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TECHNISCHE UNIVERSITÄT WIEN
Vienna University of Technology

DIPLOMARBEIT

SYNTHESIS OF POTENTIAL ANTI INFLAMMATORY AGENTS INSPIRED BY NATURE

AUSGEFÜHRT AM INSTITUT FÜR

ANGEWANDTE SYNTHESECHEMIE
DER TECHNISCHEN UNIVERSITÄT WIEN

UNTER ANLEITUNG VON

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WIEN, 15. APR. 2014

für meine Eltern

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Key

All compounds prepared in this thesis are labeled with bold Arabic numbers. Compounds unknown to the literature are additionally underlined. General structures and compounds presented as literature examples are numbered in bold Roman numerals.

Literature citations are indicated by superscript Arabic numbers.

Abstract

$PPAR_\gamma$ belongs to the superfamily of nuclear receptor proteins and upon activation by ligands acts as a transcription factor and regulates very important genes. The expressed genes are involved in glucose metabolism, lipid metabolism, and cellular differentiation. Furthermore, activation of $PPAR_\gamma$ shows anti-inflammatory effects. Clinically used agonists (thiazolidinediones) are potent full agonists but have serious side effects. Recently, 3 different neolignans (dieugenol, tetrahydrodieugenol and magnolol) were found to be $PPAR_\gamma$ partial agonists. Partial agonism is hypothesized to reduce side effects. In the frame of this thesis a further development of magnolol as a $PPAR_\gamma$ ligand was attempted. Preliminary molecular dockings studies and the crystal structure of $PPAR_\gamma$ and magnolol revealed that two copies of magnolol bind to the active binding site of the receptor, simultaneously. In consequence, our cooperation partners performed computational studies where the two magnolol molecules were linked covalently. The hypothesis was established that such a magnolol dimer would potentially display increased affinity to the receptor. The predicted structure to be synthesized can be seen in **Figure 1**.

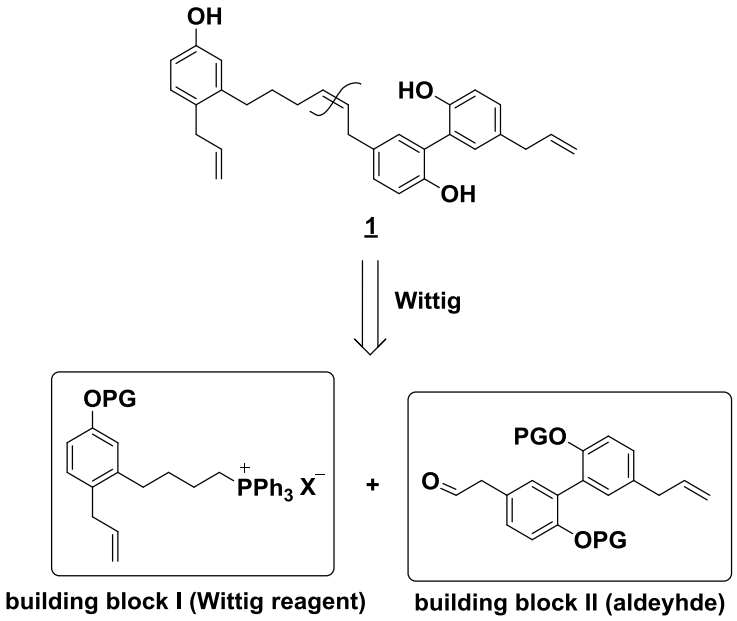


Figure 1

For the synthesis of target compound **1** a classical Wittig reaction was envisioned as the crucial step to introduce the olefin in the required Z-configuration. Both building blocks were successfully synthesized starting from commercially available anisoles. Subsequent Wittig olefination gave the desired Z-isomer, exclusively. Pharmacological probe **1** was obtained in good yields over 7 steps and was submitted for evaluation of the biological activity on $PPAR_\gamma$.

Deutsche Kurzfassung

$PPAR_\gamma$ gehört zur Gruppe der intrazellularen Rezeptor Proteine, fungiert nach Aktivierung durch Liganden als Transkriptionsfaktor und reguliert dadurch wichtige Gene. Die exprimierten Gene sind beteiligt am Zuckerstoffwechsel, Fettstoffwechsel und an der Differenzierung von Zellen. Außerdem hat Aktivierung von $PPAR_\gamma$ entzündungshemmende Vorgänge zur Folge. Klinisch angewandte Agonisten (Thiazolidindione) sind wirksame volle Agonisten, haben jedoch ernsthafte Nebenwirkungen. Vor Kurzem wurde 3 verschiedenen Neolignane (Dieugenol, Tetrahydrodieugenol und Magnolol) als partiale $PPAR_\gamma$ Agonisten identifiziert. Partialer Agonismus könnte weniger Nebenwirkungen zur Folge haben. Im Rahmen dieser Arbeit wurde die Optimierung von Magnolol als $PPAR_\gamma$ Ligand angestrebt. Einleitende in silico Bindungsstudien und die Kristallstruktur von $PPAR_\gamma$ mit Magnolol hatten zum Ergebnis, dass zwei Magnolol Moleküle gleichzeitig die aktiven Bindungsstellen besetzten. In Folge haben Kooperationspartner durch Anwendung Computer-unterstützter Methoden die Möglichkeit einer kovalenten Bindung der beiden Magnolol Moleküle vorgeschlagen. Es wurde die Hypothese erstellt, dass ein solches Magnolol-Dimer eine erhöhte Affinität zum Rezeptor aufweisen würde. Die vorgeschlagene Struktur, die es zu synthetisieren galt, ist in **Abbildung 1** zu sehen.

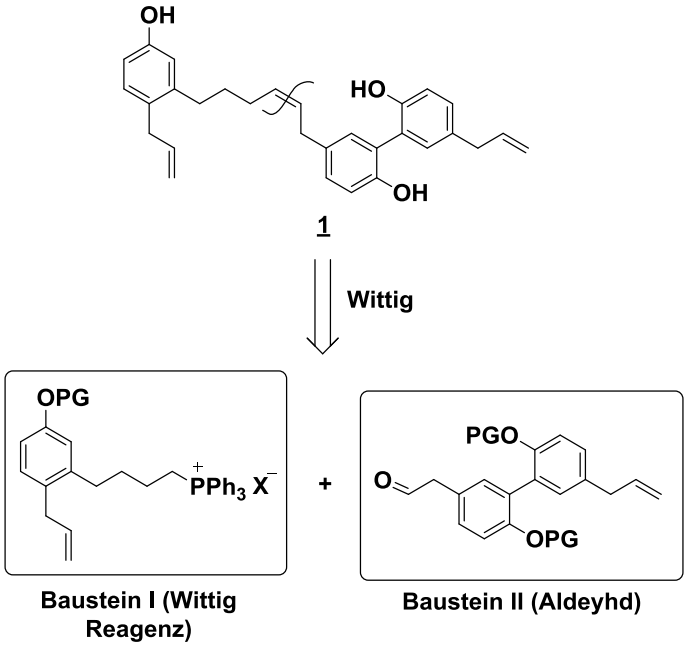


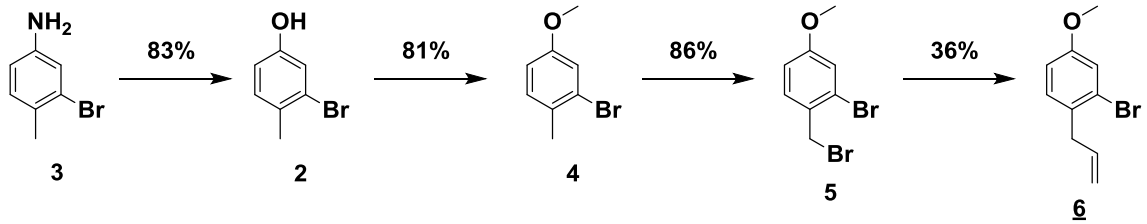
Abbildung 1

Für die Synthese der Zielverbindung **1** war eine klassische Wittig Reaktion geplant um in diesem kritischen Schritt die Z-Konfiguration des Olefins einzuführen. Die Bausteine wurden erfolgreich synthetisiert ausgehend von kommerziell erhältlichen Anisolen. Wittig Olefinierung lieferte ausschließlich das benötigte Z-Isomer. Die pharmakologische Testsubstanz **1** wurde in guten Ausbeuten über 7 Stufen erhalten und wurde zur Ermittlung der biologischen Aktivität auf $PPAR_\gamma$ übermittelt.

Table of contents

General schemes

Synthesis of building block I (Wittig reagent)



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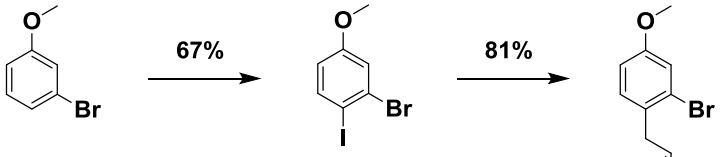

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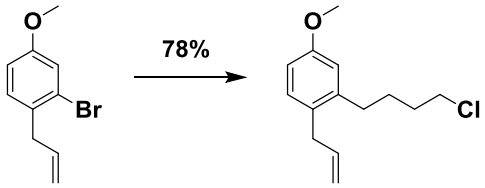

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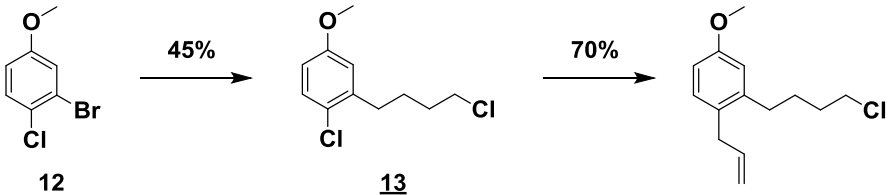

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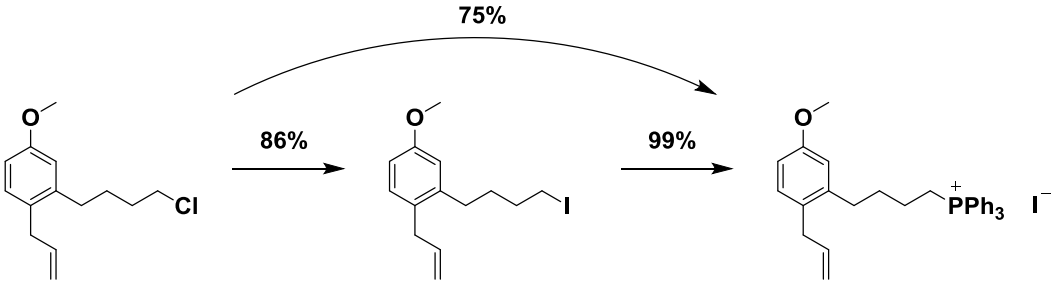

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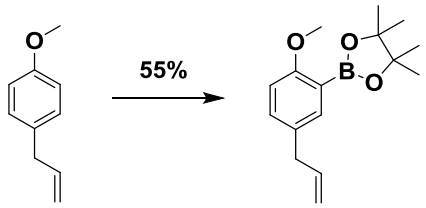
Synthesis of building block II (aldehyde)



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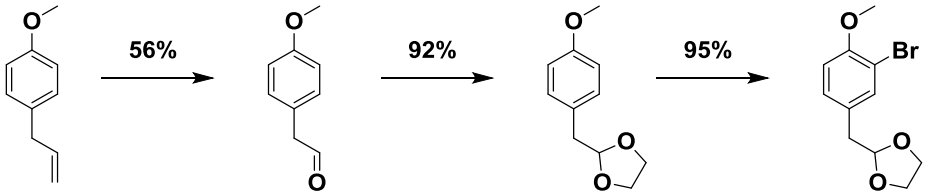

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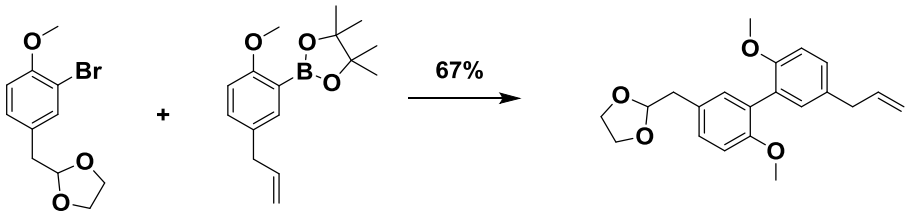

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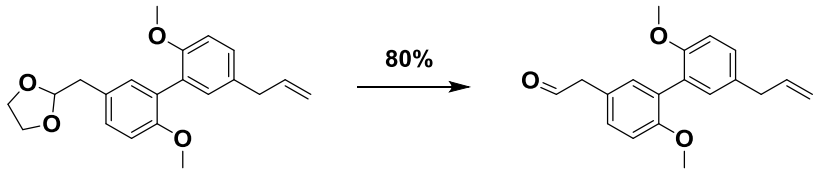

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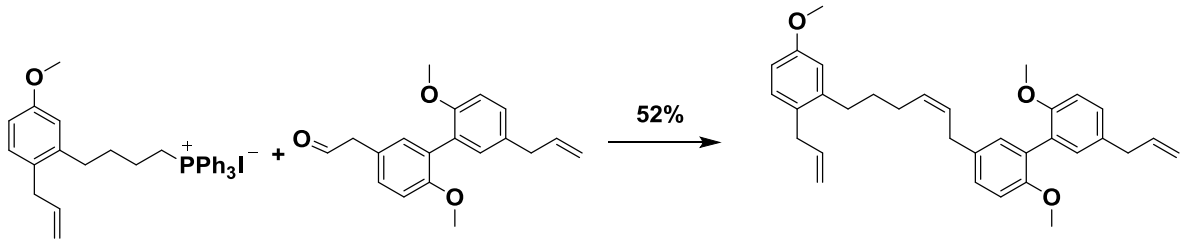
Synthesis of biological probes



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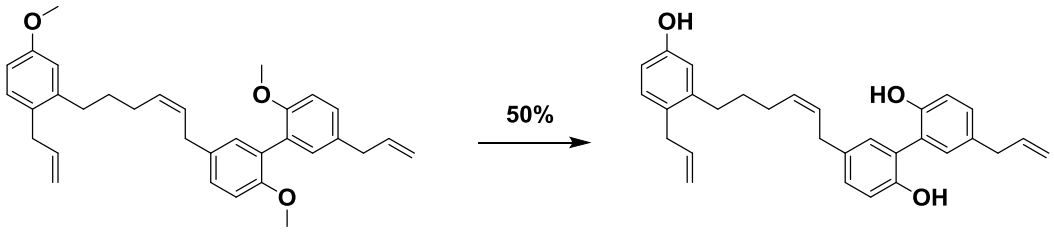


25 1

1. Introduction

1.1. Inflammation

Inflammation can be a painful condition as physicians have found these five signs - pain, redness, heat, swelling and loss of function – to be characteristic for an inflammatory process already thousands of years ago. This process is initiated by a pathogen invading the human body and therefore causing a response of the immune system in order to fight the threat. Lipid signaling molecules (e.g. prostaglandins) and protein signaling molecules (cytokines) arrange the inflammatory response at the site of the infection. Some of the signaling molecules attract cells which help to fight the pathogens while others cause fever. The increased body temperature supports the adaptive immune responses as they are more potent at higher temperatures while viral pathogens are less potent at the same time. Other signaling molecules cause occluding of local blood vessels as a result of blood clotting. This prevents the infection from spreading over the whole body. While inflammatory processes are indispensable to life, they may have severe effects in case of a disseminated infection (*sepsis*). A systemic inflammatory response results in dilation of blood vessels and loss of plasma volume. This combination leads to a dramatic drop in blood pressure which is described as shock. With blood clotting going on at the same time this might lead to a septic shock which is often fatal. Furthermore, inflammation is involved in chronic diseases like arthritis and asthma. In addition, some pathogens have developed abilities to exploit the inflammatory response in order to spread the infection. Some bacteria, such as *Salmonella*, are able to invade macrophages, which are recruited at the site of the initial infection. They then get a free ride to other tissues in the body and cause further harm.[1]

Several reports have found that inflammation is linked to diabetes, obesity, cancer, Parkinson's and Alzheimer's disease.[2-5] Naproxen, Ibuprofen and Aspirin (**Figure 2**) are examples for currently used non-steroidal anti-inflammatory drugs (NSAIDs). They inhibit the cyclooxygenase enzyme (COX) which is responsible for the biosynthesis of prostaglandins, the above mentioned lipid signaling molecules.[6-7]

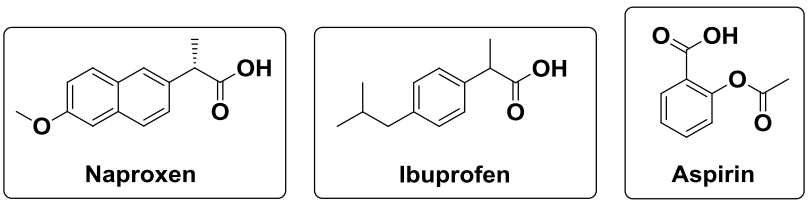


Figure 2

An alternative target for tackling inflammation is $PPAR_\gamma$ (peroxisome proliferator-activated receptor gamma) as several groups reported $PPAR_\gamma$ ligands to reduce the release of inflammatory cytokines (e.g. TNF-α and IL-6) from macrophages.[8-9] Regarding the mechanism, inhibition of NF-κB, AP1, and STAT signaling by $PPAR_\gamma$

was proposed.[10] Furthermore, activation of $PPAR_\gamma$ and subsequent recruitment of co-activators leads to competition for limited amounts of these co-activators as they are shared with other transcription factors which induce inflammatory responses.[11]

1.2. $PPAR_\gamma$

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptor proteins. These receptors can be activated by ligands and then act as transcription factors. PPARs regulate gene expression of proteins that are involved in lipid and glucose metabolism.[12-13] There exist 3 different isoforms, namely $PPAR_\alpha$, $PPAR_{\beta/\delta}$ and $PPAR_\gamma$. $PPAR_\gamma$ is mostly present in adipose tissue and is involved in adipogenesis and enhances insulin sensitivity.[14]

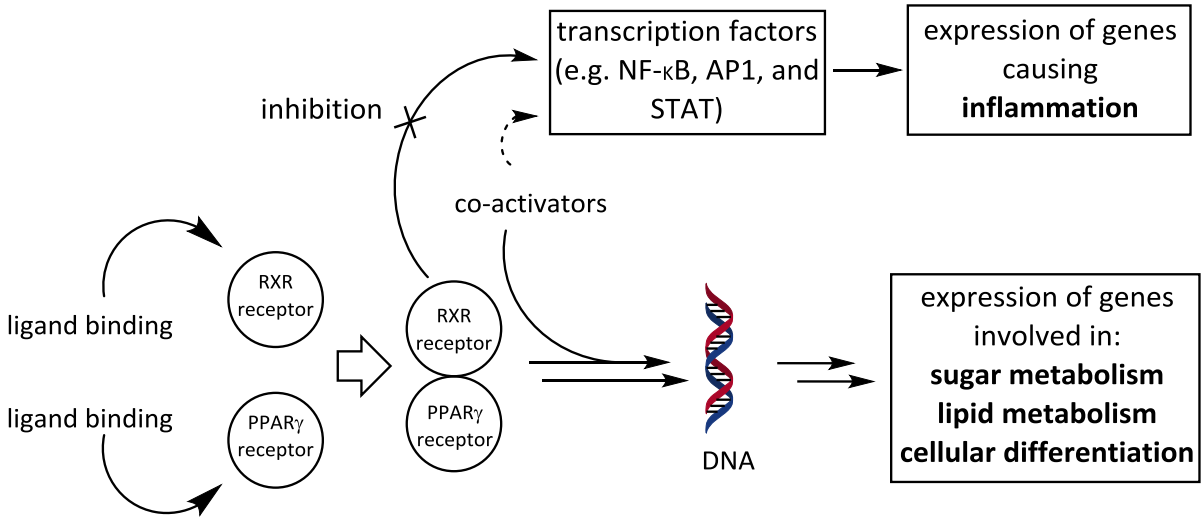


Figure 3

Upon activation by activators, $PPAR_\gamma$ migrates into the nucleus where it forms a heterodimer with the retinoid X receptor (RXR). RXR is a ligand-activated nuclear receptor protein itself and occurs in 3 different isoforms. This heterodimer then binds to the PPAR response elements (PPREs) in the promoter region of suitable genes.[15] Subsequent recruitment of co-activators leads to transcriptional regulation.[16] (**Figure 3**) At the moment, $PPAR_\gamma$ is targeted to fight type 2 diabetes and the metabolic syndrome. Therefore, $PPAR_\gamma$ ligands are commonly called insulin sensitizers.[17] Hardly surprising, PPARs are considered to be important drug targets.[18]

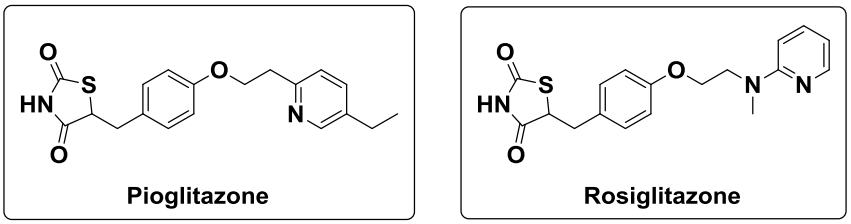


Figure 4

At the moment, Pioglitazone and Rosiglitazone (**Figure 4**) are clinically used $PPAR_\gamma$ agonists. However, these thiazolidinediones (TZDs) have multiple serious side effects like weight gain, increased bone fracture, fluid retention and heart failure.[19] As type 2 diabetes is often associated with metabolic diseases, the prescription of TZDs resulting in weight gain of already obese patients is a rather paradox problem. In recent years the hope emerged that the side effect profile could be favorably affected by applying partial agonists instead of full agonists (as TZDs are).[20]

1.3. Neolignans as $PPAR_\gamma$ ligands

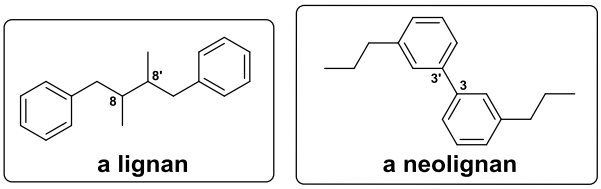


Figure 5

Lignans represent a group of compounds found in plants. These secondary metabolites act as antioxidants in the plant's defense and feature a large diversity of biological activities.[21] Structurally, lignans are characterized by a dimeric structure of propylbenzene. If the two units are linked *via* their C8 atoms (benzene ring is numbered from 1 to 6, starting from the propyl group; propyl group is numbered from 7 to 9 starting from the benzene ring) then the compound is an actual lignan. If the connection is of any other nature then the compound is termed a neolignan (**Figure 5**).[22]

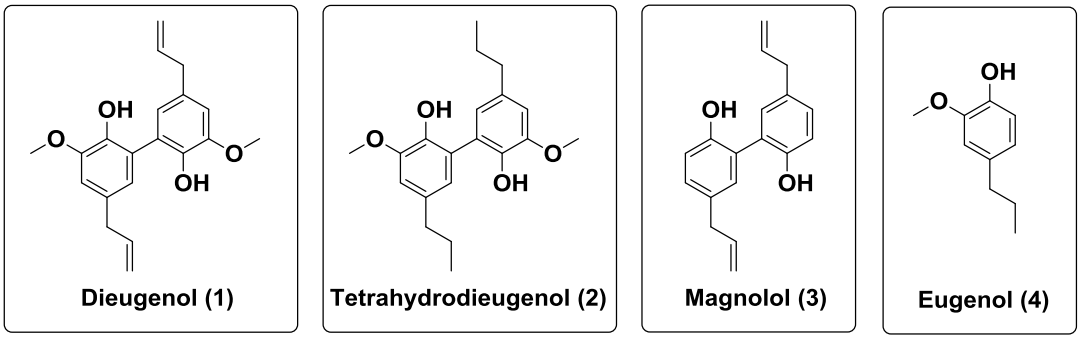


Figure 6

Fakhrudin et. al. recently found the neolignans dieugenol, tetrahydrodieugenol and magnolol (**Figure 6**) to be novel $PPAR_\gamma$ ligands.[23] EC_{50} values in the nanomolar range were detected which is similar to the clinically used agonist Pioglitazone. This suggests a similar binding pattern. The coactivator study (**Figure 7**) demonstrates that these neolignans act as partial agonists.

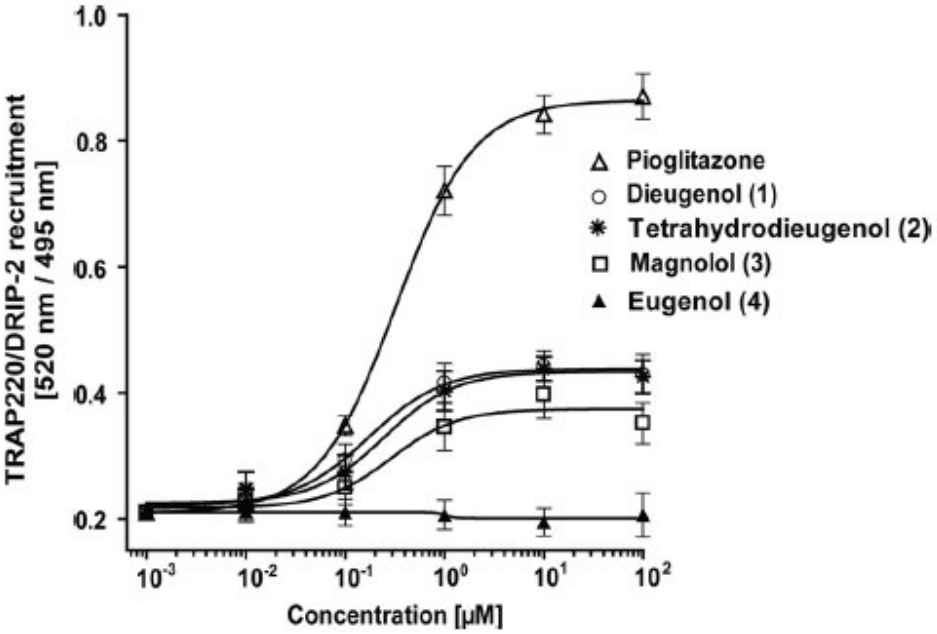


Figure 7

In a previous report Itoh et. al. crystallized $PPAR_{\gamma}$ with a fatty acid as a ligand.[24] Crystal structure revealed that two molecules of the agonist occupied the binding site, simultaneously. Fakhrudin et. al. carried out molecular docking studies which lead to the suggestions that the above mentioned neolignans bind to $PPAR_{\gamma}$ in a dimeric fashion as well.[23] This was later found to be the case by Zhang et. al. by determining the crystal structure.[25]

1.4. Objective

The aim of this thesis was to optimize magnolol as a $PPAR_{\gamma}$ ligand. This should not be conducted by synthesizing a compound library but rather by exploiting the fact that two magnolol molecules bind to the receptor, simultaneously. The general idea and how the target molecule was chosen will be presented in the next chapter.

2. Results and discussion

2.1. Optimization of magnolol as a $PPAR_{\gamma}$ ligand

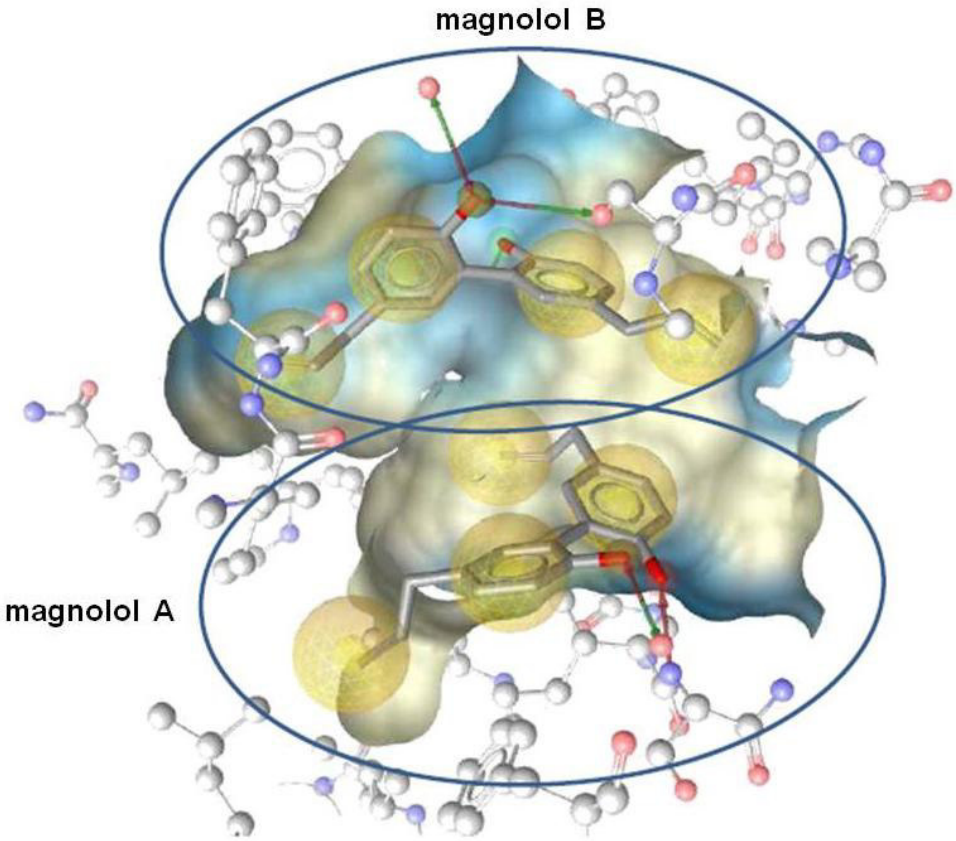


Figure 8

As already discussed in the introduction, two copies of magnolol bind to the ligand binding site of $PPAR_{\gamma}$, simultaneously. In **Figure 8** the interactions of these two magnolol molecules with the binding pocket of $PPAR_{\gamma}$ (X-ray crystal structure) are shown. The front magnolol (labeled magnolol A) interacts *via* its π-system with hydrophobic areas of the protein (marked with yellow spheres). Furthermore it is anchored by one hydrogen bond originating from a hydroxyl directly with the protein; another hydrogen bond is mediated *via* one water molecule. The back magnolol (labeled magnolol B) provides the same interactions but has one additional hydrogen bond.

In our ambition to find a selective $PPAR_{\gamma}$ ligand, we recognized the promising possibility to design a potent ligand by exploiting the fact of two molecules of magnolol to bind to the receptor. Therefore, we hypothesize that if we create a molecule that combines the structural features of two magnolol molecules within one structure, this molecule could potentially fit into the active binding site of $PPAR_{\gamma}$ in a very selective way. We could fulfill this requirement by linking two magnolol molecules together *via* a spacer resulting in the formation of a magnolol dimer.

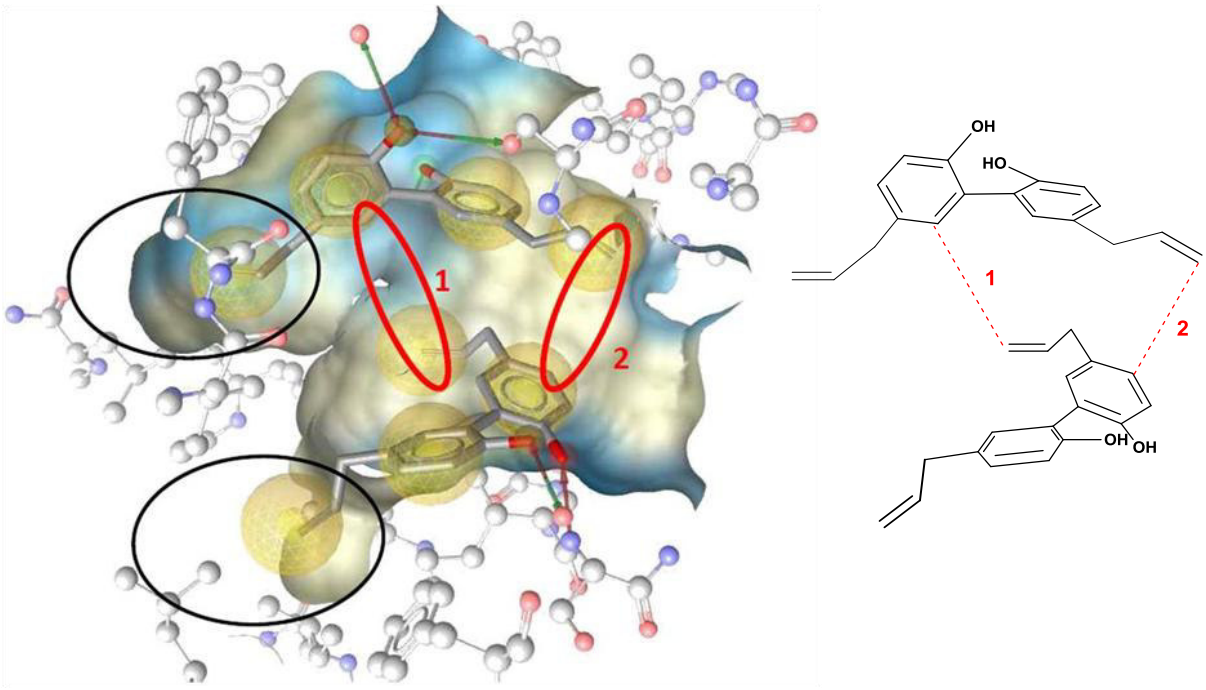


Figure 9

Therefore, the sterical features of the binding pocket have to be considered in order to decide where to place the linkage between two magnolol molecules. In **Figure 9** two possibilities were identified for such a connection. Both link one allyl group of one magnolol molecule with one benzene ring of the other magnolol molecule. In the first case, this results in a 1,2,3,4-tetrasubstituted benzene ring and in the second case in a 1,2,4,5-tetrasubstituted benzene ring. The other two allyl groups (marked with a black circle) offer no possible connection point as they are completely surrounded by amino acids from the receptor.

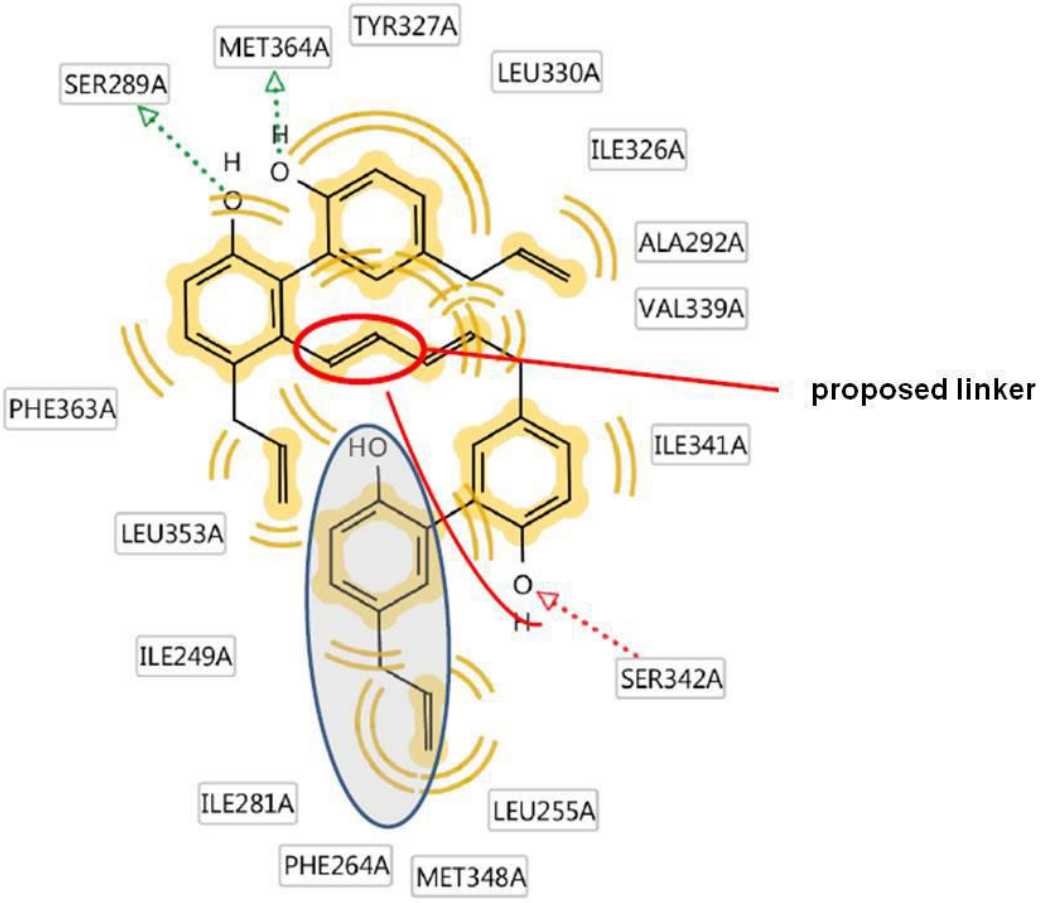


Figure 10

In **Figure 10** the first of the two proposed magnolol dimers can be seen embedded by the surrounding amino acids. Green arrows represent hydrogen bond donors while red arrows represent hydrogen bond acceptors. Structural features which are marked with a yellow sphere represent hydrophobic contacts. The proposed linker is a double bond in E-configuration. Alternatively, a single bond could be used but then the fixation between SER342 and the hydroxyl group is predicted to be weaker as the molecule gets more flexible and therefore, more unlikely to adapt the correct binding orientation.

The second proposed dimer can be found in **Figure 11**. The linker is a C_3H_6-spacer and the adjacent double bond must be in Z-configuration. It is predicted that with this dimer a new interaction between HIS449 and one hydroxy group will be established.

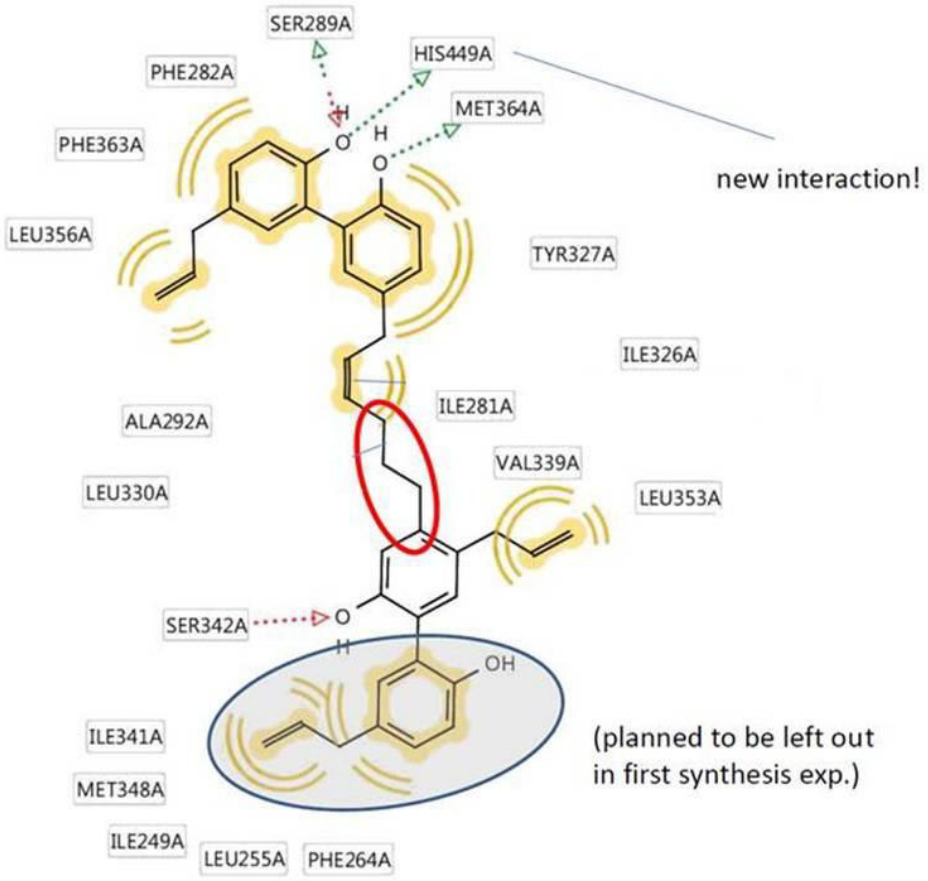
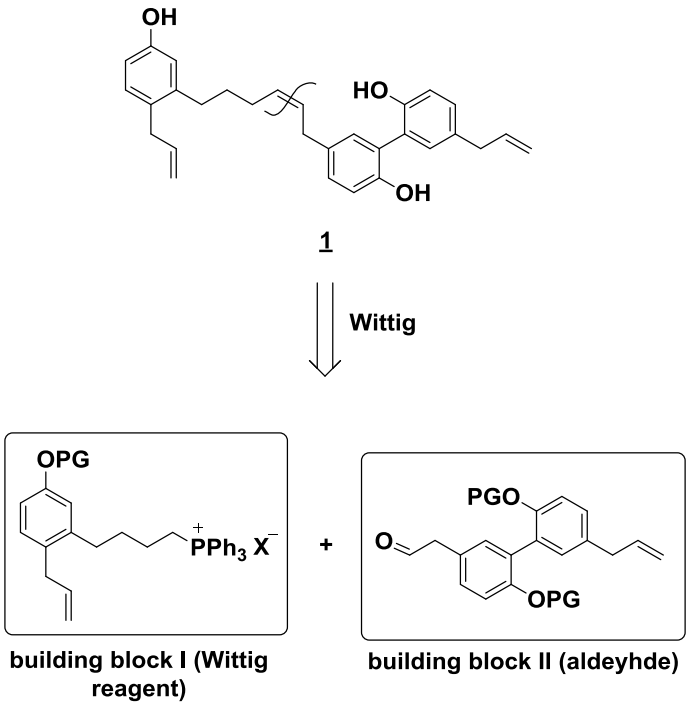


Figure 11

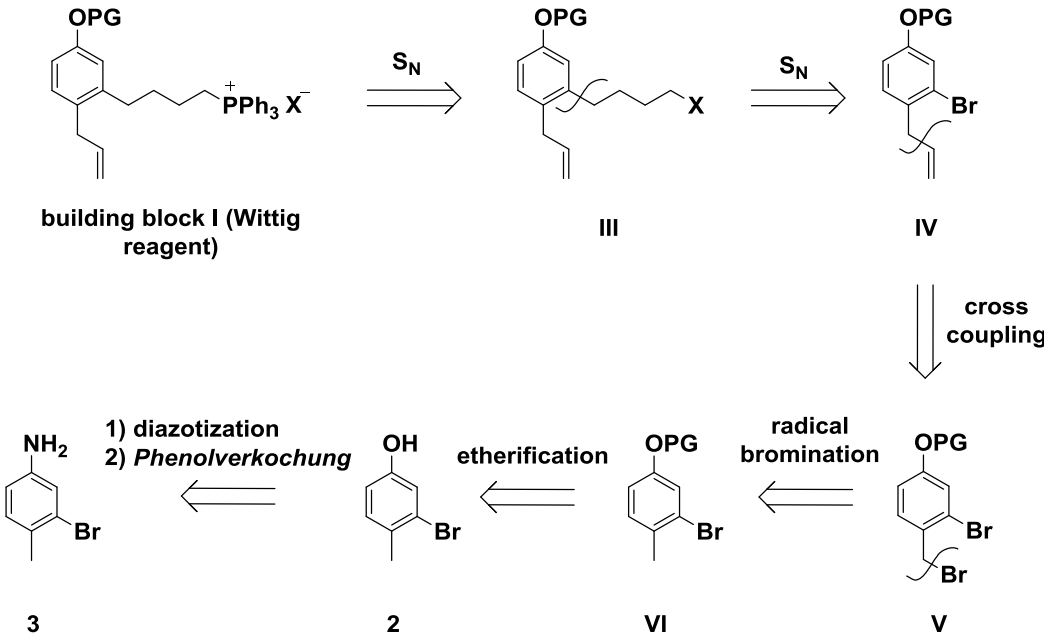
Within this master thesis we aimed to synthesize the second proposed magnolol dimer. We favored the second dimer over the first in the light of the predicted new interaction with HIS449; this seemed a more promising target also for higher activity. Furthermore, a sterically crowded 1,2,3,4-tetrasubstituted benzene is much more difficult to synthesize. In order to establish a synthesis of this dimer we set out to prepare a simplified version first which corresponds to a model system. Leaving out one half of a magnolol motif (labeled with a blue circle in **Figure 11**) seemed a reasonable simplification as this would still feature the combination of two ligands and the synthesis effort is manageable. The target structure is the simplified magnolol dimer (Z)-5-allyl-5'-(6-(2-allyl-5-hydroxyphenyl)hex-2-en-1-yl)-[1,1'-biphenyl]-2,2'-diol **1** (sesqui-magnolol; see **Scheme 1**) and the synthesis of the non simplified dimer was considered for a later stage of this project.

2.2. Retrosynthetic analysis



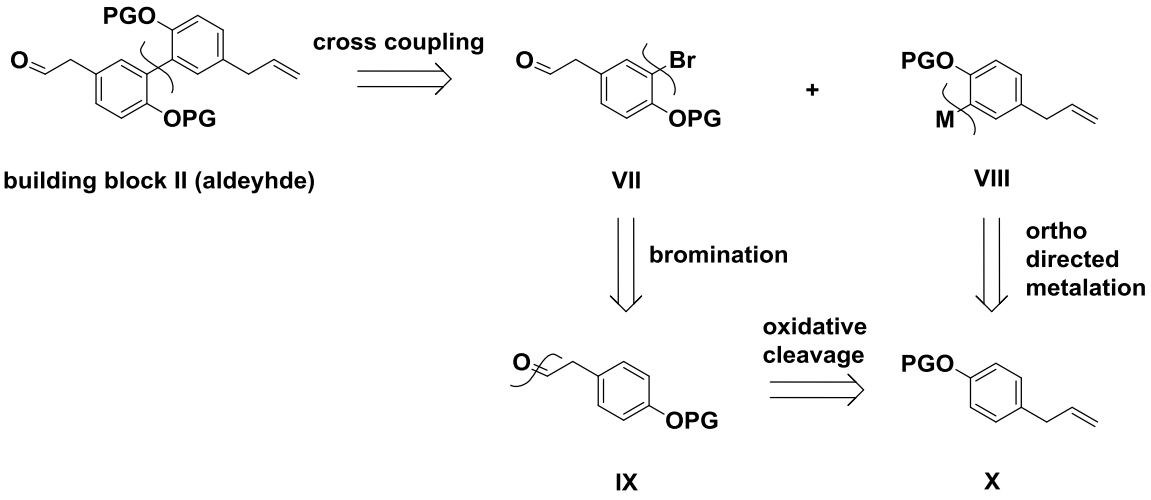
Scheme 1

The analysis of target structure **1** (**Scheme 1**) reveals a biphenylic motif, three phenolic hydroxy groups and three allylic domains, where one of them is actually a disubstituted olefin and is required in Z-configuration. Following the guidelines for a rational retrosynthesis[26], one should cut the desired molecule into two molecules of similar size. Therefore the disconnection of the olefin is a reasonable first cut. Wittig olefination[27] (and modifications thereof[28,29]), Julia olefination[30], Peterson olefination[31] and olefin metathesis[32] should be considered as widespread methods for the synthesis of olefins. Regarding stereochemistry, Julia olefination and olefin metathesis give the thermodynamically favored E-olefin. While Peterson olefination would give the E olefin upon basic hydrolysis, the Z isomer would be accessible through acidic hydrolysis, however, potentially causing isomerization of double bonds. The E isomer would be the product of a Wittig reaction when using stabilized ylides (ylides with electron withdrawing groups on the ylidic carbon, causing a stabilization of the carbanion; e.g. the Horner-Wadsworth-Emmons modification[29]). When using unstabilized ylides in a Wittig olefination, the resulting olefin can be expected in Z configuration, selectively. For target molecule **1** the used ylide would be unstabilized, no matter of where to place the ylide in the two possible starting materials. Therefore, a Wittig reaction is the reaction of choice. We wanted to place the aldehyde in the allylic position as this results in a shorter sequence overall. Protection (protecting group = PG) of the hydroxyl groups is necessary and we end up with building block **I** (Wittig reagent) and building block **II** (aldehyde) (see **Scheme 1**).



Scheme 2

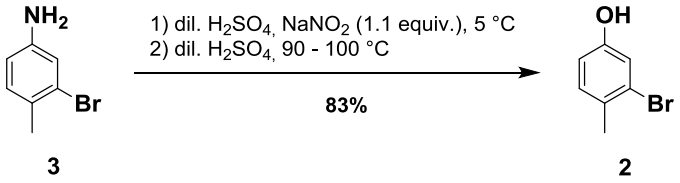
Scheme 2 summarizes the retrosynthetic analysis of the Wittig reagent **I**. This building block can be obtained from the corresponding halide **III**. For the introduction of the alkyl halide one option would be a sp^2-sp^3 cross coupling reaction and a subsequent transformation to the desired halide. A more elegant approach could be a nucleophilic substitution using a butane dihalide. When using a mixed dihalide (1-bromo-4-chlorobutane is commercially available) oligomerization should be prevented. This strategy requires a Grignard species or a lithium organyl based on aryl bromide **IV**. As bromination of an oxygen substituted benzene would predominantly give the *ortho*-bromide (if *para* position is already substituted) we should choose a starting material with the bromine in meta position already in place. Therefore, the next disconnection tackles the allylic domain. With a sp^3-sp^2 coupling in mind we could choose dibromide **V** which is readily available by radical bromination of the corresponding toluene derivative **VI**. The protecting group is obviously installed starting from 3-bromo-4-methylphenol **2**, which can be obtained by transforming the commercially available 3-bromo-4-methylaniline **3** into the phenol *via* diazotization and *Phenolverkochung*.



Scheme 3

Synthesis planning of building block **II** (aldehyde) is outlined in **Scheme 3**. The biphenylic structure can be synthesized without a doubt by a number of cross coupling reactions. Therefore we need to decide on which aryl to place the halide as well as the metal species (M). In either case, the bromine is in *ortho* position and can therefore be introduced *via* electrophilic aromatic substitution. However, in the case of the allyl substituted benzene, the double bond will be brominated first and we would require a subsequent dehalogenation step. This is a published procedure for the synthesis of 4-allyl-2-bromo-1-methoxybenzene[33] but we might consider a more atom economic possibility. Hence we should start from bromide **VII** and metal coupling partner **VIII**. Bromide **VII** leads back to aldehyde **IX**. Usually when the metal coupling partner is not available commercially, it is synthesized from the corresponding halide which would lead to the already mentioned problem of bromination in presence of a double bond. A much more atom economic way would be a direct metalation. With the *ortho* directing ability of oxygen substituted structures in mind we should consider compound **X** as a reasonable starting material. Furthermore, we could recognize the same compound **X** as a common starting material if we plan to synthesize aldehyde **IX** *via* oxidative cleavage of the double bond.

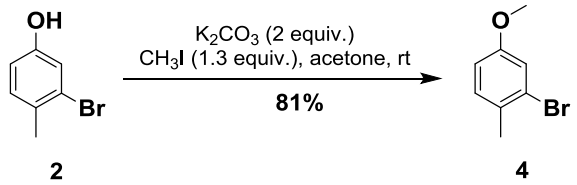
2.3. Synthesis of building block I (Wittig reagent)



3 2

Scheme 4

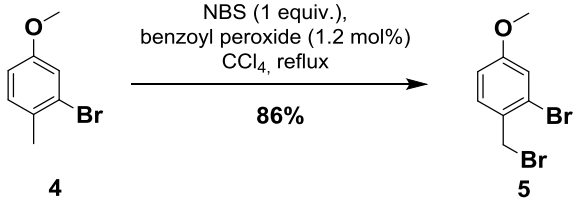
The first step in the synthetic sequence was the transformation of commercially available aniline **3** into the corresponding 3-bromo-4-methylphenol **2** (**Scheme 4**). When adding diluted H_2SO_4 to the substrate, the material solidified and was not dissolved. In one experiment diazotization was carried out anyway with big solid particles present. This resulted in incomplete conversion. Remaining starting material was recovered and isolation of the product gave 53% yield. By heating the starting material mixture to temperatures above 85°C the substrate dissolved completely but precipitated when cooled again. Applying literature conditions[34] resulted in a non stirrable mixture due to a very high concentration. Therefore, a higher amount of acid was used. Upon addition of aqu. $NaNO_2$ at 5°C the reaction became homogeneous in course of the diazotization. Heating the reaction resulted in formation of the phenol which could not be isolated in pure form by alternating acidic and basic extractions as it was stated in the original publication. After purification by flash column chromatography, pure phenol **2** was obtained in 83% yield.



2 4

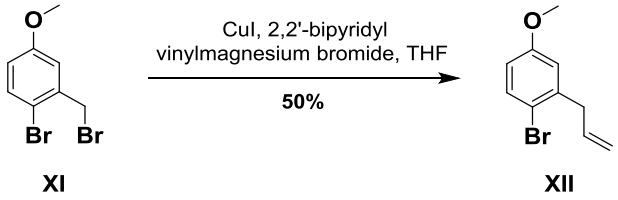
Scheme 5

When planning the forward synthesis we recognized the need of protecting the phenol. We decided to use a simple methoxy group, knowing that methyl ethers can be cleaved upon treatment with BBr_3.[35] As we will need to have protected phenols on the second building block as well, we considered to choose protecting groups in a way that deprotection of all hydroxy groups in one single operation (global deprotection) will be possible in the end. Therefore, using methoxybenzenes seems to be a good choice. Hence the next step was the etherification towards 2-bromo-4-methoxy-1-methylbenzene **4** (**Scheme 5**). Standard etherification conditions using K_2CO_3 as base and CH_3I gave anisole **4** in 81% isolated yield after flash column chromatography.



Scheme 6

In order to make the benzylic position available for a subsequent cross coupling reaction to form the allylic part of the building block, we had to introduce bromine into this position by radical bromination using NBS as brominating reagent and benzoyl peroxide as initiator. The reaction was carried out in dry and degassed CCl_4 as solvent giving 86% of 2-bromo-1-(bromomethyl)-4-methoxybenzene **5** after purification by flash column chromatography (**Scheme 6**). Although the reaction worked in high yields, it has to be noted that in some cases formation of a side product was observed. GC-MS analysis gave a mass of 234, 236 and 238 and the characteristic pattern of compounds containing one bromine and one chlorine. This finding can be explained if the benzylic position is not brominated but chlorinated. Under radical conditions the used CCl_4 might enable a competing chlorination reaction. In ^{1}H-NMR spectra an additional singlet at 4.68 ppm was observed which is in accordance with the spectral data for 2-bromo-1-(chloromethyl)-4-methoxybenzene.[36] Since retention time of the two compounds is the same, a chromatographic separation was not feasible. However the contamination was in the range of 5% and in some cases it was not observed at all. Moreover, the chlorinated product is not expected to cause problems in the next step.



Scheme 7. Original report by Hazimeh et. al.

With a sufficient amount of dibromide **5** in hand we envisioned a Cu^I catalyzed Kumada coupling[37] for establishing the allyl group on this part of the molecule. Several reports using CuI and 2,2-bipyridyl as a catalytic system encouraged us in this intention.[38-39] One report[39] used 1-bromo-2-(bromomethyl)-4-methoxybenzene **XI** as starting material which is isomeric to our substrate (**Scheme 7**). When applying these conditions (10 mol% catalyst loading, dry THF, 1.1 equiv. Grignard reagent), we observed full consumption of our starting material. Unfortunately GC-MS and ^{1}H-NMR analysis showed some debrominated starting material **4** (5%) and significant amounts of the biaryl 2,2'-bis(bromomethyl)-5,5'-dimethoxy-1,1'-biphenyl **7** (19%) (**Scheme 8**) to be present in the crude mass. The stated values are calculated from the integrals in ^{1}H-NMR and therefore represent mol% of the crude material. As biaryl

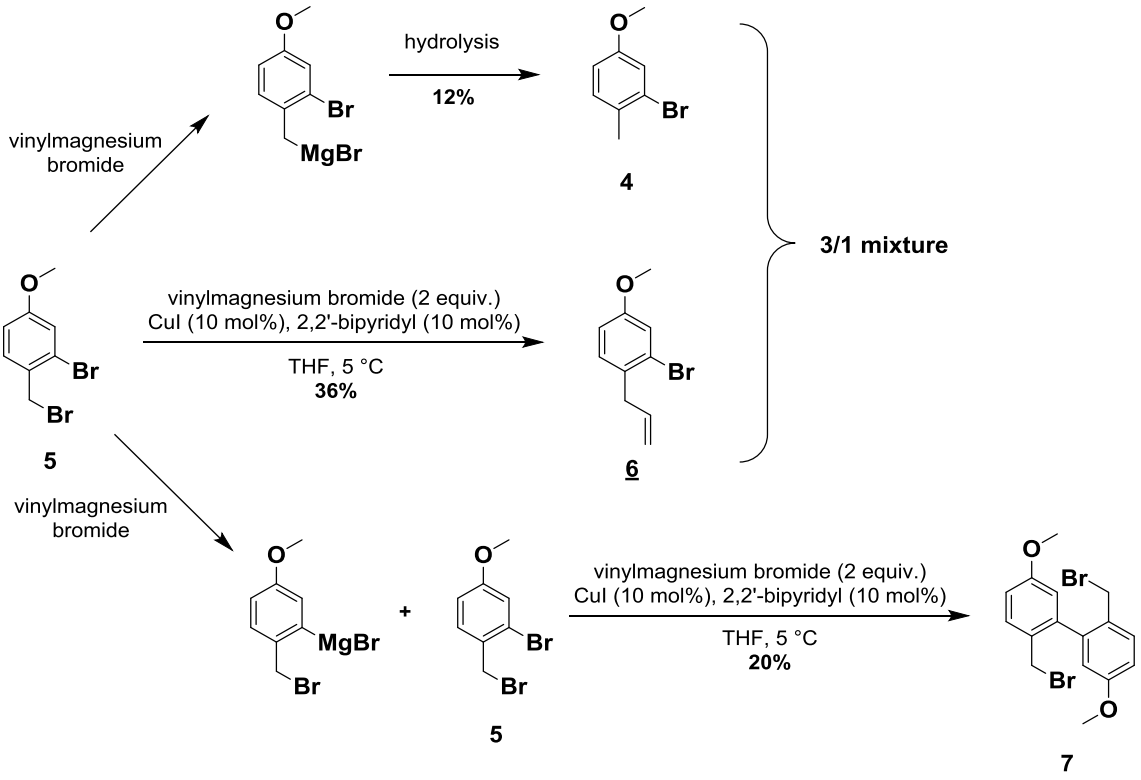
7 contains 2 molecules of the starting material **5** the yield of biaryl formation would be twice the value (38% in this case). Crude mass was submitted to flash column chromatography and the product was obtained as a mixture with the debrominated starting material **4** (5%) as separation on silica gel was not successful. A theoretical yield of 33% was calculated by considering the amount of contaminant.

Changing the solvent to dry toluene did not improve the situation.

It was attempted to carry out the reaction under iron catalysis as well (5 mol% $Fe(acac)_3$, 10 mol% TMEDA, 5 mol% hexamethylenetetramine) in dry THF as it was reported by Cahiez et. al.[40] but several side products were detected by GC-MS and this approach was abandoned.

Next we wanted to investigate addition of the starting material to a mixture of the Grignard reagent and the catalyst. This could ensure a high concentration of the Grignard reagent in the beginning of the reaction and therefore the formation of the product would probably be favored over biaryl formation. This experiment gave less biaryl **7** (10%, 20% yield respectively) on the one hand but more debrominated starting material **4** (10%) on the other hand.

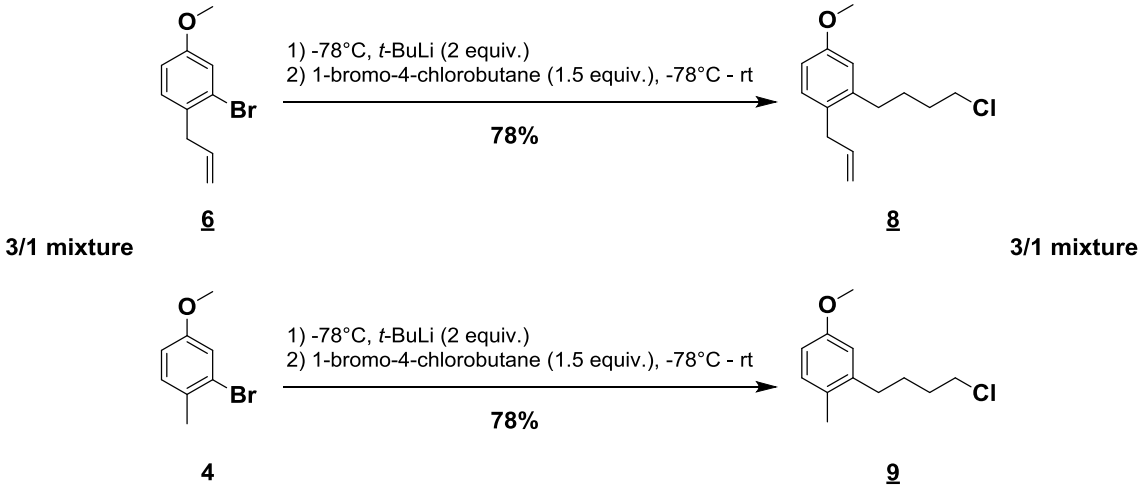
Both side products are probably caused by a halogen magnesium exchange, which is outlined in **Scheme 8**. If the benzylic bromide got exchanged and the resulting intermediate would not participate in a coupling reaction, compound **4** would be obtained upon work-up. If the exchange occurs on the sp^2 carbon and the intermediate would couple with another starting material molecule in an aryl-aryl coupling, side product **7** would be obtained under the assumption that the two benzylic bromides would not couple with vinylmagnesium bromide. Therefore, we wanted to analyze, if the hypothetical magnesium halogen exchange can be avoided when adding the Grignard reagent so slowly, that the Grignard reagent would react predominantly towards the product and would not end up in an exchange. A similar approach was carried out by Feringa and coworkers when they used lithium organyls (which conduct lithium halogen exchange very readily) in cross coupling reactions in the presence of aryl bromides.[41] To do so we used a syringe pump to add the Grignard reagent continuously over one hour. The reaction was monitored by GC-MS every 15 minutes. Surprisingly, there was no conversion after 15 minutes but after 30 minutes the reaction did proceed and was nearly finished when one equiv. of Grignard reagent had been added. Unfortunately, the side products were formed in similar quantities as in previous experiments.



Scheme 8

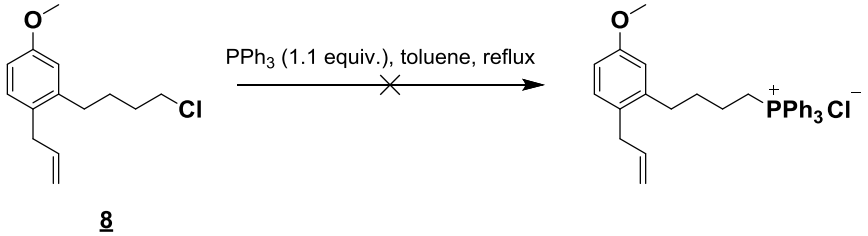
To proceed in our synthetic plan we wanted to synthesize compound **6** in a large scale experiment. As expected, product was obtained as a mixture with debrominated starting material **4** after flash column chromatography. A composition of 3 to 1 in favor of product **6** was calculated from ^{1}H-NMR intergrals (3/1 mixture) and a theoretical yield of 36% was calculated for the product and 12% for the debrominated starting material **4**. Biaryl **7** was isolated in 20**%** yield.

For the introduction of the alkyl side chain we were inspired by a publication by Back et. al.[42] They converted an aryl bromide into the corresponding lithium species *via* lithium halogen exchange and reaction with 1-bromo-6-chlorohexane resulted in the introduction of an alkyl side chain with a terminal chloride.



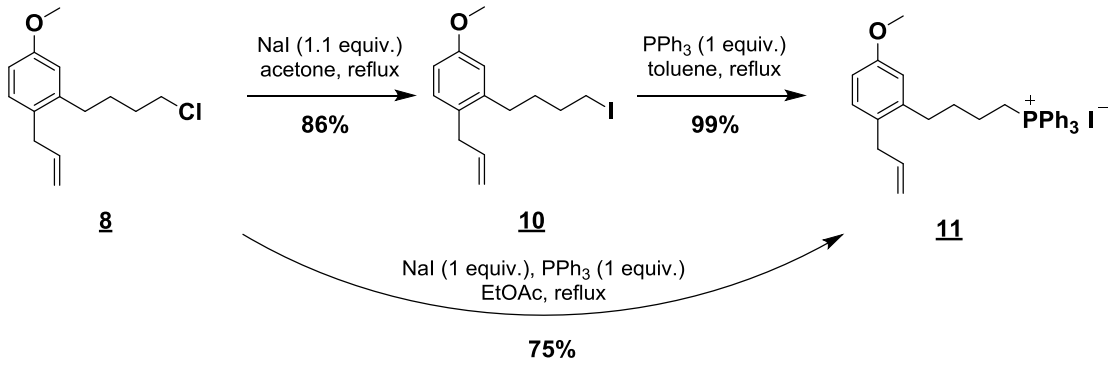
Scheme 9

For our target molecule a C_4 chain was required as the terminal carbon would become an olefinic carbon in the Wittig reaction. Therefore, commercially available 1-bromo-4-chlorobutane was the required reagent. Treating the starting material mixture (3/1 mixture of **6** and **4**) with *t*-BuLi gave rapid formation of the lithium organyl at -78°C. Using a second equiv. of the lithium reagent ensured the removal of *t*-butyl bromide as the bromide would compete in the alkylation step. Addition of the halogen reagent resulted in the desired transformation after the reaction was allowed to warm up. As starting material **6** was contaminated with compound **4** the reaction resulted in formation of 1-allyl-2-(4-chlorobutyl)-4-methoxybenzene **8** and 2-(4-chlorobutal)-4-methoxy-1-methylbenzene **9**. Unfortunately, separation of these two products was again not successful by flash column chromatography on silica gel and the product was therefore again contaminated with the toluene analog (3/1 mixture, calculated from ^{1}H-NMR intergrals). A theoretical yield of 78% for product **8** and for the contaminant **9** was calculated (**Scheme 9**). However, we were subsequently able to separate the mixture on $AgNO_3$ doped silica (5%) gel. Product **8** contains an allyl group while product **9** does not and therefore compound **8** was retained more efficiently due to complexation with the silver salt.



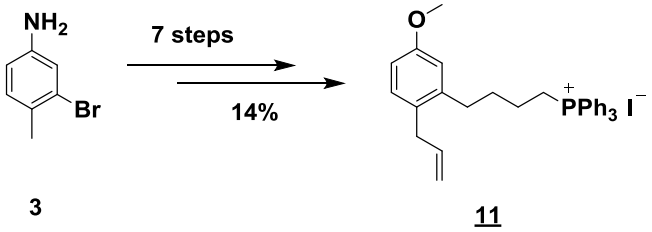
Scheme 10

In the next step we sought to transform the chloride **8** into the corresponding phosphonium chloride (**Scheme 10**). Refluxing the starting material with PPh_3 in dry toluene over night gave no conversion. Therefore we wanted to replace the chloride by an iodide as a better leaving group *via* Finkelstein reaction[43].



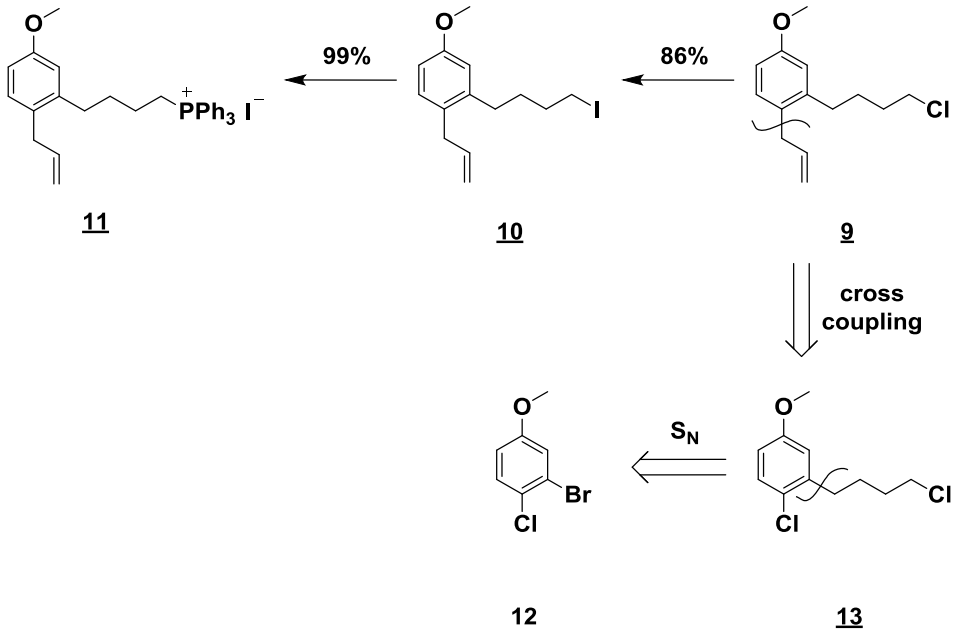
Scheme 11

Refluxing chloride **8** with NaI in acetone afforded 1-allyl-2-(4-iodobutyl)-4-methoxybenzene **10** in 86% isolated yield after column chromatography (**Scheme 11**). Further transformation with PPh_3 in refluxing toluene gave (4-(2-allyl-5-methoxyphenyl)butyl)triphenylphosphonium iodide **11** nearly quantitatively. Product was obtained in pure form as it formed an oily phase in the course of the reaction facilitating easy work-up. In order to obtain Wittig reagent **11** in crystalline form, the oil was stirred with refluxing diethyl ether which caused crystallization. Furthermore, a one pot procedure was applied.[44] Using stoichiometric amounts of NaI and PPh_3 in refluxing EtOAc afforded Wittig reagent **11** in 75% yield although starting material was never consumed completely. Conversion did not proceed after 36 - 48 hours. Although the achieved yield in the one pot protocol is lower by 10%, a chromatographic purification of the iodide intermediate **10** was not necessary and therefore this method is a good alternative.



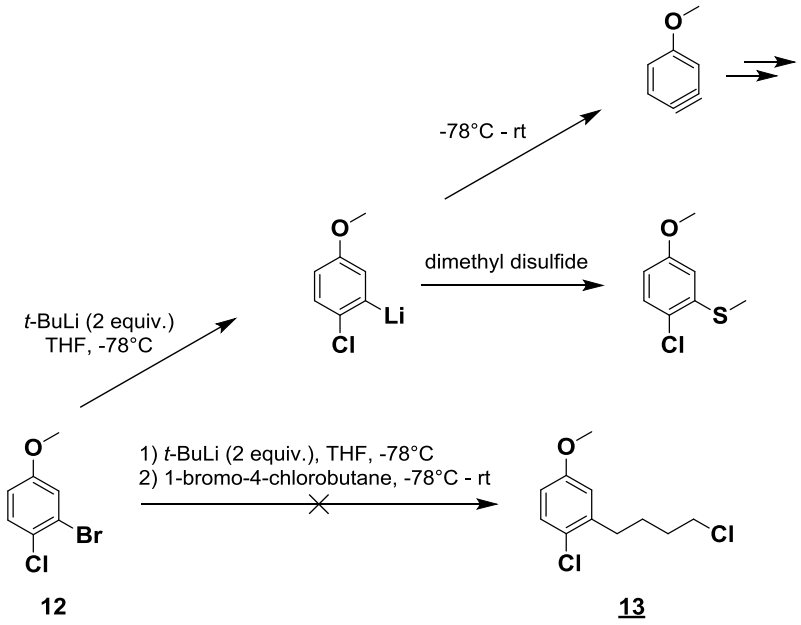
Scheme 12

Summarized, Wittig reagent **11** was obtained in 14% overall yield in seven steps starting from aniline **3** (**Scheme 12**). All steps worked reasonably well except for one. The CuI catalyzed Kumada coupling of dibromide **5** gave only 36% isolated yield and therefore affects the overall yield, significantly. Furthermore, starting material gets debrominated in this reaction step resulting in a side product with nearly identical retention behavior on unmodified silica gel, therefore preventing separation of these two compounds by chromatography. As efforts to suppress side product formation failed, an alternative synthetic strategy would be highly desirable.



Scheme 13

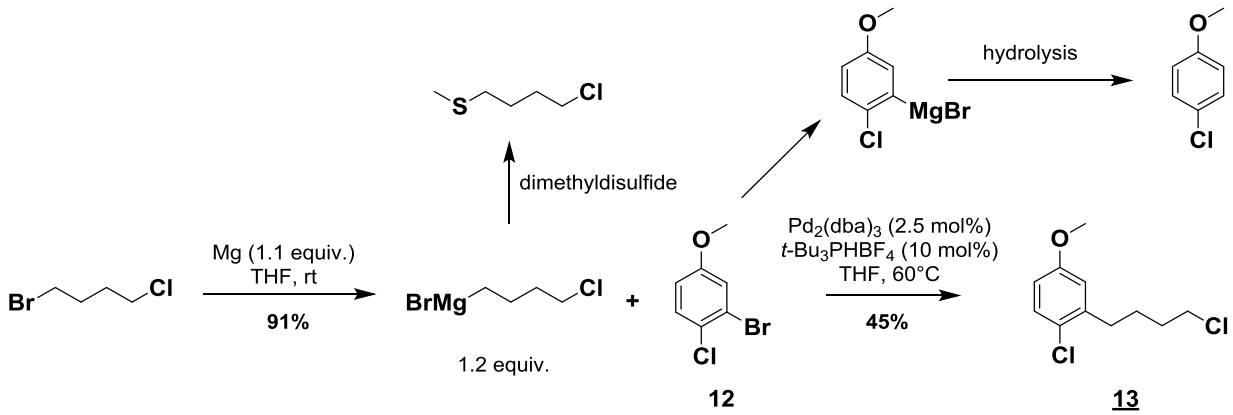
Following the original synthetic route, we established the allyl group *via* introduction of a vinyl residue on the benzylic carbon already in place. Hence, one could think of introducing the allyl group directly on the benzene ring *via* a cross coupling reaction using an allyl metal reagent. For the introduction of the alkyl chain the already established procedure could be used exploiting lithium halogen exchange and subsequent nucleophilic attack on 1-bromo-4-chlorobutane (**Scheme 13**). As an aryl bromide is required for the alkylation step, a chloride is needed as the second halide due to selectivity issues making 2-bromo-1-chloro-4-methoxybenzene **12** a suitable starting material. 1-Chloro-2-(4-chlorobutyl)-4-methoxybenzene **13** is then the logical substrate for the cross coupling reaction.



Scheme 14

There are examples where 2-bromo-1-chlorobenzenes were treated with *t*-BuLi to undergo lithium-halogen exchange and the lithium organyl was then reacted with an aldehyde or ketone as the electrophile.[45-46] In a first attempt aryl bromide **12** was stirred with 2 equiv. of *t*-BuLi at -78°C followed by addition of 1.5 equiv. of 1-bromo-4-chlorobutane (**Scheme 14**). After warming the reaction to room temperature only little conversion towards the product was observed. GC-MS showed full consumption of starting material but a lot of unreacted 1-bromo-4-chlorobutane and several unknown side products. In order to validate whether the lithiation is working, a reaction sample (after treatment with *t*-BuLi) was quenched with dimethyldisulfide as a strong electrophile. The corresponding quenching product would give a mass of 188 in GC-MS. When adding a sample into a solution of dimethyldisulfide in dry solvent, only a little amount of the quench product was observed. However, when taking up a sample by syringe which was previously charged with quenching solution, GC-MS gave a very prominent peak of the quenching product. Therefore, it can be concluded that the lithiation works but the lithium organyl is very reactive at temperatures above -78°C. Hence, we carried out the lithiation as before and added the alkylating reagent but kept the temperature at -78°C which gave no conversion. Slow warming led to undesired transformations as expected.

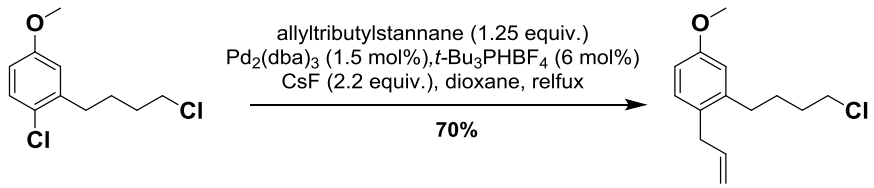
The 1,2-relationship between lithium and chloride makes aryne formation possible upon elimination of LiCl as it was suggested for (2-chlorophenyl)lithium.[47] The very reactive aryne species could then readily react in a number of possibilities leading to several unwanted side products. As the literature reports only deal with aldehydes and ketones, it can be suggested that the alkyl bromide is just not electrophilic enough and therefore, aryne formation is favored. Hence, this approach was abandoned.



Scheme 15

Another possibility to introduce the alkyl chloride is a coupling reaction. As 1-bromo-4-chlorobutane was already available, the usage of its Grignard reagent in a Kumada coupling was an obvious alternative. Preparation of (4-chlorobutyl)magnesium bromide was carried out in dry THF (Scheme 15). A sample was quenched with dimethyldisulfide and GC-MS analysis showed that Grignard formation occurred selectively on the bromide (mass of quench product: 138). Titration of the Grignard

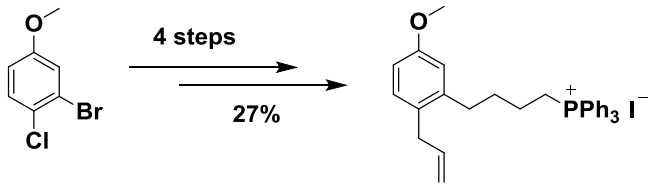
reagent with 2-butanole gave a yield of 91%. However, when the prepared Grignard reagent was stored over night at room temperature, concentration decreased to approximately 50% and unknown side products were observed by GC-MS. Therefore, the Grignard reagent was prepared freshly for every experiment. For the coupling step the catalytic system $Pd_2(dba)_3$ and *t*-Bu_3PHBF_4 was used as it was described for similar substrates.[48] When carrying out the reaction in dry THF, 50% of debrominated starting material was detected on average by GC-MS and ^{1}H-NMR analysis. When Fürstner and coworkers tried to couple aryl (pseudo) halides with Grignard reagents under iron catalysis, they observed significant dehalogenation of aryl iodides and aryl bromides (46% – 50%) as a limiting factor for their application.[49] Investigation of the reaction included varying the catalyst loading and the amount of Grignard reagent. It was observed that a higher amount of Grignard reagent favored the formation of the debrominated starting material. In consequence, by using a syringe pump for the slow addition of the Grignard reagent (1.2 equiv.) over one hour, we could slightly improve the situation but debromination remained to be a major problem. After purification by flash column chromatography compound **13** was isolated in 45% yield while in previous experiments yields in the range from 26% to 34% were achieved.



13 **8**

Scheme 16

The next step was the allylation of the aryl chloride **13**. 1-Chloro-4-methoxybenzenes are very electron rich substrates and, therefore, deactivated with respect to oxidative addition. Littke et. al. published a general procedure for the Stille coupling of aryl chlorides.[50] One example was the allylation of 1-chloro-4-methoxybenzene. By applying these conditions (**Scheme 16**) complete conversion to **8** was achieved after refluxing for three days and the desired product was obtained in 70% yield after flash column chromatography.

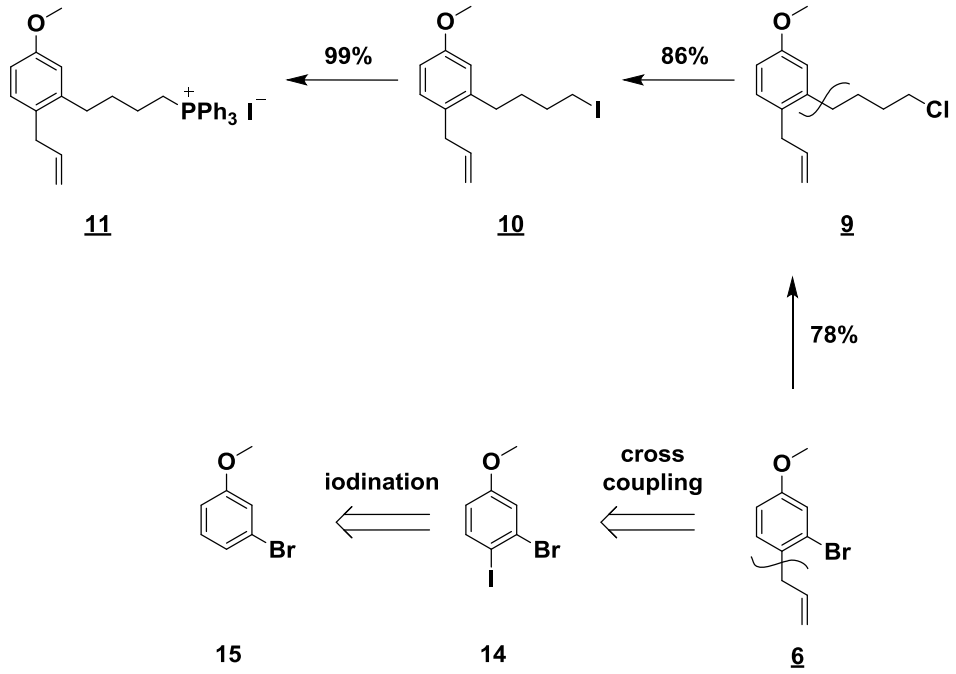


12 **11**

Scheme 17

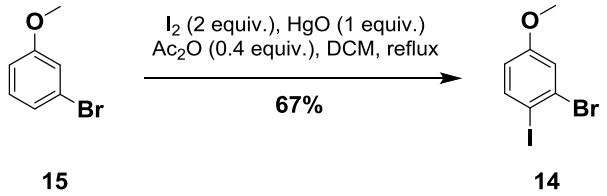
Although the desired transformation from starting material **12** to intermediate **13** *via* lithium halogen exchange and subsequent nucleophilic attack on 1-bromo-4-chlorobutane failed, the overall yield for the Wittig reagent **11** could nearly be doubled from 14% to 27%. Moreover the required steps for this building block were decreased from 7 to 4 (**Scheme 17**).

Nevertheless, also in this new synthetic route, the use of a Grignard reagent caused some trouble. As the allyl group was successfully introduced *via* Stille coupling another alternative synthetic route was developed.



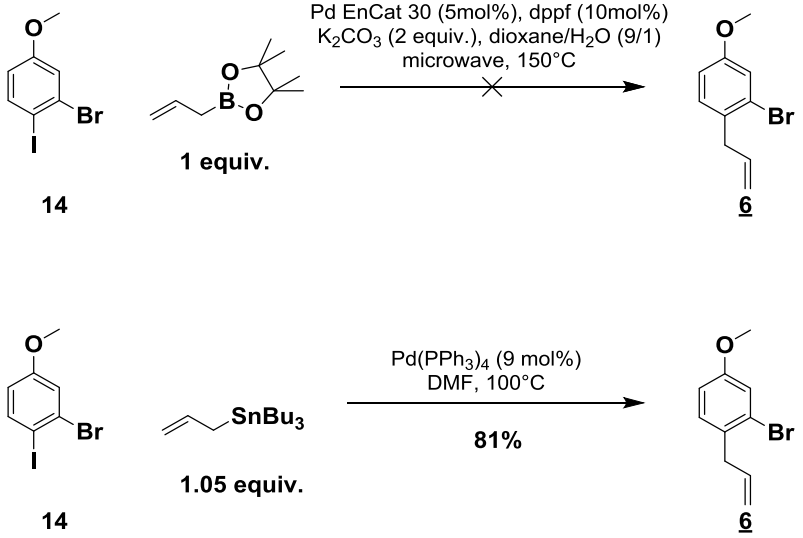
Scheme 18

As the alkylation step from compound **6** to compound **9** worked much better in the old route (78% versus 45%), it would be rational to keep this transformation and seek for a shortcut to synthesize compound **6**. Encouraged by the previous transformation, allylation *via* cross coupling before introducing the alkyl chloride could be a reliable reaction. Therefore, 2-bromo-1-iodo-4-methoxybenzene **14** would be the required starting material to selectively introduce the allyl group into the desired position. Compound **14** in turn could be accessed by iodination of 1-bromo-3-methoxybenzene **15**, which is a really cheap starting material (**Scheme 18**).



Scheme 19

1-Bromo-3-methoxybenzene **15** should be iodinated selectively in the 6 position as methoxy is a good *ortho* & *para* directing substituent and the two *ortho* positions (2 & 4) are sterically hindered. As iodine itself is not very electrophilic, oxidants are used to generate more reactive iodine species in *situ*.[51] For the preparation of aryl iodide **14** one protocol[52] exists where HgO is used as an activating oxidant, oxidizing I_2 to I_2O which then iodinates the substrate[53]. When applying the reported conditions conversion stopped after approximately 18 hours and the characteristic purple color caused by iodine was gone. Addition of more iodine led to full consumption of the starting material after refluxing overnight. Crude product was obtained nearly quantitatively but GC-MS and ^{1}H-NMR revealed 90% of the desired product and 10% of the *ortho* isomer. Only traces of the diiodide were detected. The two isomers turned out to have very similar chromatographic retention behavior. Therefore, separation *via* flash column chromatography was elaborate and the desired iodide **14** was obtained in 67% yield while mixed fractions had to be discarded (**Scheme 19**).

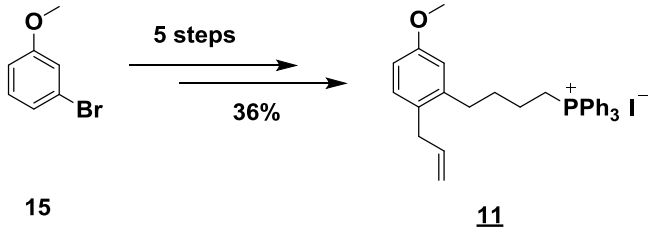


Scheme 20

For the allylation of 2-bromo-1-iodo-4-methoxybenzene **14**, first a Suzuki reaction was envisioned. Therefore, conditions which were developed within our research group for the allylation of 4-bromo-2-chlorophenol were applied. Encapsulated palladium and dppf as the ligand were used as the catalytic system. The original procedure gave full conversion after heating to 150°C in the microwave oven within 7 minutes for 4-bromo-2-chlorophenol. However, when applying these conditions to starting material **14**, no conversion at lower temperatures and only little conversion after 5 minutes at 150°C were observed. Therefore, the reaction was heated to 150°C by microwave for another hour. Surprisingly, product which had already been present had vanished. A lot of starting material was consumed and several side products were detected by GC-MS. As product was obviously formed in the first place, it can be suggested that a subsequent Heck reaction might be possible and would lead to undesired products, e.g. *via* polymerization. As the former yellow

mixture turned black in the course of the reaction, decomposition might have been occurred as well.

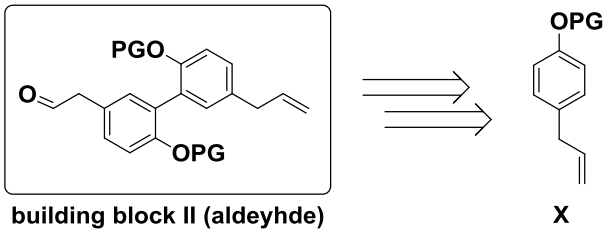
As the Stille coupling of compound **13** worked well, this kind of transformation was carried out next. Using $Pd(PPh_3)_4$ as the catalyst, rapid conversion was observed when heating to 100°C in DMF within 30 minutes. Addition of aqu. KF to the reaction solution caused precipitation of the stannane species which made work up quite facile as separation from stannane reagents can be complicated. Compound **6** was obtained in 81% yield after flash column chromatography (**Scheme 20**).

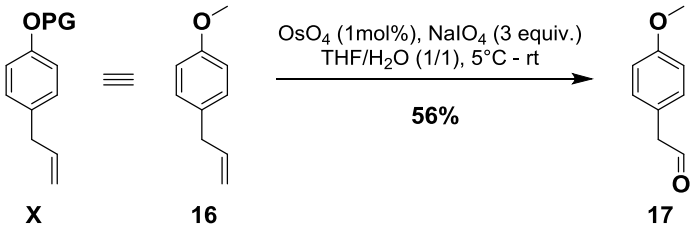


Scheme 21

By iodination of compound **15** and subsequent Stille coupling, the overall yield for the synthesis of Wittig reagent **11** could be further optimized. Compared to the very first synthetic route towards this building black, the number of necessary steps was also decreased from 7 to 5 (**Scheme 21**).

2.4. Synthesis of building block II (aldehyde)



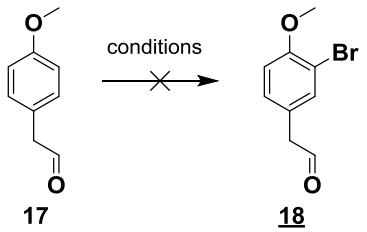


Scheme 22

In the restrosynthetic analysis for building block **II** the protected phenol **X** was found to be a suitable starting material. In the synthesis of building block I a methoxy group was used for protecting the phenolic hydroxy group. Consequently, a methoxy group was used as protecting group in the route towards building block **II** as well to enable

global deprotection in the end and furthermore, 1-allyl-4-methoxybenzene **16** is commercially available. For the preparation of 2-(4-methoxyphenyl)acetaldehyde **17** an oxidative cleavage of the double bond was the desired transformation. Nicolaou and coworkers published a methodical study on this kind of reaction using OsO_4 as the oxidant, $PhI(OAc)_2$ as co-oxidant which recycles OsO_4 and 2,6-lutidine with 1-allyl-4-methoxybenzene **16** being one example.[54] For the required transformation they reported a yield of 97%. When applying the exact literature conditions incomplete conversion was observed and the reaction did not proceed any further. Additionally, 4-methoxybenzaldehyde was detected by GC-MS and ^{1}H-NMR as a side product which would correspond to degradation by one CH_2 unit. The amount of 4-methoxybenzaldehyde increased slowly with time. Literature research revealed that such an unexpected transformation was already observed by Duchek et. al.[55] when deprotecting a structurally related acetal to the aldehyde.

When repeating the reaction with a higher catalyst loading (5 mol% instead of 2 mol%) conversion got better but was still incomplete. Increasing the amount of co-oxidant from 2.3 equiv. to 3 equiv at a catalyst loading of 2 mol% did not improve the transformation as much as a higher catalyst loading did. When using KIO_4 as co-oxidant no conversion was observed at all. Hence, we applied different literature conditions.[56] Stirring a solution of starting material **16** with $NaIO_4$ (3 equiv.) and OsO_4 (1 mol%) in THF/H_2O (1/1) gave complete conversion after 20 minutes (**Scheme 22**). Unfortunately, isolation of the aldehyde **17** by flash column chromatography failed as decomposition occurred while running the column. Hence, the product was obtained by *Kugelrohr* distillation and a yield of 56% was achieved. In the residues of distillation the corresponding carboxylic acid was found. In future experiments a lower amount of $NaIO_4$ should be tried which may result in higher yields due to less over-oxidation.

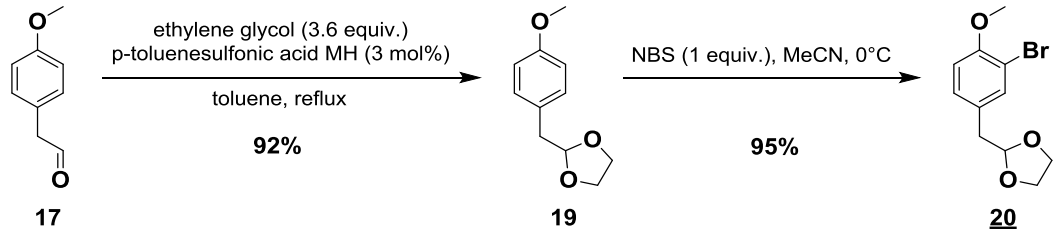


17 **18**

Scheme 23

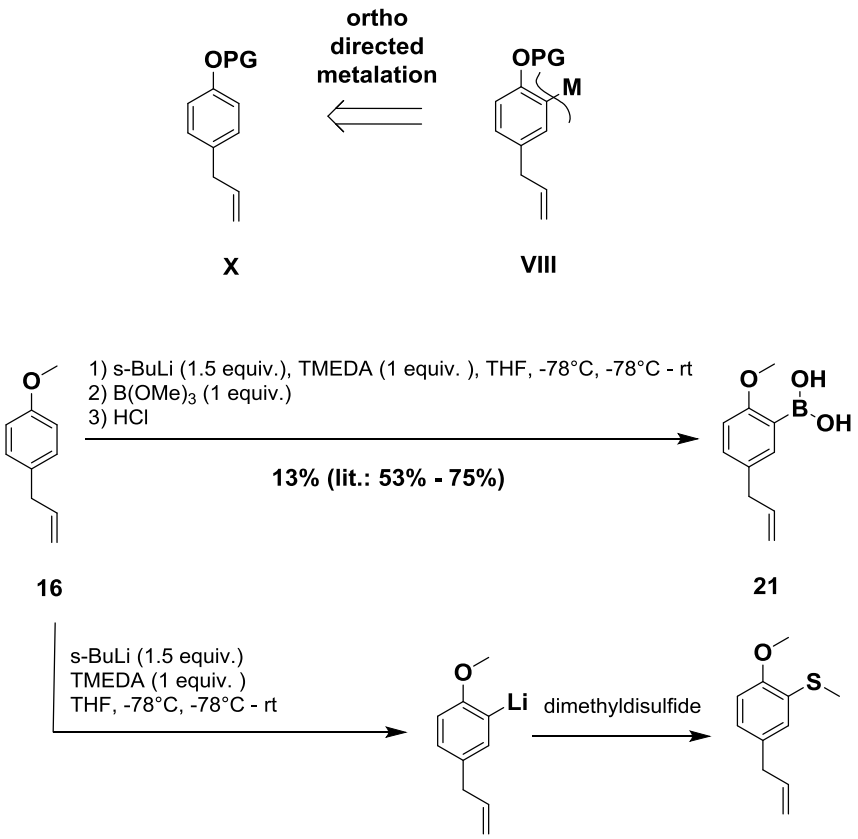
Next the bromination of aldehyde **17** to 2-(3-bromo-4-methoxyphenyl)acetaldehyde **18** was envisioned. In test reactions three different bromination conditions were applied. Pyridinium tribromide in acetic acid gave no detectable product by GC-MS but only one unknown side product with a mass of 281. Bromine in acetic acid and NBS in acetonitrile gave good conversion while bromination by NBS looked more promising. However, ^{1}H-NMR spectrum of the crude mass displayed another peak present in the aldehyde region. As it was a singulet and this kind of signal had already been observed in the preparation of aldehyde **17**, it can be suggested that CH_2 degradation happens again. When trying to purify the crude mass by flash

column chromatography only little amounts of impure material were obtained. Moreover, the storage stability of aldehyde **17** is limited as significant amounts of the corresponding carboxylic acid were found in stored samples. As the presence of the aldehyde group caused so much problems (no chromatography on silica gel possible, oxidation to carboxylic acid, degradation to corresponding benzaldehyde) it was decided to protect the aldehyde as we would need to keep the aldehyde intact for another step and would need to have purified material in the end (coupling product **II** would not be possible to purify by distillation).



Scheme 24

Hence, aldehyde **17** was protected as cyclic acetal applying general protection conditions. The water which forms in the course of the reaction was stripped of by refluxing the reaction on a Dean-Stark apparatus. After work-up 2-(4-methoxybenzyl)-1,3-dioxolane **19** was obtained in 92% yield and as purity was proven to be very good by ^{1}H-NMR, the product was used in the bromination step without purification. As bromination with NBS in acetonitrile gave very good conversion using aldehyde **17** as a starting material, the same conditions were applied to acetal **19**. Stirring the reaction mixture at 0°C gave clean conversion to 2-(3-bromo-4-methoxybenzyl)-1,3-dioxolane **20** within 2 hours and the product was obtained after work-up in analytical pure form with a yield of 95% (**Scheme 24**).

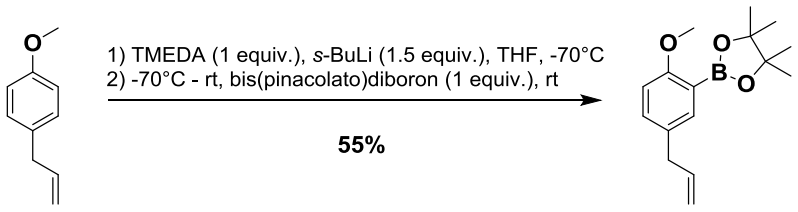


Scheme 25

With bromide **20** in hand the corresponding coupling partner **VIII** was to be synthesized next. In the restrosynthetic analysis a metalation of starting material **X** was recognized as a very elegant and economic transformation. Alternatively the metal species **VIII** can be synthesized from the corresponding bromide. A lithium halogen exchange would make the desired position available for introduction of a metal species. Exploiting the *ortho* directing ability of oxygen substituents we wanted to introduce the metal species directly on the unfunctionalized substrate resulting in a shorter sequence and hopefully a better yield as well. Furthermore, a much higher atom economy would be achieved. For the starting material **X** 1-allyl-4-methoxybenzene **16** was chosen for the same reasons already mentioned before. Snieckus has published an excellent review on the topic of *ortho* directed metalation.[57] Although the methoxy group is a rather poor *ortho* directing group, we were encouraged by publications of Denton et. al. where they synthesized (5-allyl-2-methoxyphenyl)boronic acid **21** *via ortho* directed lithiation starting from compound **16**.[58-59] Therefore, literature conditions were reproduced using boronic acid **21** in a subsequent Suzuki coupling. In the original procedure starting material **16** was reacted with *s*-BuLi (1.5 equiv.) and TMEDA (1 equiv.) in THF at -78°C for one hour. After warming to room temperature the reaction was stirred for one hour followed by the addition of $B(OMe)_3$ (1 equiv.) and stirring for 24 hours. Acidifying with 1 N HCl and stirring for one hour gave boronic acid **21**. After work-up and purification by chromatography the authors reported a yield of 53%[58] and 75%[59] respectively

(**Scheme 25**). Upon reproduction of these literature conditions, boronic acid **21** was only obtained in 13% yield. According to TLC analysis conversion was not complete and several spots were detected. When flash column chromatography was performed to separate these compounds, only low quantities of impure compounds were obtained and their structure could not be determined. Surprisingly the desired product itself was obtained from fractions, where TLC analysis gave no spot under UV and staining with different dip reagents gave only ambiguous informations. As it was not clear whether the lithiation did not work properly or the subsequent boronation caused the numerous side products, quenching of several reaction samples during the course of the reaction was performed using dimethyldisulfide in dry THF. It was observed that lithiation proceeds at -78°C within an hour although it is not complete. When stirring the reaction longer, the ratio of quench product and starting material gets worse in GC-MS suggesting that the lithium species is not stable very long under these conditions. In accordance with this observation also a decolorization of the former orange-red solution was witnessed. When letting the reaction reach room temperature after one hour at -78°C and stirring the reaction for another hour at room temperature, full conversion of starting material towards the quench product was found in analytical samples. A decoloration was not observed as well. It seems that the increase in reaction temperature is necessary to achieve complete lithiation. Furthermore, the lithiated aryl stayed intact much longer after warming to room temperature than staying at -78°C. It might be suggested that this is due to decomposition of excessive *s*-BuLi at room temperature while the aromatic lithium species is more stable.

It can be concluded that the lithiation step works just fine but the subsequent boronation step does not. Surprisingly the intermediate boronic ester was never detected by GC-MS although it can be expected to get into gas phase in the analytical procedure. Attempts to improve the situation by using triisopropyl borate, varying equivalents and varying reaction time were not successful.

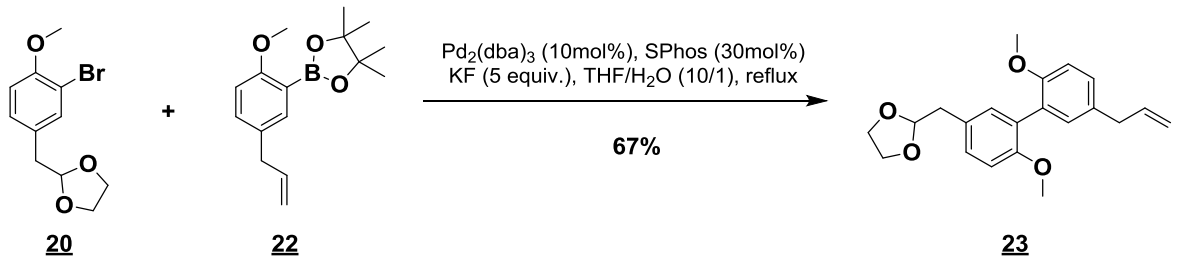


16 **22**

Scheme 26

With a working lithiation protocol in hand we envisioned a different coupling partner to take part in the subsequent cross coupling. Pinacol esters of boronic acids react in a Suzuki coupling as well.[60] Therefore, an alternative approach was to synthesize 2-(5-allyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **22**. Adding bis(pinacolato)diboron to the lithium species led to formation of the desired pinacol ester **22** (**Scheme 26**). When 1 equiv. of the boron reagent was used, full

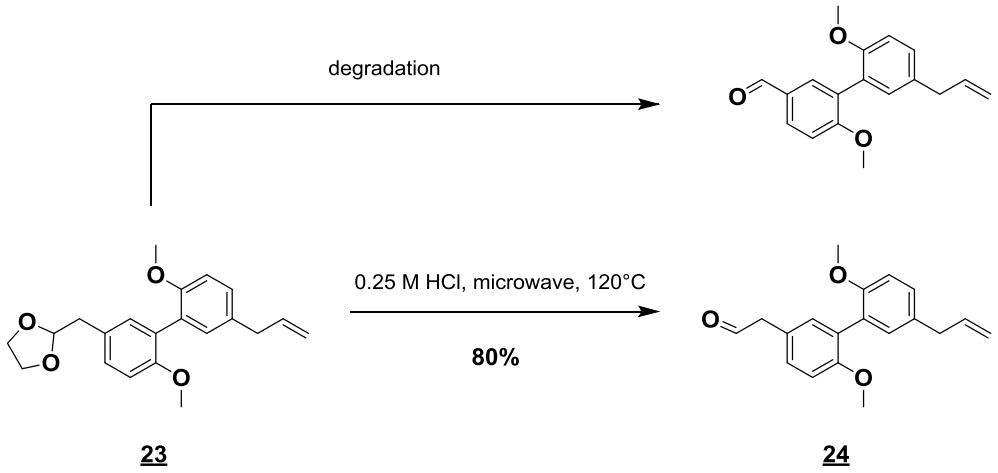
consumption of the starting material **16** was observed but ^{1}H-NMR and GC-MS of the crude mass revealed unreacted boron reagent to be present. When using only 0.65 equiv. of the boron reagent, ^{1}H-NMR and GC-MS analysis gave nearly only product and full consumption of the starting material which is surprising as there should by still starting material left. However, this was repeatedly the case and no significant amounts of side products were found in GC-MS and ^{1}H-NMR. On ordinary TLC plates decomposition of the product was observed. Hence, flash column chromatography was carried out with eluents containing 3% NEt_3. Pinacol ester **22** was isolated in 40% yield. As chromatographic separation was problematic (analyzing fractions by TLC led to several spots due to decomposition and pinacol ester **22** could not be detected under UV and gave no spots upon staining with different dip reagents when using NEt_3 doped eluents) and GC-MS and ^{1}H-NMR analysis of crude mass seemed more promising than the isolated yield of 40%, loss of product was suspected during work-up and purification. Therefore, the content of product in crude mass was determined by ^{1}H-NMR. An aliquot of the crude mass was taken and mixed with a known quantity of DMSO. ^{1}H-NMR was measured and by comparing the integral of the singulet of DMSO with the integral of the doublet of the product at 7.49 ppm (H6), a yield of 55% was determined. As GC-MS and ^{1}H-NMR gave no hint of other substances to be present in higher quantities, LC-MS was measured but also there no significant amounts of side products were found. As purity of the crude mass was rated to be good, product was not isolated but used crude in the subsequent cross coupling.



Scheme 27

For the Suzuki coupling of bromide **20** and pinacol ester **22** conditions were needed where the allyl group stays intact as Pd catalyzes not only the cross coupling reaction but also the isomerization of the double bond.[61] Denton and coworkers reported such a method for structurally related compounds.[62] They faced substantial isomerization in various solvents when PPh_3 was used as ligand and Na_2CO_3 or K_2CO_3 as base. On the contrary when KF was used as the base and SPhos as ligand, no isomerization occurred. Hence, bromide **20** (1 equiv.) and crude pinacol ester **22** (1.5 equiv.) were reacted following this protocol. Although the less reactive pinacol ester **22** had to be used instead of the boronic acid **21**, full conversion was achieved within

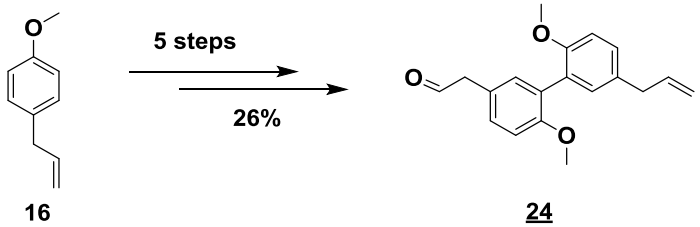
24 hours and only traces of isomerized product were detected. When the crude material was submitted to flash column chromatography, the desired product 2-((5'-allyl-2',6-dimethoxy-[1,1'-biphenyl]-3-yl)methyl)-1,3-dioxolane **23** was not obtained in pure form as the product was contaminated with bis(pinacolato)diboron from the crude pinacol ester mixture. Therefore, product was submitted to chromatography once again (1% – 5% MeCN in toluene) and was obtained in pure form in 43% yield. This problem was tackled by reducing the amount of pinacol ester **22** from 1.5 equiv. to 1.1 equiv. which proved to be sufficient Further improvement in the chromatographic separation allowed the isolation of acetal **23** in 67% yield (**Scheme 27**).



Scheme 28

As we had to introduce the acetal functionality on compound **19** in order to protect the corresponding aldehyde due to several practical issues, deprotection was required at this step of the synthesis. First, it was tried to cleave the acetal by stirring a solution of starting material **23** dissolved in THF with 2 N HCl for 24 hours at room temperature followed by another 14 hours at 40°C as conversion got very slow. In the course of the reaction an increasing amount of side product with a mass of 282 (14 less than desired product) was detected by GC-MS. In crude ^{1}H-NMR the expected product 2-(5'-allyl-2',6-dimethoxy-[1,1'-biphenyl]-3-yl)acetaldehyde **24** was present but there was also another singulet in the aldehyde region. Comparison with the side product formation in the synthesis of aldehyde **17** and aldehyde **18** led to the conclusion that again degradation by one CH_2 unit caused formation of this side product. A degradation of a structurally related 2-phenylacetaldehyde to a benzaldehyde analog was described by Duchek et. al. recently.[55] Starting from the corresponding diol, they proposed an oxidation in the benzylic position by atmospheric oxygen and loss of formic acid leading to a benzaldehyde derivative. By using degassed solvents they were able to suppress this transformation to a content of 5%. As this is an unexpected transformation, it would be interesting to evaluate whether this reaction is of any preparative value in future experiments.

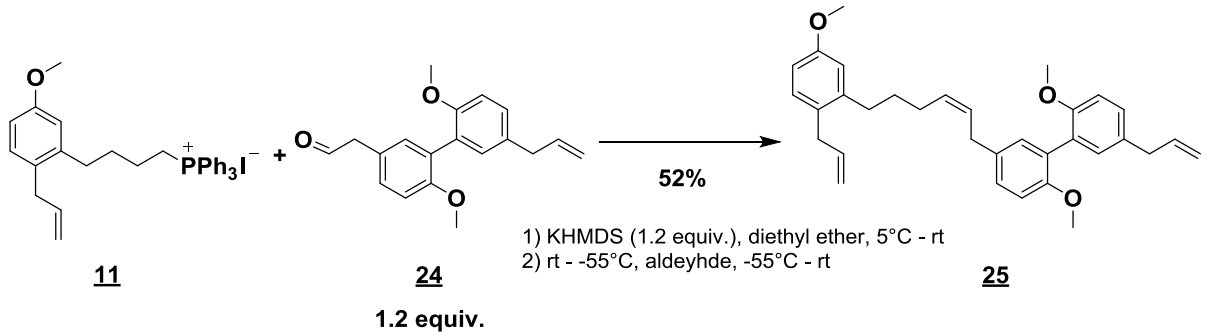
Consequently, solvents were carefully degassed prior to use. Furthermore, a microwave assisted procedure published by Procopio et. al. seemed very interesting as they claimed to cleave acetals under neutral aqu. conditions.[63] Unfortunately after heating acetal **23** with H_2O in the microwave oven for 40 minutes at 120°C as it was reported for a structurally related dimethyl acetal, no conversion was observed which can be explained by the higher stability of the cyclic acetal. Hence, different concentrations of HCl and different reaction times were applied. Higher concentrations of HCl (1 M) resulted in the formation of an unknown side product whereas lower concentrations required longer reaction time. Optimal conditions were found with 0.25 M HCl and an irradiation time of 60 minutes at 120°C (**Scheme 28**). GC-MS assumed a clean conversion towards aldehyde **24**. However, ^{1}H-NMR looked good as well but the integral of the aldehyde proton and the adjacent CH_2 group did not correspond to the expected values of 1 and 2 respectively but gave values of 0.8 and 1.6 respectively. As there were no other signals in ^{1}H-NMR and C-NMR was pure as well, a purity of 80% was assumed while crude mass was obtained quantitatively. Therefore, a yield of 80% was assigned and the product was used in the subsequent Wittig reagent as obtained. Furthermore, it was tried to purify the crude mass by flash column chromatography but obtained fractions had a worse quality than the crude mass indicating decomposition as already observed in earlier experiments.



Scheme 29

Summarized the desired building block **II** was obtained in 26% yield over 5 steps starting from commercially available 1-allyl-4-methoxybenzene **16**. The metal coupling partner for the Suzuki coupling was successfully obtained from the same starting material; by exploiting ortho directed lithiation the required metal species was obtained in one single step. The aldehyde motif had to be protected as several problems emerged when the aldehyde was present.

2.5. Synthesis of biological probes



Scheme 30

With robust synthetic routes established for both building blocks, the most important reaction was the following Wittig reaction. In a preliminary experiment *n*-BuLi was used to deprotonate the Wittig reagent **11**. After addition of the base at -78°C the starting material partly dissolved. When the reaction was allowed to reach room temperature, the reaction turned dark brown indicating an undesired reaction. After addition of aldehyde **24** several new spots were detected by TLC analysis and separation by flash column chromatography gave only low quantities of unknown compounds whose structure could not be determined. In consequence another base had to be used. A procedure for structurally similar substrates was available where the authors used potassium bis(trimethylsilyl)amide (KHMDS) as a strong but non-nucleophilic base.[64] A suspension of the Wittig reagent **11** in dry diethyl ether was treated with a 0.5 M solution of KHMDS in toluene at 0°C (**Scheme 30**). The formation of the ylide-yliden tautomeric pair caused the mixture to become homogeneous and deep orange. The solution was cooled to -78°C where upon addition of the aldehyde **24** a precipitant appeared which would be in accordance with the expected formation of triphenylphosphine oxide. TLC analysis showed one new apolar spot and probably some unreacted Wittig reagent. There was no hint for the presence of a product pair of the E- and Z-isomer. After work-up and purification by flash column chromatography 52% of colorless oil was obtained. To verify the obtained product, a ^{1}H-NMR spectrum was recorded on a 400 MHz spectrometer. The two new olefinic protons were expected to give a pair of doublets of triplets. In **Figure 12** the calculated signal for the desired (Z)-5-allyl-5'-(6-(2-allyl-5-methoxyphenyl)hex-2-en-1-yl)-2,2'-dimethoxy-1,1'-biphenyl **25** can be seen. The prediction was obtained by first measuring the actual compound and then using the obtained values for the chemical shifts to calculate the expected coupling pattern. By comparison with the recorded signal (**Figure 13**) the obtained product can be confirmed to be in Z configuration. No hint was given that any E-olefin is formed.

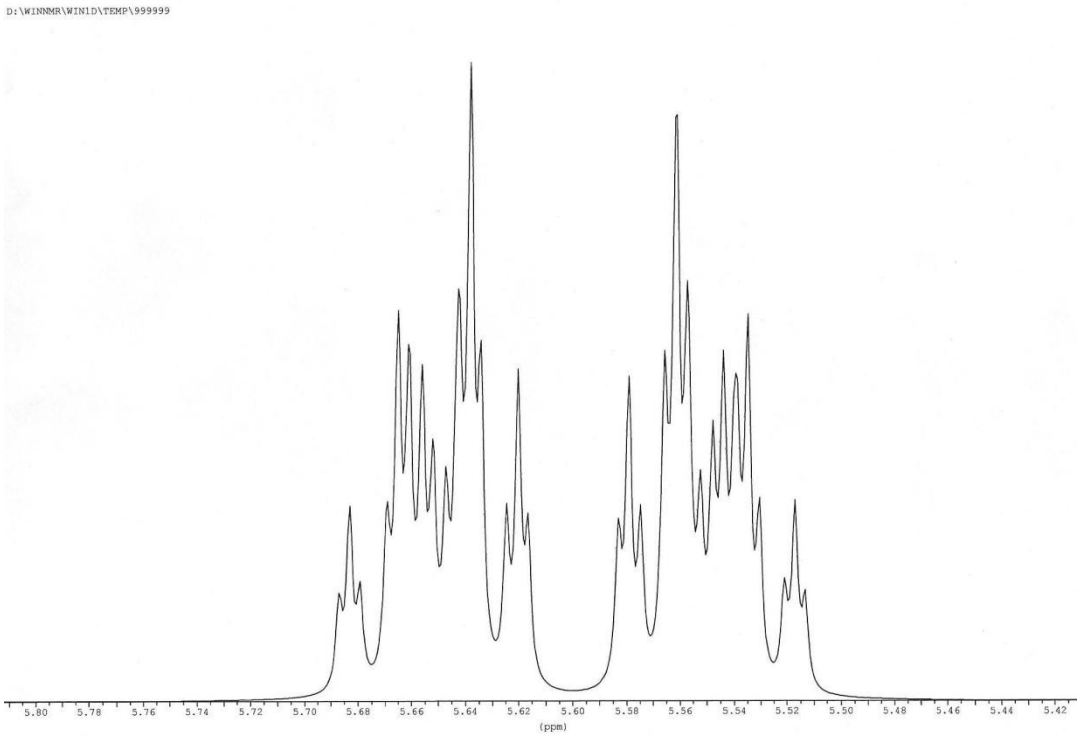


Figure 12 calculated signal for the two new olefinic protons

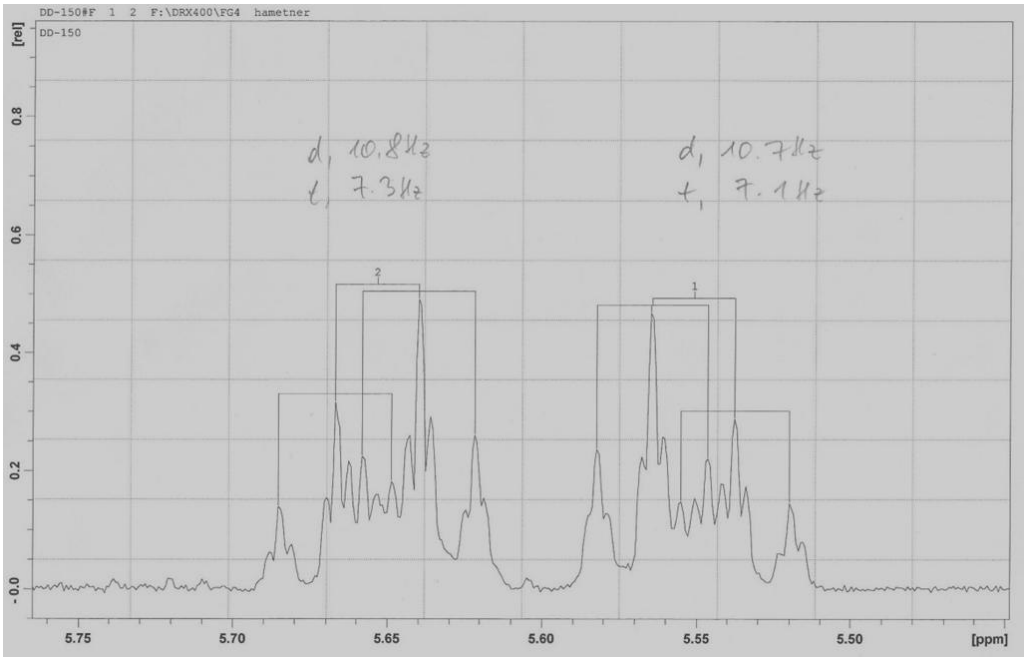
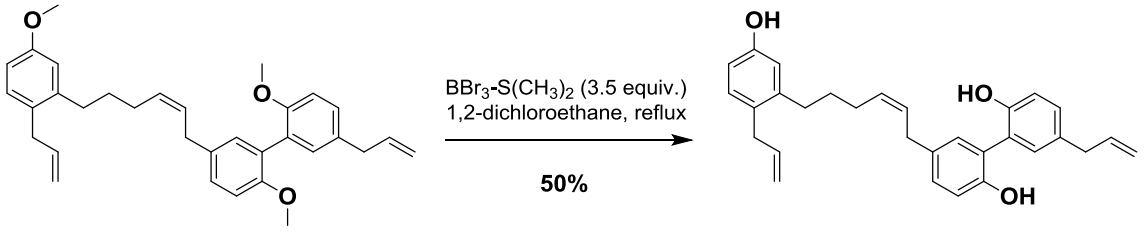


Figure 13 measured signal for the two new olefinic protons

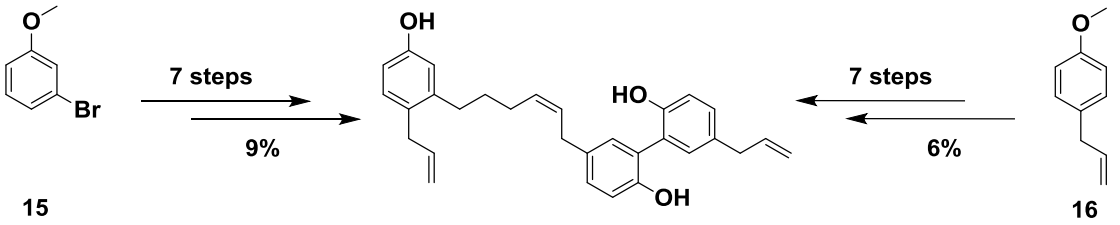


25 **1**

Scheme 31

As the final step of the synthesis a global deprotection was necessary. To demethylate compound **25** a protocol which was used to demethylate 1-allyl-4-methoxybenzene **16** was applied.[65] Starting material **25** was refluxed with 3.5 equiv. of BBr_3-SMe_2 in 1,2-dichloroethane (**Scheme 31**). The reaction was followed by LC-MS. Starting material was completely consumed after 2 hours. An intermediate bearing still one methoxy group was present much longer and was finally consumed after 21 hours. If this intermediate is the product with the phenol on the left still protected, one could think of applying this intermediate to ortho directed lithiation conditions and after a subsequent coupling step the second half of a magnolol molecule could be introduced to obtain the non-simplified magnolol dimer (see **Figure 11**). After work-up and isolation by flash column chromatography the desired simplified magnolol dimer **1** (sesqui-magnolol) was obtained in 50% yield. As far as it can be evaluated, no isomerization of any double bond occurred.

2.6. Conclusion



15 16

1

Scheme 32

Starting from aniline **3**, Wittig reagent **11** was successfully obtained as one of the two necessary building blocks for a subsequent Wittig reaction. Following the initial route several problems arose (debromination when applying Grignard reagent, inseparable side products, low yield) and a moderate yield of 14% over 7 steps was achieved. Changing the systematics in the formation of the allyl group by coupling reactions led to significant improvements in two alternative routes. Starting from anisole **12** gave Wittig reagent **11** in 27% yield over only 4 steps while starting from anisole **15** further increased the yield to 36% over 5 steps.

The aldehyde **24** as the second necessary building block was obtained in 26% yield over 5 steps starting from commercially available **16** as a common starting material. Protection of the aldehyde was necessary as degradation to the benzaldehyde analog was observed throughout the synthetic route which caused serious problems on the one hand but is an interesting transformation on the other hand and could be addressed in future projects.

With both building blocks in hand, the desired simplified magnolol dimer **1** (sesqui-magnolol) was successfully synthesized *via* Wittig reaction and subsequent global deprotection. For most transformations good (67%) to excellent (99%) yields were achieved. Some lower yielding reactions (50% - 56%) affected the overall yield; however, as the main goal of this project was to synthesize the target molecule as a pharmaceutical probe, the challenge was successfully tackled. Starting from compound **15** an overall yield of 9% was obtained while starting from compound **16** 6% yield was accomplished (**Scheme 32**).

Compounds **25** and **1** were submitted to our cooperation partners and are currently investigated towards their biological activity.

3. Experimental part

3.1. General notes

Chemicals

Chemicals were purchased from commercial suppliers and used without further purification unless otherwise noted.

Dry solvents

Dry THF, dry diethyl ether and dry toluene were obtained by distilling pre-dried solvents freshly from Na/benzophenone ketyl radical.

Dry TMEDA was distilled from NaH and was stored under argon and molecular sieves.

Dry CCl_4 was distilled freshly from P_4O_{10}.

Dry dioxane was obtained by passing pre-dried material through a cartridge containing activated alumina *via* a solvent dispensing system and stored under argon and over molecular sieve.

Microwave reactions

Microwave reactions were performed using a Biotage Initiator EXP EU Microwave Synthesizer.

Chromatography (TLC, MPLC)

TLC was performed on aluminum coated silica gel 60 F_{254} from Merck and spots were visualized with UV light and/or staining with various dip reagents. In general, cerium-ammonium-molybdate and phosphomolybdic acid dip reagents were used. For compounds containing allyl groups, basic $KMnO_4$ was used as dip reagent.

Flash column chromatography was performed on a Büchi Sepacore™ MPLC system, using silica gel 60 (40-63 µm) from Merck.

Distillation

Kugelrohr distillation was carried out using a Büchi GKR-51 apparatus.

Melting points

Melting points were determined using a Stanford Research Systems MPA100 OptiMelt Automatic Melting Point System. Data is given in 0.5 °C intervals.

GC-MS

A Thermo Finnigan Focus GC / DSQ II using a standard capillary column BGB 5 (30 m x 0.25 mm ID) or a Thermo Trace 1300 / ISQ LT using a standard capillary column

BGB 5 (30 m x 0.25 mm ID) were used for GC-MS runs. The following settings were used as standard:

Ionization method: Electron ionization (70 eV)
Injection: 1 µL (hot needle-technique), split-injection (ratio 1:8)
Flow: 2 mL/min helium
Injectorblock temperature: 250 °C
MS-transferline temperature: 280 °C

Reported are:
all fragment signals at/over mass (m/z) 100 and at/over 10 % relative intensity
all molecular peaks (regardless the relative intensity)
all peaks with 100 % intensity (regardless the mass)

HR-MS

HR-MS was carried out by Prof. E. Rosenberg at Vienna University of Technology, Institute for Chemical Technologies and Analytics.

Analytical method: All samples were analyzed by LC-IT-TOF-MS with electrospray-ionization (ESI) and atmospheric pressure chemical ionization (APCI) in only positive ion detection mode upon recording of MS spectra. For the evaluation in the following, only positive ionization spectra were used (where the quasi-molecular ion is the one of $[M+H]^+$ or $[M+Na]^+$), and further data or information were not taken into consideration.

Instrumental parameters: Shimadzu Prominence HPLC, consisting of: solvent degassing unit (DGU-20 A3), binary gradient pump (2 x LC-20AD), auto-injector (SIL-20A), column oven (CTO-20AC), control module (CBM-20A), and diode array detector (SPD-M20A)

MS-system: Shimadzu IT-TOF-MS with ESI and APCI interface.

Chromatography (parameters: Short_Col_PI_NI_MS2): column: Phenomenex ODS(3), 4 mm x 4.6 mm, 5 µm particles, operated at 40 °C; column flow: 0.5 ml/min; injection volume: 2 µl; gradient: A: H_2O + 0.1 % formic acid, B: MeOH; MS parameters as in autotune. Data recorded with detector voltage at autotune value. Scan range: 100 - 1000 amu for both, MS (PI and NI)-detection. ES ionization. Cycle time <0.6 s. CDL-temperature 200 °C, Heating block temperature: 200 °C, scan range 200-400 nm

NMR-Spectroscopy

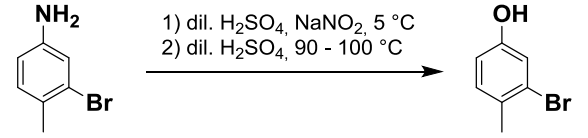
^1H- and ^{13}C-NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 200 (200 MHz) or on a Bruker Avance UltraShield 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm relative to the nominal residual solvent signal of $CDCl_3$: ^1H: 7.26 ppm, ^{13}C: 77.0 ppm. Annotations of the structures were carried out in accordance with nomenclature unless otherwise noted-.

3.2. Abbreviations

approx.	approximately
aqu.	aqueous
bs	broad singlet (NMR)
d	doublet (NMR)
dba	dibenzylideneacetone
dd	doublet of doublets (NMR)
dil.	diluted
dppf	1,1‘-bis(diphenylphosphino)ferrocen
dt	doublet of triplets (NMR)
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
equiv.	equivalent
GC-MS	gas chromatography - mass spectrometry hyphenation
HR-MS	high resolution mass spectrometry
J	coupling constant (NMR)
KHMDS	potassium bis(trimethylsilyl)amide
LC-MS	liquid chromatography – mass spectrometry hyphenation
LP	light petroleum (boiling point approx. 40 – 60 °C)
m	multiplet (NMR)
MPLC	medium pressure liquid chromatography
NBS	N-bromosuccinimide
NMR	nuclear magnetic resonance
$PhI(OAc)_2$	(diacetoxyiodo)benzene
ppm	parts per million (NMR)
p-toluenesulfonic acid MH	p-toluenesulfonic acid monohydrate
R_f	retention factor (TLC)
rt	room temperature
s	singlet (NMR)
s-BuLi	*sec*-butyllithium
satd.	saturated
SPhos	2-Dicyclohexylphosphino-2‘,6‘-dimethoxyphenyl
t	triplet (NMR)
t-BuLi	*tert*-butyllithium
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
q	quartet (NMR)
quin	quintet (NMR)

3.3. Synthesis of building block I (Wittig reagent)

3.3.1. 3-Bromo-4-methylphenol (2)



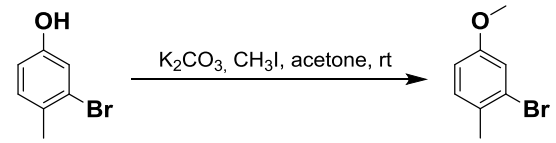
3
M = 186.05

2
M = 187.04

3-Bromo-4-methylphenol **2** was synthesized according to a modified literature protocol.[34] A 500 mL flask was charged with 3-bromo-4-methylaniline **3** (5.015 g, 27.0 mmol, 1 equiv.) and hot diluted H_2SO_4 (80 mL H_2O + 54 mL H_2SO_4) was added whereupon the starting material solidified. The mixture was heated up till the starting material was completely dissolved (approx. 85°C). While the reaction solution was allowed to cool again, starting material precipitated as fine crystals resulting in a stirrable mixture which was cooled with an ice bath. When the temperature dropped below 5°C $NaNO_2$ (2.05 g, 29.7 mmol, 1.1 equiv, dissolved in 20 mL H_2O) was added dropwise maintaining the temperature below 5°C. After addition was complete, the reaction mixture was stirred for 5 minutes and became homogeneous within this time. Then the ice bath was removed, diluted H_2SO_4 (35 mL H_2O + 35 mL H_2SO_4) was added and the reaction solution was heated to 90 - 100°C for 15 minutes. The reaction solution was cooled to room temperature and extracted with diethyl ether (3 x 100 mL). The organic phases were combined and washed with brine (100 mL). When this aqu. phase was poured into the remaining aqu. Phase from EtOAc extraction, another organic phase formed. Therefore the two phases were separated and the new organic phase was washed with brine (30 mL) again. The combined organic phases were dried over $MgSO_4$. After filtration and evaporation of the solvent in *vacuo* a brown oil was obtained. Purification by flash column chromatography (crude mass/SiO_2 = 1/35, LP → 5% EtOAc in LP) provided the desired product. After drying in high vacuum the former liquid became solid. Spectral data[66] and melting point[67] were in accordance with literature data.

Yield: 83% (4.185 g, 22.4 mmol)
Appearance: pale red solid
Melting point: 55.0 – 55.5 °C (lit.[67]: 55.2 – 55.4 °C)
TLC: R_f (LP/EtOAc = 5/1) = 0.52
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3H, CH_3), 5.06 (s, 1H, OH), 6.70 (dd, J = 8.2 Hz & 2.7 Hz, 1H, H6), 7.05 – 7.11 (m, 2H, H2 & H5) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 21.81 (q, CH_3), 114.52 (d, C6), 119.27 (d, C2), 124.83 (s, C3), 130.10 (s, C4), 131.25 (d, C5), 153.81 (s, C1) ppm.
GC-MS:
Main fragments: 188 (68, M^+), 187 (27), 186 (75, M^+), 185 (26), 108 (10), 107 (100), 105 (12)

3.3.2. 2-Bromo-4-methoxy-1-methylbenzene (4)



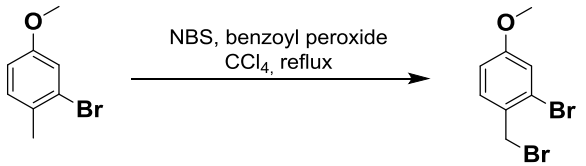
2
M = 187.04

4
M = 201.06

A 250 mL flask was charged with 3-bromo-4-methylphenol **2** (4.04 g, 21.6 mmol, 1 equiv.), acetone (110 mL), and K_2CO_3 (5.97 g, 43.2 mmol, 2 equiv.). The mixture was stirred for 10 minutes. Then methyl iodide (3.99 g, 28.1 mmol, 1.3 equiv.) was added and the mixture was stirred at room temperature for 24 hours. Solvent was removed in *vacuo* and the residue was distributed between diethyl ether (50 mL) and H_2O (50 mL). The two phases were separated and the aqu. phase was extracted with diethyl ether (2 x 25 mL). The combined organic layers were dried over $MgSO_4$. After filtration and evaporation of the solvent in *vacuo* a red liquid was obtained. Purification by flash column chromatography (crude mass/SiO_2 = 1/22, LP → 2% EtOAc in LP) provided the desired product. Spectral data are in accordance with literature reports.[68]

Yield: 81% (3.54 g, 17.6 mmol)
Appearance: colorless liquid
TLC: R_f (LP/EtOAc = 5/1) = 0.7
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.32 (s, 3H, Ar-CH_3), 3.77 (s, 3H, O-CH_3), 6.76 (dd, *J* = 8.4 Hz & 2.6 Hz, 1H, H5), 7.08 – 7.15 (m, 2H, H3 & H6) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 21.80 (q, Ar-CH_3), 55.51 (q, O-CH_3), 113.38 (d, C5), 117.53 (s, C3), 124.85 (d, C2), 129.68 (s, C1), 130.97 (d, C6), 158.19 (s, C4) ppm.
GC-MS:
Main fragments: 202 (59, M^+), 201 (17), 200(63, M^+), 199 (13), 121 (100), 105 (17)

3.3.3. 2-Bromo-1-(bromomethyl)-4-methoxybenzene (5)



4
M = 201.06

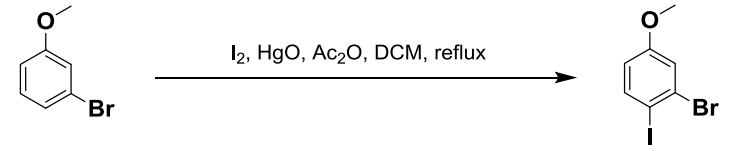
5
M = 279.96

2-Bromo-1-(bromomethyl)-4-methoxybenzene **5** was synthesized according to a modified literature protocol.[69] A 250 mL flask was charged with 2-bromo-4-methoxy-1-methylbenzene **4** (1.18 g, 5.89 mmol, 1 equiv.), NBS (1.05 g, 5.89 mmol, 1 equiv.), and benzoyl peroxide (17 mg, 0.07 mmol, 1.2 mol%). Dry and degassed CCl_4 (74 mL) was added under argon atmosphere and the reaction mixture was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature and was washed with 2N HCl (74 mL), satd. aqu. $NaHCO_3$ (74 mL), H_2O (74 mL), and brine (74 mL). The organic phase was dried over Na_2SO_4. After filtration and evaporation in *vacuo* a yellow solid was obtained. Purification by flash column chromatography (crude

mass/SiO_2 = 1/55, 2% EtOAc in LP) provided the desired product. Spectral data and melting point are in accordance with literature data.[70]

Yield: 86% (1.42 g, 5.06 mmol)
Appearance: colorless crystals
Melting point: 59.0 – 60.5°C (lit.: 59 – 60 °C)
TLC: R_f (LP/EtOAc = 5/1) = 0.7
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.80 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.83 (dd, J = 8.5 Hz & 2.6 Hz, 1H, H5), 7.12 (d, J = 2.6 Hz, 1H, H3), 7.36 (d, J = 8.5 Hz, 1H, H6) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 33.76 (t, CH_2), 55.62 (q, CH_3), 114.05 (d, C5), 118.47 (d, C3), 125.09 (s, C2), 129.05 (s, C1), 131.91 (d, C6), 160.24 (s, C4) ppm.
GC-MS:
Main fragments: 201 (96, M^+), 199 (100, M^+), 120 (10), 105 (13)

3.3.4. 2-Bromo-1-iodo-4-methoxybenzene (14)



15
M = 187.04

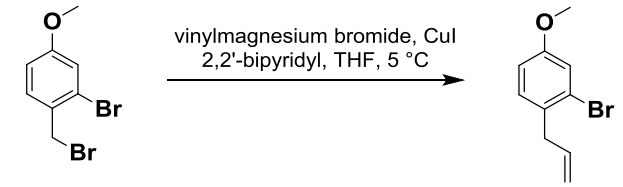
14
M = 312.93

2-Bromo-1-iodo-4-methoxybenzene **14** was synthesized according to a modified literature procedure.[52] 1-Bromo-4-methoxybenzene **15** (642 mg, 3.43 mmol, 1 equiv.), HgO (744 mg, 3.43 mmol, 1 equiv.), Ac_2O (0.13 mL, 1.37 mmol, 0.4 equiv.), and DCM (12.7 mL) were placed in a 25 mL flask. The mixture was heated to reflux. Freshly sublimed I_2 (1220 mg, 4.81 mmol, 1.4 equiv.) was added and the reaction mixture was refluxed for 19 hours. Due to incomplete reaction progress, more I_2 (523 mg, 2.06 mmol, 0.6 equiv.) was added and the reaction mixture was stirred for another 15 hours (34h in total). The reaction mixture was filtered through a pad of Celite and the pad was washed with DCM (in total 30 mL) and satd. aqu. $Na_2S_2O_3$ (10 mL). The two phases were separated and the aqu. phase was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. After evaporation of the solvent in *vacuo* and purification by flash column chromatography (crude mass/SiO_2 = 1/230, cyclohexane) the product was obtained. Spectral data are in accordance with the literature.[71]

Yield: 67% (721 mg, 2.30 mmol)
Appearance: colorless liquid
TLC: R_f (cyclohexane) = 0.24
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.78 (s, 3H, CH_3), 6.60 (dd, J = 8.8 Hz & 2.9 Hz, 1H, H5), 7.19 (d, J = 2.9 Hz, 1H, H3), 7.69 (d, J = 8.8 Hz, 1H, H6) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.62 (q, CH_3), 89.53 (s, C1), 115.39 (d, C5), 118.40 (d, C3), 129.96 (s, C2), 140.26 (d, C6), 160.23 (s, C4) ppm.

GC-MS:
Main fragments: 314 (97, M^+), 312 (100, M^+), 299 (20), 297 (21), 271 (14), 269 (14), 172 (27), 170 (28), 157 (13), 142 (10), 127 (11)

3.3.5. 1-Allyl-2-bromo-4-methoxybenzene (6)

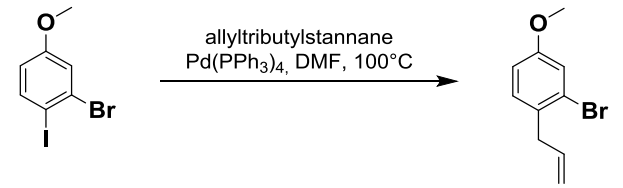


5
M = 279.96

6
M = 227.10

1-Allyl-2-bromo-4-methoxybenzene **6** was synthesized by modification of a method published by Knight and Parsons.[38] CuI (204 mg, 1.07 mmol, 10 mol%) and 2,2'-bipyridyl (167 mg, 1.07 mmol, 10 mol%) were charged into a 50 mL flask. The flask was closed with a septum and evacuated and flushed with argon on a Schlenk line 3 times and finally placed in an ice bath. Vinylmagnesium bromide (21.4 mL, 21.4 mmol, 2 equiv., 1M in THF) was added *via* syringe. A solution of 2-bromo-1-(bromomethyl)-4-methoxybenzene **5** (2994 mg, 10.7 mmol, 1 equiv.) in dry THF was added dropwise *via* syringe. The reaction mixture was stirred at 5 °C for 1 hour. Satd. aqu. NH_4Cl (60 mL), diethyl ether (60 mL), and concentrated ammonia (4.5 mL) were added. The two phases were separated and the aqu. phase was extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with 2N HCl (75 mL) and satd. aqu. $NaHCO_3$ (75 mL) before drying over $MgSO_4$. The solvent was removed in *vacuo*. A brown liquid was obtained. The crude material was purified by flash column chromatography (crude mass/SiO_2 = 1/35, LP → 2% EtOAc in LP). The product was obtained as a mixture with 2-bromo-4-methoxy-1-methylbenzene **3** (25 mol%, determined by H-NMR) as a side product. From other fractions 2,2'-bis(bromomethyl)-5,5'-dimethoxy-1,1'-biphenyl **7** was isolated as a side product.

Yield: 36 % (874 mg, 3.85 mmol)



14
M = 312.93

6
M = 227.10

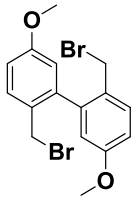
In an alternative approach 1-allyl-2-bromo-4-methoxybenzene **6** was synthesized *via* Stille coupling.[72] 2-Bromo-1-iodo-4-methoxybenzene **14** (944 mg, 3.02 mmol 1 equiv.), allyltributylstannane (1049 mg, 3.17 mmol, 1.05 equiv.), $Pd(PPh_3)_4$ (314 mg, 0.27 mmol, 9 mol%), and dry DMF (9.5 mL) were placed in an oven dried 25 mL flask. The flask was flushed with argon and was attached to a reflux condenser. Reaction solution was heated to 100°C for 45 minutes. H_2O (45 mL) was added and

the mixture then was extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with aqu. KF (10%, 10 mL), which caused precipitation. The mixture was filtered and the organic phase was again washed with aqu. KF (10%, 2 x 10 mL) and brine (10 mL) and was dried over $MgSO_4$. After evaporation of the solvent in *vacuo* and purification by flash column chromatography (crude mass/SiO_2 = 1/70, LP → 2% EtOAc in LP) the desired product was obtained.

Yield: 81 % (555 mg, 2.44 mmol)

Appearance: colorless liquid
TLC: R_f (LP/EtOAc = 5/1) = 0.83
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.44 (d, J = 6.5 Hz, 2H, Ar-CH_2-), 3.78 (s, 3H, CH_3), 4.98 – 5.13 (m, 2H, -CH=C$\underline{H}_2$), 5.84 – 6.05 (m, 1H, -C$\underline{H}$=CH_2), 6.81 (dd, J = 8.5 Hz & 2.6 Hz, 1H, H5), 7.09 – 7.15 (m, 2H, H3 & H6) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 39. 25 (t, Ar-CH_2-), 55.51 (q, CH_3), 113.67 (d, C5), 116.10 (t, -CH=$\underline{C}H_2$), 117.84 (d, C3), 124.56 (s, C2), 130.72 (d, C6), 131.35 (s, C1), 136.06 (d, -$\underline{C}$H=CH_2), 158.51 (s, C4) ppm.
GC-MS:
Main fragments: 228 (66, M^+), 226 (69, M^+), 201 (29), 199 (30), 147 (100), 146 (39), 132 (39), 131 (50), 117 (22), 116 (22), 115 (53), 104 (31), 103 (64), 102 (22)
HR-MS: $[M+H]^+$ m/z (predicted) = 227.0066, m/z (measured) = 227.0061, difference = 2.2 ppm

3.3.6. 2,2'-Bis(bromomethyl)-5,5'-dimethoxy-1,1'-biphenyl (7)



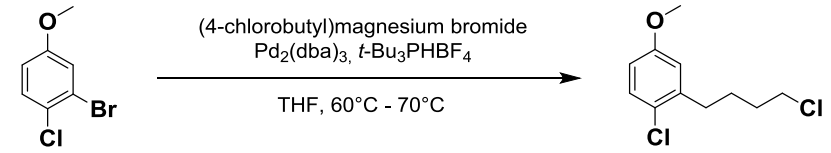
7
M = 400.11

Isolated as a side product in the preparation of 1-allyl-2-bromo-4-methoxybenzene **6**.

Yield: 20 % (428 mg, 1.07 mmol)

Appearance: beige solid
Melting point: 114.0 – 115.5 °C (lit.[73]:113 – 114 °C)
TLC: R_f (LP/EtOAc = 5/1) = 0.67
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.94 (s, 4H, CH_2), 3.78 (s, 3H, CH_3), 6.77 (dd, J = 8.5 Hz & 2.6 Hz, 2H, H4 & H4'), 7.03 – 7.12 (m, 4H, H3, H3', H6 & H6') ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 35.81 (t, CH_2), 55.50 (q, CH_3), 113.58 (d, C4 & C4'), 117.82 (d, C6 & C6'), 124.49 (s, C2 & C2'), 130.93 (d, C3 & C3'), 132.65 (s, C1 & C1'), 158.44 (s, C5 & C5') ppm.
GC-MS:
Main fragments: 402 (M+), 400 (M+), 398 (M+), 201 (93), 200 (10), 199 (100)

3.3.7. 1-Chloro-2-(4-chlorobutyl)-4-methoxybenzene (13)



12
M = 221.48

13
M = 233.13

For the preparation of the Grignard reagent a literature protocol was modified.[74] Magnesium (126 mg, 5.18 mmol, 1.1 equiv.) was placed in an oven dried 8 mL vial. The vial was closed with a screw cap with septum and was evacuated and flushed with argon on a Schlenk line 3 times. Dry THF (4 mL) was added *via* syringe. The mixture was stirred vigorously and 1-bromo-4-chlorobutane (921 mg, 4.71 mmol, 1 equiv.) was added by syringe. After the reaction started it was stirred for another 30 minutes while cooled with a water bath. Active base was determined by titration with 2-BuOH (1M solution in dry THF) to be 1.07M (91%). The Grignard solution was taken up by a syringe.

For the cross coupling of the Grignard reagent with 2-bromo-1-chloro-4-methoxybenzene **12** a protocol for similar substrates was modified.[48] Water free K_2CO_3 (41 mg, 0.30 mmol) and tri-*tert*-butylphosphine tetrafluoroborate (58 mg, 0.20 mmol) were placed in an oven dried 8 mL vial. The vial was closed with a screw cap with septum and was evacuated and flushed with argon on a Schlenk line 3 times. Dry THF (4 mL) was added. The reaction mixture was stirred for 2 hours. 2-Bromo-1-chloro-4-methoxybenzene **12** (332 mg, 1.50 mmol, 1 equiv.) was placed in an oven dried 10 mL flask. $Pd_2(dba)_3$ (34 mg, 0.04 mmol, 2.5 mol%) was added and the flask was closed with a septum and was evacuated and flushed with argon on the Schlenk line for 3 times. The ligand solution (3 mL, resulting in a concentration of 10 mol% ligand) was added *via* syringe. The stirred solution was heated on an oil bath (oil bath temperature 72°C). Grignard solution (1.68 mL, 1.80 mmol, 1.2 equiv.) was added *via* syringe pump over 1 hour. The reaction mixture was then stirred at this temperature for another 25 minutes. H_2O (5 mL) and diethyl ether (30 mL) were added. The two phases were separated and the aqu. phase was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (2 x 25 mL) and dried over Mg_2SO_4. After evaporation of the solvent in *vacuo* and purification by flash column chromatography (crude mass/SiO_2 = 1/55, LP → 2% EtOAc in LP) the product was obtained.

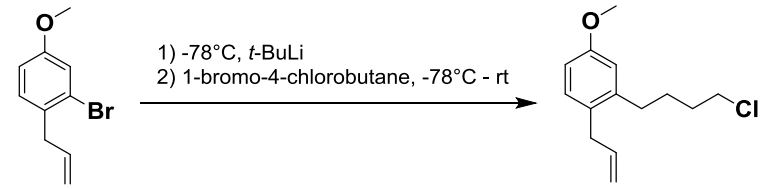
Yield: 45% (157 mg, 0.67 mmol)
Appearance: colorless liquid
TLC: R_f (LP/EtOAc = 5/1) = 0.55
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.68 – 1.94 (m, 4H, -C$\underline{H_2}$-C$\underline{H_2}$-CH_2Cl), 2.72 (t, J = 7.3 Hz, 2H, Ar-C$\underline{H_2}$-), 3.67 (t, J = 6.3 Hz, 2H, -CH_2Cl), 3.78 (s, 3H, CH_3), 6.69 (dd, J = 8.6 Hz & 2.9 Hz, 1H, H5), 6.76 (d, J = 2.8 Hz, 1H, H3), 7.24 (d, J = 9.0 Hz, 1H, H6) ppm.

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 26.98 & 32.17 & 33.00 (t, -($\underline{C}H_2$)$_3$-CH_2Cl), 44.80 (t, -CH_2Cl), 55.42 (q, CH_3), 112.67 (d, C3 or C5), 115.92 (d, C3 or C5), 125.26 (s, C1), 130.02 (d, C6), 140.41 (s, C2), 158.32 (s, C4) ppm.

GC-MS:

Main fragments: 234 (19, M^+), 232 (31, M^+), 158 (15), 157 (34), 156 (45), 155 (100), 125 (21), 121 (35)

3.3.8. 1-Allyl-2-(4-chlorobutyl)-4-methoxybenzene (8)

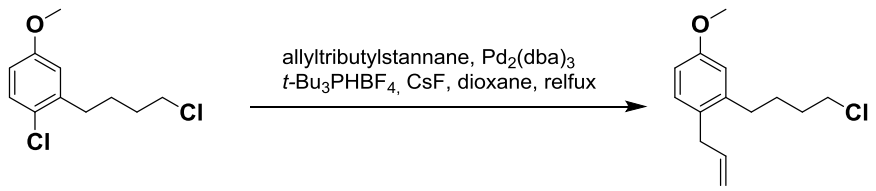


6
M = 227.10

8
M = 238.75

For the synthesis of 1-allyl-2-(4-chlorobutyl)-4-methoxybenzene **8** a procedure from Back et. al. was applied.[42] 1-Allyl-2-bromo-4-methoxybenzene **6** (798 mg, 3.51 mmol, 1 equiv.; contaminated with 238 mg (1.18 mmol) 2-bromo-4-methoxy-1-methylbenzene **4**) was placed in a 25 mL flask and dissolved in dry THF (9.4 mL). The flask was closed with a septum and the reaction solution was cooled to -78 °C. A solution of *t*-BuLi in pentane (5.53 mL, 9.40 mmol, 2 equiv., 1.7 M in pentane) was added dropwise *via* syringe and the reaction solution was stirred for 15 minutes at -78 °C, then 10 minutes at -50°C. The mixture was again cooled to -78°C and 1-bromo-4-chlorobutane (1208 mg, 7.05 mmol, 1.5 equiv.) was added whereupon the mixture was warmed to room temperature to be stirred subsequently for 1 hour. The reaction solution was then partitioned between satd. aqu. NH_4Cl (30 mL) and DCM (30 mL). The aqueous layer was extracted with DCM (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent in *vacuo* a nearly colorless liquid was obtained. The crude material was purified by flash column chromatography (crude mass/SiO_2 = 1/65, 5% - 15% DCM in LP). The product was obtained as a mixture with 2-(4-chlorobutyl)-4-methoxy-1-methylbenzene **9** (23 mol%, determined by H-NMR) as a side product. Subsequently the mixture was successfully separated on $AgNO_3$ doped (5%) silica gel by flash column chromatography (LP).

Yield: 78% (654 mg, 2.74 mmol)



13
M = 233.13

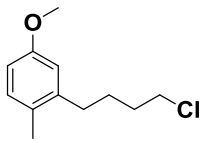
8
M = 238.75

In an alternative attempt 1-allyl-2-(4-chlorobutyl)-4-methoxybenzene **8** was prepared by Stille coupling.[50] CsF was dried prior to use by heating up to 100°C under high vacuum for several hours. 1-Chloro-2-(4-chlorobutyl)-4-methoxybenzene **13** (100 mg, 0.43 mmol, 1 equiv.), allyltributylstannane (149 mg, 0.45 mmol, 1.05 equiv.), $Pd_2(dba)_3$ (6 mg, 0.006 mmol, 1.5 mol%), tri-*tert*-butylphosphine tetrafluoroborate (7.5 mg, 0.026 mmol, 6 mol%), and CsF (143 mg, 0.94 mmol, 2.2 equiv.) were placed in an oven dried 8 mL vial. The vial was closed with a screw cap with septum and was evacuated and flushed with argon on a Schlenk line for 3 times. Dry dioxane (0.43 mL) was added *via* syringe. The reaction mixture was stirred while heated on a thermo block which was adjusted to 120°C for 50 hours. As GC-MS analysis showed more equivalents of remaining starting material than the stannane reagent to be present, another 0.2 equiv. of allyltributylstannane (28 mg, 0.086 mmol) were added and the reaction mixture was stirred while heated on a thermo block which was adjusted to 120°C for another 24 hours (74 hours in total). H_2O (2 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 2 mL). The combined organic layers were washed with aqu. KF (10%, 2 mL), which caused precipitation. The mixture was filtered through a pad of Celite; after washing, the organic phase was again washed with aqu. KF (10%, 2 x 2 mL) and brine (3 mL) and was dried over $MgSO_4$. After evaporation of the solvent in *vacuo* and purification by flash column chromatography (crude mass/SiO_2 = 1/130, LP) the desired product was obtained.

Yield: 70% (72 mg, 0.30 mmol)

Appearance: colorless liquid
TLC: R_f (LP/EtOAc = 5/1) = 0.82
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.65 – 1.94 (m, 4H, -C$\underline{H_2}$-C$\underline{H_2}$-CH_2Cl), 2.61 (t, *J* = 7.6 Hz, 2H, Ar-C$\underline{H_2}$-CH_2-), 3.34 (d, *J* = 6.3 Hz, 2H, -C$\underline{H_2}$-CH=), 3.56 (t, *J* = 6.4 Hz, 2H, CH_2Cl),3.79 (s, 3H, CH_3), 4.91 – 5.08 (m, 2H, - CH=C$\underline{H_2}$), 5.84 – 6.05 (m, 1H, -C$\underline{H}$=CH_2), 6.67 – 6.75 (m, 2H, H3 & H5),7.03 – 7.10 (m, 1H, H6) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 27.96, 32.09 & 32.40 (t, -($\underline{C}H_2$)$_3$-CH_2Cl), 36.30 (t, -$\underline{C}H_2$-CH=), 44.86 (t, -CH_2Cl), 55.20 (q, -CH_3), 111.15 (d, C5), 114.93 (d, C3), 115.34 (t, -CH=$\underline{C}H_2$), 129.68 (s, C1), 130.65 (d, C6), 137.69 (d, -$\underline{C}$H=CH_2), 141.29 (s, C2), 158.09 (s, C4) ppm.
GC-MS:
Main fragments: 240 (9, M^+), 238 (30, M^+), 209 (11), 161 (40), 148 (11), 147 (100), 146 (13), 131 (13), 129 (10), 128 (12), 121 (13), 117 (11), 115 (21)
HR-MS: $[M+H]^+$ m/z (predicted) = 239.1197, m/z (measured) = 239.1193, difference = 1.7 ppm

3.3.9. 2-(4-Chlorobutyl)-4-methoxy-1-methylbenzene (9)



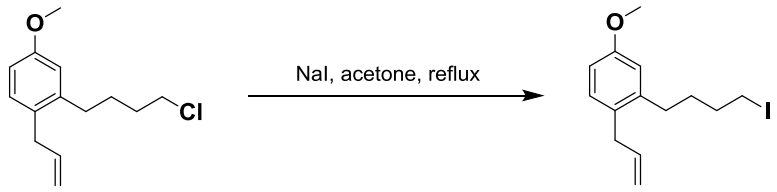
9
M = 212.72

Isolated as a side product in the preparation of 1-allyl-2-(4-chlorobutyl)-4-methoxybenzene **8** using the compound mixture from the synthesis of **6**.

Yield: 78% (196 mg, 0.92 mmol)

Appearance: colorless oil
TLC: R_f (LP/EtOAc = 5/1) = 0.78
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.66 – 1.96 (m, 4H, -C$\underline{H}_2$-C$\underline{H}_2$-CH_2Cl), 2.26 (s, 3H, Ar-CH_3), 2.62 (t, J = 7.5 Hz, 2H, Ar-CH_2-), 3.59 (t, J = 6.4 Hz, 2H, -CH_2Cl), 3.77 (s, 3H, O-CH_3), 6.65 – 6.75 (m, 2H, H3 & H5), 7.07 (d, J = 8.0 Hz, 1H, H6) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 18.39 (q, Ar-CH_3), 27.32 & 32.40 & 32.72 (t, -($\underline{C}H_2$)$_3$-CH_2Cl), 44.90 (t, -CH_2Cl), 55.23 (q, -CH_3), 110.87 (d, C5), 114.76 (d, C3), 127.87 (s, C1), 130.95 (d, C6), 141.29 (s, C2), 157.86 (s, C4) ppm.
GC-MS:
Main fragments: 214 (8, M+), 212 (25, M+), 136 (38), 135 (100), 121 (13)

3.3.10. 1-Allyl-2-(4-iodobutyl)-4-methoxybenzene (10)



8
M = 238.75

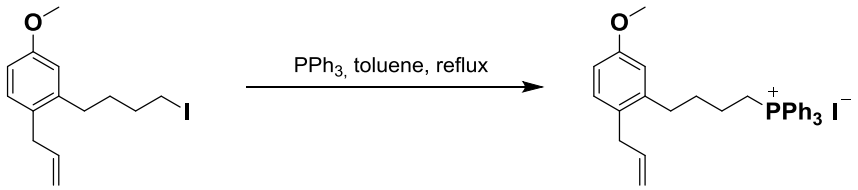
10
M = 330.21

1-Allyl-2-(4-iodobutyl)-4-methoxybenzene **10** was prepared from the corresponding chloride *via* Finkelstein reaction.[43] A 8 mL vial was charged with 1-allyl-2-(4-chlorobutyl)-4-methoxybenzene **8** (119 mg, 0.50 mmol, 1 equiv.), NaI (82 mg, 0.55 mmol, 1.1 equiv.), and acetone (2.5 mL). After closing with a septum the solution was stirred while heated on a thermo block which was adjusted to 75°C for 24 hours. The mixture was cooled to room temperature, filtered through a small pad of silica gel and the pad was washed with acetone. After evaporation of the solvent in *vacuo* and purification by column chromatography (crude mass/SiO_2 = 1/20, 5% EtOAc in LP) the desired product was obtained.

Yield: 86% (141 mg, 0.43 mmol)
Appearance: colorless liquid
TLC: R_f (LP/EtOAc = 5/1) = 0.83

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.62 – 1.80 (m, 2H, -C<u>H</u>$_2$-CH_2-CH_2I), 1.84 – 2.00 (m, 2H, -C<u>H</u>$_2$-CH_2I), 2.62 (t, *J* = 7.7 Hz, 2H, Ar-C<u>H</u>$_2$-CH_2-), 3.23 (t, *J* = 6.8 Hz, 2H, -CH_2I), 3.37 (d, *J* = 6.3 Hz, 2H, -C<u>H</u>$_2$-CH=), 3.81 (s, 3H, -CH_3), 4.95 – 5.12 (m, 2H, -CH=C<u>H</u>$_2$), 5.87 – 6.08 (m, 1H, -C<u>H</u>=CH_2), 6.70 – 6.77 (m, 2H, H3 & H5), 7.06 – 7.13 (m, 1H, H6) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 6.76 (t, -CH_2I), 31.64, 31.82 & 33.33 (t, -(<u>C</u>H$_2$)$_3$-CH_2I), 36.36 (t, -<u>C</u>H$_2$-CH=), 55.24 (q, -CH_3), 111.20 (d, C5), 114.98 (d, C3), 115.42 (t, -CH=<u>C</u>H$_2$), 129.67 (s, C1), 130.70 (d, C6), 137.74 (d, -<u>C</u>H=CH_2), 141.25 (s, C2), 158.15 (s, C4) ppm.
GC-MS:
Main fragments: 330 (37, M^+), 207 (10), 162 (22), 161 (100), 159 (16), 147 (72), 146 (20), 145 (12), 135 (11), 131 (19), 129 (16), 128 (20), 127 (11), 121 (16), 117 (16), 115 (30), 103 (15)
HR-MS: $[M+H]^+$ m/z (predicted) = 331.0553 , m/z (measured) = 331.0568, difference = 4.5 ppm

3.3.11. (4-(2-Allyl-5-methoxyphenyl)butyl)triphenylphosphonium iodide (<u>11</u>)

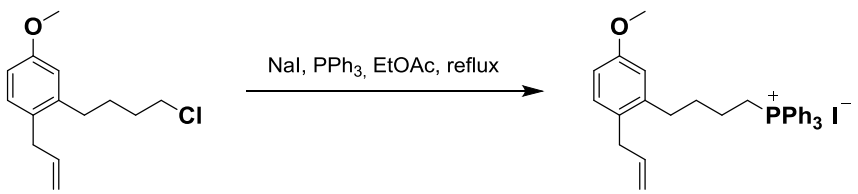


<u>10</u>
M = 330.21

<u>11</u>
M = 592.50

(4-(2-Allyl-5-methoxyphenyl)butyl)triphenylphosphonium iodide **<u>11</u>** was prepared by a standard literature procedure.[75] 1-Allyl-2-(4-iodobutyl)-4-methoxybenzene **<u>10</u>** (130 mg, 0.39 mmol, 1 equiv.), PPh_3 (103 mg, 0.39 mmol, 1 equiv.), and toluene (2 mL) were placed in a 8 mL vial. The vial was flushed with argon and was closed with a screw cap. The solution was stirred while heated on a thermo block which was adjusted to 130°C for 12 hours. An oily phase was formed. The upper toluene phase was removed by syringe and the oily residue was washed with LP (2 x 1.5 mL) and dried in high vacuum. NMR analysis gave very good purity (>95%). In order to obtain the Wittig salt in a crystalline form the oil was stirred with refluxing diethyl ether prompting the oil to crystallize. After cooling to room temperature the solvent was decanted and after drying in high vacuum the product was obtained as beige crystals.

Yield: 99% (231 mg, 0.39 mmol)



<u>8</u>
M = 238.75

<u>11</u>
M = 592.50

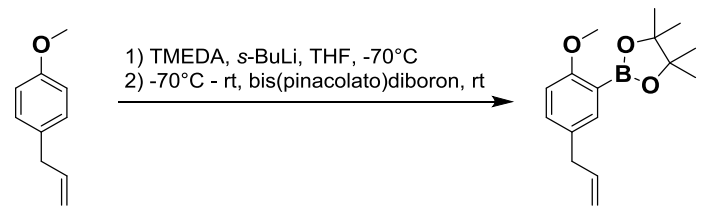
For a convenient one pot synthesis of the Wittig reagent **11** a protocol from Linares et. al. was applied.[44] 1-Allyl-2-(4-chlorobutyl)-4-methoxybenzene **8** (113 mg, 0.47 mmol, 1 equiv.), NaI (71 mg, 0.47 mmol, 1 equiv.), PPh_3 (124 mg, 0.47 mmol, 1 equiv.), and EtOAc (2.37 mL) were placed in a 8 mL vial. The vial was flushed with argon and was closed with a screw cap. The solution was stirred while heated on a thermo block which was adjusted to 95°C for 65 hours. Solvent was removed in *vacuo*, $CHCl_3$ was added and after stirring for 5 minutes the mixture was filtered through a pad of Na_2SO_4. After evaporation of the solvent in *vacuo* and drying in high vacuum an oil was obtained. Stirring with refluxing diethyl ether prompted the oil to crystallize. After cooling to room temperature the solvent was decanted and after drying in high vacuum the product was obtained as beige crystals.

Yield: 75% (210 mg, 0.35 mmol)

Appearance: beige crystals
Melting point: 121 – 124 °C
TLC: R_f (EtOAc) = 0
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.62 – 1.73 (m, 2H, Ar-CH_2-C$\underline{H}_2$-), 1.92 – 2-00 (m, 2H, -C$\underline{H}_2$-CH_2PPh_3), 2.60 (t, *J* = 7.5 Hz, 2H, Ar-C$\underline{H}_2$-CH_2-), 3.22 (d, *J* = 6.1 Hz, 2H, -C$\underline{H}_2$-CH=), 3-68 – 3.77 (m, 2H, -CH_2-C$\underline{H}_2PPh_3$), 3.75 (s, 3H, CH_3), 4.82 – 4.94 (m, 2H, -CH=C$\underline{H}_2$), 5.79 – 5.89 (m, 1H, -C$\underline{H}$=CH_2), 6.65 (dd, *J* = 8.3 Hz & 2.7 Hz, 1H, H4), 6.69 (d, *J* = 2.7 Hz, 1H, H6), 6.98 (d, *J* = 8.2 Hz, 1H, H3), 7.65 – 7.71 (m, 6H, PPh_3), 7.75 – 7.81 (m, 9H, PPh_3) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.17 (t, d, $^3J_{C\text{-}P}$ = 4.2 Hz, Ar-CH_2-C$\underline{H}_2$-), 23.09 (t, d, $^1J_{C\text{-}P}$ = 49.9 Hz, -CH_2-C$\underline{H}_2PPh_3$), 30.84 (t, d, $^2J_{C\text{-}P}$ = 15.4 Hz, -C$\underline{H}_2$-CH_2PPh_3), 31.94 (t, Ar-C$\underline{H}_2$-CH_2-), 36.26 (t, -C$\underline{H}_2$-CH=), 55.54 (q, CH_3), 111.80 (d, C4), 114.59 (d, C6), 115.29 (t, -CH=C$\underline{H}_2$), 118.16 (s, d, $^1J_{C\text{-}P}$ = 85.9 Hz, 3C, PPh_3), 129.54 (s, C2), 130.53 (d, d, $^2J_{C\text{-}P}$ = 12.4 Hz, 6C, PPh_3), 130.64 (d, C3), 133.71 (d, d, $^3J_{C\text{-}P}$ = 10.0 Hz, 6C, PPh_3), 135.08 (d, d, $^4J_{C\text{-}P}$ = 3.0 Hz, 3C, PPh_3), 135.10 (d, 15C, PPh_3), 137.74 (d, -C$\underline{H}$=CH_2), 140.49 (s, C1), 158.08 (s, C5) ppm.
HR-MS: $[M\text{-}I^-]^+$ m/z (predicted) = 465.2342 , m/z (measured) = 465.2352, difference = 2.2 ppm

3.4. Synthesis of building block II (aldehyde)

3.4.1. 2-(5-Allyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (22)



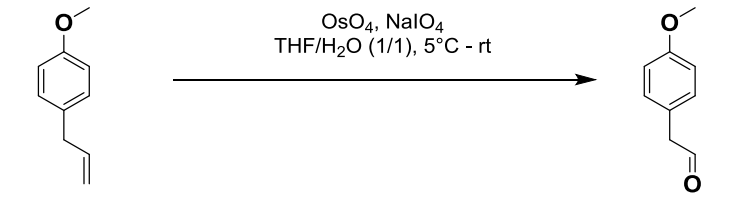
16
M = 148.20

22
M = 274.17

2-(5-Allyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **22** was prepared according to a modified literature procedure for the corresponding boronic acid.[59] Freshly distilled 1-allyl-4-methoxybenzene **16** (1000 mg, 6.75 mmol, 1 equiv.) was charged into an oven dried 50 mL flask. The flask was closed with a septum and was evacuated and flushed with argon on a Schlenk line for 3 times. Dry. THF (25 mL) was added *via* syringe and the solution was cooled to -70°C. Dry TMEDA (1.01 mL, 6.75 mmol, 1 equiv.) was added *via* syringe. *s*-BuLi (9.55 mL, 10.12 mmol, 1.5 equiv, 1.35M in cyclohexane, reagent was titrated prior to use according to a literature protocol[76]) was added dropwise *via* syringe over 3 minutes while a temperature of -75°C - -70°C was maintained. The reaction solution was stirred for 1 hour while the temperature was maintained between -70°C and -75°C. Then the reaction solution was allowed to reach room temperature (10 - 15 minutes) and was stirred for 30 minutes at room temperature. A solution of bis(pinacolato)diboron (1713 mg, 6.75 mmol, 1 equiv.) in dry THF (5mL) was added dropwise *via* syringe. The reaction solution was stirred at room temperature for 1 hour. EtOAc (130 mL) was added and the reaction solution was washed with satd. aqu. NH_4Cl (85 mL). The two phases were separated and the aqu. phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with satd. aqu. $NaHCO_3$ (100 mL) and brine (100 mL) to be finally dried over $MgSO_4$. The mixture was filtered and after evaporation of the solvent in *vacuo* the crude product was obtained. For quantification of the crude product an aliquot of the crude mass was mixed with DMSO and the yield was determined by ^{1}H-NMR to be 55%. According to GC-MS and ^{1}H-NMR analysis the only prominent impurity is not consumed bis(pinacolato)diboron. Crude product was used without purification for the subsequent coupling step.

Yield: 55%, not isolated (3.71 mmol)
Appearance: pale yellow oil
TLC: R_f(LP/EtOAc = 5/1) = 0.55
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.36 (s, 12H, 4 x CH_3), 3.33 (d, J = 7.2 Hz, Ar-CH_2), 3.81 (s, 3H, O-CH_3), 4.99 – 5.12 (m, 2H, CH-CH_2), 5.85 – 6.06 (m, 1H, CH), 6.80 (d, J = 8.4 Hz, H3), 7.21 (dd, J = 8.5 & 2.4 Hz, H4), 7.49 (d, J = 2.3 Hz, H6) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 24.79 (q, 4C, 4 x CH_3), 39.23 (t, Ar-CH_2), 55.96 (q, O-CH_3), 83.43 (q, 2C, 2 x $\underline{C}$-$(CH_3)_2$), 110.64 (d, C3), 115.32 (t, CH-$\underline{C}H_2$), 131.42 (s, C5), 132.48 (d, C4), 136.72 (d, $\underline{C}$H-CH_2 or C6), 137.96 (d, $\underline{C}$H-CH_2 or C6), 162.72 (q, C2) ppm. C1 not visible
GC-MS:
Main fragments: .274 (71, M^+), 273 (19), 201 (39), 175 (26), 174 (100), 173 (69), 159 (21), 158 (31), 157 (15), 147 (38), 146 (29), 145 (27), 143 (20), 131 (70), 129 (22), 117 (27), 116 (38), 115 (76)
HR-MS: $[M+Na]^+$ m/z (predicted) = 297.1635, m/z (measured) = 297.1626, difference = 3.0 ppm

3.4.2. 2-(4-Methoxyphenyl)acetaldehyde (17)



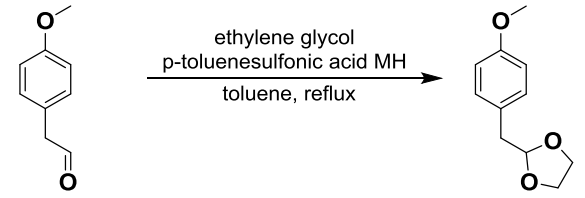
16
M = 148.20

17
M = 150.18

2-(4-Methoxyphenyl)acetaldehyde **17** was prepared according to the literature.[56] OsO_4 (17 mg, 0.01 mmol, 1mol%) and $NaIO_4$ (4280 mg, 20.01 mmol, 3 equiv.) were added to an ice bath cooled solution of 4-allylanisole **16** (1000 mg, 6.75 mmol, 1 equiv.) in degassed THF/H_2O (40 mL, 1/1) under argon. The ice bath was removed and the solution was stirred at room temperature until TLC indicated complete consumption of the starting material (25 minutes).The reaction mixture was quenched with satd. aqu. $Na_2S_2O_3$ (40 mL). Then the reaction mixture was extracted with diethyl ether (2 x 40 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed in *vacuo* and after purification by *Kugelrohr* distillation in high vacuum (100°C at 0.5 mbar) the product was obtained. Spectral data are in accordance with literature reports.[77]

Yield: 56% (568 mg, 3.78 mmol)
Appearance: colorless oil
TLC: R_f (LP/EtOAc = 5/1) = 0.5
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.63 (d, J = 3.6 Hz, 2H, CH_2), 3.81 (s, 3H, CH_3), 6.87 – 6.94 (m, 2H, H3 & H5), 7.10 – 7.17 (m, 2H, H2 & H6), 9.72 (t, J = 2.3 Hz, CHO) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 49.69 (t, CH_2), 55.28 (q, CH_3), 114.44 (d, 2C, C3 & C5), 123.70 (s, C1), 130.67 (d, 2C, C2 & C6), 158.96 (s, C4), 199.72 (d, CHO) ppm.
GC-MS:
Main fragments: 150 (17, M^+), 122 (10), 121 (100)

3.4.3. 2-(4-Methoxybenzyl)-1,3-dioxolane (19)



17
M = 150.18

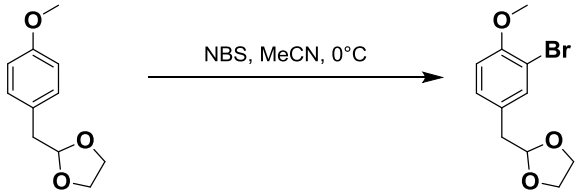
19
M = 194.23

2-(4-Methoxybenzyl)-1,3-dioxolane **19** was prepared by a standard literature procedure.[78] A 100 mL flask was charged with 2-(4-methoxyphenyl)acetaldehyde **17** (3.54 g, 23.6 mmol, 1 equiv) and p-toluenesulfonic acid monohydrate (134 mg, 0.71 mmol, 3 mol%) under argon, then dry toluene (34 mL) and ethylene glycol (5.27 g, 84.9 mmol, 3.6 equiv) were added. The reaction solution was stirred under reflux on a Dean-Stark apparatus for 24 hours. Then the reaction solution was cooled to room

temperature and was washed with satd. aqu. $NaHCO_3$ (40 mL) and brine (3 x 40 mL) before being dried over Na_2SO_4. The mixture was filtered and evaporation of the solvent in *vacuo* provided the desired product. Spectral data are in accordance with literature reports.[79]

Yield: 92% (4.231 g, 21.8 mmol)
Appearance: orange liquid
TLC: R_f(LP/EtOAc = 5/1) = 0.5
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.91 (d, J = 4.9 Hz, 2H, Ar-CH_2-), 3.79 (s, 3H, CH_3), 3.82 – 3.96 (m, 4H, -O-CH_2-CH_2-O-), 5.03 (t, J = 4.8 Hz, 1H, CH), 6.85 (d, J = 8.6 Hz, 2H, H3 & H5), 7.20 (d, J = 8.6 Hz, H2 & H6) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 39.82 (t, Ar-CH_2-), 55.21 (q, CH_3), 64.95 (t, 2C, -CH_2-CH_2-), 104.80 (d, acetal-CH), 113.78 (d, 2C, C3 & C5), 128.16 (s, C1), 130.61 (d, 2C, C2 & C6), 158.34 (s, C4) ppm.
GC-MS:
Main fragments: 194 (9, M^+), 121 (32), 73 (100)

3.4.4. 2-(3-Bromo-4-methoxybenzyl)-1,3-dioxolane (<u>20</u>)



19
M = 194.23

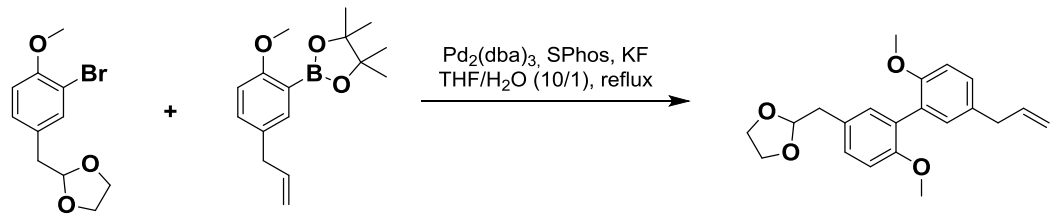
<u>20</u>
M = 273.13

2-(3-Bromo-4-methoxybenzyl)-1,3-dioxolane **<u>20</u>** was synthesized according to a literature protocol.[80] A 100 mL flask was charged with 2-(4-methoxybenzyl)-1,3-dioxolane **19** (1000 mg, 5.15 mmol, 1 equiv.) and MeCN (30 mL) and the reaction solution was cooled to 0 °C. NBS (916 mg, 5.15 mmol, 1 equiv.) was added and the reaction solution was stirred at 0°C for 2 hours. The solvent was removed in *vacuo*. The residue was distributed between diethyl ether (40 mL) and H_2O (40 mL) and the two phases were separated. The aqu. phase was extracted with diethyl ether (2 x 15 mL) and the combined organic layers were dried over Na_2SO_4. After the solvent was removed in *vacuo* the product was obtained. As analysis showed good purity (>95% according to ^{1}H-NMR), no further purification was necessary.

Yield: 95% (1336 mg, 4.89 mmol)
Appearance: dark-orange oil
TLC: R_f(LP/EtOAc = 5/1) = 0.34
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.88 (d, J = 4.7 Hz, 2H, Ar-CH_2-), 3.87 (s, 3H, CH_3), 3.79 – 3.98 (m, 4H, -O-CH_2-CH_2-O-), 5.02 (t, J = 4.7 Hz, 1H, CH), 6.83 (d, J = 8.4 Hz, 1H, H5), 7.17 (dd, J = 8.4 Hz & 2.1 Hz, 1H, H6), 7.47 (d, J = 2.1 Hz, 1H, H2) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 39.39 (t, Ar-CH_2-), 56.20 (q, CH_3), 65.00 (t, 2C, -CH_2-CH_2-), 104.31 (d, acetal-CH), 111.32 (s, C3), 111.75 (d, C5), 129.32 (s, C1), 129.74 (d, C6), 134.38 (d, C2), 154.60 (s, C4) ppm.

GC-MS:
Main fragments: 274 (2, M^+), 272 (2, M^+), 73 (100)

3.4.5. 2-((5'-Allyl-2',6-dimethoxy-[1,1'-biphenyl]-3-yl)methyl)-1,3-dioxolane (23)



20
M = 273.13

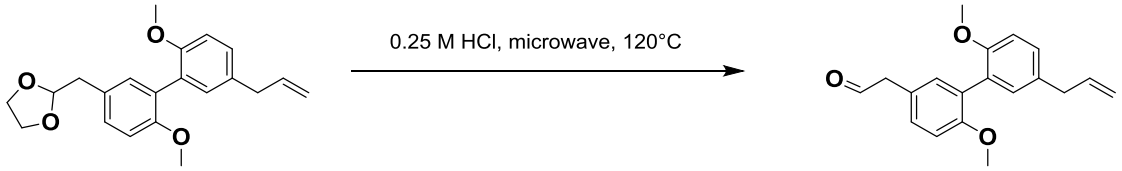
22
M = 274.17

23
M = 340.42

2-((5'-Allyl-2',6-dimethoxy-[1,1'-biphenyl]-3-yl)methyl)-1,3-dioxolane **23** was prepared following a literature procedure for similar coupling partners.[62] 2-(3-Bromo-4-methoxybenzyl)-1,3-dioxolane **20** (720 mg, 2.64 mmol, 1 equiv.), 2-(5-allyl-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **22** (2.90 mmol, 1.1 equiv., crude mixture), $Pd_2(dba)_3$ (241 mg, 0.26 mmol, 10mol%), SPhos (325 mg, 0.79 mmol, 30mol%), KF (766 mg, 13.18 mmol, 5 equiv.), THF (24 mL), and H_2O (2.4 mL) were charged into a 50 mL flask. The flask was closed with a septum and was evacuated and flushed with argon on a Schlenk line for 3 times. The flask was attached to a reflux condenser and was stirred under reflux for 24 hours. The reaction solution was cooled to room temperature and was diluted with EtOAc (75 mL). The reaction solution was washed with satd. aqu. NH_4Cl (50 mL). The two phases were separated and the aqu. phase was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$. After evaporation of the solvent in *vacuo* and purification by flash column chromatography (crude mass/SiO_2 = 1/55, 5 → 15% EtOAc in LP) the desired product was obtained.

Yield: 67% (601 mg, 1.77 mmol)
Appearance: colorless oil
TLC: R_f(LP/EtOAc = 5/1) = 0.28
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.96 (d, J = 4.9 Hz, 2H, -CH_2-acetal), 3.38 (d, J = 6.8 Hz, 2H, -C<u>H</u>$_2$-CH=), 3.77 (s, 6H, 2 x CH_3), 3.81 – 4.03 (m, 4H, -CH_2-CH_2-), 5.03 – 5.17 (m, 3H, -CH=C<u>H</u>$_2$ & acetal CH), 5.90 – 6.12 (m, 1H, -C<u>H</u>=CH_2), 6.92 (dd, J = 8.2 Hz & 2.0 Hz, 2H, H4 & H4'), 7.07 – 7.28 (m, 4H, H2, H5, H3', H6') ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 39.42 & 39.96 (t, 2 x Ar-CH_2-), 55.80 & 55.86 (q, 2 x –CH_3), 64.96 (t, -CH_2-CH_2-), 104.91 (d, acetal CH), 111.07 & 111.18 (d, C5 & C3'), 115.49 (t, -CH=<u>C</u>H_2), 127.75 & 127.85 (s, C1 & C1'), 128.43 & 129.63 (d, C4 & C4'), 131.69 (d, C6'), 131.72 (s, C3 and/or C5'), 132.67 (d, C2), 137.86 (d, -<u>C</u>H=CH_2), 155.52 & 155.90 (s, C6 & C2') ppm.
GC-MS:
Main fragments: .340 (5, M^+), 73 (100)
HR-MS: $[M+H]^+$ m/z (predicted) = 341.1747, m/z (measured) = 341.1759, difference = 3.5 ppm

3.4.6. 2-(5'-Allyl-2',6-dimethoxy-[1,1'-biphenyl]-3-yl)acetaldehyde (24)



23
M = 340.42

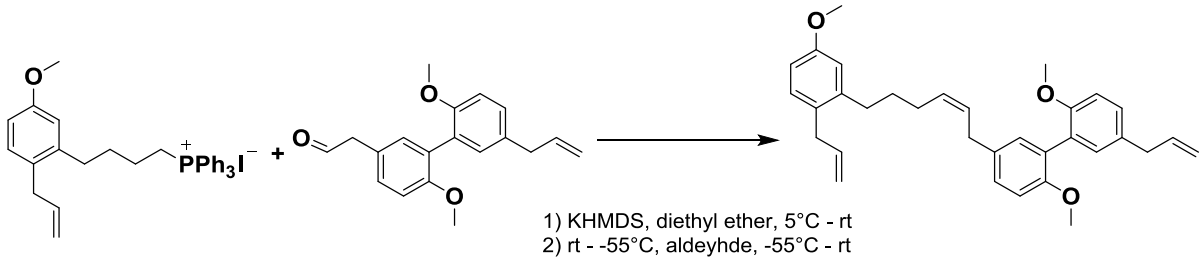
24
M = 296.37

2-(5'-Allyl-2',6-dimethoxy-[1,1'-biphenyl]-3-yl)acetaldehyde **24** was obtained by applying modified literature conditions.[63] 2-((5'-Allyl-2',6-dimethoxy-[1,1'-biphenyl]-3-yl)methyl)-1,3-dioxolane **23** (120 mg, 0.35 mmol) was placed in a 2 mL microwave vial. The vial was closed with a septum and evacuated and flushed with argon on a Schlenk line for 3 times. 0.25 M degassed HCl (1.07 mL) was added by syringe. The reaction mixture was heated in the microwave oven (absorption level: high, 120°C) for 1 hour. The reaction mixture was extracted with EtOAc (3 x 1.5 mL). The combined organic layers were dried over $MgSO_4$. After evaporation of the solvent in *vacuo* the crude product was obtained quantitatively. As the aldehyde could not be applied to column chromatography due to facile decomposition and NMR-analysis indicated good purity, the material was used without purification for the next step. Purity was determined by ^{1}H-NMR. The aldehyde signal and the signal from the adjacent methylene group were referenced to the signal from the allylic CH. A purity of 80% was obtained while crude yield was quantitatively.

Yield: 80% (0.28 mmol)
Appearance: colorless oil
TLC: R_f(LP/EtOAc = 5/1) = 0.34
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.36 (d, J = 7.0 Hz, 2H, -C$\underline{H}_2$-CH=), 3.62 (d, J = 2.3 Hz, 2H, -C$\underline{H}_2$-CHO), 3.74 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 5.02 – 5.12 (m, 2H, -CH=C$\underline{H}_2$), 5.92 – 6.03 (m, 1H, -C$\underline{H}$=CH_2), 6.90 (d, J = 8.4 Hz, H3'), 6.95 (d, J = 8.5 Hz, H5), 7.05 (d, J = 2.2 Hz, H6'), 7.08 (d, J = 2.2 Hz, H2), 7.12 – 7.17 (m, 2H, H4 & H4'), 9.74 (t, J = 2.5 Hz, CHO) ppm.
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 39.39 (t, -$\underline{C}H_2$-CH=CH_2), 49.73 (t, -$\underline{C}H_2$-CH=O), 55.83 & 55. 86 (q, 2 x –CH_3), 111.18 & 111.62 (d, C5 & C3'), 115.59 (t, -CH=$\underline{C}H_2$), 123.40 (s, C3), 127.21 (s, C1'), 128.60 (s, C1), 128.73 (d, C4'), 129.67 (d, C4), 131.54 (d, C6'), 131.84 (s, C5'), 132.67 (d, C2), 137.77 (d, -$\underline{C}$H=CH_2), 155.44 (s, C2'), 156.52 (s, C6), 199.92 (d, CHO) ppm.
GC-MS:
Main fragments: 296 (48, M^+), 268 (19), 267 (100), 221 (10), 211 (17), 194 (10), 165 (16), 152 (11), 133 (23)
HR-MS: $[M+H]^+$ m/z (predicted) = 297.1485, m/z (measured) = 297.1489, difference = 1.4 ppm

3.5. Synthesis of biological probes

3.5.1. (Z)-5-Allyl-5'-(6-(2-allyl-5-methoxyphenyl)hex-2-en-1-yl)-2,2'-dimethoxy-1,1'-biphenyl (25)

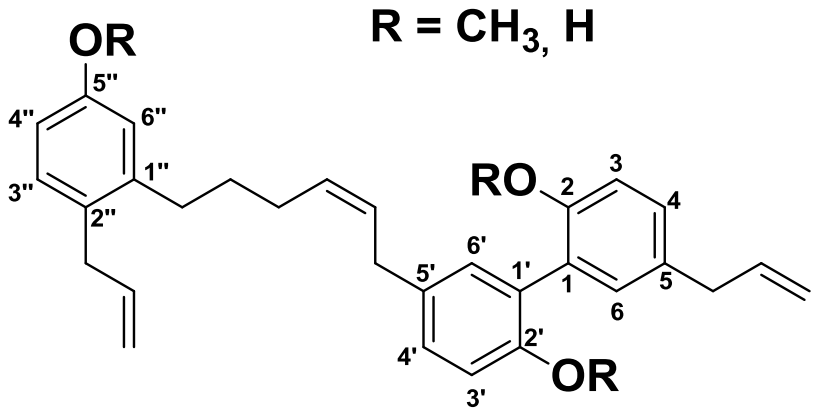


11 M = 592.50 **24** M = 296.37 **25** M = 482.66

(Z)-5-allyl-5'-(6-(2-allyl-5-methoxyphenyl)hex-2-en-1-yl)-2,2'-dimethoxy-1,1'-biphenyl **25** was synthesized applying a modified literature protocol.[64] (4-(2-Allyl-5-methoxyphenyl)butyl)triphenylphosphonium iodide **11** (121 mg, 0.20 mmol, 1 equiv.) was charged in an oven dried 8 mL vial. The vial was closed with a screw cap with septum and was evacuated and flushed with argon on a Schlenk line for 3 times. Dry diethyl ether (1.02 mL) was added. The reaction mixture was cooled with an ice bath. KHMDS (0.49 mL, 0.25 mmol, 1.2 equiv., 0.5 M in toluene) was added *via* syringe. Then the reaction solution was stirred for 5 minutes while cooled and 20 minutes at room temperature. Afterwards the reaction solution was cooled to -55°C and 2-(5'-allyl-2',6-dimethoxy-[1,1'-biphenyl]-3-yl)acetaldehyde **24** (73 mg, 0.25 mmol, 1.2 equiv.) was added as a solution in dry diethyl ether (0.5 mL), cooling was removed and the reaction mixture was stirred for 5 hours. Then the reaction mixture was filtered through a pad of Na_2SO_4. After evaporation of the solvent in *vacuo* and purification by flash column chromatography (crude mass/SiO_2 = 1/70, 1 → 5% EtOAc in LP) the desired product was obtained.

Yield: 52% (51 mg, 0.11 mmol)
Appearance: colorless oil
TLC: R_f(LP/EtOAc = 5/1) = 0.64

Assignment of carbons and protons in NMR-spectra of compounds **25** and 1 were carried out as follows:

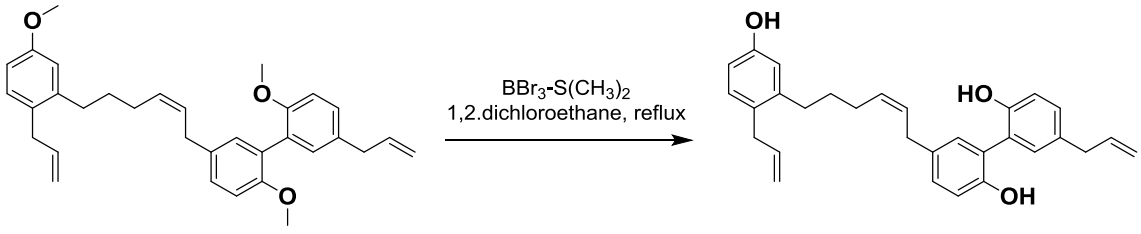


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.68 (quin, *J* = 7.7 Hz, 2H, -CH_2-C<u>H</u>$_2$-CH_2-CH=CH-), 2.23 (q, *J* = 7.2 Hz, 2H, -CH_2-CH_2-C<u>H</u>$_2$-CH=CH-), 2.60 (t, *J* = 8.2 Hz, 2H, -C<u>H</u>$_2$-CH_2-CH_2-CH=CH-), 3.30 – 3.39 (m, 6H, 3 x Ar-CH_2-), 3.74 & 3.75 & 3.77 (s, 9H, 3 x CH_3), 4.93 – 5.12 (m, 4H, 2 x -CH=C<u>H</u>$_2$), 5.55 & 5.66 (dt, *J* = 10.8 Hz, & 7.2 Hz, 2H, -CH=CH-), 5.87 – 6.03 (m, 2H, 2 x -C<u>H</u>=CH_2), 6.70 (dd, *J* = 8.1 Hz & 2.9 Hz, 1H, H4''), 6.72 (d, *J* = 2.7 Hz, 1H, H6''), 6.89 & 6.89 (d, *J* = 8.4, 2H, H3 & H3'), 7.03 – 7.06 (m, 3H, H6 & H6' & H3''), 7.10 – 7.14 (m, 2H, H4 & H4') ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.26 (t, -CH_2-CH_2-<u>C</u>H_2-CH=CH-), 30.89 (t, -CH_2-<u>C</u>H_2-CH_2-CH=CH-), 32.64 & 32.67 (t, -<u>C</u>H_2-CH_2-CH_2-CH=CH- & Ar-<u>C</u>H_2-CH=CH-), 36.34 & 39.43 (t, 2 x Ar-CH_2-), 55.20 & 55.88 & 55.93 (q, 3 x CH_3), 111.12 & 111.16 & 111.25 (d, C3 & C3' & C4''), 114.90 (d, C6''), 115.34 & 115.52 (t, 2 x -CH=<u>C</u>H_2), 127.90 (s, 2C. C1 & C1'), 128.19 & 128.44 (d, C4 & C4'), 129.12 & 130.06 (d, -CH=CH-) 129.77 (s, C2''), 130.55 & 131.42 & 131.64 (d, C6 & C6' & C3''), 131.78 (s, C5), 132.75 (s, C5'), 137.81 & 137. 86 (d, 2 x –<u>C</u>H=CH_2), 141.94 (s, C1''), 155.40 & 155.53 (s, C2 & C2'), 158.09 (s, C5'') ppm.

HR-MS: $[M+H]^+$ m/z (predicted) = 483.2894 m/z (measured) = 483.2906, difference = 2.5 ppm

3.5.2. (Z)-5-allyl-5'-(6-(2-allyl-5-hydroxyphenyl)hex-2-en-1-yl)-[1,1'-biphenyl]-2,2'-diol (<u>1</u>)



<u>25</u>
M = 482.66

<u>1</u>
M = 440.58

(Z)-5-Allyl-5'-(6-(2-allyl-5-hydroxyphenyl)hex-2-en-1-yl)-[1,1'-biphenyl]-2,2'-diol **<u>1</u>** was obtained by applying literature reported deprotection conditions.[65] (Z)-5-Allyl-5'-(6-(2-allyl-5-methoxyphenyl)hex-2-en-1-yl)-2,2'-dimethoxy-1,1'-biphenyl **<u>25</u>** (40 mg, 0.08 mmol, 1 equiv.) and BBr_3-$S(CH_3)_2$ complex (91 mg, 0.29 mmol, 3.5 equiv.) were placed in an oven dried 8 mL vial. The vial was closed with a screw cap with septum

and was evacuated and flushed with argon on a Schlenk line 3 times. 1,2-Dichloroethane (2 mL) was added *via* syringe. The mixture was stirred while heated on a thermo block which was adjusted to 105°C for 21 hours. H_2O (2 mL) was added and the two phases were separated. The aqu. phase was extracted with 1,2-dichloroethane (3 x 2 mL) and the combined organic layers were washed with brine (4 mL) and dried over $MgSO_4$. After evaporation of the solvent in *vacuo* and purification by flash column chromatography (crude mass/SiO_2 = 1/100, 1% CH_3OH in CH_3Cl) the desired product was obtained.

Yield: 50% (18 mg, 0.04 mmol)
Appearance: beige oil
TLC: $R_f(CH_3OH/CHCl_3 = 1/19) = 0.37$
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.64 (quin, *J* = 7.6 Hz, 2H, -CH_2-C<u>H</u>$_2$-CH_2-CH=CH-), 2.20 (q, *J* = 7.1 Hz, 2H, -CH_2-CH_2-C<u>H</u>$_2$-CH=CH-), 2.55 (t, *J* = 7.9 Hz, 2H, -C<u>H</u>$_2$-CH_2-CH_2-CH=CH-), 3.27 – 3.39 (m, 6H, 3 x Ar-CH_2-), 4.78 (bs, OH), 4.92 – 5.12 (m, 4H, 2 x -CH=C<u>H</u>$_2$), 5.51 – 5.67 (m, 4H, -CH=CH- & 2 x OH), 5.86 – 6.01 (m, 2H, 2 x -C<u>H</u>=CH_2), 6.57 – 6.62 (m, 2H, 2 x Ar-H), 6.93 – 7.00 (m, 3H, 3 x Ar-H), 7.06 – 7.09 (m, 2H, 2 x Ar-H), 7.11 - 7.15 (m, 2H, 2 x Ar-H) ppm.
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.24 (t, -CH_2-CH_2-<u>C</u>H$_2$-CH=CH-), 30.75 (t, -CH_2-<u>C</u>H$_2$-CH_2-CH=CH-), 32.40 & 32.66 (t, -C<u>H</u>$_2$-CH_2-CH_2-CH=CH- & Ar-<u>C</u>H$_2$-CH=CH-), 36.40 & 39.47 (t, 2 x Ar-CH_2-),112.99 (d, C4''), 115.46 & 115.99 (t, 2 x -CH=<u>C</u>H$_2$), 116.02 & 116.79 & 116,88 (d, C3, C3' & C6''), 123.77 & 123.82 (s, C1 & C1'), 128.69 (d), 129.87 (d), 129.92 (s, C2''), 130.16 (d), 130.75 (d), 130.90 (d), 131.03 (d), 131.27 (d), 133.38 & 134.39 (s, C5 & C5'), 137.62 & 137.87 (d, 2 x –<u>C</u>H=CH_2), 142.12 (s, C1''), 151.16 & 151.32 (s, C2 & C2'), 154.00 (s, C5'') ppm.
HR-MS: $[M+H]^+$ m/z (predicted) = 441.2424 m/z (measured) = 441.2436, difference = 2.7 ppm

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Curriculum vitae

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