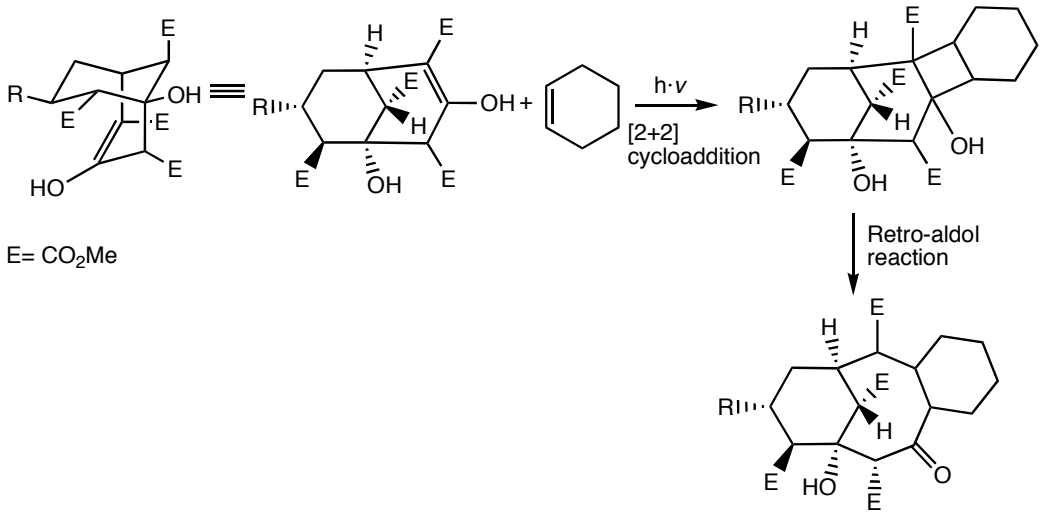


Figure 1.3. Idea for photchemical synthesis of taxanes from bicyclo[3.3.1]nonane derivatives [7].

These experiments proved unproductive but did inspire researchers to try and develop new synthetic strategies.

A method for ring expansion of cyclopentanones which had structural similiarities to the polysubstituted bicyclo[3.3.1]nonanes was developed by Rodriguez and co-workers (**Figure 1.4**) [8].

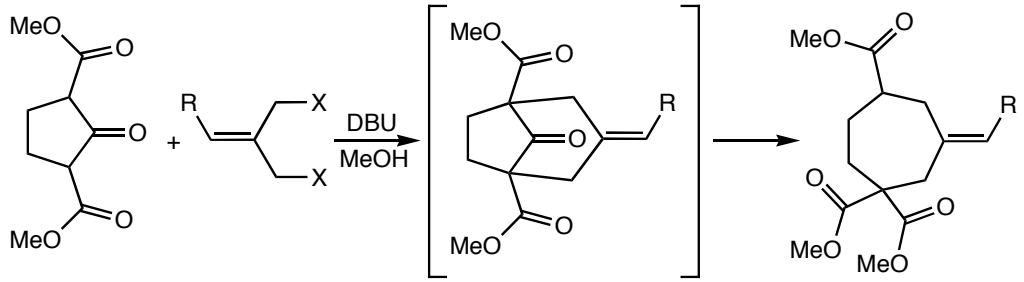


Figure 1.4. Ring expansion of cyclopentanones to cycloheptanes [8].

In an attempt to bring about similar ring expansion, Geirsson and co-workers at SI tried refluxing an acetone solution of a bicyclo[3.3.1]nonane, dibromopropane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) which yielded an unexpected crystalline product (**Figure 1.5**).

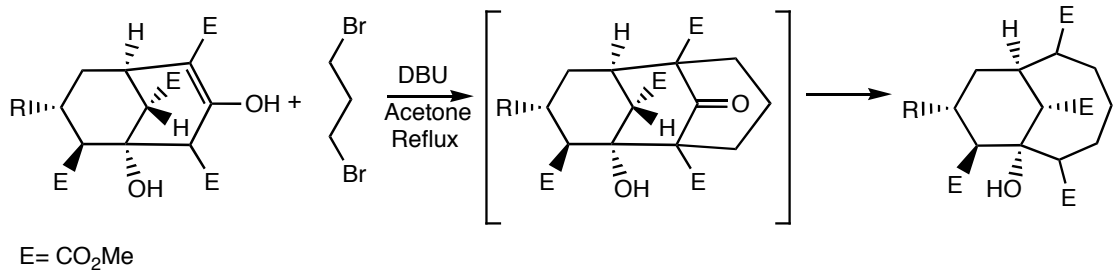
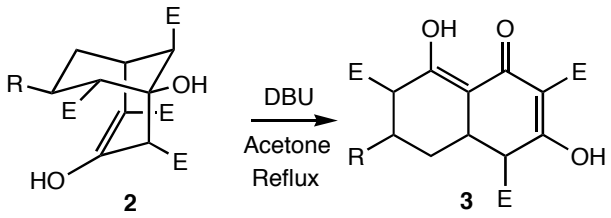


Figure 1.5. The ring expansion attempt which led to an unexpected product [7,9].

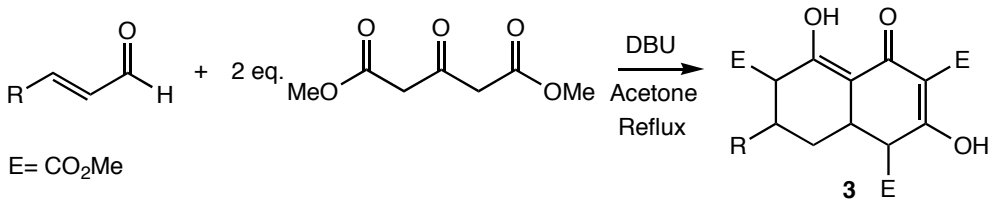
^{1}H and ^{13}C NMR spectra later revealed that no alkylation had occurred.
Extensive studies of NMR spectra and single crystal X-ray crystallography of these isolated compounds indicated that instead of the expected alkylation, a rearrangement of the polysubstituted bicyclo[3.3.1]nonane had taken place resulting in a polysubstituted bicyclo[4.4.0]decane (type **3** compound) (**Figure 1.6**) [7].



E= CO_2Me

Figure 1.6. An unexpected bicyclo[4.4.0]decane was formed in an attempt to expand the ring structure of bicyclo[3.3.1]nonanes.

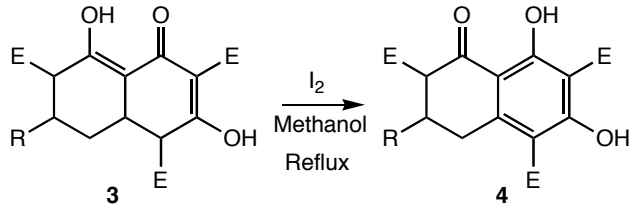
Since the unexpected discovery of these bicyclo[4.4.0]decanes or decalone derivatives, Geirsson and his coworkers have also observed that the precursors used in synthesis of bicyclo[3.3.1]nonanes are stirred in acetone at reflux with DBU, also yielded decalones (**Figure 1.7**) [7,9].



E= CO_2Me

Figure 1.7. One-step synthetic route for bicyclo[4.4.0]decanes.

The unexpected bicyclic framework aroused interest because it can be viewed as a naphthalene precursor and prompted researchers to explore the possibility of aromatizing one or both of the six-membered rings. Aromatization experiments on type **3** compounds resulted in one of the two rings being aromatized (**Figure 1.8**) [7].



E= CO_2Me

Figure 1.8. Aromatization of bicyclo[4.4.0]decanes of type **3**.

The aromatic compounds (type **4** compounds) obtained from these experiments can be either viewed as derivatives of 1-tetralones or resorcinol, both of which are biologically

active compounds. They are also present as substructures of many biologically active compounds and pharmaceuticals [10-12] (**Figure 1.9**).

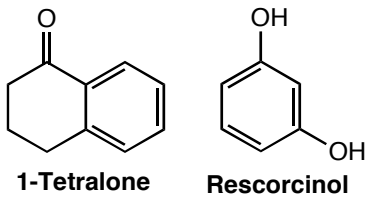


Figure 1.9. Chemical structures of 1-tetralone and resorcinol.

Substantial research has since then been conducted and further reactions and reaction conditions have been developed [7,9]. The general reaction conditions used thus far are shown in **Figure 1.10**. Various novel derivatives of both type **3** and type **4** compounds have been synthesized and submitted to NCI for anti-cancer activity screening with promising results [9].

The main goal of this project was to increase anti-cancer activity of novel type **4** compounds. This was to be achieved by:

1. Synthesizing novel bicyclo[4.4.0]decanes (type **3** and type **4** compounds) bearing various aromatic substituents. This was decided in light of the fact that type **2** compounds with aromatic moieties have shown the most cytotoxic activity and because most bicyclo[4.4.0]decanes that had already been synthesized had been obtained from aliphatic aldehydes [5,9] . Synthesis of aromatic α,β-unsaturated aldehydes (type **1** compounds) as precursors was therefore required (Chapter 2).
2. Attempting to incorporate biologically active side chains to type **4** compounds, preferably by alkylation or arylation of hydroxyl groups (Chapter 2). Since most biologically active compounds include one or more heterocycles, the incorporation of a heterocycle was also an objective.
3. Developing a synthetic strategy for the formation of chiral type **2** compounds. Since type **2** compounds can be used as precursors for type **3** and **4** compounds, synthesis of chiral type **3** and **4** compounds would hopefully be achieved in succession (Chapter 3).

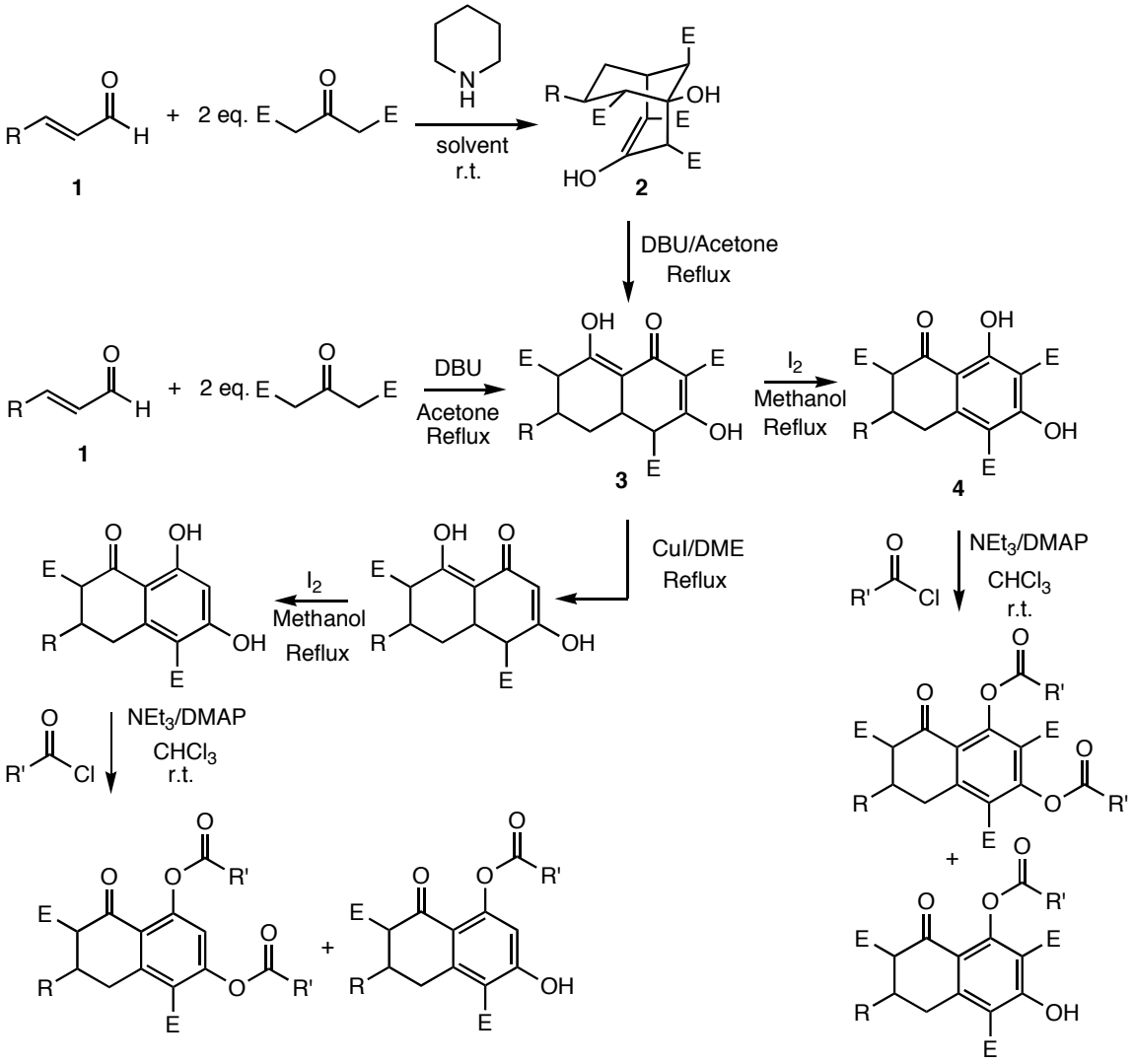


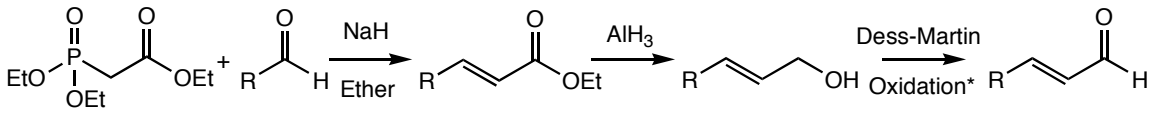
Figure 1.10. Various novel derivatives of type **3** and type **4** compounds have been synthesized under various conditions [7,9].

All novel compounds were to be sent to NCI for *in vitro* cytotoxicity testing.

2 Synthesis of bicyclo[4.4.0]decanes

2.1 Synthesis of α,β-unsaturated aldehydes

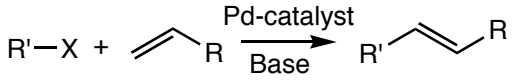
In order to synthesize type **3** and subsequently type **4** compounds, an α,β-unsaturated aldehyde is needed. Unfortunately, α,β-unsaturated aldehydes (especially aldehydes bearing an aromatic group) are not commonly commercially available. Therefore, a practical synthetic method for α,β-unsaturated aldehydes needed to be devised.
In their previous work, Geirsson and co-workers implemented a three-step synthetic route towards α,β-unsaturated aldehydes. This reaction sequence involved a Horner-Wadsworth-Emmons reaction of a phosphonate ester and an aldehyde, followed by a reduction of the resulting ester thus yielding an alcohol which would finally be oxidized to yield an aldehyde (**Figure 2.1**) [4,13].



*Dess-Martin oxidation involves the use of
Dess-Martin periodinane/$NaHCO_3$/pyridine in $CHCl_3$

Figure 2.1. Three-step reaction sequence for the formation of α,β-unsaturated aldehydes that was used at SI [4,13].

This process proved to be both time-consuming and involved difficult work up procedures as well as providing rather poor yields.
The Heck reaction has been known and studied for almost four decades and has been modified diversely, providing one of the most utile coupling reactions used to form C-C bonds between aryl and alkenyl halides and alkenes [14,15]. The reaction typically takes place in the presence of an organopalladium catalyst and a strong base (**Figure 2.2**).

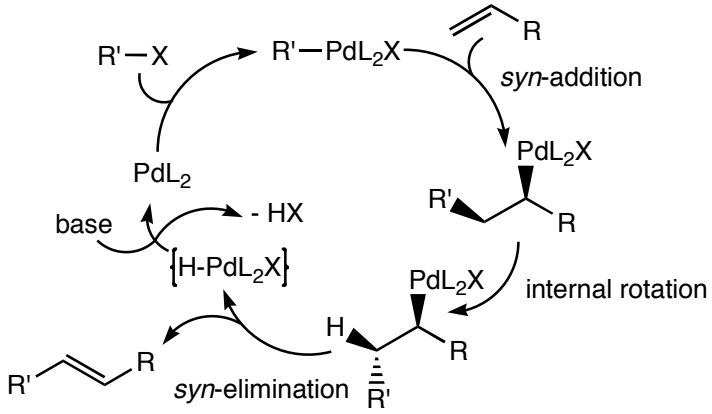


R'= alkenyl or aryl

Figure 2.2. The Heck coupling reaction.

Various catalysts, such as palladium dibenzalacetone complexes, tetrakis(triphenylphosphine)palladium(0) and palladium(II) acetate have been used as well as various organic and inorganic bases [14].

Mechanistically, the Heck reaction is believed to be similar to other well known transition metal-catalyzed coupling reactions like the Kumada, Suzuki, Stille and Negishi coupling reactions [14,15]. A general reaction mechanism is shown in **Figure 2.3** [4,14].



R'= alkenyl or aryl

Figure 2.3. General reaction mechanism of the Heck reaction [4,14].

The first step of the reaction is believed to be an oxidative addition of the alkenyl or aryl halide to a palladium complex and thus forming a σ-alkenyl- or σ-arylpalladium(II) complex. As a result, the electrophilicity of the Pd-complex is enhanced and it readily bonds to an alkene which adds *syn* to the complex. The resulting complex will then undergo internal rotation and subsequent *syn* eliminiation of a hydropalladium halide providing the desired alkene product. Regeneration of the active catalyst is then aided by an added base [4,14].

A variant of the Heck coupling reaction for the synthesis of α,β-unsaturated aromatic aldehydes was developed at SI by Óttar Rolfsson, which involves the coupling of aryl iodides with acrolein (**Figure 2.4**) [4].

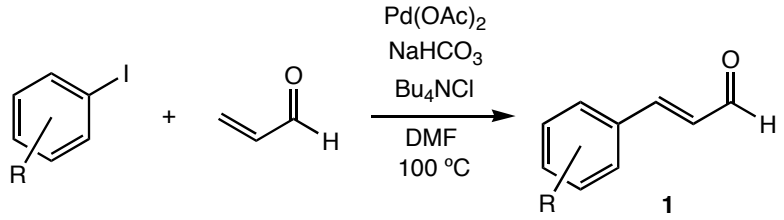
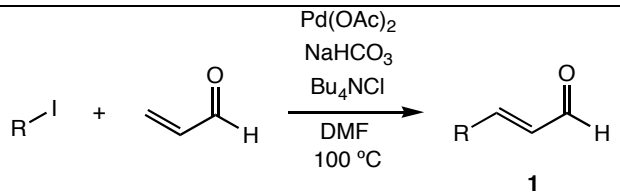


Figure 2.4 General synthetic route towards α,β-unsaturated aromatic aldehydes devised by Óttar Rolfsson [4].

The method utilizes palladium(II)acetate as a catalyst and sodium bicarbonate as a base and is carried out in DMF. Tetrabutylammonium chloride, a phase-transfer catalyst, is also implemented because it allows for the reaction to be carried out at lower temperatures and thereby reducing the risk of polymerization of acrolein.
Four α,β-unsaturated aromatic aldehydes were synthesized by Óttar Rolfsson in fairly good yields [4].

Using this Heck variant as a template, it was decided to try to synthesize new α,β-unsaturated aldehydes from various aryl iodides which then would be further reacted with dimethyl 1,3-acetonedicarboxylate to form type **3** compounds.
All reactions were carried out in a similar manner. One molar equivalent of aryl iodide was stirred with 1 molar equivalent of $NaHCO_3$, 1 molar equivalent of Bu_4NCl and 0,1 molar equivalent of palladium acetate in 25 mL of DMF at 100 °C. Two molar equivalents of acrolein were then added to the solution and the resulting solution stirred for 2 to 6 hours depending on the reactants.
The yields and structures of substituted aldehydes are shown in **Table 2.1**.



1

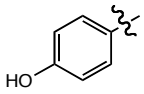
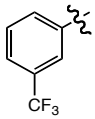
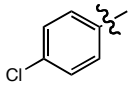
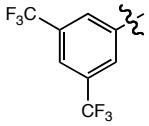
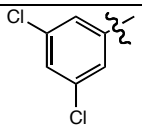
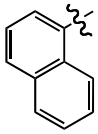
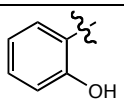
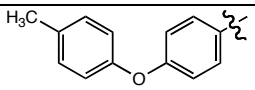
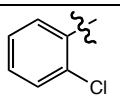
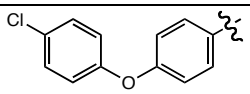
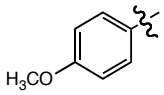
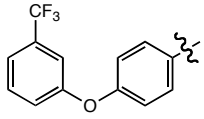
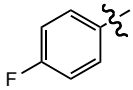
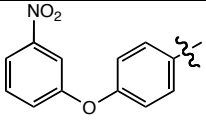
ID	R-substituent	Yield (%)	ID	R-substituent	Yield (%)
1a		89 %	**1h**		81 %
1b		90 %	**1i**		32 %
1c		82 %	**1j**		80 %
1d		74 %	**1k**		45 %
1e		96 %	**1l**		61 %
1f		91 %	**1m**		64 %
1g		75 %	**1n**		54 %

Table 2.1. Yields of type **1** compounds synthesized.

Structures of the aldehydes were confirmed by ^{1}H and ^{13}C NMR spectroscopy. All type **1** compounds gave a distinctive doublet around δ 9,65-9,86 ppm (J=7,5-8,0 Hz) downfield from TMS in the proton NMR spectra, representing aldehyde protons. The α-proton resonated as a doublet of doublets through coupling with the aldehyde proton (J=7,5-8,0 Hz) and from coupling with the β-proton (J=15,8-16,1 Hz). The α-proton signal was observed around δ 6,6-6,8 ppm. Aryl groups gave corresponding signals in the aromatic region. Signals representing β-protons were observed around δ 7,3-8,3 ppm (J=15,8-16,1

Hz). Aldehydes which include other types of protons, e.g. the hydroxyl group on **1a** and the methoxyl group on **1f**, also gave distinctive singlets with appropriate intensities. As an example, ^{1}H NMR spectrum of **1a** is shown in **Figure 2.5**.

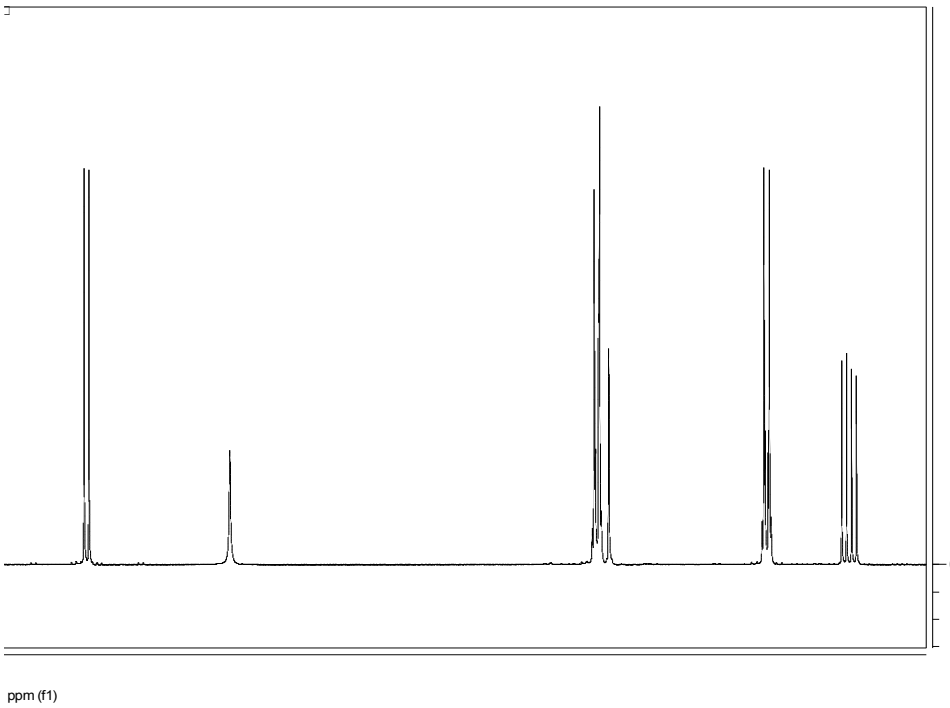


Figure 2.5. An example of a ^{1}H NMR spectrum of a type **1** compound (**1a**).

All of the aldehydes produced, were purified by column chromatography and were used in further reactions.

2.2 Synthesis of decalone derivatives

As mentioned before, the synthesis of decalone derivatives or type **3** compounds from type **2** compounds was discovered by chance when attempting a ring expansion (**Figure 1.5** and **Figure 1.6**) [7].

After isolation and structure determination of this unexpected product, a mechanism for the formation of the new compound was formulated (**Figure 2.6**) [7,16].

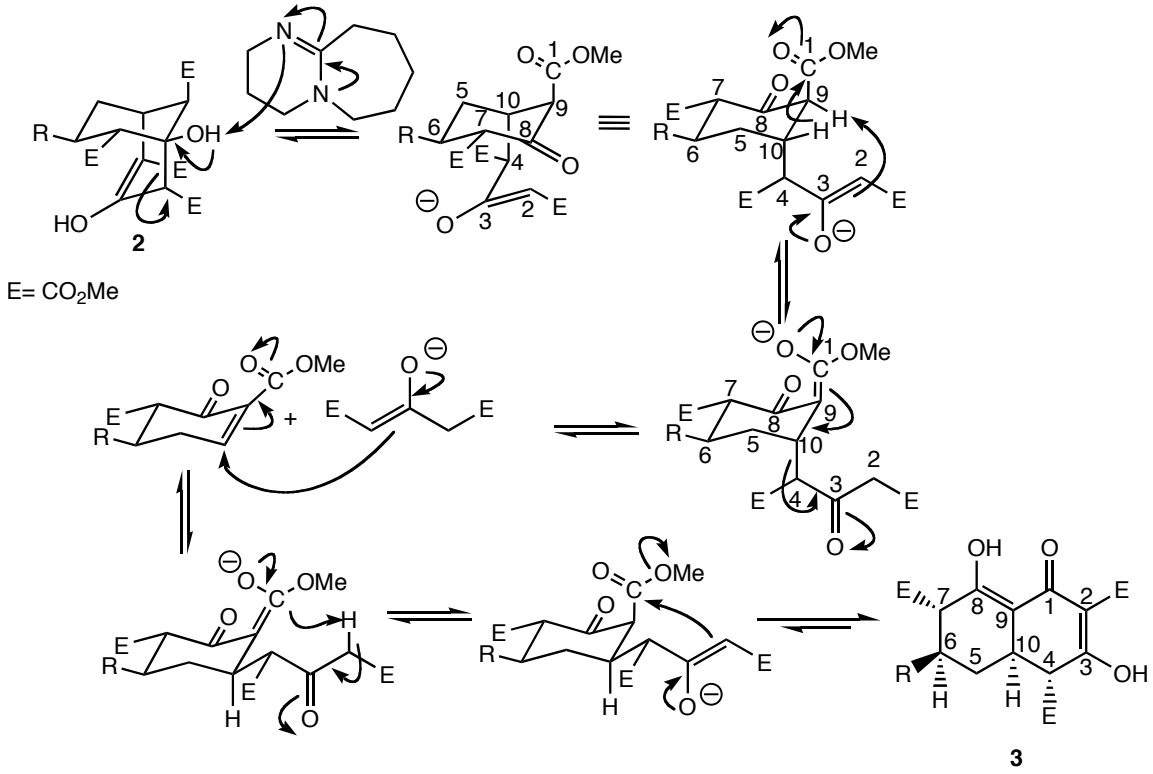


Figure 2.6. Proposed reaction mechanism for the formation of type **3** compounds from type **2** compounds [7,16].

The suggested mechanism is based on extensive studies of ^{1}H NMR spectra and X-ray crystallographic data. The spectral and crystallographic data indicated that the formation of type **3** compounds was highly stereospecific [16]. The stereochemistry of type **3** compounds is shown in **Figure 2.6**.

The first step of the reaction is believed to involve the deprotonation of the tertiary alcohol which leads to the opening of the bicyclic system. The resulting enolate anion

then undergoes rearrangement to form a new enolate anion bearing a negative charge around C-9. Then another rearrangement is believed to occur leading to the formation of a cyclohexenone intermediate and an enolate anion of dimethyl 1,3-acetonedicarboxylate. This step is essential for the observed stereochemistry. Crystallography shows the hydrogen atoms on C-6 and C-10 are in a *cis* conformation. Therefore, the next step is the conjugate addition of the enolate anion of dimethyl 1,3-acetonedicarboxylate to the cyclohexenone intermediate, adding to the *Re* face and thus bonding equatorially to the ring. The resulting enolate anion then rearranges leading to the last step of the reaction. The final step is a nucleophilic addition to an ester group and simultaneous elimination of a methoxy group and subsequent ring closure.

According to NMR spectra and crystal structure analysis, the carbonyl groups on C-8 and C-3 tautomerize towards the enol form. Although generally less commonly observed, the enol tautomer is quite common in 1,3-dicarbonyl and 1,3,5-tricarbonyl compounds like type **3** compounds [17]. The enol form predominates because of stabilization through intramolecular hydrogenbonding with a nearby carbonylgroup (**Figure 2.8**).

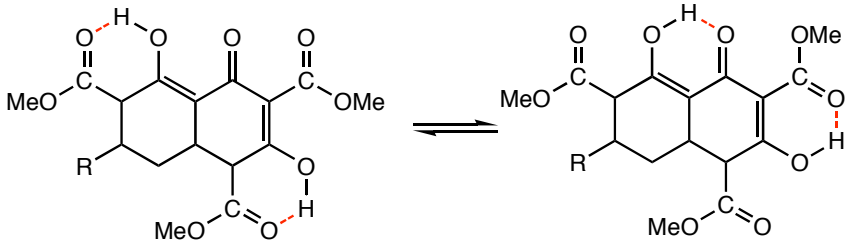


Figure 2.8. Stabilizing intermolecular hydrogenbonding in type **3** compounds.

Type **3** compounds have also been synthesized by refluxing α,β-unsaturated aldehydes and dimethyl 1,3-acetonedicarboxylate with DBU in acetone [7,9,13]. The reaction is believed to occur in a similar manner as the synthesis from type **2** compounds. A possible reaction mechanism is shown in **Figure 2.9**.

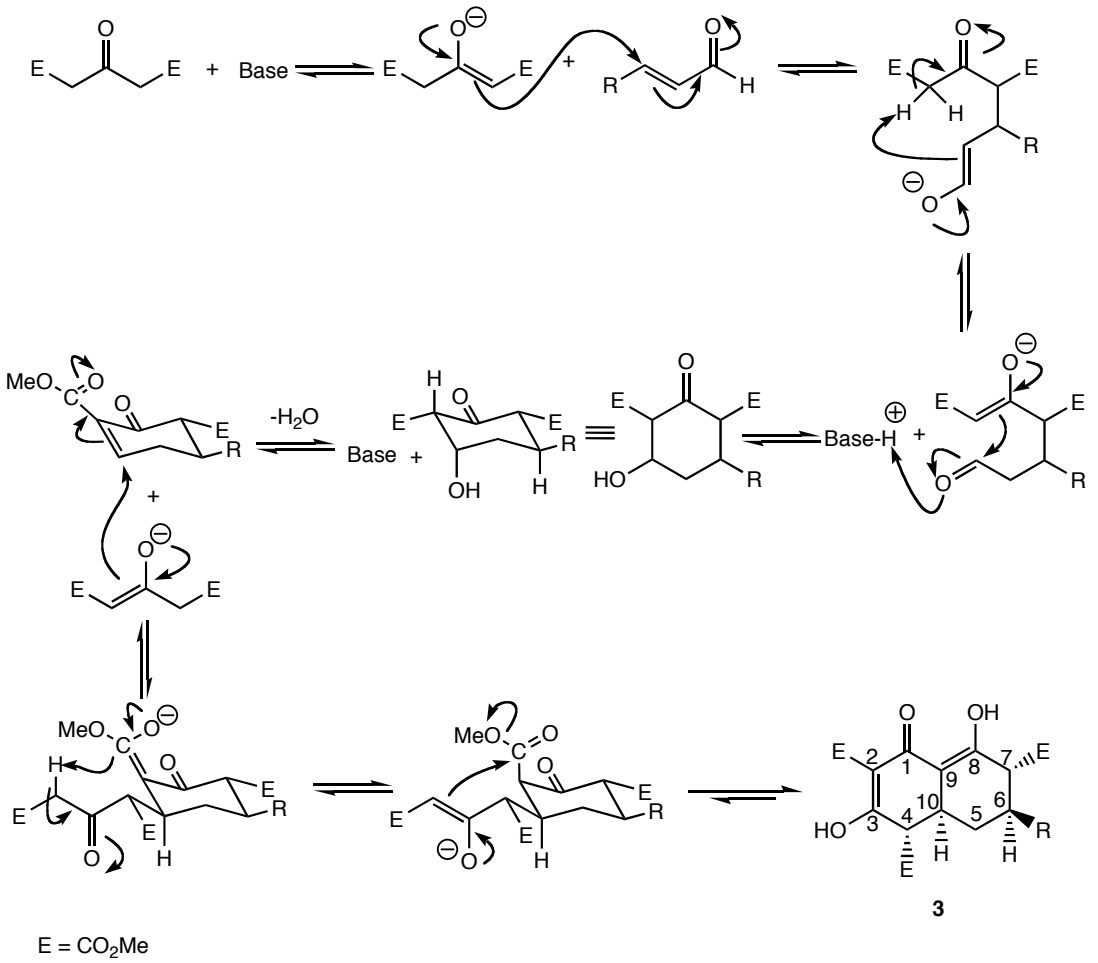
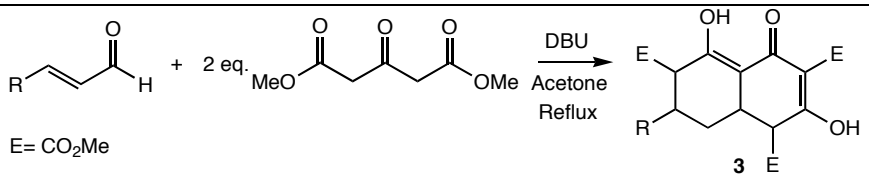


Figure 2.9. Reaction mechanism for the formation of type **3** compounds from α,β-unsaturated aldehydes and dimethyl 1,3-acetonedicarboxylate.

In this research project, the latter route was taken i.e. type **3** compounds were synthesized directly from aldehydes and dimethyl 1,3-acetonedicarboxylate.

All reactions were carried out in a similar manner. One molar equivalent of aldehyde and 2 molar equivalents of dimethyl 1,3-acetonedicarboxylate were stirred in ca. 25 mL of acetone. While heating towards reflux temperature, 2,5 molar equivalents of DBU, dissolved in 5 mL of acetone, were added dropwise and the resulting solution stirred at reflux for 12-24 hours.

The yields and structures of substituents are shown in **Table 2.2**.



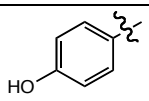
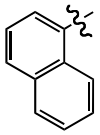
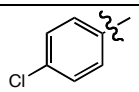
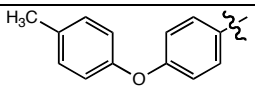
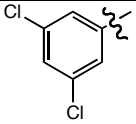
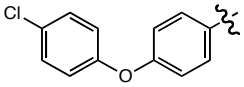
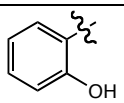
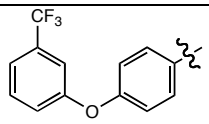
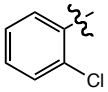
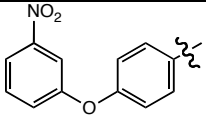
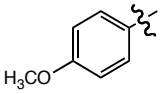
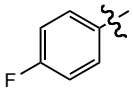
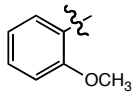
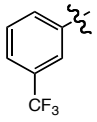
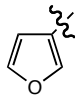
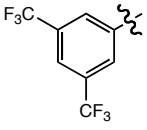
ID	R-substituent	Yield (%)	ID	R-substituent	Yield (%)
3a		78 %	**3j**		83 %
3b		55 %	**3k**		45 %
3c		67 %	**3l**		90 %
3d		70 %	**3m**		32 %
3e		84 %	**3n**		49 %
3f		90 %	**3o**		79 %
3g		87 %	**3p**		84 %
3h		92 %	**3q**		56 %
3i		36 %			

Table 2.2. Yields of type **3** compounds synthesized.

The structure of every compound was confirmed by NMR specroscopy. The enolic protons on C-3 and C-8 resonated as distinctive singlets in between δ 15,6 and 16,0 ppm

and between δ 14,7 and 15,0 ppm respectively. The relatively high chemical shifts are due to deshielding effects because of aforementioned hydrogen bonding to adjacent carbonyl groups. Multiplets in the aromatic region were also observed. The methyl ester groups gave 3 distinctive singlets around δ 3,5-4,0 ppm. Another characteristic signal for decalone compounds is a doublet of doublets (1H) generally observed around δ 3,6-3,7 ppm. This signal represents the proton on C-7. The observed split pattern is due to vicinal coupling with the proton on C-6 (J=11,0-11,8 Hz) and long range coupling with the proton on C-10 (J=2,0-2,7 Hz). The protons on C-5 give two separate signals representing the axial or pseudo-axial proton and the equatorial or pseudo-equatorial with identical split patterns (ddd). One of these signals is generally observed around δ 3,30-3,40 ppm. This signal represents the proton that is located axially (or pseudo-axially) and the observed split pattern is because of coupling with the proton on C-10 (J=2,0-2,7 Hz) and coupling with the proton on C-6 (J=4,4-5,3 Hz) and geminal coupling with the other proton on C-5 (J=10,9-13,3 Hz). The equatorial proton gives a doublet of doublet of doublets around δ 1,8-2,4 ppm (J=2,2-2,7 Hz, J=4,2-5,0 Hz and J=12,5-13,1 Hz). The proton positioned on C-10 gives a complex multiplet around δ 3,2-3,5 ppm because of aforementioned long range coupling with the proton on C-6, both protons on C-5 and the proton on C-4. The proton on C-6 gives a doublet of triplets around δ 1,6-1,9 ppm. The observed split pattern is because of coupling with the proton on C-7 (J=10,7-11,0 Hz) and because of coupling with both protons on C-5 (J=12,7-13,0 Hz in both cases) (**Figure 2.10**).

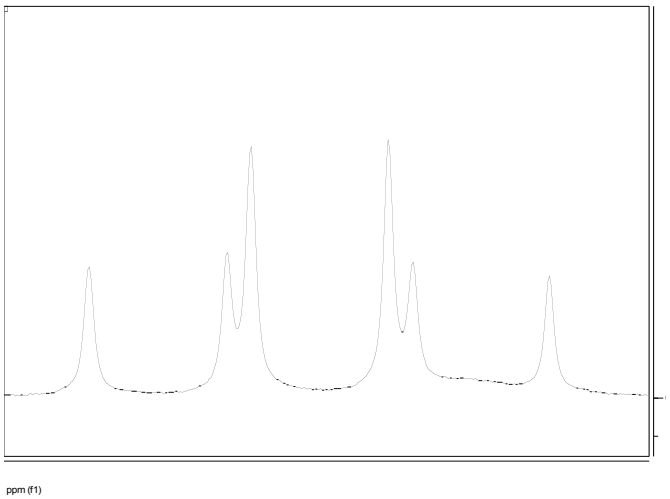


Figure 2.10. Typical observed split pattern for the proton on C-6 (**3q**).

An exemplary ^{1}H NMR spectrum for type **3** compounds is shown in **Figure 2.11**.

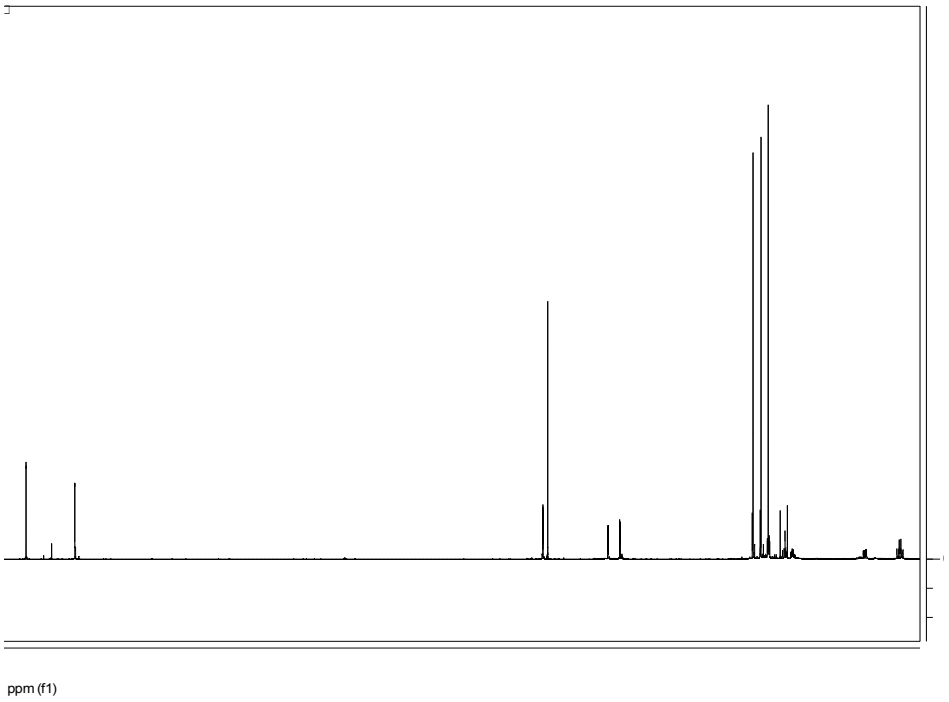


Figure 2.11. An example of a ^{1}H NMR spectrum of a type **3** compound (**3q**).

All in all, synthesis of decalone derivatives were successful but isolation of these compounds was often frustrating and difficult. For example, when attempts were made to purify type **3** compounds with silica gel column chromatography resulted in decompositon of the compounds. All the compounds had to be crystallized from methanol and more often than not, several attempts were needed to do so.

The use of an alternative, structurally similar base to DBU proved to be a viable choice. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) was used in the synthesis of a phenyl-substituted type **3** compound in a fairly good yield (**Figure 2.12**).

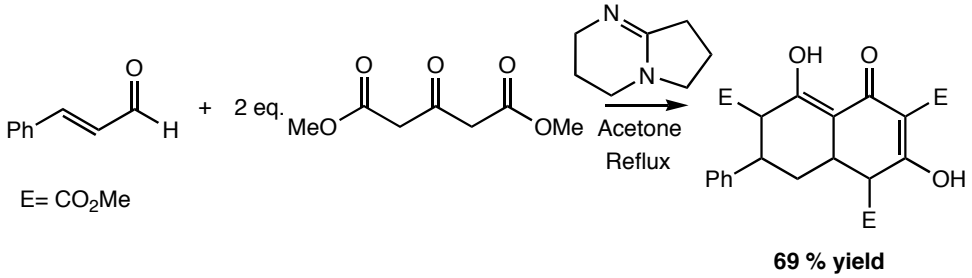


Figure 2.12. DBN could also be used to catalyze formation of decalones.

2.3 Synthesis of 1-tetralone derivatives

There are several known methods for synthesis of 1-tetralones [10-12]. For example, Shimada and co-workers have reported their synthesis by Lewis acid catalyzed intramolecular Friedel-Crafts reactions of 4-arylbutyric acid derivatives (**Figure 2.13** and **Figure 2.14**) [12].

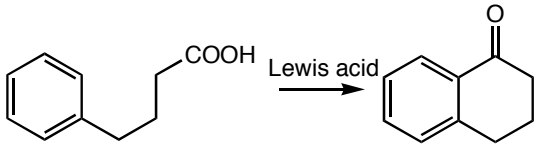


Figure 2.13. Synthesis of 1-tetralones as reported by Shimada et al. [12].

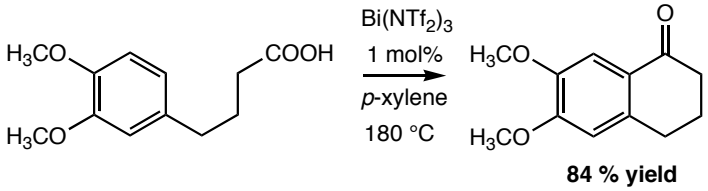


Figure 2.14. An example of a 1-tetralone synthesized by Shimada et al. [12].

As mentioned before, one-step synthesis of 1-tetralones from decalones of type **3** can be achieved by refluxing decalones with iodine in methanol (**Figure 1.8**) [7,9,13].
A plausible reaction mechanism is shown in **Figure 2.15**.

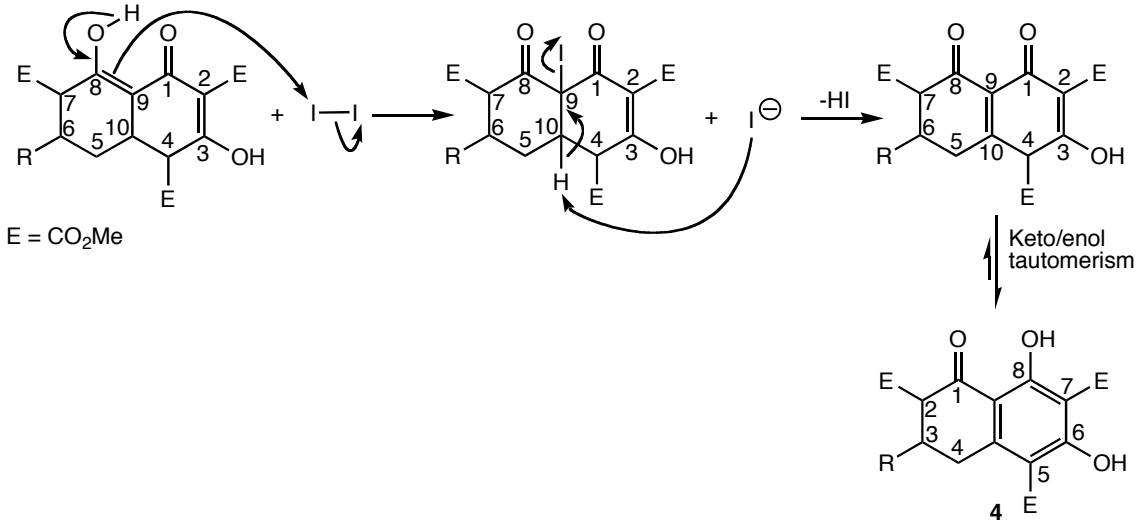


Figure 2.15. Reaction mechanism for formation of type **4** compounds.

The first step of the reaction is a nucleophilic attack of the enolic double bond on iodine resulting in the substitution of an iodine atom on C-9. Then an elimination of hydrogen iodide occurs resulting in a double bond between C-9 and C-10. The molecule then tautomerizes towards the more stable aromatic form yielding a 1-tetralone derivative. The general method used in this research project was stirring 1 molar equivalent of type **3** compound with 3 molar equivalents of iodine crystals in methanol at reflux for 20-24 hours depending on the reaction. The yields and structures of the 1-tetralones synthesized are shown in **Table 2.3**.

Structure of type **4** compounds were confirmed by NMR spectroscopy.The ^{1}H NMR spectra showed characteristic signals i.e. singlets between δ 14,1-14,3 ppm and δ 12,8-13,1 ppm which are representative for the phenolic protons. As expected, multiplets in the aromatic region were also observered representative for aryl-substituents on C-3. Other characteristic signals observed were three singlets around δ 3,5-4,0 ppm representative for methyl ester groups. A doublet of doublets (1H) was generally observed around δ 3,4-4,2 ppm which represents the proton on C-2. The split pattern is due to coupling with the proton on C-3 which is a chiral carbon. The axial-axial coupling has a larger constant (J=11,2-12,5 Hz) than the corresponding axial-equatorial coupling (J=1,2-2,0 Hz). A doublet of triplets (1H) was observed around δ 1,6-1,9 ppm representing the proton on C-3. The observed split pattern is due to coupling with proton on C-2 (J=4,5 Hz) and with protons on C-4 (J= 11,9-12,5 Hz).

^{1}H NMR spectrum of compound **4o** is shown in **Figure 2.16**.

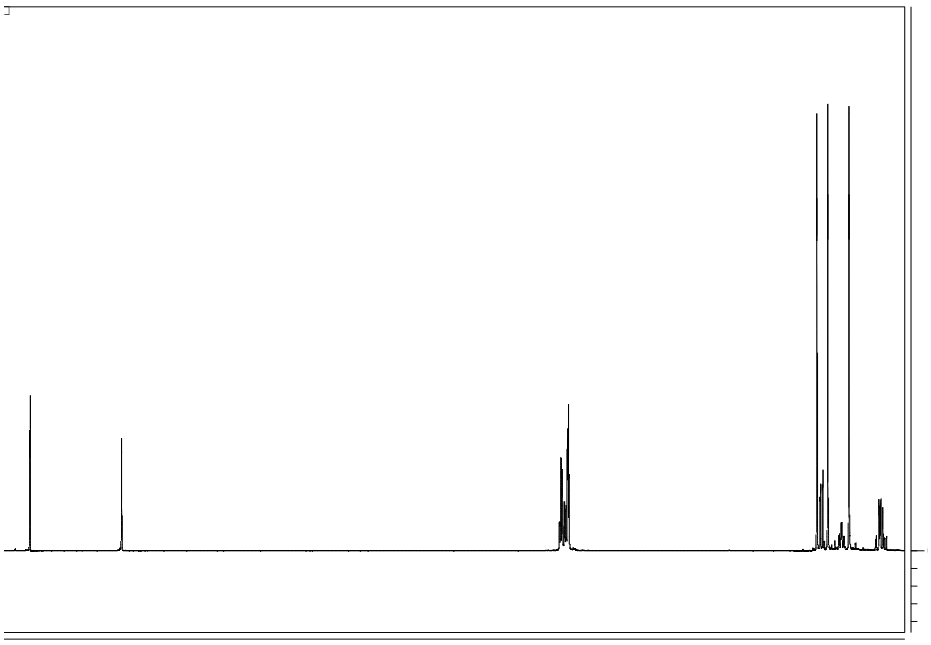
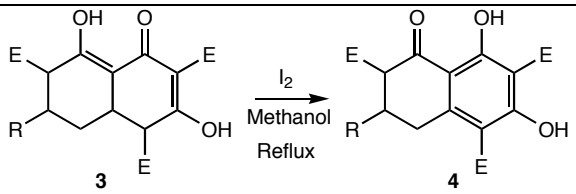


Figure 2.16. An example of a ^{1}H NMR spectrum of a type **4** compound (**4o**).

Syntheses of type **4** compounds were generally successful. All compounds were formed in excellent yields and were isolated in a relatively simple manner.



E= CO_2Me

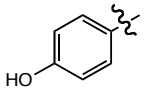
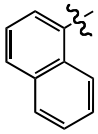
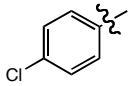
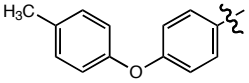
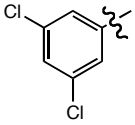
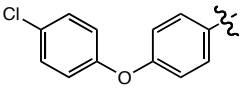
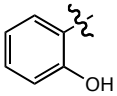
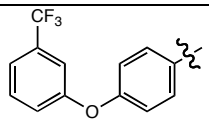
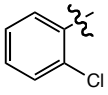
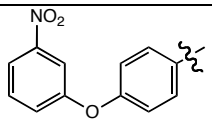
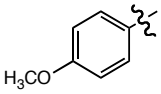
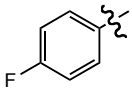
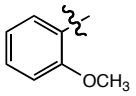
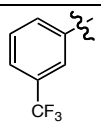
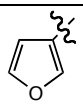
ID	R-substituent	Yield (%)	ID	R-substituent	Yield (%)
4a		87 %	**4j**		86 %
4b		93 %	**4k**		82 %
4c		96 %	**4l**		92 %
4d		75 %	**4m**		85 %
4e		72 %	**4n**		79 %
4f		81 %	**4o**		88 %
4g		79 %	**4p**		90 %
4h		77 %	**4q**		89 %

Table 2.3. Yields of type **4** compounds synthesized.

2.4 Arylation of 4-iodophenol and 4-hydroxycinnamaldehyde

Phenolic groups of 1-tetralone derivatives of type **4** are known to undergo acylation when reacted with acid chlorides in good yields (**Figure 2.17**) [9].

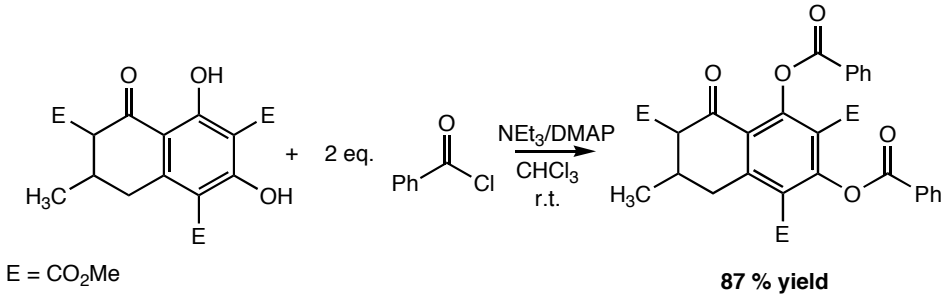


Figure 2.17. An example of acylation of a type **4** compound [9].

Esters are susceptible to hydrolysis and drug components that contain esters are likely to be hydrolyzed *in vivo*. For that reason, alkylation of these phenolic groups was of interest as ether bonds are less likely to be hydrolyzed.

Williamson ether synthesis is one of the simplest and most widely used methods in formation of ethers. Williamson ether reactions are typically base promoted reactions between alcohols or phenols and alkyl halides or tosylates [18].

Bases most commonly used in Williamson reactions involving phenols are inorganic bases e.g. carbonates or hydroxides.

The use of hydroxides was deemed impractical for the purposes of alkylating type **4** compounds as it would increase risk of side reactions. For example, the carbonyl and carboxyl groups present in type **4** molecules are highly reactive towards hydroxides.

Alkylation of phenol derivatives has been achieved by reaction with potassium carbonate in acetone (**Figure 2.18**) [19].

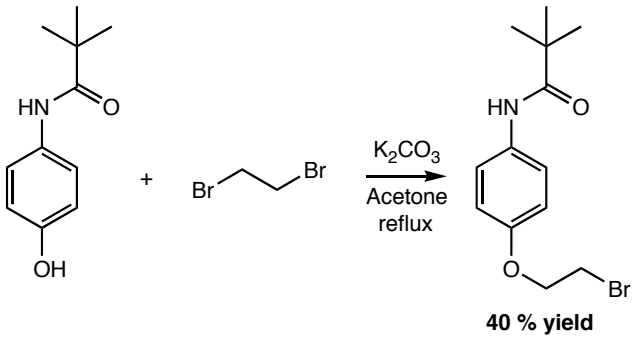


Figure 2.18. Alkylation of a phenol derivative by Williamson ether synthesis [19].

Model experiments were conducted similar to the example above. For these model experiments, carbonate catalyzed reaction between phenyl-substituted 1-tetralone (**4o**) and benzyl bromide was attempted in three different solvents (**Figure 2.19**). Benzyl bromide was selected because it was readily available at the lab and because aromatic moieties are known to be biologically active.

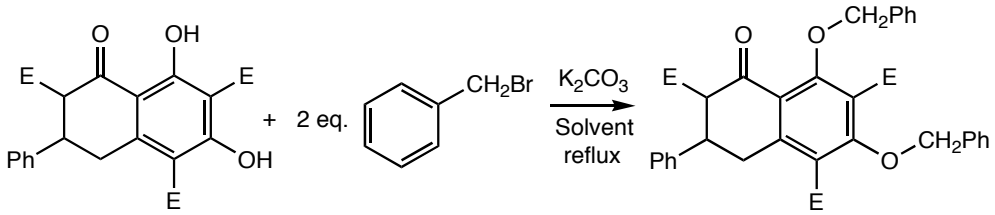


Figure 2.19. Model reaction scheme for benzylation of tetralones using K_2CO_3 as a base.

Reaction attempts were carried out in acetone, DMF and DME at reflux in each case but unfortunately no alkylation had occurred according to NMR spectra.

Similar attempts were made using various amine bases under various conditions. Amine bases are often relatively strong bases but are less nucleophilic than negatively charged hydroxides. Bases and solvents tried are listed in **Table 2.4**.

Base	Solvent	Comment
1,4-diazabicyclo[2.2.2]octane (DABCO)	$CHCl_3$	No reaction
1,4-diazabicyclo[2.2.2]octane (DABCO)	THF	No reaction
1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)	$CHCl_3$	No reaction
1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)	THF	No reaction
1,5-diazabicyclo[4.3.0]non-5-ene (DBN)	$CHCl_3$	No reaction
Triethylamine (TEA)	THF	No reaction
Triethylamine (TEA)	$CHCl_3$	No reaction
4-Dimethylaminopyridine (DMAP)	$CHCl_3$	No reaction
2,6-ditertbutylpyridine (DTBPy)	$CHCl_3$	No reaction
Piperidine	THF	No reaction

Table 2.4. Amines and solvents tried in alkylation attempts.

After these rather dissappointing results, a final attempt was made using sodium hydride in THF which did not result in alkylation either.
It was therefore decided to investigate possibilities other than the Williamson approach.

Chan-Lam coupling is a highly efficient and practical method for carbon-heteroatom bond formation. The reaction is a base-promoted, copper-catalyzed, cross-coupling reaction of boronic acid derivatives and heteroatomic compounds (**Figure 2.20**).

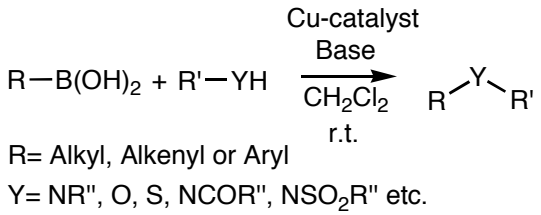


Figure 2.20. General Chan-Lam coupling reaction [20-23].

Substrates that have successfully been used include various phenols, amines, N-H containing heteroarenes, anilines, amides, imides, ureas, carbamates, and sulfonamides [20-23].
Every example of phenols encountered involved arylation and not alkylation. Examples of such arylations is shown in **figure 2.21** [20,21].

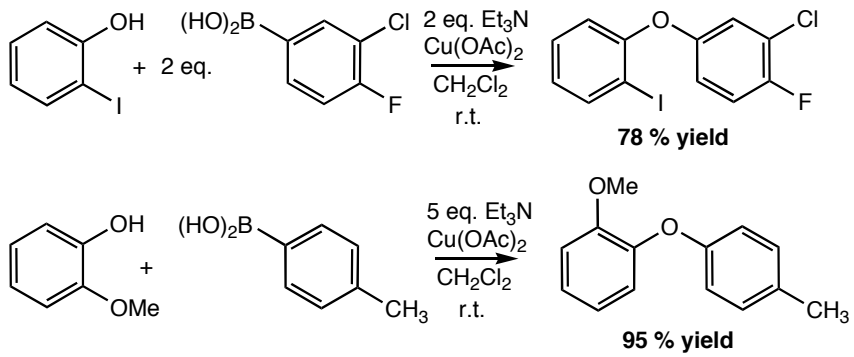


Figure 2.21. Examples of O-arylation of phenol derivatives [20,21].

A general reaction mechanism for Chan-Lam coupling of phenols and arylboronic acids is shown in **Figure 2.22** [20].

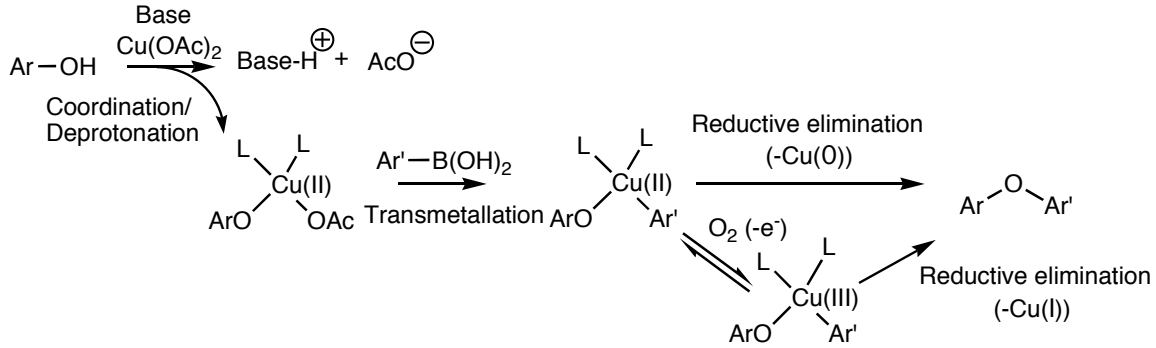
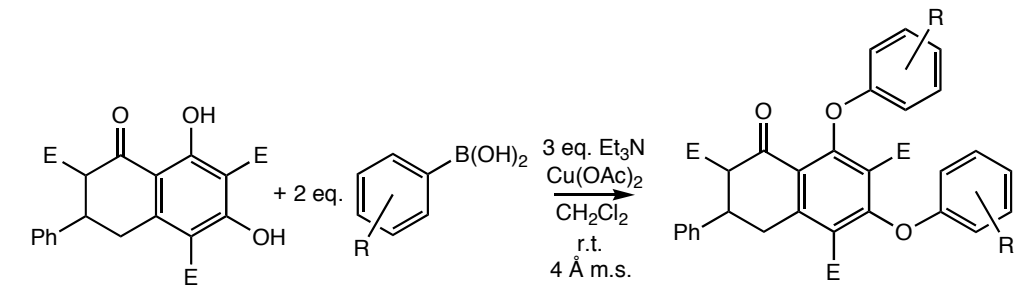


Figure 2.22. Chan-Lam cross-coupling reaction mechanism as proposed by Chan et al. [20].

The reaction mechanism sequence is deprotonation of the amine, coordination of the amine to the copper(II) followed by transmetallation (transferring the alkyl boron group to copper and the copper acetate group to boron). It has been postulated that oxidation of Cu(II) to Cu(III) then occurs by facilitation of oxygen and finally reductive elimination of Cu(III) to Cu(I) with formation of the product. Direct reductive elimination of Cu(II) to Cu(0) may also take place but is somewhat slower.

There was substantial interest in developing similar reactions involving type **4** compounds and aryl boronic acid derivatives which would hopefully lead to arylation of phenol groups. Reaction conditions similar to those reported in references were

implemented [20-23]. As a model compound, tetralone **4o** was used with four readily available different aryl boronic acids (**Figure 2.23**).

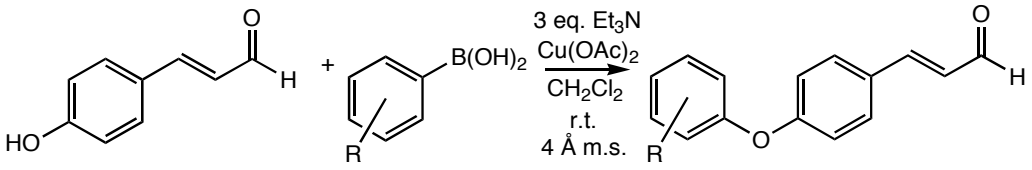


E = CO_2Me

R = *m*-NO_2, *p*-CH_3, *p*-Cl, *m*-CF_3

Figure 2.23. Attempts were made to arylate **4o** with four different aryl boronic acids.

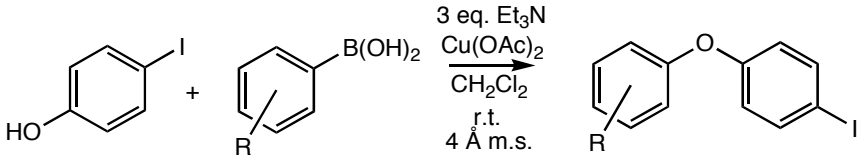
These model experiments were yet another dissapointment. No arylation was observed to take place in any of the attempts made according to both TLC and NMR analysis.
There was, however, another possible binding site for arylation reactions. Compound **4a** has a phenol group on C-3 which could be arylated. Because none of the arylation attempts with **4o** proved viable, it was decided to try yet another synthetic route i.e. arylation of the *p*-hydroxycinnamaldehyde (**1a**) which is a precursor of decalone **3a** and tetralone **4a** (**Figure 2.24**).



R = *m*-NO_2, *p*-CH_3, *p*-Cl, *m*-CF_3

Figure 2.24. Arylation of *p*-hydroxycinnamaldehyde.

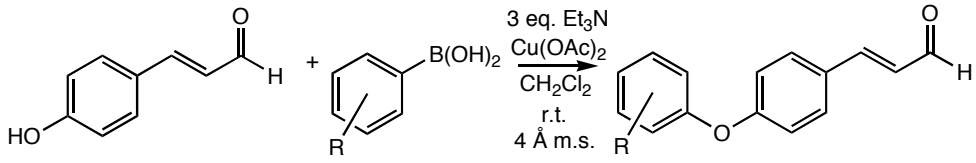
Noticing the success of Chan et al. in arylating 2-iodophenol, it was also decided to attempt arylation of 4-iodophenol which is a precursor of aldehyde **1a** (**Figure 2.25**) [20].



R = *m*-NO_2, *p*-CH_3, *p*-Cl, *m*-CF_3

Figure 2.25. Arylation of 4-iodophenol.

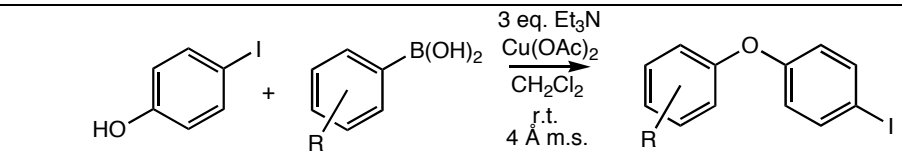
The resulting aryl iodides could then be reacted with acrolein under Heck reaction conditions, thus forming suitable precursors for type **3** and **4** compounds.
Both routes proved to be possible but arylation of 4-iodophenol resulted in substantially better yields. Results are shown in **Table 2.5** and **Table 2.6**.



R = *m*-NO_2, *p*-CH_3, *p*-Cl, *m*-CF_3

R (substituent)	Yield
m-NO_2	26 %
p-CH_3	37 %
p-Cl	32 %
m-CF_3	30 %

Table 2.5. Yields from arylation of *p*-hydroxycinnamaldehyde.



R = *m*-NO_2, *p*-CH_3, *p*-Cl, *m*-CF_3

R (substituent)	Yield
m-NO_2	67 %
p-CH_3	90 %
p-Cl	85 %
m-CF_3	43 %

Table 2.6. Yields from arylation of 4-iodophenol.

All aryl iodides were reacted further to form the corresponding aldehydes. Results from those reactions are shown in **Table 2.1**.

NMR spectral analysis confirmed the structures of the compounds synthesized. An example of ^{1}H NMR spectrum of aryl iodide is shown in **Figure 2.26**.

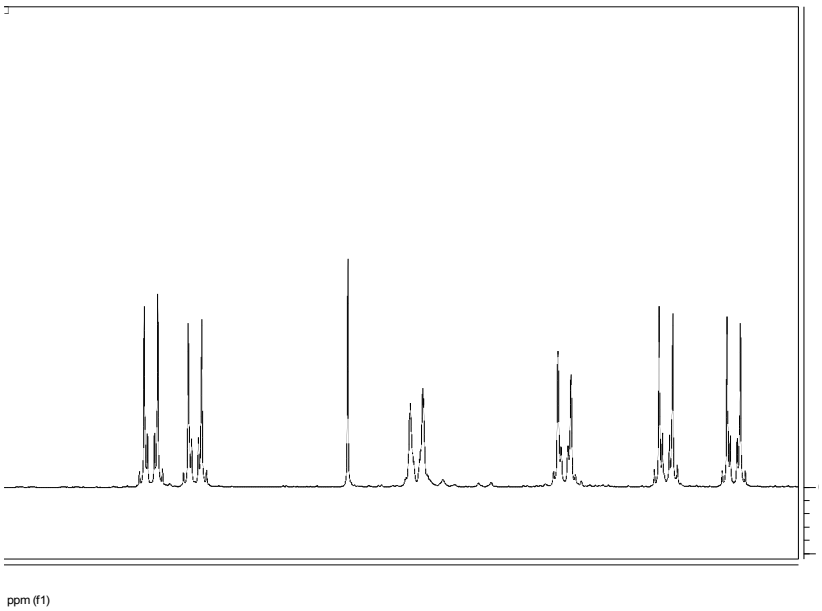


Figure 2.26. ^{1}H NMR spectrum of 1-iodo-4-(*p*-tolyloxy)benzene.

An exemplary ^{1}H NMR spectrum of arylated aldehyde is shown in **Figure 2.27**.

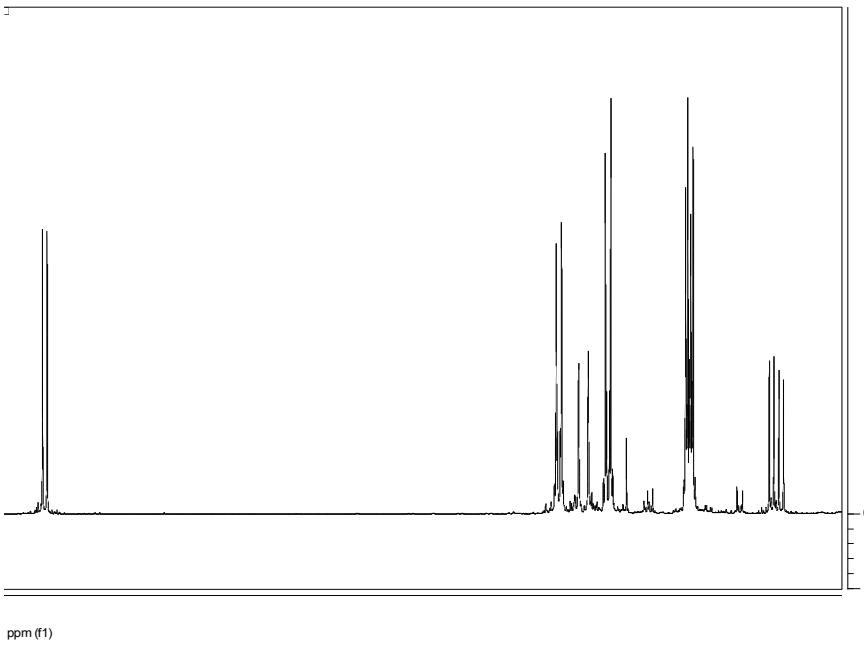


Figure 2.27. ^{1}H NMR spectrum of *trans*-3-(4-(4-chlorophenoxy)phenyl)acrylaldehyde.

3 Asymmetric synthesis of bicyclo[3.3.1]nonanes

3.1 Introduction

The world is chiral. That is to say, the vast majority of the organic compounds and biomolecules found in our biosphere are chiral. Molecular asymmetry affects the properties and interactions of molecules in a vast and diverse way which pervades our daily life such as the antibacterial activity of drugs, the smell of plants and the taste of fruits and herbs [24,25]. The chiral drug industry represents near to a third of the world drug market. This is a result of the increased regulatory control of enantiomeric composition of drug candidates and the potential of isomerically pure drugs to provide improvements over the previously available racemates [26].

Most, if not all enzymes and cell receptors react or interact better, and in some cases solely, with one enantiomeric form of a given compound [4,24].

This is due to the fact that these sites of action are constructed from chiral building blocks such as amino acids and/or carbohydrates, making the enzyme or receptor itself chiral. Being natural compounds, the amino acids and/or carbohydrates are present as single enantiomers thus combine to form a resulting biomolecule as a single enantiomer. Consequently, a given compound interacting with a given biomolecule of the type described before, will interact differently depending on which of the enantiomeric forms is interacting with the aforementioned biomolecule. Enantiomers of a given compound possess different levels of activity and can in some cases exhibit different types of activity. Consequently, when using a racemic mixture of a particular biologically active compound, it is equivalent to using a mixture of two different biologically active compounds [25].

Synthesis of chiral compounds is therefore, and indeed has been, of great interest and importance to chemists, particularly organic chemists and chemists working in the field of pharmaceutical chemistry.

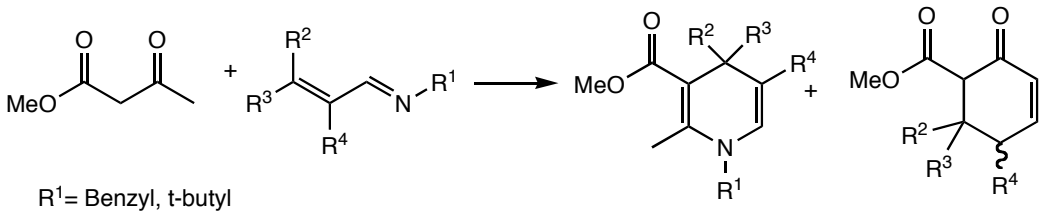
As stated before, there has been some research conducted on asymmetric synthesis of type **2** compounds in Prof. Geirsson's research group. Based on that research, the

possibility of synthesizing a chiral tetralone derivative via a chiral bicyclo[3.3.1]nonane was investigated, since the bicyclo[3.3.1]nonane of type **2** can be used as precursors for bicyclo[4.4.0]decanes or type **3** compounds (**Figure 1.10**). Consequently, if a chiral type **2** compound could be synthesized, it could lead to the synthesis of a chiral type **3** compound. Those type **3** compounds could then be aromatized to yield chiral tetralones of type **4**.

In order to devise a synthetic strategy towards a chiral type **2** compound, it was imperative to look in detail at reaction mechanism and stereochemistry of the formation of type **2** compounds.

3.2 Stereochemistry of bicyclo[3.3.1]nonanes

The formation of compounds of type **2** was encountered at the Science Institute while exploring reactions between 1-aza-1,3-butadienes and 1,3-dicarbonylcompounds [2-4]. The goal was to synthesize 1,4-dihydropyridines and/or substituted cyclohexenones but the formation of bicyclo[3.3.1]nonane compounds was observed upon reaction of dimethyl 1,3-acetonedicarboxylate was used as the 1,3-dicarbonyl component and an enimine obtained from either cinnamaldehyde or crotonaldehyde (**Figures 3.1** and **3.2**).



R^1= Benzyl, t-butyl
R^2= Methyl, Ethyl, Phenyl
R^3= H, Methyl
R^4= H, Methyl

Figure 3.1. Reaction of various 1-aza-1,3-butadienes and 1,3-dicarbonylcompounds. Work on this type of reactions led to the formation of bicyclo[3.3.1]nonane compounds [2-4].

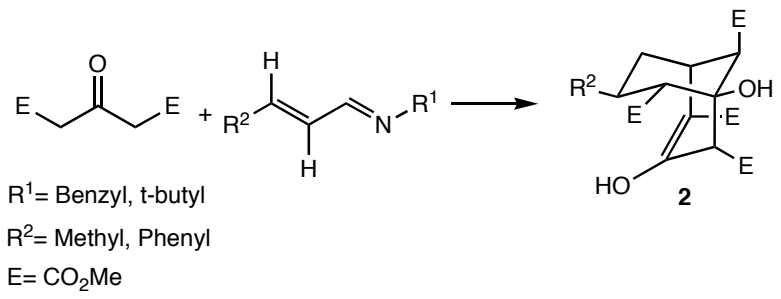


Figure 3.2. Unexpected discovery of a synthetic route towards bicyclo[3.3.1]compounds [1-3].

The formation of type **2** compounds is an example of a tandem chemical reaction. Further research and development on reaction conditions for this type of reaction led researchers to the method still being used by Geirsson's group in synthesis of type **2** compounds (**Figure 3.3**) [2-4,6,27].

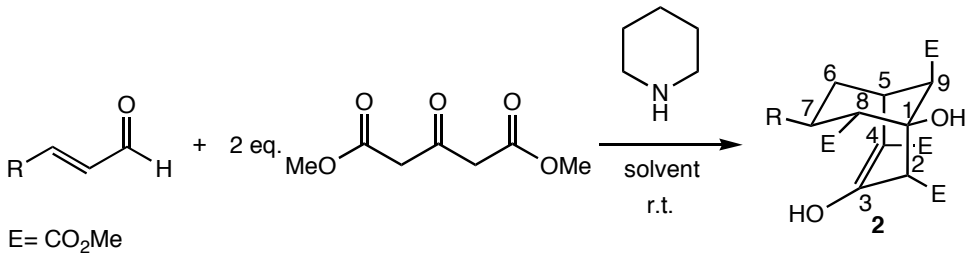


Figure 3.3. Synthetic pathway to type **2** compounds which is still used at the Science Institute [2-4,27].

Only catalytic amounts of piperidine are needed for this transformation. Studies have also led researchers to formulating a reaction mechanism which has been referred to as a sequential Michael addition-intramolecular aldol condensation mechanism (**Figure 3.4**).

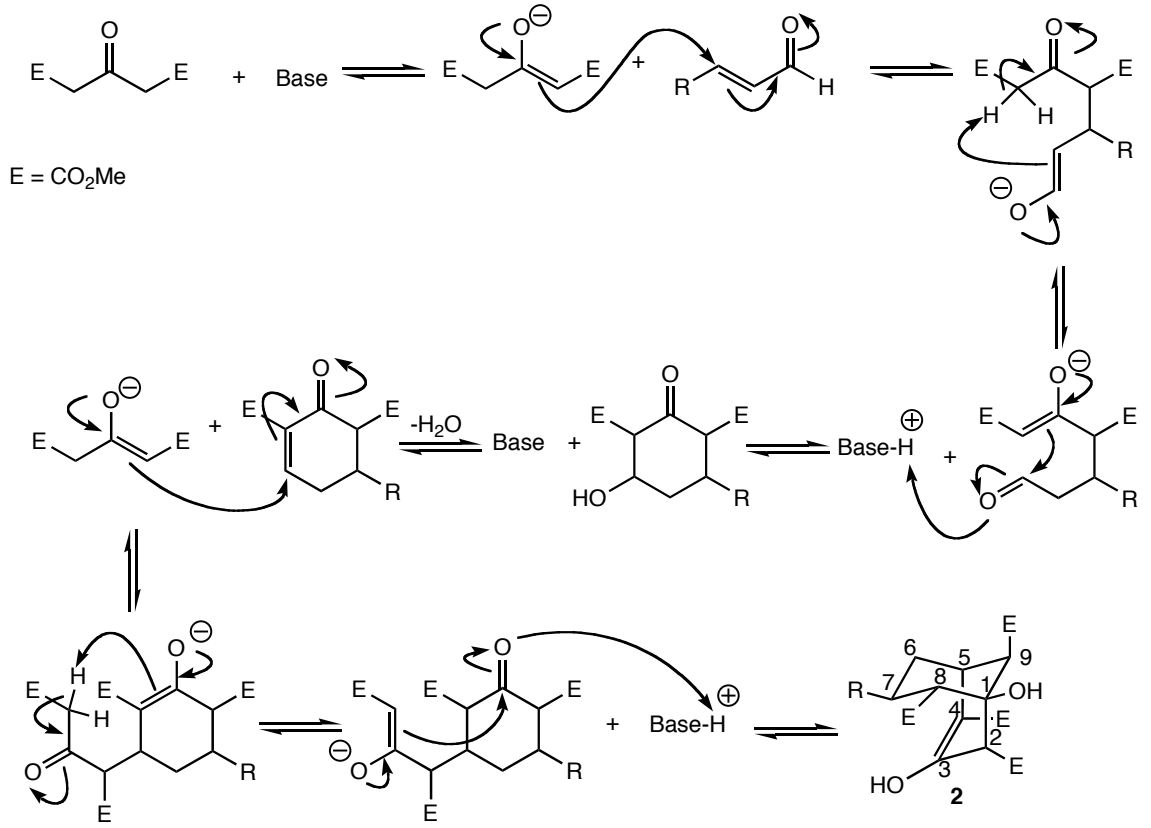


Figure 3.4. The sequential Michael addition-intramolecular aldol condensation mechanism.

The first step of the reaction is the deprotonation of dimethyl 1,3-acetonedicarboxylate followed by a Michael addition of an enolate to an α,β-unsaturated aldehyde. Then an intramolecular aldol condensation occurs. Although not yet isolated, a cyclohexenone intermediate is believed to be formed and the second equivalent of dimethyl 1,3-acetonedicarboxylate adds via 1,4-conjugate addition to the aforementioned cyclohexenone intermediate. The formation of this proposed cyclohexenone intermediate is supported by the fact that when a α,β-unsaturated ketone, such as penta-3-en-2-one, is reacted with dimethyl 1,3-acetonedicarboxylate under the same conditions, the sole product is a cyclohexenone compound identical to the proposed intermediate except of course for a methyl group on the β-carbon [4,27].The last step is an intramolecular aldol reaction and the keto group tautomerizes towards the enol form.

Through studies of ^{1}H NMR spectra of type **2** compounds as well as X-ray crystallographic data it became evident that the reaction is highly stereospecific. There

are six stereocenters generated upon formation of type **2** compounds (at C-1, C-2, C-5, C-7, C-8 and C-9) which could theoretically lead to the formation of 64 (2^6) stereoisomers. However, the NMR and crystallographic data reveals the fact that there exist essentially only one racemic diastereomer [4] (**Figure 3.5**). If the proposed reaction mechanism is analyzed in context with the results from the spectroscopic and crystallographic analysis, it becomes clear that the first Michael addition to the α,β-unsaturated aldehyde is the controlling factor in the resulting stereochemistry of the bicyclic compound. The formation of the cyclohexenone intermediate through the first Michael addition and subsequent aldol condensation determines the stereochemistry of C-7, C-8 and C-9. Stereochemistry at C-9 is not relevant at this point because of the dehydration reaction following the nucleophilic aldol reaction of the aldehyde group resulting in a double bond.

X-ray crystallography and ^{1}H NMR spectra of type **2** compounds indicate that the R-substituent on C-7 and the ester moiety on C-8 are always in a *trans* conformation and therefore it could be postulated that they are also in a *trans* conformation on the cyclohexenone intermediate. If that is the case, the two stereoisomers out of the four possible stereoisomers of the cyclohexenone intermediate must be formed as precursors to type **2** compounds.

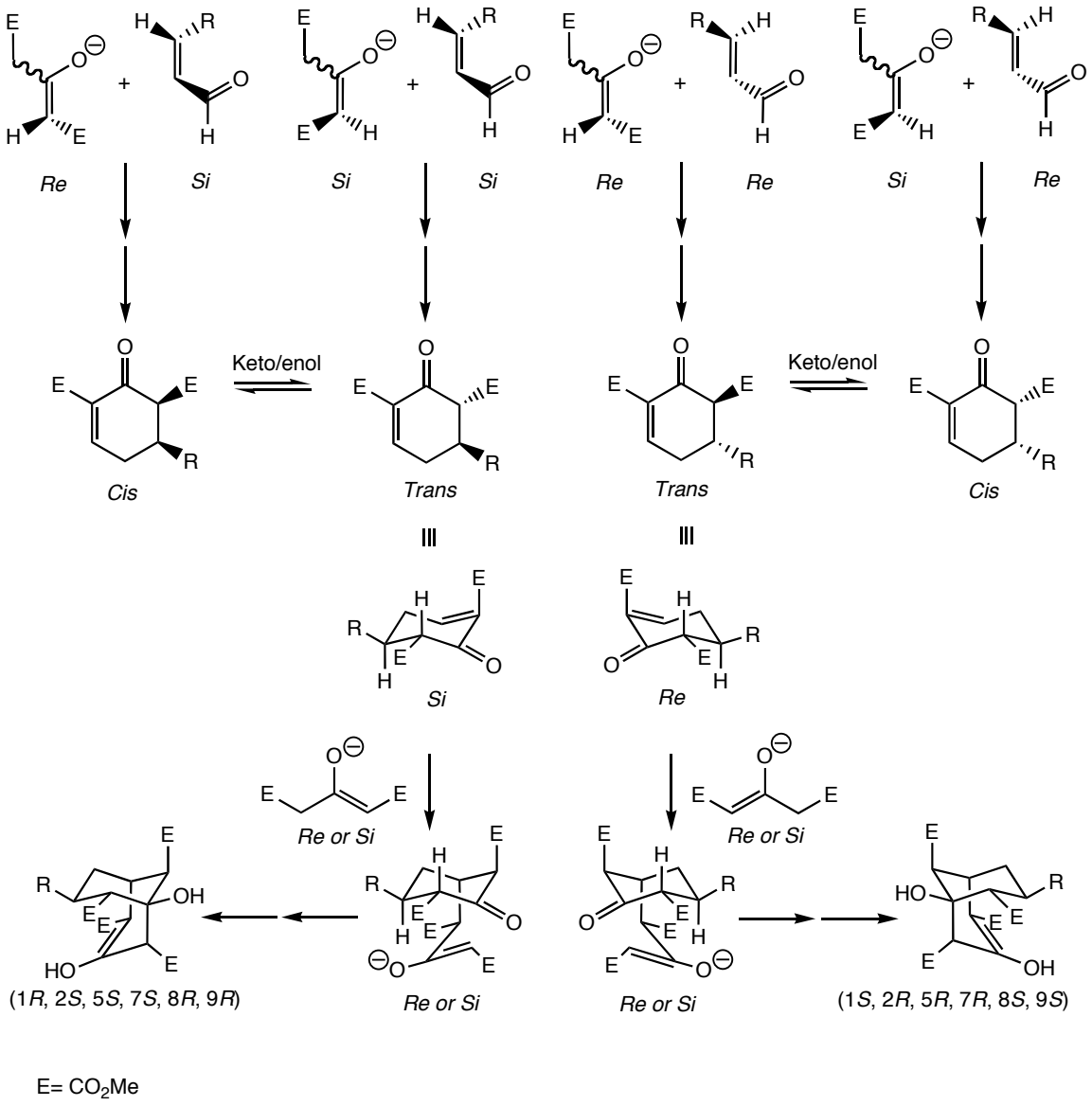


Figure 3.5. Stereochemistry of the formation of bicyclo[3.3.1]nonenols or type **2** compounds. There are essentially one possible racemic [4].

The Michael addition of the second enolate and the following aldol reaction controls the stereochemistry at C-1, C-2 and C-5. The enolate is equally likely to attack from either plane (*Re* or *Si*) so the stereochemistry of the addition of the second enolate is irrelevant to the stereochemistry of the final product. The last step of the reaction, the aldol reaction, can take place from either the *Re* or *Si* plane of the donor (enolate) so that does not govern the stereochemistry of the final product either. The product then tautomerizes towards the enol form thus forming the final product.

The spectral and crystallographic data also indicate that the R-substituent on C-7 is also found to always be in the equatorial (thermodynamically more stable) plane. Therefore, the ester group on C-8 is also in an *eq* position.
According to this stereochemical analysis, it is essentially the first Michael addition that is the decisive step in the stereochemistry of type **2** compounds. If the addition takes place towards the *Si* plane of the aldehyde it results in a (1*R*, 2*S*, 5*S*, 7*S*, 8*R*, 9*R*) configuration. If however, the addition takes place towards the *Re* plane of the aldehyde it results in the (1*S*, 2*R*, 5*R*, 7*R*, 8*S*, 9*S*) configuration. It is therefore evident that in order to achieve asymmetric synthesis of type **2** compounds, stereochemical control of the first step is necessary.

3.3 Methods in asymmetric synthesis

> "*Asymmetric synthesis is a reaction or reaction sequence that selectively creates one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on heterotopic faces, atoms, or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate.*"[1]

In order to achieve asymmetric synthesis, at least one component involved in the reaction must be chiral and non-racemic. If there are no asymmetric components involved in the reaction, the transtion states which lead to enantiomers will themselves be enantiomeric, equal in energy and a racemic mixture will form. Therefore, in designing a reaction scheme leading to asymmetric synthesis one of the following must be involved:

1. A chiral reagent. The simplest approach towards asymmetric synthesis as the reagent itself is chiral and if the reaction does not affect the chirality, the product should also be chiral. In principle this is an excellent approach, since the substrate and product should require minimal or no synthetic manipulations. However there are disadvantages, one being that commercially available enantiomerically pure reagents are in most cases

[1] Gawley, R.E., Aubé, J., *Principles of asymmetric synthesis*; 1. ed.; Elsevier Science: Oxford, 1996; Vol.14. p.4.

expensive and are as of yet, quite rare. Considerable efforts could also be involved in the preparation of the reagent and stoichiometric amounts are required.

2. A chiral solvent. In some cases, the use of a chiral solvent will lead to asymmetric synthesis as the solvent is likely to be somehow involved in the transition states. There are however very few procedures available and it is not a general method [25].

3. A chiral solvating agent. A rather promising approach is the use of chiral, non-racemic solvating agents (in a normal achiral solvent) which preferentially solvate a reaction component. An example of the use of chiral solvating agent in an asymmetric aldol reaction is shown in **Figure 3.6**. A tin(II)enolate is complexed with (S)-1-[(1-Methyl-2-pyrrolidinyl)methyl]piperidine before reaction with an aldehyde. The resulting product was obtained in 75% enantiomeric excess [25,28].

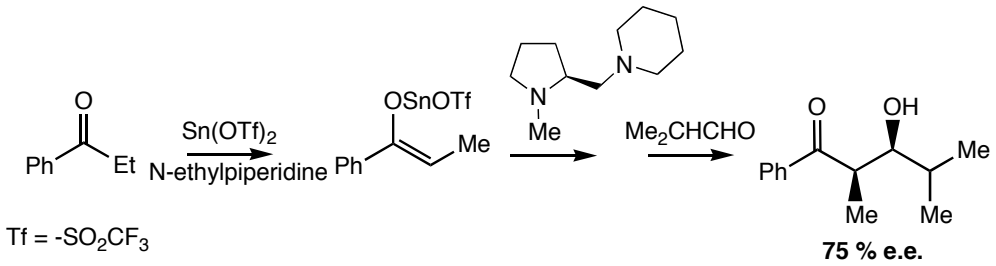


Figure 3.6. An example of the use of a chiral solvating agent in asymmetric synthesis.

4. A chiral auxiliary. The use of chiral auxiliaries is a highly advantageous approach to asymmetric synthesis, provided that the auxiliaries used will fulfil certain requirements. A chiral auxiliary must be enantiomerically pure and preferably not expensive. It needs to be obtainable in larger quantities and easily attached to substrate. The control of stereoselectivity must be high and predictable and the auxiliary must also be easily removable from the product to provide the chiral, non-racemic product. An example of the use a chiral oxaolidinone auxiliary is shown in **Figure 3.7** [25,29].

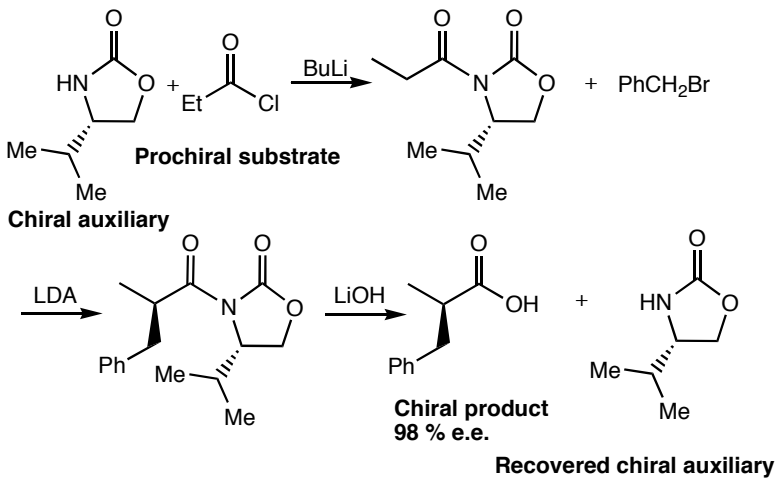


Figure 3.7. An example of the use of a chiral oxazolidinone auxiliary.

There are currently only relatively few chiral auxiliaries that meet all of the previously mentioned requirements [4,25].

5. A chiral catalyst. The use of a chiral catalyst is probably the most ideal approach to asymmetric synthesis. Catalytic transformations provide the best "atom-economic" approach because the stoichiometric introduction and removal of chiral auxiliaries can be avoided or minimized [26,30]. But the use of chiral catalysts has also some disadvantages. Many chiral catalysts are only usable under specific conditions and therefore they do not provide general, applicable methods for asymmetric synthesis [4,30].

Furthermore, catalysts that are applicable to a wider variety of substrates and reaction conditions do not neccesarily provide products in high yields or more importantly, in high enantiomeric or diastereomeric excesses [25].

Undoubtedly, the most elegant and economically attractive way to introduce chirality into a molecule is by using a catalytic amount of a chiral controller to induce the chiral transformation [26].

There is a relatively young and promising field in organic chemistry called asymmetric organocatalysis. Since the formation of type **2** compounds is organocatalyzed, it seemed logical to investigate the possibility of asymmetric organocatalysis in forming chiral bicyclo[3.3.1]nonanes.

3.4 Asymmetric organocatalysis

Until recently, the catalysts employed for the enantioselective synthesis of organic compounds fell almost exclusively into two categories: transition metal complexes and enzymes. Over the last decade or so, there has however been exponential growth in the field of organocatalysis [26,30]. Organocatalysis is the use of "small" organic compounds in catalytic amounts to bring about a chemical reaction.

Most of the known catalysts used in asymmetric organocatalysis are amines or aminebased and of which the most widely used and cited is probably the amino acid L-proline. For instance the Hajos-Parrish-Eder-Sauer-Wiechert reaction, an enantioselective intramolecular cyclization reaction which is generally thought of as marking the dawn of asymmetric organocatalysis involves the use of L-proline (**Figure 3.8**) [26,30-37].

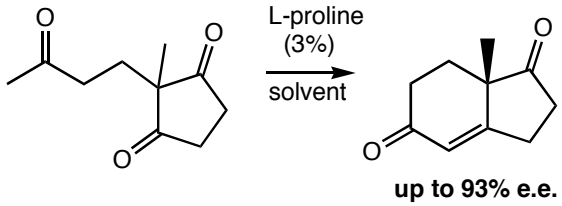


Figure 3.8. The Hajos-Parrish-Eder-Sauer-Wiechert reaction. The reaction has been carried out in various solvents such as DMF, DMSO and acetonitrile [26,30-37].

This reaction has had a vast impact on the field of asymmetric aminocatalysis since it was discovered in the 1970's, especially studies of reaction mechanisms [33-37].

Benjamin List and co-workers have researched asymmetric, aminocatalyzed reactions quite extensively. They have proposed a general mechanism for aminocatalysis with secondary amines such as L-proline and carbonyl compounds. It is their belief that there are two catalytic pathways when working with secondary amines, namely iminium catalysis and enamine catalysis (**Figure 3.9**) [26,33-37]. If an iminium ion is formed, the carbonyl compound is more reactive towards nucleophilic attacks. Therefore, the *acceptor* is activated by iminium ion formation. Conversely, enamine catalyzed reactions of carbonyl compounds involve the activation of the *donor*. Enamines are formed with deprotonation of iminium ions and are essentially enolate equivalents and therefore reactive towards electrophiles.

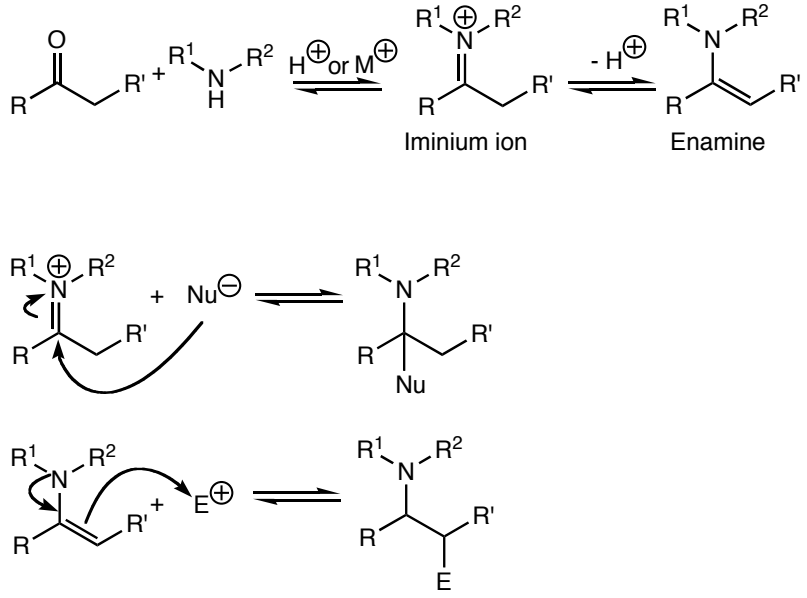


Figure 3.9. Condensation of secondary amines and carbonyl compounds yields iminium ions and enamines [26,30,33,38].

The condensation of secondary amines and carbonyl compounds is a well known reaction with a wide use in organic chemistry [18,38]. In most cases the reaction yields an enamine preferably over the cationic iminium tautomer. The condensation of primary amines and a carbonyl compound yield imines. These imines do however exist in a tautomeric equilibrium between the imine and secondary enamine forms, athough in the absence of some additional stabilization factors, the imine is often the only detectable tautomer. Nevertheless, the enamine tautomer of secondary enamines (enamines derived from condensations of primary amines and carbonyl compounds) is very reactive towards Michael acceptors and reactions do occur readily. The use of enamines in asymmetric Michael addition reactions can be a practical choice because the reaction is also inherently regiospecific due to the mechanism of the reaction. Asymmetrical ketones like 2-methylcyclohexanone are alkylated at the less substituted position via tertiary enamines whereas the more hindered position is alkylated preferentially with secondary amines (**Figure 3.10**) [24].

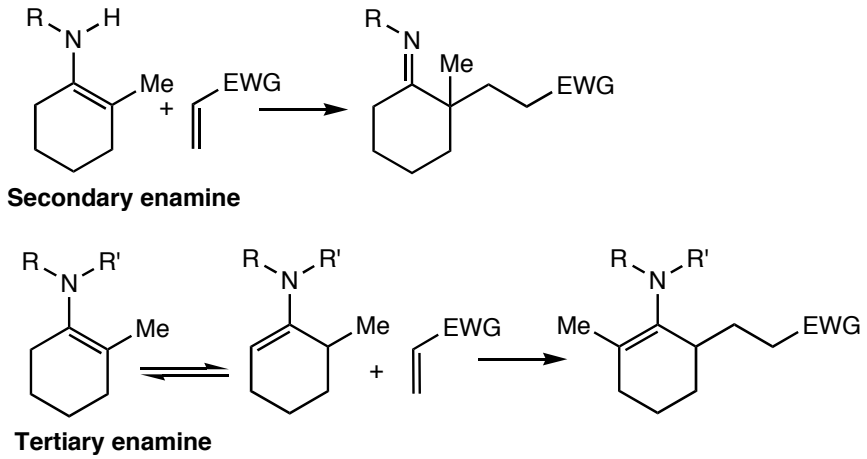


Figure 3.10. Regioselectivity of enamine-based Michael reaction of 2-methylcyclohexanone and Michael acceptor [24].

Aminocatalysis is essentially a biomimetic strategy based on the mechanism of action of enzymes. Enzymes such as class I aldolases catalyze reactions by enamine catalysis and ketoacid decarboxylases use iminium catalysis.

List et al. have studied L-proline catalyzed reactions quite extensively. Their research has been focused, amongst many others, on L-proline catalyzed aldol reactions. An example of a proline catalyzed aldol reaction can be seen in **Figure 3.11**.

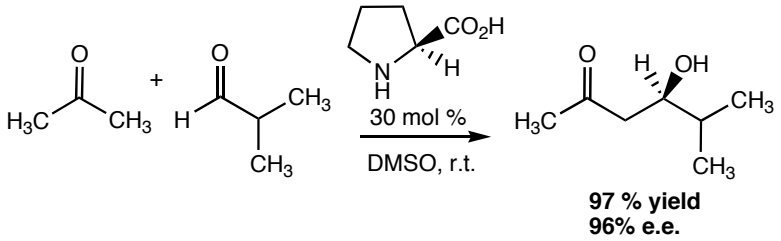


Figure 3.11. Proline catalyzed aldol reaction of acetone and isobutyraldehyde. The reaction is believed to be enamine catatlyzed [30,33,35-37].

According to their findings, this reaction is an enamine catalyzed reaction i.e. the donor is activated by formation of a tertiary enamine. List et. al proposed a reaction mechanism shown in **Figure 3.12**. L-proline acts as a "microaldolase" with the secondary amine as a nucleophilic enamine catalyst and the carboxylic acid as a general cocatalyst [30,33,35-37].

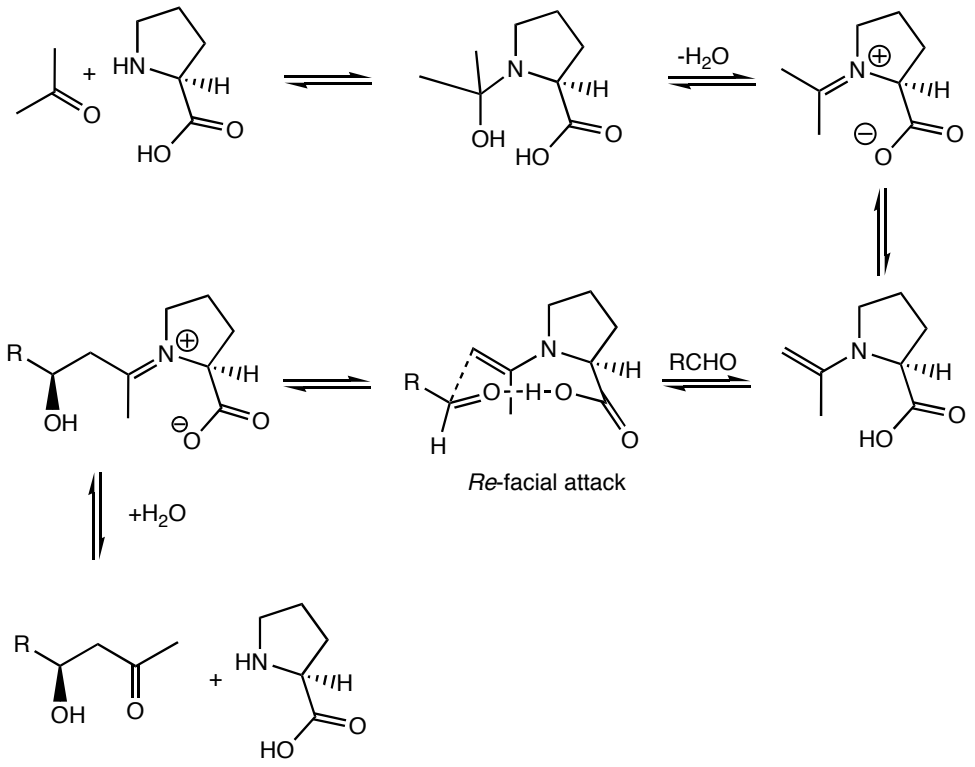


Figure 3.12. Mechanism of the proline catalyzed aldol reaction as proposed by List et al. [33].

The basis for this reaction mechanism are concepts originally proposed by Eschenmoser and Agami on the Hajos-Parrish-Eder-Sauer-Wiechert reaction [30-35]. Similar research has been carried out by Barbas et al. [39].

List and associates have also reported the combined use of both iminium and enamine catalysis in an in situ three component, proline-catalyzed Knoevenagel reaction followed by a hetero Diels-Alder reaction (**Figure 3.13**).

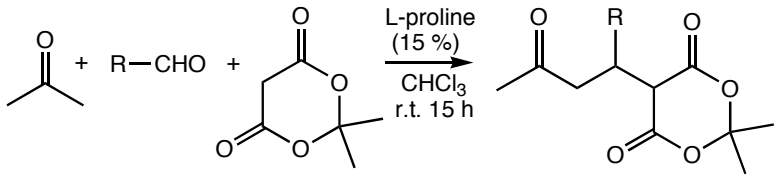


Figure 3.13. Three component reaction involving both iminium and enamine catalysis.

The reaction involves an iminium catalyzed aldol condensation of a Meldrum´s acid and an aldehyde producing an α,β-unsaturated carbonyl compound. What follows is then an enamine catalyzed hetero Diels-Alder reaction of acetone and the α,β-unsaturated

carbonyl compound obtained from the previous step, making the overall reaction a carba-acetalization. They have also proposed a fascinating mechanism for this catalytic cycle (**Figure 3.14**).

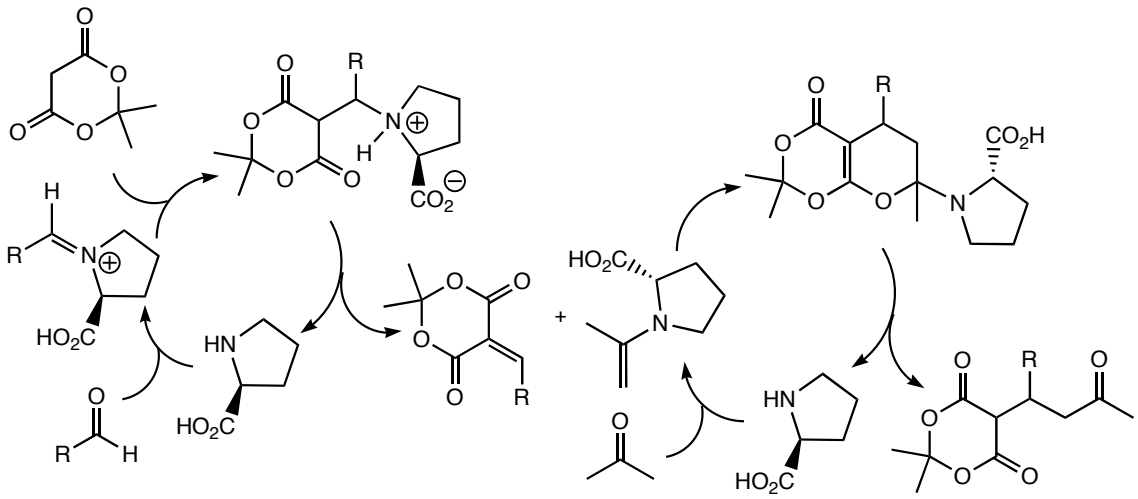


Figure 3.14. Reaction mechanism of the carba-acetalization as proposed by List et al. [33].

Unfortunately, the reaction is not enantioselective and the compounds isolated are essentially racemic, but it is nonetheless an elegant synthesis of Meldrum´s acid derivatives which clearly shows the diverse application of aminocatalysis [33].
Many iminium-, enamine- and phosphoramide based organocatalyzed reactions have been reported including cycloadditions, Michael additions, aldol reactions, nucleophilic substitutions and various other transformations with excellent enantioselectivities and in many cases, good yields [30].
As previously stated, stereochemical control over the first step towards type **2** compounds seems to be required for asymmetric synthesis. Since the first step is a conjugate addition, a method for an asymmetric conjugate addition was needed.

3.5 Enantioselective Michael addition reactions

Michael addition is the conjugate 1,4-addition of a nucleophile e.g. an organometallic compound, heteroatom nucleophile (e.g. amine or sulfide) or enolate to Michael acceptors such as α,β-unsaturated aldehydes, ketones, esters, nitriles, sulfones and nitro compounds [25].

Conjugate addition involves a nucleophilic attack on a double bond. The addition of the nucleophile requires the alkene to be electron deficient by virtue of an electron withdrawing group (EWG) which is often a carbonyl or carboxyl group. In this type of process two new chirality centers can be created along with the formation of the two new bonds.

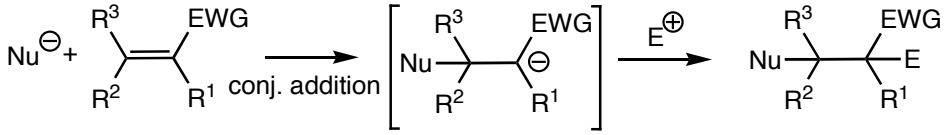


Figure 3.15. General conjugate addition reaction mechanism [25].

The active nucleophile (Nu^-) is usually generated by deprotonation of a precursor (NuH). For example the addition of a nucleophile to a prochiral α,β-unsaturated carbonyl compound (**Figure 3.16**). A new chirality center at the β-carbon is generated and a further reaction with an electrophile (E^+) can form a second center of chirality at the α-carbon.

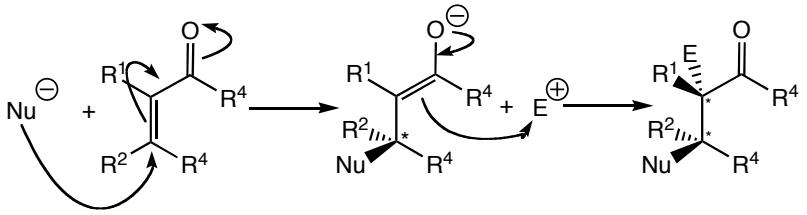


Figure 3.16. Generation of new stereocenters by nucleophilic Michael addition to a carbonyl compound [30].

Enantiofacial differentation in the addition to the β-carbon can be achieved by using a chiral base in the deprotonation of NuH resulting in a chiral ion-pair which can be expected to add to the Michael acceptor asymmetrically (**Figure 3.17**).

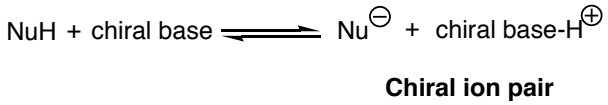


Figure 3.17. The use of a chiral base results in a chiral ion pair which in turn can result in asymmetric synthesis.

N-Alkylated cinchonium derivatives have been knonwn to mediate the enantioselective conjugate addition of carbanions to α,β-unsaturated carbonyl compounds by generation of a chiral ion pair. An example of such use is the Michael addition of 2-carbomethoxyindanone to methylvinylketone catalyzed by quinine (**Figure 3.18** and **Figure 3.19**) [30].

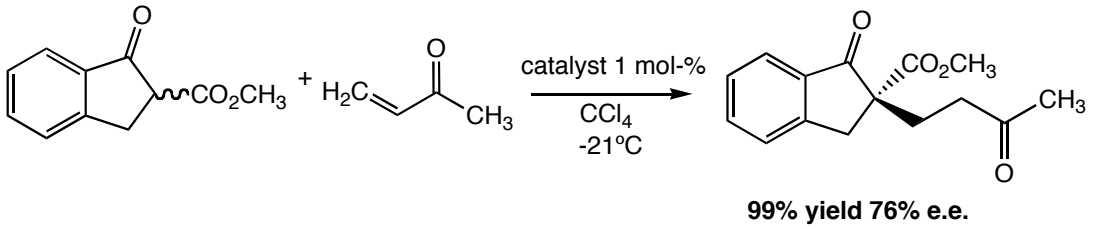


Figure 3.18. Michael addition of 2-carbomethoxyindanone to methylvinylketone catalyzed by quinine. An example of the use of a chiral ion pair in asymmetric synthesis [30].

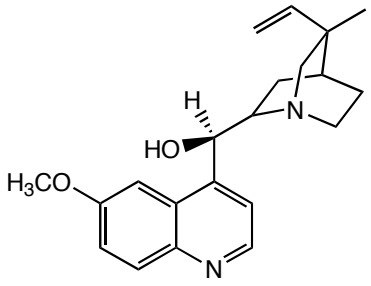
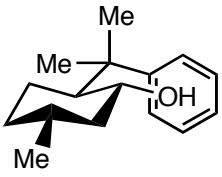


Figure 3.19. Quinine. A chiral organic base used in organocatalyzed asymmetric synthesis.

The reaction mechanism may vary with reaction conditions and reagents, making the Michael reaction highly variable in stereoselectivity. The level and sense of stereoselectivity depends on the conformation of both the donor and acceptor. Nevertheless, highly enantioselective asymmetric conjugate addition reactions have been carried out using chiral ligands, chiral auxiliaries and chiral catalysts. For example 8-

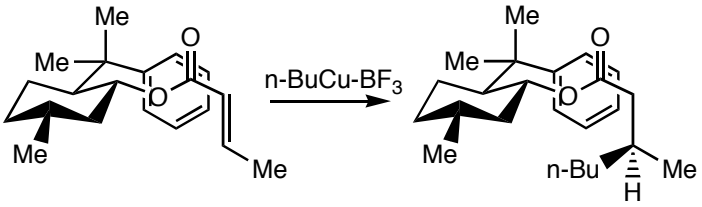
phenylmenthol has been used as a chiral auxiliary in the formation of *(S)*-3-methylheptanoic acid from *trans*-butanoic acid (**Figure 3.20** and **Figure 3.21**) [4,25].



8-phenylmenthol

Figure 3.20. 8-phenylmenthol.

The phenylgroup hinders the conjugate addition to the *Si*-face of the Michael acceptor giving an ester in 98 % diastereomeric excess. The resulting ester can then be hydrolyzed to yield the highly enantiomerically pure carboxylic acid derivative.



98 % d.e.

Figure 3.21. 8-phenylmenthol used as a chiral auxiliary [25].

Aminocatalyzed asymmetric Michael reactions are quite well known and widely reported [26,30,31,32,33]. A more common and efficient alternative to the "classical acid-base" and auxiliary based approaches described above, is the activation of Michael acceptors by reversible iminium ion formation (**Figure 3.22**). If a chiral secondary amine is reacted with a prochiral α,β-unsaturated carbonyl compound, a chiral α,β-unsaturated iminium ion is formed which is more reactive than the carbonyl compound itself because of the positive charge. More importantly, the chirality of the iminium ion intermediate controls the stereochemistry of the resulting transition state when it is reacted with a nucleophile.

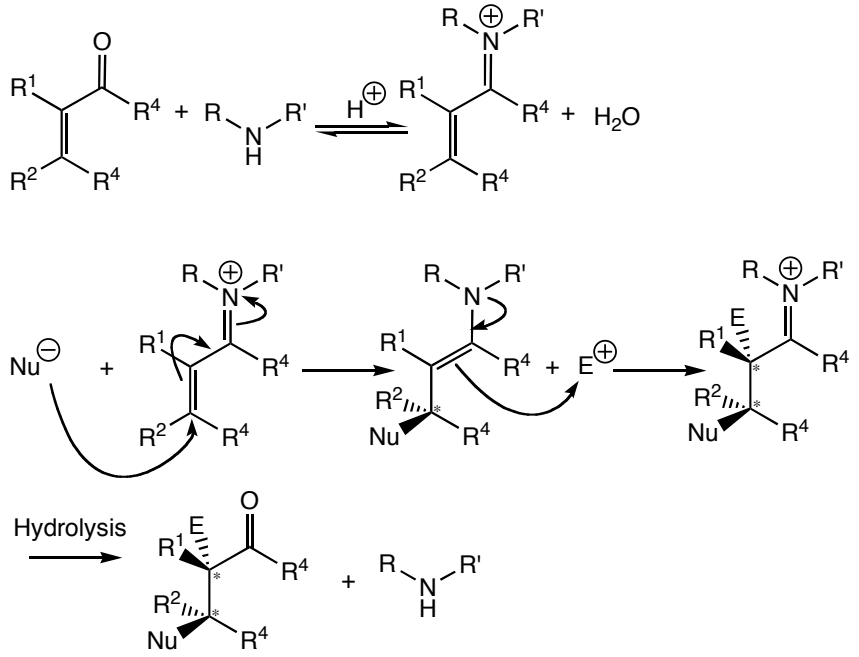


Figure 3.22. Activation of a Michael acceptor by iminium ion formation [30].

Another possibility is to activate the Michael donor with a chiral amine. If the donor is for example an enolate anion, it can be replaced by chiral enamine, formed reversibly from the original carbonyl compound and a chiral amine (**Figure 3.23**).

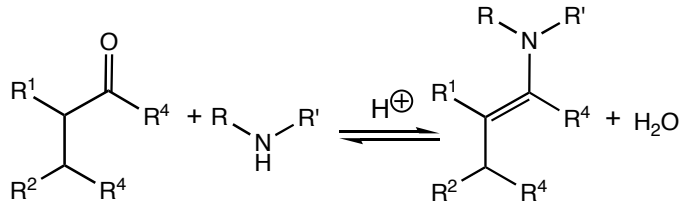


Figure 3.23. Activation of a Michael donor by enamine formation [30].

The chiral enamine would then be reacted with a Michael acceptor and subsequently hydrolyzed in a similar manner as in the case of an iminium catalyzed Michael addition.

Ishii et al. have researched the enamine catalyzed Michael addition of cyclohexanones to various nitrostyrenes and proposed an acyclic, synclinal transition state (**Figure 3.24**). In their research they used chiral pyrrolidine-pyridine conjugate bases as catalysts. What induces the enantioselectivity is that the pyridinium ring shields the *Si*-face of the enamine double bond making the *Re*-facial bonding more feasible.

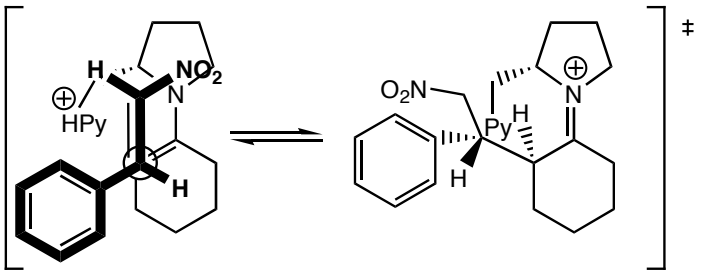


Figure 3.24. Transition state of a Michael addition of cyclohexanone to nitrostyrene as proposed by Ishii et al. [40].

The proposed transition state is based on ideas from mechanisms proposed for the Hajos-Parrish-Eder-Sauer-Wiechert reaction [30,33-37].

It is evident from the examples considered so far that enantioselectivity in asymmetric organocatalyzed reactions is governed by the stereochemical interactions in their transition states. The stereochemistry of products obtained from asymmetric reactions is often a result of steric interactions making one enantiomer more likely to form over the other.

It was decided after becoming familiar with literature on enantioselective aminocatalysis to try and develop a synthetic route towards chiral bicyclo[3.3.1]nonanes using chiral amines.

3.6 Enantioselective aminocatalyzed synthesis of bicyclo[3.3.1]nonanes

The first experiments with chiral organic catalysts and syntheses of type **2** compounds at the Science Institute were done in 2005 by Óttar Rolfsson (**Figure 3.25**) [4].

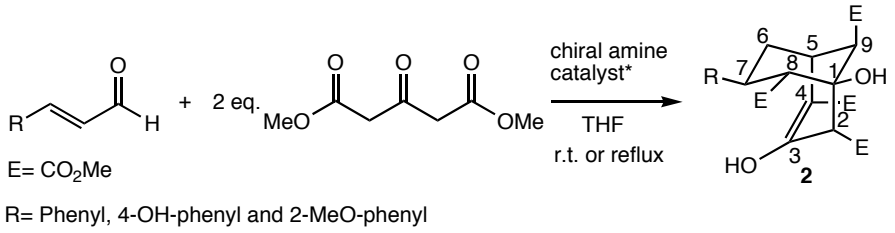


Figure 3.25. Aminocatalyzed synthesis of bicyclo[3.3.1]nonanes using chiral amines [4].

Four chiral amines were implemented in catalytic amounts in these reactions with three seperate enals.

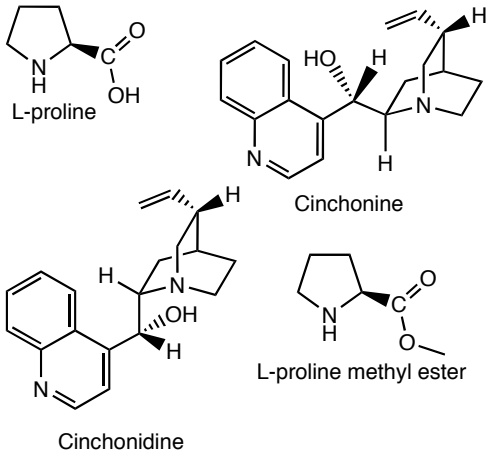


Figure 3.26. Structures of chiral bases used in aminocatalysis carried out in 2005.

The enals used were selected because the racemic mixtures of type **2** compounds obtained from these aldehydes had shown promising anti-cancer activity. In each case the chiral amine was stirred with dimethyl 1,3-acetonedicarboxylate for 20 minutes and then the aldehyde was added to the solution. Yields were in the range of 9-56% of purified type **2** compounds. More importantly, the enantiomeric ratios were determined with HPLC analysis using a Daicel CHIRALPAK®AD column. Results from these HPLC runs are given in **Table 3.1**. It should be noted that there were no attempts made to distinguish

between the two possible enantiomers so the results do not show which of the enantiomers was formed in excess. The results were not as good as had been anticipated but they did none the less show some promise.

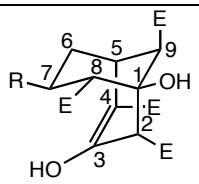
				
Chiral amine	**T (°C)**	**R= Phenyl** (enantiomeric excess)	**R= 4-OH-phenyl** (enantiomeric excess)	**R= 2-MeO-phenyl** (enantiomeric excess)
L-Proline	25	0 % *e.e.*	34 % *e.e.*	15 % *e.e.*
	80	0 % *e.e.*	0 % *e.e.*	0 % *e.e.*
L-Proline methyl ester	25	19 % *e.e.*	50 % *e.e.*	38 % *e.e.*
	80	8 % *e.e.*	25 % *e.e.*	22 % *e.e.*
Cinchonine	25	78 % *e.e.*	42% *e.e.*	20 % *e.e.*
	80	22 % *e.e.*	29 % *e.e.*	28 % *e.e.*
Cinchonidine	25	70 % *e.e.*	18 % *e.e.*	37 % *e.e.*
	80	8 % *e.e.*	18 % *e.e.*	30 % *e.e.*

Table 3.1. Results from aminocatalyzed reactions towards three type **2** compounds carried out in 2005.

In order to try and understand the reaction leading to the formation of type **2** compounds better, a series of model experiments involving prochiral amines was devised. It was decided to try four different prochiral amines under the standard conditions used for synthesis of type **2** compounds in order to find out whether they would yield the desired products. Standard conditions were the use of 10 mol % of amine base in THF at room temperature. The amines used were piperidine, pyrrolidine, tertbutylamine and benzylamine (**Figure 3.27**).

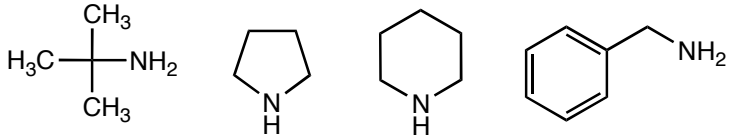


Figure 3.27. Structures of amines used in model reactions.

If these prochiral amines used would yield type **2** compounds in a fairly good yield, the method was to be optimized and a chiral analogous amine derivative was to be implemented to see whether they would lead to enantioselective synthesis. Chiral analogues of all these compounds are available commercially (**Figure 3.28**).

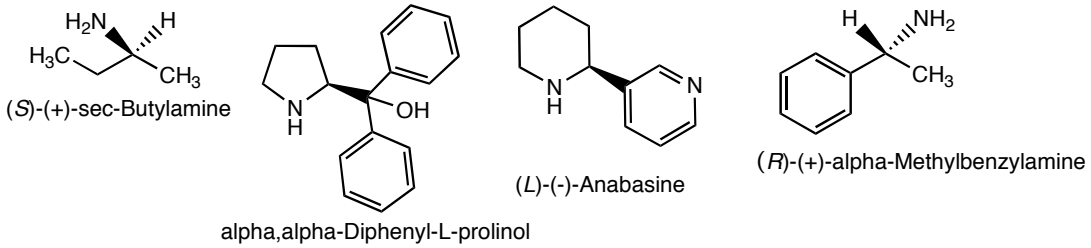


Figure 3.28. Examples of chiral analogues of the prochiral amines used in model reactions.

Secondary and tertiary amines had been used in the synthesis of type **2** compounds before but primary amines had never been used.

For these model experiments, the α,β-unsaturated aldehydes used were crotonaldehyde and cinnamaldehyde because they were readily available. Cinnamaldehyde was also selected due to the fact that type **2** compounds bearing a substituted phenyl moiety, have shown more anticancer activity than those bearing aliphatic moieties.

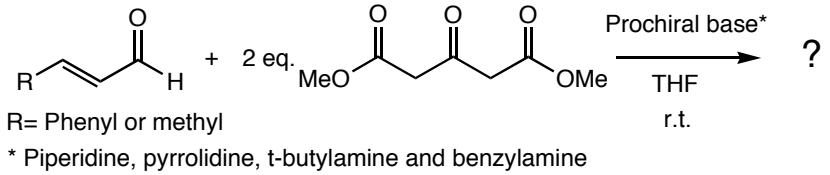


Figure 3.29. Model reactions devised in order to investigate asymmetric synthesis of type **2** compounds.

As expected, piperidine catalysis lead to formation of type **2** compounds in good yields. Pyrrolidine did also yield **2** compounds but in slightly worse yields. However, the reaction of crotonaldehyde and dimethyl 1,3-acetonedicarboxylate catalyzed by the primary amine bases, yielded only polysubstituted cyclohexanone derivatives and not even trace amounts of type **2** compounds (**Table 3.2**).

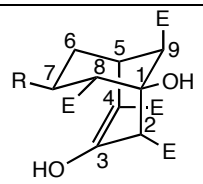
		
Amine base	**R= Phenyl (Yield)**	**R= Methyl (Yield)**
Piperidine	79 %	82 %
Pyrrolidine	64 %	59 %
Benzylamine	-	0 %
Tert-Butylamine	-	0 %

Table 3.2. Results from model experiments.

Reactions involving cinnamaldehyde and primary amines were not carried out since the formation of type **2** compounds was not observable when primary amines were used. Furthermore, the cyclohexanone derivatives were only isolated in a 36 % yield when catalyzed with benzylamine and in a 20 % yield when t-butylamine was used.
The formation of these cyclohexanone derivatives was reported by the Geirsson group in 2004 [41]. They observed the concomitant formation of polysubstituted cyclohexanones when using sodium or lithium methoxide in methanol to catalyze the formation of type **2** compounds. Formation of cyclohexanones in a reaction between an α,β-unsaturated aldehyde and dimethyl 1,3-acetonedicarboxylate is a result of 1,2-addition of an enolate to the aldehyde instead of the conjugate 1,4-addition which leads to the formation of bicyclo[3.3.1]nonanes. A possible reaction mechanism is shown in **Figure 3.30**.

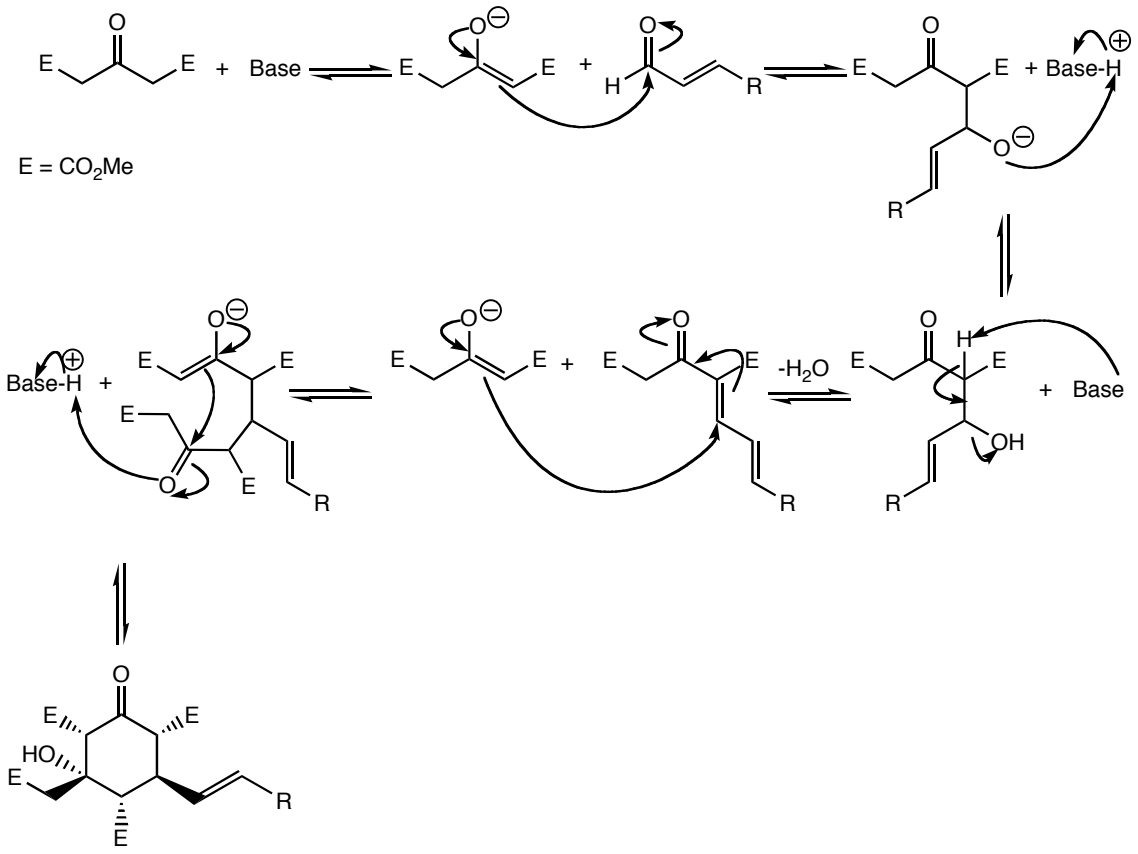


Figure 3.30. Reaction mechanism for the formation of cyclohexanone derivatives.

Like the formation of type **2** compounds, the formation of these cyclohexanone derivatives has been found to be highly stereospecific. NMR spectra and X-ray crystallography have confirmed that all the hydrogen atoms attached to ring are in axial positions as well as the hydroxyl group [41] (**Figure 3.31**).

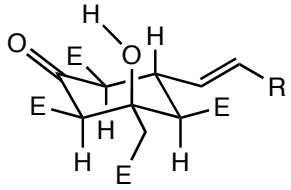


Figure 3.31. Proposed stereochemistry of cylohexanones with the largest groups in equatorial positions.

These results are in accordance with what might be expected since the more bulky groups are located in equatorial positions, thereby minimizing unfavorable 1,3-diaxial interactions and thus making the compound more stable.

The results from these experiments raised questions about the reaction mechanism in the formation of bicyclo[3.3.1]nonanes. Use of primary amine bases yielded cyclohexanone derivatives as sodium and lithium methoxide had been reported to yield as well. Methoxide ions do catalyze the reaction by deprotonation of the 1,3,5-tricarbonyl compound yielding an enolate ion which subsequently adds to the aldehyde. The amine bases could however form covalent bonds with either the aldehyde or dimethyl 1,3-acetonedicarboxylate.

It was then postulated that maybe the first step in the formation of type **2** compounds was not deprotonation and perhaps it was either catalyzed by enamine or iminium ion formation similar to the asymmetric aldol and Michael reactions mentioned before (**Figures 3.9**, **3.12**, **3.22** and **3.23**).

It was therefore decided to monitor the reaction of dimethyl 1,3-acetonedicarboxylate and an α,β-unsaturated aldehyde in the presence of pyrrolidine or piperidine with ^{1}H NMR to try and decide whether it was catalyzed by deprotonation or by enamine or iminium ion formation.

In order to monitor the reaction with ^{1}H NMR, it needed to be established that it could be carried out in a solvent which was also readily available deuterated. Deuterated chloroform is the cheapest and most common solvent used in NMR spectroscopy and was therefore the first choice.

Two molar equivalents of dimethyl 1,3-acetonedicarboxylate and one molar equivalent of piperidine were stirred together in $CHCl_3$ at room temperature and monitored with TLC (CH_2Cl_2/EtOAc (1:2). This was done in order to explore the possibilty of enamine formation.

After one hour of stirring and no visible change according to TLC, one molar equivalent of crotonaldehyde was added to the solution. Immediately after the addition of the aldehyde there was observable change seen by TLC. In only two hours the dimethyl 1,3-acetonedicarboxylate had been consumed and a single spot was observable with an Rf value around 0,62 which is typical for type **2** compounds. After workup of the reaction, NMR spectra confirmed that a type **2** compound had indeed been formed in 90 % yield. The same exact procedure was applied with pyrrolidine instead of piperidine which also

yielded a type **2** compound in 65 % yield. It was however not possible to say whether the reaction took place via enamine formation based solely on TLC analysis.

It was evident from these experiments that bicyclo[3.3.1]nonanes could be formed in chloroform so the next step was to monitor the reaction with ^{1}H NMR.

The same procedure was used as in the experiments before with $CDCl_3$ instead of $CHCl_3$ as a solvent. The reaction was carried out on a smaller scale (0,07 mmol of aldehyde as compared to 1 mmol) than in the previous experiments. The 1,3,5-tricarbonylcompound was stirred with one molar equivalent of piperidine for a few minutes at room temperature and then NMR spectra was obtained. According to our postulation there would be observable changes in ^{1}H NMR spectra if an enamine was formed (**Figure 3.32**).

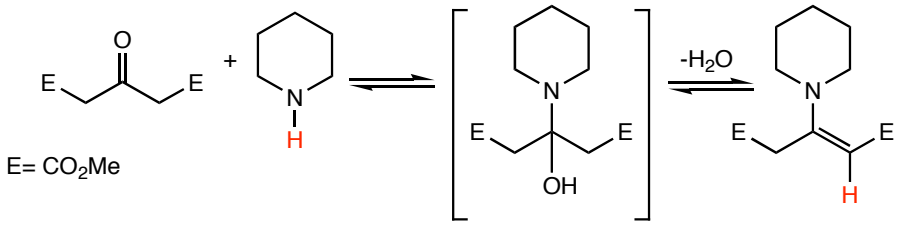


Figure 3.32. Possible enamine formation from piperidine and dimethyl 1,3-acetonedicarboxylate. The red proton on piperidine would no longer be observable and the red proton on the enamine would however be observable.

The N-H proton in piperidine around δ 2,8 ppm would no longer be visible if an enamine was formed and a double bond proton around δ 4,0-6,0 ppm should then be observable. Rather dissappointingly, neither of the aforementioned changes were observed and the ^{1}H NMR spectra was inconclusive. Crotonaldehyde was then added to the solution and the reaction monitored further by NMR in order to see whether any indications of enamine catalysis were observable in the presence of the Michael acceptor. Again, the NMR spectra did not indicate enamine formation but a type **2** compound was formed nonetheless.

Same procedure was repeated with pyrrolidine instead of piperidine with similar results. This led to reevaluation of the proposed enamine mechanism. The original idea was that type **2** compounds were formed with enamine catalysis in the presence of secondary amines via a carbinolamine intermediate (**Figure 3.32**). However, reported reactions

involving enamines almost always require the presence of a Brønsted or Lewis acid catalyst. They are also believed to be more often formed via iminum ion formation (**Figure 3.9**). Formation of enamines almost always requires heating and is less likely to occur at room temperature [18,26,30,33,38] .

Following reevaluation, it was also concluded that there was probably little to be gained by preforming an enamine in order to achieve asymmetric synthesis. Dimethyl 1,3-acetonedicarboxylate is a symmetrical molecule and therefore bonding to either the *Re* or *Si* face is equally likely to occur, even if a chiral amine is used. A hypothetical example is shown in **Figure 3.33** where a chiral pyrrolidine derivative forms an enamine with the 1,3,5-tricarbonyl compound. This would probably result in a racemic mixture because the 1,3,5-tricarbonyl compound is symmetrical.

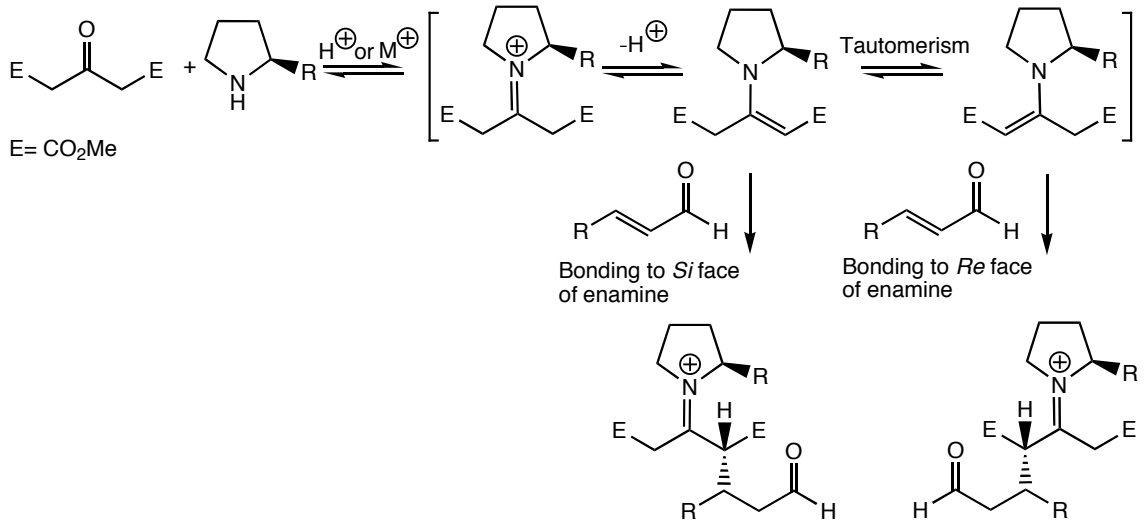


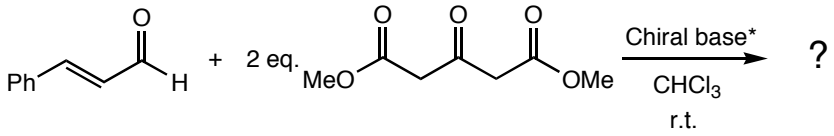
Figure 3.33. Bonding to either *Re* or *Si* face of enamine is equally likely to occur which in all likelihood leads to a racemic mixture.

Formation of an iminium ion from a chiral base and the Michael acceptor would therefore probably be likelier to yield a chiral final product.

In light of the results obtained in 2005 by Óttar Rolfsson and in view of the fact that the results obtained from these model experiments were indefinitive, it was decided to see whether the use of catalytic amounts of chiral amine bases would yield chiral bicyclo[3.3.1]nonanes with deprotonation and formation of a chiral ion pair similar to those mentioned in section **3.5** (**Figures 3.17 and 3.18**). This was also done to see

whether these amines would at all yield type **2** compounds and subsequentally optimize a HPLC analytical method for type **2** compounds.

Reaction conditions were the same as in previous model experiments i.e. the reaction was carried out in $CHCl_3$ using 1,5 mmol of aldehyde and 10 mol % base at room temperature (**Figure 3.34**). It was decided to use cinnamaldehyde and not crotonaldehyde since the final goal was preferably to synthesize chiral compounds bearing an aromatic moiety.



*L-cinchonidine, Cinchonine, L-Proline,
(S)-(+)-2-methylpiperidine, L-(-)-Anabasine,
alpha, alpha-Diphenyl-L-Prolinol,
(S)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine,

Figure 3.34. Reaction scheme with chiral amine bases.

Structures of the chiral amines used are shown in **Figure 3.35**.

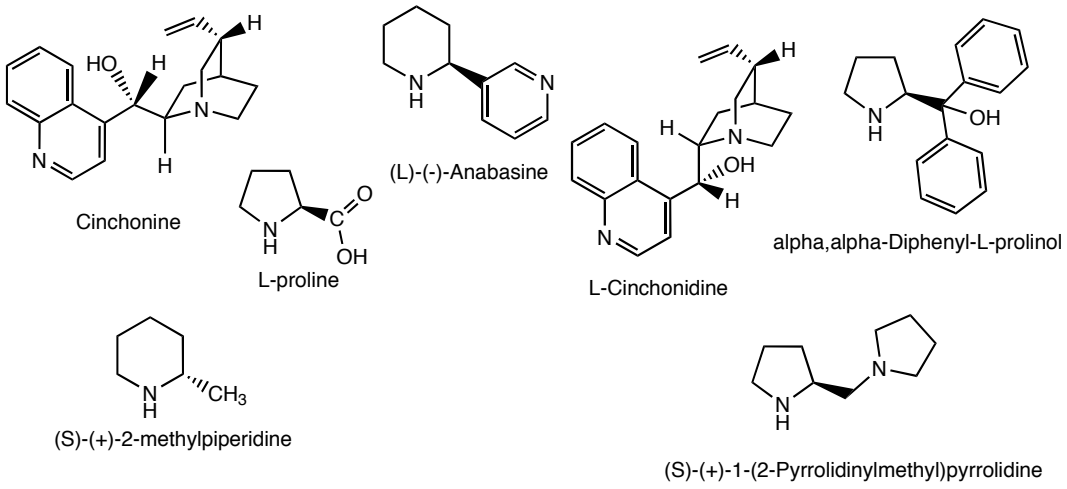


Figure 3.35. Structures of chiral amines used in attempted synthesis of chiral bicyclo[3.3.1]nonanes.

Both cinchona alkaloids and proline only yielded cyclohexanone derivatives like the primary amines had done in previous experiments (**Figures 3.30 and 3.31**). The other four amines catalysed formation of type **2** compounds although unfortunately, in rather poor yields.

The compounds obtained from theses syntheses were purified by column chromatography and recrystallization.

After purification, an analytical method was developed using a phenyl substituted type **2** compound (obtained from a piperidine catalyzed reaction) as a standard since it should be racemic. HPLC analysis later confirmed that it was indeed racemic.

Enantiomers were then separated on a Daicel CHIRALPAK®AD column with hexane/isopropanol (80:20) mobile phase at a flow rate of 1,0 mL/min.

The results from the HPLC analysis are shown in **Table 3.3** along with isolated yields.

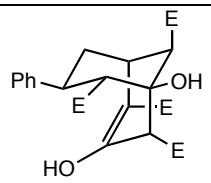
		
Chiral amine base	**Yield (%)**	**Enantiomeric excess (%)**
(S)-(+)-2-methylpiperidine	34 %	12 %
L-(-)-Anabasine	39 %	9 %
α,α-Diphenyl-L-Prolinol	22 %	10 %
(S)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine	10 %	7 %

Table 3.3. Results from chiral amine base catalyzed reactions.

Since the bicyclo[3.3.1]nonanes were essentially racemic, there were no attempts made to distinguish between the two possible enantiomers. The results do therefore not show which of the enantiomers was formed in excess. However, it should be noted that the enantiomer that was first eluted of the column was always the one formed in excess.

These results were disappointing but could maybe have been anticipated. Reported cases of aminocatalyzed Michael reactions are more often either iminium or enamine catalyzed rather than being catalyzed by deprotonation with a chiral base [11]. There is also a similar problem as with the postulated enamine catalyzed Michael reaction of dimethyl 1,3-acetonedicarboxylate and an α,β-unsaturated aldehyde, in that dimethyl 1,3-acetonedicarboxylate is symmetrical. The deprotonation is equally likely to occur on either side of the keto group and thus negating the use of a chiral base (**Figure 3.36**). The

enolate anion can also tautomerize causing the use of a chiral base to be ineffective (**Figure 3.37**). The subsequent addition to a Michael acceptor is therfore equally likely to take place on the *Re* and *Si* faces of the enolate and would almost definitely result in a racemic product.

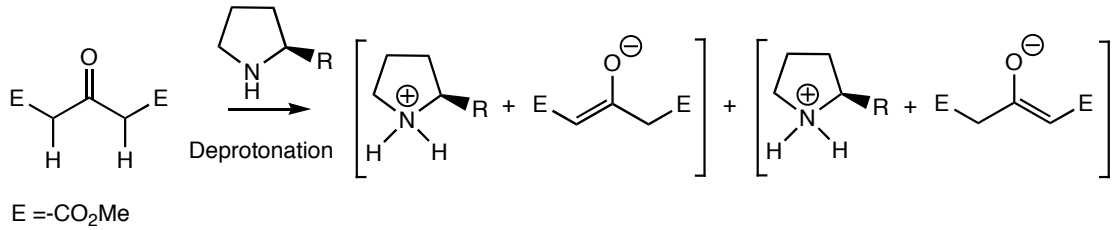


Figure 3.36. Deprotonation of dimethyl 1,3-acetonedicarboxylate is equally likely to occur on either side of the keto group.

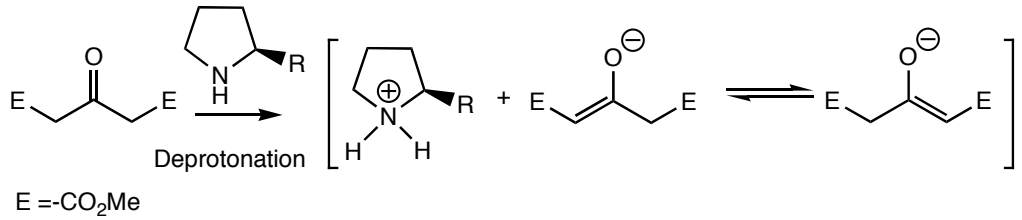


Figure 3.37. Tautomerism leads to equally likely transition states.

It can therefore be concluded that the iminium ion activation of the α,β-unsaturated aldehyde with a chiral amine is probably the only possible aminocatalytic path to a chiral bicyclo[3.3.1]nonane.

In 2008, Jørgensen et al. published a method for the formation of enantiopure bicyclo[3.3.1]nonanes. This method involves both asymmetric organocatalysis as well as an "old-fashioned" acid-base reaction. A chiral pyrrolidine derivative is used to induce enantioselectivity and piperidine, an achiral organic base, is subsequently added resulting in a one-pot, cascade reaction of an α,β-unsaturated aldehyde and dimethyl 1,3-acetonedicarboxylate resulting in the formation of bicyclo[3.3.1]nonanes identical to those synthesized at the Science Institute (**Figure 3.38**) [42].

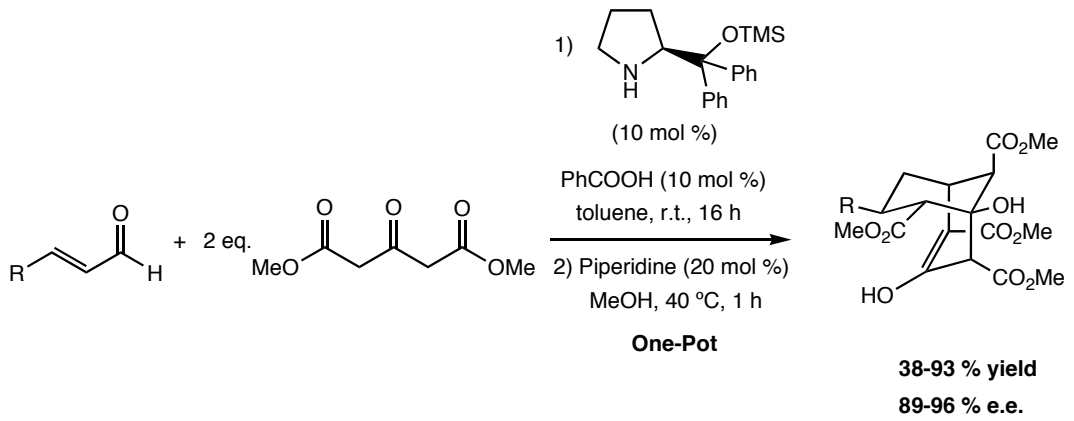


Figure 3.38. Two-base cascade reaction resulting in enantiomerically pure bicyclo[3.3.1]nonanes [42].

Various aliphatic, aromatic and heteroaromatic α,β-unsaturated aldehydes, were sucessfully subjected to the reaction conditions resulting in optically active bicyclo[3.3.1]nonanes in good yields and excellent enantiomeric purity.

The first step of the reaction is the benzoic acid catalyzed iminium formation of (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethyl silyl ether and an aldehyde thus making it more reactive towards the subsequent Michael addition of the tricarbonyl compound. The iminium intermediate also controls the stereoselectivity of the reaction. Piperidine is then added to catalyze both the aldol reaction and the second Michael addition. The reaction mechanism has been postulated as two catalytic cycles (**Figure 3.39**).

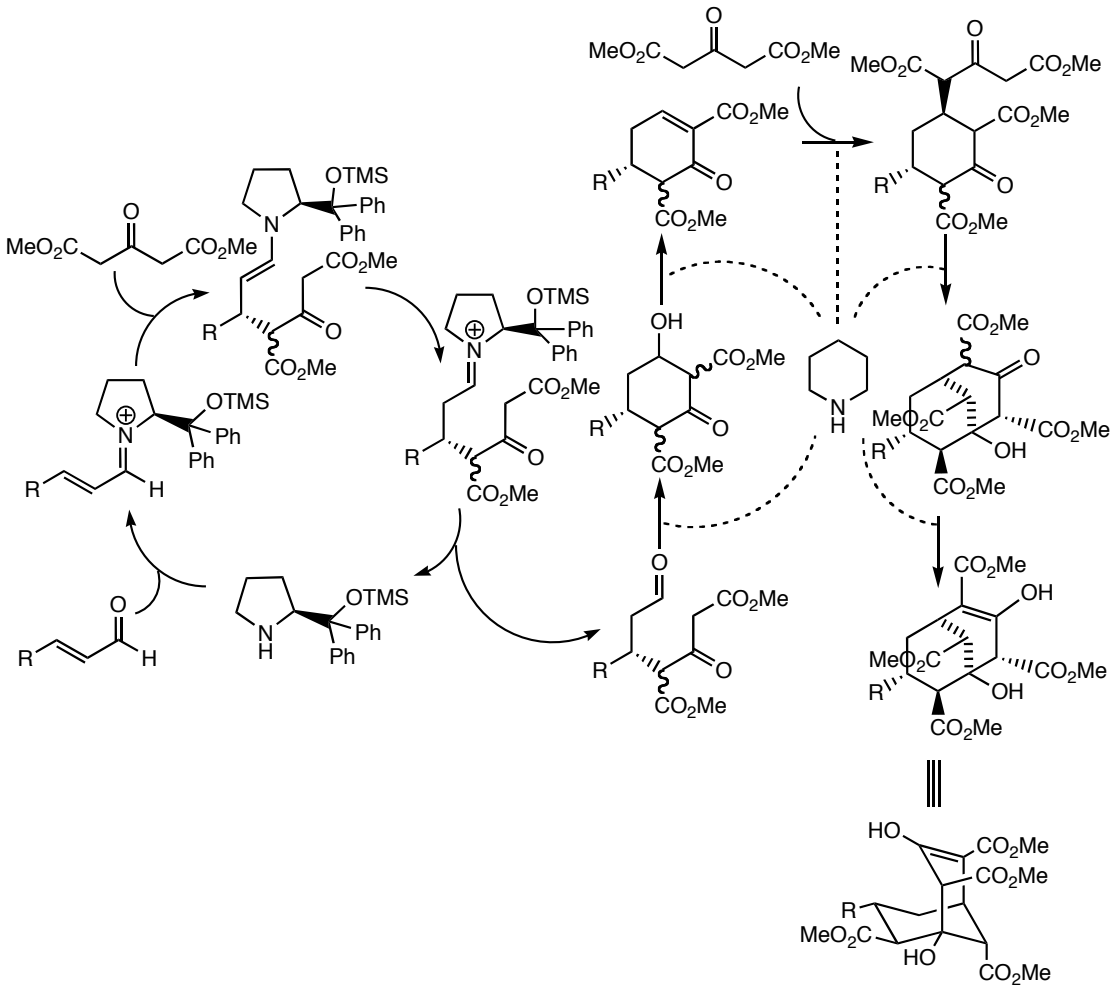


Figure 3.39. Organocatalytic cycles for the formation of enantiomerically pure bicyclo[3.3.1]nonanes [42].

At the precedent of the Jørgensen group, a similar reaction scheme between cinnamaldehyde and dimethyl 1,3-acetonedicarboxylate was devised. That scheme involved the same components and conditions in every aspect except that α,α-diphenyl-L-prolinol was used as the chiral catalyst since it was available at the lab (**Figure 3.40**). Essentially, the chiral amine used by the Jørgensen group is a trimethylsilylether derivative of α,α-diphenyl-L-prolinol so similar results were anticipated.

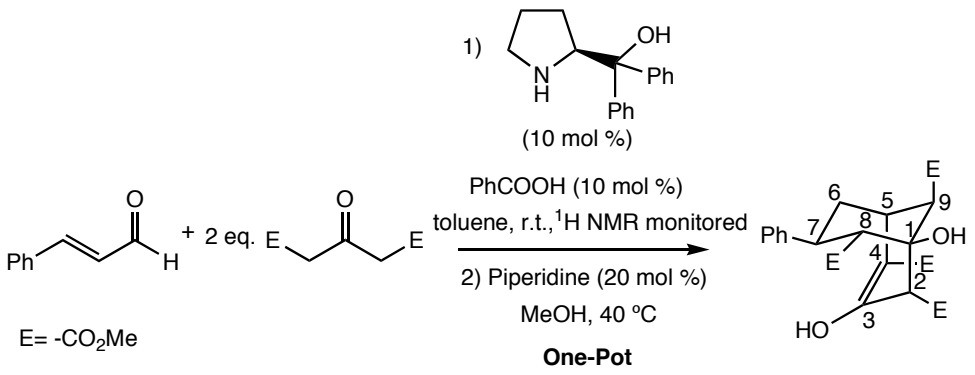


Figure 3.40. Reaction scheme devised at the example of Jørgensen et al.

The reaction was carried out by stirring 0,5 mmol of cinnamaldehyde with 0,05 mmol of α,α-diphenyl-L-prolinol and 0,05 mmol of benzoic acid in 250 μL of toluene for 25 minutes. Then 1,0 mmol of dimethyl 1,3-acetonedicarboxylate was added to the solution. The progress of the reaction was then monitored by ^{1}H NMR every two hours for the first 8 hours and then again after 20 hours and 24 hours. When ^{1}H NMR spectra showed full consumption of the aldehyde after 24 hours, 0,1 mmol of piperidine, dissolved in 2 mL of methanol, was added to the solution and stirred at 40 °C. TLC analysis showed completion of the reaction 2 hours later so it was stopped and the solvent was removed under reduced pressure. The crude mixture was then submitted to column chromatography for purification. NMR spectra verified that the expected resulting type **2** product had been formed in 38 % yield.

The next step was the determination of enantiomeric ratios. As before, the enantiomers were separated on a Daicel CHIRALPAK®AD column with hexane/isopropanol (80:20) mobile phase at a flow rate of 1,0 mL/min. For some reason not yet clear, the enantiomeric excess was only 12 %, which is similar to the aforementioned results (**Table 3.3**). This came as a surprise since the Jørgensen group had been able to synthesize an identical phenyl substituted bicyclo[3.3.1]nonane from the same precursors and under almost identical conditions. They had isolated that phenyl substituted bicyclo[3.3.1]nonane in a 70 % yield and more importantly in a 93 % enantiomeric excess [42]. The only difference between the reactions was the chiral amine used and essentially one trimethyl silyl substituent, so the difference in results can probably be attributed to that trimethyl silyl substituent.

Unfortunately, further research on these reaction conditions could not be done due to lack of time.

In spite of the fact that these experiments did not result in a general method for the asymmetric synthesis of type **2** compounds, there was one positive aspect to the research of these reactions. The HPLC analytical method developed by the Jørgensen group was exactly the same as the one developed during the process of the model experiments which was pleasing as it confirmed that HPLC analysis was at least being done right.

4 Conclusions and future work

Based on previously developed synthetic methods and research, fourteen various aromatic α,β-unsaturated aldehydes were synthesized in a Heck reaction variant from acrolein and various aryl iodides in fairly good yields. These aldehydes, as well as three other commercially available aldehydes, were then further reacted with 2 molar equivalents of dimethyl 1,3-acetonedicarboxylate under basic conditions yielding novel polysubstitued bicyclo[4.4.0]decanes (type **3** compounds). Formation of these decalone derivatives is achieved in a highly stereoselective tandem Michael reaction.

Decalones of type **3**, were then aromatized by reaction with iodine resulting in novel polysubstituted 1-tetralones which can also be viewed as resorcinol derivatives (type **4** compounds).

Attempts were then made to alkylate and arylate phenol groups of 1-tetralone (**4o)**, which unfortunately were not succesful. Arylation of 4-iodophenol and *p*-hydroxycinnamaldehyde was achieved by Chan-Lam coupling of arylboronic acid derivatives yielding novel aryl iodides and arylated cinnamaldehyde derivatives. The resulting novel arylated compounds were then used in syntheses of corresponding type **3** and type **4** compounds.

An enantioselective synthetic route towards bicyclo[3.3.1]nonanes using chiral amines was explored. Results were somewhat promising but a general practical method could not be devised. Research did however lead to an optimized HPLC analytical method of enantiomeric ratios. Experiments also showed that the use of primary amines lead to 1,2-addition of aldehydes and not 1,4-conjugate addition, which consequently lead to highly stereoselective formation of cyclohexanone derivatives.

All novel compounds were to be sent to the National Cancer Institute (NCI) for *in vitro* cytotoxicity testing. Unfortunately, this could not be done in time to include results in this thesis. Results from cytotoxicity testing will hopefully be obtained and published in the near future.

Further work on developing a practical synthetic method for chiral bicyclo[3.3.1]nonanes should be done in light of results obtained by the Jørgensen group [42]. For example, if (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethyl silyl ether is either purchased or synthesized from (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol and implemented under similar conditions as the Jørgensen group used, the synthesis of enantiomerically pure bicyclo[3.3.1]nonanes of type **2** should be possible.

5 Experimental

All NMR spectra were measured and recorded on a Bruker Avance 400 MHz spectrometer. Analytical thin layer chromatography was done using ALUGRAM® SIL G/UV_{254} 0.20 mm silica gel plates from Macherey-Nägel. Column chromatography was performed using silica gel (particle size 0,06-0,20 nm) from Acros Organics. High performance liquid chromatography was carried out using Hewlett Packard HP 1100 HPLC system with DAD and a Daicel CHIRALPAK®AD analytical column. All solvents and reagents that were obtained from commercial suppliers were used without further purification unless otherwise noted.

5.1 General protocol for the synthesis of α-β-unsaturated aldehydes. Heck reaction

A mixture of a corresponding aryliodide (1 mmol), tetrabutyl ammonium chloride (1 mmol), sodium bicarbonate (3 mmol) and palladium(II)acetate (0.1 mmol) dissolved in 40 mL of DMF (N,N-dimethylformamide) and stirred at 100°C for 5 minutes. 2-propenal (2 mmol), dissolved in 5 mL of DMF was then added dropwise to the solution to the solution over a period of 15 minutes. The resulting solution was then stirred at 100°C and monitored by TLC (CH_2Cl_2/EtOAc (9:1)) for 6-12 hours depending on which derivative of aryliodide was used. DMF was then removed under reduced pressure and the resulting mixture dissolved in CH_2Cl_2. The resulting organic phase was subsequently washed with 10% hydrochloric acid (3 times), H_2O (2 times) and dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure and the product purified with column chromatography (EtOAc/Petroleum ether (1:2)).

Trans-3-(4-hydroxyphenyl)acrylaldehyde. (**1a**)

Obtained from 4-iodophenol and acrolein as yellow crystals (89 %).

^{1}H (Acetone d-6) δ (ppm): 9,65 (d, J=7,7 Hz, 1H); 9,08 (s, 1H); 7,63 (m, 2H); 7,59 (d, J= 15,9 Hz, 1H); 6,95 (m, 2H); 6,63 (dd, J=7,7 Hz, J=15,9 Hz, 1H).

^{13}C (Acetone d-6) δ (ppm): 193,9; 161,4; 153,7; 131,6; 127,1; 126,8; 116,9.

Trans-3-(4-chlorophenyl)acrylaldehyde. (**1b**)

Obtained from 1-chloro-4-iodobenzene and acrolein as yellow, needlelike crystals (90 %).

^{1}H ($CDCl_3$) δ (ppm): 9,70 (d, *J*=7,6 Hz, 1H); 7,50 (m, 2H); 7,43 (d, *J*=16,0 Hz, 1H); 7,41(m, 2H); 6,69 (dd, *J*=7,6 Hz, *J*=16,0 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,4; 151,1; 137,4; 131,5; 129,7; 129,5; 129,0.

Trans-3-(3,5-dichlorophenyl)acrylaldehyde. (**1c**)

Obtained from 1,3-dichloro-5-iodobenzene and acrolein as reddish crystals (82 %).

^{1}H ($CDCl_3$) δ (ppm): 9,72 (d, *J*=7,5 Hz, 1H); 7,42 (m, 3H); 7,34 (d, *J*=16,0 Hz, 1H); 6,69 (dd, *J*=7,5 Hz, *J*=16,0 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 192,8; 148,9; 136,9; 135,9; 130,73; 130,67; 126,5.

Trans-3-(2-hydroxyphenyl)acrylaldehyde. (**1d**)

Obtained from 2-iodophenol and acrolein as yellow crystals (74 %).

^{1}H ($CDCl_3$) δ (ppm): 9,67 (d, *J*=8,0 Hz, 1H); 7,80 (d, *J*=16,0 Hz, 1H); 7,50 (m, 1H); 7,32 (m, 1H); 7,13 (s, 1H); 7,00 (dd, *J*=8,0 Hz, *J*=16,0 Hz, 1H); 6,97 (m, 2H).

^{13}C ($CDCl_3$) δ (ppm): 195,7; 155,9; 149,8; 132,8; 129,9; 129,1; 121,4; 120,9; 116,6.

Trans-3-(2-chlorophenyl)acrylaldehyde. (**1e**)

Obtained from 1-chloro-2-iodobenzene and acrolein as yellow needlelike crystals (96 %).

^{1}H ($CDCl_3$) δ (ppm): 9,72 (d, *J*=7,7 Hz, 1H); 7,90 (d, *J*=16,0 Hz, 1H); 7,64 (m, 1H); 7,35 (m, 3H); 6,67 (dd, *J*=7,67 Hz, *J*=16,0 Hz 1 H).

^{13}C ($CDCl_3$) δ (ppm): 193,6; 162,6; 148,0; 135,1; 132,0; 130,5; 130,3; 127,9; 127,4.

Trans-3-(4-methoxyphenyl)acrylaldehyde. (**1f**)

Obtained from 4-methoxyphenyl iodide and acrolein as yellow crystals (91 %).

^{1}H ($CDCl_3$) δ (ppm): 9,65 (d, *J*=7,8 Hz, 1H); 7,52 (m, 2H); 7,42 (d, *J*=15,9 Hz, 1H); 6,94 (m, 2H); 6,60 (dd, *J*=7,8 Hz, *J*=15,8 Hz, 1H); 3,86 (s, 3H).

^{13}C ($CDCl_3$) δ (ppm): 193,7; 162,2; 152,7; 130,4; 126,9; 126,6; 114,6; 55,5.

Trans-3-(4-fluorophenyl)acrylaldehyde. (**1g**)

Obtained from 4-fluorophenyl iodide and acrolein as white crystals (75 %).

^{1}H ($CDCl_3$) δ (ppm): 9,69 (d, *J*=7,6 Hz, 1H); 7,44 (d, *J*=16,0 Hz, 1H); 7,13 (m, 2H); 6,64 (dd, *J*=7,6 Hz, *J*=16,0 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,5; 165,8; 163,3; 151,3; 130,6; 130,5; 128,4; 116,5; 116,3.

Trans-3-(3-trifluoromethylphenyl)acrylaldehyde. (**1h**)

Obtained from 3-trifluoromethylphenyl iodide and acrolein as yellow crystals (81 %).

^{1}H ($CDCl_3$) δ (ppm): 9,74 (d, *J*=7,5 Hz, 1H); 7,68 (m, 5H); 7,51 (d, *J*=16,0 Hz, 1H); 6,77 (dd, *J*=7,5 Hz, *J*=16,0 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,3; 170,9; 150,5; 134,9; 134,8; 131,3; 130,0; 129,8; 127,6 (q); 119,2.

Trans-3-(3,5-bis(trifluoromethyl)phenyl)acrylaldehyde. (**1i**)

Obtained from 3,5-bis(trifluoromethyl)phenyl iodide and acrolein as darkbrown crystals (32 %).

^{1}H ($CDCl_3$) δ (ppm): 9,80 (d, *J*=7,3 Hz, 1H); 8,10 (m, 3H); 7,56 (d, *J*=16,1 Hz, 1H); 6,86 (dd, *J*=7,3 Hz, *J*=16,1 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 192,5; 148,0; 140,4; 136,1; 134,8; 133,1; 132,7; 131,5; 127,5 (q); 125,5 (q); 100,1.

Trans-3-(naphthalen-1-yl)acrylaldehyde. (**1j**)

Obtained from 1-iodonaphthalene and acrolein as yellow crystals (80 %).

^{1}H ($CDCl_3$) δ (ppm): 9,86 (d, *J*=7,7 Hz, 1H); 8,33 (d, *J*=15,7 Hz, 1H); 8,19 (m, 1H); 7,96 (m, 1H); 7,91 (m, 1H); 7,82 (m, 1H); 7,63 (m, 1H); 7,54 (m, 2H);
6,85 (dd, *J*=7,7 Hz, *J*=15,7 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,7; 149,4; 133,8; 131,7; 131,2; 131,02; 131,01; 129,1; 127,3; 126,5; 125,8; 125,5; 122,8.

Trans-3-(4-(*p*-tolyloxy)phenyl)acrylaldehyde. (**1k**)

Obtained from 1-iodo-4-(*p*-tolyloxy)benzene and acrolein as yellow crystals (45 %).

^{1}H (Acetone d-6) δ (ppm): 9,68 (d, *J*=7,7 Hz, 1H); 7,73 (m, 2H); 7,66 (d, *J*=15,9 Hz, 1H); 7,26 (m, 2H); 7,05 (m, 4H); 6,69 (dd, *J*=7,7 Hz, *J*=15,91 Hz, 1H); 2,34 (s, 3H).

^{13}C (Acetone d-6) δ (ppm): 193,9; 161,6; 151,5; 152,8; 135,0; 131,45; 131,43; 129,9; 128,4; 120,8; 118,7; 20,8.

Trans-3-(4-(4-chlorophenoxy)phenyl)acrylaldehyde. (**1l**)

Obtained from 1-chloro-4-(4-iodophenoxy)benzene and acrolein as white crystals (61 %).

^{1}H ($CDCl_3$) δ (ppm): 9,67 (d, *J*=7,7 Hz, 1H); 7,54 (m, 2H); 7,44 (d, *J*=15,9 Hz, 1H); 7,34 (m, 2H); 7,00 (m, 4H); 6,69 (dd, *J*=7,7 Hz, *J*=15,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,7; 160,0; 154,5; 152,0; 130,5; 130,1; 129,6; 129,1; 127,7; 121,2; 118,5.

Trans-3-(4-(3-(trifluoromethyl)phenoxy)phenyl)acrylaldehyde. (**1m**)

Obtained from 1-(4-iodophenoxy)-3-(trifluoromethyl)benzene and acrolein as white crystals (64 %).

^{1}H ($CDCl_3$) δ (ppm): 9,65 (d, *J*=7,7 Hz, 1H); 7,59(m, 2H); 7,47 (d, *J*=15,9 Hz, 1H); 7,40 (m, 1H); 7,26 (m, 1H); 7,19 (m, 1H); 7,01 (m, 2H);
6,62 (dd, *J*=7,7 Hz, *J*=15,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,6; 162,6; 159,2; 158,4; 151,8; 130,7; 130,5; 129,7; 127,9; 122,8; 120,8 (q); 119,0.

Trans-3-(4-(3-nitrophenoxy)phenyl)acrylaldehyde. (**1n**)

Obtained from 1-(4-iodophenoxy)-3-nitrobenzene and acrolein as light brown crystals (54 %).

^{1}H ($CDCl_3$) δ (ppm): 9,70 (d, *J*=7,6 Hz, 1H); 8,49(m, 1H); 8,30 (m, 1H); 8,23 (m, 2H); 8,02 (m, 1H); 7,97 (m, 1H); 7,86 (m, 1H); 7,47 (d, *J*=15,9 Hz, 1H); 7,01 (m, 2H);
6,68 (dd, *J*=7,7 Hz, *J*=15,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,8; 159,1; 158,5; 157,1; 153,4; 151,9; 130,74; 130,70; 129,3; 125,2; 123,5; 119,5.

5.2 General protocol for the synthesis of decalone derivatives. Type 3 compounds

Dimethyl 1,3-acetonedicarboxylate (2 mmol) and an α-β-unsaturated aldehyde (1 mmol) were dissolved in 25 mL of acetone and stirred at room temperature for 10 minutes. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2,5 mmol), dissolved in 10 mL of acetone was then added dropwise to the solution and the resulting solution stirred at reflux. The reaction was monitored using TLC (Acetone) which showed completion after 12-24 hours, depending on the aldehyde. After completion, acetone was removed under reduced pressure and the resulting yellow oil dissolved in CH_2Cl_2. The organic phase was succesively washed with 1 M H_2SO_4 (twice), H_2O (twice) and lastly dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure. The pure product was obtained after crystallization from methanol.

Trimethyl 2,5-dihydroxy-7-(4-hydroxyphenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3a**)

Obtained from **1a** and dimethyl 1,3-acetonedicarboxylate as orange crystals (78 %).

^{1}H (Acetone d-6) δ (ppm): 15,99 (s, 1H); 14,76 (s, 1H); 8,30 (s, 1H); 7,12(m, 2H) 6,80 (m, 2H); 3,93 (s, 3H); 3,78 (s, 3H); 3,72 (dd, *J*=2,1 Hz, *J*=11,6 Hz, 1H); 3,55 (s, 3H); 3,31 (ddd, *J*=2,3 Hz, *J*=5,3 Hz, *J*=13,1 Hz, 1H); 3,26 (m, 1H); 3,19 (dt, *J*=3,3 Hz , *J*=11,9 Hz, 1H); 1,84 (dt, *J*=2,3 Hz, *J*=5,0 Hz, *J*=12,1 Hz, 1H).

^{13}C (Acetone d-6) δ (ppm): 187,0; 185,3; 171,2; 169,7; 157,4; 157,3; 133,6; 129,0; 116,4; 116,3; 56,2; 55,9; 53,1; 52,9; 52,3; 42,5.

Trimethyl 2,5-dihydroxy-7-(4-chlorophenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3b**)

Obtained from **1b** and dimethyl 1,3-acetonedicarboxylate as yellow crystals (55 %).

^{1}H ($CDCl_3$) δ (ppm): 15,65 (s, 1H); 14,87 (s, 1H); 7,30 (m, 2H); 7,12 (m, 2H); 3,96 (s, 3H); 3,79 (s, 3H); 3,61 (dd, *J*=2,6 Hz, *J*=11,1 Hz, 1H); 3,60 (s, 3H); 3,35 (ddd, *J*=2,2 Hz, *J*=4,4 Hz, *J*=10,8 Hz, 1H); 3,26 (m,1H); 1,96 (ddd, *J*=2,7 Hz, *J*=4,2 Hz, *J*=12,6 Hz, 1H); 1,62 (dt, *J*=10,9 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,1; 184,5; 172,6; 172,0; 168,8; 139,8; 133,4; 129,2; 128,4; 103,3; 102,9; 54,8; 53,4; 53,3; 52,9; 52,6; 41,6; 34,5; 34,1.

Trimethyl 2,5-dihydroxy-7-(3,5-dichlorophenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3c**)

Obtained from **1c** and dimethyl 1,3-acetonedicarboxylate as white crystals (67 %).

^{1}H ($CDCl_3$) δ (ppm): 15,62 (s, 1H); 14,89 (s, 1H); 7,27 (m, 1H); 7,07 (m, 2H); 3,96 (s, 3H); 3,81 (s, 3H); 3,64 (s, 3H); 3,59 (dd, *J*=2,2 Hz, *J*=11,6 Hz, 1H); 3,34 (ddd, *J*=2,2 Hz, *J*=4,4 Hz, *J*=10,9 Hz, 1H); 3,25 (m, 1H); 1,96 (ddd, *J*=2,7 Hz, *J*=4,5 Hz, *J*=12,7 Hz, 1H); 1,61 (dt, *J*=11,0 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,0; 184,4; 172,1; 171,9; 170,1; 168,7; 144,6; 135,5; 127,9; 125,7; 103,2; 102,8; 54,5; 53,3; 53,2; 53,0; 52,7; 41,7; 34,0; 33,9.

Trimethyl 2,5-dihydroxy-7-(2-hydroxyphenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3d**)

Obtained from **1d** and dimethyl 1,3-acetonedicarboxylate as yellow crystals (70 %).

^{1}H ($CDCl_3$) δ (ppm): 15,67 (s, 1H); 14,86 (s, 1H); 8,30 (s, 1H); 7,37 (m, 1H); 7,27 (m, 2H); 7,19 (m, 1H); 3,97 (s, 3H); 3,79 (s, 3H); 3,61 (s, 3H); 3,59 (dd, *J*=2,3 Hz, *J*=11,5 Hz, 1H); 3,41 (ddd, *J*=2,2 Hz, *J*=4,5 Hz, *J*=11,1 Hz, 1H); 3,38 (m,1H); 2,43 (ddd, *J*=2,6 Hz, *J*=4,5 Hz, *J*=12,6 Hz, 1H); 1,90 (dt, *J*=10,9 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,1; 184,5; 173,0; 172,0; 170,1; 168,8; 138,3; 133,7; 130,3; 130,4; 128,6; 127,5; 103,5; 102,8; 53,5; 53,2; 52,9; 52,5; 34,1.

Trimethyl 2,5-dihydroxy-7-(2-chlorophenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3e**)

Obtained from **1e** and dimethyl 1,3-acetonedicarboxylate as yellow crystals (84 %).

^{1}H ($CDCl_3$) δ (ppm): 15,67 (s, 1H); 14,86 (s, 1H); 7,37 (m, 1H); 7,26 (m, 2H); 7,19 (m, 1H); 3,96 (s, 3H); 3,79 (s, 3H); 3,61 (s, 3H); 3,60 (dd, *J*=2,3 Hz, *J*=11,5 Hz, 1H); 3,41 (ddd, *J*=2,2 Hz, *J*=4,5 Hz, *J*=11,1 Hz, 1H); 3,38 (m,1H); 2,43 (ddd, *J*=2,6 Hz, *J*=4,5 Hz, *J*=12,6 Hz, 1H); 1,90 (dt, *J*=10,9 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,1; 184,5; 172,9; 172,0; 170,1; 168,8; 138,3; 133,7; 130,3; 130,4; 128,6; 127,5; 103,5; 102,8; 53,5; 53,2; 52,9; 52,5; 34,1.

Trimethyl 2,5-dihydroxy-7-(4-methoxyphenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3f**)

Obtained from **1f** and dimethyl 1,3-acetonedicarboxylate as yellow crystals (90 %).

^{1}H ($CDCl_3$) δ (ppm): 15,64 (s, 1H); 14,85 (s, 1H); 7,10 (m, 2H); 6,85 (m, 2H); 3,96 (s, 3H); 3,79 (s, 3H); 3,78 (s, 3H); 3,62 (dd, *J*=2,2 Hz, *J*=11,8 Hz, 1H); 3,59 (s, 3H); 3,34 (ddd, *J*=2,2 Hz, *J*=4,4 Hz, *J*=10,9 Hz, 1H); 3,22 (m, 1H); 1,97 (ddd, *J*=2,7 Hz, *J*=4,3 Hz, *J*=12,7 Hz, 1H); 1,62 (dt, *J*=11,0 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 188,1; 184,5; 173,0; 172,0; 170,7; 168,9; 158,9; 133,3; 128,0; 114,3; 103,4; 102,8; 55,3; 55,2; 53,5; 53,2; 52,8; 52,4; 41,4; 34,8; 34,2.

Trimethyl 2,5-dihydroxy-7-(4-fluorophenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3g**)

Obtained from **1g** and dimethyl 1,3-acetonedicarboxylate as yellow crystals (90 %).

^{1}H ($CDCl_3$) δ (ppm): 15,65 (s, 1H); 14,89 (s, 1H); 7,15 (m, 2H); 7,01 (m, 2H); 3,96 (s, 3H); 3,79 (s, 3H); 3,62 (dd, *J*=2,2 Hz, *J*=11,8 Hz, 1H); 3,59 (s, 3H); 3,35 (ddd, *J*=2,2 Hz, *J*=4,4 Hz, *J*=10,9 Hz, 1H); 3,27 (m, 1H); 1,97 (ddd, *J*=2,7 Hz, *J*=4,3 Hz, *J*=12,7 Hz, 1H); 1,62 (dt, *J*=11,0 Hz, *J*=12,8 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,0; 184,5; 172,7; 172,0; 170,5; 168,9; 163,3; 137,0; 115,9 (d); 103,3; 102,8; 53,4; 53,2; 52,9; 52,5; 41,5; 34,6; 34,1.

Trimethyl 2,5-dihydroxy-7-(3-trifluromethylphenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3h**)

Obtained from **1h** and dimethyl 1,3-acetonedicarboxylate as white crystals (92 %).

^{1}H ($CDCl_3$) δ (ppm): 15,67 (s, 1H); 14,89 (s, 1H); 7,46 (m, 5H); 3,97 (s, 3H); 3,80 (s, 3H); 3,65 (dd, *J*=2,2 Hz, *J*=11,6 Hz, 1H); 3,59 (s, 3H); 3,36 (m, 1H); 2,00 (ddd, *J*=2,7 Hz, *J*=4,4 Hz, *J*=12,7 Hz, 1H); 1,62 (dt, *J*=10,9 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,0; 184,5; 172,4; 172,0; 170,3; 168,8; 142,2; 131,5; 131,1; 130,4; 129,5; 124,6 (q); 122,6; 103,3; 102,8; 54,7; 53,4; 53,2; 52,9; 52,5; 42,0; 34,1; 34,0.

Trimethyl 2,5-dihydroxy-7-(3,5-bis(trifluoromethyl)phenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3i**)

Obtained from **1i** and dimethyl 1,3-acetonedicarboxylate as yellow crystals (36 %).

^{1}H ($CDCl_3$) δ (ppm): 15,68 (s, 1H); 14,93 (s, 1H); 7,80 (m, 1H); 7,64 (m, 2H); 3,97 (s, 3H); 3,82 (s, 3H); 3,64 (dd, *J*=2,2 Hz, *J*=11,7 Hz, 1H); 3,61 (s, 3H); 3,40 (ddd, *J*=2,2 Hz, *J*=4,5 Hz, *J*=10,8 Hz, 1H); 3,24 (m, 1H); 2,02 (ddd, *J*=2,7 Hz, *J*=4,4 Hz, *J*=12,6 Hz, 1H); 1,72 (dt, *J*=10,7 Hz, *J*=12,8 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 185,9; 184,4; 171,9; 171,8; 169,9; 168,6; 143,9; 132,5; 132,2; 127,4; 124,4; 121,8 (m); 103,2; 102,8; 54,5; 53,24; 53,23; 53,0; 52,7; 41,9; 33,9; 33,8.

Trimethyl 2,5-dihydroxy-7-(naphthalen-1-yl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3j**).

Obtained from **1j** and dimethyl 1,3-acetonedicarboxylate as white crystals (83 %).

^{1}H ($CDCl_3$) δ (ppm): 15,72 (s, 1H); 14,88 (s, 1H); 8,05 (m, 1H); 7,87 (m, 1H); 7,77 (m, 1H); 7,51 (m, 4H); 3,98 (s, 3H); 3,76 (dd, *J*=2,2 Hz, *J*=11,6 Hz, 1H); 3,72 (s, 3H); 3,46 (m, 1H); 3,45 (s, 3H); 2,11 (ddd, *J*=2,6 Hz, *J*=3,8 Hz, *J*=13,3 Hz, 1H); 1,67 (dt, *J*=11,0 Hz, *J*=13,0 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,1; 184,6; 173,5; 172,1; 168,8; 137,5; 134,0; 131,1; 129,4; 129,3; 128,9; 128,0; 124,6; 126,5; 125,8; 125,5; 123,0; 122,5; 103,4; 102,7; 54,3; 53,5; 53,3; 52,8; 52,4; 35,8; 34,5.

Trimethyl 2,5-dihydroxy-7-(4-(*p*-tolyloxy)phenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3k**)

Obtained from **1k** and dimethyl 1,3-acetonedicarboxylate as orange crystals (45 %).

^{1}H ($CDCl_3$) δ (ppm): 15,65 (s, 1H); 14,86 (s, 1H); 7,12 (m, 4H); 6,91 (m, 4H); 3,96 (s, 3H); 3,80 (s, 3H); 3,62 (dd, *J*=2,2 Hz, *J*=11,6 Hz, 1H); 3,61 (s, 3H); 3,35 (ddd, *J*=2,2 Hz, *J*=4,4 Hz, *J*=10,9 Hz, 1H); 3,25 (m, 1H); 1,99 (ddd, *J*=2,7 Hz, *J*=4,2 Hz, *J*=12,7 Hz, 1H); 1,63 (dt, *J*=10,9 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,0; 184,5; 172,9; 172,0; 170,5; 168,8; 157,2; 154,4; 135,5; 133,3; 130,4; 128,2; 119,4; 118,5; 103,3; 102,7; 55,2; 53,5; 53,1; 52,8; 52,5; 41,4; 34,6; 34,2; 20,7.

Trimethyl 2,5-dihydroxy-7-(4-(4-chlorophenoxy)phenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3l**)

Obtained from **1l** and dimethyl 1,3-acetonedicarboxylate as white crystals (90 %).

^{1}H ($CDCl_3$) δ (ppm): 15,65 (s, 1H); 14,87 (s, 1H); 7,29 (m, 2H); 7,14 (m, 2H); 6,93 (m, 4H); 3,96 (s, 3H); 3,80 (s, 3H); 3,62 (dd, *J*=2,2 Hz, *J*=11,6 Hz, 1H); 3,61 (s, 3H); 3,36 (ddd, *J*=2,2 Hz, *J*=4,4 Hz, *J*=10,9 Hz, 1H); 3,27 (m, 1H); 1,99 (ddd, *J*=2,7 Hz, *J*=4,4 Hz, *J*=12,7 Hz, 1H); 1,64 (dt, *J*=10,9 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,0; 184,5; 172,7; 172,0; 170,5; 168,9; 156,4; 155,6; 136,4; 129,8; 128,6; 128,4; 120,3; 119,1; 103,3; 102,8; 55,1; 53,5; 53,2; 52,9; 52,5; 41,5; 34,6; 34,1.

Trimethyl 2,5-dihydroxy-7-(4-(3-(trifluoromethyl)phenoxy)phenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3m**)

Obtained from **1m** and dimethyl 1,3-acetonedicarboxylate as yellow crystals (32 %).

^{1}H ($CDCl_3$) δ (ppm): 15,66 (s, 1H); 14,87 (s, 1H); 7,40 (m, 2H); 7,18 (m, 4H); 6,98 (m, 2H); 3,97 (s, 3H); 3,80 (s, 3H); 3,64 (dd, *J*=2,2 Hz, *J*=11,6 Hz, 1H); 3,62 (s, 3H); 3,37 (ddd, *J*=2,2 Hz, *J*=4,4 Hz, *J*=10,9 Hz, 1H); 3,29 (m, 1H); 1,99 (ddd, *J*=2,7 Hz, *J*=4,4 Hz, *J*=12,7 Hz, 1H); 1,66 (dt, *J*=10,9 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,0; 184,5; 172,7; 172,0; 170,6; 168,9; 157,6; 155,6; 137,0; 130,4; 128,7; 121,8; 119,9; 119,7; 115,3 (m); 103,4; 102,7; 55,1; 53,5; 53,2; 52,9; 52,4; 41,5; 34,6; 34,1.

Trimethyl 2,5-dihydroxy-7-(4-(3-nitrophenoxy)phenyl)-4-oxo-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3n**)

Obtained from **1n** and dimethyl 1,3-acetonedicarboxylate as red crystals (49 %).

^{1}H ($CDCl_3$) δ (ppm): 15,66 (s, 1H); 14,88 (s, 1H); 8,51 (m, 1H); 8,20 (m, 2H); 7,97 (m, 1H); 7,22 (m, 2H); 7,01 (m, 2H); 3,97 (s, 3H); 3,82 (s, 3H); 3,65 (dd, *J*=2,2 Hz, *J*=11,6 Hz, 1H); 3,63 (s, 3H); 3,35 (ddd, *J*=2,4 Hz, *J*=4,5 Hz, *J*=11,0 Hz, 1H); 3,29 (m, 1H); 2,03 (ddd, *J*=2,6 Hz, *J*=4,4 Hz, *J*=12,7 Hz, 1H); 1,67 (dt, *J*=10,9 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 185,9; 184,6; 172,9; 172,0; 170,5; 168,8; 158,3; 154,8; 140,4; 137,8; 133,1; 130,5; 130,3; 129,9; 128,3; 124,5; 123,4; 120,5; 117,3; 115,4; 113,4; 102,7; 55,1; 53,5; 53,2; 52,9; 52,4; 41,6; 34,5; 34,1.

Trimethyl 2,5-dihydroxy-4-oxo-7-phenyl-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3o**)

Obtained from cinnamaldehyde and dimethyl 1,3-acetonedicarboxylate as white crystals (79 %).

^{1}H ($CDCl_3$) δ (ppm): 15,65 (s, 1H); 14,86 (s, 1H); 7,25 (m, 5H); 7,01 (m, 2H); 3,96 (s, 3H); 3,78 (s, 3H); 3,67 (dd, *J*=2,2 Hz, *J*=11,6 Hz, 1H); 3,58 (s, 3H); 3,36 (ddd, *J*=2,2 Hz, *J*=4,5 Hz, *J*=10,9 Hz, 1H); 3,28 (m, 1H); 2,00 (ddd, *J*=2,7 Hz, *J*=4,4 Hz, *J*=12,7 Hz, 1H); 1,67 (dt, *J*=10,8 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,0; 184,6; 173,0; 172,0; 170,6; 168,9; 141,3; 129,0; 127,5; 127,0; 103,5; 102,8; 55,0; 53,5; 53,2; 52,9; 52,5; 42,1; 34,6; 34,2.

Trimethyl 2,5-dihydroxy-4-oxo-7-(2-methoxyphenyl)-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate. (**3p**)

Obtained from 2-methoxycinnamaldehyde and dimethyl 1,3-acetonedicarboxylate as yellow crystals (84 %).

^{1}H ($CDCl_3$) δ (ppm): 15,67 (s, 1H); 14,82 (s, 1H); 7,23 (m, 1H); 7,11 (m, 1H); 6,89 (m, 2H); 4,02 (dd, *J*=2,1 Hz, *J*=11,6 Hz, 1H); 3,96 (s, 3H); 3,82 (s, 3H); 3,77 (s, 3H); 3,56 (s, 3H); 3,32 (m, 1H); 3,28 (m, 1H); 1,89 (m, 2H).

^{13}C ($CDCl_3$) δ (ppm): 186,0; 184,6; 173,6; 172,1; 170,9; 169,0; 157,4; 128,7; 128,5; 120,8; 111,1; 103,6; 102,8; 55,3; 53,5; 53,1; 52,8; 52,7; 52,2;; 34,2; 32,8.

Trimethyl 2,5-dihydroxy-4-oxo-7-(furan-3-yl)-1,4,6,7,8,8a-hexahydronaphthalene-1,3,6-tricarboxylate (**3q**)

Obtained from 3-furylacrylaldehyde and dimethyl 1,3-acetonedicarboxylate as yellow crystals (56 %).

^{1}H ($CDCl_3$) δ (ppm): 15,64 (s, 1H); 14,86 (s, 1H); 7,33 (m, 1H); 6,28 (m, 1H); 6,00 (m, 1H); 3,95 (s, 3H); 3,83 (s, 3H); 3,71 (dd, *J*=2,2 Hz, *J*=11,4 Hz, 1H); 3,71 (s, 3H); 3,45 (m, 1H); 3,33 (ddd, *J*=2,2 Hz, *J*=4,5 Hz, *J*=11,0 Hz, 1H); 2,15 (ddd, *J*=2,8 Hz, *J*=4,5 Hz, *J*=12,8 Hz, 1H); 1,59 (dt, *J*=10,9 Hz, *J*=12,9 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 186,1; 184,5; 172,2; 172,0; 170,6; 168,9; 154,1; 142,2; 110,3; 105,7; 103,4; 102,7; 53,4; 53,2; 52,9; 52,7; 52,3; 35,8; 33,5; 32,1.

5.3 General protocol for the synthesis of 1-tetralone derivatives. Type 4 compounds

A decalone derivative of type **3** (1 mmol) and iodine crystals (3 mmol) were dissolved in 25 mL of methanol and stirred at reflux. The reaction was monitored using TLC (Acetone) which showed completion after 20-24 hours. After completion of the reaction, methanol was removed under reduced pressure and the resulting crude dissolved in CH_2Cl_2. The organic phase was then washed with saturated Na_2SO_3 (once), H_2O (once), saturated NaCl (once) and lastly dried over anhydrous magnesium sulfate. The solvent was then removed under reduced pressure. The pure product was obtained after crystallization from methanol.

Trimethyl 2,4-dihydroxy-5-oxo-7-(4-hydroxyphenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4a**)

Obtained from **3a** as yellow crystals (87 %).

^{1}H (Acetone d-6) δ (ppm): 14,14 (s, 1H); 12,81 (s, 1H); 8,39 (s, 1H); 7,23 (m, 2H); 6,82 (m, 2H); 4,27 (dd, *J*=1,8 Hz, *J*=12,8 Hz, 1H); 3,96 (s, 3H); 3,85 (s, 3H); 3,61 (dt, *J*=4,5 Hz, *J*=12,1 Hz, 1H); 3,55 (s, 3H); 3,24 (dq, *J*=8,2 Hz, *J*=17,5 Hz, 2H).

^{13}C (Acetone d-6) δ (ppm): 200,7; 170,0; 169,6; 167,9; 167,7; 166,8; 157,7; 157,6; 150,7; 132,5; 129,4; 116,2; 116,1; 104,1; 61,3; 53,2; 52,9; 52,3; 43,3; 36,2.

Trimethyl 2,4-dihydroxy-5-oxo-7-(4-chlorophenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4b**)

Obtained from **3b** as white crystals (93 %).

^{1}H ($CDCl_3$) δ (ppm): 14,23 (s, 1H); 13,10 (s, 1H); 7,32 (m, 2H); 7,20 (m, 2H); 4,01 (s, 3H); 3,90 (dd, *J*=1,2 Hz, *J*=12,4 Hz, 1H); 3,88 (s, 3H); 3,67 (dt, *J*=4,5 Hz, *J*=12,1 Hz, 1H); 3,62 (s, 3H); 3,14 (dq, *J*=8,1 Hz, *J*=17,6 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 197,7; 170,0; 168,6; 167,7; 167,1; 166,9; 148,3; 138,4; 133,8; 129,3; 128,6; 113,3; 109,0; 102,1; 60,2; 53,2; 52,9; 52,6; 42,3; 34,8.

Trimethyl 2,4-dihydroxy-5-oxo-7-(3,5-dichlorophenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4c**)

Obtained from **3c** as yellow crystals (96 %).

^{1}H ($CDCl_3$) δ (ppm): 14,14 (s, 1H); 13,11 (s, 1H); 7,29 (m, 1H); 7,16 (m, 2H); 4,00 (s, 3H); 3,91 (dd, *J*=1,2 Hz, *J*=12,4 Hz, 1H); 3,89 (s, 3H); 3,66 (s, 3H); 3,62 (dt, *J*=4,5 Hz, *J*=12,1 Hz, 1H); 3,12 (dq, *J*=8,2 Hz, *J*=17,5 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 191,2; 170,0; 168,3; 167,6; 167,1; 166,8; 147,8; 143,3; 135,6; 128,3; 125,9; 113,2; 108,9; 102,1; 59,7; 53,2; 52,9; 52,7; 42,3; 34,4.

Trimethyl 2,4-dihydroxy-5-oxo-7-(2-hydroxyphenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4d**)

Obtained from **3d** as brown crystals (75 %)

^{1}H ($CDCl_3$) δ (ppm): 14,31 (s, 1H); 13,30 (s, 1H); 8,34 (s,1H): 7,61 (m, 1H); 7,33 (m, 3H); 4,04 (s, 3H); 3,94 (dd, *J*=1,2 Hz, *J*=12,4 Hz, 1H); 3,90 (s, 3H); 3,65 (s, 3H); 3,61 (dt, *J*=4,5 Hz, *J*=12,1 Hz, 1H); 3,10 (dq, *J*=8,1 Hz, *J*=17,5 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 195,3; 172,7; 170,8; 168,9; 167,1; 166,7; 160,4; 148,5; 143,5; 131,9; 130,8; 124,2; 123,9; 113,7; 105,1; 102,1; 54,7; 52,5; 51,9; 51,7; 48,7; 34,6.

Trimethyl 2,4-dihydroxy-5-oxo-7-(2-chlorophenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4e**)

Obtained from **3e** as yellow crystals (72 %)

^{1}H ($CDCl_3$) δ (ppm): 14,19 (s, 1H); 13,06 (s, 1H); 7,38 (m, 1H); 7,26 (m, 3H); 4,25 (dt, *J*=4,3 Hz, *J*=11,8 Hz, 1H); 3,98 (s, 3H); 3,87 (dd, *J*=1,3 Hz, *J*=12,6 Hz, 1H); 3,85 (s, 3H); 3,61 (s, 3H); 3,02 (dq, *J*=8,1 Hz, *J*=17,7 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 197,8; 169,8; 168,4; 167,5; 167,1, 166,8; 148,3; 137,1; 133,9; 130,5; 128,9; 127,4; 127,1; 112,9; 108,9; 102,1; 58,6; 53,1; 52,7; 52,6; 38,8; 33,5.

Trimethyl 2,4-dihydroxy-5-oxo-7-(4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4f**)

Obtained from **3f** as yellow crystals (81 %)

^{1}H ($CDCl_3$) δ (ppm): 14,27 (s, 1H); 13,07 (s, 1H); 7,17 (m, 2H); 6,86 (m, 2H); 3,99 (s, 3H); 3,90 (dd, *J*=1,4 Hz, *J*=12,5 Hz, 1H); 3,86 (s, 3H); 3,79 (s, 3H); 3,61 (dt, *J*=4,6 Hz, *J*=12,5 Hz, 1H); 3,59 (s, 3H); 3,13 (dq, *J*=8,1 Hz, *J*=17,6 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 198,1; 169,9; 168,7; 167,5; 166,8; 166,7; 158,9; 148,7; 131,8; 128,1; 114,2; 113,0; 108,9; 101,7; 60,5; 55,1; 52,9; 52,6; 52,3; 42,0; 35,0.

Trimethyl 2,4-dihydroxy-5-oxo-7-(4-fluorophenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4g**)

Obtained from **3g** as yellow crystals (79 %)

^{1}H ($CDCl_3$) δ (ppm): 14,24 (s, 1H); 13,10 (s, 1H); 7,23 (m, 2H); 7,04 (m, 2H); 4,00 (s, 3H); 3,90 (dd, *J*=2,8 Hz, *J*=12,5 Hz, 1H); 3,88 (s, 3H); 3,79 (s, 3H); 3,67 (dt, *J*=4,5 Hz, *J*=12,0 Hz, 1H); 3,61 (s, 3H); 3,14(dq, *J*=8,1 Hz, *J*=17,6 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 197,6; 170,1; 168,7; 167,5; 166,9; 166,8; 163,3; 160,9; 148,3; 138,7; 138,5; 135,6; 129,9; 128,7; 120,7; 112,9; 108,9; 101,9; 60,4; 53,1; 52,8; 52,5; 42,1; 34,9.

Trimethyl 2,4-dihydroxy-5-oxo-7-(3-trifluoromethylphenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4h**)

Obtained from **3h** as yellow crystals (77 %)

^{1}H ($CDCl_3$) δ (ppm): 14,21 (s, 1H); 13,12 (s, 1H); 7,52 (m, 4H); 4,01 (s, 3H); 3,96 (dd, *J*=1,2 Hz, *J*=12,4 Hz, 1H); 3,88 (s, 3H); 3,75 (dt, *J*=4,5 Hz, *J*=12,1 Hz, 1H); 3,60 (s, 3H); 3,19 (dq, *J*=8,2 Hz, *J*=17,6 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 197,4; 170,0; 168,3; 167,6; 167,0; 166,8; 148,0; 140,8; 135,6; 130,3; 129,6; 128,3; 124,8 (q); 113,2; 108,9; 102,0; 99,9; 60,0; 53,1; 52,8; 52,5; 42,6; 34,6.

Trimethyl 2,4-dihydroxy-5-oxo-7-(naphthalen-1-yl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4j**)

Obtained from **3j** as light brown crystals (86 %).

^{1}H ($CDCl_3$) δ (ppm): 14,30 (s, 1H); 13,11 (s, 1H); 8,10 (m, 1H); 7,89 (m, 1H); 7,79 (m, 1H); 7,54 (m, 2H); 7,43 (m, 2H); 4,65 (dt, *J*=4,1 Hz, *J*=11,2 Hz, 1H); 4,00 (s, 3H); 3,80 (s, 3H); 3,55 (s, 3H); 3,42 (dd, *J*=4,2 Hz, *J*=17,9 Hz, 1H); 3,41 (dq, *J*=8,2 Hz, *J*=17,9 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 198,3; 170,1; 168,8; 167,6; 168,97; 168,95; 148,8; 136,2; 134,2; 131,0; 129,2; 128,4; 128,8; 128,1; 125,4; 123,3; 122,5; 113,1; 109,2; 102,3; 59,9; 53,15; 52,8; 52,6; 37,2; 35,0.

Trimethyl 2,4-dihydroxy-5-oxo-7-(4-(*p*-tolyloxy)phenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4k**)

Obtained from **3l** as greenish crystals (82 %).

^{1}H ($CDCl_3$) δ (ppm): 14,29 (s, 1H); 13,09 (s, 1H); 7,19 (m, 2H); 7,14 (m, 2H); 6,94 (m, 2H); 6,91 (m, 2H); 4,01 (s, 3H); 3,91 (dd, *J*=4,2 Hz, *J*=12,4 Hz, 1H); 3,89 (s, 3H); 3,66 (dt, *J*=4,2 Hz, *J*=12,0 Hz, 1H); 3,63 (s, 3H); 3,16 (dq, *J*=8,1 Hz, *J*=17,6 Hz, 2H); 2,34 (s, 3H).

^{13}C ($CDCl_3$) δ (ppm): 198,1; 170,2; 168,8; 167,7; 167,0; 166,9; 157,6; 154,2; 148,7; 134,1; 133,4; 130,4; 128,4; 119,4; 118,4; 113,3; 109,1; 101,9; 60,6; 53,1; 52,8; 52,5; 42,2; 35,0; 20,8.

Trimethyl 2,4-dihydroxy-5-oxo-7-(4-(4-chlorophenoxy)phenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4l**)

Obtained from **3l** as white crystals (92 %).

^{1}H ($CDCl_3$) δ (ppm): 14,28 (s, 1H); 13,10 (s, 1H); 7,30 (m, 2H); 7,22 (m, 2H); 6,96 (m, 2H); 6,94 (m, 2H); 4,02 (s, 3H); 3,91 (dd, *J*=4,2 Hz, *J*=12,4 Hz, 1H); 3,89 (s, 3H); 3,69 (dt, *J*=4,3 Hz, *J*=11,9 Hz, 1H); 3,64 (s, 3H); 3,17 (dq, *J*=8,0 Hz, *J*=17,6 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 197,8; 170,2; 168,7; 167,7; 167,0; 166,9; 156,7; 155,5; 148,6; 135,0; 129,9; 128,8; 128,7; 120,5; 119,0; 113,4; 109,1; 101,9; 60,6; 53,2; 52,8; 52,5; 42,2; 34,9.

Trimethyl 2,4-dihydroxy-5-oxo-7-(4-(3-(trifluoromethyl)phenoxy)phenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4m**)

Obtained from **3m** as yellow crystals (85 %).

^{1}H ($CDCl_3$) δ (ppm): 14,27 (s, 1H); 13,11 (s, 1H); 7,46 (m, 1H); 7,37 (m, 1H); 7,27 (m, 2H); 7,22 (m, 1H); 7,17 (m, 1H); 7,00 (m, 2H); 4,02 (s, 3H); 3,92 (dd, *J*=4,2 Hz, *J*=12,4 Hz, 1H); 3,90 (s, 3H); 3,70 (dt, *J*=4,4 Hz, *J*=11,9 Hz, 1H); 3,63 (s, 3H); 3,18 (dq, *J*=8,1 Hz, *J*=17,6 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 197,9; 170,1; 168,8; 167,8; 167,0; 166,9; 157,4; 155,9; 148,5; 135,6; 132,2; 130,5; 128,8; 125,1; 121,9; 120,1 (q); 119,7; 119,0; 113,4; 109,1; 101,9; 60,6; 53,2; 52,9; 52,5; 42,3; 34,9.

Trimethyl 2,4-dihydroxy-5-oxo-7-(4-(3-nitrophenoxy)phenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4n**)

Obtained from **3n** as brown crystals (79 %).

^{1}H ($CDCl_3$) δ (ppm): 14,25 (s, 1H); 13,10 (s, 1H); 8,49 (m, 1H); 8,27 (m, 2H); 7,97 (m, 1H); 7,30 (m, 2H); 7,03 (m, 2H); 4,00 (s, 3H); 3,92 (dd, *J*=4,2 Hz, *J*=12,4 Hz, 1H); 3,89 (s, 3H); 3,70 (dt, *J*=4,4 Hz, *J*=11,9 Hz, 1H); 3,64 (s, 3H); 3,20 (dq, *J*=8,1 Hz, *J*=17,6 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 197,8; 170,1; 168,8; 167,7; 167,0; 166,8; 158,2; 155,2; 149,3; 149,0; 148,5; 136,4; 133,1; 130,6; 129,1; 128,9; 124,5; 123,3; 120,1; 118,1; 115,9; 60,5; 53,2; 52,9; 52,6; 42,3; 34,8.

Trimethyl 2,4-dihydroxy-5-oxo-7-phenyl-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4o**)

Obtained from **3o** as pale yellow crystals (88 %)

^{1}H ($CDCl_3$) δ (ppm): 14,29 (s, 1H); 13,10 (s, 1H); 7,32 (m, 5H); 4,02 (s, 3H); 3,96 (dd, *J*=4,2 Hz, *J*=12,4 Hz, 1H); 3,88 (s, 3H); 3,70 (dt, *J*=4,7 Hz, *J*=11,9 Hz, 1H); 3,60 (s, 3H); 3,19 (dq, *J*=8,1 Hz, *J*=17,7 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 198,0; 170,1; 168,7; 167,7; 166,9; 148,7; 139,9; 129,0; 127,9; 127,1; 113,3; 109,1; 101,9; 60,4; 53,1; 52,8; 52,4; 42,8; 34,9.

Trimethyl 2,4-dihydroxy-5-oxo-7-(2-methoxyphenyl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4p**)

Obtained from **3p** as yellow crystals (84 %).

^{1}H ($CDCl_3$) δ (ppm): 14,38 (s, 1H); 13,05 (s, 1H); 7,25 (m, 1H); 7,11 (m, 1H); 6,90 (m, 2H); 4,00 (s, 3H); 3,92 (dt, *J*=4,2 Hz, *J*=11,7 Hz, 1H) 3,87 (s, 3H); 3,86 (dd, *J*=4,2 Hz, *J*=12,4 Hz, 1H 3,85 (s, 3H); 3,58 (s, 3H); 3,37 (dq, *J*=8,1 Hz, *J*=17,5 Hz, 2H)

^{13}C ($CDCl_3$) δ (ppm): 199,1; 170,2; 168,2; 167,8; 167,2; 166,6; 162,6; 157,7; 149,9; 129,0; 127,7; 121,0; 113,3; 111,4; 109,2; 101,7; 58,1; 55,4; 53,0; 52,9; 52,6; 39,6; 32,7.

Trimethyl 2,4-dihydroxy-5-oxo-7-(furan-3-yl)-5,6,7,8-tetrahydronaphthalene-1,3,6-tricarboxylate. (**4q**)

Obtained from **3q** as yellow crystals (89 %).

^{1}H ($CDCl_3$) δ (ppm): 14,28 (s, 1H); 13,08 (s, 1H); 7,34 (m, 1H); 6,28 (m, 1H); 6,10 (m, 1H); 4,00 (s, 3H); 3,93 (dd, *J*=4,2 Hz, *J*=12,4 Hz, 1H); 3,93 (s, 3H); 3,67 (dt, *J*=4,7 Hz, *J*=9,7 Hz, 1H); 3,74 (s, 3H); 3,27 (dq, *J*=8,2 Hz, *J*=17,6 Hz, 2H).

^{13}C ($CDCl_3$) δ (ppm): 197,2; 170,0; 168,7; 167,7; 167,0; 166,9; 153,0; 148,1; 142,5; 113,2; 110,4; 109,2; 106,7; 102,1; 57,7; 53,1; 52,9; 52,8; 36,2; 31,3.

5.4 General protocol for arylation of 4-iodophenol and *p*-hydroxycinnamaldehyde. Chan-Lam cross coupling

4-iodophenol (or *p*-hydroxycinnamaldehyde) (1 mmol), an aryl boronic acid derivative (1 mmol) and dry copper(II) acetate (1 mmol), were stirred with a few 4 Å molecular sieves in ca. 15 mL of CH_2Cl_2 at room temperature for 15 minutes. Triethylamine (3 mmol), dissolved in 5 mL of CH_2Cl_2, was then added and the resulting solution stirred at room temperature for 48-72 hours. The progress of the reaction was monitored by TLC (Acetone). After completion of the reaction, the molecular sieves were removed and most of the solvent removed under reduced pressure. The crude mixture was then submitted to column chromatography (EtOAc/Petroleum ether (1:9)) after preabsorbtion to silica gel for isolation and purification.

1-iodo-4-(*p*-tolyloxy)benzene.

Obtained from 4-iodophenol and *p*-tolylboronic acid as clear, white crystals (90 %).

^{1}H ($CDCl_3$) δ (ppm): 7,58 (m, 2H); 7,51 (m, 2H); 6,74 (m, 2H); 6,63 (m, 2H); 2,18 (s, 3H).

^{13}C ($CDCl_3$) δ (ppm): 158,0; 155,6; 138,6; 138,5; 130,4; 120,4; 119,4; 117,9; 20,8.

1-chloro-4-(4-iodophenoxy)benzene.

Obtained from 4-iodophenol and 4-chlorophenylboronic acid as clear crystals (85 %).

^{1}H ($CDCl_3$) δ (ppm): 7,62 (m, 2H); 7,30 (m, 2H); 6,93 (m, 2H); 6,76 (m, 2H).

^{13}C ($CDCl_3$) δ (ppm): 155,0; 155,2; 138,7; 138,3; 129,8; 120,8; 120,3; 117,8.

1-(4-iodophenoxy)-3-(trifluoromethyl)benzene.

Obtained from 4-iodophenol and 3-(trifluoromethyl)phenylboronic acid as clear, white crystals (43 %).

^{1}H ($CDCl_3$) δ (ppm): 7,57 (m, 2H); 7,34 (m, 1H); 7,28 (m, 1H); 7,16 (m, 1H); 7,07 (m, 1H); 6,70 (m, 2H).

^{13}C ($CDCl_3$) δ (ppm): 157,1; 156,3; 139,0; 138,5; 132,1; 130,4; 121,8; 121,3; 120,2 (q); 87,1.

Trans-3-(4-(3-nitrophenoxy)phenyl)acrylaldehyde.

Obtained from *p*-hydroxycinnamaldehyde and *m*-nitrophenylboronic acid as light brown crystals (26 %).

^{1}H ($CDCl_3$) δ (ppm): 9,70 (d, *J*=7,64 Hz, 1H); 8,49(m, 1H); 8,30 (m, 1H); 8,23 (m, 2H); 8,02 (m, 1H); 7,97 (m, 1H); 7,86 (m, 1H); 7,47 (d, *J*=15,90 Hz, 1H); 7,01 (m, 2H); 6,68 (dd, *J*=7,67 Hz, *J*=15,93 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,8; 159,1; 158,5; 157,1; 153,4; 151,9; 130,74; 130,70; 129,3; 125,2; 123,5; 119,5.

Trans-3-(4-(*p*-tolyloxy)phenyl)acrylaldehyde.

Obtained from *p*-hydroxycinnamaldehyde and *p*-tolylboronic acid as yellow crystals (37 %).

^{1}H (Acetone d-6) δ (ppm): 9,68 (d, *J*=7,67 Hz, 1H); 7,73 (m, 2H); 7,66 (d, *J*=15,93 Hz, 1H); 7,26 (m, 2H); 7,05 (m, 4H); 6,69 (dd, *J*=7,67 Hz, *J*=15,91 Hz, 1H); 2,34 (s, 3H).

^{13}C (Acetone d-6) δ (ppm): 193,9; 161,6; 151,5; 152,8; 135,0; 131,45; 131,43; 129,9; 128,4; 120,8; 118,7; 20,8.

Trans-3-(4-(4-chlorophenoxy)phenyl)acrylaldehyde.

Obtained from *p*-hydroxycinnamaldehyde and 4-chlorophenylboronic as white crystals (32 %).

^{1}H ($CDCl_3$) δ (ppm): 9,67 (d, *J*=7,71 Hz, 1H); 7,54 (m, 2H); 7,44 (d, *J*=15,88 Hz, 1H); 7,34 (m, 2H); 7,00 (m, 4H); 6,69 (dd, *J*=7,70 Hz, *J*=15,90 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,7; 160,0; 154,5; 152,0; 130,5; 130,1; 129,6; 129,1; 127,7; 121,2; 118,5.

Trans-3-(4-(3-(trifluoromethyl)phenoxy)phenyl)acrylaldehyde.

Obtained from *p*-hydroxycinnamaldehyde and 3-(trifluoromethyl)phenylboronic acid as white crystals (30 %).

^{1}H ($CDCl_3$) δ (ppm): 9,65 (d, *J*=7,68 Hz, 1H); 7,59(m, 2H); 7,47 (d, *J*=15,90 Hz, 1H); 7,40 (m, 1H); 7,26 (m, 1H); 7,19 (m, 1H); 7,01 (m, 2H);
6,62 (dd, *J*=7,68 Hz, *J*=15,93 Hz, 1H).

^{13}C ($CDCl_3$) δ (ppm): 193,6; 162,6; 159,2; 158,4; 151,8; 130,7; 130,5; 129,7; 127,9; 122,8; 120,8 (q); 119,0

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