Higher Marine Phenylpropanoids: Synthesis and Biology of Maculalactones and Ophiodilactones

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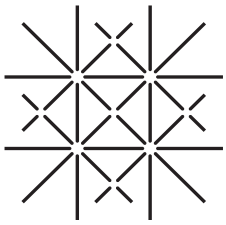

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Ideologie ist Ordnung auf
Kosten des Weiterdenkens

Friedrich Dürrenmatt

This thesis was supervised by Prof. Dr. Karl Gademann from September 2010 to February 2014 at the University of Basel, Department of Chemistry.

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ABSTRACT

Phenylpropanoids, consisting of the characteristic C_6C_3 subunits, are one of the most prevalent secondary metabolites in nature. While terrestrial plants produce a wide variety of these natural products, few examples from marine prokaryotes are known. In this thesis, we will discuss our investigations on the synthesis and biology of two marine natural product families. The maculalactones were isolated from the marine cyanobacterium *Kyrtuthrix maculans*. While maculalactone A was found to be a potential antifouling agent, maculalactone E exhibits interesting activities against human tumor cell lines. The structurally related ophiodilactones, isolated from *Ophiocoma scolopendrina*, showed comparable cytotoxicities against leukemia cells.

All three literature known syntheses of maculalactone A possess yields below 10%. In our optimization, we investigated shortcuts of the known routes and a butenolide formation by metathesis. Finally, we obtained maculalactone A in an overall yield of 45% utilizing a rare, intramolecular butenolide synthesis.

In our concept for the antifouling protection of metal surfaces, we envisioned connecting maculalactone A through a linker to a catechol anchor. An appropriate derivative of the natural product for this purpose was identified in a small SAR study. We then labeled the active maculalactone A analogue with a rhodamine B fluorophore. *In vivo* experiments in *Artemia salina* demonstrated a selective accumulation of this molecular probe along the intestine.

Unfortunately, our efforts towards the total synthesis of ophiodilactone A and B over two independent strategies were unsuccessful. In a linear strategy, a bisallylic precursor was desymmetrized via a Sharpless epoxidation. After Payne rearrangement and nucleophilic epoxide opening, we successfully elongated the linear chain. However, the steric repulsion of the benzyl- and protecting groups prevented further conversion. In an alternative, protecting group-free approach, maculalactone A was added to cinnamaldehyde in a diastereo- and enantioselective vinylogous Michael addition by phase transfer catalysis. Despite attempts with various reagents, the subsequent oxidation of the butenolide double bond was not achieved. In addition, different strategies to work around the insufficient reactivity of the olefin were investigated.

In conclusion, we developed an efficient synthesis of maculalactone A and used this material for our biological investigations. Furthermore, we achieved the synthesis of the ophiodilactone A carbon skeleton in five steps.

ZUSAMMENFASSUNG

Die Phenylpropanoide sind die wohl häufigsten sekundären Metaboliten in der Natur. Während diese Naturstoffe in grosser Variation in Pflanzen vorkommen, sind sie in im Meer lebenden Prokaryoten selten zu finden. In der hier vorliegenden Arbeit diskutieren wir unsere Erkenntnisse in der Synthese und Biologie zweier mariner Naturstofffamilien. Die Maculalactone wurden aus dem Cyanobakterium *Kyrtuthrix maculans* isoliert. Maculalacton A zeigt Potential als Antifouling Mittel und bei Maculalacton E wurden interessante Aktivitäten gegen menschliche Krebszellen nachgewiesen. Die strukturell ähnlichen Ophiodilactone wurden aus dem Seestern *Ophiocoma scolopendrina* isoliert und wirken cytotoxisch gegenüber Leukämiezellen.

Die drei in der Literatur beschrieben Maculalacton A Synthesen erreichen Ausbeuten unter 10%. In unserer Optimierung untersuchten wir eine Synthese des Butenolids mittels Metathese und konnten Maculalacton A schlussendlich über eine seltene intramolekulare Zyklisierung in vier Schritten und einer Ausbeute von 45% herstellen.

In unserem Konzept zum Biofoulingschutz von Metaloberflächen verbanden wir Maculalacton A über einen Linker mit einem unserer Catechol Anker. Ein geeignetes Derivat des Naturstoffes wurde in einer kleinen SAR Studie gefunden. Dieses Maculalacton A Analogon wurde ausserdem mit einem Rhodamin B Fluorophor markiert. In einem *in vivo* Experiment mit *Artemia salina* konnten wir eine Akkumulierung des Markers entlang des Darmes beobachten.

Zwei verschiede Strategien zur Totalsynthese von Ophiodilacton A und B waren leider erfolglos. In einer linearen Route desymmetrisierten wir einen Bisallylalkohol mittels Sharpless Epoxidierung. Das Epoxid konnte nach einer Payne Umlagerung nukleophil geöffnet werden. Die Verlängerung der linearen Kette konnte ereichte werden, jedoch verhinderte die sterische Abschirmung der Schutz- und Benzylgruppen sämtliche Folgereaktionen. In einer alternativen, Schutzgruppen freien Strategie wurde Maculalacton A in einer enantio- und diastereoselektiven Reaktion mittels Phasentransferkatalysator an Zimtaldehyd addiert. Die folgende Oxidation der Doppelbindung des Butenolids konnte weder mit verschiedenen Reagenzien noch über reaktivere Intermediat erreichten werden.

Zusammenfassend entwickelten wir eine effiziente Synthese von Maculalacton A und nutzen diese zur Untersuchung der biologischen Eigenschaften. Ausserdem konnten wir das Kohlenstoffgerüst von Ophiodilacton A in 5 Stufen aufbauen.

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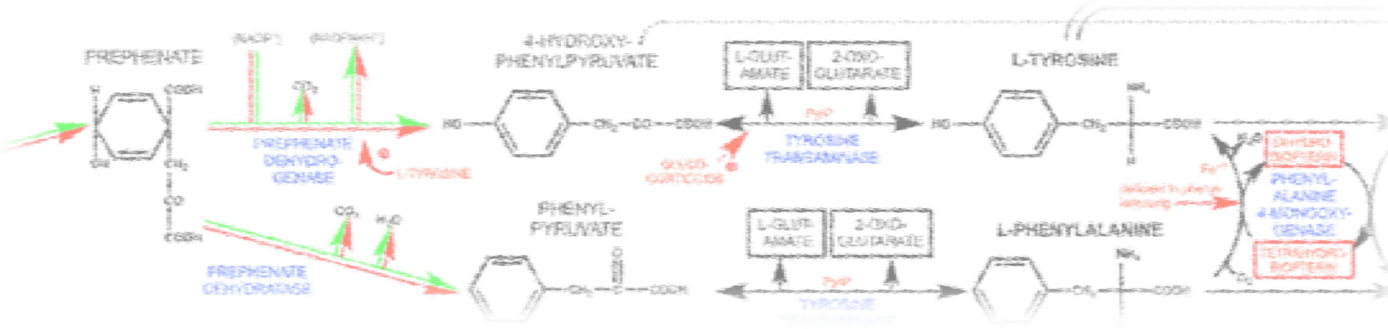
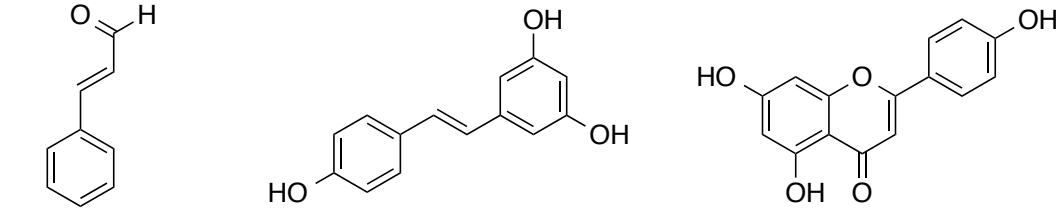
1 - INTRODUCTION



1.1 Phenylpropanoids

Phenylpropanoids might be most prevalent secondary metabolites in nature and are most frequently found in terrestrial plants.[1,2] In the colonization of landmass by plants 500 million years ago, these pioneering organisms had to adapt to stresses such as UV radiation, desiccation and microbial attacks. Along with other evolutions, the emergence of the phenylpropanoid metabolic pathway was crucial (Section 1.2). In plants, low-molecular-weight phenylpropanoids play various roles such as antibiotics, UV protectants, insect repellents, flower pigments and signaling molecule in plant-microbe interactions.[3] Furthermore, high-molecular-weight, polymeric phenylpropanoids are important components in surface and support structures. Due to these diverse biological functions, phenylpropanoids adopt various molecular structures, which consists of C_6C_3 subunits.[4] In addition, other phenylpropanoid subunits such as C_6C_2 and C_6C_1 or acetate-derived C_2 and aromatic C_6 units and, in some cases, various primary and secondary metabolites can be present.



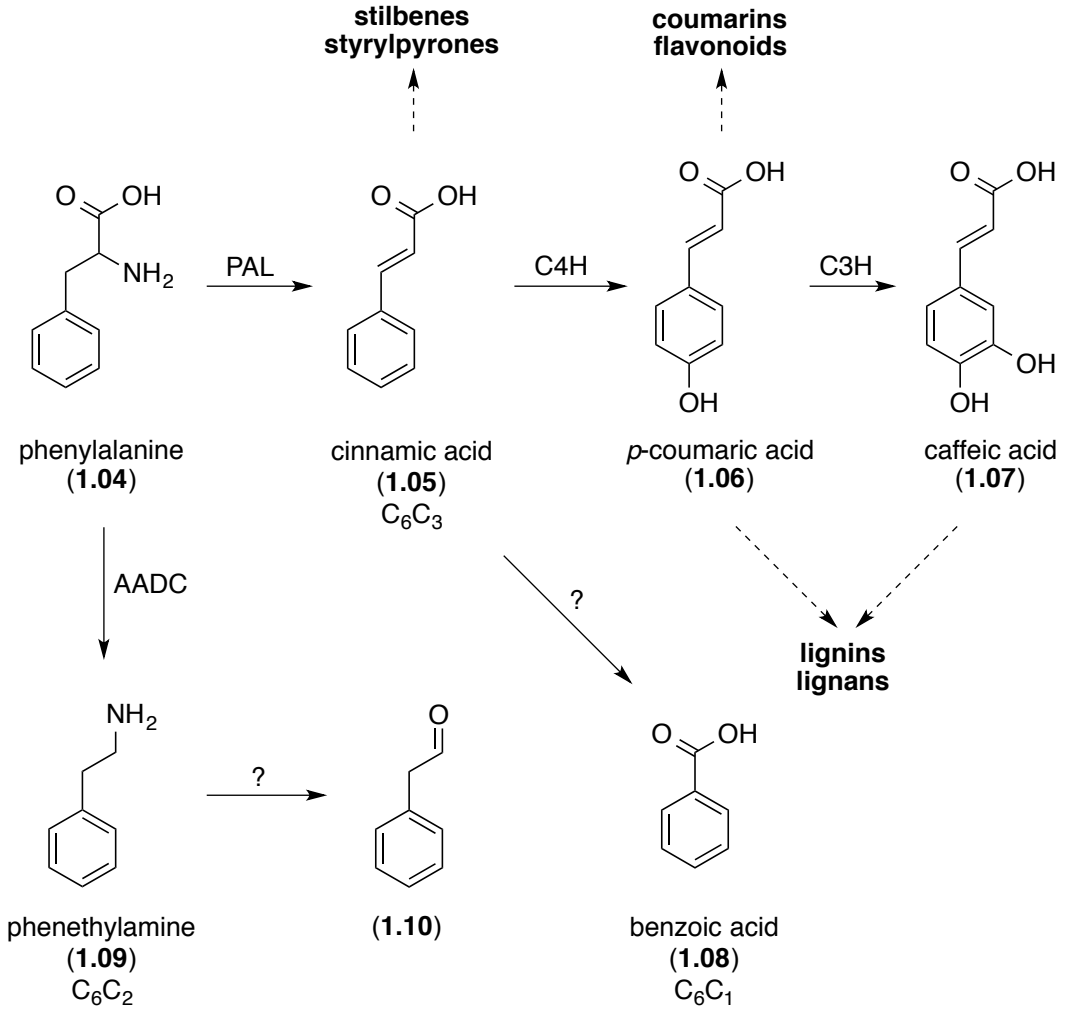
cinnamaldehyde (**1.01**) resveratrol (**1.02**) apigenin (**1.03**)

Figure 1.1: Selected examples of phenylpropanoids from different plant sources.[4,5]

Selected examples of well-known phenylpropanoids are depicted in figure 1.1.[4,5] The least complex phenylpropanoid, cinnamaldehyde (**1.01**), consists of a single C_6C_3 unit and is known to cause the unique odor of cinnamon tree bark. Resveratrol (**1.02**) is present in grapes and red wine, and it's suspected anti-aging effects are still debated. Resveratrol consists of one C_6C_3 phenylpropanoid subunit and an additional aromatic ring constructed from three acetate-derived C_2 units. Therefore, it belongs to the family of stilbenes. Arylic hydroxyl groups are a typical feature of phenylpropanoids. The more complex, apigenin (**1.03**), belongs to the family of flavones and can be found in several herbs including parsley, thyme and peppermint.

1.2 Biosynthesis of Phenylpropanoids

Despite intensive studies on the biosynthesis of phenylpropanoids in the last decades, many details have yet to be revealed.[1–4,6,7] The fundamental first steps of the biogenesis resulting in the different families of phenylpropanoids will be discussed (Scheme 1.1). Most of the described transformations are also known for the corresponding CoA-esters.



Scheme 1.1: Parts of the phenylpropanoid metabolism in terrestrial plants. The enzymes are abbreviated as follows: phenylalanine ammonia lyase (PAL), cinnamate-4-hydroxylase (C4H), coumarate-3-hydroxylase (C3H) and aromatic amino acid decarboxylase (AADC). In some species, *p*-coumaric acid can be accessed from tyrosine. The required enzyme tyrosine ammonia lyase (TAL) is manly found in grasses.[4]

In the first step, the proteogenic amino acid phenylalanine (**1.04**) is converted to the unsaturated cinnamic acid (**1.05**), representing the most elementary C_6C_3 subunit.[4] Subsequent oxidation by C4H results in the formation of *p*-coumaric acid (**1.06**) and further oxidation by C3H gives caffeic acid (**1.07**). As indicated in scheme 1.1, these three phenylpropanoids are the main building blocks of the many more complex

structures such as lignans (Section 1.3). It is assumed that benzoic acid (**1.08**), a C_1C_6 unit, is produced from cinnamic acid.[7] However, this has not been proven thus far and benzoic acid can also be accessed from other metabolites. Recently, Tieman *et al.* discovered the first step of the biosynthesis of C_2C_6 subunits.[8] The enzyme AADC is responsible for the one carbon deletion of **1.04**, giving phenethylamine (**1.09**). Then, the amine group is assumed to be removed by oxidation to ketone **1.10**.

Crucial for the biosynthesis of phenylpropanoids is PAL, required to obtain the C_6C_3 building block cinnamic acid (**1.05**). While this enzyme is found in all vascular plants, it is absent in animals and most algae. Therefore, this protein has been assumed to be a result of the evolutionary adoption of the plants during the colonization of the land (Section 1.1). However, the isolation of phenylpropanoid secondary metabolites from none plant organisms put this assumption in question. In 2007, Moffitt *et al.* characterized the first cyanobacterial PALs from *Anabaena variabilis* and *Nostoc punctiforme*.[9] In combination with similar findings in other organisms, it is now debated if this enzyme has a prokaryotic origin and was transported to the vascular plants by a horizontal gene transfer.[2]

1.3 Lignans

Lignans are a family of phenylpropanoid natural products consisting of two C_6C_3 units, linked by a C8-C8' carbon bond.[4,10] These secondary metabolites are widely distributed in the plant kingdom and are biosynthesized and deposited in significant amounts in the heartwood region of trees. Lignans show interesting biological properties and some members of this family are used in medicine and as nutritional supplements, such as podophyllotoxin-derivatives in cancer therapies and sesamin in health and nutrition. Additionally, the lignans are of special interest to us, as they are closely structurally related to the marine secondary metabolite families, the maculalactones and ophiodilactones.

1.3.1 Classification and Biosynthesis

Lignans are classified in eight subgroups, determined by the cyclization pattern and whether oxygen is present in the skeleton (Figure 1.2).[10,11] Some of these subgroups are further divided to account for the oxidation state of the C9- and C9'-position, which is installed in the beginning of the biosynthesis. Furthermore, the members of each

subgroup vary substantially in the oxidation levels of the alkyl chains and the aromatic rings.

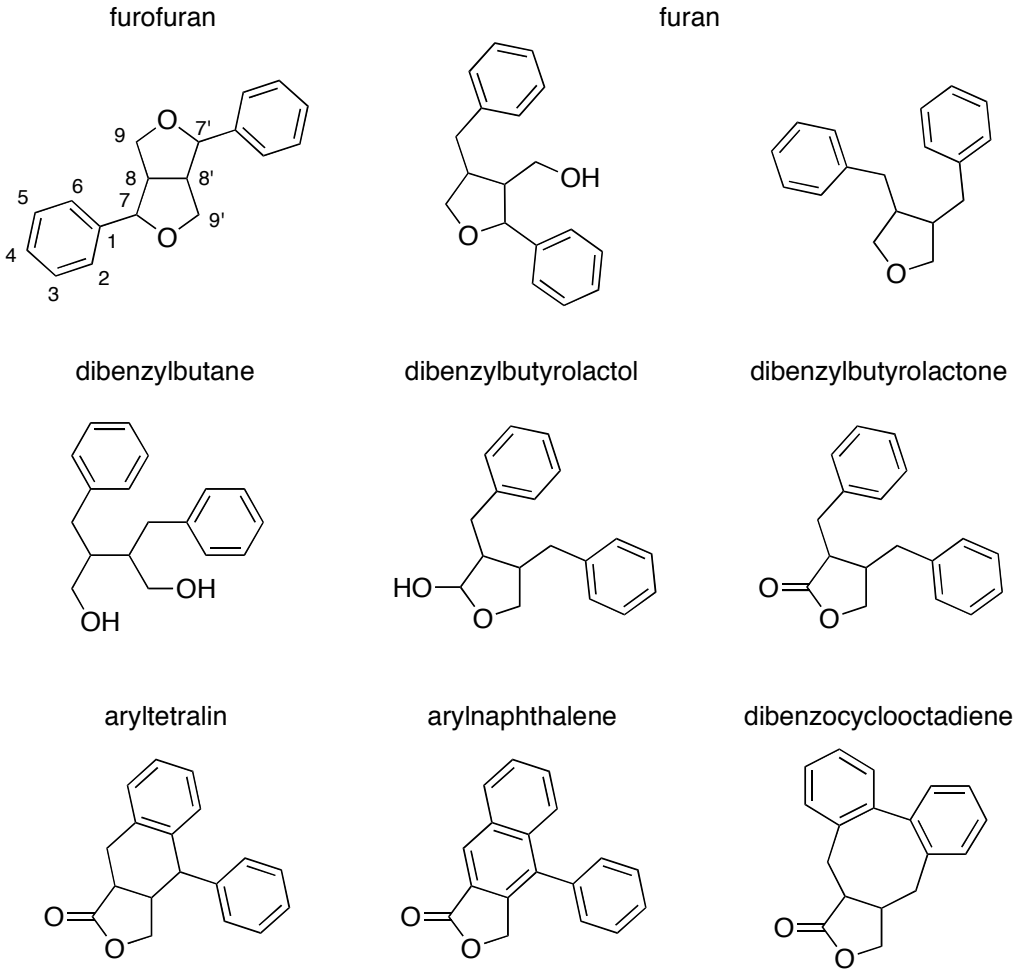
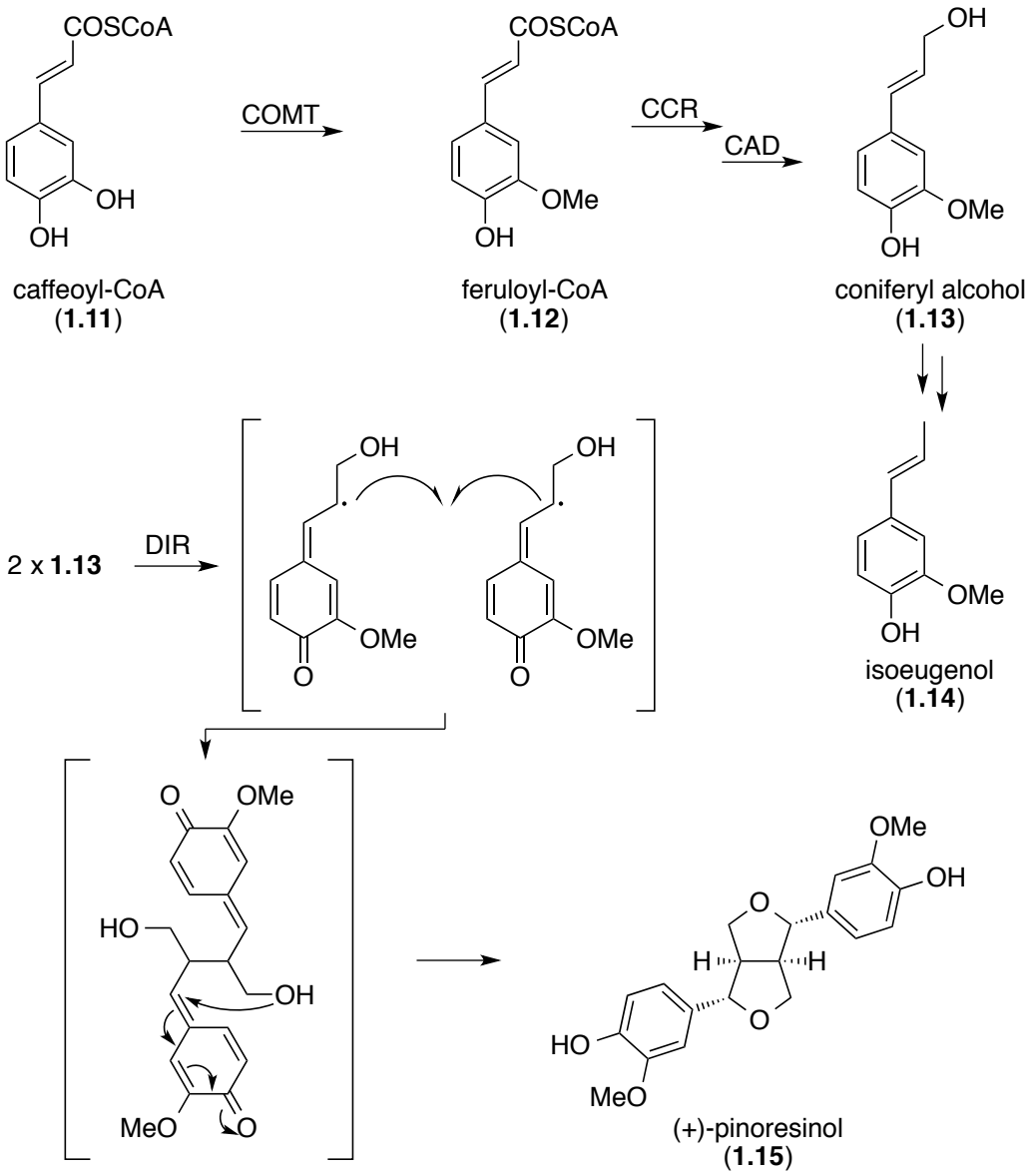


Figure 1.2: Subgroups of Lignans. The members without oxygen at the C9(C9')-position were omitted for clarity.[10]

Compared to the other lignans, the biosynthesis of the C9(C9')-oxidized members is the most explored.[7,11] In the initial steps of the biogenesis, *p*-caffeoyl-CoA (**1.11**) is converted to the dimerization precursor coniferyl alcohol (**1.13**) (Scheme 1.2). The regioselective methylation in the 3-position by COMT results in the formation of feruloyl-CoA (**1.12**). Subsequently, the CoA ester is reduced with NADPH in two steps to the corresponding alcohol **1.13**. The formed coniferyl alcohol is a precursor of not only lignans, but also lignins.

In the presence of DIR and an oxidase or a single electron oxidant, coniferyl alcohol (**1.13**) is dimerized to afford the C8(C8') coupled pinoresinol (**1.15**).[10] This reaction proceeds via a regioselective carbon-carbon bond formation of two resonance-stabilized radicals. Lignans without oxygen at the C9(C9')-position or two acid groups

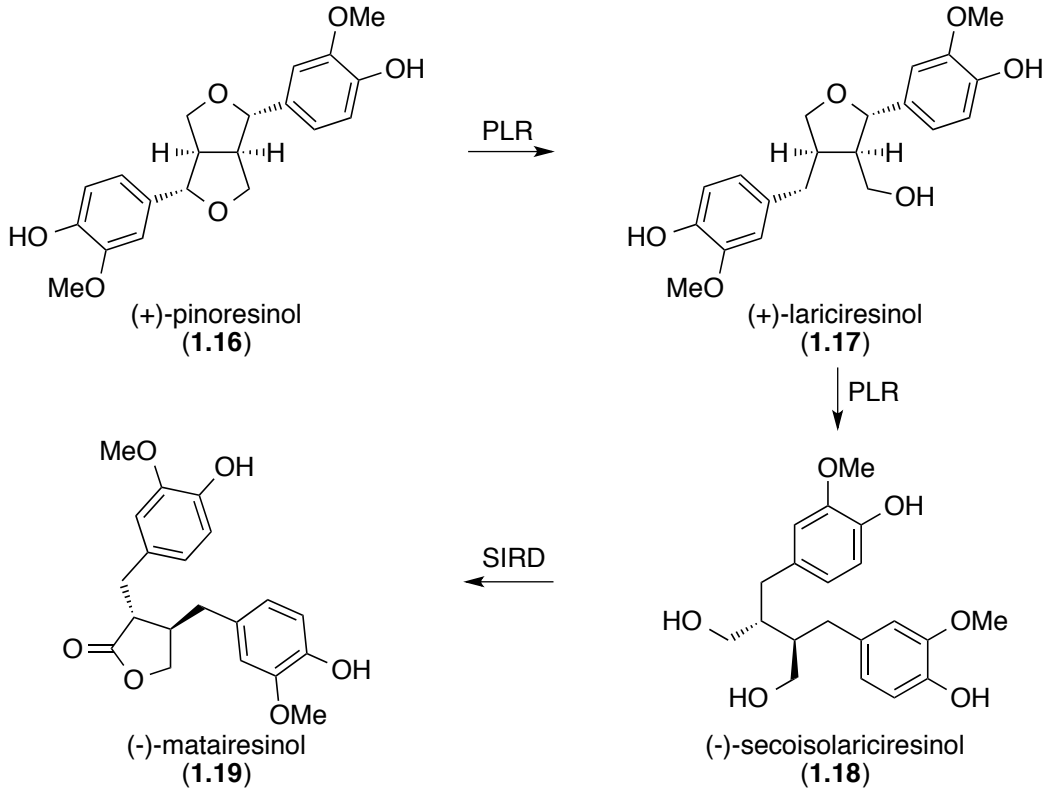
originate from a similar reaction with isoeugenol (**1.14**) or caffeic acid (**1.07**), respectively. In contrast to similar reactions in the biogenesis of lignins, these radical dimerizations are enantioselective. Lignans from natural sources are isolated either enantiopure or with an excess of one enantiomer. The absolute configuration of pinoresinol and all derived natural products can vary with plant species.



Scheme 1.2: Biosynthesis of coniferyl alcohol and subsequent dimerization to (+)-pinoresinol.[4,10] The enzymes are abbreviated as follows: caffeic acid methyltransferase (COMT), cinnamoyl-CoA reductase (CCR), cinnamyl alcohol dehydrogenase (CAD) and dirigent protein (DIR).

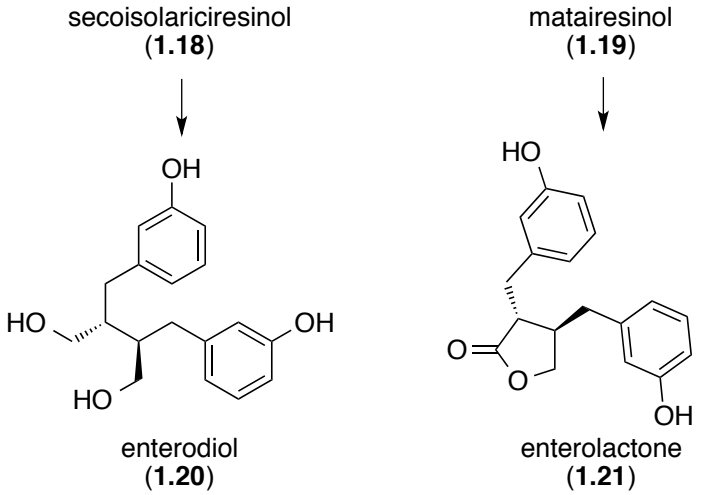
The formed pinoresinol (**1.15**) is the central intermediate in the synthesis of all C9(C9')-oxidized lignans and can be converted to the remaining seven subgroups (Figure 1.2). The biosynthetic pathway affording dibenzylbutyrolactones, which possess

a similar structure as maculalactone A (**1.34**) (Section 1.4), is well understood.[4,10] In the beginning of this process, the benzylic ethers are cleaved by PLR in the presence of NADPH to afford lariciresoinol (**1.17**) first and secoisolariciresinol (**1.18**) second (Scheme 1.3). This is followed by a regioselective oxidation of one of the two primary alcohols, resulting in the formation of matairesinol (**1.19**).



Scheme 1.3: Biosynthesis of (-)-matairesinol.[4,10] The enzymes are abbreviated as follows: pinoresinol/lariciresinol reductase (PLR) and secoisolariciresinol dehydrogenase (SIRD).

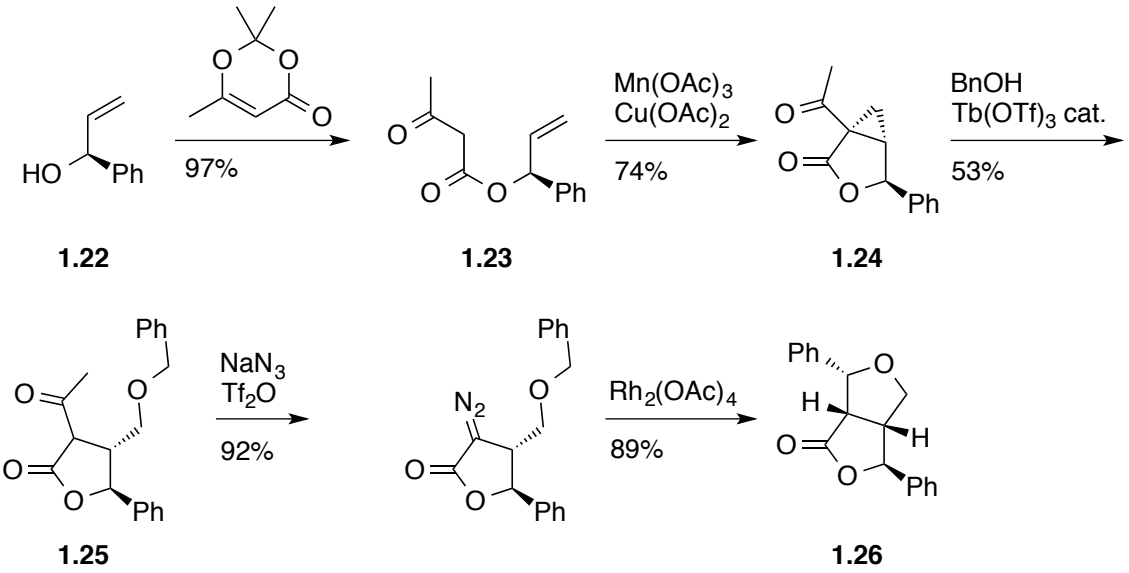
Secoisolariciresinol and matairesinol occur in numerous foodstuffs such as oilseeds, whole grains, vegetables and fruits.[12] During the digestion of these foods, intestinal bacteria convert these lignans into enterodiol (**1.20**) and enterolactone (**1.21**), respectively (Scheme 1.4).[4] These "mammalian" lignans are known to provide preventative effects including reduced risk of breast[13] and lung[14] cancer, as well as a reduction of vascular inflammations.[15]



Scheme 1.4: Transformation to enterodiol and enterolactone by intestinal bacteria.[4]

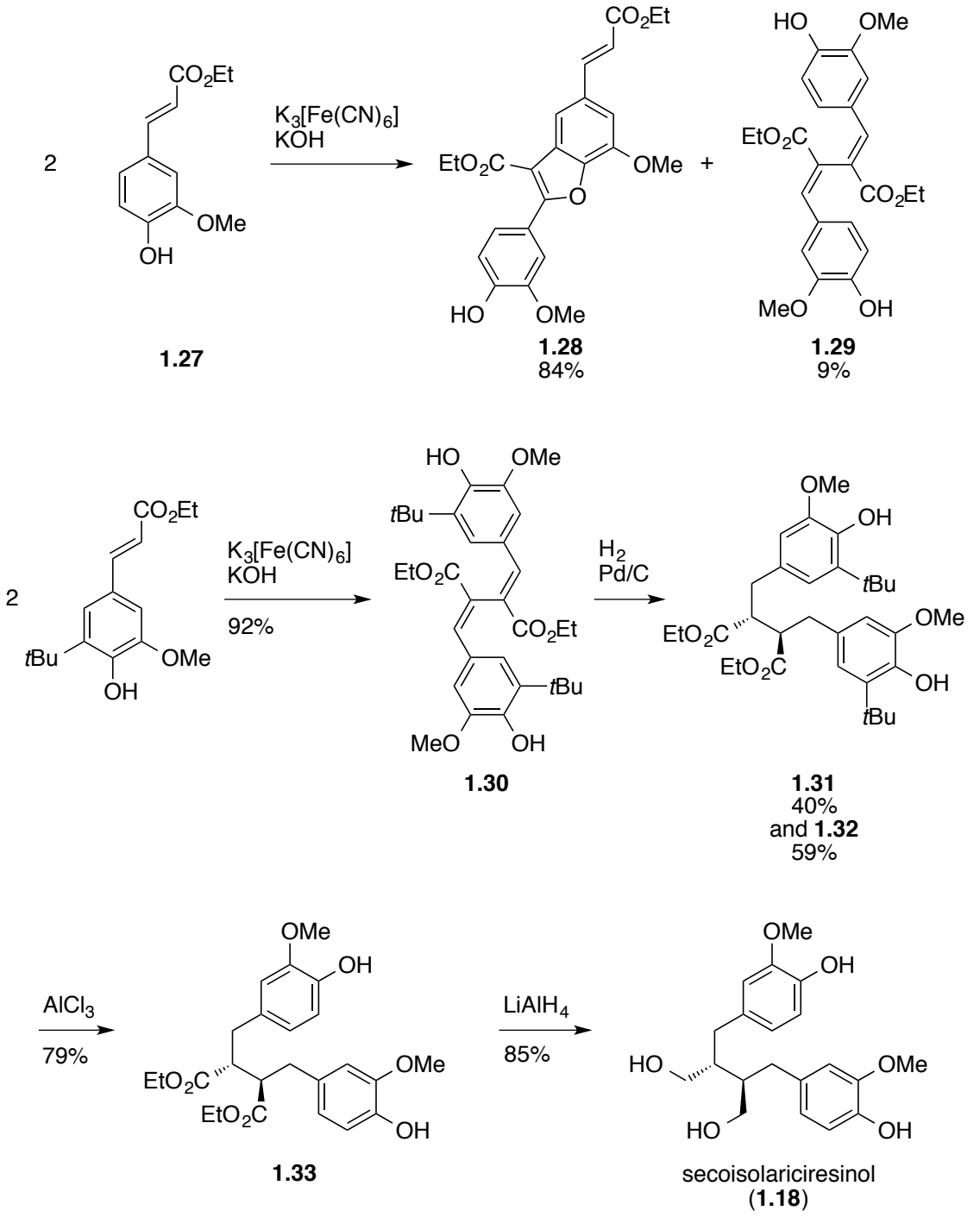
1.3.2 Synthesis

The promising biological properties and the interesting chemistry of the lignans has attracted much attention by synthetic groups.[16–19] A modern synthetic route yielding four different furofuran lignans has been reported by Bruton an co-workers.[20] Key steps of the synthesis include a Mn(III)-mediated intramolecular cyclopropanation and a carbene C-H insertion (Scheme 1.5). Enantiomerically enriched 1-phenylallyl alcohol (**1.22**) is converted to β-keto ester **1.23**. A diastereoselective cyclopropanation affords intermediate **1.24**, which is subsequently transformed to the ring-opened lactone **1.25**. A deacetylative diazo-transfer was followed by a rhodium catalyzed C-H insertion to provide **1.26**. The furofuran core was established after reduction of the lactone in two further steps. The natural occurring lignans were accessed by the same strategy from the appropriately substituted analogues.



Scheme 1.5: Stereoselective synthesis of furofuran lignans as reported by Bruton and co-workers.[20]

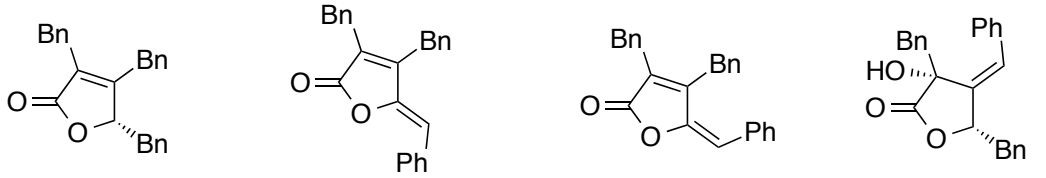
Other groups focused on more biomimetic approaches. While single electron oxidations of ethyl ferulate (**1.27**) have been known for years, selectivity issues resulting from the mesomeric delocalization of the radical could not be overcome. Instead of the desired C8(C8') coupled bisester **1.29**, the C8(C5') linked product **1.28** was observed as the major product (Scheme 1.6).[21,22] Recently, Wang *et al*. reported a method to prevent the undesired formation of product **1.28**. By blocking the arylic five position with a *tert*-butyl residue, the desired C8(C8') linked product **1.30** was isolated in excellent yield and selectivity from the same reaction conditions. Olefin reduction gave the diastereomeric compounds **1.31** and **1.32**. Subsequent removal of the *tert*-butyl groups by a retro Friedel-Crafts alkylation resulted in the formation of bisester **1.33**. Reduction of the ester moieties afford *rac*-secoisolariciresinol (**1.18**). The diastereomeric compound **1.32** was transformed in the same manner.



Scheme 1.6: Biomimetic synthesis of lignans after blockage of the C5 position as reported by Wang *et al.*[21]

1.4 Maculalactones

In 1996, the group of Brown published the isolation of a new secondary metabolite from the cyanobacteria *Kyrtuthrix maculans*.[23] This organism forms colonies in high intertidal zones on rocky shores in Vietnam, Thailand, Australia, China, Japan, India, Hawaii and the Mediterranean. In Hong Kong, where the samples for isolation were collected, *K. maculans* dominates the moderately exposed shores and covers approximately about 50% of the rock surface.

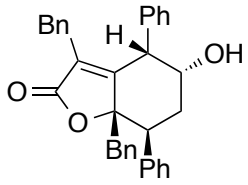


maculalactone A (**1.34**) | maculalactone B (**1.35**) | maculalactone C (**1.36**) | maculalactone L (**1.37**)

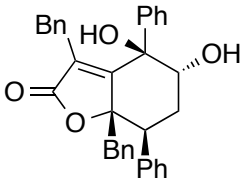
Figure 1.3: Butenolide secondary metabolites isolated from *K. maculans*.[23–25] The relative stereochemistry of maculalactone L was established within this work (Chapter 6). Maculalactone A was later also isolated from *Ophioplocus japonicus*.[26]

The isolated secondary metabolite was identified as an unsaturated γ-lactone substituted by three benzyl groups and was named maculalactone A (**1.34**) (Figure 1.3).[23] The absolute configuration of the stereocenter was determined during the first total synthesis of **1.34** by the same group.[27] Interestingly, isolated maculalactone A was found to be not optically pure. The probes from natural sources exhibit an enantiomeric excess of the (4*S*) enantiomer of 70 to 90%. A racemization during the isolation could be excluded. Neither racemic nor optically pure natural products are often observed in the family of the lignans (Section 1.3.1).

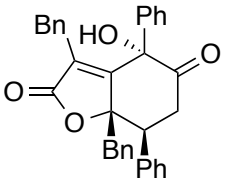
In 1998, Brown and coworkers reported the structure of ten new compounds, isolated from the same cyanobacterium.[24] Maculalactone B (**1.35**) and C (**1.36**) possess the same carbon skeleton as maculalactone A **(1.34**), but include an additional double bond in the γ-position. In contrast, maculalactone D (**1.38**), E (**1.39**), F (**1.40**), G (**1.41**), H (**1.42**), I (**1.43**), J (**1.44**) and K (**1.45**) are more complex and the structure is extended by another C_6C_3 unit, resulting in the tetrahydrobenzofuranone core of these new compounds (Figure 1.4). While the carbon skeletons of these maculalactones are identical, they can be differentiated by the oxidation patterns.



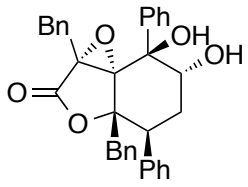
maculalactone D
(**1.38**)



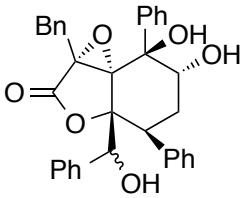
maculalactone E
(**1.39**)



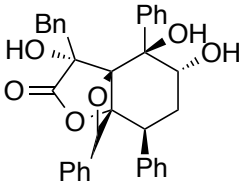
maculalactone F
(**1.40**)



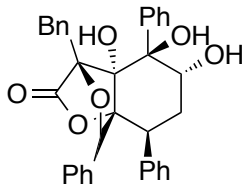
maculalactone G
(**1.41**)



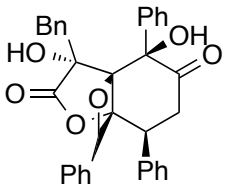
maculalactone H
(**1.42**)



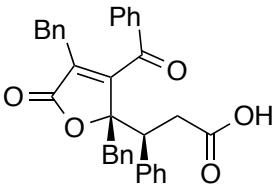
maculalactone I
(**1.43**)



maculalactone J
(**1.44**)



maculalactone K
(**1.45**)



maculalactone M
(**1.46**)

Figure 1.4: Tetrahydrobenzofuranone secondary metabolites isolated from *K. maculans*.[24,28] Maculalactone E was also isolated from *O. japonicus* and the absolute configuration was determined.[26] All other absolute configurations are unknown, but were assumed to be the same.

In the following years, two new members of this family were isolated from the same organism. Maculalactone L (**1.37**) possesses the carbon-skeleton of maculalactone A and is an oxidized analogue of this compound.[25] Maculalactone M (**1.46**) is suspected to originate from an oxidative carbon bond cleavage, resulting in its ring open structure.[28]

Recently, Wang *et al.* described the isolation of maculalactone A (**1.34**) and E (**1.39**) from the brittle star *Ophioplocus japonicus*.[26] Furthermore, the absolute configuration of lactone **1.39** was determined by a modified Mosher method. It is here assumed that all other maculalactones with a tetrahydrobenzofuranone core exhibit the same absolute configuration.

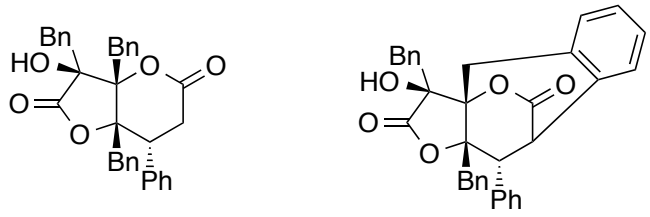
The biological properties of the maculalactones are not well investigated. Only the most abundant maculalactone A (**1.34**) was intensively studied by Brown and co-workers.[29] Along with other experiments, the toxicity of maculalactone A against

potential grazers was determined. Furthermore, the use of maculalactone A as antifouling agent was investigated (Section 3.1.2).[30] In their activity driven isolation from *O. japonicus*, Wang *et al.* examined the cytotoxicity of macualactone A (**1.34**) and E (**1.39**) against five human tumor cell lines (A549, SK-OV-3, SK-MEL-2, XF498, HTC15).[26] While maculalactone A showed only modest activity, maculalactone E exhibited good IC_{50} values between 2.8 and 3.7 μg/ml.

In accordance to the structure, oxidation pattern and the extent of aromatic moieties, the maculalactones are assumed to be a result of the phenylpropanoid metabolic pathway.[24] Similarly saturated γ-lactones are known from lignans (Section 1.3). The biosynthesis is not yet understood, but the butenolide is assumed to be the result of a condensation of three C_6C_3 units. This would however require the loss of two carbons during this process. Alternatively, the core could be formed from two C_6C_3 and one C_6C_1 units. The tetrahydrobenzofuranone bicycle is assumed to originate from an additional C_6C_3 unit.

1.5 Ophiodilactones

In 2009, Ueoka *et al.* reported the isolation of similar compounds from *Ophiocoma scolopendrina*.[31] This ophiuroid inhabits intertidal zones in the Indo-Pacific and is therefore a potential grazer of *K. maculans*. In contrast to the tetrahydrobenzofuranone bicycle of the maculalactones, the isolated compounds ophiodilactone A (**1.47**) and B (**1.48**) possess a second δ-lactone (Figure 1.5). It has been estimated that these dilactones are metabolites of the *K. maculans* nutrition.[26]



ophiodilactone A (**1.47**) ophiodilactone B (**1.48**)

Figure 1.5: Ophiodilactone A and B isolated from the ophiuroid *Ophiocoma scolopendrina*.[31] The absolute stereochemistry has been determined from CD data.

To our knowledge, the γ,δ-dilactone core structure of ophiodilactone A (**1.47**) has been isolated for the first time from a biological sample. Only two examples of similar synthetic γ,δ-dilactones were found in literature, of which both exhibit minimal substitution. Even more fascinating is the additional connection between the aryl- and

the α-lactonic position in ophiodilactone B (**1.48**).[32] Both compounds were found to exhibit cytotoxic activity against P388 murine leukemia cells with IC_{50} values of 5.0 and 2.2 μg/ml for ophiodilactone A and B, respectively.[31]

Recently, Matsubara *et al.* published their total synthesis of ophiodilactone A (**1.47**) and B (**1.48**).[33,34] In their route, the assumed direct conversion of **1.47** to **1.48** by a radical mechanism was demonstrated.[31]

1.6 Thesis Outlook

This discussion will present our efforts to understand more about the chemistry and biology of the maculalactones and the ophiodilactones. Chapter 2 focuses on a new high yielding synthesis of maculalactone A (**1.34**). Our biological studies and investigations towards an antifouling application are discussed in chapter 3. Our efforts towards our main goal, the total synthesis of ophiodilactone A (**1.47**) and B (**1.48**), are described in chapters 4 and 5. Preliminary studies towards the synthesis of other maculalactones are presented in chapter 6.

1.7 References

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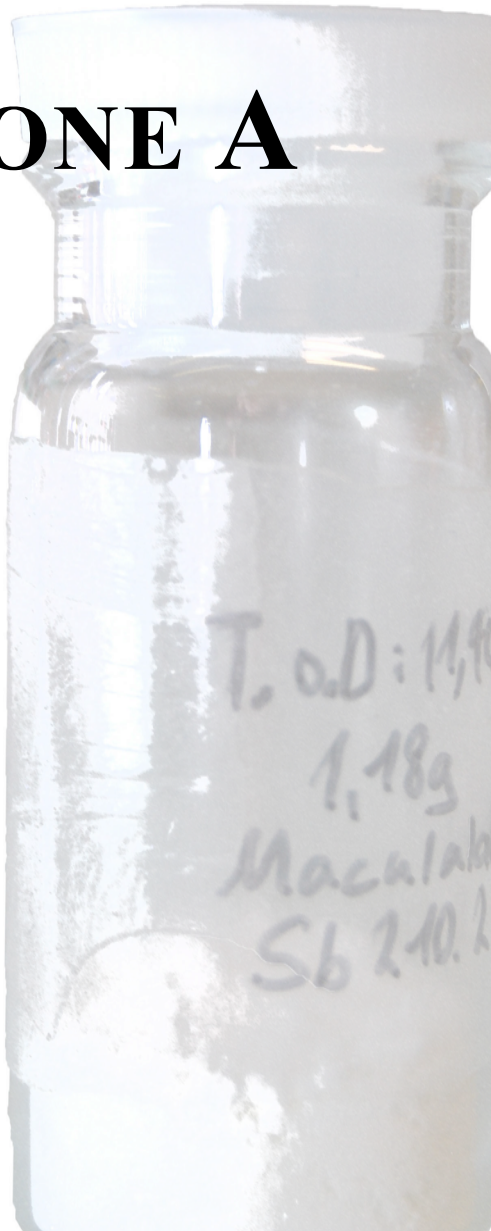
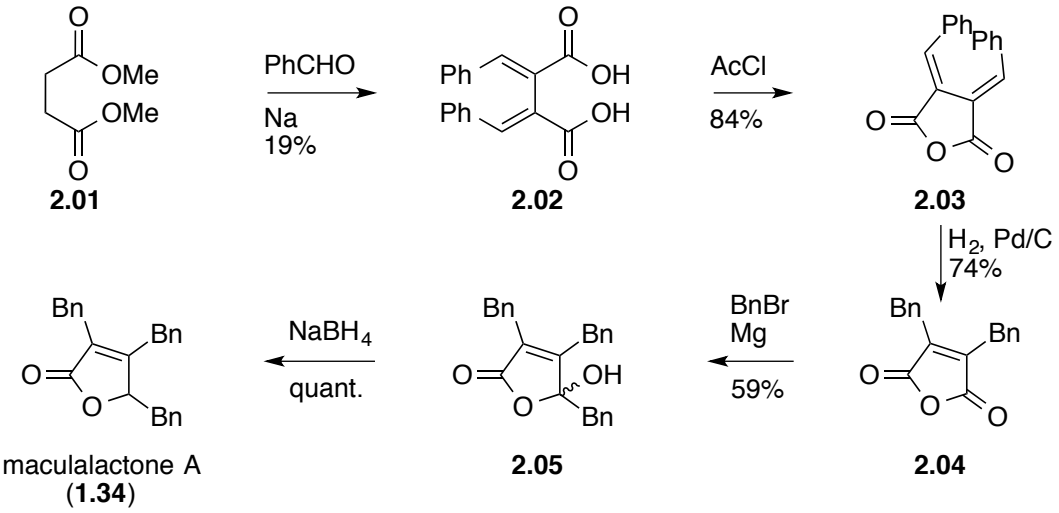
2 - An Improved Synthesis of Maculalactone A



2.1 Introduction

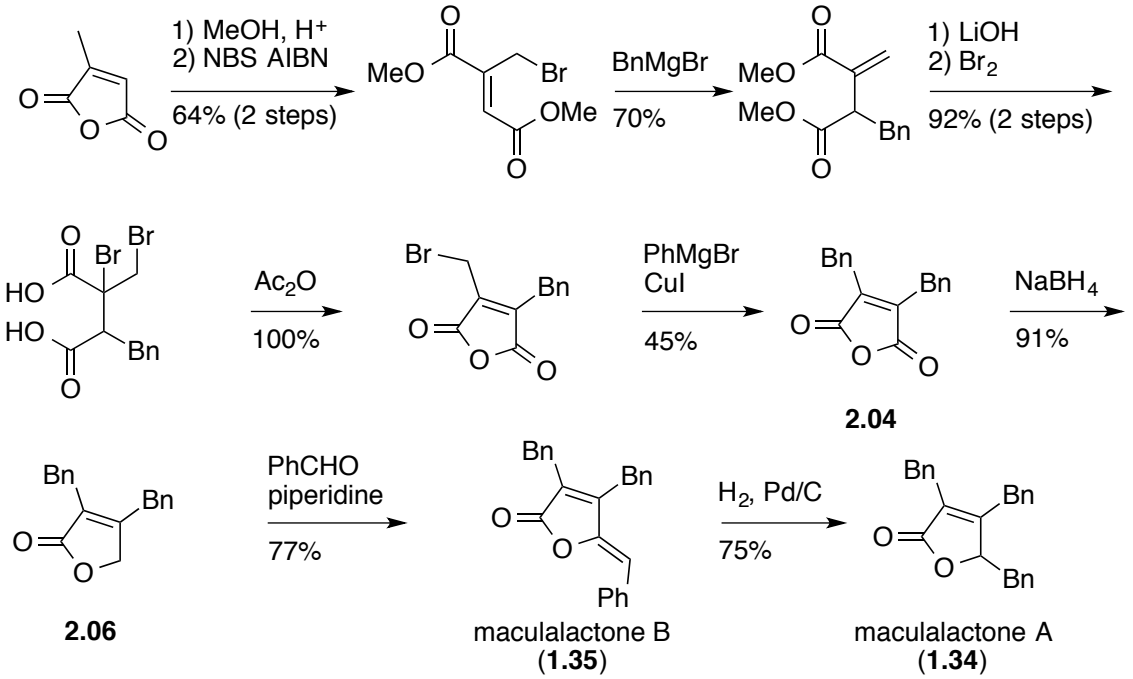
2.1.1 Previous Approaches Reported in the Literature

In literature, three different groups have completed the total synthesis of maculalactone A (**1.34**). The first synthesis was published in 2004 by Brown and co-workers (Scheme 2.1).[1] Their route accessed racemic maculalactone A in five steps and in an overall yield of 7%. Additionally, maculalactone B (**1.35**), C (**1.36**) and enantiomerically enriched maculalactone A were synthesized. A main reason for the low yield of this route is the Stobbe condensation forming bisacid **2.02** in the first step. This intermediate is in principle commercially available, but starting from dimethyl succinate (**2.01**) is more economical. Despite the low yielding first step, this route offers considerably high yields.



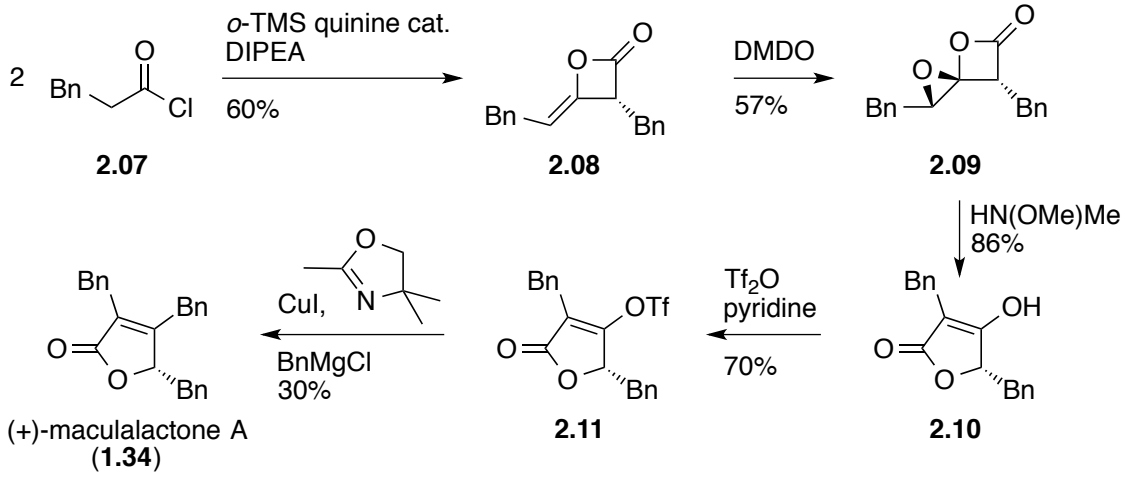
Scheme 2.1: Synthesis of racemic maculalactone A in five steps and 7% overall yield as published by Brown and co-workers.[1]

One year later, the group of Argade published the second total synthesis of maculalactone A (**1.34**) in 10 steps and an overall yield of 10% (Scheme 2.2).[2] This low yield is mainly a result of the high number of synthetic steps and an especially low yielding step of allylic substitution to afford anhydride **2.04**. However, this synthesis shows similarities to the route of Brown *et al.,* with anhydride **2.04** as common intermediate.



Scheme 2.2: Synthesis of racemic maculalactone A in 10 steps and 10% overall yield as published by Argade and co-workers.[2,3]

In 2009, Romo and co-workers published the third total synthesis (Scheme 2.3).[4] In the process of their investigations on the synthesis of tetronic acids, maculalactone A (**1.34**) was synthesized in five steps and in an overall yield of 6%. The sequence starts with the asymmetric synthesis for ketene dimer **2.08** from **2.07** according to Calter *et al*.[5] This olefin is then epoxidized to the spiro compound **2.09**.



Scheme 2.3: Synthesis of enantiomerically enriched maculalactone A in five steps and 6% overall yield as published by Romo and co-workers.[4]

The required tetronic acid derivative **2.10** is formed after a base-induced rearrangement in a yield of 30% over the three steps. The following substitution of the

β-position by a benzyl group was found to be more problematic. The copper catalyzed coupling on lactone **2.11** affords (+)-maculalactone A in 30% yield, reducing the overall yield of the synthesis dramatically.

2.1.2 Systematic Analysis of the Synthetic Problems

In respect to the considerably high yield of Brown's route, this route was chosen for the preparation of maculalactone A (**1.34**). Although the synthesis was successful, two problematic steps were identified. The hydrogenation and subsequent isomerization of diene **2.03** had selectivity issues. The following Grignard reaction was also found to be challenging, due to the tendency of benzyl Grignard reagents to dimerize and the difficult generation.

These problematic steps encouraged us to compare the published syntheses in more detail. Despite the low number of steps, all routes possess low overall yields. These low yields of the syntheses revel a common problem. In a survey, the lowest yielding step in all three routes was found in the installation of a benzyl group on the finished butenolide core. Besides the Stobbe condensation in Brown's synthesis, this step is typically performed with a nucleophilic benzyl species.[1]

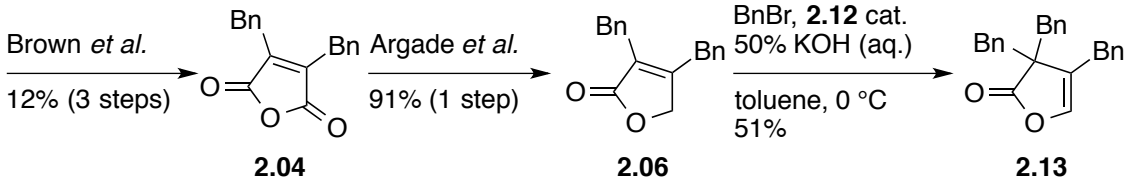
The second lowest yielding step in the synthesis of Brown *et al.* is the nucleophilic addition of a benzyl Grignard reagent to anhydride **2.04**.[1] The synthesis of Argade involves the same intermediate, but the last benzyl group is introduced in an electrophilic addition to **2.06**, followed by a reduction of the formed double bond.[2] A combination of these procedures would bypass the nucleophilic benzylation. However, the additionally required hydrogenation of **1.35** in moderate yield makes this combination not favorable.

These considerations lead to two principles for an improved synthesis of maculalactone A. First, the benzyl groups should be introduced in a non-nucleophilic fashion and second, these groups should be introduced as early in the synthesis as possible. Ideally, the benzyl substituents would already be present in the starting materials, implying that the phenylic and benzylic bonds should not be formed in the synthesis. In principle, this is only possible if the butenolide is formed at the end of the synthesis.

2.2 Substitution by Electrophilic Addition

Our first attempts focused on a combination of Brown's synthesis and an electrophilic introduction of the last phenyl moiety.[1] In contrast to the condensation in the synthesis of Argade, we proposed a substitution on an electrophilic halogen alkane.[2] This would not only remove one step in the route, but it also might allow for an enantioselective version of the reaction.

Therefore, butenolide **2.06** was reacted with benzyl bromide in the presence of the cinchona alkaloid derived phase transfer catalyst **2.12**[6] and a base (Scheme 2.4). Further information concerning these reaction conditions and a detailed optimization of the reaction conditions with a different substrate can be found in section 4.3.2. In contrast to the reaction with benzaldehyde, we observed a clear addition to the α-position giving lactone **2.13**. This regioselectivity can be attributed to the nature of the electrophile. The same behavior was observed with other substrate described in section 6.2.3 and in literature.[7] The addition to the α-position is kinetically favored. With benzaldehyde, this addition is reversible and the thermodynamically favored condensation product is formed. Since this selectivity cannot be overcome, no further investigations of this strategy were performed.

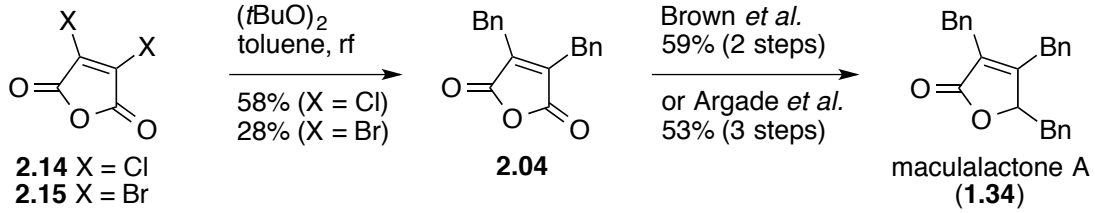


Scheme 2.4: Synthesis of lactone **2.06** and addition of benzyl bromide under phase transfer catalysis (PTC).[1,2] **2.12** is a cinchona alkaloid derived PTC[6] and was synthesized according to literature (Section 4.3.2).[8]

2.3 Substitution by Radical Addition

In 2008, the group of Messorosh published a new procedure for the addition of benzyl radicals to 2,3-dichloromaleic anhydride (**2.14**) (Scheme 2.5).[9] The radical species are generated by the decomposition of di-*tert*-butyl peroxide in toluene. This method offers an alternative in the total synthesis of Brown and Argade, as it gives access to anhydride **2.04** in one step.[1,2] However, the chlorinated compound **2.14** is expensive and cannot be prepared in the lab. We investigated the same system with the

brominated analogue **2.15**, which was prepared from cheap starting material as described by Dubernet *et al.*[10]



Scheme 2.5: Synthesis of anhydride **2.04** by radical substitution.[1,2,9]

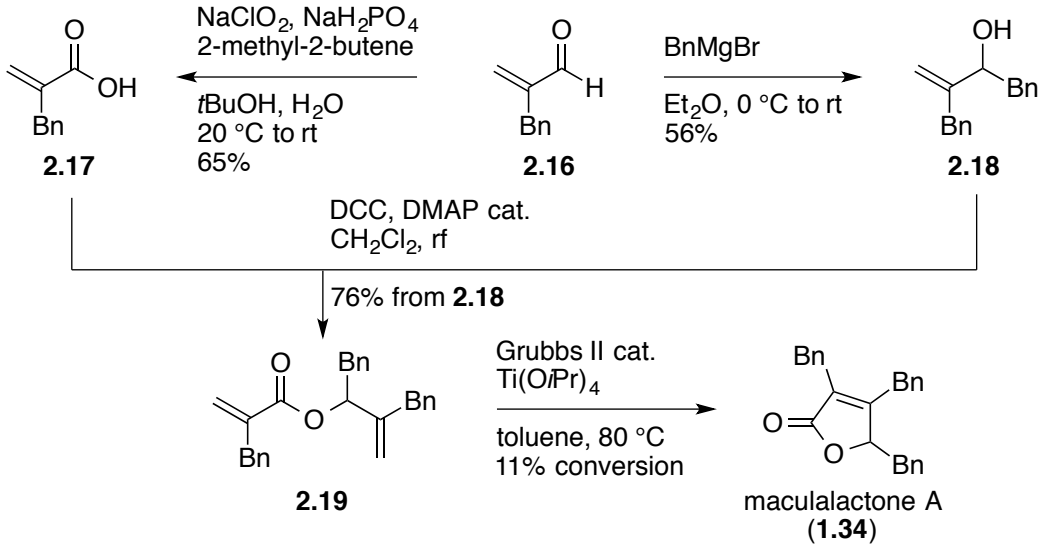
The yield of the radical substitution of the brominated maleic anhydride was found to be only 28%. Therefore, maculalactone A could theoretically be synthesized in five steps and an overall yield to 17%. Despite this first success, other synthetic strategies giving maculalactone A were investigated.

2.4 Late Stage Ring-Closing Metathesis

As described above, the optimization of the known total synthesis offered only little improvements. Therefore we decided to develop a completely new synthesis of maculalactone A (**1.34**). Due to the problematic formation of the phenylic or benzylic bonds, our strategy was to install these groups initially and form the lactone in a later stage of the synthesis. In literature, various procedures are known for the formation of butenolides.[11–13] However, only some of these procedures are compatible with triple substituted lactones. An example is the ring closing metathesis, which has been successfully applied by various research groups.[14–16]

Enone **2.16** was synthesized by a Mannich reaction, as described by Pihko and co-workers (Scheme 2.6).[17] Consequently, the enone was converted to acid **2.17** by a Pinnick oxidation and to allylic alcohol **2.18** by a 1,2-addition. The latter proceeded nicely, despite the use of a nucleophilic benzyl Grignard reagent. The two fragments were then combined in a Steglich esterification to give diene **2.19**.

With this convergent approach, ester **2.19** was synthesized in four steps and in 42% and 38% overall yields, respectively. However, the following metathesis with Grubbs second generation catalyst[18] resulted in no conversion. Some literature reports a beneficial effect with similar system by the addition of Lewis acids.[16,19] In our case, the addition of titanium isopropoxide gave a maximal conversion of 11%.



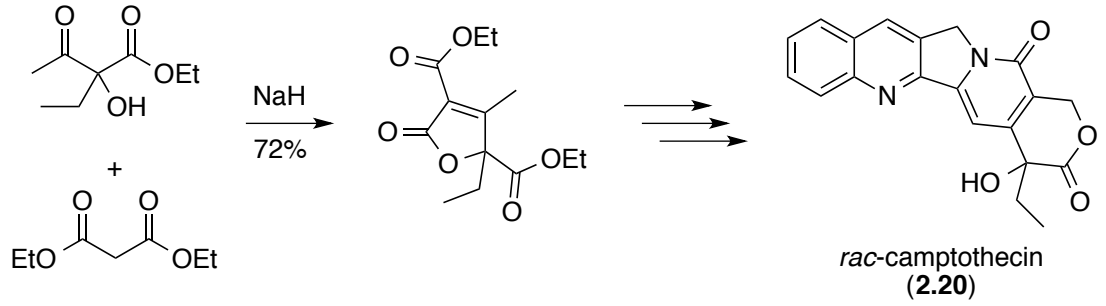
Scheme 2.6: Synthesis of maculalactone A by a late-stage ring closing metathesis. The stated conversion in the metathesis is the maximally obtained value (^{1}H-NMR).

Eventually, the low conversion could be improve by an extensive catalyst screening or a relay strategy, how Hoye *et al.*[20] introduced it, could overcome the problematic electronics and the steric hindrance. The latter would, however, complicate the synthesis of the precursor, as well as reduce the atom economy. Nevertheless, the synthesis of ester **2.19** in good yields acknowledged our efforts towards a convergent route with an early introduction of the benzyl moieties.

2.5 Late Stage Ring Closure of an Activated Methylene

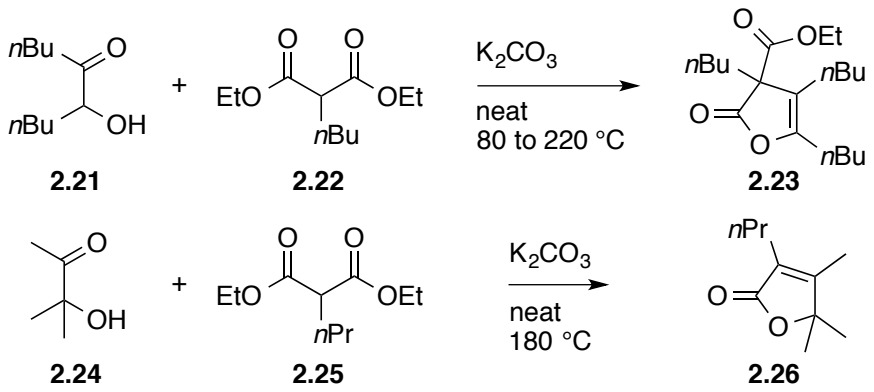
2.5.1 Butenolide Synthesis by Knoevenagel Condensation

The Knoevenagel condensation is a well known synthesis of α,β-unsaturated ester and various examples can be found in literature.[21,22] Advantages include the mild conditions, high conversion and high tolerance of diverse functional groups. Not surprisingly, the Knoevenagel reaction has also been used for the synthesis of butenolides (Scheme 2.7). An advantage of this process is the spontaneous formation of the lactone under mild reaction conditions, as in the example of the total synthesis of camptothecin (**2.20**) by Peters *et al.*[23] Disadvantages include the requirement of a strong electron acceptor in the α-position of the lactone. Although the decarboxylation of such substrates is well known, the late introduction of the required benzyl group would undermine our strategy.



Scheme 2.7: Butenolide formation in the synthesis of camptothecin.[23]

Since the formation of the double bond by the elimination of water is the driving force and the final irreversible step of this reaction, very little work has been done on substituted malonic esters, which might inherently block this crucial elimination. We postulated that we could combine the elimination of carbon dioxide with the formation of the double bond. As literature examples show, β-lactones are known to eliminate carbon dioxide at higher temperatures.[24–26] After the initial nucleophilic attack of the malonate, the formed alkoxide is in close proximity to the malonic ester. We suggested that an intramolecular attack on the carbonyl would occur by a transesterification to a β-lactone. Under higher temperatures, this could form the desired product via a [2+2] cycloelimination.



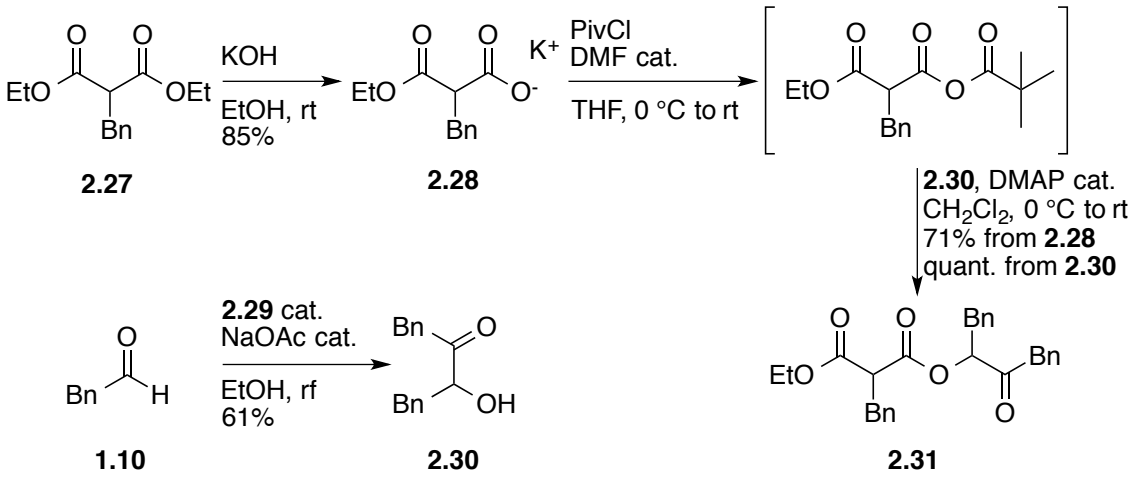
Scheme 2.8: Condensation of α-hydroxy ketones with malonic esters and analogs.[27,28]

Only one example by Avetisyan *et al.*[27] in 1981 and a later application in an industrial setting[28] of such a reaction with substituted malonic esters was found (Scheme 2.8). They investigated the condensation of α-hydroxy ketones with the substituted 1,3-electron acceptors **2.22** and **2.25**. Using secondary alcohol **2.21**, elimination of water occurred in the opposite direction giving β,γ-unsaturated lactone **2.23**. Similar results were observed when β-keto esters were used. If the γ-position was blocked by an additional substituent as in tertiary alcohol **2.24**, the

unexpected product **2.26** was formed. However, the required reaction conditions are rather harsh.

2.5.2 Synthesis of Key Intermediate Ester 2.31

An intermolecular reaction was assumed to be challenging, as the aromatic substituent on the ketone raises the acidity of the α-protons, promoting side reactions of the formed enolate. To increase not only the selectivity, but also to stabilize the quaternary intermediate after the nucleophilic attack and thereby accelerate the reaction rate, we focused on an intramolecular reaction. The properly substituted α-hydroxy ketone **2.30** was synthesized by an Umpolung reaction, as described by the group of Stetter (Scheme 2.9).[29] The commercially available malonic ester **2.27** was transformed to potassium salt **2.28,** as described by Goel *et al.*[30] This salt was then reacted with pivaloyl chloride to the mixed anhydride. The activation of the acid by a mixed anhydride was found to be superior to other methods, as the mild conditions suppress the competitive decarboxylation. The mixed anhydride was then reacted with alcohol **2.30** to the required ester **2.31** as a mixture of diastereomers.



Scheme 2.9: Synthesis of ester **2.31** in five steps as a mixture of diastereomers. Compounds **2.30**[29] and **2.28**[30] were synthesized according to literature procedures. Compound **2.29** is Stetter's catalyst (3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride).

2.5.3 Optimization of the Late Stage Cyclization

The cyclization was first tried with similar conditions as described by Avetisyan *et al.* (Table 1, entry 1).[27] While the expected product maculalactone A was formed, the yield was considerably low. Variations of the reaction conditions, showed only little influence on the yield (entries 2 to 6). Different catalysts, solvents and additives were evaluated. While catalysts such as 2,6-lutidine, diisopropylamine,

Li_2CO_3, NaOAc, CsOAc, aq. NaOH and Na_2SO_4 showed no product formation, Cs_2CO_3 was found to be superior compared to K_2CO_3 (results not shown). The addition of crown ethers accelerated the reaction with Cs_2CO_3 and K_2CO_3 as base. Other additives like Lewis acids such as $FeCl_3$ and $AlCl_3$ gave no improvement. Reactions with Cs_2CO_3 were performed in THF, toluene, CH_3CN and *t*BuOH, but THF showed the best results (results not shown).

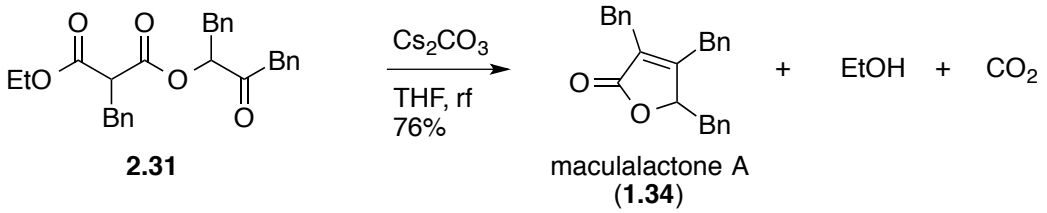
Entry	Catalyst (eq.)	Solvent	Temp. [°C]	Time	Yield [%]
1	K_2CO_3 (1.5)	Diglyme	160	45 min	33
2	K_2CO_3 (2.0)	Diglyme	110	2.5 h	32
3	K_2CO_3 (2.0)	Diglyme	110	4 h	23
4	K_2CO_3 (0.2)	Diglyme	120	9.5 h	30
5	K_2CO_3 (3.2) $KHCO_3$ (0.9)	Diglyme	110	3 h	33
6	K_2CO_3 (2.0)	Dioxane	100	4 h	35
7	Cs_2CO_3 (2.0)	THF	rf	45 min	70
8	Cs_2CO_3 (1.5)	THF	rf	55 min	70
9	Cs_2CO_3 (0.2)	THF	rf	2.5 h	65
10[a]	Cs_2CO_3 (0.2)	THF	rf	3 h	76

Table 2.1: Optimization of the cyclization. [a]The refluxing THF was run over a bed of activated 4 Å molecular sieves.

Further optimizations of the conditions were carried out with cesium carbonate. No crown ethers were used, as the acceleration was no advantage in context of the purification of the reaction mixture. The amount of base could be reduced to 20 mol%, while the reaction time had to be extended (entry 7 to 9).

However, ^{1}H-NMR measurements of the crude product showed significant amounts of keto alcohol **2.30**. Ethanol, formed in the course of the elimination, can attack ester **2.31** under the reaction conditions, affording diethyl malonate **2.27** and the observed keto alcohol **2.30**. To circumvent this transesterification, the ethanol had to be removed from the reaction mixture. This was accomplished by a special reaction setup

as depicted in section 9.5.1. Thereby, the condensate of the refluxing reaction was run over a bed of activated 4 Å molecular sieves. While ethanol and carbon dioxide are small enough to get adsorbed by the molecular sieve, the solvent runs back into the reaction. With the removal of residual ethanol, the transesterification could be suppressed below ^{1}H-NMR detection limits, increasing the yield to 76% (entry 9 and 10) (Scheme 2.10). The remaining lack in the mass balance can be explained by diffuse polymerization, as these yellow-colored side products are easily removed by filtration over silica gel.



Scheme 2.10: Cyclization of ester **2.31** to afford maculalactone A.

Finally, an intermolecular cyclization of keto alcohol **2.30** and malonate **2.27** under the optimized reaction conditions was tested. Within three hours, first traces of maculalactone A could be observed. However, neither a reaction time of two days, nor a higher concentration could bring the conversion over 15% as determined by ^{1}H-NMR.

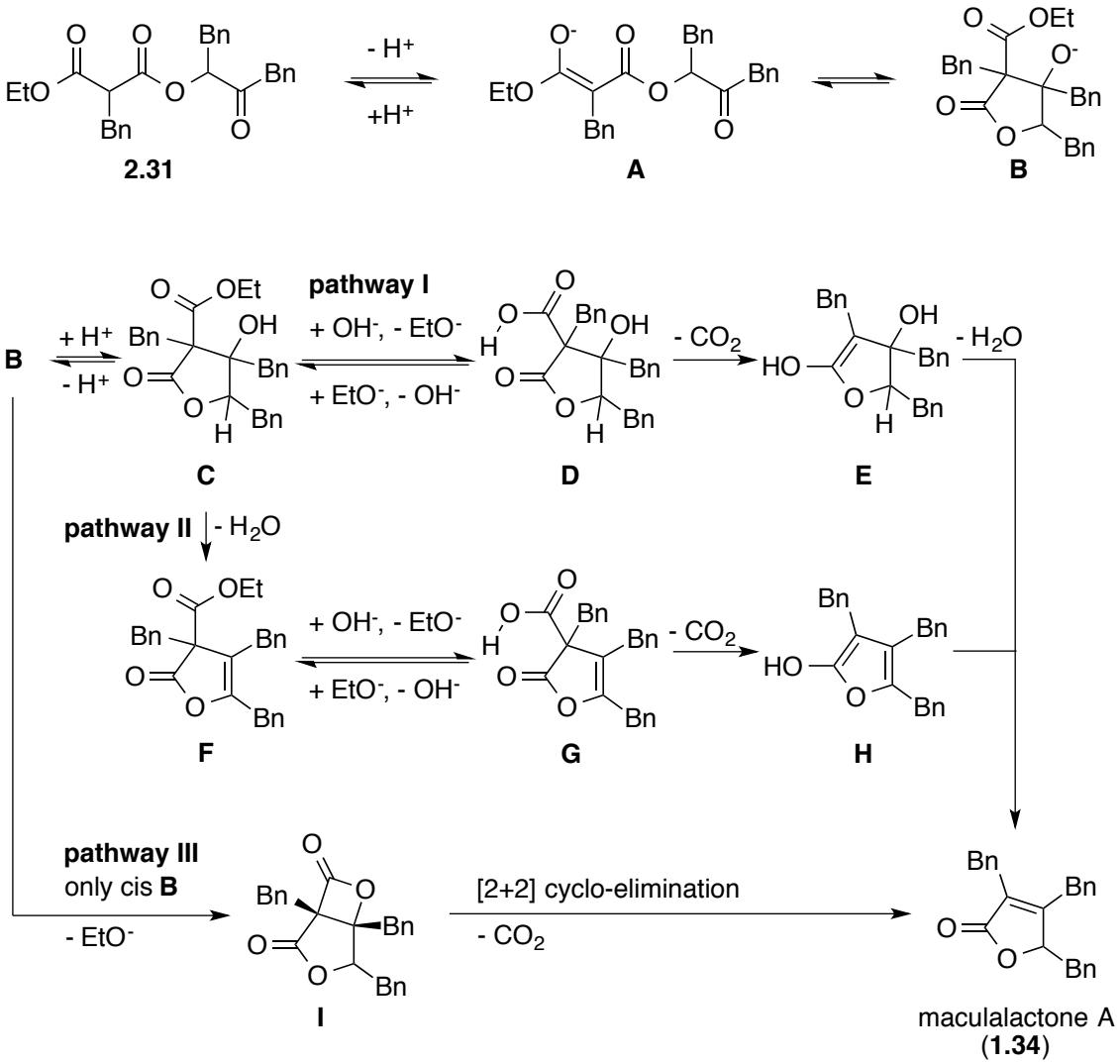
Our newly developed method of a late stage cyclization, allowed the synthesis of maculalactone A (**1.34**) from inexpensive commercial starting material in three steps in the longest sequence and an overall yield of 45%. Additionally, only one short column chromatography is necessary, making this procedure easy to scale-up. This reaction sequence was performed up to a scale of 5 g of maculalactone A. The final product could be crystallized directly from the filtered reaction mixture in high purity.

2.5.4 Proposed Mechanism of the Cyclization

In their publication, Avetisyan *et al.*[27] describe the β,γ-unsaturated lactone **2.23** as the condensation product of secondary keto alcohol substrates. Only for tertiary keto alcohols, the α,β-unsaturated lactone was observed (Scheme 2.8). In contrast, our intramolecular cyclization of the secondary ester **2.31** provides maculalactone A with the double bond in α,β-position. To explain this difference, we considered the mechanism. In a first step, the methylene group of ester **2.31** is deprotonated by cesium carbonate to form the anion **A** (Scheme 2.11).[31] This is followed by a nucleophilic addition to the keto group to give alkoxide **B**. Both of these steps are reversible. In a

Knoevenagel condensation, this would than be followed by the protonation of the alcohol and an E_1cb elimination of water. However, the activated methylene in intermediate **B** has no available protons.

We then proposed three different mechanisms for conversion of intermediate **B** to the final product of our synthesis. In the first two, the alkoxide could be protonated, as in a classical Knoevenagel condensation, affording **C**. In pathway I, the ester moiety of this intermediate could then be hydrolyzed in solution, resulting in the formation of acid **D**. Such 3-carbonyl acids are prone to decomposition in basic solutions. Carbon dioxide would be liberated affording enol ester **E**. By an overall 1,4-elimination of water, this reactive intermediate **E** would be converted to the final product maculalactone A.



Scheme 2.11: Proposed mechanisms for the cyclization to give maculalactone A.

Alternatively, as in pathway II, alcohol **C** could eliminate water, forming relatively stable lactone **F**. While this was the major product in the reaction described by

Avetisyan *et al.*[27], we did not find any evidence for its formation. However, as in the first mechanism, the decarboxylation would be introduced by a saponification to acid **G**. Following CO_2 liberation, intermediate **H** could tautomerize to give the conjugated product, maculalactone A (**1.34**).

The third mechanistic hypothesis (pathway III), would include the formation of a β-lactone as in dilactone **I** (Section 2.5.1). The formation of this second lactone would only be possible if the carbonyl group and the alkoxide were in a *cis*-relationship. Since the open form **A** and lactone **B** are in equilibrium, the *trans*-compound could be converted to the *cis*-form. Maculalactone A would be generated by the release of carbon dioxide from β-lactone **I** in a cyclo-elimination step.

The investigation of the mechanism proved to be difficult. The intramolecular nature of the reaction, together with the potentially acid, base or thermal instability of the intermediate, tolerate only certain analytic methods such as NMR, IR or UV. In a first attempt, we wanted to determine the reaction order of the different starting materials. Therefore, two concentrations of ester **2.31** and two amounts of Cs_2CO_3 were reacted at 80 °C for 3.5 hours. To run the reactions in parallel, a reduced reaction setup with sealed tubes was used. Surprisingly, the reactions with usual concentrations of ester **2.31** showed no product formation and the three times diluted reactions showed only a minimal maculalactone A formation. Nevertheless, other unknown compounds were detected. However, to gain more information about the actual mechanism, further experiments are required. Tracking the reaction with IR in a setup, allowing refluxing, could give more information on the reaction speed, potential intermediates and the rate-limiting step.

2.6 Conclusion

To date, three groups have published total syntheses of maculalactone A, but all routes possess an overall yield below 10%.[1,2,4] While we reproduced the synthesis of Brown *et al.*, we identified the late nucleophilic introduction of benzyl groups as an obstacle in all reported syntheses.[1] In a first attempt, we tried to work around such a nucleophilic substitution. While an electrophilic benzylation was unsuccessful, a radical reaction affording anhydride **2.04** in two-steps, was found to be more promising. This shortcut in the synthesis of Brown *et al.* enabled the synthesis of maculalactone A (**1.34**) in five steps and an overall yield of 17%.

In addition, an alternative route that prevented a late-stage benzylation was developed. This was accomplished by an early installation of all benzyl groups and a ring closure in the last step. In a first attempt, we planned to close the lactone by metathesis. While the synthesis of diene **2.19** was accomplished in sufficient yield, a maximal conversion of 11% in the metathesis could not be overcome.

We then proposed a cyclization initiated by an intramolecular addition of an activated methylene, resulting in olefin formation by the elimination of ethanol and carbon dioxide. The synthesis of the cyclization precursor **2.31** was accomplished in three steps. In a first attempt, the desired maculalactone A (**1.34**) was isolated in 30% yield. As changes of the catalyst amount, temperature and reaction time had little influence on the yield, other catalysts, solvents and additives were screened. Cesium carbonate as catalyst doubled the yield, while optimization of the reaction set-up increased the yield to 76%. With our newly developed route, maculalactone A was synthesized from inexpensive commercially available starting materials in overall four steps and a yield of 45%. Additionally, only one short column chromatography is necessary, making the procedure easy to scale-up.

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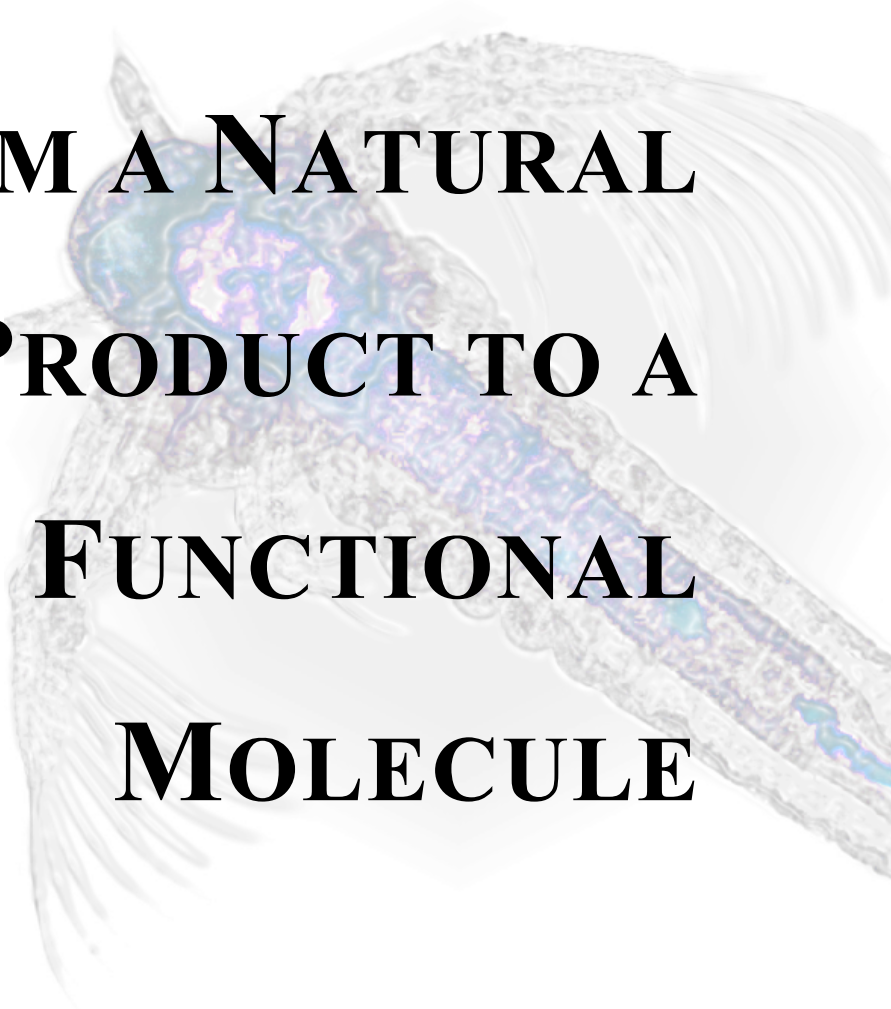
3 - From a Natural Product to a Functional Molecule



3.1 Introduction

3.1.1 Biofouling, an Unsolved Problem

The term biofouling describes the undesired accumulation of biological material on underwater structures such as platforms, jetties and ship hulls or inside water containing structures such as pipes, tanks and other technical equipment (Figure 3.1).[1,2] The formation of such bio-films causes adverse effects such as faster corrosion, a reduced lifetime and changed surface properties.

In marine trade, these biological settlements can cause additional problems such as dispersion of adhered species and a higher frictional resistance.[1–5] Due to biofouling, fuel consumption of a ship can increase by up to 40%.[2] In the marine environment, these problems were successfully prevented by the use of tributyltin compounds (TBT) as antifouling coatings. In the end of the last century, TBT was found to cause serious damage to the marine environment, forcing the international maritime organization to ban the use of TBT coatings.[2,5,6] Since TBT coatings protected about 70% of the marine vessels, alternatives coatings are necessary.

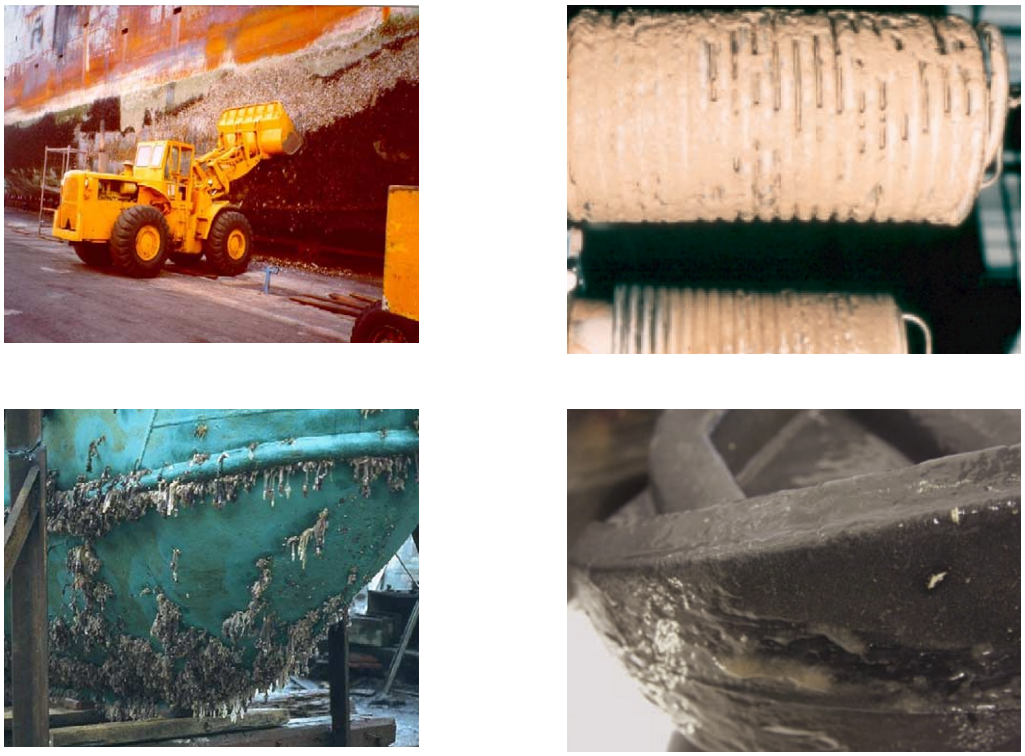


Figure 3.1: Left, heavily fouled ship hulls.[2] Upper right, heat exchangers of a pump after six month of operation. Lower right, biofilm formation on a valve in a drinking water system.[7]

In fresh water systems, biofilm formation is typically slower. Nevertheless, biofouling can cause problems such as drinking water contamination, changed surface properties such as a decreased thermal transmittance, reduced flow and pipes obstruction. In the past, these issues in fresh-water systems were addressed in a similar manner as in the marine environment.

Heat exchangers in power stations or chemical plants, driven by fresh-water, are also strongly affected by biofouling.[8–11] The build-up decreases not only the lifetime of the equipment, but also reduces also the heat transfer rate, which can lead to obstruction of parts or the entire apparatus. The methods to control the bio-film formation include filtration of the water supply, abrasive cleaning with sponge balls, or the use of highly toxic chemicals such as hypochlorite.

3.1.2 Maculalactone A as an Antifouling Agent

In contrast to man-made structures, marine organisms are usually less affected by biofouling. Nature developed different strategies to prevent the settlement of other species. One is the production of chemical compound such as secondary metabolites, often referred as natural products, to deter adhesion and grow.[4,11,12] In recent years, butenolide systems moved into the focus of interest, as they show not only anti-fouling properties, but can also inhibit quorum sensing.[13] Various antifouling butenolide structures from marine sources are described in literature,[14–16] of which 5-octylfuran-2[5H]-one is a great example.[17–19]

Figure 3.2: *K. maculans* growing on a Hong Kong rocky shore.[20]

The slow growing cyanobacterium *Kyrtuthrix maculans* forms pure colonies on moderately exposed shores (Figure 3.2). The low reproduction rate combined with the lack of other organisms in the colonies indicates an antifouling protection. Since the

colonies lack a kind of specialized surface, the cyanobacterium has been suggested to produce a chemical defense. In 1996, the group of Brown reported the isolation of (+)-maculalactone A (**1.34**) from *K. maculans* (Section 1.4).[21] In addition to the isolation of other secondary metabolites from *K. maculans* and the first total syntheses of maculalactone A, B (**1.35**) and C (**1.36**), Brown and co-workers were also interested in the antifouling properties of maculalactone A. The capability of maculalactone A to act as a chemical defense was investigated in a toxicity study. The LC_{50} concentrations of the four potential herbivores *Tetraclita japonica*, *Balanus amphitrite*, *Ibla cumingii* and *Artemina salina* were found between 1.1 and 5.2 μg/ml.[20] This moderate to high toxicity suggests maculalactone A to be a potential antifouling agent.

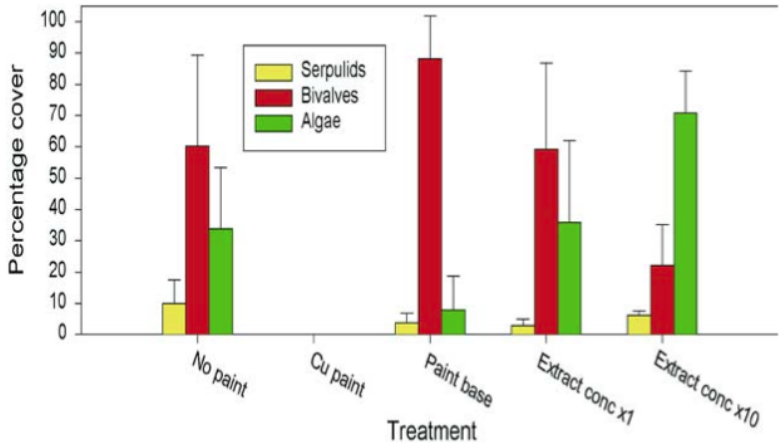


Figure 3.3: Extent of fouling of painted PVC plates after exposure to seawater for 12 weeks.[20]

In a further study, synthetic racemic maculalactone A (**1.34**) was incorporated in commercial "house-hold" paints with no anti-fouling activity.[20] Both the natural and the ten-fold concentration of maculalactone A were used. Consequently, PVC plates were painted either with a copper containing antifouling paint, the unmodified household paint or the maculalactone A-containing paints. The plates were submerged for 12 weeks in the Hong Kong Sea, before the surface coverage with marine organisms was determined (Figure 3.3). The addition of maculalactone A to the paint resulted in a reduction of settlement of bivalves. Although this reduction was partially compensated by increased algae growth, this test showed the potential of maculalactone A (**1.34**) as antifouling agent.

3.1.3 Biomimetic Surface Modification

In the recent years, our group developed a system for the chemical modification of metal oxide surfaces. In early systems, this technology based was on the observation

that the siderophore anachelin (**3.01**)[22] strongly binds to metal oxides (Figure 3.4). The metal oxide binding side was identified as the catechol moiety (indicated in red). As metal surfaces are usually covered by a metal oxide layer, these catechols were thought to be the appropriate tool to modify such surfaces. In first studies, this anchor moiety was isolated and modified with a methylated PEG chain (**3.02**)[23,24] and later connected to vancomycin, to afford antimicrobial surfaces.[25,26]

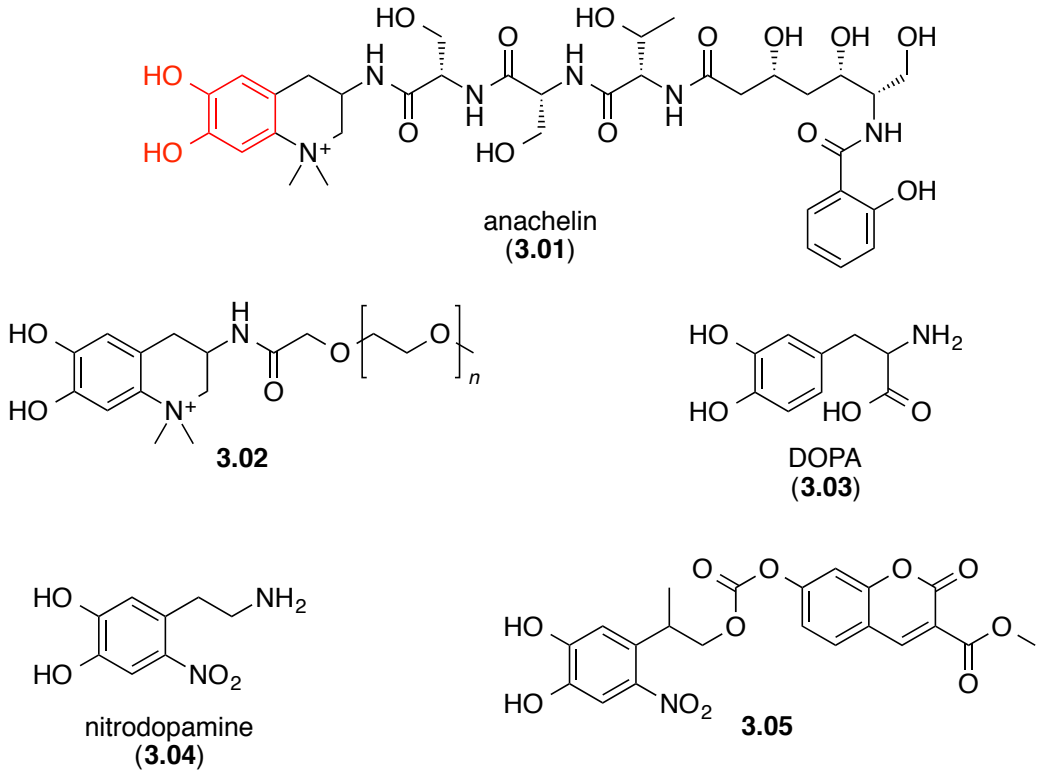


Figure 3.4: Various catechol based anchors.[23,27–29]

In parallel, an anchor inspired by the mussel adhesive protein (MAP) was developed by other groups.[30–34] MAP consists of up to 27 mol% of 3,4-dihydroxyphenylalanine (DOPA, **3.03**), facilitating the strong adhesive properties of this protein. Both anchors show distinct similarities and a combination of both was found to be superior.[28] Nitrodopamine (**3.04**) combines the easy accessibility of DOPA derivatives with the strong binding affinity of the electron sufficient catechols, as in the anachelin-derived systems. Such a nitrodopamine was, for example, used as anchor in the modulation of quorum sensing.[35] Recently, the modified functional hybrid **3.05** was employed in a light induced surface release system.[29]

Despite these various anchors and the multiple applications, there are still some issues with this system. The attachment of the cargo to the anchor is often realized by

ester or carbonate functions and little is known about the long-term stability of such compounds in water. Furthermore, the high affinity of these compounds to any metal oxide including silicon oxide makes the handling challenging. Often a protection of the catechol is necessary, causing further problems in the final deprotection step.

3.2 Concept for the Antifouling Protection of Metal Surfaces with Maculalactone A

The emerging biofouling issues after the ban of TBT and the promising biomimetic antifouling properties of maculalactone A (**1.34**) stimulated us to come up with a new concept for the protection of metal surfaces. In combination with our experience in surface modifications, we designed a functional hybrid combining the antifouling activity of maculalactone A with the surface stability of one of our anchors (Figure 3.5). The hybrid consists of three different, covalently linked parts. The anchor immobilizes the system on the metal surface and keeps the hybrid in place. A linker increases the flexibility of the hybrid and enhances the accessibility of the warhead. PEG linkers are often used for such applications, but also other chains are possible. The third part is the maculalactone A warhead, facilitating the antifouling protection.

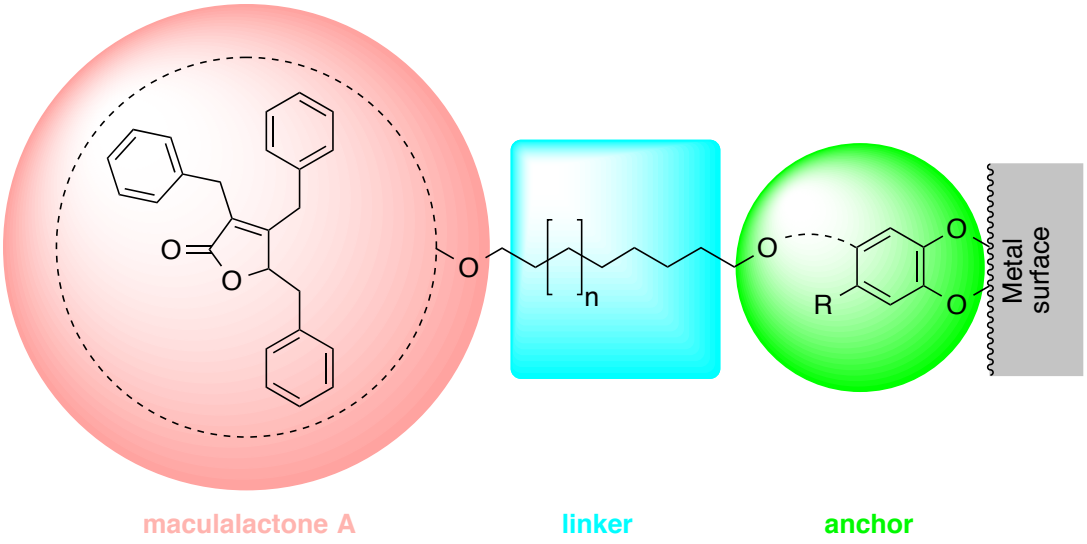


Figure 3.5: Concept for the antifouling protection of metal surfaces with a bifunctional hybrid.

With this functional hybrid in hand, it could be immobilized on various metal surfaces through a dip and rinse procedure. Ideally, already a low density of the hybrid would be sufficient to protect the surface from biofouling, while a majority of the surface would remain free. Therefore the often-required properties of metal surfaces

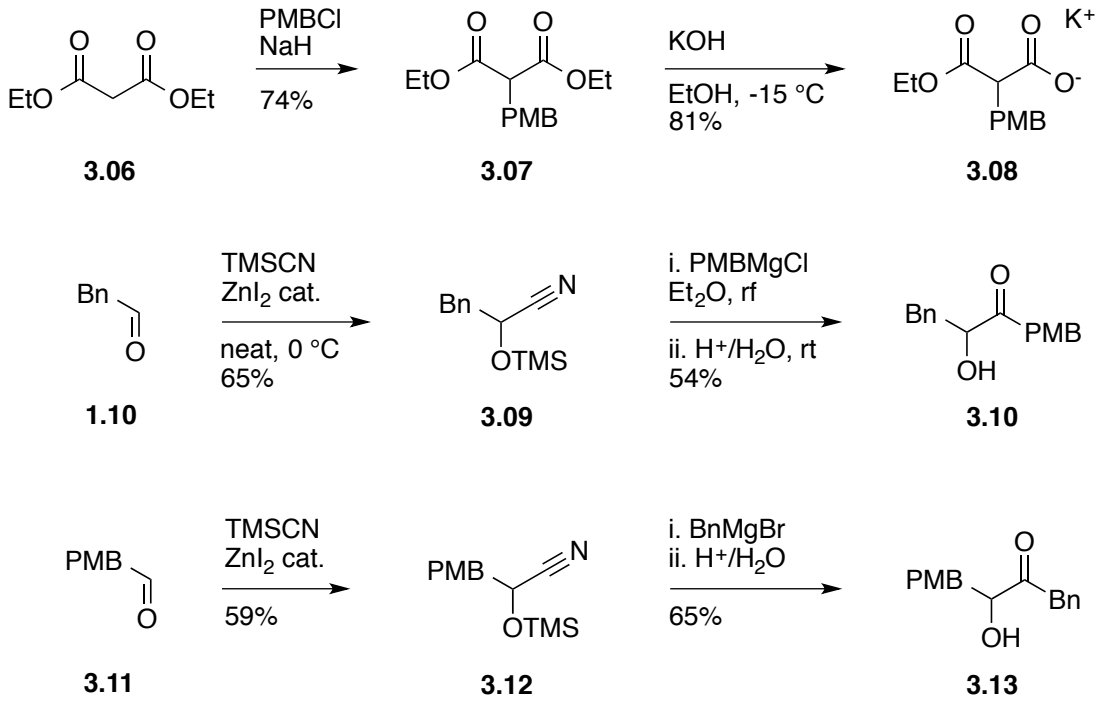
would stay intact. This is of particular interest in heat exchangers and other technical equipment. However, such an application is only promising if the hybrid exhibits good long-term stability and if large quantities can be produced by a simple and inexpensive procedure.

This concept and first results of the following studies were awarded with the first price of the Clariant CleanTech award 2012.

3.3 Maculalactone A Analogues for Covalent Attachment and SAR Study

3.3.1 Synthesis of Substituted Maculalactone A Analogues

To enable a covalent linkage to the anchor, a modification site of maculalactone A needed to be devised. The *para*-position of one benzyl moiety was thought to have the least influence on the biological properties. The introduction of a methoxy group was found to offer the highest scope for later modifications and sufficient orthogonality for the synthesis.



3.06 **3.07** **3.08**

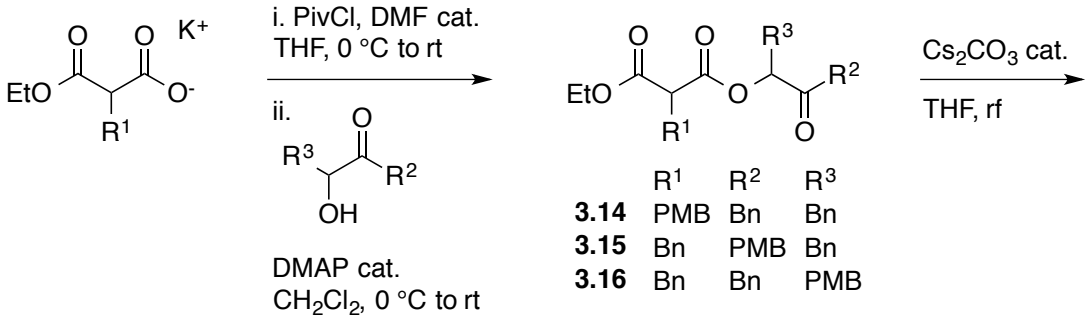
1.10 **3.09** **3.10**

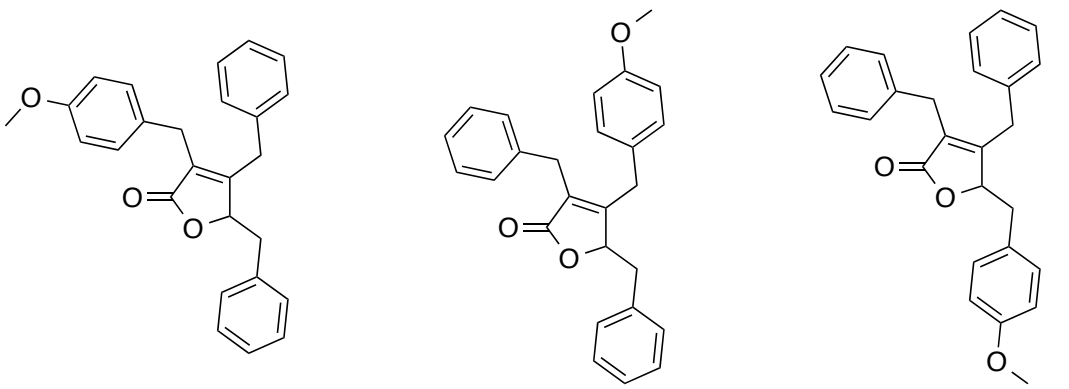
3.11 **3.12** **3.13**

Scheme 3.1: Synthesis of modified maculalactone A precursors. PMB = *p*-methoxybenzyl. Synthesis of **3.07** as described in literature.[36] Synthesis of **3.13** was conducted by a procedure from Pattenden *et al.* and **3.10** was synthesized in a similar fashion.[37]

Consequently, the three methoxy-substituted precursors **3.08**, **3.10** and **3.13** were synthesized (Scheme 3.1). Malonic ester **3.07** was accessed as described by Shiotani

et al.[36] and converted to malonate **3.08** at reduced temperature in 81% yield. The asymmetrically substituted α-hydroxy ketones **3.10** and **3.13** were synthesized either by or similar to a procedure by Pattenden *et al.*[37] Therefore, the aldehydes were converted to the TMS protected cyanohydrins **3.09** and **3.12**. After the addition of the corresponding Grignard reagent, the resulting imines were hydrolyzed and the TMS protecting group was removed under acidic conditions.





3.17
69% (2 steps)

3.18
60% (2 steps)

3.19
41% (2 steps)

Scheme 3.2: Synthesis of modified maculalactone A analogues.

Finally, the modified precursors were first converted to the corresponding esters **3.14**, **3.15** and **3.16** (Scheme 3.2). Subsequently, these were cyclized to the maculalactone A analogues **3.17**, **3.18** and **3.19**. This transformation was achieved under the same conditions as described earlier for the synthesis of maculalactone A (Section 2.5).

3.3.2 SAR Study of Modified Maculalactone A Derivatives

To identify a position that allows modifications, the biological properties of the three analogues have to be compared with the one of maculalactone A (**1.34**). Ideally, the antifouling capacity would be quantified. However, such assays are not standardized, vary widely and require incubation periods of several weeks.

In accordance with the work of Brown, an alternative was found in toxicity assays. Such standardized tests are commercially available, deliver reproducible results and can be accomplished in two to three days. *Thamnocephalus platyurus* together with *Artemia franciscana* were used as test organisms. The latter is a close relative of *A. salina*, which was employed in the studies of Brown.[20]

The toxicity assays were obtained from MicrobioTest Inc. in Belgium and conducted by the standard method. Five concentrations of maculalactone A and analogues were analyzed in three repetitions. The mortality is the ratio between dead organisms and the total number in each repetition (Figure 3.6).

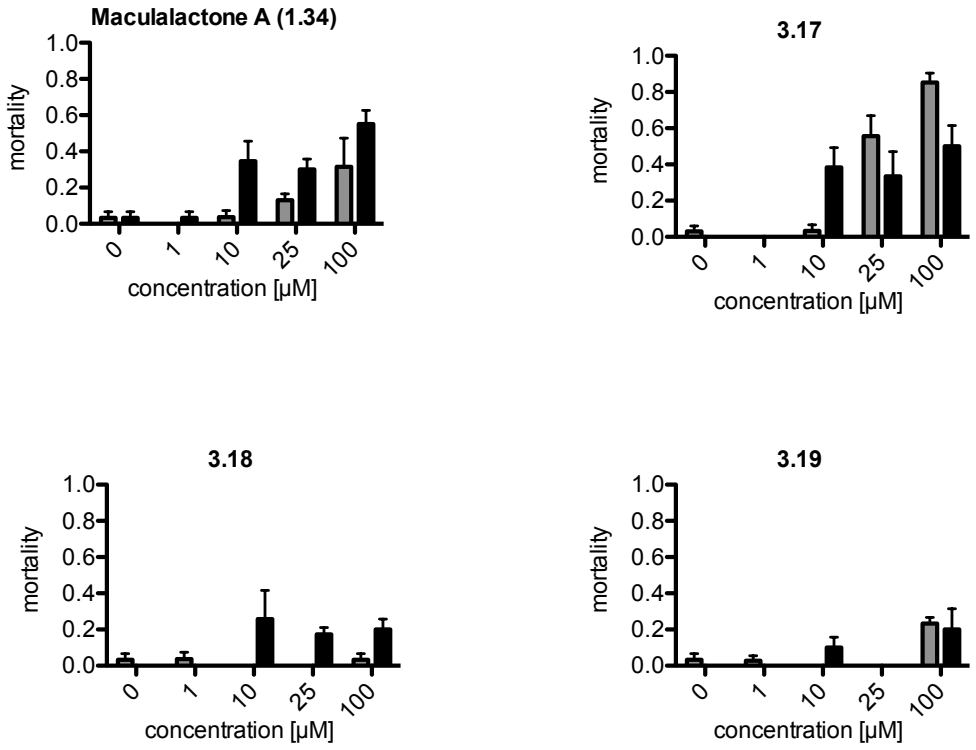


Figure 3.6: SAR study of modified maculalactone A analogues. Grey: *A. franciscana*. Black: *T. platyurus*. Values are given as the mean of three independent experiments with ten animals, error bars denote the standard error of the mean (SEM).

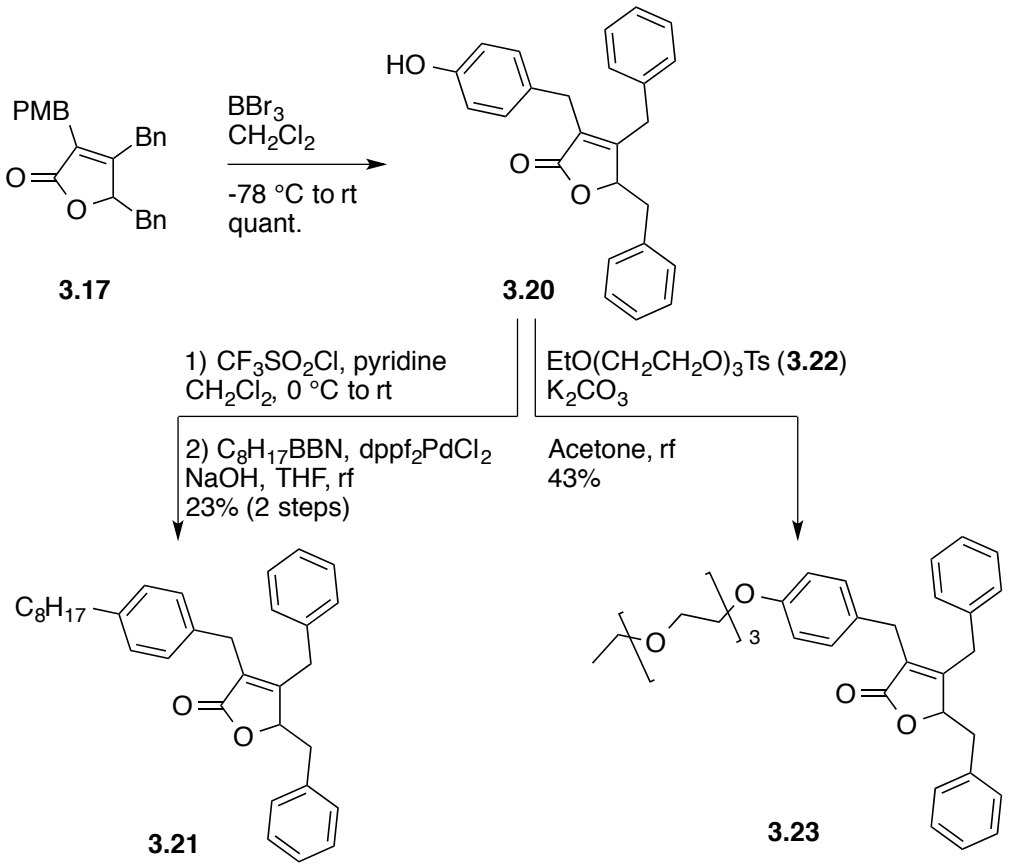
The assay shows a slightly lower toxicity of the synthetic maculalactone A (**1.34**), as compared to the findings of Brown *et al.*[20] This is either caused by the racemic nature of the synthetic **1.34** or is a result of the differences in the conducted assays.

Compared to maculalactone A, analogue **3.17** exhibited an increased toxicity in *A. franciscana* and similar values in *T. platyurus*. In contrast, the modified analogues **3.18** and **3.19** showed a reduced or no effect on the test organisms. According to these findings, analogue **3.17** is the appropriate candidate for further investigations.

Beside the measured toxicity, the assays exposed a strong effect on the swimming ability of the organisms. While they show a normal movement in a 1 μM maculalactone A solution, they lose their ability to swim in a controlled manner at a concentration of 10 μM.

3.3.3 Validation of the Methoxy Platform

Finally, the usage of the methoxy group as linkage point for further modifications was validated (Scheme 3.3). In a first step, the methyl group was removed in the presence of boron tribromide to give phenol **3.20** in quantitative yield. As the nature of the linker was not yet specified, two potential connections were investigated.



Scheme 3.3: Deprotection of **3.16** and validation of the methoxy functionalization as linkage position for further modifications. $EtO(CH_2CH_2O)_3Ts$ (**3.21**) was prepared as described in literature.[38,39]

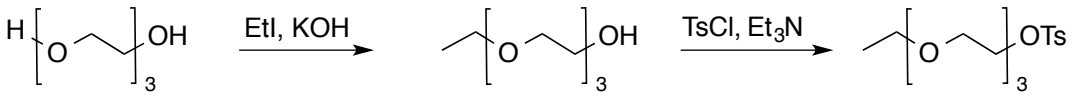
To investigate the alkylation of phenol **3.20**, it was first converted to the corresponding triflate by standard procedures. This intermediate was elongated through a Suzuki cross coupling with an aliphatic chain to give derivative **3.21** with a carbon-carbon type linkage.[40] PEGylation was achieved by reacting phenol **3.20** with

the activated PEG chain **3.22** in the presence of a mild base. This Williamson etherification afforded compound **3.23** in modest yield.

3.4 Studies Towards an Inexpensive PEGylated Anchor System

3.4.1 Concept for the Desymmetrization of Longer PEG Chains

Modifications of short PEG chain ends like the one used for the synthesis of maculalactone A analogue **3.23**, have a big influence on the physical and chemical properties. In the preparation of the activated PEG **3.22** described by Baena *et al.*[38] and Watanabe[39], the unsubstituted symmetrical chain **3.24** is ethylated on one side (Scheme 3.4). This changes the properties of the compounds to allow for separation of the mono-alkylated **3.25** by distillation.



3.24 **3.25** **3.22**

Scheme 3.4: Preparation of the activated PEG chain **3.22,** as described in literature.[38,39]

Increasing the length of the PEG chain causes the separation of the single side modified species to become more challenging. Additionally, more expensive separation methods, such as column chromatography on silica gel, reversed phase columns chromatography or size exclusion chromatography have to be used. Thus, the longer single side modified PEG chains are much more expensive, and can, therefore, only be used for selected applications were the cost is not limiting (Section 3.6). In contrast to the usual modifications like protecting groups, the introduction of one of our anchors would offer an additional separation method. Since theses anchors are catechols, they can be deprotonated by strong bases. However, the miscibility of PEG with water and organic solvents prevents a separation from the coupling reaction by acid-base extraction. Alternatively, the acidic anchors could be isolated by solid phase extraction using a basic cationic ion exchange resin.

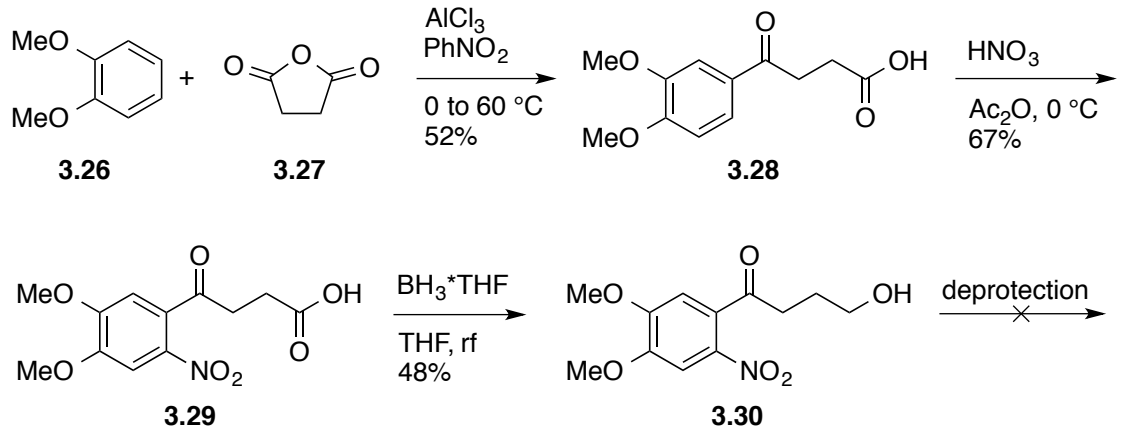
In the here-described concept, a large excess of PEG would be used in the coupling reaction to the anchor. This would prevent double anchor attachment to the PEG chain. After the reaction, the modified PEG could be isolated from the non-modified PEG by

an appropriate work-up. Potential limitations in this plan include the unprotected catechol and a good base stability of the used functional groups.

3.4.2 PEGylated Anchor Synthesis

To obtain an inexpensive PEGylated anchor, the synthesis has to avoid expensive materials and the target has to be reached in a limited number of steps and high yield. Additionally, purification by crystallization or distillation would be ideal. Furthermore, the anchor should have good hydrolytic stability. For this reason, ester, amide and carbonate connections were avoided and the first heteroatom was planned to be at least three carbons away from the anchor to prevent cleavage by UV light.[29]

In our first approach, the anchor was synthesized with a protected catechol moiety, which would be liberated readily after the PEG coupling. In this manner, veratrole (**3.26**) was reacted in a Friedel-Crafts acylation with succinic anhydride (**3.27**) in accordance to a procedure described by Ghosh *et al.* (Scheme 3.5).[41] The formed acid **3.28** was then nitrated under standard conditions to give nitrocatechol **3.29**. The acid was then reduced in the presence of borane to alcohol **3.30**. The remaining γ-carbonyl group was thought to decrease the aromatic electron density and, thereby, increasing the stability of the anchor attachment to metal surfaces.

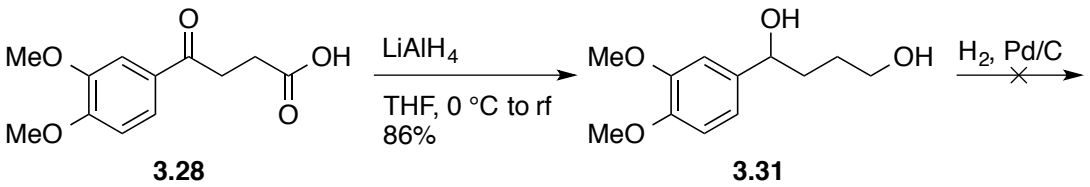


Scheme 3.5: Preparation of protected catechol **3.30**. The deprotection was tried with boron tribromide in CH_2Cl_2 at -78 °C to room temperature and sodium ethanthiolate in THF and dioxane at temperatures up to 150 °C.

To test the catechol deprotection without the PEG chain, alcohol **3.30** was subjected to standard conditions with boron tribromide or sodium ethanthiolate.[42] In both cases, this led to complete decomposition. With boron tribromide and under certain conditions, the potential desired product was observed in the crude mixture, but decomposed during further workup. As such nitro catechols are usually stable, this has

to be a result of the additional carbonyl group. It is likely that, the negative mesomeric effect promotes the formation of the quinone methide, which can then undergo various side reactions.

Consequently, we tried to remove the carbonyl group (Scheme 3.6). Such benzylic heteroatoms can be removed under reductive conditions. Therefore acid **3.28** was treated for two days with lithium aluminium hydride in refluxing THF. While all additional functionalities were reduced to give product **3.31**, the oxygen remained in the benzylic position. Further reduction of diol **3.31** with palladium on activated carbon and hydrogen was unsuccessful. Other known methods would allow the conversion, but this would increase the reagent costs and the number of steps, which was undesirable for this work.



3.28 **3.31**

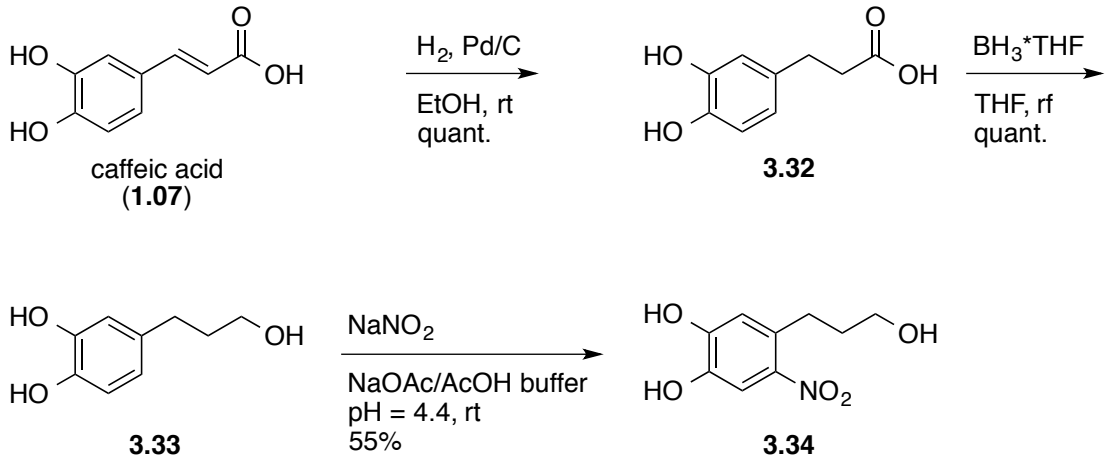
Scheme 3.6: Removal of the carbonyl group under reductive conditions. The hydrogenation was tried with 10% palladium on activated coal in MeOH and EtOAc, with and without the addition of acetic acid at room temperature and at 50 °C.

The addition ot the carbonyl group through the Friedel-Crafts acylation hinders the viability of the route. Furthermore, protection of the catechol moiety was not favorable due to deprotection issues.

3.4.3 Protecting Group Free PEGylated Anchor Synthesis

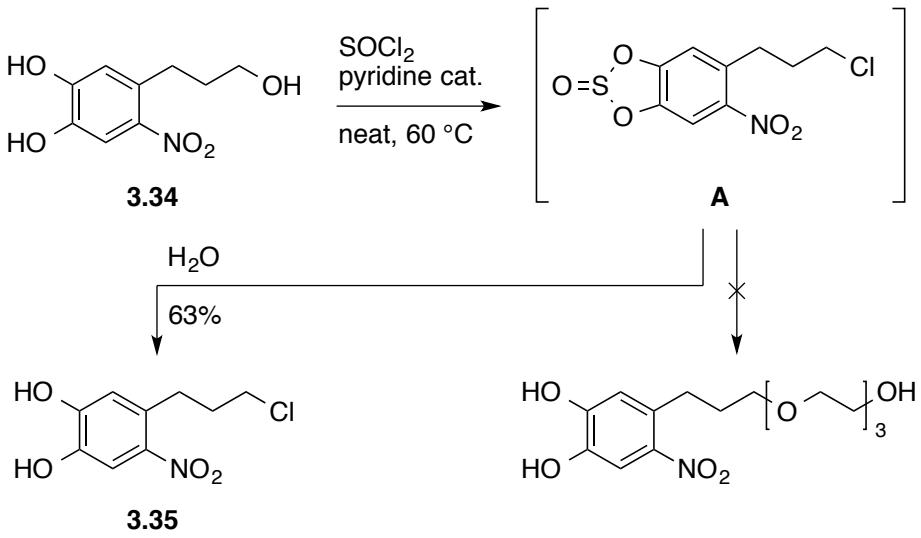
A new precursor with a three-carbon chain and an unprotected catechol was found in caffeic acid (**1.07**) (Scheme 3.7). This phenylpropanoid natural product is inexpensive and can be easily converted to alcohol **3.32** by catalytic hydrogenation and reduction with borane. Such free catechols are known to be extremely reactive in electrophilic aromatic substitutions. Therefore, a procedure with sodium nitrite in an acidic solution was used. A similar procedure was already applied in the synthesis of the nitrodopamine anchor (**3.04**).[43,44] In the reaction with dopamine, the crystallization of the semi-sulfate product after the first substitution prevents the double nitration. In the synthesis of nitrocatechol **3.34**, the over nitration was avoided by buffering the system to a pH of 4.4 as it was described for similar substrates by de la Bretèche *et al.*[45] With this route, the

nitrocatechol anchor **3.34** was synthesized in three step and 55% yield in sufficient purity without chromatography.



Scheme 3.7: Synthesis of the caffeic acid derived nitrocatechol anchor **3.34**.

For the following etherification, we planned to activate the hydroxy function of **3.34** and substitute it with PEG. However, free phenol groups are better nucleophiles and could potentially lead to polymerization of the anchor. For this reason, the catechol had to be inactivated for the next step.

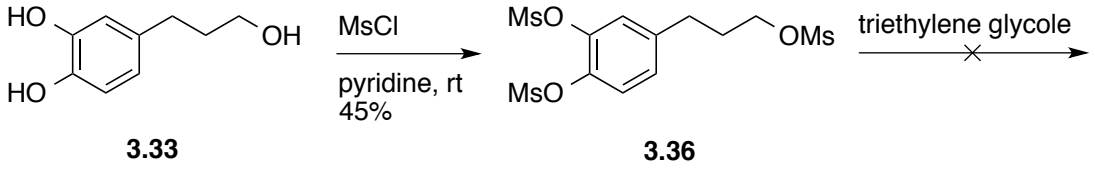


Scheme 3.8: Attempted PEGylation of anchor **3.34** over the dioxosulfinylbenzoid **A** and synthesis of the chlorinated intermediate **3.35**.

Reports by Frederick *et al.* and the group of Feller describe the surprisingly high stability of dioxosulfinylbenzoids, resulting from the treatment of catechols with thionyl chloride.[46,47] With our anchor **3.34**, this reaction leads not only to a deactivation of the catechol, but also to the activation of the hydroxy group by chlorination (Scheme 3.8).

It was at this point not clear if the bidentate nature of the dioxosulfinylbenzoid **A** was sufficient to prevent a nucleophilic substitution at the sulfur by PEG, liberating the phenols. After the chlorination of anchor **3.34**, the excess thionyl chloride was removed by distillation and triethylene glycol was added as test substrate. Neither the addition of strongly basic sodium hydride nor the elevated temperatures were sufficient to show product formation by UPLC-MS. However, after quenching with water, chlorinated product **3.35** could be isolated.

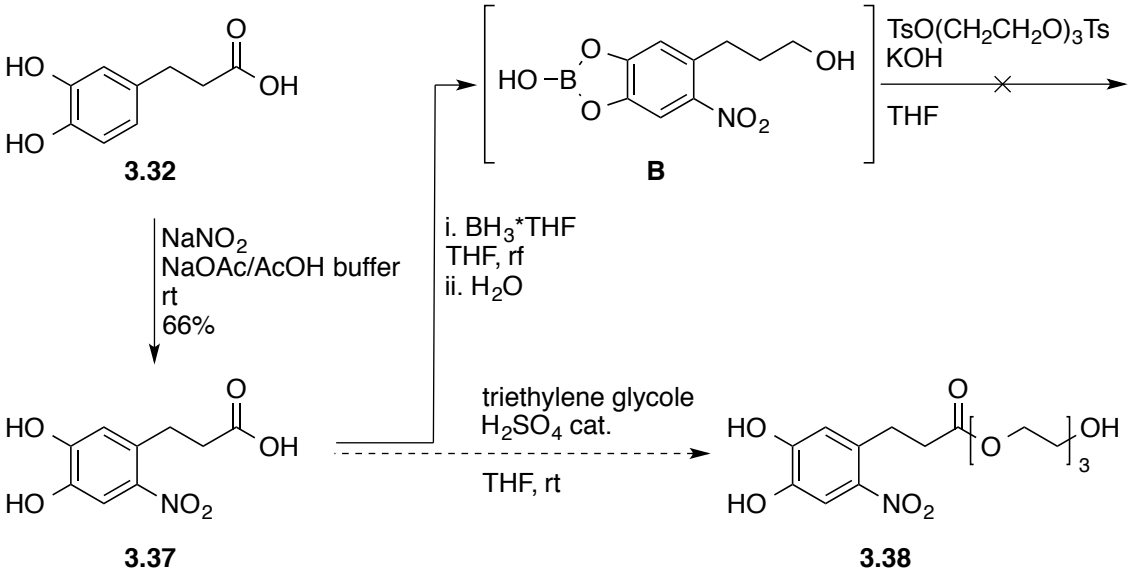
To overcome the low reactivity the chloride, an alternative activation of the hydroxy group by mesylation was tried. In this study, the more easily accessed catechol **3.33** was used. After treatment with methansulfonyl chloride, trisubstituted intermediate **3.36** was isolated (Scheme 3.9). However, under etherification conditions with triethylene glycol, none of the desired product was observed. An analysis of the reaction mixture by UPLC-MS showed mesylated triethylene glycol, resulting from a transesterification at the sulfur. The simultaneously liberated phenol is thought to lead to the observed polymerization of the anchor.



3.33 **3.36**

Scheme 3.9: Tried PEGylation of anchor **3.33** over the triple mesylated intermediate **3.36**.

A second possibility to overcome the low reactivity of this substrate was to switch the role of the reaction partners. A tosylated PEG derivative, as it was used earlier, is a better electrophile due to the neighbor group effect of the adjacent oxygen (Section 3.3.3).[48] To mask the catechol function, the synthesis was reordered. Acid **3.32** was directly nitrated to give nitrocatechol **3.37** (Scheme 3.10). The degree of nitration was controlled by the pH of the reaction solution and the addition speed of the sodium nitrite solution. However, this reaction proved to be more difficult, as the nitration of alcohol **3.33** and the conditions had to be optimized after every scale-up step. The acid was then reduced with borane, affording intermediate boronic ester **B** with masked phenol groups only after the addition of stoichiometric amounts of water.[49] However, the following substitution of the tosylated triethylene glycol was not successful.



Scheme 3.10: Nitration of acid **3.32**, reduction to the alcohol and masking of the catechol followed by a substitution. Alternative esterification of acid **3.37** with triethylene glycol.

Alternatively, acid **3.37** formed ester **3.38** in the presence of ten equivalents of triethylene glycol under acidic catalysis in complete conversion. However, the ester is not base stable and isolation by solid phase extraction was not possible. Alternatively, neutral ion exchange resins are known to absorb phenols respectively catechols.[50–52] A separation of ester **3.38** from remaining triethylene glycol by ion exchange chromatography showed initial positive results, but a method affording pure material was not achieved in the available time.

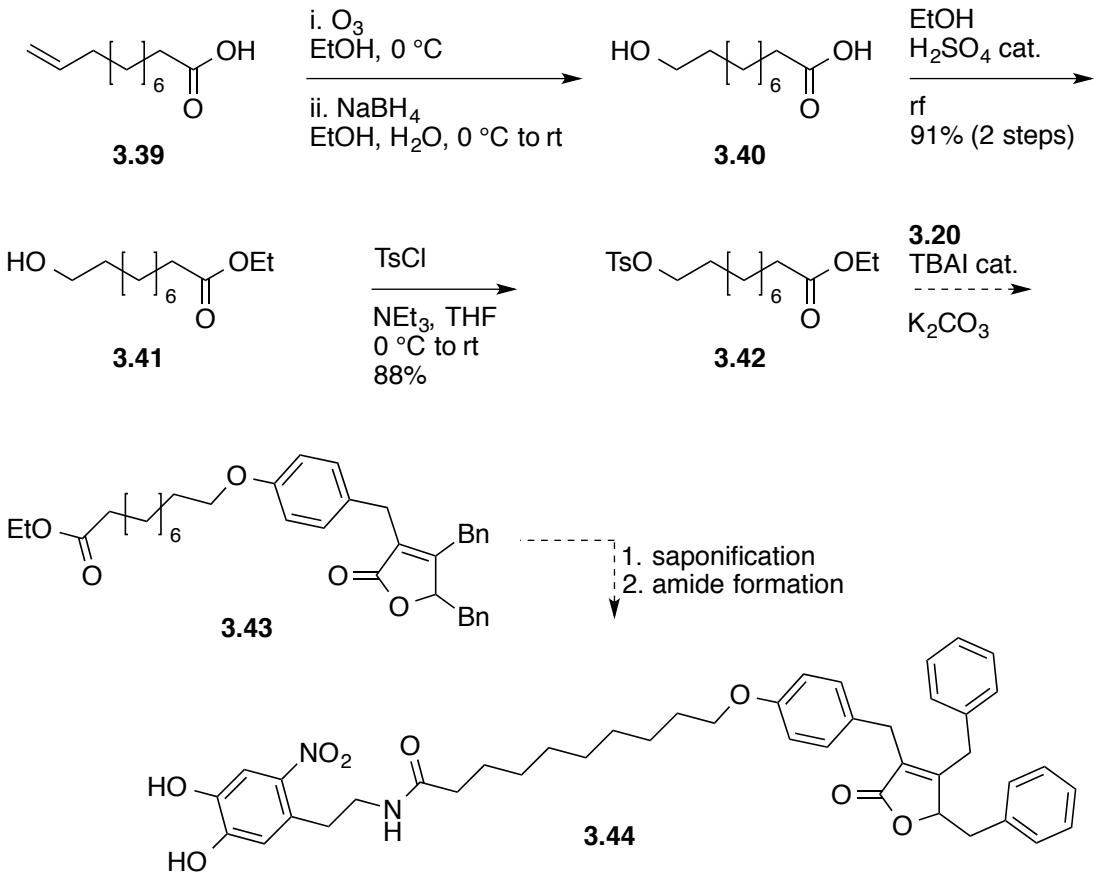
In conclusion, these results show some interesting aspects of an inexpensive PEGylated anchor system, major issues still remain. One problem is the etherification of the anchor and the PEG chain. Further investigations are necessary to accomplish the goal of this project. If these issues could be overcome, the presented concept would give access to an affordable linker anchor couple. Furthermore, PEGylated anchors such as ester **3.38** have already been used to form protein resistant surfaces and prevent biofouling.[23,24,53,54]

3.5 Synthesis of the Anchored Maculalactone A Hybrid

In interest of time, a shorter and more straightforward hybrid was designed and synthesized. A shorter bifunctional fatty acid derived linker was chosen. Undecylenic acid (**3.39**) is isolated from castor oil by cracking under pressure and subsequent steam

distillation in good purity.[55] As a result, this eleven-carbon fatty acid is the least expensive in the family of ω-unsaturated fatty acids.

Acid **3.39** was converted to ω-hydroxy acid linker **3.40** by ozonolysis and subsequent reduction with $NaBH_4$ as Diaper *et al.* described it (Scheme 3.11).[56] The acid is then protected as ethyl ester **3.41** by a known procedure.[57] Subsequently, the ω-hydroxy group is tosylated to obtain activated linker **3.42**. The next steps are in the process of being optimized. Initial experiments of the Williamson etherification with tetrabutylammonium iodide as the catalyst show promise. The formed ester **3.43** will then be hydrolyzed before it is coupled to our dopamine anchor, as it was earlier demonstrated by Gomes *et al.*[35] The dopamine anchor has been chosen due to the higher hydrolytic stability of the formed amide compared to an ester. The synthesized functional hybrids will then be coated on metal plates by a dip and rinse procedure. The surface properties of the plates will be measured and consequently, the antifouling activity will be examined by submerging the plates in our biofouling test facility.

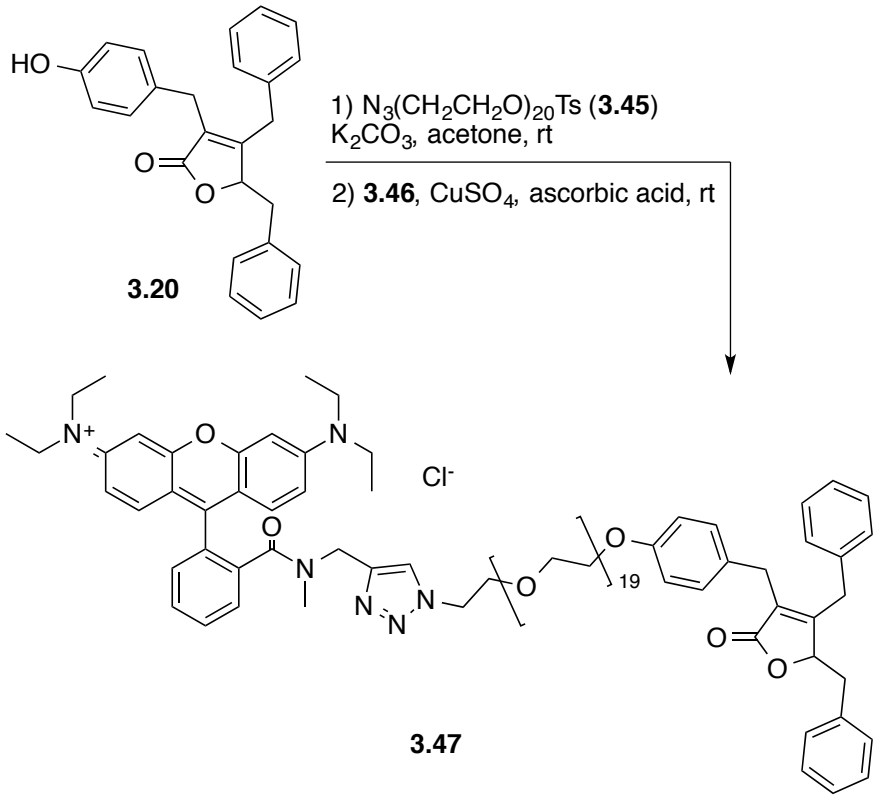


Scheme 3.11: Synthesis of anchored maculalactone A hybrid **3.44** with a ω-hydroxy fatty acid linker.

3.6 *In Vivo* Studies

3.6.1 Synthesis of a Rhodamine B Labeled Maculalactone A Analogue

While the toxicity of maculalactone A (**1.34**) is well described, nothing is known about the actual mode of action. A deeper understanding of this is certainly desirable and a first piece was found in our structure activity relationship study (Section 3.3.2).



Scheme 3.12: Synthesis of the labeled maculalactone A analogue **3.47**. Compound **3.46** is the *N*-methyl-*N*-propargyl amid of rhodamine B, synthesized as described by Yan *et al.*[58]

The modified maculalactone A analogue **3.17**, which was found as candidate for an antifouling coating, can also be used to collect some evidence about the molecular target (Scheme 3.12). Therefore, the corresponding phenol **3.20** was elongated with the activated PEG azide **3.45**. By a Click reaction, the azide was connected to the rhodamine B derivative **3.46**,[58] giving fluorescently labeled maculalactone A analogue **3.47**. Additionally, the negative control **3.48** with a free hydroxyl group instead of the maculalactone A moiety was prepared. However, this compound was found to be predisposed for amide hydrolysis and could only be synthesized in very low quantity.

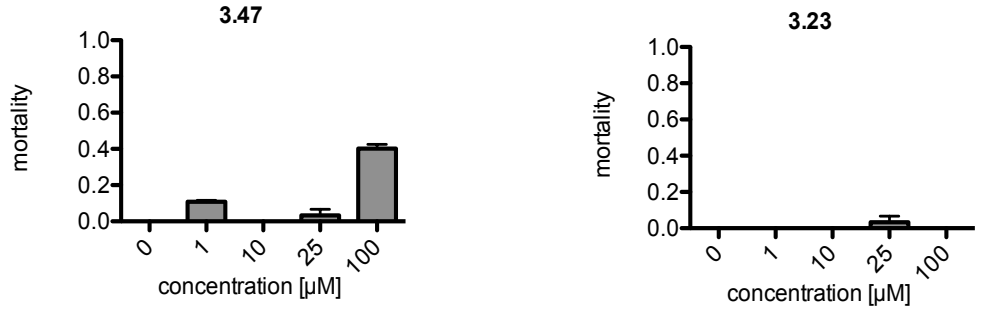


Figure 3.7: Toxicity assay of marker **3.47** and analogue **3.23** with *A. franciscana*. Values are given as the mean of three independent experiments with ten animals, error bars denote the standard error of the mean (SEM).

Consequently, the validity of the synthesized marker **3.47** proved in a toxicity assay with *A. franciscana* (Figure 3.7). Additionally, the toxicity of analogue **3.23** with the short PEG chain was determined. In dissent to all earlier results, compound **3.23**, bearing a short PEG residue, showed no toxicity at all. In contrast, the rhodamine B marker **3.47** exhibits a toxicity comparable to the one of maculalactone A. These partially positive results encouraged us to continue our investigations.

3.6.2 Visualization of Maculalactone A Interactions in *Artemia Salina*

Marker **3.47** needed to be validated through selective and specific staining in the *in vivo* experiments. In addition to the marker **3.47**, the negative control **3.48 (**without the maculalactone A moiety) was employed. Furthermore, pure rhodamine B and a blank control of DMSO were incorporated in this first experiment.

For a microscope examination, the organisms should be fixed in a formalin solution. However, the media of *A. franciscana* was found to be incompatible with the fixation. Therefore, a more robust strain of *A. salina* was employed for the *in vivo* experiments. A concentration of 1 µM was found to be optimal, as no toxic side effects were expected and a sufficient fluorescence contrast was achieved.

The two-days-old organisms were incubated for 24 hours in the staining solutions containing either **3.47**, **3.48**, rhodamine B or the blank control. This was followed by a washing procedure where the organisms were twice transferred to fresh media and incubated for three hours. Finally the larvae were fixed in a formalin solution in PBS buffer.

The stained organisms were examined by fluorescent microscopy under identical lighting conditions (Section 8.3). While rhodamine B caused general staining of the entire body, the negative control **3.48** did not show any fluorescence at all. In contrast,

the maculalactone A marker **3.47** showed a selective staining of specific organs. Since the control experiments excluded a selective staining caused by the fluorophore or the linker, the stained regions show the specific areas that had accumulated maculalactone A.

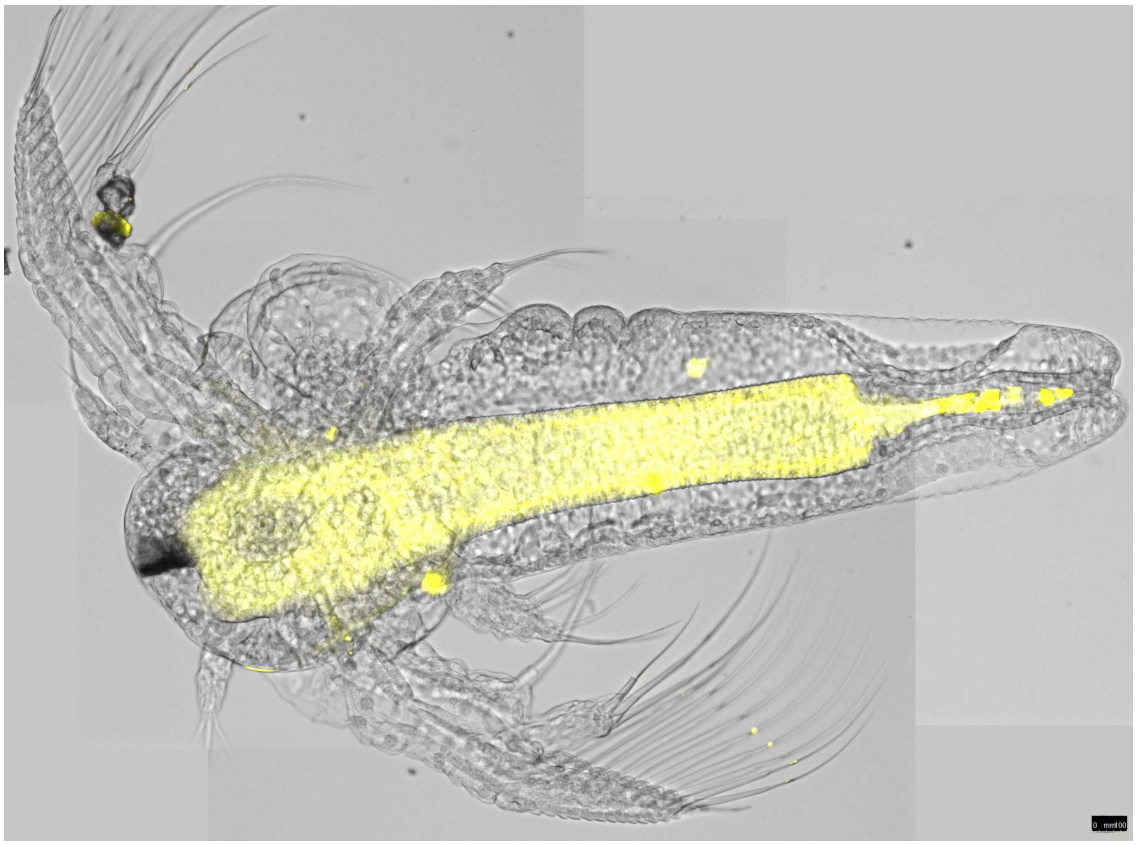


Figure 3.8: A combination of four microscope pictures of an *A. salina* nauplia stained with compound **3.47**. Visual and fluorescence images, scale bar =100 µm.

Initial images showed a highly stained, rod-shaped organ in the center of the body, which appears to be related to the intestine (Figure 3.8).[59] At the tail of the animal, the stained tissue ends in a sharp line. Additionally, a cell like texture instead of a homogeneous staining was observed. The head area could not be completely focused and eventually a circular dyed shape was observed.

Examination by bifocal microscopy gave more insight. Slices through the tail revealed a tube like structure, which is in agreement with a staining of the intestine wall and not it's content (Figure 3.9). Consequently, it can be assumed that the labeled maculalactone A **3.47** was accumulated in the intestine wall or a related tissue.

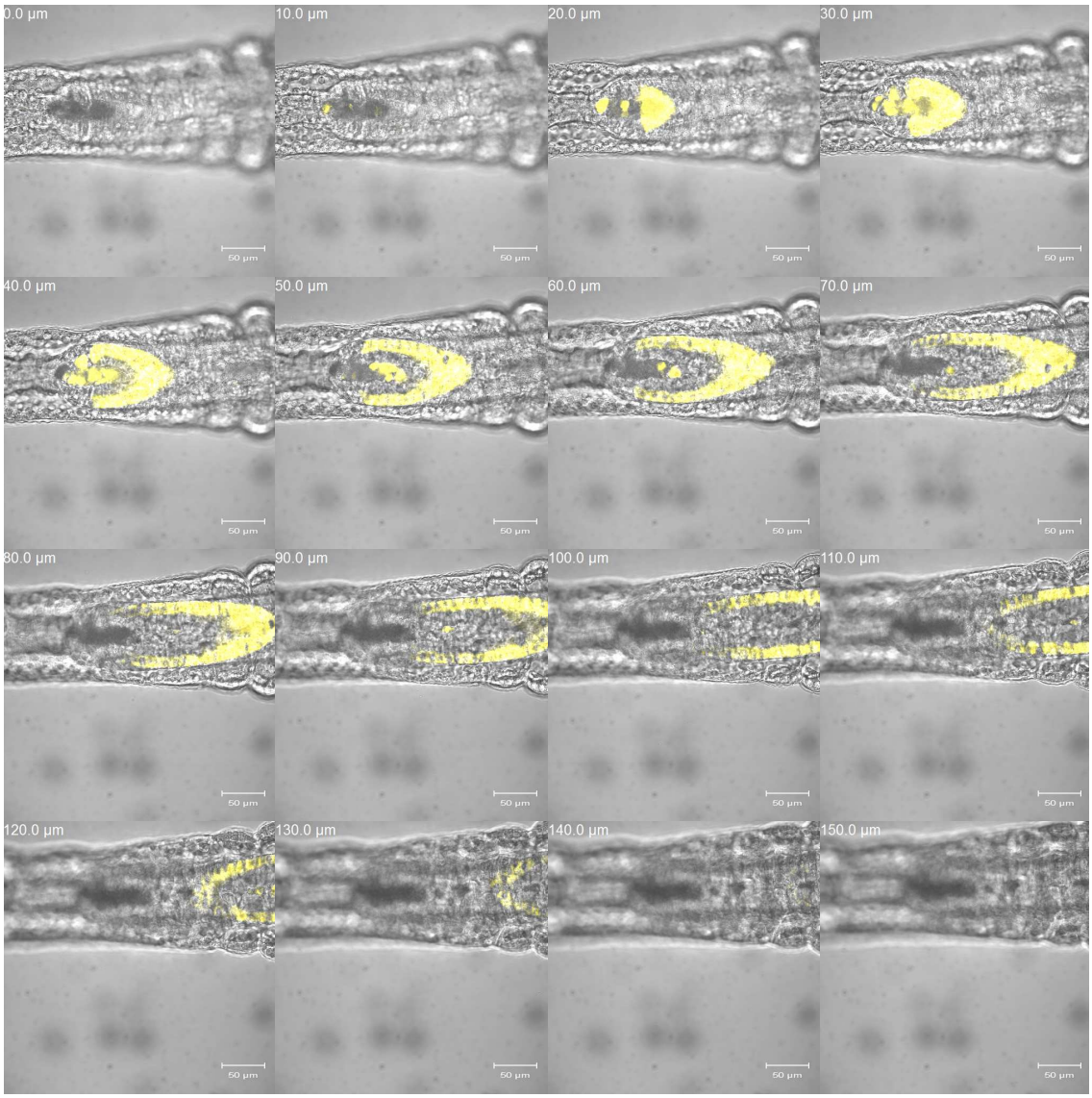


Figure 3.9: Tail images of an *A. salina* nauplia stained with compound **3.47**. Visual and fluorescence images, 10 µm slides in the z-axis, scale bar = 50 µm.

Interesting to note are the sharp borders of dyed tissue towards the end of the organism, as well as along the structure (Figures 3.9 and 3.10). This excludes the possibility of an unspecific staining by diffusion from the gut into the body.

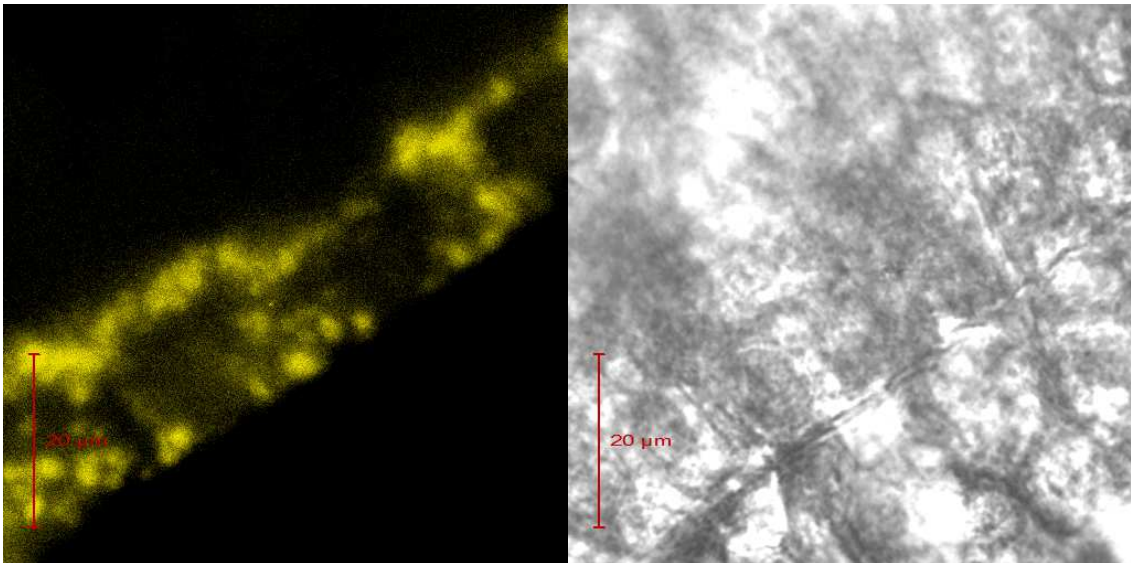


Figure 3.10: Magnification of the tail of an *A. salina* nauplia stained with compound **3.47**. Left: fluorescence, right: visual image, scale bar = 20 µm.

Images of the head revealed another dyed structure above the intestine, enclosed by a strongly stained ring. However, we have not yet been able to indentify this tissue.

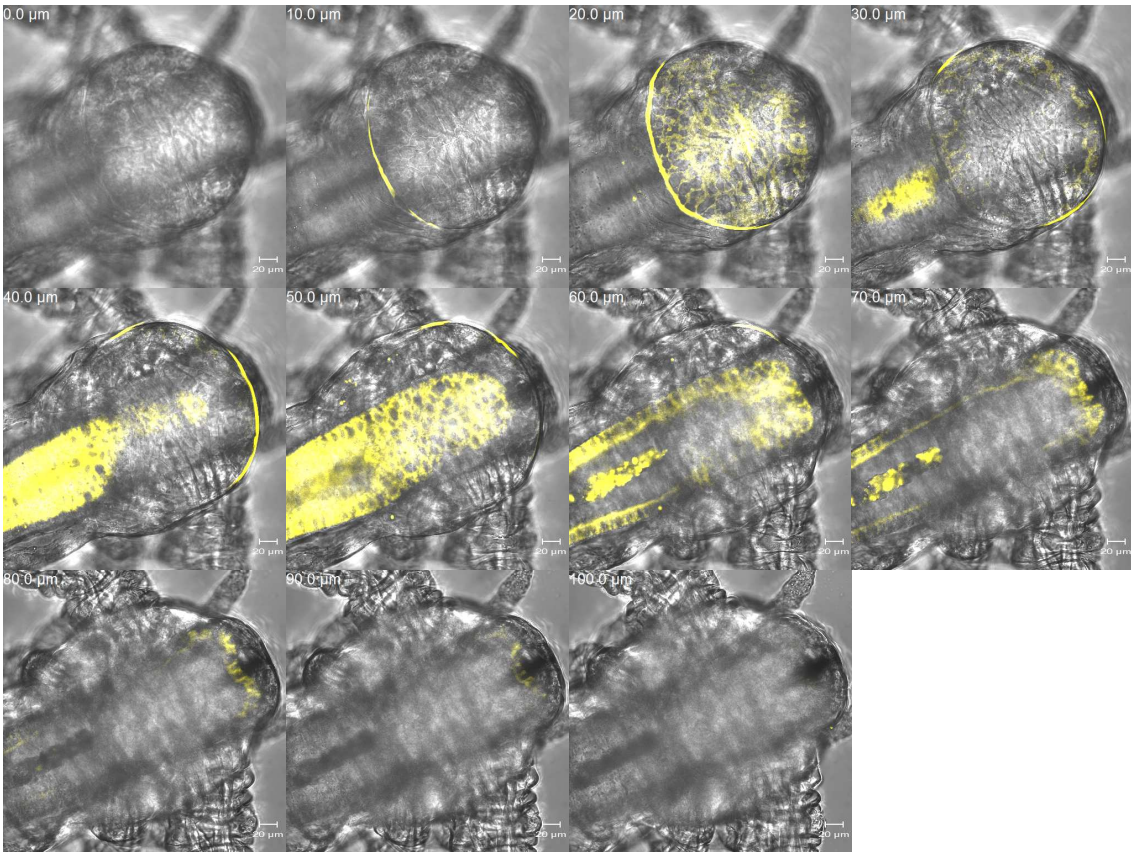


Figure 3.11: Head of an *A. salina* nauplia stained with compound **3.47**. Visual and fluorescence images, 10 µm slides in the z-axis, scale bar = 20 µm.

Although *A. salina* is regularly employed in toxicity assays, little is known about the anatomy of its larvae stages. Therefore, a definitive assignment of the stained tissues would require further experiments with other organisms as well as with cell cultures. However, with these experiments we visualize the tissues targeted in *A. salina* and were able to get an initial look at the mode of action.

3.7 Conclusion

The accumulation of biological material, referred as biofouling, is a serious threat for many surfaces in contact with fluids.[1,2,5,6,8–11] In contrast to man-made structures, biological organisms are usually less affected by biofouling.[4,11,12] The slowly growing cyanobacterium *K. maculans* is suspected to produce maculalactone A (**1.34**) as a chemical defense against biofouling. [20] This compound showed promising activities against the settlement of bivalves.

Together with our expertise in surface modifications, we developed a novel concept for the biofouling protection of metal surfaces. Thereby, we planned to form a covalent linkage between maculalactone A and one of our nitrocatechol anchors. With this functional hybrid, a metal surface could be coated in a dip and rinse procedure and would be protected from biofouling by the biological properties of maculalactone A. This concept and preliminary results were awarded in 2012 with the first prize of the Clariant CleanTech award.

In a first phase of the project, three different maculalactone A derivatives for a covalent linkage were synthesized. The formed analogues were then compared in a SAR study and lactone **3.17** was found to be equally or more active as maculalactone A.

Commercially viable surface coatings need to be made from inexpensive building blocks. Effort were made to build a system that would allow for the synthesis of inexpensive single side substituted PEG linkers. Towards this end, various new anchors were synthesized. Our idea was to connect one of these anchors to a PEG chain and use the acidic properties of the catechol to isolate the substituted linker from the reaction mixture. While significant progress was made toward the synthesis and purification of these anchors, further investigation are required.

In the meantime, the biologically active lactone **3.47** was connected over a PEG linker with a rhodamine B fluorophore. Consequently, this marker was used to visualize the contribution of maculalactone A in *A. salina*. Interestingly, only defined tissues around the intestine and in the head of the organisms were stained. To disclose more

details about the mode of action of maculalactone A, further experiments with better known organisms or cells cultures are required.

3.8 References

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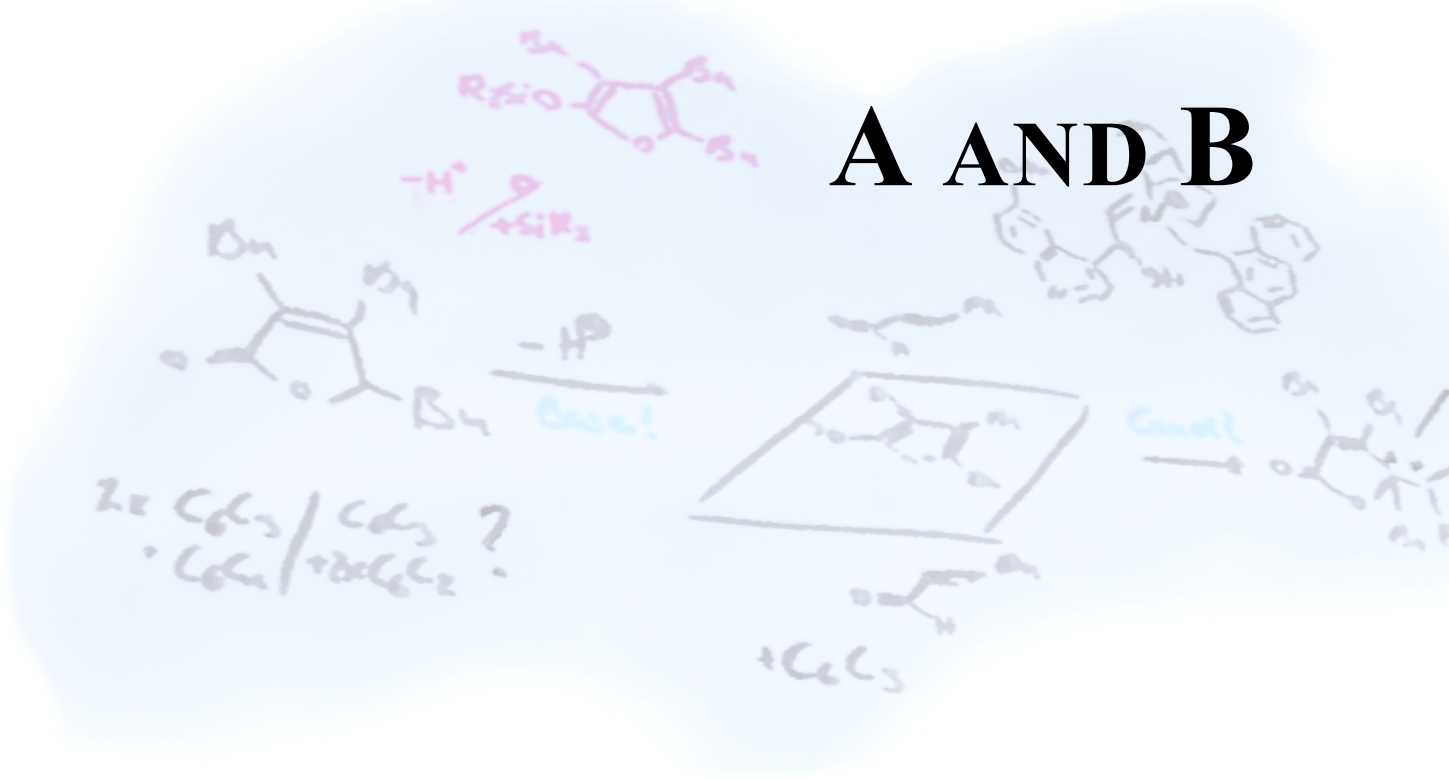
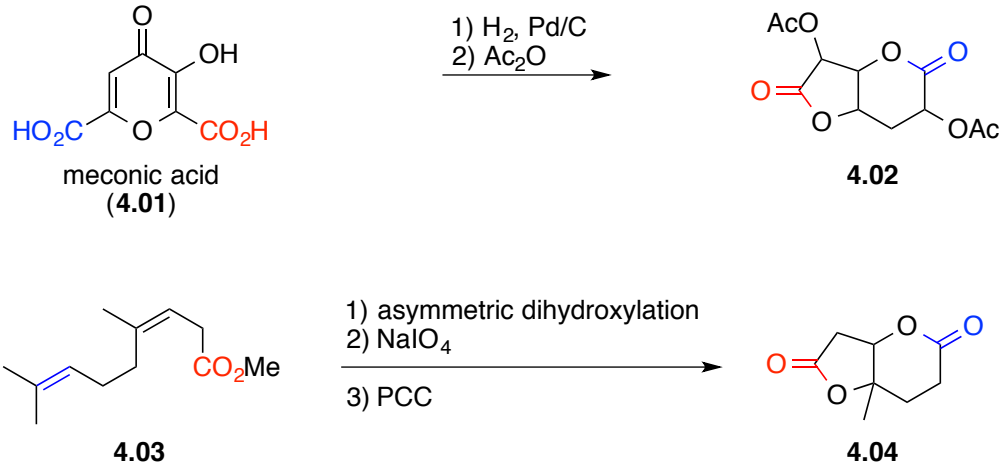
4 - Synthetic Studies on Ophiodilactone A and B



4.1 Introduction

4.1.1 Early Synthetic Examples of the γ,δ-Dilactone Core

As described in section 1.5, the core structure of ophiodilactone A (**1.47**) and B (**1.48**) is unique among natural products. When we started our investigations, only two synthetic compounds were known bearing such a γ,δ-dilactone moiety (Scheme 4.1). In 1916, Borsche published his investigations on the structure of meconic acid (**4.01**).[1] Following a catalytic reduction and treatment with acetic anhydride, he obtained the dilactone **4.02**. About 90 years later, the group of Brückner described the dihydroxylation of trisubstituted β,γ-unsaturated ester derivative.[2] After double dihydroxylation of the geranyl derivative **4.03**, followed by an oxidative cleavage and oxidation, dilactone **4.04** was isolated.



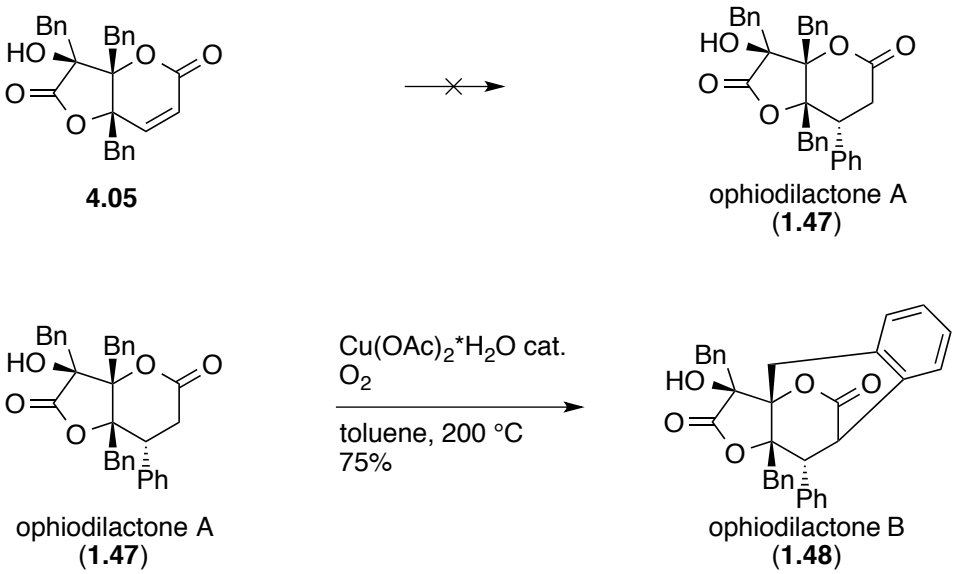
Scheme 4.1: The established synthetic examples of γ,δ-dilactone structures.[1,2]

While both of these strategies would be unsuitable for the substitution pattern of the ophiodilactones, they provide interesting insights into this core. The intermediate after hydrogenation of **4.01** consists of two acids and four hydroxyl groups, allowing various structural isomers. However, the dehydration with acidic anhydride delivers selectively the required γ,δ-dilactone **4.02**.

4.1.2 Established Synthetic Efforts

Early synthetic efforts in the Gademann group were conducted by Jean-Yves Wach and are discussed in section 5.1.3. The applied strategy focuses on a linear approach including a desymmetrization and is summarized, together with my work on this route, in chapter 5.

In 2012, Matsubara *et al.* published preliminary results towards the total synthesis of ophiodilactone A (**1.47**) and B (**1.48**).[3] While the γ,δ-dilactone was synthesized successfully, they could not achieve the introduction of the last phenyl group by a nucleophilic 1,4-addition on **4.05** (Scheme 4.2).



Scheme 4.2: Selected examples from the total synthesis of ophiodilactone A and B by Matsubara *et al.*[3,4]

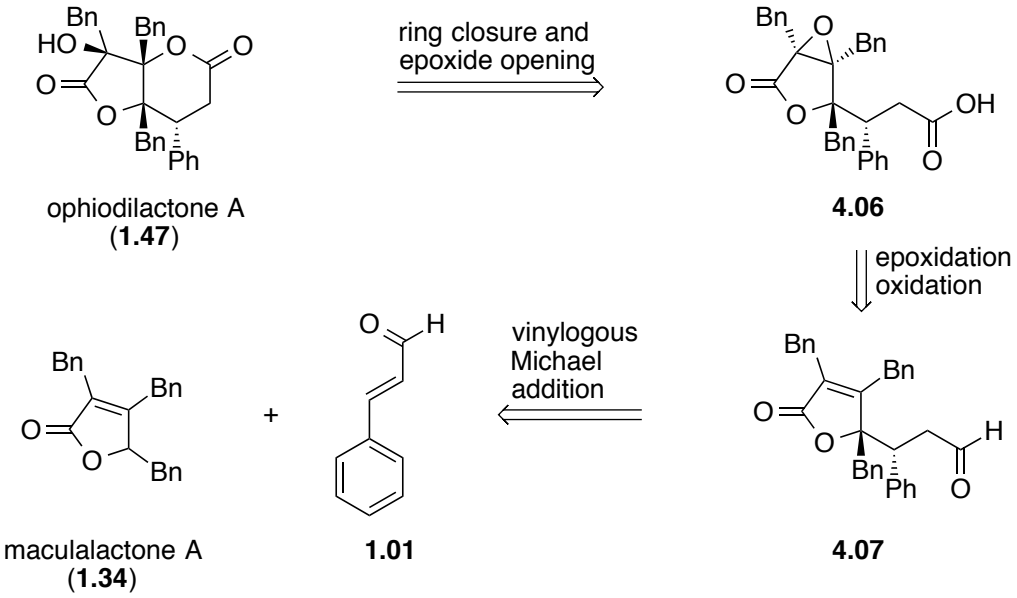
Very recently, the same group communicated their successful total synthesis of ophiodilactone A in 17 steps and a overall yield of 14%.[4] Furthermore, Matsubara *et al.* presented the one step conversion of ophiodilactone A (**1.47**) to ophiodilactone B (**1.48**). Their employed strategy shows only little similarities to ours and interesting steps will be discussed at the appropriate position within this chapter. This includes especially the epoxidation and epoxide opening.

4.2 Synthetic Strategy from Maculalactone A to Ophiodilactone A and B

Ueoka *et al.* speculated in the isolation publication, that a radical reaction converts ophiodilactone A (**1.47**) to B (**1.48**).[5] Therefore, we focused our efforts on the synthesis of ophiodilactone A, to later be converted to ophiodilactone B.

As maculalactone A (**1.34**) possesses already most of the carbon skeleton of ophiodilactone A, our synthetic strategy was straightforward. The dilactone can be formed from the corresponding acid **4.06** by a nucleophilic epoxide opening (Scheme 4.3). The epoxide is generated from the double bond of the butenolide **4.07**.

The elongation of maculalactone A (**1.43**) by another phenylpropanoid unit is the key step of the synthesis and can be achieved by a vinylogous Michael addition to cinnamaldehyde or an appropriate derivative. Due to the loss of chirality in the vinylogous addition, racemic maculalactone A can be used. However, this requires an enantioselective method for the phenylpropanoid elongation.



Scheme 4.3: Synthetic strategy leading from maculalactone A (**1.34**) to ophiodilactone A (**1.47**).

4.3 Elongation by a Phenylpropanoid Unit[6]

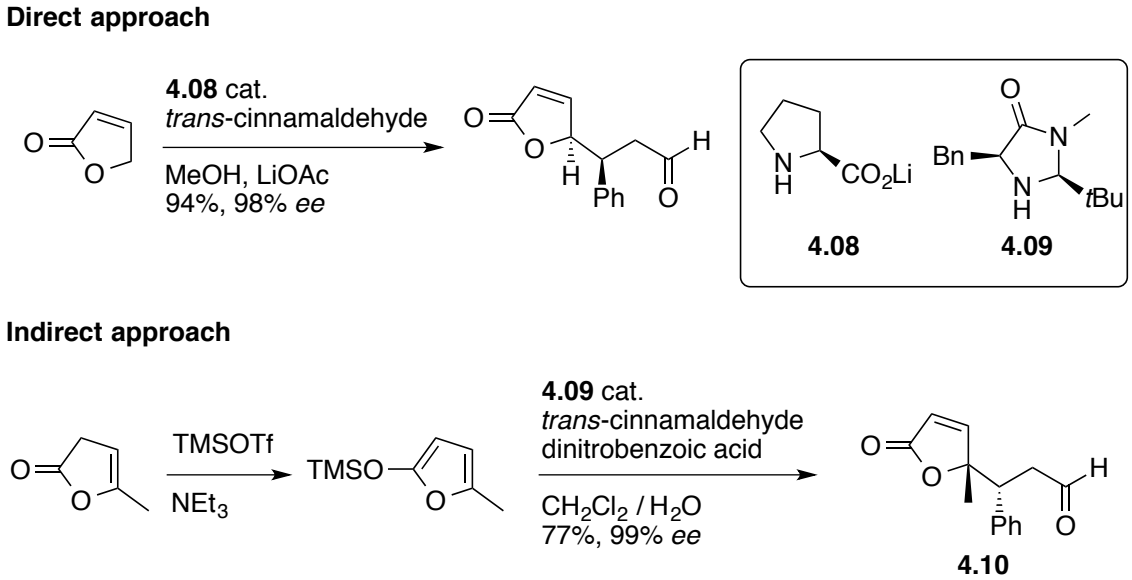
4.3.1 Additions with γ-Lactones

The proton in γ-position of butenolides is relatively acidic and can be removed by weak bases. The formed anion can then be used for nucleophilic substitutions and additions. Depending on the electrophile, either the α or the γ-position is modified. Such processes have been extensively used in the last few years. An example for a modification in γ-positions has already been described in the maculalactone A synthesis by Kar *et al.* (Scheme 2.2).[7] Throughout our synthetic studies we observed a substitution in α-position, affording compound **2.13** (Scheme 2.4).

Various methods have been studied for the addition of such nucleophilic butenolides to Michael acceptors. Most of these methods can be condensed to two principal systems (Scheme 4.4).[8,9] In the direct approach, the butenolide is deprotonated *in situ* and directly reacted with the electrophile. More recently, enantioselective versions these

[6] The vinylolous Michael addition was developed by Michael Lüscher during his Master thesis.[6]

reactions can be facilitated by the addition of organocatalysts, such as proline derivatives[10–12], amines[13–17] and cinchona alkaloids[18,19] or a combination of these.



Scheme 4.4: Examples of direct[10] and indirect[20] vinylogous Michael additions with butenolides.

In the indirect method, the butenolide is first converted to the silyloxy furan, followed by addition to the Michael acceptor in a Mukaiyama-type reaction. While racemic methods had been known, an enantioselective system was first developed by Kitajima *et al.*[21] and eventually optimized by the group of Macmillan,[20] where secondary amides are used as iminium catalysts.

However, most of the established methods are applied on un- or little-substituted butenolides. The behavior of the densely substituted maculalactone A under these reaction conditions is hard to predict. This could include reduced reactivity due to steric hindrance and unknown changes in the acidity of the γ-proton.

4.3.2 Implementation of the Vinylogous Michael Addition

The direct reaction was more attractive. Therefore, our first experiments focused on the *in situ* generation of the nucleophile by weak bases (Table 4.1). In this early stage, manly achiral catalysts were tested. Under standard conditions with pyrrolidine, no reaction was observed (Entry 1). The addition of Lewis and Bronsted acids to pyrrolidine had no effect (Entries 2 and 3). The addition of equimolar amounts of pyrrolidine lead to decomposition of the starting material (Entry 4). The same was found with the more basic DBU (Entry 7). However, whit an excess of triethylamine, no

reaction was observed (Enties 5 and 6). Furthermore, no product was observed in the presence of primary diamines (Entries 8 and 9).

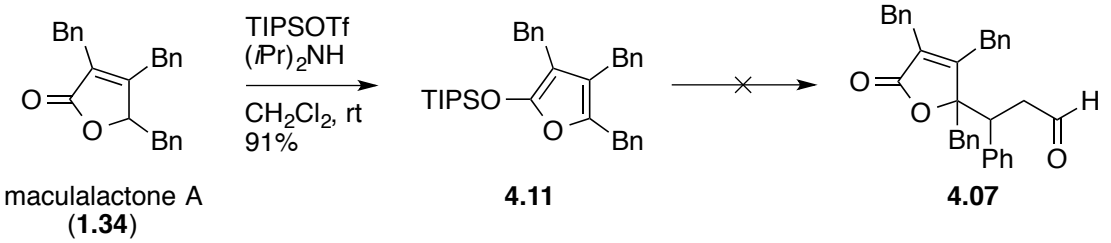
Entry	Enone [eq.]	Catalyst (eq.)	Additive (eq.)	Temperature [°C]	Solvent	Yield [%]
1	3.0	Pyrrolidine (0.2)	-	rt to 50	MeOH	0[a]
2	3.0	Pyrrolidine (0.2)	LiCl (0.2)	rt to 50	MeOH	0[a]
3	3.0	Pyrrolidine (0.2)	AcOH (0.2)	rt to 50	MeOH	0[a]
4	3.0	Pyrrolidine (1.0)	-	rt	MeOH	0[b]
5	1.5	NEt_3 (2.0)	-	rt to 40	MeOH	0[a]
6	1.5	NEt_3 (2.0)	-	rt to 40	CH_2Cl_2	0[a]
7	1.0	DBU (1.0)	-	0 to rt	CH_2Cl_2	0[b]
8	2.0	(±)-*trans*-Diamino-cyclohexane (0.2)	AcOH (0.4)	rt to 40	MeOH	0[c]
9	2.0	(±)-*trans*-Diamino-cyclohexane (0.2)	AchOH (0.4)	rt to 40	CH_2Cl_2	0[c]

Table 4.1: Direct vinylogous Michael addition of maculalactone A (**1.34**) to cinnamaldehyde (**1.01**) with weak bases. The reaction times vary between 24 and 72 hours. The following experiments were conducted according to literature procedures: 1-4[10], 8+9[13]. [a]No reaction. [b]Mainly byproducts with traces of the desired product. [c]Almost no reaction with traces of byproducts and no desired product.

We then turned our attention to the indirect method, first employed by Macmillan.[20] The catalyst **4.09** was synthesized according to literature.[22] Unfortunately, generation of the silyloxy furan species from maculalactone A was problematic. Literature examples are usually less substituted and, thus, can be isolated by distillation. However, this was not possible with our substrate. Additionally, the trimethylsilyloxy furan was found to be extremely instable and readily hydrolyzed. Different silylating agents including TESOTf, TBDMSOTf, TIPSOTf were tested. Finally, the triisopropylsilyloxy furan **4.11** could be isolated by extraction at 0°C in 91% yield (Scheme 4.5).

However, no conversion to product **4.07** was observed when the nucleophile **4.11** was reacted with *trans*-cinnamaldehyde in the presence of catalyst **4.09**. Most of the starting material hydrolyzed to maculalactone A (**1.34**). Also the addition of TFA instead of 2,4-dinitrobenzoic acid had no positive influence. TFA was used in the

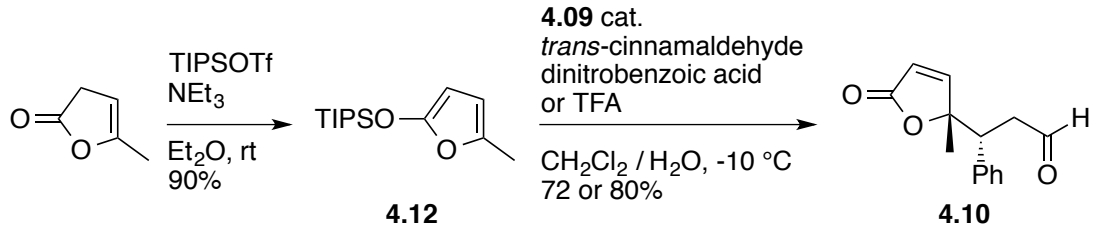
literature to activate triisopropylsilyloxy furans.[11] To reduce the steric repulsion of the formed iminium ion, the pyrrolidine TFA salt was used as catalyst. In our reaction, little conversion to the desired product was observed by ^{1}H-NMR, most of the silyloxy furan hydrolyzed to maculalactone A.



maculalactone A (**1.34**) **4.11** **4.07**

Scheme 4.5: Indirect vinylogous Michael addition utilizing Macmillan's method.[20] The second step was tried with 3.0 eq. *trans*-cinnamaldehyde, 2.0 eq. water in THF at 0 to 40 °C with either **4.09***TFA or pyrrolidine*TFA as catalyst.

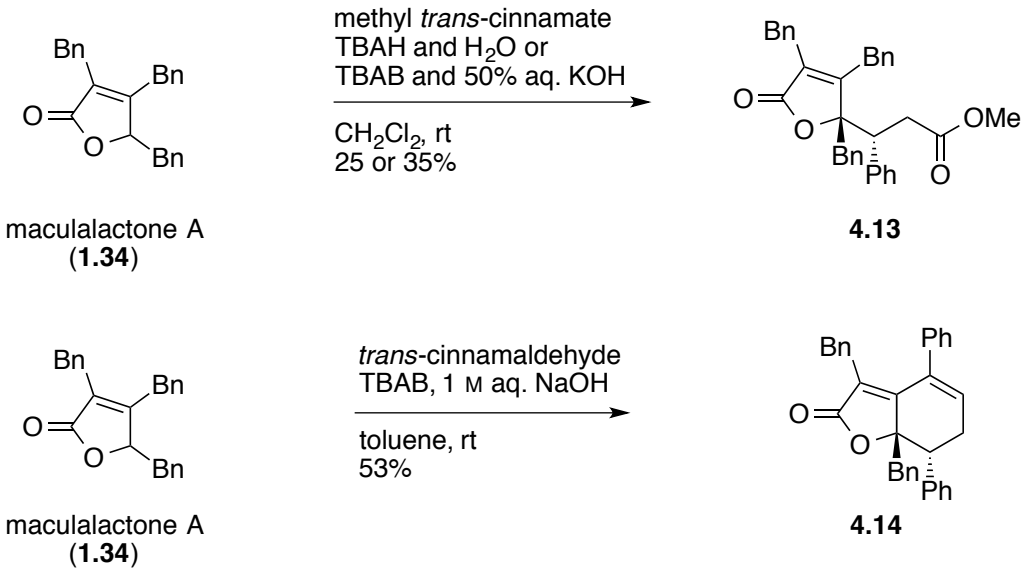
To exclude a potential low reactivity of the triisopropylsilyloxy furan, we repeated the reaction described by Macmillan with the corresponding TIPS compound **4.12** (Scheme 4.6). With an elongated reaction time, the expected conversion and a similar yield of **4.10** was observed, while the diastereoselectivity decreased to 75:25. Using TFA as an acidic additive, the reaction time was cut in half. These results reveal a problem with the steric hindrance, rather then with the reactivity, in our substrate.



4.12 **4.10**

Scheme 4.6: Indirect vinylogous Michael addition with triisopropylsilyloxy furan **4.12**. The second reaction was either promoted with 2,4-dinitrobenzoic acid or TFA.

In the third approach, we studied reactions promoted by phase transfer catalysts (PTC). The advantages of these systems include the used strong bases, providing the necessary reactivity and no need for iminium ion formation. First experiments with achiral tetrabutylammonium salts as the PTC and methyl *trans*-cinnamate as electrophile showed promising results (Scheme 4.7). The isolation of ester **4.13** in moderate yield as a single diastereomer indicated strong substrate control. However, the employed PTCs were not stable under the reaction conditions and had to be added in portions over the reaction time to ensure full conversion of maculalactone A.



Scheme 4.7: Direct vinylogous Michael addition under PTC conditions. TBAH = tetrabutylammonium hydroxide in aqueous solution. TBAB = tetrabutylammonium bromide

To improve the yield, the more reactive cinnamaldehyde was used as electrophile. Interestingly, the unexpected product **4.14** was isolated. This product is the result of a second deprotonation in the benzylic position, followed by a vinylogous Aldol reaction. Traces of the corresponding ring open intermediate **4.13** were observed in the reaction mixture by ^{1}H-NMR. However, bicycle **4.14** seems to be an important intermediate in the synthesis of maculalactone D to K and M and is discussed in chapter 6. Additionally, compound **4.14** was crystallized and the relative configuration of the product was determined by X-ray diffraction analysis (Figure 4.1).

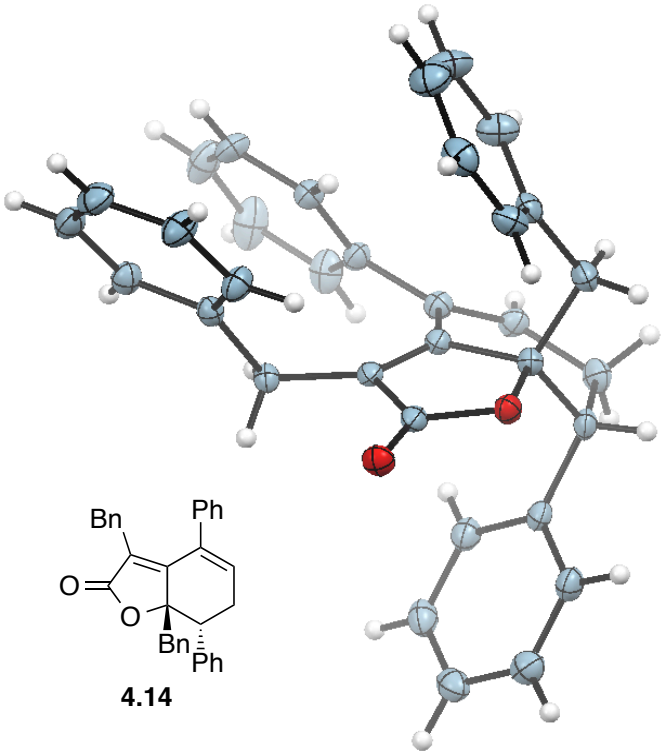


Figure 4.1: X-ray crystal structure of bicycle **4.14**.

Various enantioselective phase transfer catalysts have been developed in the recent years.[23] Asymmetric quaternary ammonium salts are the most promising for our purposes, of which the cinchona alkaloid derivatives are easily accessible (Figure 4.2).[24] Different third generation cinchona alkaloid PTCs introduced by Lygo (**2.12**)[25] and by Corey (**4.15**, **4.16**)[26] were synthesized according to literature.

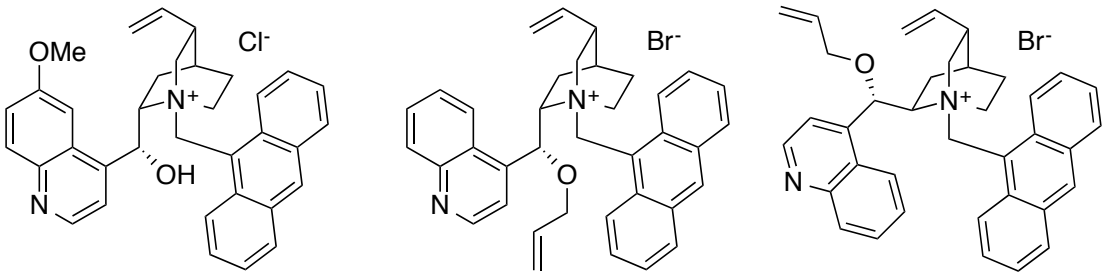
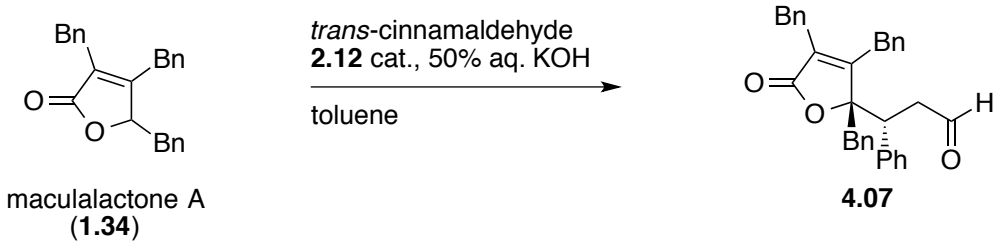


Figure 4.2: Synthesized cinchona alkaloid derived PTCs. Synthesis of **2.12**[27], **4.15**[26] and **4.16**[28] according to literature. **4.15** and **4.16** are pseudoenantiomers.

Regrettably, the synthesized PTCs showed almost no reactivity towards methyl *trans*-cinnamate under the same conditions as in the racemic approach in scheme 4.7. Only Lygo's catalyst (**2.12**) gave a low yield of 9%. To improve the conversion, the more reactive trans-cinnamaldehyde was used as electrophile (Scheme 4.8). As

expected, faster conversion to product was observed. But in contrast to earlier results with the tetrabutylammonium bromide catalyst, no second cyclization was observed and desired aldehyde **4.07** was obtained in sufficient yield.



Scheme 4.8: Reaction of maculalactone A with cinnamaldehyde to key intermediate **4.07**.

The different outcome of the PTC reactions with cinnamaldehyde can be explained by different mechanisms. While the reaction with tetrabutylammonium bromide proceeds by an extraction mechanism, the cinchona alkaloids usually favor an interfacial mechanism. A detailed discussion of the mechanism is beyond the scope of this chapter, but can be found in literature.[6,23] To confirm that the stereochemical outcome of the formed product are the same in both reactions, aldehyde **4.07** was converted with tetrabutylammonium bromide under phase transfer conditions to bicycle **4.14** (Section 6.3).

4.3.3 Optimization of the Vinylogous Michael Addition

In a first optimization, the reaction conditions were adjusted to improve the yield and diastereoselectivity (Table 4.2). Different temperatures, catalysts and catalyst loadings were investigated. The reactions were run until complete conversion of the starting material was observed.

As in the reactions with methyl *trans*-cinnamate, catalyst **2.12** showed the highest reactivity and selectivity (Entries 1 to 3). Lower temperatures elongate the reaction time, but were found to increase the diastereoselectivity (Entries 1, 4 to 6). The longer reaction time had a slight negative effect on the yields. Finally, different catalyst concentrations were tested (Entries 6 to 8). While higher loadings reduced the reaction time, no beneficial effect on the yield or the diastereoselectivity was observed. The optical rotations measured from the product indicated no further enantioenrichment.

Entry	Catalyst (mol %)	Temp. [°C]	Time [h]	d.r.[a]	Yield[b] [%]
1	**2.12** (5)	0 to 5	24	82:18	58
2	**4.15** (5)	0 to 5	48	77:23	43
3	**4.16** (5)	0 to 5	48	77:23	39
4	**2.12** (5)	-20	120[c]	87:13	39[3]
5	**2.12** (5)	-10 to -5	36	84:16	55
6	**2.12** (5)	-15	96	87:13	52[d]
7	**2.12** (10)	-15	72	67:14	50
8	**2.12** (20)	-15	60	88:12	47[e]

Table 4.2: First round optimization of the vinylogous Michael addition as depicted in scheme 4.8. Conditions: 5.0 eq. *trans*-cinnamaldehyde, 6.5 eq. 50% aq. KOH, toluene. [a]Diastereomeric ratio was determined by ^{1}H-NMR. [b]Yield of desired diastereomer **4.07**. [c]Incomplete conversion. Optical rotations $[\alpha]_D$ are [d]-70.5° (c = 0.43, $CHCl_3$) and [e]-72.3° (c = 0.58, $CHCl_3$).

A determination of the enantiomeric excess was at this stage not possible, as aldehyde **4.07** decomposed under chiral HPLC or GC conditions. However, after a mild reduction, alcohol **4.17** could be separated on HPLC and the enantiomeric excess was measured (Scheme 4.9). A racemic sample of alcohol **4.17** was obtained by subsequent reduction of racemic ester **4.13** with DIBAL and $NaBH_4$.

In a second optimization round, we focused on improving the enantioselectivity (Table 4.3). As in the first round, catalyst **2.12** showed the highest selectivity, which is reflected in the high enantiomeric excess and the diastereomeric ratio (Entries 2 to 4). As expected, pseudoenantiomeric catalyst **4.16** gave a small excess of the opposite enantiomer (Entry 4). Additionally, we observed that the reaction temperature greatly influenced the enantioselectivity (Entry 5).

Entry	Catalyst (mol%)	Temp. [°C]	d.r.	*ee* [%]
1[a]	**TBAB** (1 eq.)	rt	<95	0[a]
2	**2.12** (5)	0 to 5	92:18	30
3	**4.15** (5)	0 to 5	77:23	5
4	**4.16** (5)	0 to 5	77:23	8[b]
5	**2.12** (5)	-15	87:13	68

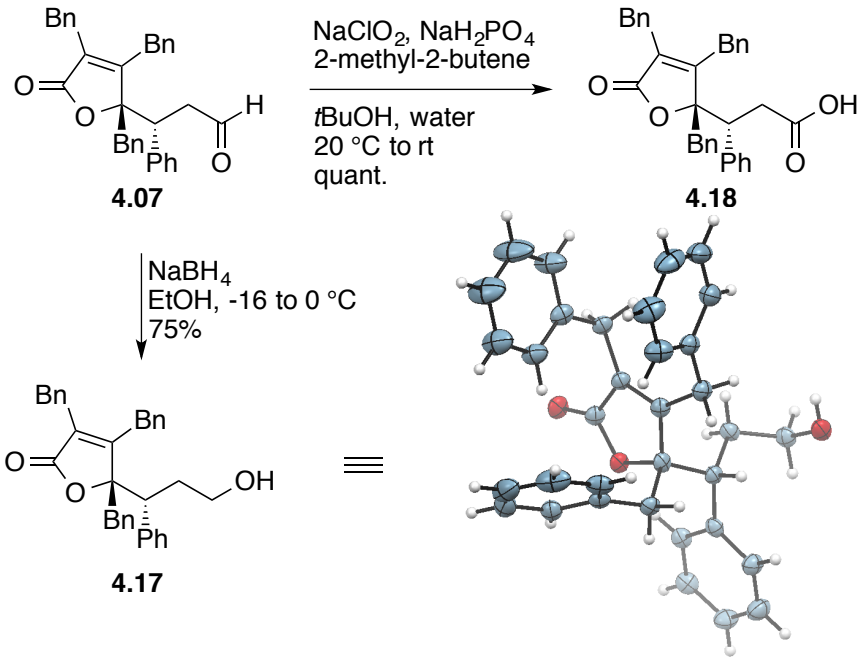
Table 4.3: Second round optimization of the vinylogous Michael addition. Conditions: 5.0 eq. *trans*-cinnamaldehyde, 6.5 eq. 50% aq. KOH, toluene. The enantiomeric excess was determined after $NaBH_4$ reduction by chiral HPLC (Appendix 9.3.1). [a]Racemic material was observed after reduction of **4.13**, synthesized as depicted in scheme 4.7. [b]Excess of the opposite enantiomer.

Due to the biphasic nature of the reaction system and the high influence of appropriate stirring, this reaction was found to be problematic during scale-up. While similar yields were obtained with more equivalents of base, reduced enantiomeric excess was observed. Upon optimization, we were able to conduct the synthetic key step of this strategy in a reasonable yield of 52% of the desired diastereomer and a high selectivity with a diastereomeric ratio of 87 to 13, and an enantiomeric excess of 68%.

4.4 Oxidation of the Butenolide Double Bond

4.4.1 Different Oxidation States

As the aldehyde is a rather sensitive functionality and we knew that compound **4.07** would easily cyclize, we converted this moiety into the corresponding alcohol **4.17** and acid **4.18** (Scheme 4.9). While the alcohol was easier to handle, we postulated that it could open the formed epoxide and give an undesired oxane ring. It was later demonstrated by Matsubara *et al.* that only harsh conditions could promote epoxide opening.[4] Regardless, utilizing the acid **4.18** would give directly the correct product and thereby reducing the number of steps.



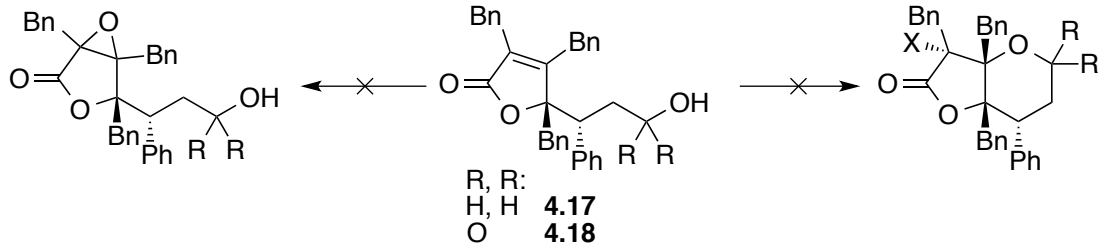
Scheme 4.9: Synthesis of acid **4.18** and alcohol **4.17** and X-ray crystal structure of the latter.

Alcohol **4.17** was accessed by a mild reduction with $NaBH_4$ in ethanol. The pure product could be crystallized and analyzed by X-ray diffraction to confirm the configuration. The corresponding acid **4.18** was synthesized by Pinnick oxidation.

4.4.2 Reagent Screening

Consequently, alcohol **4.17** and acid **4.18** were submitted to various epoxidation methods described in literature (Scheme 4.10). The conditions are summarized in table 4.4 and, if available, a literature example with a similar substrate is mentioned.

The electronic properties of this double bond are difficult to predict. Therefore, nucleophilic and electrophilic reagents were used. Furthermore, dihydroxylation reagents were also applied. Unfortunately, most reactions showed no conversion within several days and the reaction temperatures were stepwise increased until decomposition of the starting material was observed. With DMDO, interconversion of the alcohol to the acid was observed. However, none of the reactions showed even traces of the desired product.



Scheme 4.10: Unsuccessful epoxidation and halolactonisation of acid **4.18** and alcohol **4.17**. Applied reaction conditions are listed in table 4.4.

Alternatively, we attempted to form the second ring in an intramoleculat halolactonisation. These reaction conditions can be found in the table 4.4. As in the epoxidation, most reactions showed no conversion and were then pushed until decomposition of the starting material.

	With acid **4.18**	With alcohol **4.17**
Nucleophilic epoxidation	H_2O_2, NaOH[29,30]; H_2O_2, KOH; NaOCl, pyridine[31]; H_2O_2, TBAH; H_2O_2, H_2SO_4[32]; *t*BuOOH, triton B[33]; *t*BuOOH, DBU[34]	*t*BuOOH, BuLi[35]; *t*BuOOH, DBU[34]; H_2O_2, KOH
Electrophilic epoxidation	MCPBA; O_3; DMDO; peroxytrifluoroacetic acid; NaOCl, H^+; $KMnO_4$, cis-dicyclohexano-18-crown-6[36,37]	DMDO; OsO_4, $NaIO_4$[38]
Halolactonisation	I_2, $NaHCO_3$, AgOTs; $(SEt_2)I_2Cl_7Sb$[39]; NBS; TMSI, BBr_3	

Table 4.4: Reagents used for epoxidation and halolactonisation of acid **4.18** and alcohol **4.17**. No reaction showed traces of the desired product. The reaction temperatures were increased until decomposition of the starting material was observed. Analytics were conducted by TLC and UPLC-MS. If available, a literature example with a similar substrate is noted. The following reagents were synthesized or purified according to literature: MCPBA[40], DMDO[41], peroxytrifluoroacetic acid[42], $(SEt_2)I_2Cl_7Sb$[39].

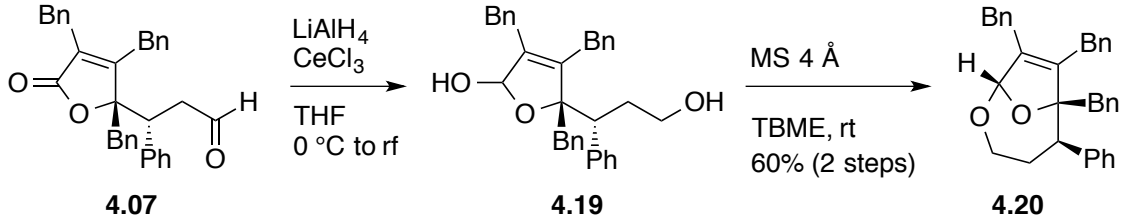
At this point of our investigations, it was not clear whether the lack of reactivity was caused by the steric repulsion or the electronics of the double bond. As it is not possible to remove any of the substituents in this stage of the synthesis, we changed the electronics of the double bond.

4.4.3 Oxidation of a More Electron Rich Substrate

One easy way to increase the electron density on the double bond is to reduce the adjacent carbonyl group. Cane *et al.* described this in an elegant way on a similar substrate.[43] After reduction to the lactone, the intermediate hemiacetal was used to direct a vanadyl acetylacetonate catalyzed allylic epoxidation. The lactol epoxide was consequently oxidized to the lactone with the Jones reagent.

The reduction of the aldehyde moiety was combined with the lactone reduction under Luche conditions (Scheme 4.11). While the first step worked well, the second step required more harsh conditions in refluxing THF to give lactol **4.19**. However, the consequential epoxidation with vanadyl acetylacetonate could not be achieved.

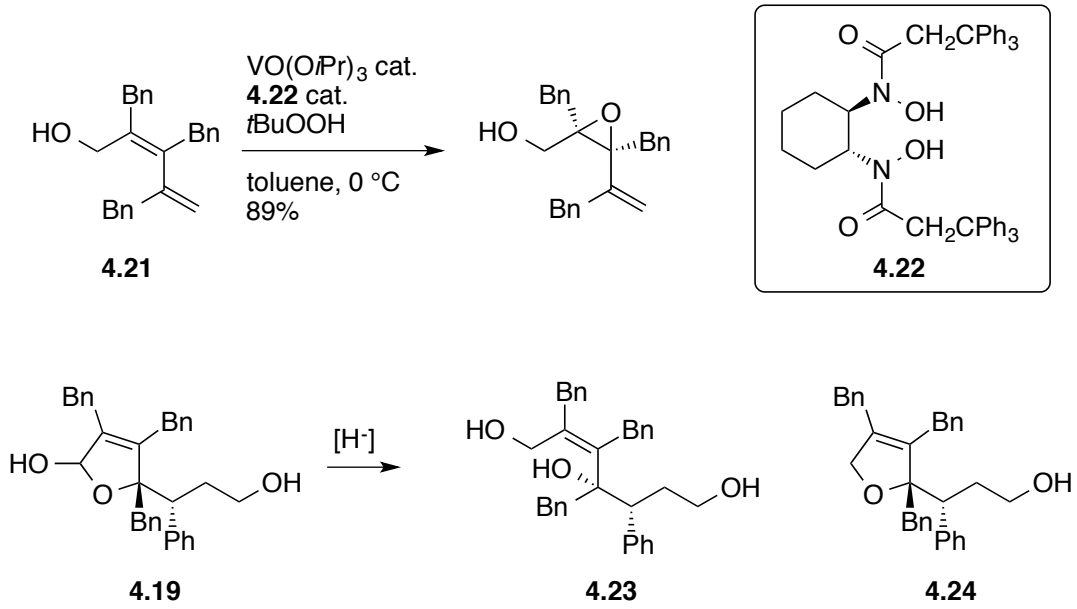
To test other epoxidation reagents, we attempted to isolate lactol **4.19**. Thereby, it was found to be unstable and reacted spontaneously to the bicyclical acetal **4.20** by dehydration. Stirring **4.19** in the presence of molecular sieves accelerated this process.



Scheme 4.11: Reduction of aldehyde **4.07** under Luche conditions. The formed lactol reacted spontaneously to acetal **4.20**, a process accelerated under dehydrating conditions.

Acetal **4.20** was then treated with the following reagents to achieve an epoxidation. If available, a literature reference with a similar substrate is given: MCPBA[44]; MCPBA, K_2CO_3[45,46]; DMDO; MCPBA, $NaHCO_3$, $Cu(ACN)_4PF_6$[47]; peroxyacetic acid, Na_2CO_3; O_3; $FeCl_3$, $NaIO_4$; $RuCl_3$, $NaIO_4$[48]; $RuCl_3$, $NaIO_4$, 2,2'-dipyridin[49]; OsO_4, $NaIO_4$; OsO_4, NMO[50]; peroxytrifluoroacetic acid, Na_2HPO_4; H_2O_2; H_2O_2, various acids and bases; H_2O_2, $MgBr_2$. Most of the reactions showed no conversion. Therefore, the temperature was increased until the starting material decomposed. In case of reactions with MCPBA or H_2O_2 with $MgBr_2$, alcohol **4.17** was formed.

Matsubara *et al.* were able epoxidize the similar but less complex intermediate **4.21** in a enantioselective reaction with a vanadyl complex at 0 °C in 6 days (Scheme 4.12).[4] In principle, a similar reaction might be possible, if the lactol **4.19** is further reduced to the expected ring open structure **4.23** with two allylic hydroxy groups.[51,52] However, further reduction of lactol **4.19** was found to lead instead to dihydrofuran **4.24**.

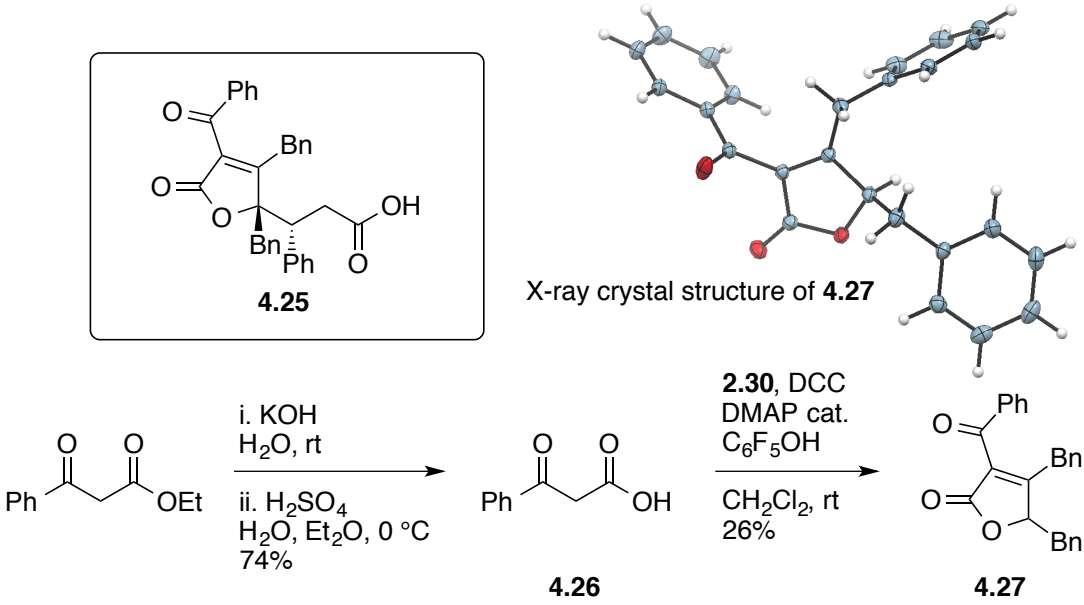


Scheme 4.12: Substrate **4.21** from the epoxidation in the total synthesis by Matubara *et al.*[4] Expected product **4.23** and found product **4.24** from a further reduction of **4.19**.

4.4.4 Oxidation of a Less Electron Rich Substrate

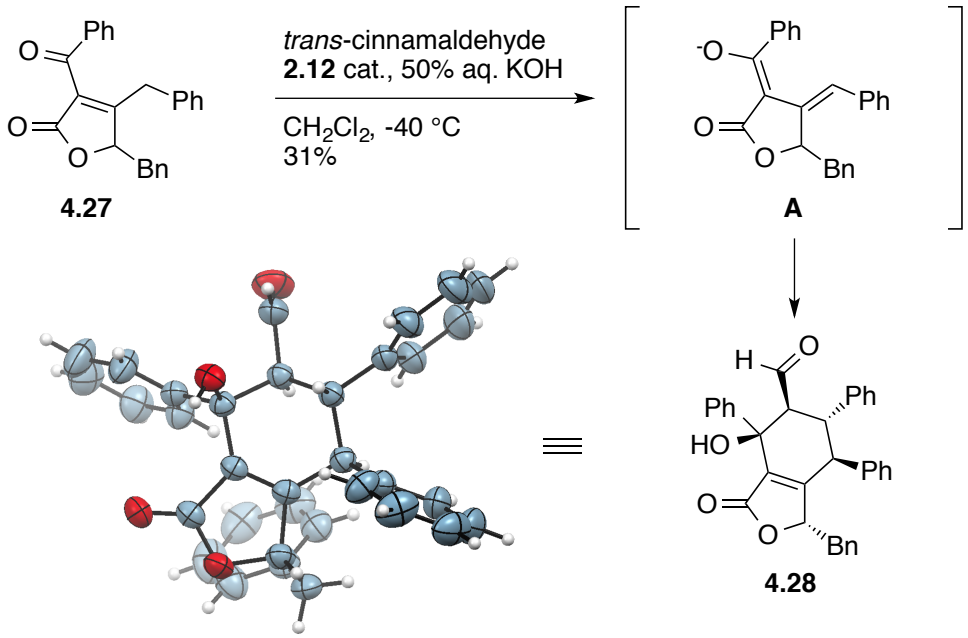
As the epoxidation of the more electron rich double bond was not successful, a new strategy with a more electrophilic double bond was developed. To accomplish this, a carbonyl functionality was introduced in the benzylic position, as depicted in intermediate acid **4.25** (Scheme 4.13). Such benzylic ketones or the corresponding alcohols can be deleted in the presence of aliphatic alcohols. As such an additional carbonyl group increases the reactivity of the substrate, we decided to introduce it in the beginning, as it will also promote the γ-lactone formation (Section 2.5) and the vinylogous Michael addition (Section 4.3).

With the additional electron acceptor, Maculalactone A derivative **4.27** could be synthesized by a standard Knoevenagel condensation (Section 2.5.1). Acid **4.26** was first synthesized as described by Cragg *et al.*[53] Subsequently, the free acid was esterificated with alcohol **2.30**, which was already used for our synthesis of maculalactone A (Section 2.5.2). While the ring-open ester was expected, the reaction conditions were surprisingly sufficient to form at least partially the Knoevenagel condensation product **4.27**. Therefore, the yield of this transformation was relatively low. However, lactone **4.27** was crystallized and analyzed by X-ray diffraction.



Scheme 4.13: Synthesis of more electron deficient lactone **4.25**. Synthesis of the corresponding maculalactone A derivative with X-ray crystal structure. Acid **4.26** was synthesized as described by Cragg *et al.*[53] Compound **2.30**, 3-oxo-3-phenylpropanoic acid, was already used in the synthesis of maculalactone A and was synthesized in accordance to a procedure by Stetter *et al.*[54] (Scheme 2.9).

Conducting the vinylogous Michael addition under the same conditions as for maculalactone A (**1.34**) (Section 4.3.3), yielded an unexpected product, with two aldehyde protons and the mass of double cinnamaldehyde addition. A reduction of the aldehyde excess to 1.2 equivalents prevented the double addition, affording a new product possessing the expected mass. The isolated product was analyzed and the structure was identified as aldehyde **4.28** (Scheme 4.14). This unexpected product **4.28** is either the result of a vinylogous Michael addition on the extra circular position followed by a Aldol reaction or a Diels-Alder reaction between deprotonated intermediate **A** and *trans*-cinnamaldehyde. To test this, the reaction temperature was decreased to – 40 °C. While reactions with maculalactone A showed no turn over at this temperature (Section 4.3.3), good conversion was achieved without increasing the reaction time. Additionally, only one diastereomer was observed. Product **4.28** was crystallized and analyzed by X-ray diffraction analysis. The configuration was in agreement with the outcome of a regular-demand endo-selective Diels-Alder reaction. Despite the use of chiral catalyst **2.12**, X-ray analysis and optical rotation revealed a racemic product.



Scheme 4.14: Transformation of maculalactone A analogue **4.27** with cinnamaldehyde to the unexpected product **4.28**. The stereochemistry was determined by X-ray diffraction analysis.

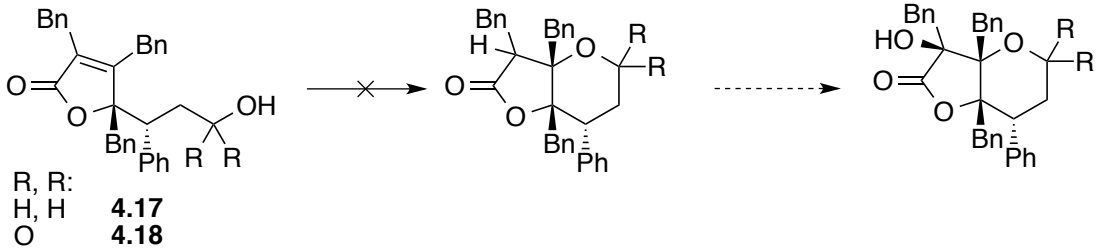
To overcome this predominant side reaction, other electrophiles as methyl *trans*-cinnamate and 3-phenyl-2-propenenitril were tested. As those showed no reactivity, singe phase systems with other bases were investigated. However, none of the expected products were observed.

4.5 Stepwise Oxidation of the Butenolide

In all previous strategies it was tried to oxidize the α- and the β-carbon of the butenolide simultaneously. Alternatively, this can be done in two separate steps, which was tried with the three following strategies.

4.5.1 Nucleophilic oxa-Michael Addition

In the first strategy, the β-carbon would be attacked in an oxa-Michael addition. The addition would be followed by a α-oxidation, for which different procedures by Rubottom and Davis are well known (Scheme 4.15).[55,56] Due to the higher nucleophilicity of hydroxy groups opposed to the corresponding carboxylate, using alcohol **4.17** in the oxa-Michael addition, would be beneficial. However, this would require a final oxidation of the oxane to the lactone, which would be achieved by a procedure with ruthenium(III) chloride described by Ramon *et al.*[57]



Scheme 4.15: Investigated intramolecular oxa-Michael addition with acid **4.18** and alcohol **4.17**. Applied reagents and conditions are discussed within the text.

Oxa-Michael additions with acids are much less known in literature, as carboxylic acids are usually bad nucleophiles. A thermal method used by Jaroszewski *et al.* was attempted first.[58] The neat acid **4.18** was warmed to 225 °C for 4.5 hours, but no reaction was observed. Also, heating with KOH in dioxane in the microwave to 200 °C showed only decomposition and none of the desired product.

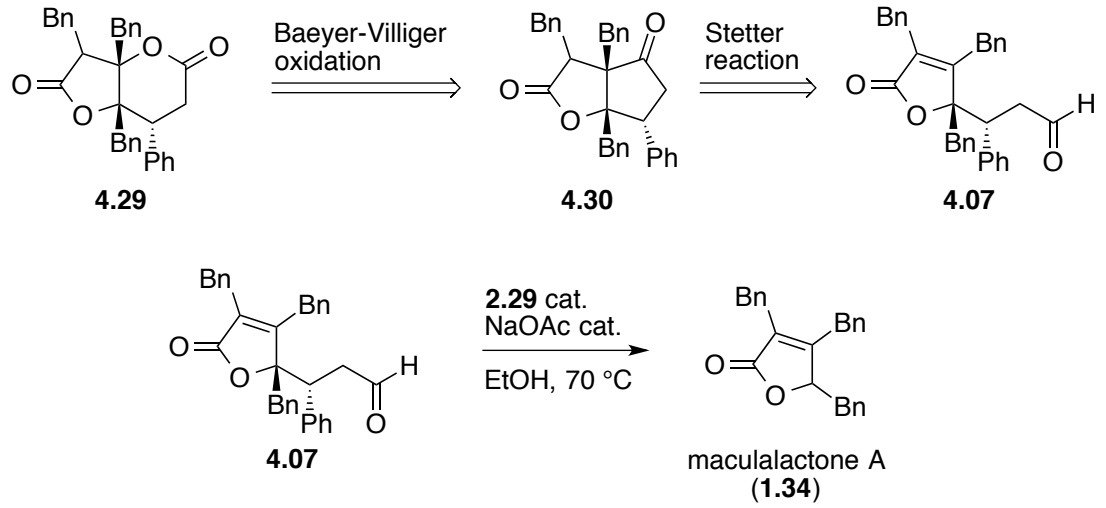
Oxa-Michael additions with hydroxy groups are better known. For example Blay *et al.* published an intramolecular addition to a butenolide.[59] Alcohol **4.17** was treated with different bases and acids to promote this reaction. All experiments showed no reactivity and were, therefore, heated until decomposition of the starting material was observed.

The driving force of these oxa-Michael additions was found to be too low to overcome the steric hindrance of the more rigid bicycle. In the accomplished total synthesis by Matsubara *et al*., the final nucleophilic attack of the acid on the more reactive epoxide in the same position required a temperature of 150 °C and gives a maximal yield of 55%.[4]

4.5.2 Umpolung Michael Addition

The low reactivity in the oxa-Michael addition due to the relative low nucleophilicity of the hydroxy group lead directly to a second indirect strategy. The idea was to use a more nucleophilic carbon nucleophile to attack the Michael acceptor (Scheme 4.16). This should deliver cyclopentanone **4.30**, which could be converted to δ-lactone **4.29** through a Baeyer-Villiger oxidation. However, this strategy requires Umpolung reactivity of the carbonyl group, resulting in a Stetter-type reaction.[60]

Under standard conditions with Stetter's thiazolium catalyst, aldehyde **4.07** was converted to maculalactone A (**1.34**) in a reversal of the vinylogous Michael addition. Other catalysts such as 1-butyl-3-methylimidazolium hexafluorophosphate led only to decomposition of the starting material.[61]



Scheme 4.16: Strategy for the synthesis of **4.31** by Umpolung and investigated Stetter reaction resulting in a retro vinylogous Michael addition giving maculalactone A (**1.34**). Compound **2.29** is Stetter's catalyst (3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride).

As a negative charge on the aldehyde carbon was not tolerated, another Umpolung strategy was employed. The carbonyl group was thereby reduced by a single electron transfer, giving the corresponding acyl radical. The additions of such nucleophilic radicals to Michael acceptors are well known in literature and samarium(II) iodide is often the reductant of choice.[62–64] Additional acyl radical generating reagents[65,66] and light induced[67–69] methods are known.

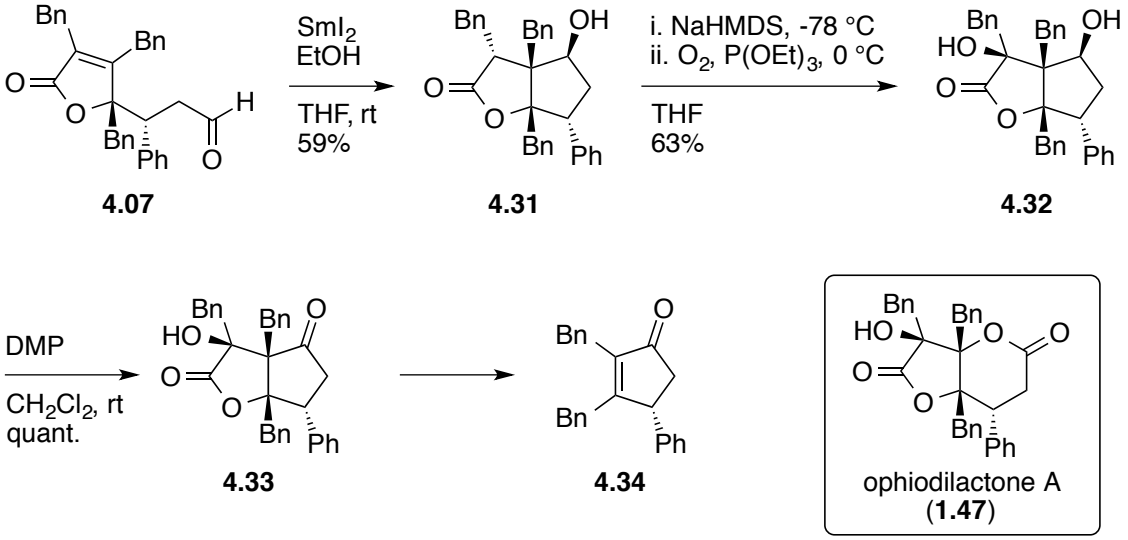
The reaction of aldehyde **4.07** with samarium(II) iodide afforded the desired product **4.31** in moderate yield (Table 4.5, Entry 1) (Scheme 4.17). The reaction conditions were further optimized. Reducing the reaction temperature and increasing the reaction time was found to be unfavorable (Entry 2). On the contrary, a shorter reaction time gave a higher yield (Entry 3). While the addition of HMPA led to a decrease in selectivity, ethanol as additive in small amounts showed a slightly positive effect (Entries 4 to 6). The samarium iodide solution was found to greatly influence the reaction. We attempted to titrate the reaction solution until the typical blue color persisted, but no improvement in yield was observed (Entry 7).

Entry	SmI_2 [eq.]	Additive (eq.)	Temp.	Time	Yield [%]
1	4	-	rt	4 h	41
2	4.9	-	-78 °C to rt	12 h	-[a]
3	4	-	rt	2 h	58
4	4	HMPA (40)	rt	1 h	-[b]
5	4	EtOH (1.2)	rt	20 min	59
6	4	EtOH (5)	rt	20 min	31
7	titr.[c]	-	60 °C	10 min	-[b]

Table 4.5: Optimization of the samarium(II) iodide induced radical Michael addition of **4.07** to **4.31**. Samarium(II) iodide was synthesized as described by Procter.[70] Reactions were conducted in dry THF. [a]No reaction observed. [b]Product formation observed, but in low purity and not isolated. [c]The reaction was titrated with samarium(II) iodide until the blue color persisted for two minutes.

As a next step, the α-position of lactone **4.31** was oxidized. While the reaction with the Davis reagent resulted in a mixture of products, another procedure with molecular oxygen, applied by Zhang *et al.* to solve a similar problem, gave diol **4.32** in good yield.[71] Conducting the oxidation at -78°C resulted surprisingly in the undesired diastereomer.

The intermediate product of the SmI_2-induced addition before quenching is, in principle, the corresponding samarium enolate. A direct oxidation of the intermediate with oxygen was found to give directly diol **4.32**, but lactone **4.31** was observed as the main product. A similar reaction with a different substrate has been published by Shi *et al.*[72]

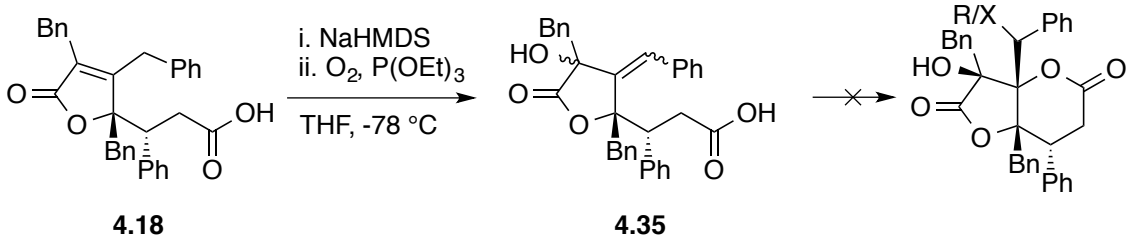


Scheme 4.17: Synthesis of precursor **4.33** by radical Michael addition, α-oxidation and DMP oxidation. The final Baeyer-Villiger rearrangement showed no reaction in the most cases and in others decomposition to ketone **4.34**. The applied conditions are listed in the text. The diastereomeric compounds of **4.31** and **4.32** were observed, but not completely characterized.

To set the stage for the Baeyer-Villiger oxidation, diol **4.32** was converted to the corresponding ketone **4.33** by oxidation with DMP. With ketone **4.33** in hand, different procedures for the Baeyer-Villiger oxidation were tested. The following conditions were tried: MCPBA, TfOH[73]; MCPBA, K_2CO_3[74]; MCPBA (s)[75]; peroxytrifluoroacetic acid; peroxytrifluoroacetic acid, KH_2PO_4[76]; peroxyacetic acid; H_2O_2, KOH, but they were not sufficient to form ophiodilactone A (**1.47**). In some reactions, decomposition product **4.34** was observed.

4.5.3 α-Oxidation

A third strategy beginning with an oxidation in the α-position was investigated (Scheme 4.18). We expected to deprotonate acid **4.18** and perform the α-oxidation under the same conditions discussed in section 4.5.2. While acid **4.35** was observed by NMR and MS, we were unable to remove an unidentified impurity for a proper characterization of the product. This prevented us from being able to determine the relative configuration of the formed stereocenters.



4.18 **4.35**

Scheme 4.18: Oxidation of acid **4.18** to intermediate **4.35**. The following addition to the double bond was not achieved. The applied reagents for the second step are listed in the text.

Due to the issues encountered with isolating intermediate acid **4.35**, we attempted to proceed with the cyclization. Different tactics were applied to facilitate the addition to the allylic double bond. However, none of the following conditions showed any conversion to the expected products: PTSA; TFA; H_2SO_4; I_2, K_2CO_3; NBS; $HgTFA_2$[77]; $(SEt_2)I_2Cl_7Sb$[39]; PhSeBr, $AgBF_4$[78]; BF_3*Et_2O; Au(I)PPh_3Cl, AgOTf[79]; $FeCl_3$[80]; $FeCl_3$, AgOTf[80]; Pd(II)OAc_2; Rh(I)PPh_3Cl.

4.6 Conclusion

The described synthetic strategy allowed us to synthesis the carbon skeleton of ophiodilactone A (**1.47**) in 5 steps from commercially available starting materials. This was achieved by the addition of cinnamaldehyde to maculalactone A (**1.34**) in a vinylogous Michael addition. Use of a chiral phase transfer catalyst in this step allowed us to obtain the product in an enantiomeric excess of 68%. Furthermore, a second vinylogous Aldol reaction, forming bicycle **4.14**, was observed. This cyclization could be a key step in the synthesis of maculalactones D – K and M (Chapter 6).

We attempted a variety of approaches and conditions to accomplish the required oxidation of the butenolide double bond. We initially tried to oxidize the double bond by an epoxidation or dihydroxylation method. As this was not successful, an alternative halo-lactonisation pathway was investigated. However, none of these methods were able to functionalize the double bond.

In a different approach, we tried to alter the electronic properties of the double bond. First, the electron density on the olefin was increased by reduction to lactol **4.19**, which dehydrated spontaneously to acetal **4.20**. Despite the higher electron density, oxidation of the double bond could not been achieved. Consequently, we decreased the electron density by adding a conjugated carbonyl group to the substrate. In the synthesis of the

required ketone **4.25**, the introduced group influenced the addition to cinnamaldehyde in a way to give unexpected bicycle **4.38**.

In the third attempt, we tried to oxidize the two carbons of the double bond individually. We first tried a oxa-Michael addition. As no conversion was achieved, a Stetter-type addition with a carbon nucleophile was attempted. Finally, the formation of bicycle **4.31** was achieved after single electron reduction with samarium(II) iodide. We then tried to convert cyclopentanone **4.33** to ophiodilactone A (**1.47**) by a Baeyer-Villiger oxidation. However, no conversion was observed. Finally, the α-carbon of the butenolide was oxidized, causing a migration of the double bond to an exocyclic benzylic position, forming **4.35**. Unfortunately, all attempts to close the second lactone by addition to this double bond failed.

While the carbon skeleton of ophiodilactone A was established in 5 steps, it was not possible to conduct the required oxidation in this late stage. Therefore, the required oxidations should be conducted in an earlier stage on less complex substrates, as Matsubara *et al.* did in their successful total synthesis.[4]

4.7 References

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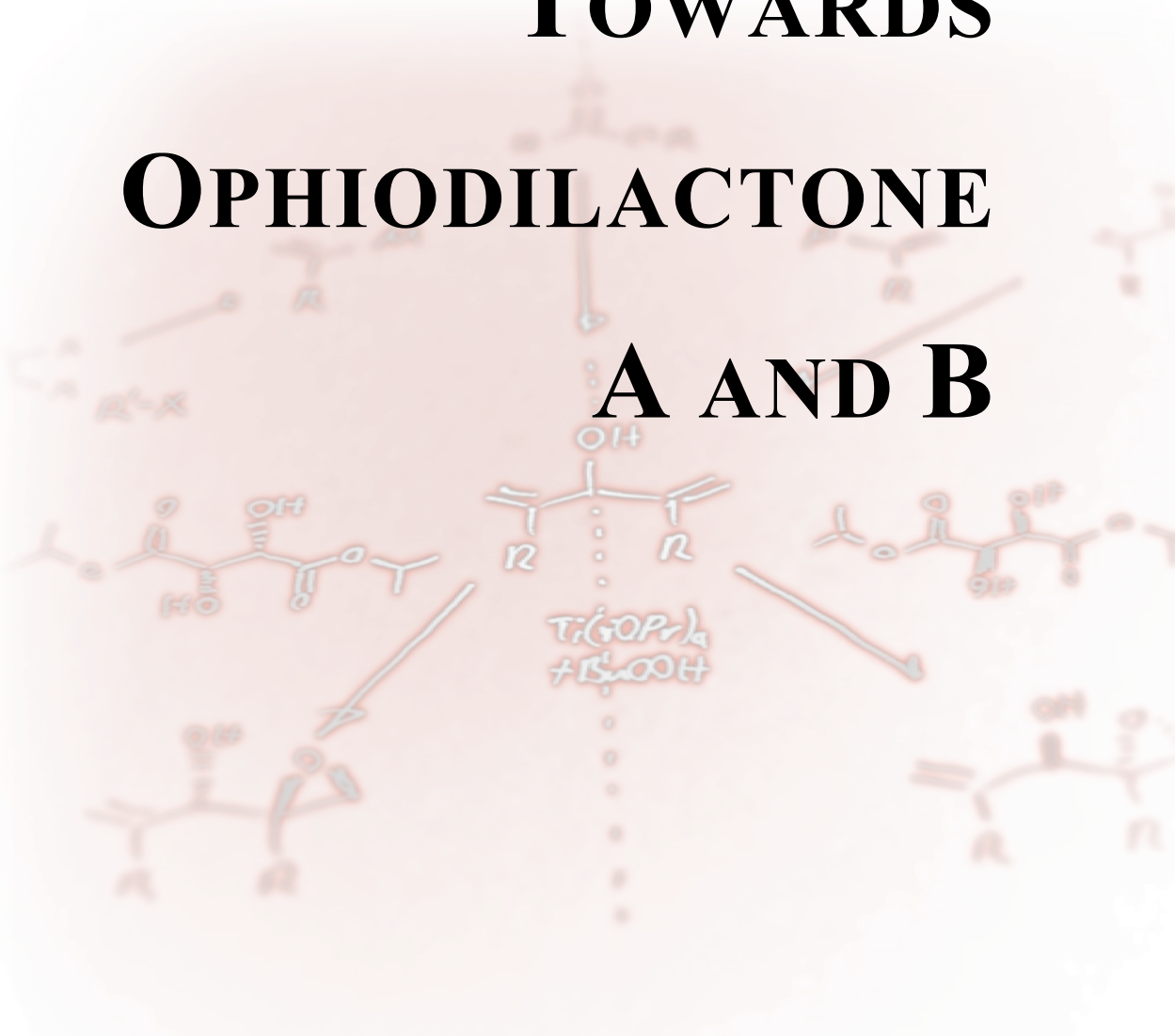
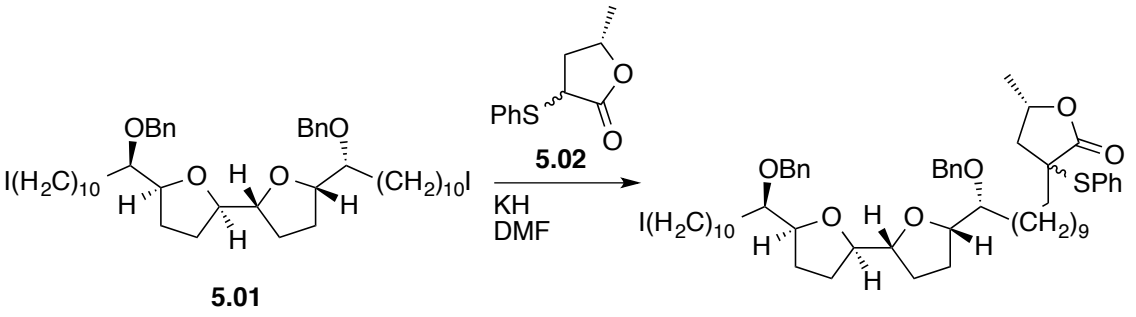
5 - Studies on a Linear Approach Towards Ophiodilactone A and B



5.1 Introduction

5.1.1 Enantioselective Synthesis by Desymmetrization

Towards the end of the last century, the Schreiber research group developed a novel method for the synthesis of carbon chains with repeating elements.[1] In contrast to the general strategy where a precursor is elongated in one direction, they proposed a bidirectional concept. Therefore, a central building block is simultaneously elongated in both directions, reducing the number of required steps by half. However, most of the synthetic targets have asymmetric chains or different chain ends. Therefore, the generated symmetrical carbon chain is desymmetrized by an appropriate and, mostly, enantioselective method. Advantageous is not only the reduced number of steps, but in some cases also the higher enantiomeric purity, as pointed out in section 5.1.2.



Scheme 5.1: Desymmetrization in the total synthesis of 14,21-*diepi*-squamocin-K.[2]

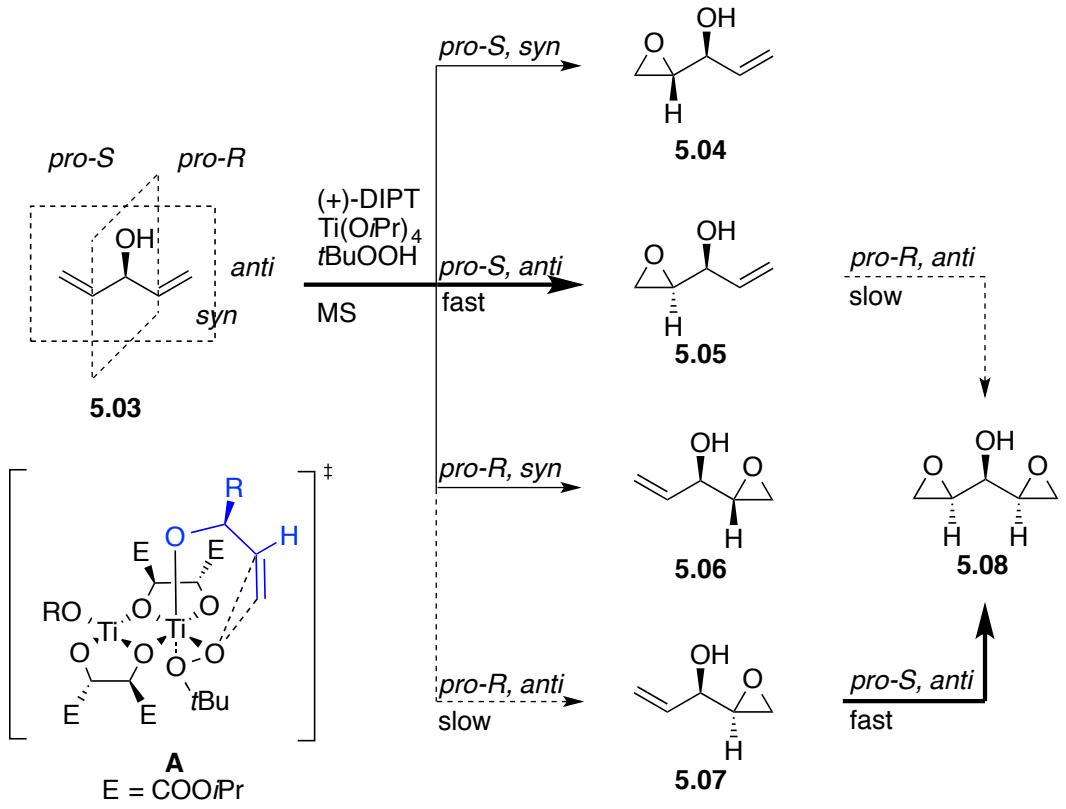
Recently, the group of Hou applied this strategy in their impressive total synthesis of 14,21-*diepi*-squamocin-K (Scheme 5.1).[2] The *meso* symmetric precursor **5.01** was synthesized in 13 steps by simultaneous elongation in both directions. The desymmetrization was accomplished by an enantioselective substitution with the chiral lactone **5.02**. The total synthesis of 14,21-*diepi*-squamocin-K was finished within another four steps. In addition to linear chains like **5.01**, this strategy was also applied in the synthesis of complex non-linear structures.[3,4]

5.1.2 Desymmetrization by Sharpless Epoxidation

Among the class of catalytic, enantioselective reactions, the Sharpless epoxidation is one of the most used.[5] Advantages include the inexpensive commercially available pre-catalyst, ligand and oxidant, as well as the usually high substrate scope, yield and enantioselectivity. Consequently, Sharpless epoxidations are regularly employed in total

synthesis. Additionally, various groups have used and studied the desymmetrization of bisallylic alcohols.[6–10]

Schreiber has made significant contributions to this field (Scheme 5.2).[7] The studied epoxidation of bisallylic alcohol **5.03** can in principle result in four different products (**5.04** to **5.07**). These products result from whether the oxygen adds to the right (*pro-R*) or to the left (*pro-S*) double bond and it comes from the same side as the alcohol (*syn*) or the other side (*anti*). The *anti* and *syn* products are enantiomers of each other.



Scheme 5.2: Desymmetrization of bisallyl alcohol **5.03** by Sharpless epoxidation through transition state **A,** substrate in blue.[7,11]

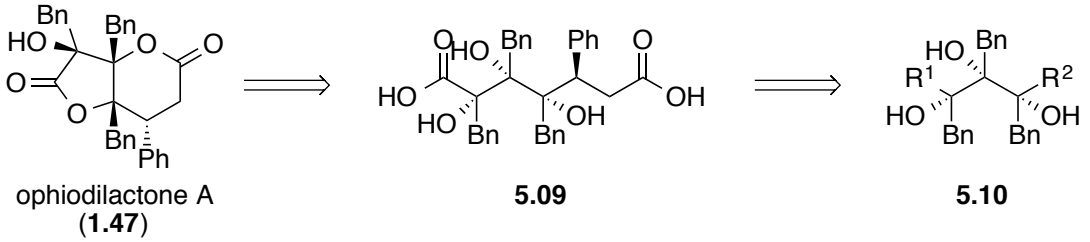
The reaction rates of this enantio- and diastereoselective process toward each of the four products are different, which is reflected in the product distribution. These reaction rates are a result of the stability of transition state **A**. The chiral information of the tartaric ester differentiates between the *pro-S* and *R* sides. The steric repulsion between residue R and the isopropyl ester is reduced if the *pro-S* face is attacked. With this catalyst control, the formation of product **5.05** is faster than the one of enantiomeric **5.07**. In such bisallyl desymmetrizations, the enantiopurity is further increased if the reaction is run past completion of the first epoxidation. Since the second epoxidation of **5.05** has to occur on the *pro-R* face, it is slow compared to the one of **5.07**. Therefore,

the undesired enantiomer is more quickly converted to bisepoxide **5.08**, which can be removed by chromatography.

In contrast to the enantioselectivity, the diastereoselectivity relays on the orientation of the double bond to the substrates alcohol group in the transition state. Usually, both groups are on the same side as shown in **A** and the addition occurs from the backside in an *anti* fashion. As the *syn*/*anti* selectivity is controlled by the substrate, different substituents can influence the selectivity. In the upper example from Schreiber *et al.*, none of the *syn* products **5.04** and **5.06** were observed.

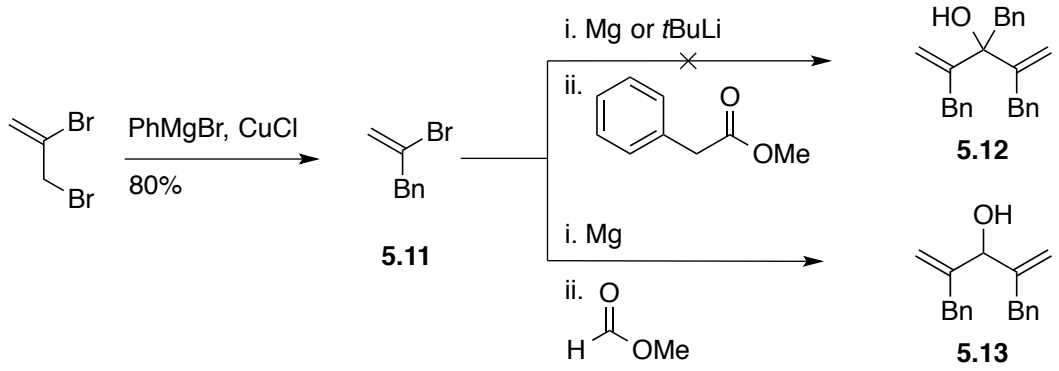
5.1.3 Asymmetric Routes Towards Triol 5.10

Ophiodilactone A (**1.47**) can be traced back to the linear precursor **5.09** by cleavage of the lactone bonds (Scheme 5.3). The central section **5.10** of this linear precursor shows C_s-symmetry, making it achiral. Thus, we postulated to synthesize ophiodilactone A through a desymmetrization process, potentially using Sharpless epoxidation.[5]



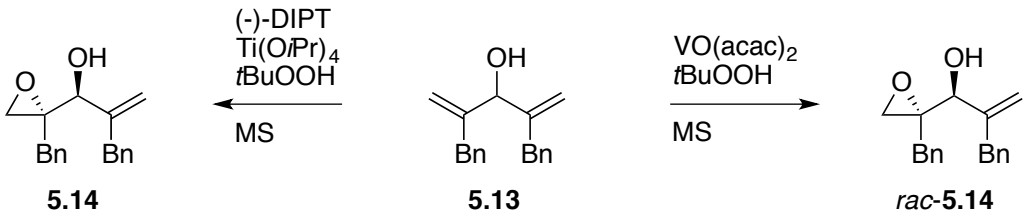
Scheme 5.3: Symmetric elements of ophiodilactone A.

In a previous work by Jean-Yves Wach, we first attempted the synthesis of a desymmetrized analogue of **5.10**.[12] While two desymmetrization approaches over cyclic intermediates were unsuccessful, a linear precursor was found to be an appropriate candidate for the desymmetrization by epoxidation (Scheme 5.4). Vinyl bromide **5.11** was synthesized by a procedure published by Breit *et al.*[13] The bromide was then converted into both a Grignard reagent and an organo lithium reagent, and consequently added to methyl 2-phenylacetate. Unfortunately, none of product **5.12** was obtained. The acidic, benzylic protons of methyl 2-phenylacetate were suggested to protonate the organometallic reagent. Luckily, the less complex bisallyl alcohol **5.13** could be synthesized, as described in literature.[13]



Scheme 5.4: Synthesis of symmetric intermediate **5.13**.[12]

Subsequently, intermediate **5.13** was desymmetrized in a Sharpless epoxidation (Scheme 5.5).[12] While first experiments with sub-stoichiometric amounts of catalyst were unsuccessful, the desired epoxide **5.14** was isolated with high diastereoselectivity and sufficient yield when 1.1 equivalents of titanium(IV) isopropoxide were used. Racemic epoxide **5.14** was synthesized by a diastereoselective epoxidation with vanadyl acetylacetonate. However, the analytical separation of the enantiomers by chromatography failed. Furthermore, all attempts to open the epoxide with a nucleophile were unsuccessful.

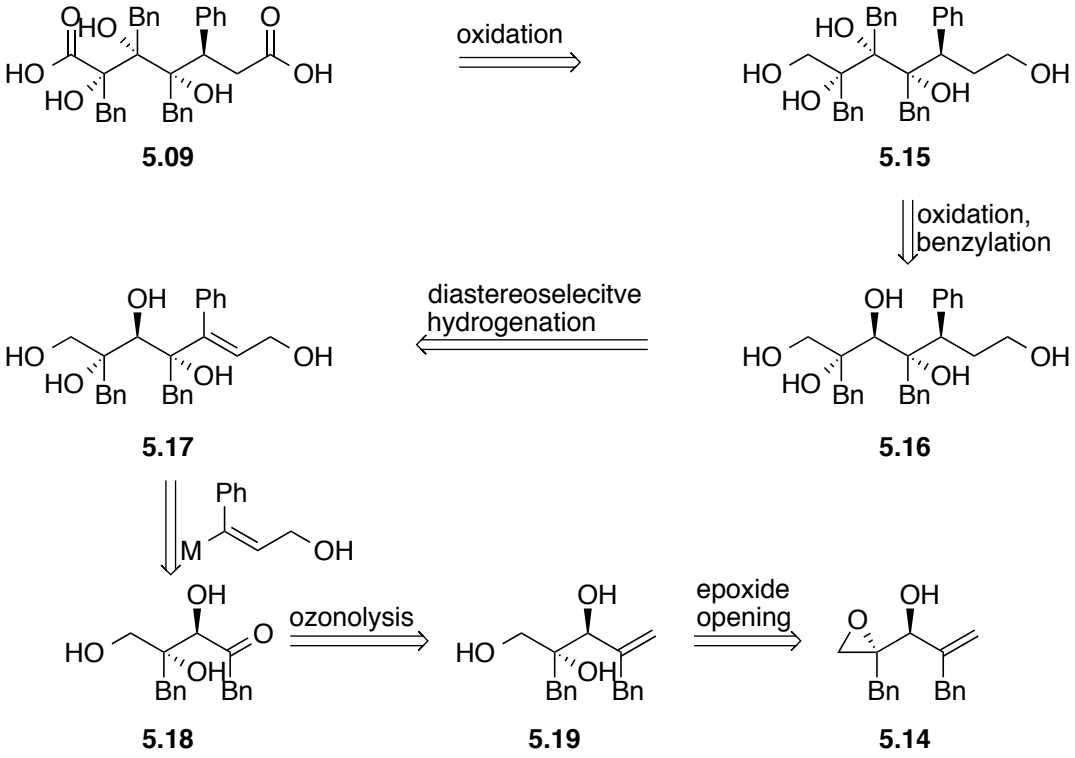


Scheme 5.5: Desymmetrization of **5.13** by Sharpless epoxidation.[12]

5.2 Synthetic Strategy by Desymmetrization

Based on these early findings, a route towards ophiodilactone A (**1.47**) through linear precursor **5.09** was developed (Scheme 5.6). The bisacid would be formed by oxidation of the primary alcohols of **5.15**. This compound would be accessible by oxidation of the secondary alcohol and subsequent benzylation of compound **5.16**. In principle, the stereoselectivity of the secondary alcohol in **5.16** is not essential, but would be determined by the *anti* selectivity of the Sharpless epoxidation. The phenyl stereocenter would be established by a selective hydrogenation of alkene **5.17**. This olefin itself would result from elongation of ketone **5.18** by an appropriate organometallic reagent.

The ketone can be formed by ozonolysis of **5.19**, following the epoxide opening of the Sharpless epoxidation product **5.14**.



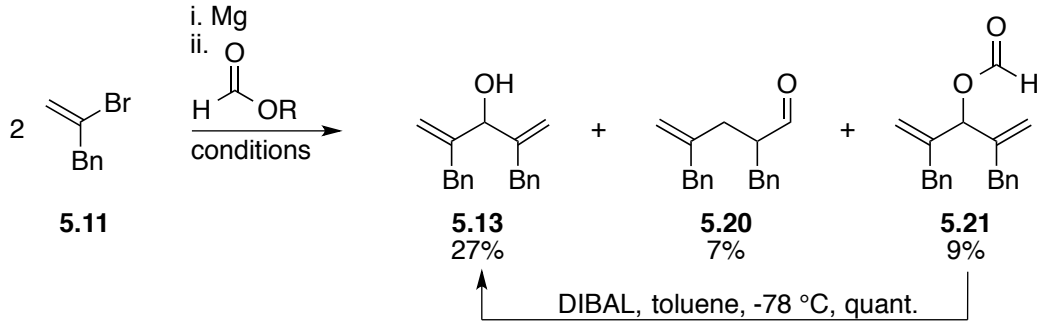
Scheme 5.6: Retro synthesis of Ophiodilactone A (**1.47**) and B (**1.48**).

5.3 Improved Synthesis of Symmetric Alcohol 5.13

5.3.1 Optimization of the Established Synthesis

While literature describes the synthesis of symmetrical intermediate **5.13** in high yield, we had reproduction issues in our lab.[12,13] The synthesis of vinyl bromide **5.11** gave similar yields, but the double Grignard addition resulted in a significantly lower yield with varied reproducibility (Scheme 5.7). In our investigations, two major side products were identified. While the 1,4-addition product **5.20** was expected, albeit in smaller quantities, we were surprised by the formation of transesterification product **5.21**. Varying the reaction temperature and time gave no improvements, so we focused on the nature of the nucleophile. We postulated that solvent stabilization of the nucleophilic center was decreased by changing the solvent from THF to Et_2O, and later to mixtures with toluene. While the resulting "harder" nucleophile should favor the 1,2-addition, no improvement was made. Filtration of the Grignard reagent had no positive effect either. In a next step, additives like LiCl, LaCl and $FeCl_3$ were employed

without any improvement of the yield. The use of *tert*-butyl formate showed no beneficial effect too.

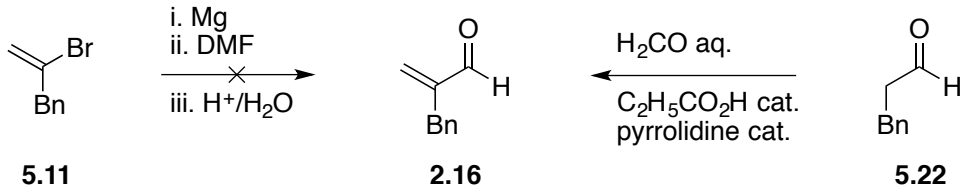


Scheme 5.7: Problematic double Grignard addition affording **5.13,** and side products **5.20** and **5.21**. Different reaction times and temperatures, solvents (Et_2O, THF, toluene), additives (LiCl, LaCl, $FeCl_3$) and electrophiles (R = Et, *t*Bu) were tested.

Despite our unsuccessful attempts to improve the reaction, the identification of ester **5.21** allowed us to transform this side product to the desired bisallyl alcohol through a quantitative reductive ester cleavage.

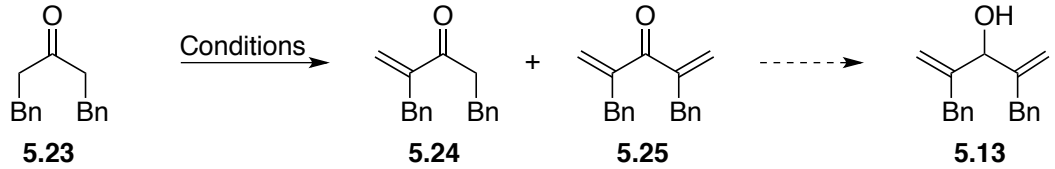
5.3.2 Synthesis of Bisallyl Alcohol 5.13

Our initial goal was to separate the two addition steps of the described Grignard reaction to better understand the chemistry and to potentially identify the synthetic problem (Scheme 5.8). Therefore, the vinyl Grignard reagent was added to DMF to give the desired unsaturated aldehyde **2.16**. Since this addition failed, a procedure published by Pihko *et al.* through a Mannich reaction was applied, to afford aldehyde **2.16** in excellent yield.[14]



Scheme 5.8: Synthesis of intermediate **2.16** by Mannich reaction.[14] For the Grignard reaction, the same conditions as for the reaction with ethyl formate were applied.

The facile Mannich reaction inspired us to change our synthetic route to bisallyl alcohol **5.13** (Scheme 5.9). Ketone **5.23** was synthesized from 1,5-diphenylpenta-1,4-dien-3-one by hydrogenation.[15] When we applied the conditions described by Pihko to this substrate, no conversion was observed (Table 5.1, Entry 1). This was likely due to the lower acidity of the ketone as compared to the aldehyde.



Scheme 5.9: Synthesis of bisallyl alcohol by double Mannich reaction and subsequent reduction. The attempted reaction conditions are listed in table 5.1.

We considered other methods to transform the ketone. While the conditions described by Connell *et al.*[16] gave no conversion (Entry 2), a reaction described by the group of Agosta[17] showed the formation of the mono-methylenated product **5.24** (Entry 3). Despite various modifications, none of the doubly reacted product **5.25** could be observed (Entries 4 and 5).

Entry	Catalyst	Solvent	Temperature [°C]	Time [h]	Product / Yield
1[a]	Pyrrolidine, propionic acid	*i*PrOH	50	72	No conversion
2[b]	$(i\text{Pr})_2\text{NH}$, TFA	Toluene	100	72	No conversion
3[a]	Piperidine, HCl	-	80	65	Traces **5.24**
4[a]	Piperidine, HCl	-	120	20	15% **5.24**
5[a]	Piperidine, H_2SO_4	-	120	72	No conversion
6[a]	Morpholine	AcOH	100	12	20% **5.24** and traces **5.25**
7[a]	Morpholine	AcOH	40 to 100	42	Slow conversion
8[b]	Morpholine	AcOH	80	12	No conversion
9[a]	Morpholine	AcOH	150	3	29% **5.25**
10[a]	Morpholine	AcOH	150[c]	1	Slow conversion

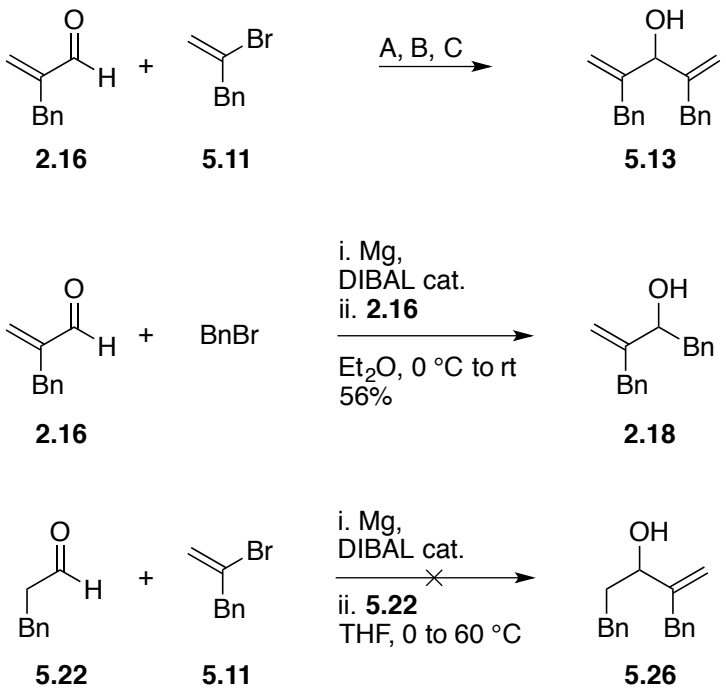
Table 5.1: Optimization of the double Mannich reaction. Conditions: [a]37% aq. formaldehyde, [b]paraformaldehyde, [c]Reaction performed in the microwave.

Finally, a procedure described by Moran *et al.* using morpholine as catalyst and acetic acid as solvent promoted not only fast conversion to **5.24**, but also traces of the desired product (Entries 6 to 8).[18] We postulated that a fast elimination of the amine following the initial addition drives the reaction to promote double methylenation. This

elimination is accelerated either by higher temperatures or by a lower pH. By heating the reaction for three hours to 150 °C, the desired product was isolated in a yield of 31% (Entry 9). As the yield after several optimizations was still low, the synthesis of bisallyl alcohol **5.13** by Mannich reaction was found to be not feasible. However, we were successful in developing this rare double Mannich reaction, affording product **5.25** in 31% yield.

5.3.3 Asymmetric Synthesis of Bisallyl Alcohol 5.13

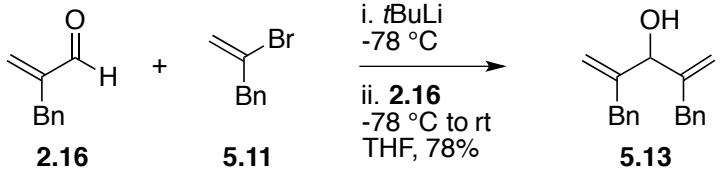
As the synthesis of bisallyl alcohol **5.13** by a double Mannich reaction was inefficient, we continued our investigations of the double Grignard reaction described in section 5.3.1. We attempted the addition of vinyl bromide **5.11** to aldehyde **2.16** under a variety of conditions (Scheme 5.10). While conditions similar to the prior reaction with ethyl formate gave comparable yields, an experiment under Barbier conditions did not show any conversion.



Scheme 5.10: Investigation on the second addition of the vinyl Grignard reagent. A: Mg, Et_2O, 0 °C to rt, 14%; B: Mg, DIBAL cat., THF, 0 to 60 °C, 12%; C: Zn, THF, NH_4Cl, EtOAc, rt, no conversion.

We then investigated the influence of the double bonds. The benzyl Grignard reaction with unsaturated aldehyde **2.16** proceeded in a good yield of 56%, but no expected allyl alcohol **5.26** was observed when the vinyl Grignard reagent was added to the simplified aldehyde **5.22**.

At this point, we identified the Grignard reagent as the problem. While it was known that the vinyl lithium reagent of **5.11** could not be added to ethyl formate,[12] the reaction proceeded with the more electrophilic aldehyde **2.16** in 78% yield (Scheme 5.11).



Scheme 5.11: High yielding synthesis of symmetrical bisallyl alcohol **5.13** from **2.16** prepared as described by Pihko *et al.*[14] and **5.11** prepared as described by Breit *et al.*[13]

5.4 Desymmetrization by Sharpless Epoxidation

We wanted to investigate the influence of the tartaric ester on the enantioselectivity of the Sharpless epoxidation (Table 5.2). The enantioselectivity was improved by the use of diisopropyl tartrate as observed in literature.[19] Using cumene hydroperoxide instead of *tert*-butyl hydroperoxide showed no improvements with our substrate.[6]

Entry	Additive	Reaction time [h]	Yield [%]	*ee* [%]	α_D (c, solvent)
1	DET	44	75	71	
2	DIPT	17	68	87	
3	DIPT	60	60	84	+21.5° (0.57, $CHCl_3$)

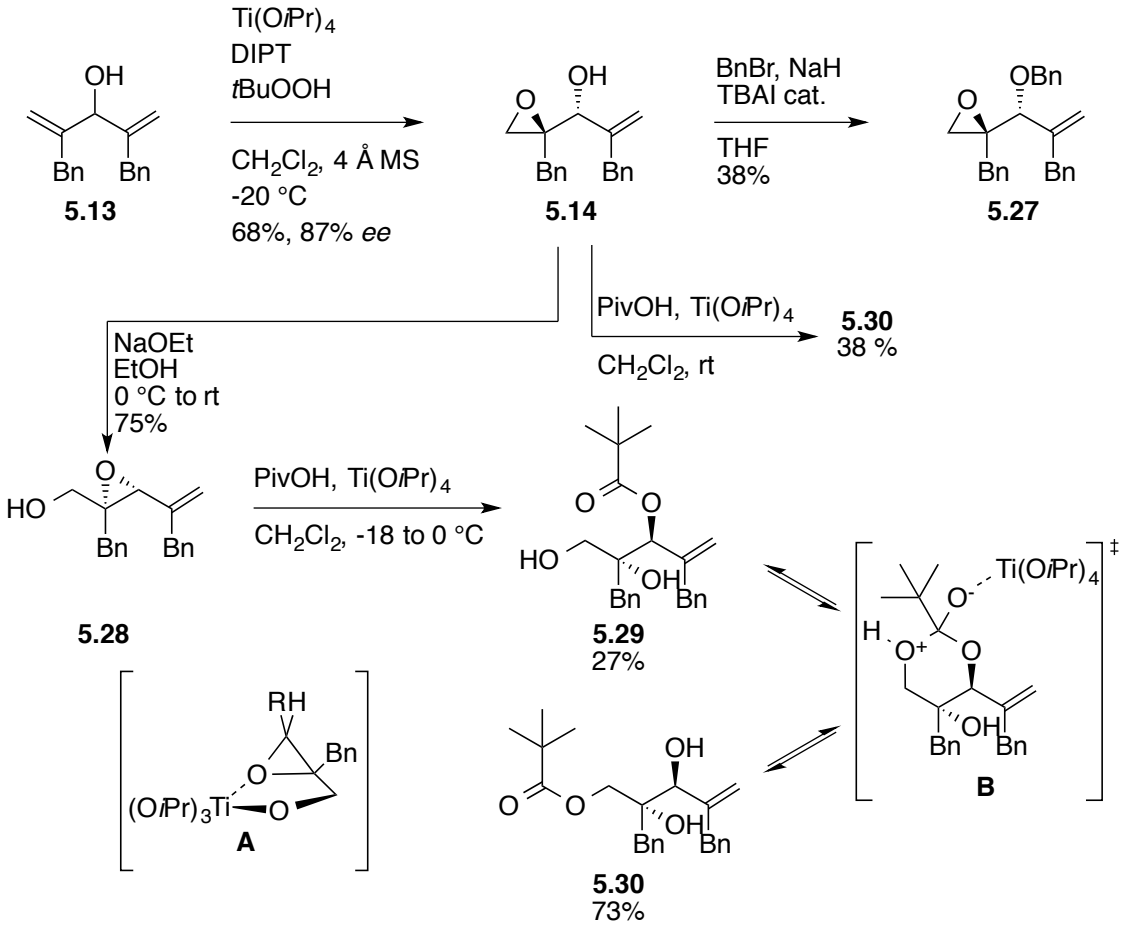
Table 5.2: Enantioselectivity of Sharpless epoxidation with diethyl tartrate (DET) and diisopropyl tartrate (DIPT). Conditions: 2.00 eq. *t*BuOOH, 1.10 eq. Ti(O*i*Pr)$_4$, 1.30 eq. DET/DIPT, pulverized molecular sieves, CH_2Cl_2, -20 °C.

5.5 Nucleophilic Epoxide Opening

As discussed in section 5.1.3, the ring opening of the epoxide **5.14** was unsuccessful in previous studies.[12] Additionally, procedures utilizing TBAF[20] and titanium(IV) isopropoxide[10] failed to give conversion to the desired product. However, the protection of the hydroxy group to give ether **5.27** was facile (Scheme 5.12).

Many literature examples describe a higher reactivity of the epoxide after a Payne rearrangement.[5,19,21] While some groups found the Payne rearrangement to be a spontaneous process in the hydrolysis of the Sharpless reaction, our substrate required stronger conditions. Using sodium hydroxide as base in a mixture of water and

methanol at 50 °C, the reaction required 30 hours for completion. Other bases as sodium hydride and triethylamine did not show any conversion. Finally, sodium ethoxide in ethanol at room temperature was found to give the rearranged epoxide **5.28** in 3.5 hours at an acceptable yield of 75%. An alternative where the Sharpless reaction was quenched with aqueous sodium hydroxide and methanol to trigger a direct Payne rearrangement, required 50 °C and four days for complete conversion, giving only 37% of the rearranged product **5.28**.



Scheme 5.12: From bisallyl alcohol **5.13** to the pivaloyl protected triol **5.30**. Intermediate **A** shows the activation in the epoxide opening.[22] Transition state **B** is part of the 1,3 ester shift.[24] Ester **5.29** rearranged spontaneously at ambient conditions and could only be characterized after protection of the diol giving **5.45**.

In literature, titanium(IV) isopropoxide has been found to be superior in the opening of hydroxy epoxides.[9,10,22] This is explained by a simultaneous coordination of titanium to the alcohol and the oxirane oxygen, thereby activating the leaving group as depicted in intermediate **A**. By this method, the epoxide could be opened with pivalic acid (Table 5.3, Entry 1). However, the product was not the expected ester **5.29**, but isomer

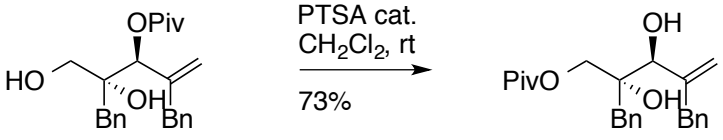
5.30 with the ester on the terminal position. Such 1,3-shifts of esters are known in literature and may occur over the transition state **B**.[23,24]

From a strategic point of view, this rearrangement is in our favor as it was part of the synthetic strategy to install a pivaloyl ester in the terminal position. Due to the Payne rearrangement, this transformation occurs with retention, changing the absolute configuration of the product. Therefore, parts of the studies were conducted with the undesired enantiomer.

Entry	PivOH [eq.]	Catalyst (eq.)	Solvent	Temperature [°C]	Yield **5.29**, **5.30** [%]
1	1.3	Ti(O*i*Pr)$_4$ (1.5)	Toluene	rt	-, 22
2	1.3	TiCl(O*i*Pr)$_3$ (1.5)	Benzene	rt	0, 0[a]
3	3.0	Ti(O*i*Pr)$_4$ (1.7)	CH_2Cl_2	0 to rt	20, 52
4	3.0	Ti(O*i*Pr)$_4$ (2.0)	CH_2Cl_2	-18 to 0	27, 73

Table 5.3: Opening of epoxide **5.28** by pivalic acid (PivOH). [a]An unknown product was formed.

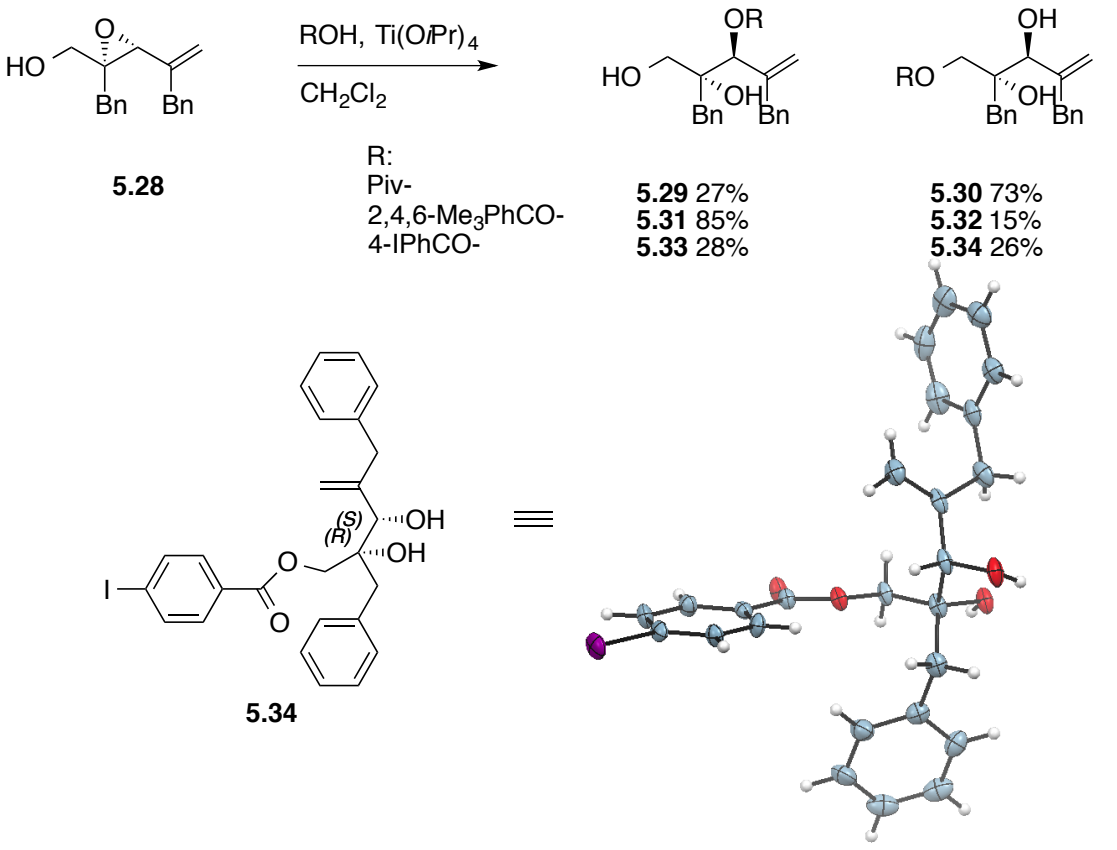
Unfortunately, epoxide opening with the more reactive TiCl(O*i*Pr)$_3$ gave an unknown product (Entry 2). Consequently, the reaction conditions were optimized by changing the solvent to CH_2Cl_2 and lowering the temperature to obtain quantitative conversion (Entries 3 and 4). These optimized reaction conditions were tested for the opening of the not rearranged epoxide **5.14**. Although the reaction required higher temperatures and a longer reaction time, 38% of the terminal pivaloyl ester **5.30** was isolated. However, the isolated product showed a similar optical rotation of α_D = -18.3° (0.58, $CHCl_3$) to the same product synthesized over the Payne rearrangement. Therefore, the direct reaction from the terminal epoxide **5.14** proceeds over the same intermediates, resulting in inversion. Furthermore, intermediate **5.28** could be observed in the reaction mixture.



5.29 **5.30**

Scheme 5.13: Isomerization of **5.29** to the thermodynamically favored **5.30** with PTSA in three days.

While the terminal pivalic ester **5.30** was isolated in high purity as a white solid, not rearranged **5.29** was unstable at ambient conditions. Locking the ester group by the protection of the remaining hydroxy functions enabled us to isolate and characterize compound **5.45**. However, the terminal ester seems to be the thermodynamically favored product. Therefore, the isomerization of ester **5.29** to **5.30** seemed feasible (Scheme 5.13). While carboxylic acids were not strong enough to accelerate the rearrangement, TFA and PTSA showed from the beginning fast conversion. With PTSA, about three days were required for the isomerization to go to completion. The long reaction time caused degradation, decreasing the isolated yield of **5.30** to 73%. A similar reaction with titanium(IV) isopropoxide over three days resulted in decomposition.



Scheme 5.14: Epoxide opening with various carboxylic acids. X-ray crystal structure of **5.34** for determination of absolute configuration. Compounds **5.31**, **5.32** and **5.33** were unstable and could not be characterized.

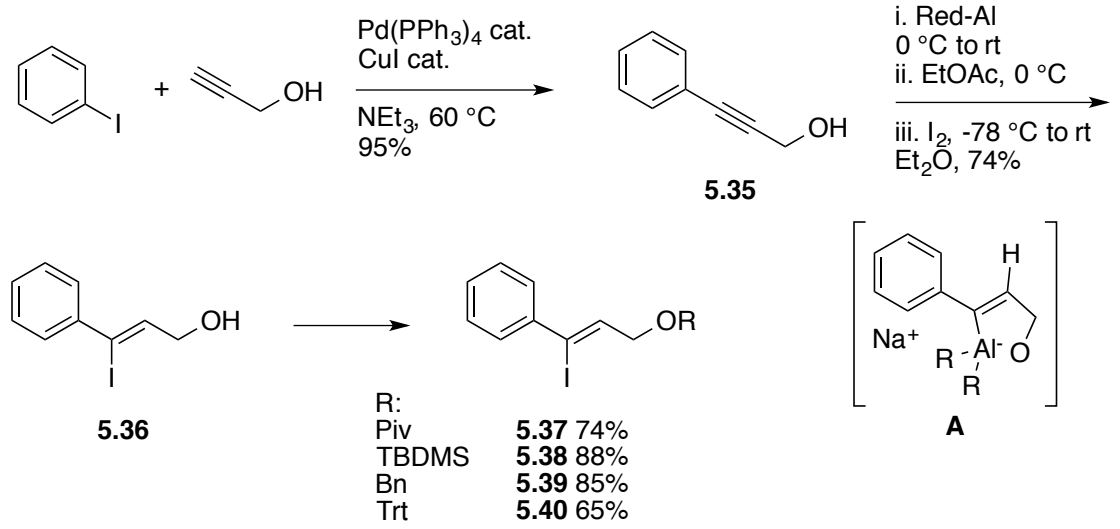
Additionally, the epoxide **5.28** was opened with other carboxylic acids (Scheme 5.14). While the equilibrium of the pivalic ester favored terminal product **5.30**, this ratio varied with other carboxylic acids. Using 2,4,6-timethylbenzoic acid, products **5.31** and **5.32** were isolated and quantified in an opposite ratio, but the spontaneous

isomerization was unavoidable and made the characterization impossible. When the epoxide was opened with *p*-iodobenzoic acid to give **5.33** and **5.34**, the terminal ester could be isolated, crystallized, analyzed by X-ray diffraction, and the absolute configuration was determined as depicted in scheme 5.14.

5.6 Evaluation of Nucleophiles for Chain Elongation

5.6.1 Synthesis of the Precursor

To yield the open bisacid **5.09**, forming the desired dilactone core, the carbon chain has to be elongated by another two carbons. Additionally, a phenyl group has to be introduced at the vinylic position. Both can be done by shortening the chain by ozonolysis and adding a nucleophilic C_6C_3 subunit.



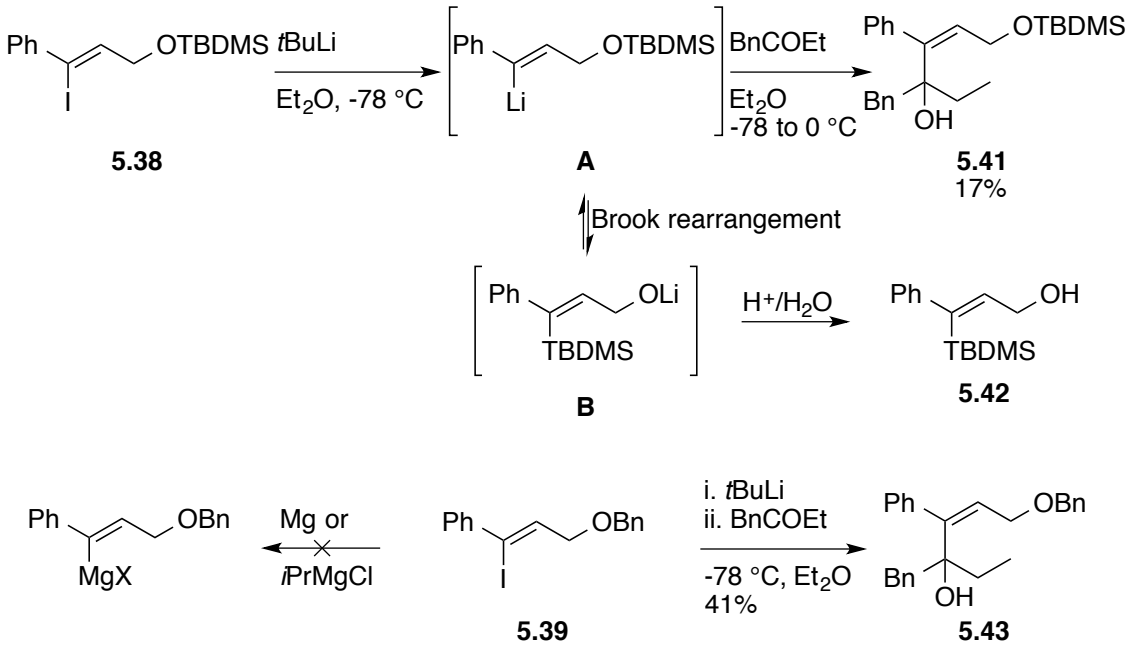
Scheme 5.15: Synthesis of protected vinyl iodides **5.37** to **5.40**, and selective reduction and iodination over intermediate **A**.[26] Conditions for alcohol protection: **5.37**: PivCl, DMAP cat., pyridine, CH_2Cl_2, rt; **5.38**: TBDMSCl, NEt_3, CH_2Cl_2, 0 °C to rt; **5.39**: BnBr, $(Bu)_4NHSO_4$ cat., NaOH, toluene, 0 °C to rt; **5.40**: TrtCl, pyridine, CH_2Cl_2, 0 °C to rt. Compound **5.40** could be crystallized and analyzed by X-ray diffraction (Section 8.4).

The vinyl iodide **5.36** was chosen as appropriate precursor (Scheme 5.15). The Sonogashira coupling giving alkyne **5.35** proceeded nicely.[25] The following reduction and selective iodination were performed in accordance to a procedure from Fürstner.[26] In this reaction, the hydroxy function coordinates to the aluminium and controls the addition to the triple bond, giving intermediate **A**.[27–29] It was found that it was important to quench the remaining excess of Red-Al with ethyl acetate before treatment with iodine. Subsequently, the hydroxy function was protected. Benzyl protection was problematic, as elimination of hydroiodic acid and formation of the protected alkyne

was observed. Sodium hydride as base for this reaction led to quantitative elimination, while sodium hydroxide under phase transfer conditions gave minor amounts of the elimination product and the desired vinyl iodide in a yield of 85%.

5.6.2 Nucleophilic Addition to a Model Substrate

We sought an appropriate protecting group, a metal for the iodine exchange and the optimal reaction conditions without consuming the valuable intermediate **5.46**. The pivalic ester **5.37** would give the same protecting group on both ends of the chain, circumventing one deprotection step. However, this protecting group was unstable to withstand the halogen metal exchange. The TBDMS-protection was found to be problematic as well. Lithiated intermediate **A** showed to be prone for a 1,4-Brook rearrangement, resulting in alcohol **5.42** (Scheme 5.16). This process has already been investigated by Kim *et al.*[29] However, this rearrangement was not quantitative and a small yield of the addition product **5.41** was obtained.



Scheme 5.16: Lithium iodine exchange to intermediate **A** and addition to test electrophile yielding **5.41** or Brook rearrangement to alcohol **5.42**.[29] Activation of iodide **5.39** with *t*BuLi and addition to the test substrate to give **5.43**. Grignard formation of **5.39** was attempted with Mg, DIBAL cat., THF, 60 °C and *i*PrMgCl, THF, rt.

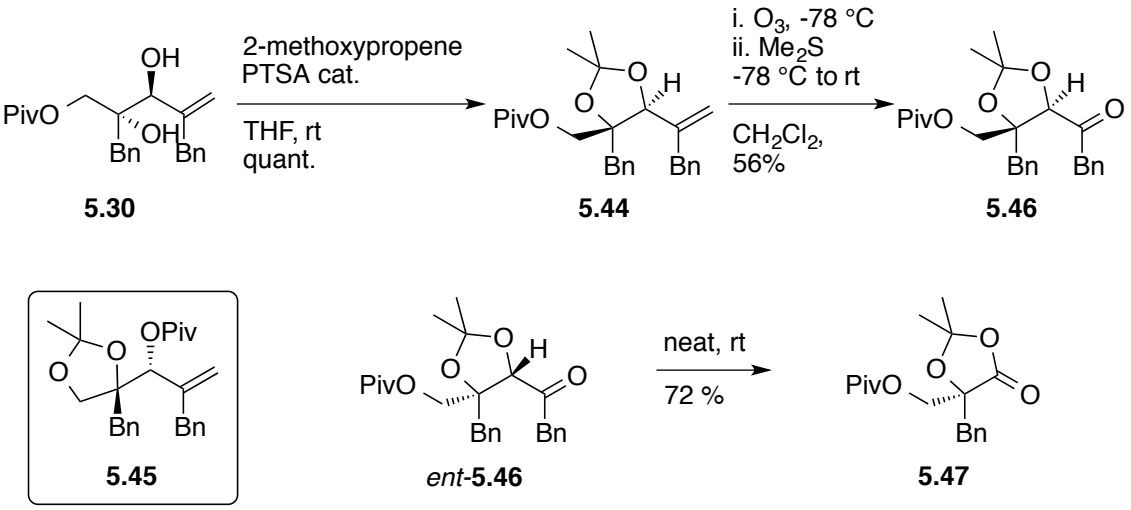
Finally, the benzylated iodide **5.39** was lithiated with *t*BuLi and added to the test substrate to obtain alcohol **5.43** in moderate yield. Other halogen metal exchange methods with metallic magnesium or with *iso*-propyl magnesium chloride failed to give any product. A direct method utilizing the unprotected alcohol **5.36** over a

deprotonation with a Grignard reagent, followed by a halogen metal exchange with butyl lithium described by Knochel *et al.* showed to be ineffective in our case.[30]

5.7 Chain Elongation

5.7.1 Electrophile Synthesis

The 1,2-diol of pivalic ester **5.30** was protected as an acetonide to give compound **5.44** (Scheme 5.17). Subsequently, the double bond was treated with ozone to yield ketone **5.46**. Over oxidation was prevented by the addition of Sudan III as an indicator.[31]



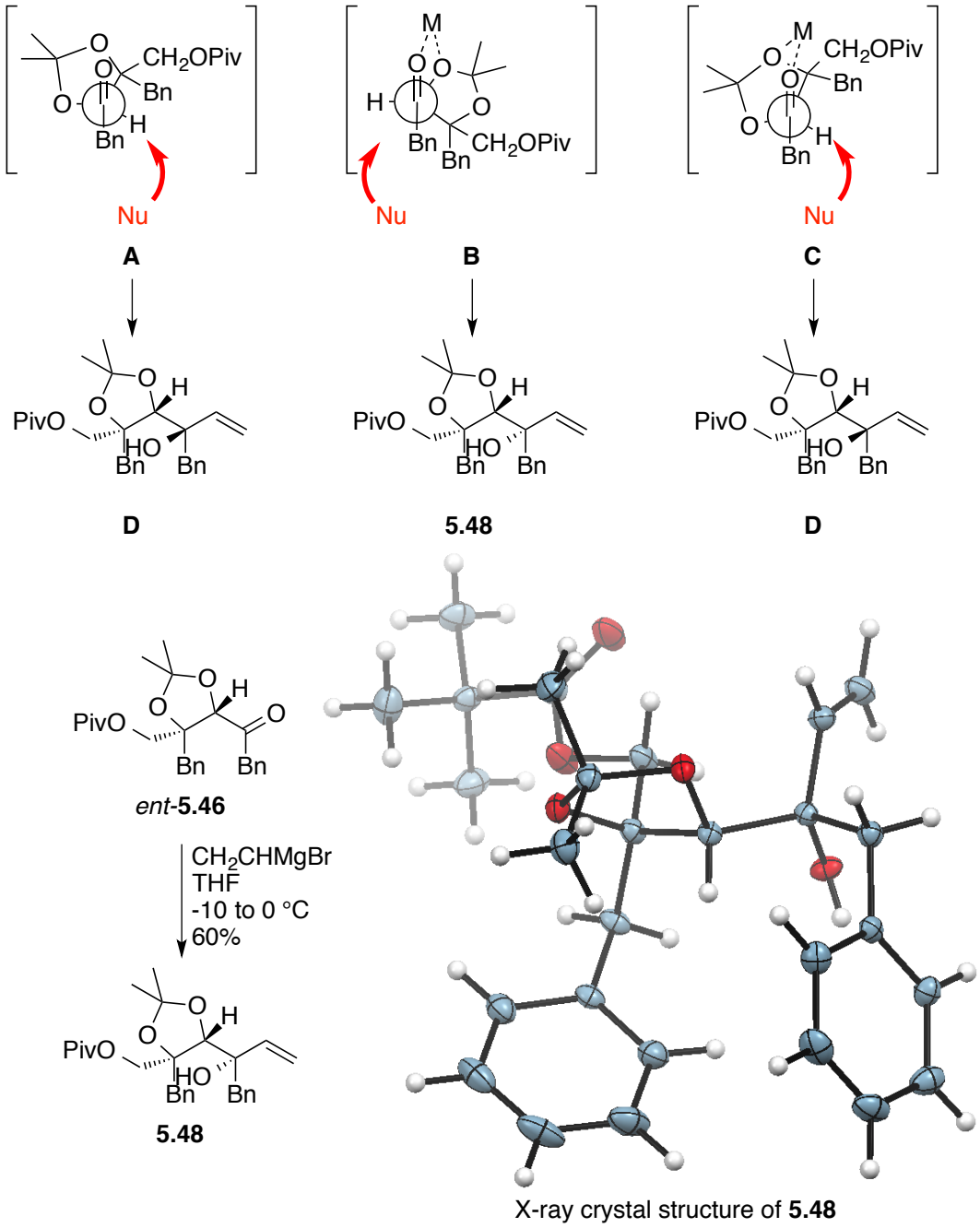
Scheme 5.17: Synthesis of ketone **5.46** in two steps and oxidative cleavage of the product while storage. Instable ester **5.29** was converted to **5.45** under the same reaction conditions affording **5.44**. The protected **5.45** could be characterized.

However, the product was found to be less stable than expected. Ketone **5.46** degraded overtime to ester **5.47**. Compound **5.47** is likely the result of an oxidative cleavage. A similar reaction was described by Carda *et al.*, enabled by the addition of sodium periodate.[32]

5.7.2 Stereoselectivity of Nucleophilic Additions

The stereoselective outcome of nucleophilic additions to carbonyl compounds bearing a chiral center has been intensively studied in the last century. Models to predict the stereoselectivity were beside others introduced by Cram *et al.*[33] and the group of Felkin[34] and further developed by Anh and co-workers[35] and Reetz *et al*.[36] Each of this model accounts for another type of substrate. With a electron withdrawing and Lewis basic group in α- and β-position, ketone **5.46** comply with three of these models. Our

first task was to evaluate which model describes our substrate. These experiments were performed with the enantiomeric ketone *ent*-**5.46**.



Scheme 5.18: Models **A**, **B** and **C** predicting the outcome of nucleophilic addition to *ent*-**5.46**. Addition of vinyl magnesium bromide and the formed product **5.48,** with measured X-ray crystal structure.

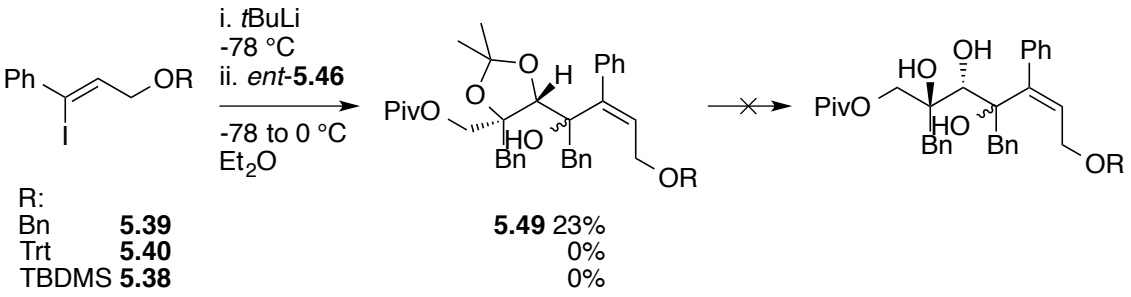
Three different models can be applied on our substrate (Scheme 5.18). In the Felkin-Anh model, intermediate **A** is the most reactive and gives **D** as the major product. The interaction between the π*-orbital of the carbonyl and the σ*-orbital of the electron withdrawing oxygen, causing a 90° angle between the two bonds, is essential

and the nucleophile then approaches from the *Re* face, giving product **D**. In his early descriptions, Cram excluded substrates with Lewis basic groups in α-position from his model, as they can build chelate complexes with certain metals. In these cases, the Cram-Chelate intermediate **B** has to be considered as most reactive intermediate. The two oxygens are both coordinated to the metal, forming an eclipsed five membered cyclic chelate. The nucleophile adds then from the *Si* face. Additionally, Reetz described a similar chelation with Lewis bases in the β-position. The six membered chelate **C** would result in a nucleophilic attack from the *Re* face.

To test which model applies for our substrate, vinyl magnesium bromide was added to the carbonyl group. The major product **5.48** was isolated and the relative configuration was determined after crystallization and X-ray diffraction analysis. The Cram-Chelate model **B** was found to predict the observed product. As expected for magnesium with its potential for coordination, the Felkin-Ahn product was not observed. Furthermore, the chelation to the α-oxygen seems to dominate over the β-position. This finding is in accordance with reports of other groups with similar substitution patterns.[37–40]

Unfortunately, the resulting stereocenter in **5.48** has the undesired orientation. With the addition over the Reetz intermediate **C** not being feasible, conditions favoring the Felkin-Ahn product had to be applied. Therefore, all further experiments were conducted with the less-coordinating lithium reagents.

5.7.3 Addition of the Lithium Reagents



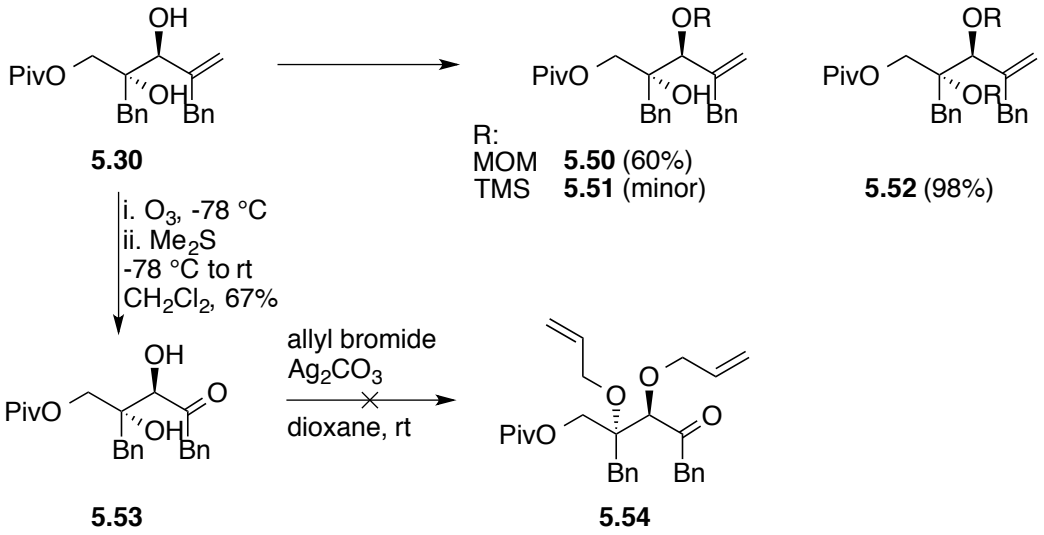
Scheme 5.19: Addition of protected vinyl iodides to ketone **5.46**.[41–43]

In accordance with the findings in the vinyl Grignard reaction (Section 5.7.2), vinyl iodides were lithiated and added to ketone *ent*-**5.46** (Scheme 5.19). While the TBDMS and trityl-protected compounds **5.38** and **5.40** gave no product, the benzylated **5.39** gave the chain-elongated tertiary alcohol **5.49** in a yield of 23%. The relative configuration of the new hydroxy group could not be determined.

However, the following deprotection of the diol under various conditions could not be accomplished. Our strategy intended the oxidation of the secondary hydroxy group, followed by benzylation. Therefore, other protecting groups and reaction orders were investigated.

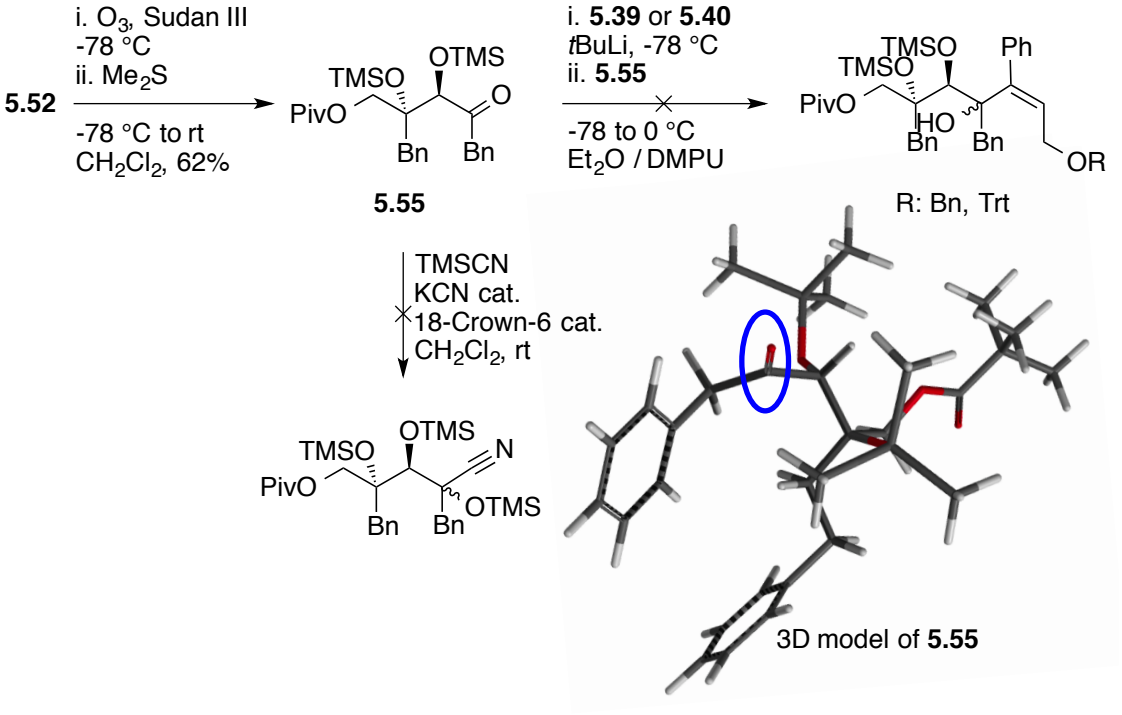
5.7.4 Further Attempts Towards Ophiodilactone A and B

Consequently, other protecting groups for the diol moiety were evaluated (Scheme 5.20). In contrast to the former acetonide, we focused on single side protecting groups. Protection with MOM was only achieved for the secondary alcohol, forming **5.50**. In contrast, the TMS group could be introduced twice to give bissilyl ether **5.52** in 98% yield.



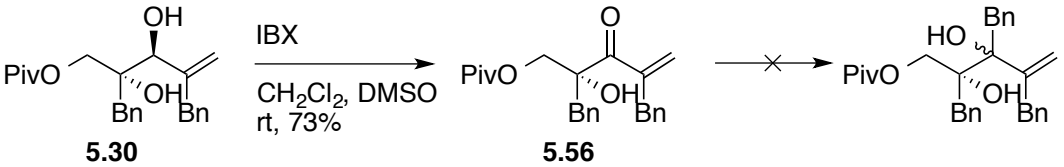
Scheme 5.20: Alternative protections of diol **5.30**. Conditions giving **5.50**: MOMCl, NaI, DIPEA, dioxane, 100 °C and **5.52**: TMSCl, imidazole, CH_2Cl_2, rt. Eventually mono-TMS product **5.51** was observed.

As allyl groups are not inert to ozonolysis conditions, the sequence was reversed and the double bond was first cleaved to ketone **5.53** (Scheme 5.21). However, the following allyl protection to afford **5.54** could not be accomplished.



Scheme 5.21: Addition of organolithium and cyanide nucleophiles to ketone **5.55**. Three-dimensional model calculated with Spartan Student version 5.0.1 (Nov 14 2011), Equilibrium Geometry with "Molecular Mechanics" MMFF.

TMS protected ketone **5.55** and unprotected ketone **5.53** were then subjected to the chain elongation conditions. In both cases, no desired product was isolated. Steric hindrance of the TMS and benzyl groups explains this result for TMS protected ketone **5.55**. A structural model shows how the carbonyl group is shielded and, therefore, not accessible for the organolithium species (Scheme 5.21). An alternative nucleophilic addition whit trimethylsilyl cyanide also showed no conversion. This result demonstrates a general problem in the synthesis of the ophiodilactones. The benzyl moieties hinder the accessibility of the central chain, and protecting groups can make the access impossible.



Scheme 5.22: Oxidation to ketone **5.56** and addition of the third benzyl group. The second step was attempted with BnMgBr, Et_2O, rt and BnLi, toluene, rf.

In a last attempt, the sequence of additions was changed. Instead of the chain elongation, we tried to introduce the remaining benzyl group (Scheme 5.22). Therefore,

the secondary hydroxy group of the allylic alcohol **5.30** was oxidized to ketone **5.56**. For the organometallic nucleophile, Grignard reagents are known for a low 1,2- to 1,4-selectivity, but benzyl lithium reagent is not well known and difficult to prepare. The latter was generated as described by Furber *et al*.[44] However, neither of these nucleophiles gave the desired product.

5.8 Conclusion

The synthesis of ophiodilactone A (**1.47**) and B (**1.48**) over the linear bisacid **5.09**, allows the application of a desymmetrization strategy. The advantage of this strategy is the bidirectional synthesis of a symmetric precursor, reducing the required amount of steps.[1] First experiments on this route were conducted by Jean-Yves Wach and revealed problems in the synthesis of symmetrical intermediates with high complexity.[12]

The relatively simple literature known bisallyl alcohol **5.13** was found to be a suitable intermediate.[13] However, the high yields stated in literature could not be reproduced in our laboratory. Therefore, a new synthetic route over a Mannich reaction and an organolithium addition was developed. While this new procedure give the bisallyl alcohol in sufficient yield, it lacked the advantages of a bidirectional synthesis, increasing the number of steps from two to three.

Consequently, bisallyl alcohol **5.13** was desymmetrized by a Sharpless epoxidation, giving epoxide **5.14** in an enantiomeric excess of 87%. The subsequent epoxide opening by pivalic acid was achieved, following a Payne rearrangement. Additionally, the ester moiety rearranged under the reaction conditions to the desired terminal hydroxy group. After protection of the diol as acetonide, the second double bond was cleaved by ozonolysis, giving ketone **5.46**.

Towards the nucleophilic three-carbon chain elongation, iodoalcohol **5.36** was protected by different groups, activated by lithium-halogen exchange and added to a test substrate. The benzyl protected vinyl iodide **5.39** was found to be superior and was added to ketone **5.46**. However, all following attempts to conduct the required deprotection of the diol failed.

Alternatively, the diol **5.30** was protected by two TMS groups. The following unsuccessful chain elongation was explained with the high steric demand of the two TMS protecting groups.

Overall, a total synthesis over an asymmetric precursor offers several advantages, including a reduction in the number of steps. In the case of ophiodilactone A and B, the

high steric demand of the benzyl groups and the high complexity of the core requires the desymmetrization to be performed at an early stage. Furthermore, the desymmetrization strategy requires a linear synthesis over the open bisacid **5.09**, necessitating the use of multiple protecting groups. However, these protecting groups were found to increase the steric bulk around the central carbon chain, shutting down the reactivity of the substrate.

5.9 References

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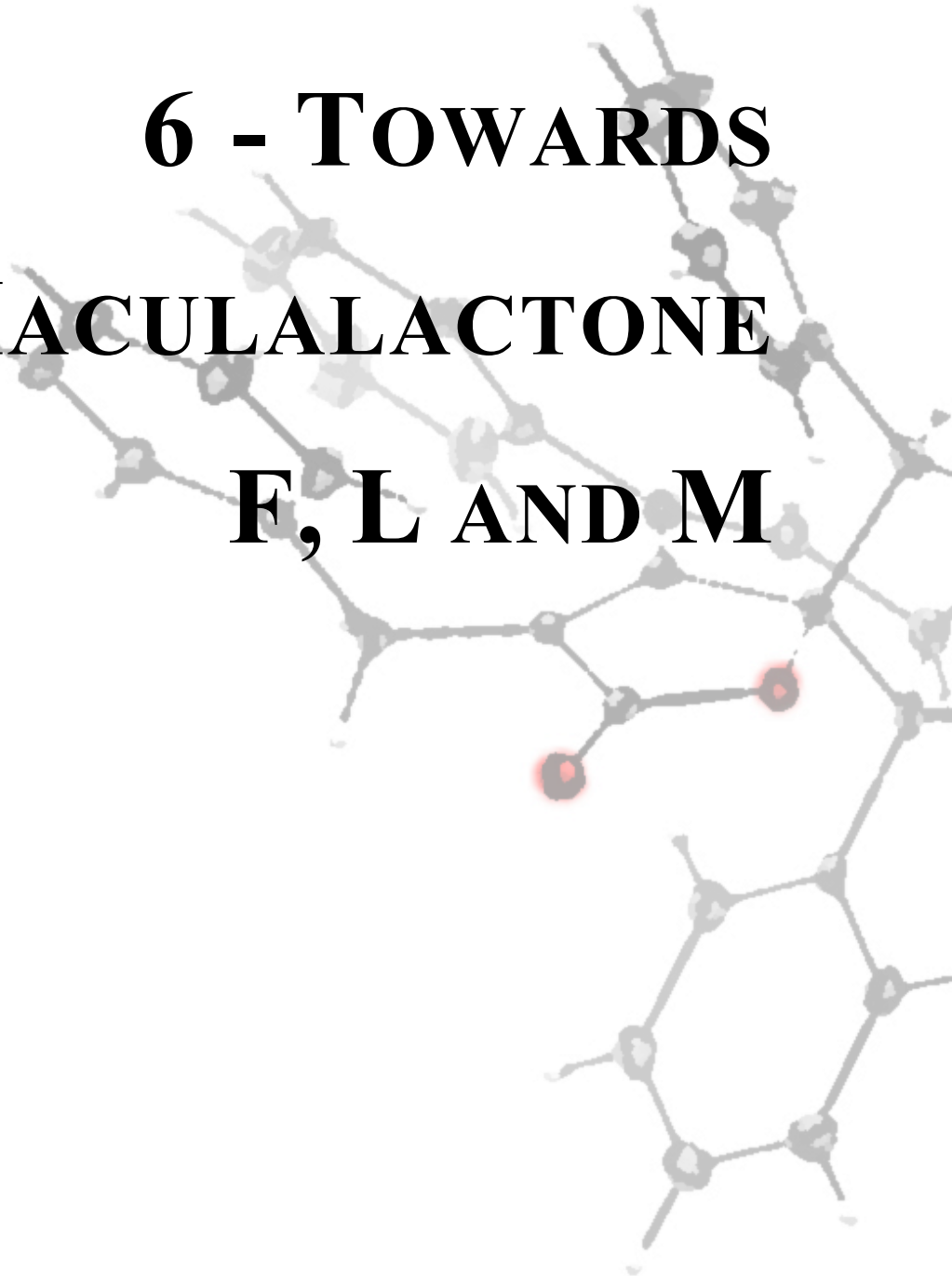
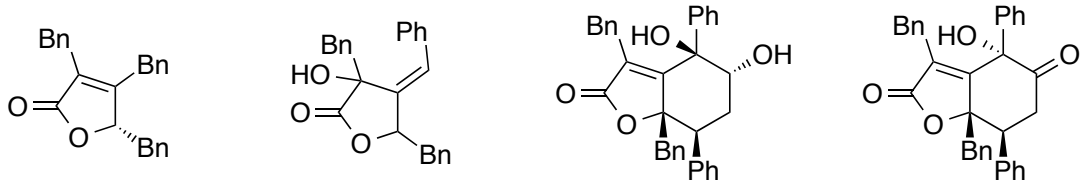
6 - Towards Maculalactone F, L and M



6.1 Introduction

To our knowledge, only maculalactone A, B and C have been synthesized so far (Chapters 1 and 2).[1–5] These three structures and maculalactone L (**1.37**) possess a butenolide core (Figure 6.1).[6] All other maculalactones, except maculalactone M, include a fourth phenylpropanoid resulting in a tetrahydrobenzofuranone skeleton.[2,7]

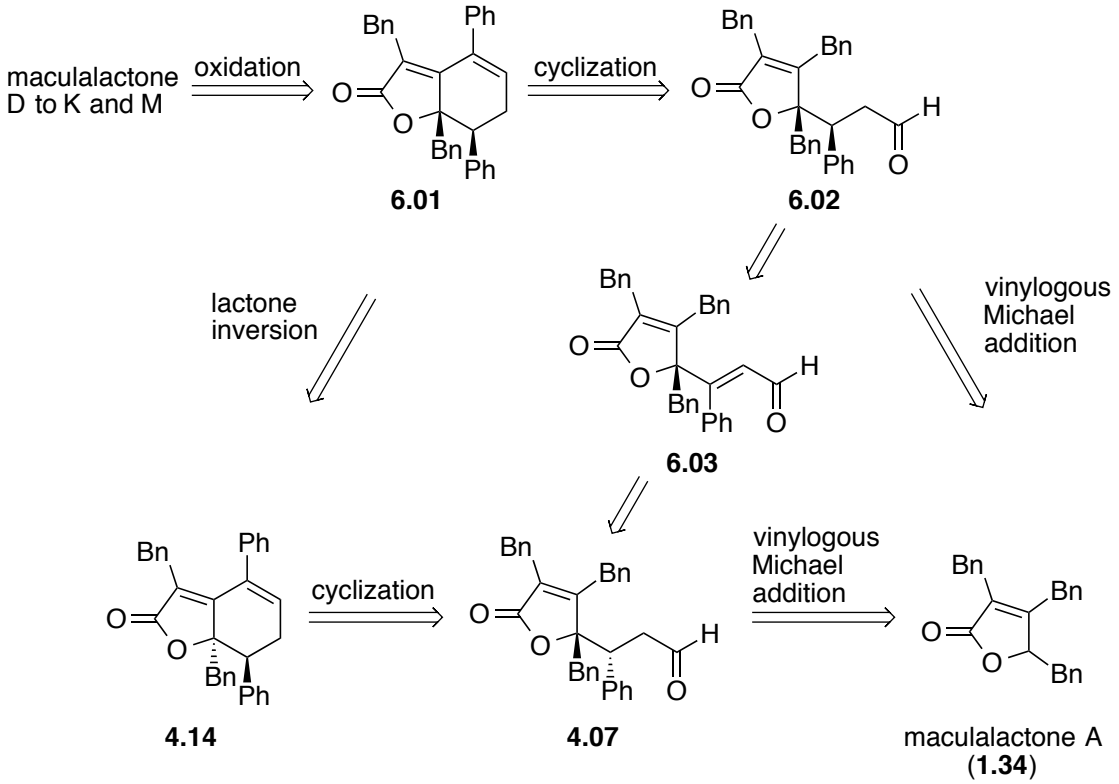


maculalactone A (**1.34**) | maculalactone L (**1.37**) | maculalactone E (**1.39**) | maculalactone F (**1.40**)

Figure 6.1: Exemplary maculalactones formed from three and four phenylpropanoid subunits.

While the biological properties of maculalactone A have been the objective of several studies (Chapters 1 and 3), little is known about the other members of this family.[8] Recently, Wang *et al.* isolated maculalactone E (**1.39**) from the brittle star *Ophioplocus japonicus* and found promising cytotoxicities against five human tumor cell lines.[9] To gain more insight into the chemistry and biology of these compounds, we investigated routes towards their total syntheses.

These studies require the addition of an additional C_6C_3 phenylpropanoid unit, as it was done in the synthesis of ophiodilactone A (**1.48**) and B (**1.48**) (Section 4.3). However, the relative configuration of the phenyl and the neighboring benzyl group should be *cis*, instead of the earlier observed *trans*-product (Scheme 6.1). To obtain the correct stereochemistry as depicted in aldehyde **6.02**, either the vinylogous Michael addition had to be changed in a way to afford the correct product, or the configuration of the phenylic stereocenter had to be inverted by the installation of a double bond and a subsequent stereoselective hydrogenation. Alternatively, the benzyl-substituted stereocenter could be inverted by a lactone opening followed by a re-closure causing inversion.



Scheme 6.1: Synthetic strategies toward common precursor **6.01**. (In case of inversion of the lactone, the enantiomeric compound should be used)

The required ring closure of the second ring, forming the dihydrobenzofuranone **6.01** should be straightforward, as this reaction was already performed with the *trans*-isomer. The inversion of the lactone seems to be more feasible after the second ring closure, as the ring strain could favor the desired *cis*-product. Finally, common precursor **6.01** has to be oxidized in an appropriate way to give the different maculalactones.

In our study, we focused on altering the stereochemical outcome of the vinylogous Michael addition over enone **6.03**.

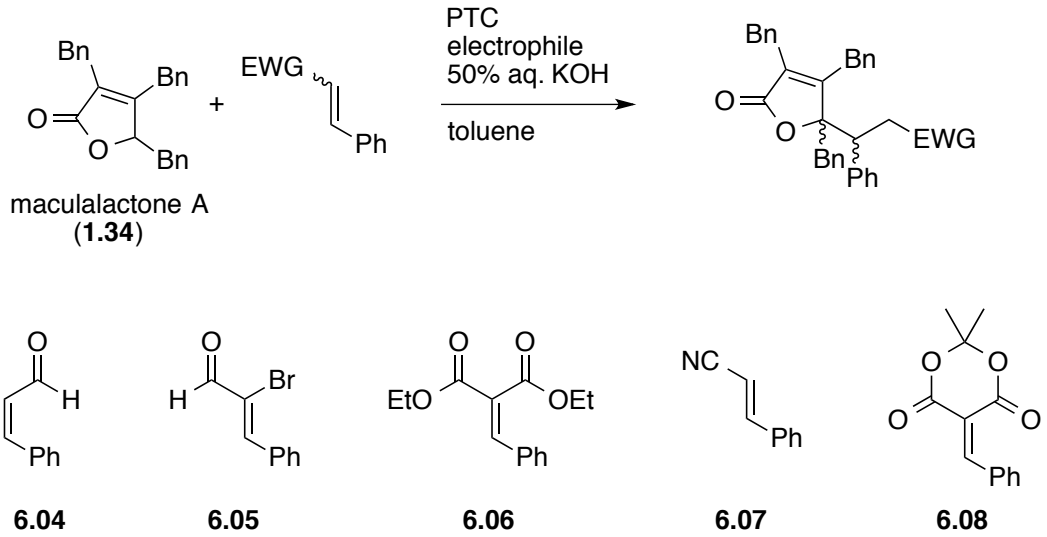
6.2 Adjusting the Stereochemistry of Bicycle 4.14[10]

6.2.1 Electrophiles in the Vinylogous Michael Addition

In the phase transfer catalyzed vinylogous Michael addition in the synthesis towards ophiodilactone A and B, a strong prevalence toward the *trans* product was found (Section 4.3). This selectivity was observed in the tetrabutylammonium-catalyzed reactions with methyl cinnamate, as well as in the cinchona alkaloid-catalyzed systems with cinnamaldehyde. Since the stereoselectivity is thought to be a result of substrate

Parts of the following study was conducted by Michael Lüscher during his Master thesis.[10]

control, alternative electrophiles were examined (Scheme 6.2).



Scheme 6.2: Vinylogous Michael addition with different electrophiles. The reactions were usually catalyzed by Lygo's PTC **2.12**.[11] Reaction temperatures were adapted to the electrophile. In some cases, further experiments with PTC **4.15** and/or $CsOH*H_2O$ as base were conducted.[12] Reaction times were adjusted to the conversion. The electrophiles **6.04**[13] and **6.08**[14,15] were prepared accordingly procedures in the stated literature.

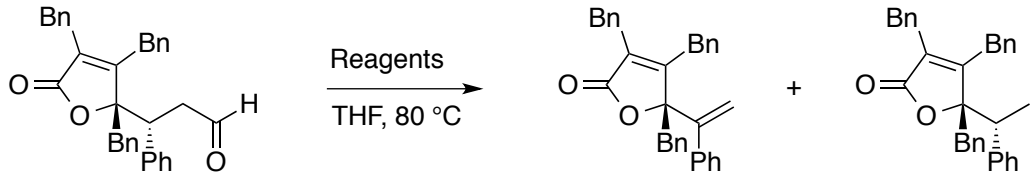
Despite multiple attempts, reactions with bromide **6.05** and nitrile **6.07** showed no conversion. Meldrum's acid derivative **6.08** and *cis*-cinnamaldehyde **6.04** were not stable under the reaction conditions. The latter isomerized under the basic conditions to the thermodynamically favored *trans*-form. The usual *trans*-product was isolated and during the reaction, isomerization of **6.04** could be observed by TLC. Finally, malonate **6.06** showed little conversion to an unidentified product.

6.2.2 Hydrogenation of the Unsaturated Aldehyde

As the usage of different electrophiles did not give the required *cis*-product **6.02**, a second strategy over enone **6.03** and subsequent hydrogenation was investigated. We first attempted to synthesize the required unsaturated compound by dehydrogenation.

The commonly used selenation, followed by oxidation and elimination, showed no conversion at lower temperatures and led to decomposition of the starting material at an elevated temperature of -40 °C. The same result was observed with IBX in DMSO, a method developed by Nicolaou *et al*.[16]

A procedure published by Shvo *et al.* with allyl diethyl phosphate as the oxidant and palladium(II) acetate as the catalyst showed the formation of small amounts of an unknown product **A** (Table 5.1, Entry 1) (Scheme 6.3).[17]



4.07 **6.09** **6.10**

Scheme 6.3: Dehydrogenation catalyzed with palladium. Decarboxylation product **6.10** was identified by NMR (^{1}H, ^{13}C, COSY, HMQC and HMBC) and ESI-MS.

As only little conversion to the potential desired product **A** was observed, a stronger base was applied, leading to the unexpected decarbonylated products **6.09** and **6.10** (Entry 2). While such palladium mediated decarbonylations are known in literature, they usually require more harsh conditions (T ≥ 150 °C).[18]

Entry	Reagents	Ratio **4.07**	Ratio **A**	Ratio **6.09**	Ratio **6.10**
1	$Pd(OAc)_2$ (0.3 eq.), allylOPO$(OEt)_2$ (2.0 eq.), $NaHCO_3$ (1.5 eq)	87	13	-	-
2	$Pd(OAc)_2$ (0.3 eq.), allylOPO$(OEt)_2$ (2.0 eq.), Na_2CO_3 (1.5 eq)	-	25	50	25
3	$Pd(OAc)_2$ (0.1 eq.), $NaHCO_3$ (1.5 eq)	-	-	50	50
4	Pd/C (10 eq.)[a]	-	-	50	50

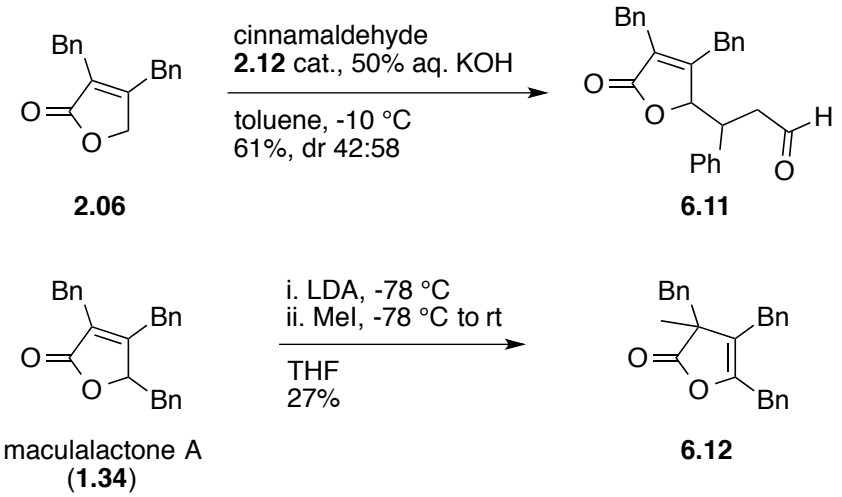
Table 6.1: Palladium mediated dehydrogenation. Conditions: THF, 80 °C. Ratios were calculated by ^{1}H-NMR data. Product **6.10** was identified by NMR (^{1}H, ^{13}C, COSY, HMQC and HMBC) and ESI-MS. [a]Reaction led to the formation of many side products.

In the absence of allyl diethyl phosphate as oxidant, a one-to-one mixture of the decarbonylated products was observed (Entry 3). A similar result was found in the presence of palladium on charcoal, even though, many side products formed (Entry 4).

6.2.3 Changing the Reaction Sequence

We then attempted to change the reaction order to give access to the *cis*-product **6.02**. In this way, the vinylogous Michael addition should be performed with the γ-unsubstituted maculalactone A derivative **2.11**, which would then be followed by benzyl group installation at this position (Scheme 6.4). The vinylogous Michael addition of the known intermediate **2.06** with cinnamaldehyde under standard

conditions afforded the desired product **6.11** as a diastereomeric mixture. Since the following step includes a deprotonation in γ-position, both products can be used.

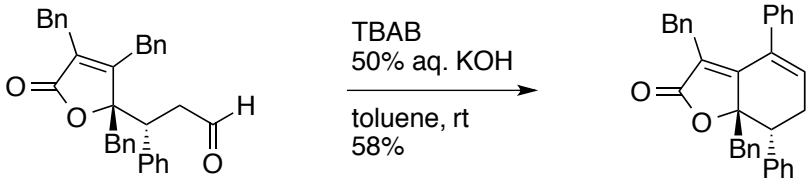


Scheme 6.4: Vinylogous Michael addition with maculalactone A precursor **2.06**. The diastereomeric ratio was determined by ^{1}H-NMR. Test reaction for the alkylation with maculalactone A.

The following benzylation was first tested by the deprotonation and subsequent alkylation of maculalactone A (**1.34**). The addition to methyl iodide resulted in the formation of the α-disubstituted lactone **6.12**. This is in accordance with earlier findings in the benzylation of lactone **2.06** and similar results were described in literature (Section 2.2).[19] The predominate α-addition makes the inverted addition to the γ-position impossible.

6.3 Synthesis of *epi*-Maculalactone F and M[10]

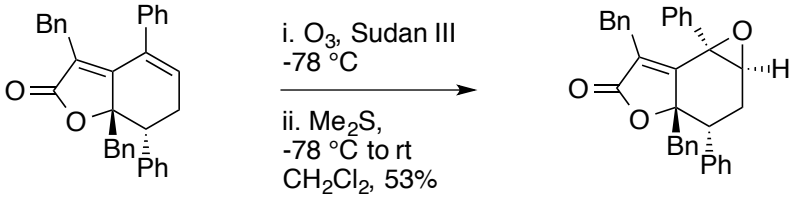
Although the synthesis of key intermediate **6.01** was not yet achieved, first experiments were conducted over diastereomeric bicycle **4.14**. This bicycle was formed in the tetrabutylammonium bromide catalyzed reaction of maculalactone A and cinnamaldehyde (Section 4.3.2) (Scheme 6.5). To obtain the enantiomerically enriched bicycle, aldehyde **4.07**, formed in the asymmetric vinylogous Michael addition, was cyclized under the same conditions.



4.07 **4.14**

Scheme 6.5: Synthesis of enantiomerically enriched **4.14** from aldehyde **4.07**.

Epi-maculalactone M (**6.14**) was chosen as first target, as it should be accessible over an oxidative cleavage of bicycle **4.14**. Such a cleavage was thought to be achieved in one step by treating this bicycle with ozone. To prevent oxidation of the second less electron dense double bond, Sudan III was added as indicator (Scheme 6.6).[20] Surprisingly, epoxide **6.13** was isolated as main product, along with minor amounts of the potential ring-opened aldehyde.

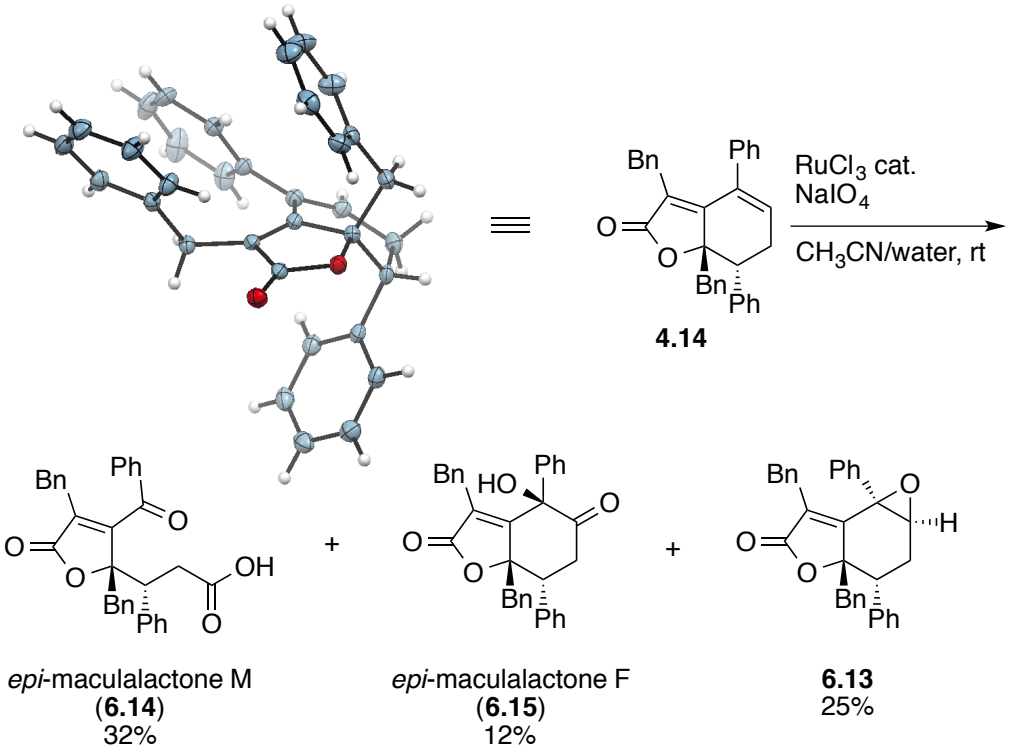


4.14 **6.13**

Scheme 6.6: Ozonolysis of bicycle **4.14** giving epoxide **6.13**.

This unusual outcome of the ozonolysis step is not well known in literature. Bailey *et al.* explains the epoxide formation with the steric hindrance.[21] In a common ozonolysis, all three oxygens of ozone take part in a [2+3]-cycloaddition, leading to the cleavage of the double bond. In sterically hindered systems, only one of the oxygens can approach the double bond, resulting in the observed epoxide formation.

An alternative procedure to obtain *epi*-maculalactone M (**6.14**) involves the dihydroxylation of the double bond, followed by an *in-situ* oxidative cleavage (Scheme 6.7). Therefore, different dihydroxylation methods were tested, of which most did not show any conversion. Finally, a method introduced by the group of Sharpless with a ruthenium tetroxide catalyst was sufficient to give *epi*-maculalactone M.[22] Additionally, epoxide **6.13** and a ketone identified as *epi*-maculalactone F (**6.15**) were also isolated.



epi-maculalactone M (**6.14**) 32%

epi-maculalactone F (**6.15**) 12%

6.13 25%

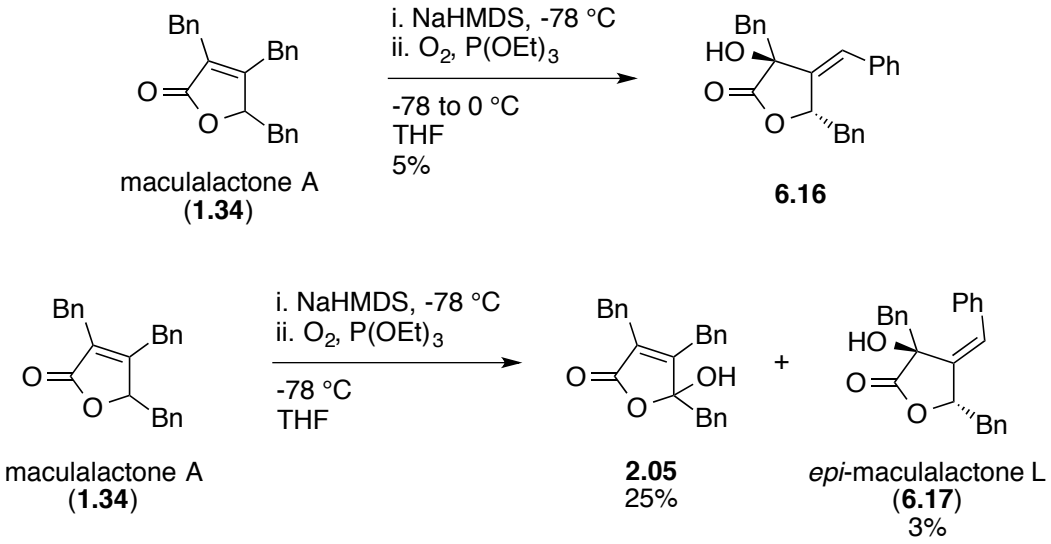
Scheme 6.7: Dihydroxylation and *in-situ* oxidative cleavage giving *epi*-maculalactone M (**6.14**), epoxide **6.13** and *epi*-maculalactone F (**6.15**). Including X-ray crystal structure of starting material **4.14**.

The diastereoselectivity of these oxygen additions is explained best with the X-ray crystal structure of bicycle **4.14**. While the phenyl group blocks the bottom face of the double bond, the oxidizing agent can only approach from the top to afford the observed product.

6.4 Synthesis of Maculalactone L Structures

While maculalactone A, B and C have been synthesized, the synthesis of maculalactone L (**1.37**) has not yet been accomplished. Furthermore, it is the only maculalactone with an unknown relative configuration.

In our studies towards ophiodilactone A and B, we performed several α-oxidations (Section 4.5.2 and 4.5.3). We postulated that maculalactone L is the result of α-oxidation of maculalactone A (**1.34**). Our initial experiment was conducted in accordance to the synthesis of **4.32** (Section 4.5.2). The oxygen addition was performed at -78 °C, but the reaction was warmed to 0 °C and stirred at this temperature for 2 hours before quenching (Scheme 6.8). While mainly decomposition was observed, compound **6.16**, possessing a similar structure as maculalactone L, was isolated.



Scheme 6.8: Oxidation of the α-position of maculalactone A to form two conformal isomers of maculalactone L. The relative configuration was determined by 2D-NMR experiments.

In a next attempt, the reaction mixture was quenched at -78 °C. While slightly less decomposition was observed, two new products were isolated. One was identified as the γ-oxidation product **2.05**, which is known from the synthesis of maculalactone A, B and C by Brown *et al.*[3] The second product possessed the same structure as maculalactone L with the correct Z orientation of the double bond. However, the NMR spectra did not match to the isolated maculalactone L. Therefore, we surmised that the structure must be *epi*-maculalactone L (**6.17**).

6.5 Conclusion

While maculalactone A, B and C have already been synthesized years ago, little is known about the synthesis of the other members of this natural product family (Section 1.4). We proposed a route to access these natural products over the bicyclic key intermediate **6.01**. While some transformations are known from our studies towards ophiodilactone A and B (Chapter 4), it is not clear how to obtain the required *cis*-orientation of the substituents in **6.02**.

In a first approach, we tried to change the outcome of the vinylogous Michael addition by varying the electrophile. However, all tested alternative Michael acceptors showed no reactivity or decomposition under the reaction conditions. Further studies were conducted on the possibility to convert aldehyde **4.07** to the corresponding enone **6.03** and to change the orientation of the β-substituent in a following stereoselective hydrogenation. While various methods were tested, the required enone

could not be observed. In a third attempt, we tried to vary the order of the steps. While the vinylogous Michael addition worked well, the following alkylation was found to result in a substitution at the α-position.

Although key intermediate **6.01** could not be synthesized, the oxidations steps were tested with the diastereomeric bicycle **4.14**. A dihydroxylation catalyzed by ruthenium tetroxide, followed by an *in-situ* oxidative cleavage afforded *epi*-maculalactone M (**6.14**) in a yield of 30%. Furthermore, a side product of the reaction was identified as *epi*-maculalactone F (**6.15**).

In an attempt to synthesize maculalactone L (**1.37**), maculalactone A was deprotonated and oxidized with molecular oxygen. Thereby, different compounds having the same composition as maculalactone L were isolated. One compound was identified as *epi*-maculalactone L (**6.17**) and helped to define the unknown relative configuration of natural maculalactone L.

6.6 References

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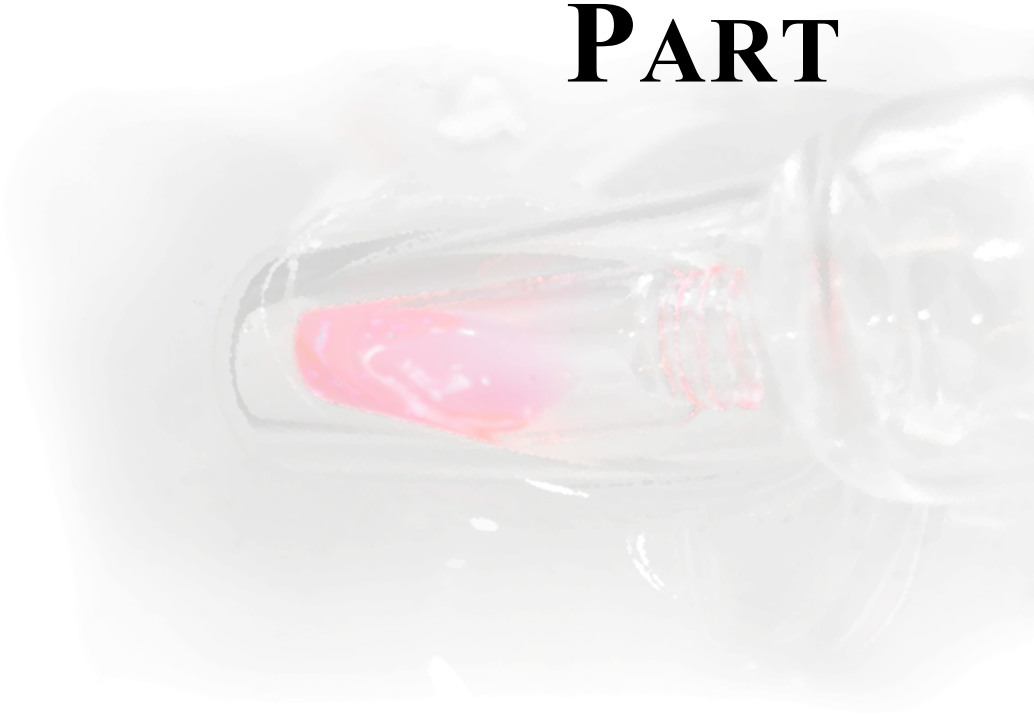
7 - CONCLUSION

In our studies on the synthesis and biology of marine, phenylpropanoid natural products, different approaches towards a more economical synthesis of maculalactone A (**1.34**) were investigated. A first attempt over a late stage ring-closing metathesis was partially successful, but the low conversion of the metathesis could not be overcome. Alternatively, a route via a late-stage intramolecular cyclization of malonic ester **2.31** gave maculalactone A in modest yield. This final key step includes a nucleophilic addition to a carbonyl moiety and subsequent loss of ethanol and carbon dioxide to establish the butenolide double bond. After careful optimization, this cyclization was achieved in 76% yield, allowing the synthesis of maculalactone A in total of four steps and 45% yield.

The same methodology was used for the synthesis of the three maculalactone A analogues **3.17**, **3.18** and **3.19**, each bearing a methoxy group on one of the benzyl moieties. The biological properties of these analogues were compared in a small SAR study with *Artemia franciscana* and *Thamnocephalus platyurus*. Subsequently, analogue **3.17** was used in our investigations on the antifouling protection of metal surfaces. Therefore, we utilized the methoxy group to connect the analogue to one of our surface anchors. In a similar manner, we synthesized the rhodamine B labeled analogue **3.47**. In an *in vivo* staining experiment with *Artemia salina*, we observed specific accumulation of maculalactone A in two tissues.

Two different strategies towards the synthesis of ophiodilactone A (**1.47**) and B (**1.48**) were investigated. In an initial linear route, we first developed a new synthesis of bisallyl precursor **5.13**, which was subsequently desymmetrized via a Sharpless epoxidation. Eventually, the epoxide was opened after a Payne rearrangement, followed by an ozonolysis, affording ketone **5.46**. While the following carbon chain elongation was successful, it was not possible to remove the protecting groups. In a second, protecting group-free strategy, maculalactone A was the starting material. By a vinylogous Michael addition, we could add the required C_6C_3 unit in 52% yield and 68% *ee*. Various efforts to achieve the required oxidation of the butenolide double bond failed. Furthermore, different approaches to alter the reactivity of the olefin or to convert it into a more reactive intermediate were unsuccessful. However, by this second strategy, we obtained the carbon skeleton of ophiodilactone A (**1.47**) in five steps and an overall yield of 23%.

8 - EXPERIMENTAL PART



8.1 General Information

Reagents and Solvents: All chemicals and solvents were purchased from Acros, Alfa Aesar, Fluka, Fluorochem, Apollo, TCI or Sigma-Aldrich and used without any prior purification if not otherwise reported. Dry solvents were purchased from Sigma-Aldrich. Technical grade solvents for extractions and chromatography were distilled before usage. NMR solvents were obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA).

Reactions: Yields refer to purified, dried and spectroscopically pure compounds. Air or moisture sensitive reactions were set up in dry glassware under nitrogen atmosphere.

Chromatography: Column chromatography was carried out on silica gel 60 with a particle size of 0.04 – 0.063 mm (230 – 400 mesh) from Merck or Silicycle. Preparative TLC was performed on the same plates, usually in a size of 20 to 20 cm. The developed plates were examined under UV light at 254 nm, the sections of interest were removed with a knife and extracted with CH_2Cl_2 or EtOAc. Preparative HPLC chromatography was performed using Varian Prep Star pumps and a Dionex UltiMate 3000 RS detector ore a Dionex P680 pump and a Dionex PDA-100 detector.

Distillation: Concentration was performed by rotary evaporation under reduced pressure at 40 to 50 °C. Kugelrohr distillation was done using a Büchi GKR-51 apparatus.

Retention Factor (Rf): Analytical thin layer chromatography (TLC) was performed either on Merck Silica gel 60 F_{254} Plates with a thickness of 0.25 mm on glass support or on Merck Silica gel 60 RP-18 F_{254} Plates with a thickness of 0.2 mm on aluminum support. The developed plates were examined under UV light at 254 nm and stained with an aqueous $KMnO_4/Na_2CO_3$ solution or an aqueous $(NH_4)_6Mo_7O_{24}/Ce(SO_4)_2/H_2SO_4$ solution.

^{1}H-, ^{13}C- and ^{19}F-Nuclear Magnetic Resonance (NMR): All spectra were recorded either using a Bruker BZH-NMR (250 MHz), a Bruker DPX-NMR (400/101/376 MHz), a Bruker Avance DRX (500/126 MHz) or a Bruker Avance III (600/151 MHz) spectrometer at room temperature if not otherwise reported. Two-dimensional spectra were recorded on a Bruker Avance DRX. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks or tetramethylsilane (TMS), coupling constants (*J*) are reported in Hertz (Hz). The multiplicities are given as: s=singlet, d=doublet, t=triplet, m=multiplet and their combination, as dd=doublet of a doublet and

so on. For multiplets the range of the chemical shift (ppm) is reported. Solvents are abbreviated as follows: chloroform-d ($CDCl_3$), water-d_2 (D_2O), methanol-d_4 (MeOD), dimethylsulfoxide-d_6 (DMSO-d_6), benzene-d_6 (C_6D_6).

Infrared Spectroscopy (IR): The spectra were recorded on a Varian 800 FT-IR ATR Spectrometer. The absorptions are reported in cm^{-1}.

Mass Spectrometry (MS): Mass spectra with electronic ionization (EI-MS) were recorded on a Finnigan MAT 95Q instrument. Fast atom bombardment mass spectrometry (FAB-MS) was measured on a Finnigan MAR 312 instrument. Mass spectra with electron spray ionization (ESI-MS) were measured on a Bruker esquire 3000 plus instrument. EI-MS and FAB-MS were performed by Dr. H. Nadig, University of Basel.

High Resolution Mass Spectroscopy (HR-MS): Mass spectra were measured by the Mass spectrometric service of the University of Bern on a Sciex QSTAR Pulsar mass spectrometer or by Dr. H. Nadig on a Bruker maXis 4G using electrospray ionization in both cases.

Elementary Analysis (EA): The elementary analysis was measured on a Perkin-Elmer Analysator 240 performed by Hr. W. Kirsch, University of Basel

Gas Chromatography with Mass Spectrometry (GC-MS): For GC-MS analysis, either a Hewlett Packard 5890 Series II gas chromatography system with a Macherey-Nagel OPTIMA 1 Me_2Si column (25 m x 0.2 mm x 0.35 μm), at 1 ml/min He-flowrate with a Hewlett Packard 5971 Series mass selective detector (EI 70 eV) or a Thermo Trace 1300 gas chromatography system with an Agilent Ultra 1 column (25 m x 0.2 mm x 0.33 μm) at 1 ml/min He-flowrate with a Thermo ISQ mass detector (EI 70 eV) was used.

Ultra Pressure Liquid Chromatography with Mass Sectrometry (UPLC-MS): For UPLC-MS analysis a Agilent 1290 Infinity instrument with an Agilent Eclipse Plus C18 column, a CH_3CN/water gradient (acidified with TFA or formic acid) and an Agilent 6130 ESI-MS detector was used.

High Performance Liquid Chomatography (HPLC): Analytic HPLC was performed on a Dionex system using a P680 pump and a PDA-100 detector.

Chiral HPLC: Chiral HPLC was performed on a Shimadzu LC-20A prominence system with a LC-20AD pump and a SPD-M20A diode array detector.

Optical Rotations ($[\alpha]_D$): Optical rotations were measured at the sodium D line using a 1 ml cell with a 1 dm path length on a Jasco P-2000 digital polarimeter and the concentration (c) is given in g/100 ml.

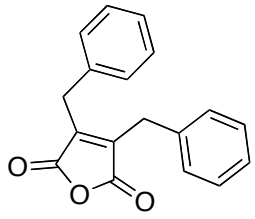
Melting point (Mp): A Büchi B545 apparatus was used. The measured temperatures are not corrected.

Absorptions spectra (UV/VIS): Spectra were recorded on a Shimadzu UV-1650 PC instrument.

Emission spectra (EM): The fluorescent emission was recorded on a Shimadzu RF-5301 PC instrument.

8.2 An Improved Synthesis of Maculalactone A

2,3-Dibenzylmaleic anhydride (2.04)



A solution of 2,3-dibromomaleic anhydride (**2.15**, 1.00 eq., 0.758 mmol, 194 mg) in toluene (1.6 ml) was heated to reflux. Subsequently, di-*tert*-butyl peroxide (0.500 eq., 0.379 mmol, 69.3 µl) was added in five portions over ten hours and the mixture was refluxed for another four hours. The reaction mixture was then cooled to room temperature and filtrated over basic aluminium oxide. The solid was washed with Et_2O. The filtrate was concentrated and purified by column chromatography (SiO_2, pentane/EtOAc (10:1)) to give the title compound **2.04** (61 mg, 0.21 mmol, 28%) as pale yellow oil.

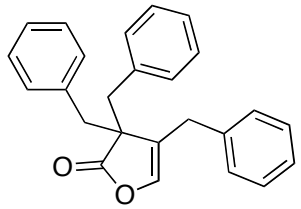
Rf (SiO_2, pentane/EtOAc (11:1)): 0.40.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.27 (m, 6 H), 7.17 – 7.10 (m, 4 H), 3.80 (s, 4 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 165.9, 143.1, 135.1, 129.2, 129.0, 127.6, 30.4.

The analytical data of product **2.04** correspond to those reported in the literature.[1–3]

3,3,4-Tribenzylfuran-2(3H)-one (2.13)



To a solution of 3,4-dibenzylfuran-2(5H)-one (**2.06**, 1.0 eq., 0.11 mmol, 29 mg) in toluene (5.4 ml) were added benzyl bromide (3.0 eq., 0.323 mmol, 38.7 µl) and the cinchona alkaloid catalyst (**2.12**, 0.05 eq., 5 mmol, 3 mg) in one portion. The mixture was cooled to 0 °C and stirred for 10 minutes before a 50% aq. KOH solution (6.5 eq., 0.701 mmol, 52.5 µl) was added within five minutes. After vigorous stirring for 30 minutes at 0 °C, the mixture was heated to room temperature and stirred for 72 hours. The resulting suspension was filtrated through a SiO_2 pad and the filtrate was

concentrated. The crude mixture was purified by column chromatography (SiO_2, pentane/EtOAc (20:1)) to give the title compound **2.13** (21 mg, 0.059 mmol, 51%) as pale yellow solid.

Rf (SiO_2, pentane/EtOAc (5:1)): 0.43.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.41 (dd, *J* = 10.2, 4.6 Hz, 2 H), 7.35 – 7.19 (m,11 H), 7.07 (d, *J* = 7.3 Hz, 2 H), 6.60 (t, *J* = 2.5 Hz, 1 H), 4.18 (d, *J* = 2.6 Hz, 2 H), 3.50 (d, *J* = 13.1 Hz, 2 H), 3.11 (d, *J* = 13.2 Hz, 2 H).

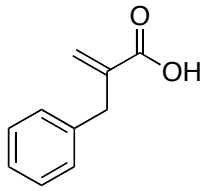
^{13}C-NMR (101 MHz, $CDCl_3$): 179.4, 137.0, 136.0, 135.7, 130.4, 129.0, 128.6, 128.5, 128.3, 128.3, 128.2, 128.1, 127.7, 127.2, 125.7, 70.2, 56.4, 45.6.

IR (neat): 3028, 2927, 1764, 1725, 1493, 1454, 1141, 1025, 698.

HR-MS: Calculated for $C_{25}H_{23}O_2$ $[M+H]^+$: 355.1693, found: 355.1696.

Mp: 102 – 103 °C.

2-Benzylacrylic acid (2.17)

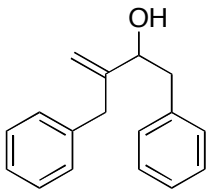


To a solution of 2-benzylacrylaldehyde (**2.16**, 1.00 eq., 3.42 mmol, 500 mg) in *tert*-butanol (4 ml) was added 2-methyl-2-butene (3.00 eq., 10.3 mmol, 1.09 ml). The reaction was cooled to 15 – 20 °C in a ice bath before a mixture of sodium chlorite (2.30 eq., 7.87 mmol, 889 mg) and monobasic sodium phosphate (2.00 eq., 6.84 mmol, 821 mg) in water (2.5 ml) was added dropwise within 30 minutes, maintaining the temperature below 20 °C. The reaction mixture was allowed to reach room temperature over two days. Subsequently, the mixture was concentrated, diluted with water and acidified to pH 3 with phosphoric acid. A white solid precipitated, which was collected by filtration to give the title compound **2.17** (197 mg, 1.2 mmol, 36%) as white solid. The filtrate was extracted three times with CH_2Cl_2. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated to give the title compound **2.17** (358 mg, 2.2 mmol, 65%) as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 (t, *J* = 7.3 Hz, 2 H), 7.22 (dd, *J* = 9.8, 7.8 Hz, 3 H), 6.38 (s, 1 H), 5.58 (d, *J* = 1.3 Hz, 1 H), 3.63 (s, 2 H).

The analytical data of product **2.17** correspond to those reported in the literature.[4]

3-Benzyl-1-phenylbut-3-en-2-ol (2.18)



Pre-dried magnesium turnings (1.40 eq., 4.79 mmol, 116 mg) were mixed with dry Et_2O (2 ml) and cooled to 0 °C. Then diisobutylaluminium hydride (1 M solution in hexane, 0.015 eq., 0.05 mmol, 0.05 ml) was added and the mixture was stirred for 10 minutes. Subsequently, benzyl bromide (1.25 eq., 4.28 mmol, 508 µl) in dry Et_2O (1 ml) was added dropwise. The resulting solution was stirred for two hours at 0 °C. To the resulting yellow suspension, a solution of 2-benzylacrylaldehyde (**2.16**, 1.00 eq., 3.42 mmol, 500 mg) in dry Et_2O (1 ml) was added dropwise. The mixture was stirred for three hours at room temperature before it was quenched with a sat. aq. NH_4Cl solution, stirred for another 30 minutes and filtrated over Celite. The layers were separated and the aq. layer was extracted three times with TBME. The org. layers were subsequently washed with water and brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (9:1)) to give the title compound **2.18** (460 mg, 1.9 mmol, 56%) as colorless oil.

Rf (SiO_2, pentane/EtOAc (9:1)): 0.29.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.27 (m, 4 H), 7.25 – 7.17 (m, 6 H), 5.17 (s, 1 H), 4.82 (d, J = 1.1 Hz, 1 H), 4.33 – 4.25 (m, 1 H), 3.52 (d, J = 15.5 Hz, 1 H), 3.39 (d, J = 15.5 Hz, 1 H), 2.95 (dd, J = 13.7, 4.1 Hz, 1 H), 2.76 (dd, J = 13.7, 8.9 Hz, 1 H), 1.58 (d, J = 3.5 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 150.7, 139.2, 138.3, 129.4, 129.2, 128.5, 128.4, 126.6, 126.3, 112.3, 75.0, 42.8, 39.4.

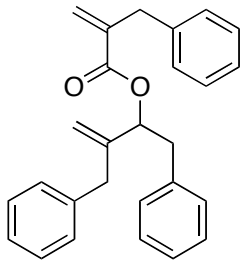
IR (neat): 3558, 3421, 3062, 3027, 2919, 1647, 1602, 1494, 1453, 1049, 1030, 906, 743, 697.

HR-MS: Calculated for $C_{17}H_{18}NaO$ $[M+Na]^+$: 261.1250, found: 261.1254.

EI-MS (70 eV) m/z (%): 238 (3, $[M]^+$), 147 (63), 146 (78), 145 (15), 130 (10), 129 (100), 117 (25), 116 (24), 115 (13), 92 (61), 91 (88), 65 (12).

The analytical data of product **2.18** correspond to those reported in the literature.[5]

3-Benzyl-1-phenylbut-3-en-2-yl 2-benzylacrylate (2.19)



To a solution of 3-benzyl-1-phenylbut-3-en-2-ol (**2.18**, 1.0 eq., 0.093 mmol, 22 mg) and 2-benzylacrylic acid (**2.17**, 1.3 eq., 0.12 mmol, 20 mg) in dry CH_2Cl_2 (2 ml) was added 4-dimethylaminopyridine (1.1 eq., 0.10 mmol, 13 mg). Five minutes later, *N*,*N*'-dicyclohexylcarbodiimide (1.5 eq., 0.14 mmol, 29 mg) was added and the mixture was heated to reflux. After five hours at reflux, the reaction was cooled to room temperature and the precipitate was filtered off. After concentrating the filtrate, the crude product was purified by preparative TLC (SiO_2, pentane/EtOAc (15:1)) to give the title compound **2.19** (27 mg, 0.071 mmol, 76%) as pale yellow oil.

Rf (SiO_2, pentane/EtOAc (15:1)): 0.73.

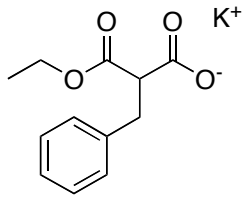
^{1}H-NMR (500 MHz, $CDCl_3$): 7.30 – 7.24 (m, 5 H), 7.24 – 7.18 (m, 4 H), 7.13 (dd, *J* = 6.9, 5.2 Hz, 4 H), 7.10 – 7.06 (m, 2 H), 6.16 (s, 1 H), 5.43 (dd, *J* = 7.9, 5.6 Hz, 1 H), 5.39 (d, *J* = 1.4 Hz, 1 H), 4.96 (s, 1 H), 4.71 (d, *J* = 1.0 Hz, 1 H), 3.54 (s, 2 H), 3.36 (d, *J* = 15.8 Hz, 1 H), 3.30 (d, *J* = 15.8 Hz, 1 H), 2.92 (dd, *J* = 13.9, 8.0 Hz, 1 H), 2.86 (dd, *J* = 14.0, 5.5 Hz, 1 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 166.0, 146.8, 140.1, 138.8, 138.7, 137.4, 129.5, 129.5, 129.1, 128.6, 128.5, 128.4, 126.6, 126.5, 126.4, 114.4, 77.7, 40.4, 39.5, 38.1.

IR (neat): 3062, 3028, 2922, 1716, 1632, 1603, 1494, 1453, 1297, 1191, 1129, 1000, 908, 737, 697.

HR-MS: Calculated for $C_{27}H_{26}NaO_2$ $[M+Na]^+$: 405.1825, found: 405.1825.

Potassium 2-benzyl-3-ethoxy-3-oxopropanoate (2.28)



A published procedure[6] was modified as follows: To a solution of diethyl benzylmalonate (**2.27**, 1.00 eq., 20.0 mmol, 5.11 g) in EtOH (20 ml) was added a freshly filtrated solution of potassium hydroxide (1.05 eq., 21.0 mmol, 1.39 g) in EtOH

(20 ml) at room temperature. The reaction was stirred for six hours at room temperature. The precipitate was filtered off and the filtrate was concentrated to a yellowish foam. The residue was suspended twice in Et_2O and again concentrated. After drying at high vacuum, the foam was triturated overnight in Et_2O (50 ml). The precipitate was filtered off, washed twice with Et_2O and dried in vacuum to give the title compound **2.28** (4.44 g, 17 mmol, 85%) as white solid.

^{1}H-NMR (400 MHz, D_2O): 7.30 – 7.22 (m, 2 H), 7.22 – 7.15 (m, 3 H), 4.06 – 3.96 (m, 2 H), 3.51 (dd, *J* = 8.8, 7.4 Hz, 1 H), 3.05 – 3.00 (m, 2 H), 1.07 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (101 MHz, D_2O): 176.0, 173.3, 139.1, 128.7, 128.6, 126.6, 62.0, 57.3, 35.0, 13.2.

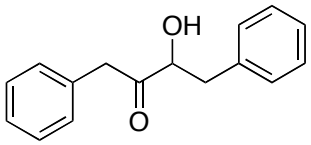
IR (neat): 3396, 2980, 1710, 1598, 1496, 1454, 1359, 1321, 1234, 1150, 1095, 1061, 1028, 950, 914, 858, 830, 745, 698.

HR-MS: Calculated for $C_{12}H_{13}O_4$ $[M-K]^-$ 221.0819, found: 221.0822.

Mp: 120 °C decomposition.

The analytical data of product **2.28** correspond to those reported in the literature.[6]

3-Hydroxy-1,4-diphenylbutan-2-one (2.30)



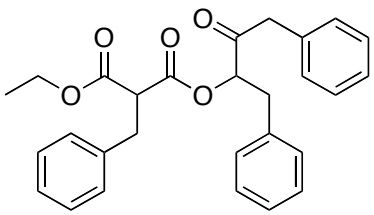
A published procedure[7] was modified as follows: To a solution of sodium acetate (0.200 eq., 4.00 mmol, 328 mg) and freshly distilled phenyl acetaldehyde (**1.10**, 2.00 eq., 40.0 mmol, 4.77 ml) in EtOH (20 ml) was added 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (**2.29**, 0.100 eq., 2.00 mmol, 540 mg). The mixture was heated to reflux for three hours, cooled down and mixed with ice water (20 ml). After stirring for another hour, the mixture was saturated with NaCl and extracted three times with EtOAc. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (7:1 to 5:1)) to give the title compound **2.30** (2.9 g, 12 mmol, 61%) as yellow liquid, which crystallized after several days.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.39 – 7.26 (m, 6 H), 7.25 – 7.12 (m, 4 H), 4.51 (ddd, *J* = 7.4, 5.5, 4.9 Hz, 1 H), 3.81 (d, *J* = 15.9 Hz, 1 H), 3.75 (d, *J* = 15.9 Hz, 1 H), 3.22 (d, *J* = 5.6 Hz, 1 H), 3.15 (dd, *J* = 14.1, 4.7 Hz, 1 H), 2.90 (dd, *J* = 14.1, 7.4 Hz, 1 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 209.2, 136.5, 133.1, 129.6, 129.5, 128.9, 128.8, 127.5, 127.2, 76.8, 45.9, 40.3.

The analytical data of product **2.30** correspond to those reported in the literature.[7,8]

1-Ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-benzylmalonate (2.31) as a mixture of diastereomers



To a suspension of potassium 2-benzyl-3-ethoxy-3-oxopropanoate (**2.28**, 1.40 eq., 72.8 mmol, 19.0 g) in dry THF (250 ml) at 0 °C was added DMF (0.050 eq., 5.20 mmol, 201 µl) followed by the dropwise addition of pivaloyl chloride (1.70 eq., 88.4 mmol, 11.0 ml) over five minutes. During the addition of pivaloyl chloride, the reaction mixture turned to a solution and after another 10 minutes to a jelly. This was then kept for one hour at 0 °C and for 2.5 hours at room temperature. During that time, the jelly dissolved and the reaction mixture could be stirred again. The resulting solution was concentrated, dried in high vacuum, again dissolved in dry CH_2Cl_2 (250 ml), concentrated and dried again in high vacuum without exceeding a temperature of 25 °C. The residue was dissolved in dry CH_2Cl_2 (250 ml) and cooled to 0 °C. The addition of 4-dimethylaminopyridine (0.100 eq., 5.20 mmol, 635 mg) to the reaction mixture was followed by the addition of a solution of 3-hydroxy-1,4-diphenylbutan-2-one (**2.30**, 1.00 eq., 52.0 mmol, 12.5 g) in dry CH_2Cl_2 (50 ml) over 10 minutes. The reaction was allowed to reach room temperature overnight before it was quenched at 0 °C with a mixture of water and a sat. aq. $NaHCO_3$ solution (1:1 v/v). The layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were washed with a sat. aq. NH_4Cl solution, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **2.31** (23.1 g, 52 mmol, quantitative) as yellowish liquid.

Rf (SiO_2, pentane/Et_2O (2:1)): 0.7.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.32 – 7.20 (m, 8 H), 7.20 – 7.15 (m, 2 H), 7.14 – 7.09 (m, 2 H), 7.06 – 6.99 (m, 3 H), 5.35 – 5.25 (m, 1 H), 4.21 – 4.04 (m, 2 H), 3.76 – 3.69 (m, 1 H), 3.58 (s, 1 H), 3.50 (d, J = 16.9 Hz, 0.5 H), 3.38 (d, J = 16.9 Hz, 0.5 H), 3.26 – 3.11 (m, 2 H), 3.06 – 2.93 (m, 2 H), 1.19 – 1.11 (m, 3 H).

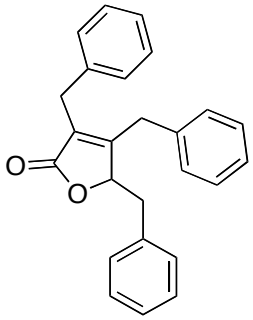
^{13}C-NMR (126 MHz, $CDCl_3$): 204.4, 204.3, 168.5, 168.4, 168.4, 168.3, 137.7, 137.6, 135.7, 135.5, 132.9, 132.9, 129.9, 129.9, 129.6, 129.6, 129.0, 129.0, 128.7, 128.7, 128.7, 127.3, 127.3, 127.2, 127.1, 127.1, 79.6, 79.4, 61.9, 61.9, 53.8, 53.7, 46.5, 46.4, 37.1, 34.7, 34.7, 14.1, 14.1.

IR (neat): 3031, 2982, 2936, 1732, 1497, 1454, 1369, 1276, 1229, 1149, 701, 633.

HR-MS: Calculated for $C_{28}H_{32}NO_5$ $[M+NH_4]^+$: 462.2275, found: 462.2274.

EI-MS (70 eV) m/z (%): 444(3, $[M]^+$), 353 (9), 205 (43), 160 (10), 159 (100), 131 (68), 91 (94).

Maculalactone A (1.34)



A two neck round bottom flask was equipped with a condenser and a device to run the condensed solvent over a bed of 4 Å molecular sieves (Section 9.5.1). In the flask, a mixture of cesium carbonate (0.200 eq., 3.78 mmol, 1.23 g) and THF (400 ml) was heated until the suspension was strongly refluxing. After refluxing for 30 minutes, a solution of 1-ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-benzylmalonate (**2.31**, 1.00 eq., 18.9 mmol, 8.40 g) in THF (20 ml) was added over 25 minutes. The reaction was further stirred under strong reflux. After 3.5 hours, the finished reaction was cooled to room temperature. The mixture was filtrated over a bed of SiO_2 and the solids were washed with TBME. The filtrate was concentrated. The crude product was dissolved in a hot mixture of MeOH/water (3:1, 300 ml) before activated carbon (90 mg) was added. After boiling for 10 minutes, the mixture was filtrated and the solids were washed with a hot mixture of MeOH/water (3:1, 20 ml). The filtrate was again heated to reflux and MeOH (22 ml) were added to get a solution. The solution was cooled down overnight and after addition of some crystals, the product started to crystallize. The resulting suspension was cooled to 0 °C before precipitate was filtered off and washed twice with a cold mixture of MeOH/water (2:1, 25 ml). The crystals were dried in high vacuum to give the title compound **1.34** (5.1 g, 14 mmol, 76%) as brownish crystals. The filtrate was concentrated and purified by column chromatography (SiO_2,

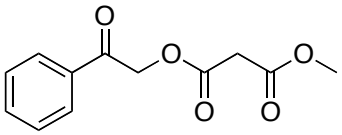
pentane/EtOAc (12:1)) to give the title compound **1.34** (290 mg, 0.82 mmol, 4%) as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.23 (m, 6 H), 7.22 – 7.10 (m, 5 H), 7.03 (d, *J* = 6.5 Hz, 2 H), 6.92 – 6.85 (m, 2 H), 4.99 – 4.89 (m, 1 H), 3.92 (d, *J* = 15.6 Hz, 1 H), 3.63 (d, *J* = 15.3 Hz, 1 H), 3.57 (d, *J* = 15.3 Hz, 1 H), 3.48 (d, *J* = 15.6 Hz, 1 H), 3.23 (dd, *J* = 14.5, 3.9 Hz, 1 H), 2.82 (dd, *J* = 14.6, 6.1 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 173.7, 161.8, 137.8, 136.1, 135.0, 129.6, 129.2, 128.8, 128.7, 128.3, 127.5, 127.3, 126.5, 81.7, 77.4, 38.1, 33.4, 29.5.

The analytical data of product **1.34** correspond to those reported in the literature.[1]

Methyl (2-oxo-2-phenylethyl) malonate



To a suspension of potassium 3-methoxy-3-oxopropanoate (1.10 eq., 1.10 mmol, 172 mg) in CH_2Cl_2 (2 ml) at 0 °C was added freshly distilled oxayl chloride (1.30 eq., 1.30 mmol, 112 µl) over five minutes. This was followed by the addition of some drops of dry DMF. The reaction was stirred for 30 minutes at 0 °C and for one hour at room temperature. The resulting mixture was concentrated, again dissolved in CH_2Cl_2 (4 ml), concentrated, dried in high vacuum and finally dissolved in CH_2Cl_2 (2 ml) and cooled to 0 °C. A mixture of 2-hydroxy-1-phenylethanone (1.00 eq., 1.00 mmol, 136 mg) and pyridine (2.00 eq., 2.00 mmol, 161 µl) in CH_2Cl_2 (2 ml) was slowly added. The resulting mixture was stirred overnight at room temperature. The reaction was cooled to 0 °C and quenched with water. Then a sat. aq. NH_4Cl solution was added and the pH was adjusted to 4 – 5 with a 1 M aq. HCl solution. The layers were separated and the aq. layer was extracted with CH_2Cl_2 and twice with EtOAc. The org. layers were washed with a mixture of water and a sat. aq. $NaHCO_3$ solution (1:1 v/v), combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O (2:1)) to give the title compound (90 mg, 0.38 mmol, 90%) as pale yellow oil.

Rf (SiO_2, pentane/Et_2O (2:1)): 0.19.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.93 – 7.89 (m, 2 H), 7.64 – 7.59 (m, 1 H), 7.52 – 7.47 (m, 2 H), 5.41 (s, 2 H), 3.78 (s, 3 H), 3.59 (s, 2 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 191.4, 166.8, 166.1, 134.2, 134.1, 129.1, 127.9, 66.9, 52.8, 41.1.

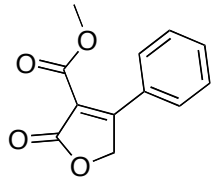
IR (neat): 3001, 2954, 1737, 1702, 1449, 1341, 1225, 1148, 1015, 973, 756, 692, 661, 609.

HR-MS: Calculated for $C_{12}H_{13}O_5$ $[M+H]^+$: 237.0757, found: 237.0759.

FAB-MS (8 kV, Xe) m/z (%): 238 (15), 237 (100, $[M+H]^+$), 137 (57), 136 (15), 119 (10), 105 (18), 101 (10), 91 (10).

The analytical data of product correspond to those reported in the literature.[9]

Methyl 2-oxo-4-phenyl-2,5-dihydrofuran-3-carboxylate



To a solution of methyl (2-oxo-2-phenylethyl) malonate (1.0 eq., 0.22 mmol, 52 mg) in THF (2.5 ml) at 0 °C was added sodium hydride (1.3 eq., 0.29 mmol, 11 mg) in one portion. The reaction was stirred for 15 minutes at 0 °C and for two hours at room temperature. The resulting suspension was quenched at 0 °C with a sat. aq. NH_4Cl solution. The layers were separated and the aq. layer was extracted six times with TBME. The org. layers were combined, washed with brine, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O (1:1)) to give the title compound (44 mg, 0.20 mmol, 92%) as yellowish solid.

Rf (SiO_2, pentane/Et_2O (1:1)): 0.21.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.57 – 7.45 (m, 5 H), 5.18 (s, 2 H), 3.90 (s, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 169.6, 165.3, 162.9, 132.4, 129.3, 128.0, 119.4, 70.7, 52.9.

IR (neat): 2956, 1744, 1721, 1634 ,1440, 1341, 1239, 1208, 1196, 1070, 1038, 767, 744, 694.

HR-MS: Calculated for $C_{12}H_{10}NaO_4$ $[M+Na]^+$: 241.0471, found: 241.0474.

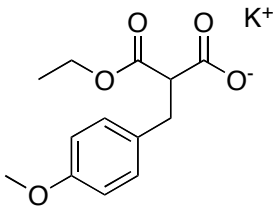
EI-MS (70 eV) m/z (%): 219 (13), 218 (100, $[M]^+$), 203 (26), 188 (20), 187 (56), 160 (27), 129 (46), 121 (32), 119 (28), 105 (26), 91 (56).

Mp: 134 – 135 °C.

The analytical data of product correspond to those reported in the literature.[9]

8.3 From a Natural Product to a Functional Molecule

Potassium 3-ethoxy-2-(4-methoxybenzyl)-3-oxopropanoate (3.08)



A solution of diethyl 2-(4-methoxybenzyl)malonate (**3.07**, 1.00 eq., 1.80 mmol, 505 mg) in dry EtOH (2 ml) was cooled to -15 °C. A freshly filtrated solution of KOH (1.05 eq., 1.89 mmol, 125 mg) in dry EtOH (2 ml) was added at -15 °C over 15 minutes. The resulting mixture was stirred for 17 hours at -15 °C before it was concentrated to give a white honey with some solid parts. This was suspended twice in Et_2O and again concentrated. The residue was triturated in Et_2O overnight. The precipitate was filtered off, washed twice with Et_2O and dried in high vacuum to give the title compound **3.08** (421 mg, 1.5 mmol, 81%) as white solid.

^{1}H-NMR (400 MHz, D_2O): 7.22 (d, *J* = 8.7 Hz, 2 H), 6.97 – 6.90 (m, 2 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 3.80 (s, 3 H), 3.56 (dd, *J* = 8.9, 7.3 Hz, 1 H), 3.07 (s, 1 H), 3.05 (d, *J* = 2.9 Hz, 1 H), 1.15 (t, *J* = 7.1 Hz, 3 H).

^{13}C-NMR (101 MHz, D_2O): 176.0, 173.4, 157.4, 131.7, 129.9, 114.1, 62.0, 57.5, 55.4, 34.2, 13.2.

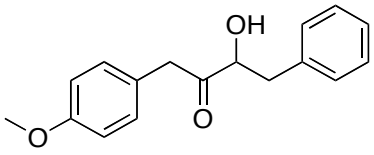
IR (neat): 3383, 1714, 1597, 1512, 1361, 1247, 1150, 1034, 818, 687.

FAB-MS (8 kV Xe) m/z (%): 291 (100, $[M+K]^+$), 281 (18), 253 (15), 252 (18), 242 (16), 121 (39), 39 (75).

HR-MS: Calculated for $C_{13}H_{16}NaO_5$ $[M+Na]^+$: 275.0890, found: 275.0890.

Mp: 129 – 130 °C.

3-Hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-2-one (3.10)



For the formation of the cyanohydrin, a published procedure[8] was modified as follows: To neat trimethylsilyl cyanide (1.00 eq., 20.0 mmol, 2.67 ml) was added a crystal of ZnI_2 and the mixture was cooled to 0 °C. Then freshly distilled phenylacetaldehyde (**1.10**, 1.00 eq., 20.0 mmol, 2.38 ml) was added over five minutes.

The reaction was stirred and allowed to reach room temperature over three hours. The TMS protected cyanohydrin was isolated by Kugelrohr distillation at 80 to 110 °C and 0.5 mbar to give the intermediate **3.09** (2.85 g, 13 mmol, 65%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.27 – 7.13 (m, 5 H), 4.41 (dd, *J* = 7.3, 6.4 Hz, 1 H), 2.98 (d, *J* = 6.4 Hz, 1 H), 2.97 (d, *J* = 7.3 Hz, 1 H), 0.00 (s, 9 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 199.6, 135.0, 129.8, 128.7, 127.6, 63.0, 42.9, -0.5.

The analytical data of the intermediate cyanohydrin correspond to those reported in the literature.[8]

A solution of the TMS protected cyanohydrin (1.00 eq., 13.0 mmol) in dry Et_2O (20 ml) was added dropwise to a solution of (4-methoxybenzyl)magnesium chloride (1.50 eq., 19.5 mmol) in dry Et_2O (60 ml) at reflux (preparation can be found after the analytical data). The mixture was stirred for five hours at reflux. A GC-MS analysis showed about 50% conversion. Therefore another portion of (4-methoxybenzyl)magnesium chloride (1.50 eq., 19.5 mmol) in dry Et_2O (70 ml) was added to the refluxing reaction. After another four hours at reflux, the GC-MS analysis showed complete conversion. The reaction was cooled down and poured on a mixture of 35% aq. HCl (60 ml) and ice (100 ml). The resulting mixture was allowed to reach room temperature overnight. The layers were separated and the aq. layer was extracted twice with TBME. The org. layers were washed with a sat. aq. Na_2CO_3 solution, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (5:1)) to give the title compound **3.10** (1.89 g, 7.0 mmol, 54%) as yellowish solid. Over both steps, a yield of 35% was achieved.

Rf (SiO_2, pentane/EtOAc (4:1)): 0.31.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.35 – 7.20 (m, 5 H), 7.09 – 7.04 (m, 2 H), 6.89 – 6.84 (m, 2 H), 4.55 – 4.47 (m, 1 H), 3.80 (s, 3 H), 3.75 (d, *J* = 16.0 Hz, 1 H), 3.69 (d, *J* = 16.0 Hz, 1 H), 3.22 (d, *J* = 5.6 Hz, 1 H), 3.15 (dd, *J* = 14.1, 4.7 Hz, 1 H), 2.89 (dd, *J* = 14.1, 7.4 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 209.5, 159.0, 136.6, 130.7 129.5, 128.8, 127.1, 125.0, 114.4, 76.7, 55.4, 45.0, 40.4.

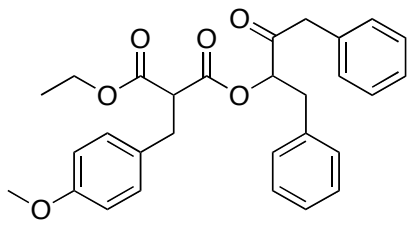
IR (neat): 3391, 2837, 1694, 1614, 1513, 1467, 1301, 1245, 1177, 1090, 1033, 798, 741.

HR-MS: Calculated for $C_{17}H_{22}NO_3$ $[M+NH_4]^+$: 288.1594, found: 288.1592.

Mp: < 50 °C.

Crucial is the generation of the Grignard reagent as benzyl magnesium compounds are prone for reductive homo couplings. A efficient method was found to be as follows. Pre-dried magnesium turnings (1.60 eq., 20.8 mmol, 506 mg) were mixed with dry Et_2O (50 ml) and cooled to -20 °C. Then diisobutylaluminium hydride (1 M solution in hexane, 0.010 eq., 0.13 mmol, 0.13 ml) was added and the solution was stirred for 10 minutes. This was followed by the addition of a solution of 1-(chloromethyl)-4-methoxybenzene (1.50 eq., 19.5 mmol, 2.66 ml) in dry Et_2O (20 ml) over two hours at -20 °C. The reaction was stirred for 17 hours at -20 °C. According to GC-MS the resulting solution consists of starting material, Grignard reagent and dimerization product in a ration of 1 to 3 to 1.

1-Ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-(4-methoxybenzyl)malonate (3.14) as mixture of diastereomers



To a suspension of potassium 3-ethoxy-2-(4-methoxybenzyl)-3-oxopropanoate (**3.08**, 1.40 eq., 1.33 mmol, 386 mg) in dry THF (6 ml) at 0 °C was added DMF (0.05 eq., 0.05 mmol, 4 µl) followed by the dropwise addition of pivaloyl chloride (1.70 eq., 1.61 mmol, 201 µl) over five minutes. The reaction was then stirred for two hours at 0 °C and for 3.5 hours at room temperature. The resulting solution was concentrated and dried in high vacuum. Then, the residue was twice dissolved in dry CH_2Cl_2 (60 ml), concentrated and dried in high vacuum without exceeding a temperature of 25 °C. The residue was dissolved in dry CH_2Cl_2 (50 ml) and cooled to 0 °C. The addition of 4-dimethylaminopyridine (0.10 eq., 0.10 mmol, 12 mg) was followed by the addition of a solution of 3-hydroxy-1,4-diphenylbutan-2-one (**2.30**, 1.00 eq., 0.95 mmol, 228 mg) in dry CH_2Cl_2 (2 ml) over five minutes. The reaction was allowed to reach room temperature overnight before it was quenched with a mixture of water and a sat. aq. $NaHCO_3$ solution (1:1 v/v). The layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were washed with a sat. aq. NH_4Cl solution, combined, dried with Na_2SO_4 and concentrated. The crude was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **3.14** (408 mg, 0.86 mmol, 91%) as yellowish oil.

Rf (SiO_2, pentane/EtOAc (8:1)): 0.42.

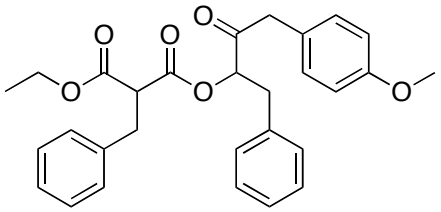
^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.22 (m, 6 H), 7.16 – 7.07 (m, 2 H), 7.07 – 6.98 (m, 4 H), 6.83 – 6.73 (m, 2 H), 5.35 – 5.26 (m, 1 H), 4.17 – 4.05 (m, 2 H), 3.76 (s, 1.3 H), 3.71 – 3.64 (m, 2.6 H), 3.58 (s, 0.9 H), 3.47 (d, *J* = 17.1 Hz, 0.6 H), 3.34 (d, *J* = 17.1 Hz, 0.6 H), 3.22 – 3.07 (m, 2 H), 3.06 – 2.93 (m, 2 H), 1.20 – 1.13 (m, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 204.4, 204.4, 168.6, 168.5, 168.4, 168.3, 158.6, 135.7, 135.6, 132.9, 132.9, 130.0, 130.0, 129.9, 129.9, 129.6, 129.6, 129.6, 129.5, 128.7, 128.7, 128.7, 127.2, 127.2, 127.2, 114.1, 79.6, 79.4, 61.8, 61.8, 55.3, 55.2, 54.1, 54.0, 46.4, 46.3, 37.1, 33.9, 33.9, 14.2, 14.1.

IR (neat): 3063, 3031, 2935, 1729, 1612, 1514, 1455, 1248, 1178, 1148, 1032, 700.

HR-MS: Calculated for $C_{29}H_{30}NaO_6$ $[M+Na]^+$: 497.1935, found: 497.1938.

1-Ethyl 3-(4-(4-methoxyphenyl)-3-oxo-1-phenylbutan-2-yl) 2-benzylmalonate (3.15) as a mixture of diastereomers



To a suspension of potassium 2-benzyl-3-ethoxy-3-oxopropanoate (**2.28**, 1.40 eq., 9.10 mmol, 2.37 g) in dry THF (40 ml) at 0 °C was added DMF (0.050 eq., 0.32 mmol, 25 µl) followed by the dropwise addition of pivaloyl chloride (1.70 eq., 11.1 mmol, 1.37 ml) over five minutes. The reaction was then kept for 1.5 hour at 0 °C and for 2.5 hours at room temperature. The resulting solution was concentrated, dried in high vacuum and then twice dissolved in dry CH_2Cl_2 (40 ml), concentrated and dried in high vacuum without exceeding a temperature of 27 °C. The residue was dissolved in dry CH_2Cl_2 (40 ml) and cooled to 0 °C. The addition of 4-dimethylaminopyridine (0.10 eq., 0.65 mmol, 79 mg) to the reaction mixture was followed by the addition of a solution of 3-hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-2-one (**3.10**, 1.00 eq., 6.50 mmol, 1.76 g) in dry CH_2Cl_2 (10 ml) over five minutes. The reaction was allowed to reach room temperature overnight before it was quenched with a mixture of water and a sat. aq. $NaHCO_3$ solution (1:1 v/v). The layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were washed with a sat. aq. NH_4Cl solution, combined, dried with Na_2SO_4 and concentrated to give the title compound

3.15 (3.33 g, 6.5 mmol, quantitative) as a yellow liquid, which started to crystallize upon long standing.

Rf (SiO_2, pentane/EtOAc (4:1)): 0.59.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 – 7.20 (m, 6 H), 7.20 – 7.15 (m, 2 H), 7.14 – 7.10 (m, 2 H), 7.04 – 7.00 (m, 1 H), 6.98 – 6.90 (m, 2 H), 6.86 – 6.81 (m, 2 H), 5.34 – 5.25 (m, 1 H), 4.17 – 4.05 (m, 2 H), 3.79 (s, 1.5 H), 3.79 (s, 1.5 H), 3.75 – 3.69 (m, 1 H), 3.52 (s, 1 H), 3.44 (d, *J* = 17.0 Hz, 0.5 H), 3.33 (d, *J* = 17.0 Hz, 0.5 H), 3.27 – 3.11 (m, 2 H), 3.06 – 2.91 (m, 2 H), 1.19 – 1.11 (m, 3 H).

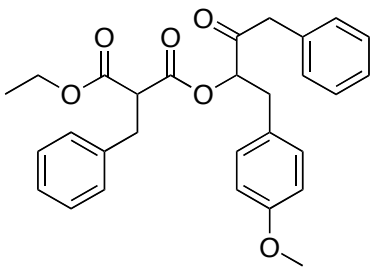
^{13}C-NMR (101 MHz, $CDCl_3$): 204.7, 204.7, 168.5, 168.4, 168.4, 168.3, 158.9, 137.7, 137.6, 135.7, 135.6, 130.9, 130.9, 129.6, 129.6, 129.0, 129.0, 128.7, 128.7, 128.7, 127.2, 127.2, 127.1, 124.8, 124.8, 114.2, 79.6, 79.4, 62.0, 61.8, 55.4, 53.8, 53.7, 45.6, 45.6, 37.1, 34.7, 34.7, 14.1, 14.1.

IR (neat): 3982, 2936, 1728, 1612, 1513, 1247, 1177, 1147, 1030, 737, 699.

HR-MS: Calculated for $C_{29}H_{30}NaO_6$ $[M+Na]^+$: 497.1935, found: 497.1934.

Mp: < 50 °C.

1-Ethyl 3-(1-(4-methoxyphenyl)-3-oxo-4-phenylbutan-2-yl) 2-benzylmalonate (3.16) as a mixture of diastereomers



To a suspension of potassium 2-benzyl-3-ethoxy-3-oxopropanoate (**2.28**, 1.40 eq., 3.75 mmol, 977 mg) in dry THF (20 ml) at 0 °C was added pivaloyl chloride (1.70 eq., 4.56 mmol, 566 µl) dropwise over five minutes followed by the addition of DMF (0.050 eq., 0.13 mmol, 10 µl). The reaction was then kept for 1.5 hour at 0 °C and for three hours at room temperature. The resulting solution is concentrated, dried in high vacuum and then twice dissolved in dry CH_2Cl_2 (20 ml), concentrated and dried in high vacuum without exceeding a temperature of 27 °C. The residue was dissolved in dry CH_2Cl_2 (20 ml) and cooled to 0 °C. The addition of 4-dimethylaminopyridine (0.10 eq., 0.27 mmol, 33 mg) to the reaction mixture was followed by the addition of a solution of 3-hydroxy-4-(4-methoxyphenyl)-1-phenylbutan-2-one (**3.13**, 1.00 eq., 2.68 mmol, 724 mg) in dry CH_2Cl_2 (10 ml) over five minutes. The reaction was allowed to reach

room temperature overnight before it was quenched with a mixture of water and a sat. aq. $NaHCO_3$ solution (1:1 v/v). The layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were washed with a sat. aq. NH_4Cl solution, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **3.16** (733 mg, 1.5 mmol, 58%) as yellowish liquid.

Rf (SiO_2, pentane/EtOAc (6:1)): 0.35.

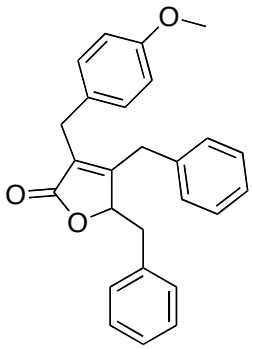
^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.21 (m, 6 H), 7.20 – 7.16 (m, 1 H), 7.15 – 7.10 (m, 1 H), 7.07 – 6.98 (m, 3 H), 6.94 – 6.90 (m, 1 H), 6.84 – 6.75 (m, 2 H), 5.30 – 5.22 (m, 1 H), 4.16 – 4.08 (m, 2 H), 3.78 (s, 1.5 H), 3.78 (s, 1.5 H), 3.74 – 3.70 (m, 1 H), 3.58 (s, 1 H), 3.49 (d, *J* = 16.9 Hz, 0.5 H), 3.37 (d, *J* = 16.9 Hz, 0.5 H), 3.28 – 3.11 (m, 2 H), 3.00 – 2.89 (m, 2 H), 1.19 – 1.13 (m, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 204.4, 204.3, 168.4, 168.1, 168.2, 168.2, 158.7, 158.7, 137.5, 137.5, 132.8, 132.8, 130.5, 130.5, 129.8, 129.7, 128.8, 128.8, 128.6, 128.6, 127.4, 127.3, 127.1, 126.9, 126.9, 114.0, 113.9, 79.7, 79.5, 61.8, 61.7, 55.3, 53.7, 53.6, 46.4, 46.3, 36.1, 34.6, 34.6, 14.0, 14.0.

IR (neat): 1727, 1612, 1514, 1455, 1246, 1177, 1146, 1030, 832, 752, 698.

HR-MS: Calculated for $C_{29}H_{30}NaO_6$ $[M+Na]^+$: 497.1935, found: 497.1943.

4,5-Dibenzyl-3-(4-methoxybenzyl)furan-2(5H)-one (3.17)



A two neck round bottom flask was equipped with a condenser and a device to run the condensed solvent over a bed of 4 Å molecular sieves (Section 9.5.1). In the flask, a mixture of cesium carbonate (0.20 eq., 0.17 mmol, 56 mg) and THF (60 ml) was heated until the suspension was strongly refluxing. After refluxing for 30 minutes, a solution of 1-ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-(4-methoxybenzyl)malonate (**3.14**, 1.00 eq., 0.860 mmol, 408 mg) in THF (8 ml) was added over five minutes. The reaction was further stirred under strong reflux. After four hours, a TLC showed only little conversion and additional cesium carbonate (0.20 eq., 0.17 mmol, 56 mg) was added.

After another four hours, the mixture was cooled down and filtrated over a bed of SiO_2. The solids were washed with TBME and the filtrate was concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **3.17** (252 mg, 0.66 mmol, 76%) as pale yellow oil.

Rf (SiO_2, pentane/EtOAc (6:1)): 0.36.

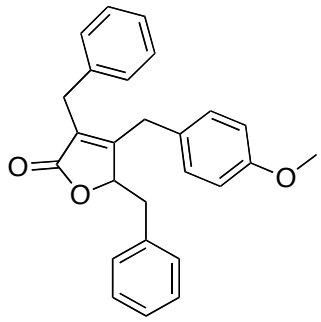
^{1}H-NMR (500 MHz, C_6D_6): 7.06 – 7.01 (m, 6 H), 6.98 – 6.95 (m, 2 H), 6.87 – 6.83 (m, 2 H), 6.73 – 6.67 (m, 4 H), 4.56 – 4.52 (m, 1 H), 3.47 (dd, *J* = 15.2, 3.8 Hz, 2 H), 3.32 (s, 3 H), 2.97 (d, *J* = 15.7 Hz, 1 H), 2.77 (dd, *J* = 14.5, 3.9 Hz, 1 H), 2.33 (dd, *J* = 14.5, 6.4 Hz, 1 H).

^{13}C-NMR (126 MHz, C_6D_6): 172.9, 160.1, 158.8, 136.7, 135.6, 130.5, 129.8, 129.7, 129.7, 129.1, 128.9, 128.7, 128.4, 128.2, 128.0, 127.2, 127.2, 114.4, 81.2, 54.8, 38.2, 33.0, 28.9.

IR (neat): 3028, 2910, 2836, 1729, 1510, 1246, 1049, 1032, 702.

HR-MS: Calculated for $C_{26}H_{24}NaO_3$ $[M+Na]^+$: 407.1618, found: 407.1618.

3,5-Dibenzyl-4-(4-methoxybenzyl)furan-2(5H)-one (3.18)



A two neck round bottom flask was equipped with a condenser and a device to run the condensed solvent over a bed of 4 Å molecular sieves (Section 9.5.1). In the flask, a mixture of cesium carbonate (0.20 eq., 0.21 mmol, 69 mg) and THF (75 ml) was heated until the suspension was strongly refluxing. After refluxing for 30 minutes, a solution of 1-ethyl 3-(4-(4-methoxyphenyl)-3-oxo-1-phenylbutan-2-yl) 2-benzylmalonate (**3.15**, 1.00 eq., 1.05 mmol, 498 mg) in THF (25 ml) was added over five minutes. The reaction was further stirred under strong reflux. After 3.5 hours, the finished reaction was cooled to room temperature. The mixture was filtrated over a bed of SiO_2 and the solids were washed with TBME. The filtrate was concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **3.18** (241 mg, 0.63 mmol, 60%) as yellowish solid.

Rf (SiO_2, pentane/EtOAc (5:1)): 0.31.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.27 – 7.23 (m, 3 H), 7.21 – 7.13 (m, 5 H), 6.95 – 6.86 (m, 4 H), 6.84 – 6.80 (m, 2 H), 4.97 – 4.90 (m, 1 H), 3.86 (d, *J* = 15.6 Hz, 1 H), 3.79 (s, 3 H), 3.62 (d, *J* = 15.3 Hz, 1 H), 3.56 (d, *J* = 15.3 Hz, 1 H), 3.42 (d, *J* = 15.7 Hz, 1 H), 3.22 (dd, *J* = 14.6, 4.0 Hz, 1 H), 2.81 (dd, *J* = 14.6, 6.2 Hz, 1 H).

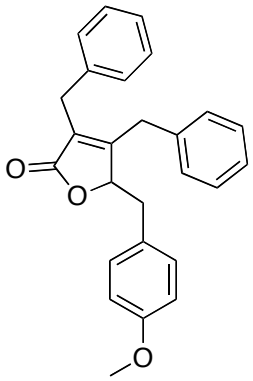
^{13}C-NMR (101 MHz, $CDCl_3$): 173.7, 162.3, 158.9, 137.9, 135.0, 129.8, 129.6, 128.8, 128.7, 128.6, 128.3, 127.9, 127.3, 126.5, 114.6, 81.7, 55.5, 38.1, 32.5, 29.4.

IR (neat): 3029, 2838, 1747, 1511, 1249, 1177, 1024, 836, 725, 698, 655.

HR-MS: Calculated for $C_{26}H_{25}O_3$ $[M+H]^+$: 385.1798, found: 385.1797.

Mp: 62 – 63 °C.

3,4-Dibenzyl-5-(4-methoxybenzyl)furan-2(5H)-one (3.19)



A two neck round bottom flask was equipped with a condenser and a device to run the condensed solvent over a bed of 4 Å molecular sieves (Section 9.5.1). In the flask, a mixture of cesium carbonate (0.20 eq., 0.17 mmol, 55 mg) and THF (60 ml) was heated until the suspension was strongly refluxing. After refluxing for 30 minutes, a solution of 1-ethyl 3-(1-(4-methoxyphenyl)-3-oxo-4-phenylbutan-2-yl) 2-benzylmalonate (**3.16**, 1.00 eq., 0.850 mmol, 403 mg) in THF (20 ml) was added over five minutes. The reaction was further stirred under strong reflux. After 7.5 hours, the finished reaction was cooled to room temperature. The mixture was filtrated over a bed of SiO_2 and the solids were washed with TBME. The filtrate was concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **3.19** (230 mg, 0.60 mmol, 70%) as yellowish solid.

Rf (SiO_2, pentane/EtOAc (6:1)): 0.25.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.24 (m, 4 H), 7.19 – 7.15 (m, 3 H), 7.09 – 7.03 (m, 4 H), 6.87 – 6.83 (m, 2 H), 6.80 – 6.75 (m, 2 H), 4.92 (t, *J* = 4.7 Hz, 1 H), 3.92 (d, *J* = 15.6 Hz, 1 H), 3.79 (s, 3 H), 3.63 (d, *J* = 15.4 Hz, 1 H), 3.56 (d, *J* = 15.3 Hz, 1 H),

3.46 (d, *J* = 15.6 Hz, 1 H), 3.20 (dd, *J* = 14.7, 4.0 Hz, 1 H), 2.80 (dd, *J* = 14.7, 5.6 Hz, 1 H).

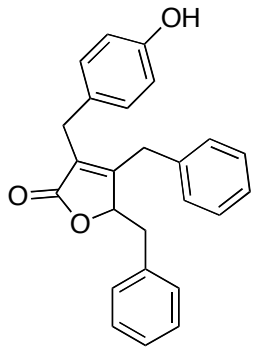
^{13}C-NMR (101 MHz, $CDCl_3$): 173.7, 161.8, 158.9, 137.8, 136.1, 130.7, 129.2, 128.8, 128.8, 128.6, 128.3, 127.4, 126.7, 126.5, 114.1, 81.8, 55.3, 37.0, 33.4, 29.5.

IR (neat): 2932, 1735, 1676, 1612, 1454, 1332, 1244, 1178, 1132, 1099, 1033, 1006, 836, 706, 658.

HR-MS: Calculated for $C_{26}H_{24}NaO_3$ $[M+Na]^+$: 407.1618, found: 407.1618.

Mp: 101 – 102 °C.

4,5-Dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (3.20)



To a solution of 4,5-dibenzyl-3-(4-methoxybenzyl)furan-2(5H)-one (**3.17**, 1.00 eq., 0.655 mmol 252 mg) in dry CH_2Cl_2 (15 ml) at -78 °C was added BBr_3 (1 M solution in CH_2Cl_2, 5.0 eq., 3.3 mmol, 3.3 ml) over 15 minutes. The reaction was allowed to reach room temperature overnight. Subsequently, the reaction mixture was cooled to 0 °C and poured on ice. The layers were separated and the aq. layer was extracted two times with CH_2Cl_2. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated to give the title compound **3.20** (258 mg, 0.66 mmol, quantitative) as brownish foam.

Rf (SiO_2, pentane/EtOAc (3:1)): 0.31.

^{1}H-NMR (500 MHz, C_6D_6): 7.07 – 6.99 (m, 6 H), 6.95 (dd, *J* = 7.4, 1.8 Hz, 2 H), 6.74 – 6.66 (m, 4 H), 6.55 – 6.49 (m, 2 H), 4.78 (s, 1 H), 4.57 – 4.47 (m, 1 H), 3.48 – 3.36 (m, 2 H), 3.28 (d, *J* = 15.0 Hz, 1 H), 2.95 (d, *J* = 15.7 Hz, 1 H), 2.75 (dd, *J* = 14.5, 3.9 Hz, 1 H), 2.31 (dd, *J* = 14.5, 6.2 Hz, 1 H).

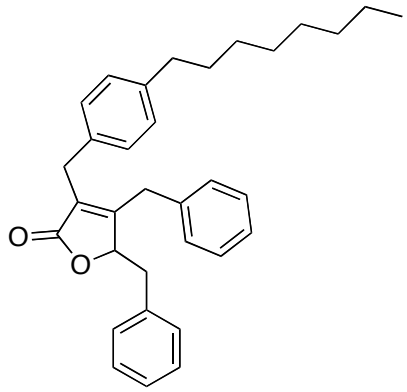
^{13}C-NMR (101 MHz, C_6D_6): 173.4, 160.5, 155.3, 136.6, 135.5, 129.8, 129.8, 129.8, 129.7, 129.1, 128.9, 128.8, 128.2, 127.9, 127.2, 115.8, 81.5, 38.1, 33.0, 28.8.

IR (neat): 3357, 3029, 2922, 1723, 1512, 1452, 1341, 1225, 1051, 831, 748, 699.

HR-MS: Calculated for $C_{25}H_{22}NaO_3$ $[M+Na]^+$: 393.1461, found: 393.1460.

EI-MS (70 eV) m/z (%): 280 (7), 279 (35, $[M]^+$), 276 (18), 107 (45), 91 (100).

4,5-Dibenzyl-3-(4-octylbenzyl)furan-2(5H)-one (3.21)



A solution of 4,5-dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (**3.20**, 1.0 eq., 0.14 mmol, 50 mg) in a mixture of dry CH_2Cl_2 (3 ml) and dry pyridine (1 ml) was cooled to 0 °C. To the cooled solution was added trifluoromethansulfonic anhydride (1.2 eq., 0.16 mmol, 28 µl) over five minutes. The reaction mixture was stirred for 30 minutes at 0 °C and 30 minutes at room temperature. Since a TLC shows only little conversion, additional trifluoromethansulfonic anhydride (1.2 eq., 0.16 mmol, 28 µl) was added at 0 °C. After stirring for 15 minutes at 0 °C and 45 minutes at room temperature a TLC confirmed complete conversion. The reaction was cooled to 0 °C and quenched with a 1 M aq. HCl solution. The layers were separated and the aq. layer was extracted twice with CH_2Cl_2. The org. layers were subsequently washed with a 1 M aq. HCl solution and a sat. aq. $NaHCO_3$ solution, combined, dried with Na_2SO_4 and concentrated to give the activated intermediate (59 mg, 0.12 mmol, 87%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.39 – 7.23 (m, 6 H), 7.19 – 7.12 (m, 2 H), 7.08 – 7.01 (m, 4 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 5.02 (t, *J* = 4.6 Hz, 1 H), 3.89 (d, *J* = 15.7 Hz, 1 H), 3.67 – 3.47 (m, 3 H), 3.30 (dd, *J* = 14.6, 4.1 Hz, 1 H), 2.88 (dd, *J* = 14.6, 5.4 Hz, 1 H).

^{19}F-NMR (376 MHz, $CDCl_3$, no ^{19}F reference): -72.86 (s).

A solution of 9-borabicyclo[3.3.1]nonane (0.5 M solution in THF, 1.4 eq., 0.16 mmol, 320 µl) was cooled to 0 °C before 1-octene (1.4 eq., 0.16 mmol, 26 µl) was added. The mixture was stirred for 30 minutes at 0 °C, giving the solution A. To a second solution of the triflate intermediate (1.0 eq., 0.12 mmol, 58 mg) and 1,1'-bis(diphenylphosphino)ferrocene-paladium(II) dichloride*CH_2Cl_2 (0.05 eq., 6 µmol, 5 mg) in dry THF (1 ml) was added a 3 M aq. NaOH solution (0.12 ml). This was followed by the addition of solution A. The reaction mixture was stirred at reflux overnight and concentrated forming a black residue. The residue was mixed with water

and extracted three times with TBME. The org layers were combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (10:1)) and subsequently by preparative TLC (SiO_2, pentane/EtOAc (9:1)) to give the title compound **3.21** (14 mg, 0.030 mmol, 26%) as pale yellow oil. Over both steps, a yield of 23% was achieved.

Rf (SiO_2, pentane/EtOAc (9:1)): 0.45.

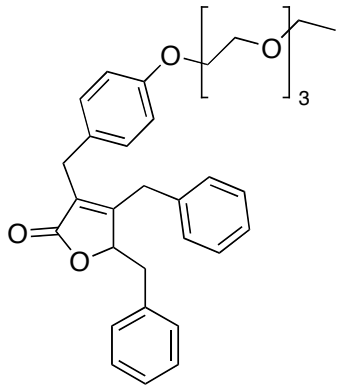
^{1}H-NMR (500 MHz, $CDCl_3$): 7.32 – 7.23 (m, 6 H), 7.17 – 7.12 (m, 2 H), 7.04 – 6.97 (m, 4 H), 6.82 (d, *J* = 7.9 Hz, 2 H), 4.96 – 4.88 (m, 1 H), 3.94 (d, *J* = 15.5 Hz, 1 H), 3.58 (d, *J* = 5.3 Hz, 2 H), 3.47 (d, *J* = 15.5 Hz, 1 H), 3.22 (dd, *J* = 14.5, 4.0 Hz, 1 H), 2.81 (dd, *J* = 14.6, 6.3 Hz, 1 H), 2.59 – 2.50 (m, 2 H), 1.60 – 1.55 (m, 3 H), 1.33 – 1.24 (m, 10 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 173.7, 161.6, 141.1, 136.2, 135.1, 135.0, 129.6, 129.2, 128.9, 128.8, 128.8, 128.7, 128.2, 127.4, 127.2, 81.7, 38.2, 35.7, 33.3, 32.1, 31.7, 29.7, 29.5, 29.4, 29.1, 22.8, 14.3.

IR (neat): 2925, 2854, 1752, 1512, 1495, 1454, 1337, 1078, 1049, 1008, 750, 700.

HR-MS: Calculated for $C_{33}H_{38}NaO_2$ $[M+Na]^+$: 489.2760, found: 489.2763.

4,5-Dibenzyl-3-(4-(2-(2-(2-ethoxyethoxy)ethoxy)ethoxy)benzyl)furan-2(5H)-one (3.23)



To a solution of 4,5-dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (**3.22**, 1.0 eq., 0.14 mmol, 50 mg) and potassium carbonate (2.0 eq., 0.27 mmol, 37 mg) in acetone (1 ml) was added triethylene glycol monoethyl ether *p*-tosylate[10,11] (**3.22**, 1.1 eq., 0.15 mmol, 54 mg). The reaction mixture was stirred for 50 hours at reflux before it was concentrated. The crude product was first purified by column chromatography (SiO_2, pentane/EtOAc (3:2)) and then by preparative HPLC chromatography (Gemini-NX 10u C18 250x21.2 mm, CH_3CN/water (95:5 to 0:100)) to give the title compound **3.23** (31 mg, 0.058 mmol, 43%) as pale yellow oil.

Rf (SiO_2, pentane/EtOAc (1:1)): 0.47.

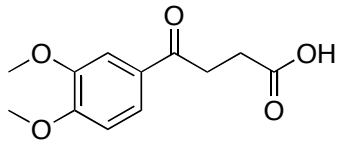
^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.23 (m, 6 H), 7.17 – 7.12 (m, 2 H), 7.07 – 7.02 (m, 2 H), 6.81 – 6.76 (m, 2 H), 6.76 – 6.70 (m, 2 H), 4.97 – 4.89 (m, 1 H), 4.14 – 4.06 (m, 2 H), 3.91 (d, *J* = 15.6 Hz, 1 H), 3.87 – 3.82 (m, 2 H), 3.77 – 3.72 (m, 2 H), 3.72 – 3.64 (m, 4 H), 3.60 (dt, *J* = 4.4, 1.6 Hz, 2 H), 3.57 – 3.49 (m, 4 H), 3.46 (d, *J* = 15.4 Hz, 1 H), 3.22 (dd, *J* = 14.5, 4.0 Hz, 1 H), 2.81 (dd, *J* = 14.5, 6.2 Hz, 1 H), 1.21 (t, *J* = 7.0 Hz, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 173.7, 161.5, 157.5, 136.1, 135.0, 130.1, 129.6, 129.3, 129.2, 129.0, 128.8, 128.7, 127.4, 127.3, 114.9, 81.7, 71.0, 70.9, 70.8, 70.0, 69.9, 67.6, 66.8, 38.1, 33.3, 28.7, 15.3.

IR (neat): 2870, 1750, 1609, 1510, 1454, 1245, 1107, 1049, 830, 749, 702.

HR-MS: Calculated for $C_{33}H_{42}NO_6$ $[M+NH_4]^+$: 548.3007, found: 548.3003.

4-(3,4-Dimethoxyphenyl)-4-oxobutanoic acid (3.28)



A published procedure[12] was modified as follows: To a solution of veratrole (**3.26**, 1.00 eq., 50.0 mmol, 6.55 ml) in nitrobenzene (30 ml) at 0 °C was added carefully aluminium chloride (2.40 eq., 120 mmol, 16.0 g) keeping the temperature below 5 °C. This was followed by the dropwise addition of succinic anhydride (**3.27**, 1.20 eq., 60.0 mmol, 6.00 g) in nitrobenzene (80 ml), keeping the temperature below 5 °C. After stirring for 10 minutes at 0 °C, the mixture was allowed to reach room temperature and stirred for one hour. Subsequently, the reaction mixture was stirred at 60 °C for three hours. The finished reaction was cooled down and poured on a mixture of ice, water and a 37% aq. HCl solution. The resulting mixture was steam distilled to remove remaining veratrole and the nitrobenzene solvent. The residue was stirred for two days before the precipitate was filtered off and washed twice with water and once with Et_2O. The solid was again suspended in water and a sat. aq. Na_2CO_3 solution was added until clear solution was formed. Activated coal was added and the mixture was boiled for 15 minutes before it was filtrated. The filtrate was cooled down to 0 °C and a 37% aq. HCl solution was added until it gets cloudy. After stirring for another 30 minutes, the pH was set to 1 by the addition of further 37% aq. HCl. The suspension was stirred for

three hours, before the precipitate was filtered off, washed twice with water and dried to give the title compound **3.28** (6.2 g, 26 mmol, 52%) as grey solid.

^{1}H-NMR (500 MHz, MeOD): 7.69 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.54 (d, *J* = 2.0 Hz, 1 H), 7.03 (d, *J* = 8.5 Hz, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.30 – 3.26 (m, 2 H), 2.71 – 2.66 (m, 2 H).

^{13}C-NMR (126 MHz, MeOD): 199.2, 176.7, 155.1, 150.4, 131.1, 124.1, 111.7, 111.5, 56.5, 56.4, 33.9, 29.0.

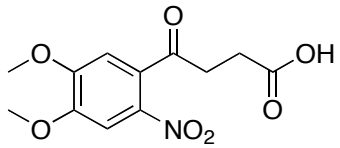
IR (neat): 3351, 1737, 1661, 1588, 1514, 1413, 1334, 1266, 1139, 1020, 876, 758.

HR-MS: Calculated for $C_{12}H_{14}NaO_5$ $[M+Na]^+$: 261.0733, found: 261.0737.

Mp: 160 °C (decomposition).

The analytical data of product **3.28** correspond to those reported in the literature.[13]

4-(4,5-Dimethoxy-2-nitrophenyl)-4-oxobutanoic acid (3.29)



To a 70% aq. HNO_3 solution (10 ml), acetic anhydride (2 ml) was added at 0 °C. To this solution, a suspension of 4-(3,4-dimethoxyphenyl)-4-oxobutanoic acid (**3.28**, 1.00 eq., 2.10 mmol, 500 mg) in acetic anhydride (3 ml) was added, keeping the temperature below 5 °C. The mixture was stirred for four hours at 0 °C before it was poured on a ice/water mixture. The precipitate was filtered off, washed three times with water and dried in vacuum. The solid was stirred in boiling toluene for 15 minutes. After cooling down, cyclohexane was added and the precipitate was isolated by filtration to give the title compound **3.29** (397 mg, 1.4 mmol, 67%) as yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6): 12.26 (s, 1 H), 7.64 (s, 1 H), 7.22 (s, 1 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.10 (t, *J* = 6.8 Hz, 2 H), 2.58 (t, *J* = 6.8 Hz, 2 H).

^{13}C-NMR (101 MHz, DMSO-d_6): 200.5, 173.5, 153.1, 149.4, 138.5, 130.6, 109.7, 107.2, 56.6, 56.4, 37.1, 28.3.

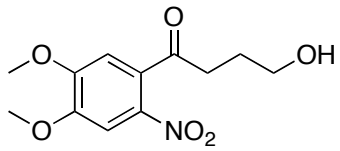
IR (neat): 2634, 1685, 1507, 1443, 1320, 1277, 1332, 1094, 1012, 877, 791, 666.

HR-MS: Calculated for $C_{12}H_{12}NO_7$ $[M-H]^-$: 282.0619, found: 282.0621.

Mp: 212 – 214 °C.

Compound **3.29** has earlier been reported.[14]

1-(4,5-Dimethoxy-2-nitrophenyl)-4-hydroxybutan-1-one (3.30)



To a refluxing solution of 4-(4,5-dimethoxy-2-nitrophenyl)-4-oxobutanoic acid (**3.29**, 1.0 eq., 0.35 mmol, 99 mg) in dry THF (5 ml) was added borane (1 M solution in THF, 1.5 eq., 0.525 mmol, 525 µl) within five minutes. The reaction was stirred for 70 minutes at reflux, before it was cooled to 0 °C and quenched with 1 M aq. HCl. The resulting mixture was extracted three times with EtOAc. The org. layers were washed with a sat. aq. Na_2CO_3 solution, combined, dried with Na_2SO_4 and concentrated. The crude solid was purified by recrystallization with water to give the title compound **3.30** (45 mg, 0.17 mmol, 48%) as brown solid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.64 (s, 1 H), 6.74 (s, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.78 (t, *J* = 6.1 Hz, 2 H), 2.86 (t, *J* = 6.9 Hz, 2 H), 2.05 (t, *J* = 6.4 Hz, 2 H).

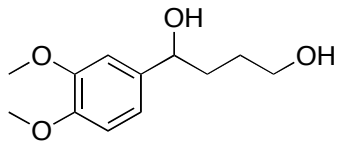
^{13}C-NMR (101 MHz, $CDCl_3$): 203.0, 154.3, 150.0, 149.7, 133.1, 108.7, 107.0, 62.0, 56.9, 56.7, 40.1, 27.0.

IR (neat): 2943, 2360, 1704, 1577, 1522, 1336, 1281, 1225, 1069, 1013, 870, 791.

HR-MS: Calculated for $C_{12}H_{15}NNaO_6$ $[M+Na]^+$: 292.0792, found: 292.0793.

Mp: 121 – 123 °C.

1-(3,4-Dimethoxyphenyl)butane-1,4-diol (3.31)



The initial goal of this procedure was to synthesize 4-(3,4-dimethoxyphenyl)butan-1-ol. To a solution of lithium aluminium hydride (1.0 eq., 0.42 mmol, 16 mg) in dry THF (5 ml) at 0 °C was added a solution of 4-(3,4-dimethoxyphenyl)-4-oxobutanoic acid (**3.28**, 1.00 eq., 0.420 mmol, 100 mg) in dry THF (5 ml) over 10 minutes. The resulting mixture was stirred for another 30 minutes at 0 °C and then heated to reflux. After stirring for two days, the reaction mixture was quenched with a 1 M aq. HCl solution (pH = 1) and again heated to reflux for another three hours. Then, the mixture was cooled down and extracted three times with EtOAc. The org. layers were combined, dried with Na_2SO_4 and concentrated to give the title compound **3.31** (82 mg, 0.36 mmol, 86%) as colorless oil.

Rf (SiO_2, pentane/EtOAc (1:3)): 0.78.

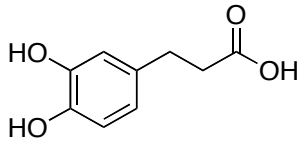
^{1}H-NMR (400 MHz, $CDCl_3$): 6.91 – 6.80 (m, 3 H), 4.86 – 4.79 (m, 1 H), 4.13 – 4.05 (m, 1 H), 3.96 – 3.84 (m, 7 H), 2.35 – 2.23 (m, 1 H), 2.08 – 1.95 (m, 2 H), 1.86 – 1.74 (m, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 149.1, 148.3, 136.0, 118.0, 111.1, 109.1, 80.7, 68.6, 56.1, 56.0, 34.6, 26.1.

IR (neat): 2945, 2871, 1593, 1515, 1464, 1263, 1235, 1139, 1028, 810, 762.

HR-MS: Calculated for $C_{12}H_{16}NaO_3$ $[M+Na]^+$: 231.0992, found: 231.0994.

3-(3,4-Dihydroxyphenyl)propanoic acid (3.32)



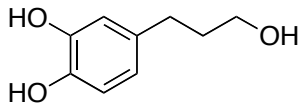
To a solution of caffeic acid (**1.07**, 1.00 eq., 5.00 mmol, 901 mg) in EtOH (25 ml), palladium (10% palladium on activated coal, 45 mg) was added. Subsequently, in a steal autoclave, a hydrogen pressure of 10 bar was applied on the reaction mixture. After stirring for three hours under this atmosphere, the pressure was released and the mixture was filtrated over Celite. The filtrate was concentrated to give the title compound **3.32** (902 mg, 5.0 mmol, quantitative) as brownish crystals.

^{1}H-NMR (400 MHz, MeOD): 6.69 – 6.66 (m, 1 H), 6.65 (d, J = 2.1 Hz, 1 H), 6.55 – 6.49 (m, 1 H), 2.75 (t, J = 7.7 Hz, 2 H), 2.56 – 2.48 (m, 2 H).

^{13}C-NMR (101 MHz, MeOD): 177.0, 146.1, 144.5, 133.8, 120.5, 116.4, 116.3, 37.1, 31.4.

The analytical data of product **3.32** correspond to those reported in the literature.[15]

4-(3-Hydroxypropyl)benzene-1,2-diol (3.33)



A solution of 3-(3,4-dihydroxyphenyl)propanoic acid (**3.32**, 1.00 eq., 5.00 mmol, 902 mg) in dry THF (25 ml) was heated to reflux. Subsequently, borane (1 M solution in THF, 5.00 eq., 25.0 mmol, 25.0 ml) was slowly added and the resulting mixture was refluxed overnight. Then, the reaction was cooled to room temperature and quenched with a 1 M aq. HCl solution and stirred for another 45 minutes. The THF was removed by vacuum distillation and the aqueous residue was extracted three times with EtOAc.

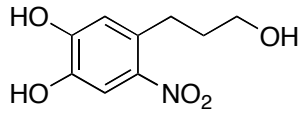
The org. layers were washed with a mixture of brine and a 0.5 M aq. $Na_2S_2O_4$ solution (1:1 v/v), combined, dried with Na_2SO_4 and concentrated. The residue was dissolved in MeOH, brought to reflux for some minutes and concentrated to give the title compound **3.33** (874 mg, 5.0 mmol, quantitative) as colorless liquid.

^{1}H-NMR (400 MHz, MeOD): 6.66 (d, *J* = 8.0 Hz, 1 H), 6.62 (d, *J* = 2.0 Hz, 1 H), 6.50 (dd, *J* = 8.0, 2.1 Hz, 1 H), 3.54 (t, *J* = 6.6 Hz, 2 H), 2.56 – 2.46 (m, 2 H), 1.77 (ddt, *J* = 13.1, 9.1, 6.5 Hz, 2 H).

^{13}C-NMR (101 MHz, MeOD): 146.1, 144.2, 135.0, 120.6, 116.5, 116.3, 62.3, 35.7, 32.4.

The analytical data of product **3.33** correspond to those reported in the literature.[16]

4-(3-Hydroxypropyl)-5-nitrobenzene-1,2-diol (3.34)



To a stirred solution of 4-(3-hydroxypropyl)-1,2-diol (**3.33**, 1.00eq., 0.600 mmol, 101 mg) in a 0.2 M aq. sodium acetate/ acetic acid buffer (pH 4.4, 4 ml) was added every hour one of four identical portions of a solution of sodium nitrite (5.00 eq., 3.00 mmol, 207 mg) in water (1 ml). After totally four hours, a 0.5 M aq. $Na_2S_2O_4$ solution was added and the mixture was stirred for 15 minutes. This solution was saturated with sodium chloride and extracted three times with EtOAc. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The formed solid was triturated in toluene first at 80 °C and then at room temperature overnight. After decanting the solvent, the solids were twice washed with toluene. Finally the remaining solid was dissolved in MeOH and again concentrated to give the title compound **3.34** (78 mg, 0.33 mmol, 55%) as brown solid.

^{1}H-NMR (500 MHz, MeOD): 7.50 (s, 1 H), 6.73 (s, 1 H), 3.60 (t, *J* = 6.5 Hz, 2 H), 2.92 – 2.84 (m, 2 H), 1.86 – 1.77 (m, 2 H).

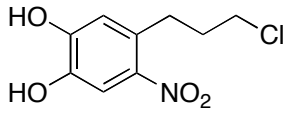
^{13}C-NMR (101 MHz, MeOD): 152.3, 144.9, 141.5, 132.5, 118.6, 113.3, 62.5, 34.6, 30.8.

IR (neat): 3481, 2942, 2582, 1597, 1531, 1496, 1439, 1323, 1277, 1195, 1154, 1052, 997, 878, 808, 757.

HR-MS: Calculated for $C_9H_{10}NNa_2O_5$ $[M-H+2Na]^+$: 258.0349, found: 258.0349.

The analytical data of product **3.34** correspond to those reported in the literature.[17]

4-(3-Chloropropyl)-5-nitrobenzene-1,2-diol (3.35)



To pure 4-(3-hydroxypropyl)-5-nitrobenzene-1,2-diol (**3.34**, 1.0 eq., 0.12 mmol, 25 mg) at 0 °C was added thionyl chloride (1 ml). This mixture was stirred for 10 minutes at 0 °C and then heated to 60 °C. After 16 hours, only little conversion was observed and pyridine (10 µl) was added. After four hours, UPLC-MS showed complete conversion and the reaction mixture was cooled to 0 °C and quenched with water. The resulting mixture was extracted three times with EtOAc. The org. layers were combined, dried with Na_2SO_4 and concentrated to give the title compound **3.35** (17 mg, 0.073 mmol, 63%) as yellowish oil.

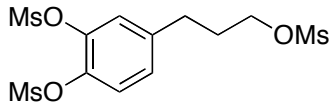
^{1}H-NMR (400 MHz, MeOD): 7.52 (s, 1 H), 6.74 (s, 1 H), 3.58 (t, *J* = 6.4 Hz, 2 H), 3.02 – 2.91 (m, 2 H), 2.13 – 2.00 (m, 2 H).

^{13}C-NMR (101 MHz, MeOD): 152.3, 145.2, 141.5, 131.2, 118.7, 113.4, 45.2, 34.5, 31.6.

IR (neat): 3341, 2968, 1599, 1532, 1330, 1286, 1195, 1047, 887, 809, 758, 547.

HR-MS: Calculated for $C_9H_9ClNO_4$ $[M-H]^-$: 230.0226, found: 230.0228.

4-(3-((Methylsulfonyl)oxy)propyl)-1,2-phenylene dimethanesulfonate (3.36)



To a solution of 4-(3-hydroxypropyl)-1,2-diol (**3.33**, 1.0 eq., 0.13 mmol, 22 mg) in CH_2Cl_2 (1 ml) at 0 °C was first added pyridine (15 eq., 2.0 mmol, 160 µl) followed by methanesulfonyl chloride (6.0 eq., 0.80 mmol, 62 µl). The reaction was allowed to reach room temperature overnight before additional methanesulfonyl chloride (3.0 eq., 0.40 mmol, 31 µl) was added. After stirring for another 24 hours, the reaction was poured on a mixture of ice and a 37% aq. HCl solution (1 ml). The resulting mixture was extracted three times with EtOAc. The org. layers were combined, dried with Na_2SO_4 and concentrated to give the title compound **3.36** (25 mg, 0.060 mmol, 45%) as pale yellow oil.

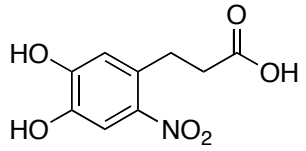
^{1}H-NMR (400 MHz, $CDCl_3$): 7.41 – 7.37 (m, 1 H), 7.30 (d, *J* = 2.1 Hz, 1 H), 7.19 (dd, *J* = 8.4, 2.1 Hz, 1 H), 4.23 (t, *J* = 6.1 Hz, 2 H), 3.24 (s, 3 H), 3.23 (s, 3 H), 3.00 (s, 3 H), 2.83 – 2.75 (m, 2 H), 2.12 – 2.03 (m, 2 H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 141.7, 141.0, 139.4, 128.5, 124.4, 124.4, 68.6, 38.7, 38.6, 37.5, 31.1, 30.3.

IR (neat): 3032, 2939, 2854, 1501, 1348, 1253, 1168, 1097, 952, 927, 853, 807, 730, 510.

HR-MS: Calculated for $C_{12}H_{22}NO_9O_3$ $[M+NH_4]^+$: 420.0451, found: 420.0453.

3-(4,5-Dihydroxy-2-nitrophenyl)propanoic acid (3.37)



To a stirred solution of 3-(4,5-dihydroxyphenyl)propanoic acid (**3.32**, 1.0 eq., 0.060 mmol, 11 mg) in a mixture of a 0.2 M aq. sodium acetate solution (344 µl) and a 0.2 M aq. acetic acid solution (56 µl) was added a solution of sodium nitrite (5.0 eq., 0.30 mmol, 21 mg) in water (0.1 ml). After stirring at room temperature for four hours, a 0.5 M aq. $Na_2S_2O_4$ solution was added and the mixture was stirred for 15 minutes. This solution was acidified with a 1 M aq. HCl solution and extracted four times with EtOAc. The org. layers were combined, dried with Na_2SO_4 and concentrated to give the title compound **3.37** (9 mg, 0.040 mmol, 66%) as brown solid.

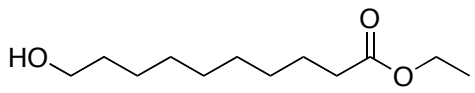
^{1}H-NMR (400 MHz, MeOD): 7.53 (s, 1 H), 6.77 (s, 1 H), 3.11 (td, *J* = 7.7, 3.9 Hz, 2 H), 2.68 – 2.58 (m, 2 H).

^{13}C-NMR (101 MHz, MeOD): 176.4, 152.4, 145.3, 141.5, 131.0, 118.7, 113.4, 35.7, 29.8.

IR (neat): 3226, 1707, 1595, 1527, 1329, 1286, 1197, 1085, 1055, 885, 809, 761.

HR-MS: Calculated for $C_9H_8NO_6$ $[M-H]^-$: 226.0357, found: 226.0357.

Ethyl 10-hydroxydecanoate (3.41)



A published procedure[18] was modified as follows: To a solution of undecylenic acid (**3.39**, 1.00 eq., 27.0 mmol, 4.98 g) in EtOH (15 ml) at 0 °C was added Sudan III (traces). Subsequently, ozone was passed through the solution until the red color disappeared. Then, the reaction was flushed with oxygen for some minutes, before the mixture was added carefully to a solution of NaOH (1.50 eq., 40.5 mmol, 1.62 g) and $NaBH_4$ (2.00 eq., 54.0 mmol, 2.08 g) in water (25 ml) and EtOH (25 ml) at 0 °C. The mixture was allowed to reach room temperature over night. The ethanol was removed in

by vacuum distillation before the mixture was carefully acidified at 0 °C with a 35% aq. HCl solution. The precipitate was filtered off and washed with ice-cold water to give 10-hydroxydecanoic acid (**3.40**) (5.09 g) as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.11 (s, 2 H), 3.93 – 3.50 (m, 2 H), 2.33 (t, *J* = 7.5 Hz, 2 H), 1.70 – 1.45 (m, 4 H), 1.42 – 1.21 (m, 10 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 179.8, 63.2, 34.2, 32.8, 29.5, 29.4, 29.3, 29.1, 25.8, 24.8.

IR (neat): 3243, 2912, 2849, 1690, 1469, 1414, 1302, 1047, 1020, 976, 719.

HR-MS: Calculated for $C_{10}H_{19}O_3$ $[M-H]^-$: 187.1340, found: 187.1341.

The analytical data of product **3.40** correspond to those reported in the literature.[18]

A published procedure[19] was modified as follows: To a solution of the previously formed 10-hydroxydecanoic acid in EtOH (65 ml) were added traces of sulfuric acid and the mixture was refluxed for 22 hours. Subsequently, the reaction mixture was cooled down and concentrated. The residue was mixed with a sat. aq. Na_2CO_3 solution and then extracted three times with TBME. The org. layers were washed with a sat. aq. Na_2CO_3 solution, combined, dried with Na_2SO_4 and concentrated to give the title compound **3.41** (5.3 g, 25 mmol, 91% over two steps) as a clear liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): 4.09 (q, *J* = 7.1 Hz, 2 H), 3.59 (t, *J* = 6.7 Hz, 2 H), 2.25 (t, *J* = 7.5 Hz, 2 H), 1.75 (s, 1 H), 1.65 – 1.48 (m, 4 H), 1.37 – 1.17 (m, 13 H).

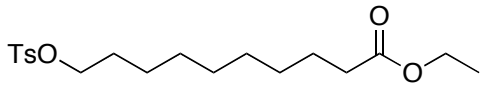
^{13}C-NMR (101 MHz, $CDCl_3$): 174.0, 63.0, 60.3, 34.4, 32.8, 29.5, 29.4, 29.2, 29.2, 25.8, 25.0, 14.3.

IR (neat): 3451, 2927, 2855, 1735, 1465, 1372, 1236, 1180, 1098, 1031.

HR-MS: Calculated for $C_{12}H_{24}NaO_3$ $[M+Na]^+$: 239.1618, found: 239.1617.

The analytical data of product **3.41** correspond to those reported in the literature.[19]

Ethyl 10-(tosyloxy)decanoate (3.42)



To a solution of ethyl 10-hydroxydecanoate (**3.41**, 1.00 eq., 2.00 mmol, 433 mg) in triethyl amine (6 ml) and dry THF (6 ml) at 0 °C was added *p*-toluenesulfonyl chloride (5.00 eq., 10.0 mmol, 1.91 g). The mixture was allowed to reach room temperature overnight. The reaction mixture was poured on a mixture of ice and a 32% aq. HCl solution (5 ml). This mixture was extracted three times with TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude

product was purified by column chromatography (SiO_2, pentane/EtOAc (12:1)) to give the title compound **3.42** (650 mg, 1.8 mmol, 88%) as clear liquid.

Rf (SiO_2, pentane/EtOAc (12:1)): 0.15.

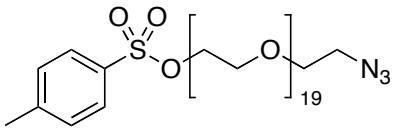
^{1}H-NMR (400 MHz, $CDCl_3$): 7.82 – 7.75 (m, 2 H), 7.34 (dd, *J* = 8.5, 0.6 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.01 (t, *J* = 6.5 Hz, 2 H), 2.44 (s, 3 H), 2.27 (t, *J* = 7.5 Hz, 2 H), 1.67 – 1.54 (m, 4 H), 1.31 – 1.19 (m, 13 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 174.0, 144.8, 133.4, 129.9, 128.0, 70.8, 60.3, 34.5, 29.3, 29.2, 29.2, 29.0, 28.9, 25.4, 25.1, 21.8, 14.4.

IR (neat): 2929, 2857, 1733, 1361, 1177, 1098, 952, 816, 664, 555.

HR-MS: Calculated for $C_{19}H_{31}O_5S$ $[M+H]^+$: 371.1887, found: 371.1890.

***O*-(2-Azidoethyl)-*O*'-tosylnonadecaethylene glycol (3.45)**



To a solution of *O*-(2-azidoethyl)nonadecaethylene (1.0 eq., 0.020 mmol, 19 mg) in dry THF (0.5 ml) and NEt_3 (0.2 ml) at 0 °C was added *p*-toluenesulfonyl chloride (3.0 eq., 0.060 mmol, 11 mg). The reaction was allowed to reach room temperature overnight. An ESI-MS measurement showed still starting material in the reaction mixture. Additional *p*-toluenesulfonyl chloride (4.1 eq., 0.082 mmol, 15 mg) was added and the reaction was stirred overnight. The finished reaction was poured on a mixture of ice and a 37% aq. HCl solution. The resulting mixture was once extracted with Et_2O. The aq. layer was saturated with NaCl and extracted four times with EtOAc. The org. layers were washed with a sat. aq. $NaHCO_3$ solution, combined, dried with Na_2SO_4 and concentrated to give the title compound **3.45** (19 mg, 0.018 mmol, 88%) as clear oil.

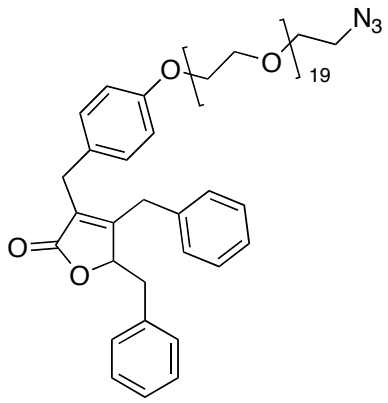
^{1}H-NMR (400 MHz, $CDCl_3$): 7.81 – 7.76 (m, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 4.14 (dd, *J* = 5.4, 4.3 Hz, 2 H), 3.69 – 3.59 (m, 72 H), 3.57 (s, 4 H), 3.41 – 3.34 (m, 2 H), 2.43 (s, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 144.9, 133.1, 129.9, 128.1, 70.9, 70.8, 70.8, 70.7, 70.7, 70.6, 70.1, 69.4, 68.8, 50.8, 21.8.

IR (neat): 2921, 2858, 2108, 1457, 1351, 1293, 1248, 1177, 1095, 1037, 923, 849, 818, 778, 664, 555.

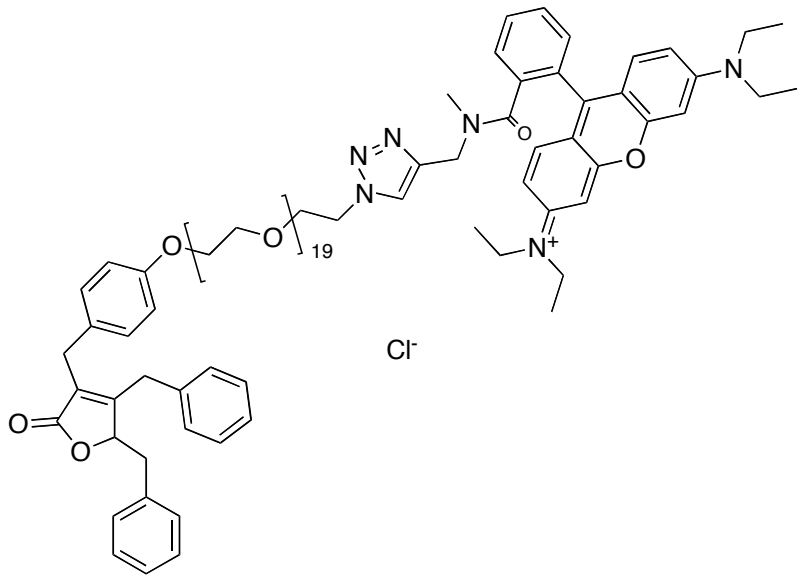
HR-MS: Calculated for $C_{47}H_{87}N_3Na_2O_{22}S$ $[M+2Na]^{2+}$ 561.7645, found: 561.7643.

3-(*O*-(2-Azidoethyl)nonadecaethylene glycol)-4,5-dibenzylfuran-2(5*H*)-one (3.47a)



To a solution of *O*-(2-Azidoethyl)-*O*'-tosylnonadecaethylene glycol (**3.45**, 1.0 eq., 0.065 mmol, 76 mg) in acetone (2 ml) was first added 4,5-dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (**3.20**, 2.0 eq., 0.13 mmol, 48 mg) followed by potassium carbonate (2.2 eq., 0.14 mmol, 20 mg). The mixture was heated to reflux for 24 hours. The reaction was filtrated and concentrated to 220 mg crude product. However, the reaction reached only 50% conversion, however the product was used for the next step without further purification.

Rhodamine B maculalactone A hybrid (3.47)



To a solution of 3-(*O*-(2-Azidoethyl)nonadecaethylene glycol)-4,5-dibenzylfuran-2(5*H*)-one (**3.47a**, 1.0 eq., 0.065 mmol, 83 mg) and *N*-(6-(diethylamino)-9-(2-(methyl(prop-2-yn-1-yl)carbamoyl)phenyl)-3*H*-xanthen-3-ylidene)-*N*-ethylethanaminium chloride (**3.46**, 1.0 eq., 0.065 mmol, 35 mg) in CH_2Cl_2 (5 ml) and water (5 ml) was added copper(II) sulfate (0.2 eq., 0.01 mmol, 2 mg) and L-ascorbic acid (0.2 eq., 0.01 mmol, 3 mg). The mixture was vigorously stirred at room

temperature. After four days, *t*BuOH (5 ml) and after seven days, additional L-ascorbic acid (0.2 eq., 0.01 mmol, 3 mg) was added. After 10 days, the reaction was concentrated and separated by preparative HPLC (Phenomenex Gemini C18, CH_3CN/water (1:4 to 3:2)) and (Phenomenex Gemini C18, CH_3CN/water + 0.1% HCO_2H (2:3 to 3:2)) to give the title compound **3.47** (26 mg, 0.014 mmol, 22%) as purple oil.

^{1}H-NMR (500 MHz, MeOD): 7.95 (d, *J* = 14.0 Hz, 0.4 H), 7.75 (t, *J* = 5.7 Hz, 2 H), 7.69 (d, *J* = 7.0 Hz, 0.6 H), 7.53 – 7.42 (m, 2 H), 7.33 – 7.13 (m, 12 H), 7.06 (d, *J* = 8.8 Hz, 0.4 H), 7.02 – 6.92 (m, 3.6 H), 6.73 (s, 4 H), 5.01 (t, *J* = 4.5 Hz, 1 H), 4.59 – 4.52 (m, 0.6 H), 4.48 – 4.39 (m, 3 H), 4.10 – 4.04 (m, 2 H), 3.96 (d, *J* = 15.5 Hz, 1 H), 3.88 (s, 0.4 H), 3.85 – 3.77 (m, 4 H), 3.73 – 3.48 (m, 81.4 H), 3.46 (s, 2 H), 3.28 (dd, *J* = 14.7, 3.9 Hz, 1 H), 2.99 (s, 2 H), 2.90 (dd, *J* = 14.6, 5.7 Hz, 1 H), 2.67 (s, 0.6 H), 1.32 (t, *J* = 6.3 Hz, 12 H).

^{13}C-NMR (126 MHz, MeOD): 175.8, 170.2, 164.3, 159.3, 159.1, 158.7, 157.2, 157.1, 156.8, 137.8, 137.0, 136.4, 133.1, 132.1, 131.7, 131.4, 131.3, 131.1, 130.8, 130.3, 130.1, 129.5, 129.5, 128.6, 128.2, 128.1, 125.4, 115.7, 115.4, 115.2, 114.8, 97.3, 83.6, 71.7, 71.6, 71.5, 71.4, 70.9, 70.3, 68.6, 51.5, 46.9, 42.8, 38.5, 38.5, 33.9, 29.1, 13.0.

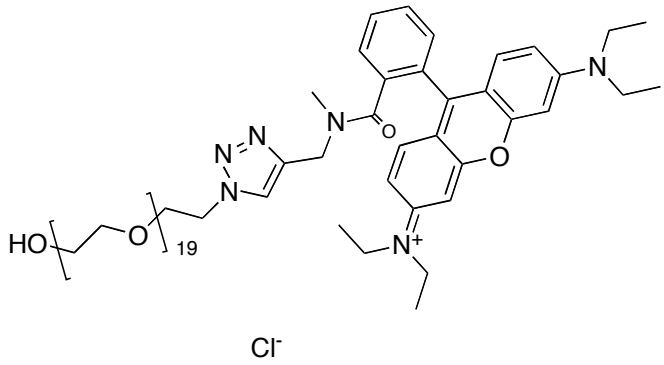
IR (neat): 3398, 2907, 2871, 2359, 2332, 1750, 1634, 1589, 1470, 1414, 1346, 1276, 1249, 1182, 1133, 1105, 684.

HR-MS: Calculated for $C_{97}H_{137}N_6Na_2O_{24}$ $[M+2Na]^{3+}$ 605.3154, found: 605.3163.

HPLC (Phenomenex Gemini C18, CH_3CN/water (5 min 2:3, in 25 min to 3:2), 1 ml/min, 540 nm): single peak at 14.5 minutes retention time.

UV/VIS: λ_{max} (H_2O) = 568 nm (Section 9.5.2).

Rhodamine B with linker (3.48)



To a solution of *O*-(2-Azidoethyl)nonadecaethylene (1.0 eq., 0.055 mmol, 54 mg) and *N*-(6-(diethylamino)-9-(2-(methyl(prop-2-yn-1-yl)carbamoyl)phenyl)-3*H*-xanthen-3-ylidene)-*N*-ethylethanaminium chloride (**3.46**, 1.0 eq., 0.055 mmol, 29 mg) in *t*BuOH (4 ml) and water (4 ml) was added copper(II) sulfate (0.5 eq., 0.03 mmol, 4 mg) and L-ascorbic acid (1.0 eq., 0.055 mmol, 11 mg). The mixture was vigorously stirred at room temperature. After five and again after six days, additional L-ascorbic acid (1.0 eq., 0.055 mmol, 11 mg) was added. After 13 days, the reaction was concentrated and separated by preparative HPLC (Phenomenex Gemini C18, CH_3CN/water + 0.1% HCO_2H (1:17 to 9:11)) and (Phenomenex Synergi Hydro-RP, CH_3CN/water + 0.1% HCO_2H (1:19 to 4:1)) giving 19 mg of still impure product. The amid was found to be instable under HPLC conditions. Therefore, the mixture was purified by preparative TLC (SiO_2, CH_2Cl_2/MeOH (4:1)) giving 10 mg still impure product. This was again separated by semi-preparative HPLC (Phenomenex Synergi Hydro-RP, CH_3CN/water + 0.1% HCO_2H (2 min 1:19, in 3 min to 3:7, in 25 min to 4:1)) to give the title compound **3.48** (2 mg, 1.2 µmol, 3%) as purple oil.

^{1}H-NMR (400 MHz, MeOD): 8.55 (s, 1 H), 8.10 (s, 0.4 H), 7.80 – 7.67 (m, 1.6 H), 7.51 – 7.42 (m, 0.6 H), 7.35 – 7.29 (m, 0.4 H), 7.27 – 7.18 (m, 2 H), 7.04 – 6.93 (m, 2 H), 6.42 – 6.33 (m, 2 H), 4.64 – 4.51 (m, 2 H), 4.49 – 4.39 (m, 2 H), 3.80 (t, *J* = 5.0 Hz, 1 H), 3.75 – 3.47 (m, 83 H), 3.42 – 3.33 (m, 4 H), 3.05 (s, 1 H), 3.00 (s, 1 H), 1.33 (t, *J* = 7.1 Hz, 6 H), 1.19 – 1.10 (m, 6 H).

IR (neat): 3485, 2871, 1618, 1590, 1512, 1468, 1414, 1349, 1276, 1249, 1181 ,1112, 949, 824, 779, 646, 609.

HR-MS: Calculated for $C_{72}H_{119}N_6O_{22}$ $[M+2H]^{3+}$ 473.2787, found: 473.2793.

HPLC (Phenomenex Synergi Hydro-RP, CH_3CN/water + 0.1% HCO_2H (2 min 1:19, in 3 min to 3:7, in 25 min to 4:1), 1 ml/min, 540 nm): single peak at 14.8 minutes retention time.

UV/VIS: λ_{max} (H_2O) = 563 nm (Section 9.5.2).

Assay with *Thamnocephalus platyurus*

The assay "Thamnotoxkit F^{TM}" was purchased from MicrobioTest Inc., Kleimoer 15, 9030 Mariakerke (Gent), Belgium. The assay was conducted as described in the standard operating procedure.

The standard freshwater (SFW) was prepared as described and oxygenated prior use by bubbling air for 30 minutes through it. Diluted standard freshwater (DFW) was prepared by mixing SFW (2.5 ml) with deionized water (17.5 ml). The *T. platyurus* cysts were hydrated in DFW (0.2 ml) for 30 minutes before they were added to DFW (10 ml) and incubated in a Petri dish for 24 hours at 25 °C under continuous light (8 W fluorescent tube lamp).

Dilutions of the test substances with concentrations of 50, 12.5, 5 and 0.5 mM in methanol were prepared. In a 24 well plate, four repetitions of each concentration were prepared by mixing 2 µl of the substance solution with 998 µl SFW giving aqueous solutions with concentrations of 100, 25, 10 and 1 µM. A blank from 2 µl methanol and 998 µl SFW was prepared. About 40 larvae were added to the first vial of each dilution by a pipette. From there, 10 larvae were transported to each of the remaining three vials of each concentration. Only these three vials were counted. The plate was covered with parafilm and incubated for 24 hours at 25 °C in the dark.

The mortality was determined by counting the dead larvae. Dead was defined as no movement within 10 seconds. The remaining larvae were killed by adding CO_2 containing water (dry ice in water) and the total amount of individuals in each vial was determined.

Test Substance	0 µM Dead/ Total	1 µM Dead/ Total	10 µM Dead/ Total	25 µM Dead/ Total	100 µM Dead/ Total
1.34	1/10	1/10	3/10	2/10	5/10
	0/10	0/10	2/11	4/10	5/11
	0/10	0/10	5/9	3/10	7/10
3.17	0/10	0/10	2/8	8/14	7/10
	0/10	0/9	3/10	1/10	3/10
	0/8	0/8	6/10	3/9	5/10
3.18	0/9	0/10	5/12	2/9	1/10
	0/11	0/10	1/10	2/10	3/10
	0/11	0/11		1/10	2/10
3.19	0/10	0/10	0/10	0/11	0/10
	0/10	0/10	2/10	0/10	2/10
	0/10	0/10	1/10	0/11	4/10

Table 8.1: Raw Data of Assay with *Thamnocephalus platyurus*. Cysts Lot: TP070512, SFW Lot: EPA200912.

Assay with *Artemia franciscana*

The assay "Artoxkit M™" was purchased from MicrobioTest Inc., Kleimoer 15, 9030 Mariakerke (Gent), Belgium. The assay was conducted as described in the standard operating procedure.

The standard seawater (SSW) was prepared as described and oxygenated prior use by bubbling air for 30 minutes trough it. The *A. franciscana* cysts were added to SSW (10 ml) and incubated in a Petri dish for 30 to 32 hours at 25 °C under continuous light (8 W fluorescent tube lamp).

Dilutions of the test substances with concentrations of 50, 12.5, 5 and 0.5 mM in methanol were prepared. In a 24 well plate, four repetitions of each concentration were prepared by mixing 2 µl of the substance solution with 998 µl SSW giving aqueous solutions with concentrations of 100, 25, 10 and 1 µM. A blank from 2 µl methanol and 998 µl SSW was prepared. About 40 larvae were added to the first vial of each dilution by a pipette. From there, 10 larvae were transported to each of the remaining three vials

of each concentration. Only these three vials were counted. The plate was covered with parafilm and incubated for 33 hours at 25 °C in the dark.

The mortality was determined by counting the dead larvae. Dead was defined as no movement within 10 seconds. The remaining larvae were killed by adding CO_2 containing water (dry ice in water) and the total amount of individuals in each vial was determined.

Test Substance	0 µM Dead/ Total	1 µM Dead/ Total	10 µM Dead/ Total	25 µM Dead/ Total	100 µM Dead/ Total
1.34	0/9	0/11	1/9	2/10	5/10
	1/10	0/11	0/11	1/11	0/10
	0/10	0/10	0/10	1/10	4/9
3.17	1/11	0/9	0/10	3/9	10/11
	0/10	0/10	1/10	7/10	9/10
	0/9	0/10	0/9	7/11	9/12
3.18	0/10	0/10	0/11	0/10	0/11
	0/9	0/10	0/10	0/11	1/10
	1/10	1/9	0/9	0/10	0/10
3.19	1/10	0/9	0/10	0/10	2/10
	0/10	0/8	0/11	0/11	3/10
	0/10	1/12	0/10	0/10	2/10
3.23	0/10	0/10	0/11	0/9	0/10
	0/9	0/7	0/11	0/10	0/9
	0/8	0/8	0/10	1/10	0/10
3.47	0/10	1/10	0/10	1/10	4/9
	0/11	1/8	0/12	0/11	4/11
	0/11	1/10	0/10	0/10	4/10

Table 8.2: Raw Data of Assay with *Artemia franciscana*. Cysts Lot: AF/F2006, SFW Lot: ASPM060712.

Staining experiments with *Artemia salina*

The *A. salina* cysts were purchased from OOO Biotrade, Peschanaya Str. 96V of 29, Barnaul, 656049, Russia. The standard seawater (SSW) was prepared by dissolving 1.4 g "Artemia Salz" (Artemia-sal. JBL GmBH & co. KG, D-67141 Neuhofen) in tab water. The SSW was oxygenated prior use by bubbling air for 30 minutes through it. 20 mg *A. salina* cysts were added to SSW (20 ml) in a Petri and illuminated for 30 minutes trough a 3 mm layer of water (20 W energy-saver lamp). The cysts were then incubated for 48 hours at 25 °C under continuous light (8 W fluorescent tube lamp).

Solutions with a concentration of 0.5 mM of rhodamine B, **3.47** and **3.48** in DMSO were prepared. In a 24 well plate, 2 µl of this solutions were diluted with 998 µl SSW giving a concentration of 1 µM. A blank from 2 µl DMSO and 998 µl SSW was prepared. With a pipette, about 25 larvae were added to each solution. The plate was covered with parafilm and incubated for 25 hours at 25 °C in the dark.

After incubation, some individuals were investigated under the fluorescence microscope (Figure 8.1).

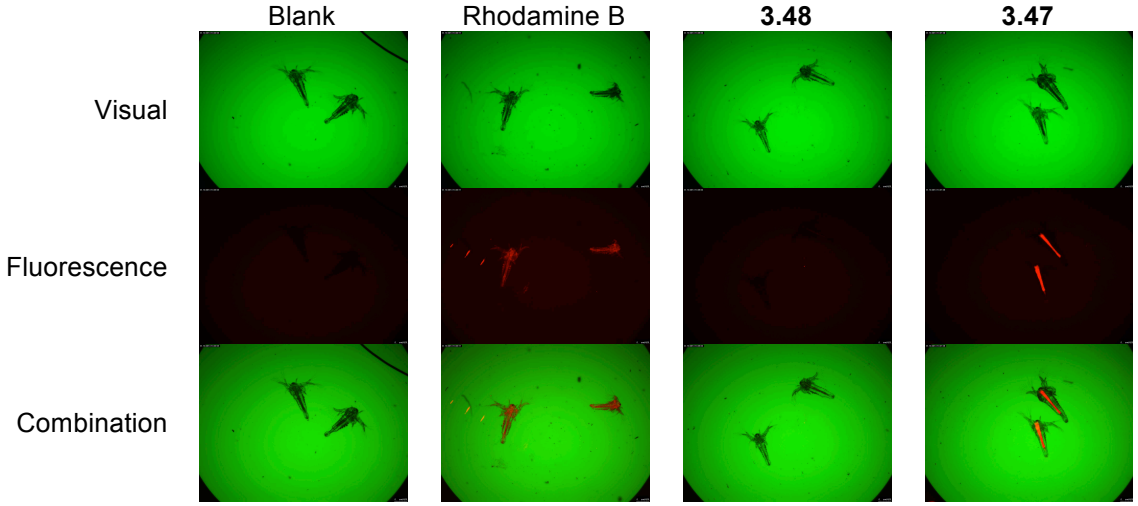


Fig 8.1: Pictures taken before washing. **3.47** results in a specific staining while **3.48** is inactive and rhodamine B colors the complete organism.

The remaining nauplia were transferred in a mixture of 2 µl DMSO and 998 µl SSW and incubated for three hours at 25 °C in the dark. The transfer was repeated and they were again incubated for three hours under the same conditions.

The larvae were transported in a mixture of formalin 10% and a standard PBS puffer (1:1 v/v). The larvae were fixed at 4 °C in the dark.

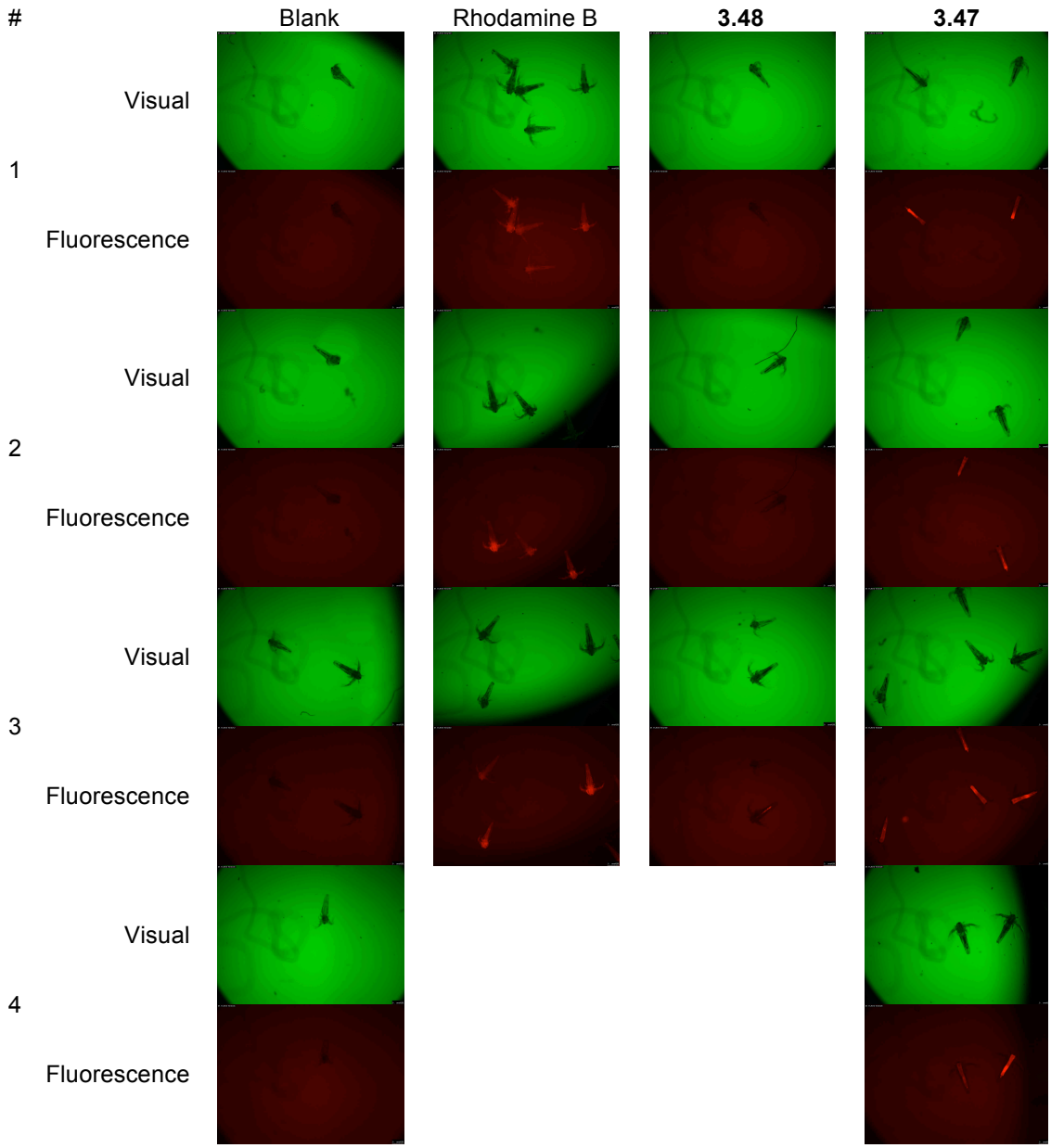
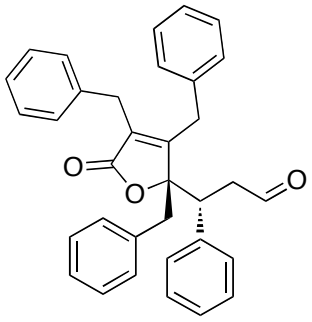


Fig 8.2: Pictures series taken after washing. While the blank and **3.48** shows no fluorescence, rhodamine B marks the complete organism and **3.47** stains only specific parts.

8.4 Synthetic Studies on Ophiodilactone A and B

3-Phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (4.07)



Method A: To a solution of maculalactone A (**1.34**, 1.0 eq., 0.13 mmol, 50 mg) in toluene (3 ml) was added *trans*-cinnamaldehyde (5.0 eq., 0.67 mmol, 85 µl). The solution was cooled to -15 °C. The mixture was stirred for five minutes at this temperature, followed by the addition of the cinchona alkaloid catalyst (**2.12**, 0.05 eq., 0.01 mmol, 4 mg). Subsequently, a 50% aq. KOH solution (6.5 eq., 0.87 mmol, 65 µl) was added over two minutes. The resulting mixture was vigorously stirred at -15 °C for three days, before it was filtrated over SiO_2. The filter cake was extensively washed with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **4.07** (34 mg, 0.069 mmol, 52%) as a white solid. Additionally, the potential diastereomer **6.02** (12 mg, 0.025 mmol, 11%) was isolated in a purity of about 80%.

Method B: This method was used to yield the racemic product. To a solution of methyl 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanoate (**4.13**, 1.0 eq., 0.10 mmol, 50 mg) in toluene (1.1 ml) at -78 °C, diisobutylaluminium hydride (1.2 M solution in toluene, 1.2 eq., 0.12 mmol, 99 µl) was added dropwise. The reaction was stirred for five hours at -78 °C. As the reaction was not finished, additional portions of diisobutylaluminium hydride (1.2 M solution in toluene, 0.55 eq., 0.050 mmol, 45 µl) were added. The finished reaction was quenched at -78 °C with a sat. aq. NH_4Cl solution. The layers were separated and the aq. layer was extracted three times with EtOAc. The org. layers were washed with brine, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (8:1)) to give the racemic title compound **4.07** (20 mg, 0.041 mmol, 41%) as white solid.

Rf (SiO_2, pentane/EtOAc (6:1)): 0.31.

^{1}H-NMR (500 MHz, $CDCl_3$): 8.92 (d, *J* = 1.5 Hz, 1 H), 7.41 (s, 2 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.31 – 7.24 (m, 4 H), 7.24 – 7.14 (m, 3 H), 7.14 – 7.04 (m, 5 H), 7.02 – 6.98 (m, 2 H), 6.52 – 6.46 (m, 2 H), 3.86 (d, *J* = 15.4 Hz, 1 H), 3.58 – 3.42 (m, 3 H), 3.35 (dd, *J* = 11.1, 2.5 Hz, 1 H), 2.87 (d, *J* = 14.6 Hz, 1 H), 2.79 – 2.69 (m, 2 H), 2.11 (dd, *J* = 17.6, 2.0 Hz, 1 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 199.2, 172.9, 161.5, 138.7, 137.1, 134.9, 134.4, 131.5, 129.9, 129.4, 129.4, 129.3, 128.7, 128.7, 128.7, 128.1, 128.0, 127.8, 127.4, 126.3, 92.4, 45.5, 44.7, 41.5, 33.7, 29.8.

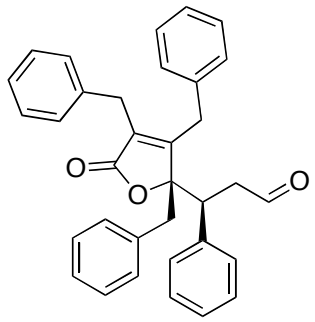
IR (neat): 3031, 2923, 2827, 2725, 1746, 1724, 1495, 1454 ,699.

HR-MS: Calculated for $C_{34}H_{31}O_3$ $[M+H]^+$: 487.2268, found: 487.2272.

$[\alpha]_D$ (c = 0.34, $CHCl_3$, 36% *ee*): -88.9°.

Mp: 75 – 76 °C.

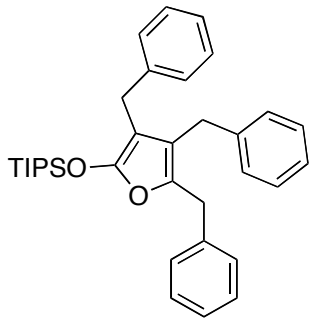
Side product **6.02** was rationalized to be the diastereomer of the desired product **4.07**. Pure **6.02** could not be isolated. Therefore, a complete characterization was not possible.



^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.70 (t, *J* = 0.9 Hz, 1 H), 7.27 – 7.19 (m, 8 H), 7.14 – 7.08 (m, 4 H), 7.02 (t, *J* = 7.6 Hz, 2 H), 6.86 (t, *J* = 7.6 Hz, 2 H), 6.47 (dd, *J* = 7.9, 0.8 Hz, 2 H), 5.94 (dd, *J* = 7.9, 0.8 Hz, 2 H), 3.90 (dd, *J* = 8.6, 4.2 Hz, 1 H), 3.61 (d, *J* = 17.6 Hz, 1 H), 3.56 (d, *J* = 17.4 Hz, 1 H), 3.51 (d, *J* = 14.4 Hz, 1 H), 3.39 (dd, *J* = 18.4, 4.2 Hz, 1 H), 3.23 (ddd, *J* = 18.4, 8.6, 1.2 Hz, 1 H), 3.01 (d, *J* = 14.4 Hz, 1 H), 2.75 (d, *J* = 15.8 Hz, 1 H), 2.66 (d, *J* = 15.9 Hz, 1 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 200.1, 173.3, 161.7, 139.0, 137.2, 134.5, 134.1, 130.5, 130.2, 129.5, 129.2, 128.9, 128.8, 128.6, 128.1, 128.0, 127.8, 127.6, 127.1, 125.6, 91.3, 47.2, 45.0, 41.5, 34.3, 29.1.

Triisopropyl((3,4,5-tribenzylfuran-2-yl)oxy)silane (4.11)

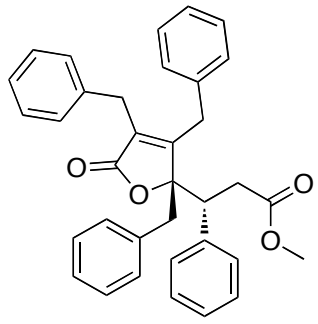


To a solution of maculalactone A (**1.34**, 1.0 eq., 0.14 mmol, 50 mg) in dry CH_2Cl_2 (2 ml), diisopropylamine (6.0 eq., 0.840 mmol, 119 µl) was slowly added. This was followed by the addition of triisopropylsilyl-trifluoromethanesulfonate (5.0 eq., 0.700 mmol, 194 µl). The resulting mixture was stirred for three hours at room temperature. The reaction mixture was cooled to 0 °C and diluted with CH_2Cl_2. This mixture was extracted at 0 °C consecutively with a sat. aq. $NaHCO_3$ solution, a 1 M aq. $CuSO_4$ solution and brine. The aq. layers were extracted with CH_2Cl_2. The org. layers were combined, dried with Na_2SO_4, concentrated and extensively dried in high vacuum to give the title compound **4.11** (65 mg, 0.13 mmol, 91%) as clear oil in sufficient purity. The formed product is highly reactive and cannot be further purified and completely characterized.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.26 – 7.10 (m, 11 H), 7.08 – 7.04 (m, 2 H), 7.01 – 6.98 (m, 2 H), 3.77 (s, 2 H), 3.53 (s, 2 H), 3.37 (s, 2 H), 1.01 (s, 18 H), 0.99 (s, 6 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 152.6, 141.4, 140.5, 139.5, 138.9, 128.7, 128.5, 128.3, 128.2, 126.1, 125.9, 125.7, 119.3, 95.5, 32.4, 30.1, 28.7, 17.7, 12.4.

***rac*-Methyl 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanoate (4.13)**



To a solution of maculalactone A (**1.34**, 1.00 eq., 0.509 mmol, 181 mg) in CH_2Cl_2 (5.5 ml) were added methyl *trans*-cinnamate (5.00 eq., 2.55 mmol, 413 mg) and tetrabutylammonium bromide (1.00 eq., 0.509 mmol, 168 mg). After stirring for five

minutes, a 50% aq. KOH solution (6.50 eq., 3.31 mmol, 246 µl) was added over five minutes. The reaction was vigorously stirred for three days at room temperature and filtrated over SiO_2. The solid was washed with CH_2Cl_2 and the filtrate was concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (7:1)) to give the title compound **4.13** (90 mg, 0.18 mmol, 35%) as colorless solid.

Rf (SiO_2, pentane/EtOAc (5:1)): 0.26.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.45 (s, 2 H), 7.34 (t, *J* = 7.5 Hz, 2 H), 7.31 – 6.95 (m, 14 H), 6.44 – 6.37 (m, 2 H), 3.80 (d, *J* = 15.7 Hz, 1 H), 3.62 (d, *J* = 15.7 Hz, 1 H), 3.48 (d, *J* = 15.7 Hz, 1 H), 3.40 (dd, *J* = 11.4, 2.7 Hz, 1 H), 3.37 – 3.31 (m, 4 H), 2.86 (d, *J* = 14.6 Hz, 1 H), 2.73 (d, *J* = 14.6 Hz, 1 H), 2.62 (dd, *J* = 16.4, 11.3 Hz, 1 H), 2.19 (dd, *J* = 16.4, 2.7 Hz, 1 H).

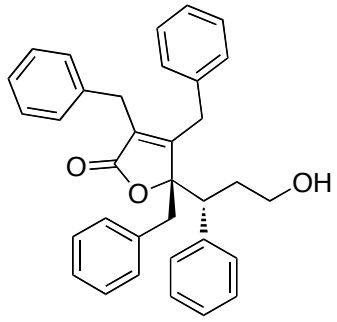
^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.0, 171.4, 161.8, 138.7, 137.1, 134.9, 134.5, 131.2, 130.0, 129.4, 129.2, 128.7, 128.7, 128.6, 128.5, 128.0, 127.8, 127.5, 127.3, 126.1, 92.4, 51.6, 47.5, 41.6, 35.5, 33.8, 29.7.

IR (neat): 3063, 3030, 2950, 1743, 1495, 1247, 1166, 910, 731, 702, 632.

HR-MS: Calculated for $C_{35}H_{33}O_4$ $[M+H]^+$: 517.2373, found: 517.2381.

Mp: < 50 °C.

3,4,5-Tribenzyl-5-(3-hydroxy-1-phenylpropyl)furan-2(5H)-one (4.17)



A solution of 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**4.07**, 1.00 eq., 0.310 mmol, 151 mg) in anhydrous EtOH (10 ml) was cooled to -16 °C. This was followed by the addition of a solution of $NaBH_4$ (1.3 eq., 0.40 mmol, 16 mg) in anhydrous EtOH (2 ml) over five minutes. The mixture was stirred for 50 minutes at -18 °C and for 30 minutes at 0 °C. The reaction was quenched with water (3 ml). The resulting mixture was diluted with brine and EtOAc. The formed layers were separated and the aq. layer was extracted three times with EtOAc. The org. layers were subsequently washed with brine, combined, dried with Na_2SO_4 and concentrated. The

crude product was purified by column chromatography (SiO_2, pentane/EtOAc (2:1)) to give the title compound **4.17** (113 mg, 0.23 mmol, 75%) as white solid. An X-ray diffraction analysis was performed after recrystallization.

Rf (SiO_2, pentane/EtOAc (3:1)): 0.27.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.40 – 7.27 (m, 7 H), 7.23 – 7.13 (m, 6 H), 7.12 – 6.98 (m, 5 H), 6.45 (dd, *J* = 7.9, 1.4 Hz, 2 H), 3.84 (d, *J* = 15.5 Hz, 1 H), 3.61 – 3.50 (m, 2 H), 3.43 (d, *J* = 15.7 Hz, 1 H), 3.13 (ddd, *J* = 10.6, 6.8, 3.7 Hz, 1 H), 2.94 (dd, *J* = 12.0, 2.6 Hz, 1 H), 2.88 (d, *J* = 14.6 Hz, 1 H), 2.76 – 2.64 (m, 2 H), 1.81 – 1.69 (m, 1 H), 1.38 (dddd, *J* = 13.6, 9.4, 6.8, 2.7 Hz, 1 H), 0.26 (s, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.3, 162.0, 139.2, 137.3, 135.5, 134.8, 130.8, 130.0, 129.8, 129.1, 128.6, 128.5, 128.1, 127.6, 127.2, 126.1, 93.0, 60.0, 48.0, 42.0, 33.8, 32.8, 29.8.

IR (neat): 3432, 3028, 2954, 1716, 1493, 1157, 754, 701.

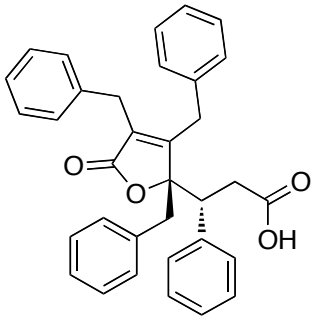
HR-MS: Calculated for $C_{34}H_{33}O_3$ $[M+H]^+$: 489.2424, found: 489.2425.

$[\alpha]_D$ (c = 0.44, $CHCl_3$): -87.0°.

Chiral HPLC (Chiralpak IC column from Daicel, heptan/*i*PrOH (80:20), 0.5 ml/min, 25 °C, 210 nm) Rt: 18.6 and 23.5 minutes.

Mp: 169 – 170 °C.

3-Phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanoic acid (4.18)



A solution of 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**4.07**, 1.0 eq., 0.19 mmol, 93 mg) in *tert*-butanol (12 ml) and water (0.8 ml) was cooled to 15 – 20 °C. First 2-methyl-2-butene (3.0 eq., 0.57 mmol, 61 µl) was added followed by the addition of a solution of sodium chlorite (2.3 eq., 0.44 mmol, 40 mg) and NaH_2PO_4*H_2O (2.0 eq., 0.38 mmol, 53 mg) in water (1.2 ml) within 15 minutes, remaining the temperature below 20 °C. The mixture was vigorously stirred for seven hours at room temperature. The *tert*-butanol was removed in vacuum from the finished reaction mixture, before additional water and CH_2Cl_2 were added. The mixture was

acidified to pH 1 by the addition of phosphoric acid. The layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were subsequently washed with a mixture of brine and a small amount of phosphoric acid. The combined org. layers were dried with Na_2SO_4 and concentrated to give the title compound **4.18** (103 mg, 0.19 mmol, quantitative) as white solid.

Rf (RP-18, CH_3CN/H_2O/TFA (10:4:0.002)): 0.34.

^{1}H-NMR (500 MHz, $CDCl_3$): 10.33 (s, 1 H), 7.44 (s, 2 H), 7.36 (dd, *J* = 13.6, 7.1 Hz, 2 H), 7.32 – 7.27 (m, 1 H), 7.23 – 7.11 (m, 5 H), 7.11 – 6.99 (m, 6 H), 6.99 – 6.96 (m, 2 H), 6.44 – 6.39 (m, 2 H), 3.81 (d, *J* = 15.5 Hz, 1 H), 3.59 – 3.48 (m, 2 H), 3.40 (d, *J* = 15.7 Hz, 1 H), 3.28 (ddd, *J* = 10.9, 8.5, 2.4 Hz, 1 H), 2.82 (d, *J* = 14.6 Hz, 1 H), 2.72 (d, *J* = 14.6 Hz, 1 H), 2.61 (ddd, *J* = 17.1, 11.4, 1.6 Hz, 1 H), 2.16 (ddd, *J* = 17.1, 8.3, 2.4 Hz, 1 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 176.0, 172.9, 161.7, 138.5, 137.0, 134.7, 134.4, 131.4, 129.9, 129.3, 129.2, 129.1, 128.7, 128.6, 128.0, 127.9, 127.7, 127.6, 127.4, 126.2, 92.4, 47.0, 41.6, 35.2, 33.7, 29.8.

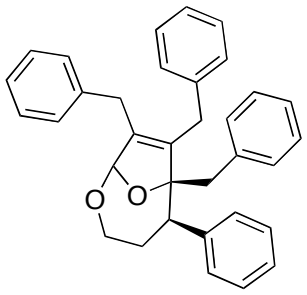
IR (neat): 2923, 2852, 1738, 1715, 1495, 1454, 1252, 1080, 1002, 915, 757, 699.

HR-MS: Calculated for $C_{34}H_{30}NaO_4$ $[M+Na]^+$: 525.2036, found: 525.2032.

$[\alpha]_D$ (c = 0.27, $CHCl_3$): -68.9°.

Mp: 82 – 83 °C.

6,7,8-Tribenzyl-5-phenyl-2,9-dioxabicyclo[4.2.1]non-7-ene (4.20)



To a solution of 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**4.07**, 1.0 eq., 0.10 mmol, 49 mg) in dry THF (4 ml) at 0 °C was added dry cerium(III) chloride (2.1 eq., 0.21 mmol, 52 mg). This was followed by the addition of $LiAlH_4$ (4.0 eq., 0.40 mmol, 15 mg) at once. The reaction was stirred for one hours at 0 °C and overnight at room temperature. To complete the conversion, the mixture was heated to reflux for 1.5 hours before it was cooled to 0 °C and quenched with water. After letting the reaction come to room temperature, it was filtrated over Celite. The solid was washed with TBME and water. The filtrate was diluted with brine before the layers

were separated. The aq. layer was extracted twice with TBME. The org. layers were combined, dried with Na_2SO_4 and concentrated. The intermediately formed lactol **4.19** reacts spontaneously to the desired product **4.20**. This process was accelerated by dissolving the lactol in TBME (5 ml). To this solution was added 4Å mole sieve (1 g) and the mixture was stirred at room temperature for 24 hours. The finished reaction mixture was filtrated over Celite and the filtrate was concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (20:1)) to give the title compound **4.20** (28 mg, 0.60 mmol, 60%) as pale colorless oil.

Rf (SiO_2, pentane/EtOAc (13:1)): 0.47.

^{1}H-NMR (500 MHz, C_6D_6): 7.27 (dd, *J* = 6.7, 2.7 Hz, 2 H), 7.19 – 7.11 (m, 9 H), 7.10 – 7.04 (m, 7 H), 6.53 (dd, *J* = 6.6, 2.5 Hz, 2 H), 5.85 (s, 1 H), 3.80 (ddd, *J* = 12.4, 6.3, 2.1 Hz, 1 H), 3.77 – 3.70 (m, 1 H), 3.45 (d, *J* = 15.4 Hz, 1 H), 3.34 (d, *J* = 15.6 Hz, 1 H), 3.22 (d, *J* = 15.4 Hz, 1 H), 3.04 (dd, *J* = 15.2, 10.4 Hz, 2 H), 2.84 (dd, *J* = 9.6, 5.6 Hz, 1 H), 2.36 (d, *J* = 14.9 Hz, 1 H), 2.25 (dtd, *J* = 14.9, 10.0, 2.1 Hz, 1 H), 1.61 (ddd, *J* = 11.8, 11.0, 5.5 Hz, 1 H).

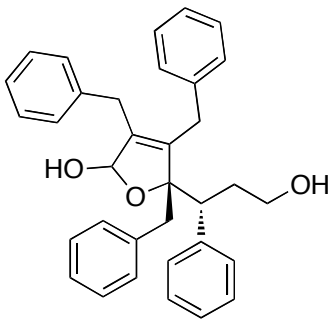
^{13}C-NMR (126 MHz, C_6D_6): 143.8, 142.0, 139.3, 138.1, 133.3, 130.9, 129.8, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 127.0, 126.9, 126.3, 106.2, 96.0, 62.1, 53.1, 42.4, 39.0, 32.8, 30.8.

IR (neat): 3026, 2950, 1601, 1493, 1453, 1084, 997, 952, 874, 417.

HR-MS: Calculated for $C_{34}H_{32}O_2$ $[M+H]^+$: 473.2475, found: 473.2473.

$[\alpha]_D$ (c = 0.30, $CHCl_3$, 68% *ee*): -55.5°.

The intermediate lactol 3,4,5-tribenzyl-5-(3-hydroxy-1-phenylpropyl)-2,5-dihydrofuran-2-ol (**4.19**) could not be characterized, as it spontaneously reacted to acetal **4.20**. Nevertheless, the intermediate lactol could be observed as crude by NMR.



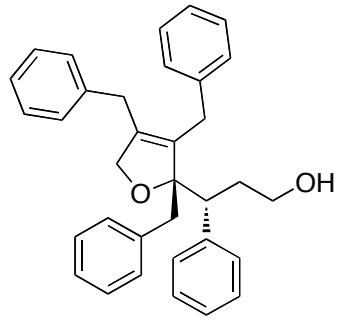
Rf (SiO_2, pentane/EtOAc (2:1)): 0.22.

^{1}H-NMR (500 MHz, C_6D_6): 7.29 – 7.01 (m, 18 H), 6.39 – 6.33 (m, 2 H), 5.35 (s, 1 H), 3.47 (d, *J* = 15.3 Hz, 1 H), 3.43 (d, *J* = 15.7 Hz, 1 H), 3.26 (d, *J* = 15.6 Hz, 1 H),

3.14 (d, *J* = 15.3 Hz, 1 H), 3.11 – 3.05 (m, 1 H), 2.83 (d, *J* = 14.0 Hz, 1 H), 2.74 – 2.65 (m, 2 H), 2.51 (d, *J* = 14.0 Hz, 1 H), 2.34 (s, 1 H), 2.06 – 1.95 (m, 1 H), 1.69 – 1.60 (m, 1 H).

^{13}C-NMR (126 MHz, C_6D_6): 142.3, 138.6, 138.4, 138.4, 138.0, 136.7, 130.6, 129.8, 128.8, 128.8, 128.6, 128.4, 128.2, 128.0, 127.0, 127.0, 126.4, 126.1, 102.5, 98.2, 60.7, 48.5, 44.0, 35.8, 32.6, 31.5.

Under more harsh conditions like refluxing overnight, the further reduced product 3-phenyl-3-(2,3,4-tribenzyl-2,5-dihydrofuran-2-yl)propan-1-ol (**4.24**) was formed as side product.



Rf (SiO_2, pentane/EtOAc (5:1)): 0.32.

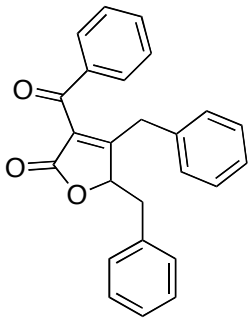
^{1}H-NMR (500 MHz, C_6D_6): 7.50 (s, 1 H), 7.23 (s, 2 H), 7.18 – 7.02 (m, 15 H), 6.39 (dd, *J* = 6.4, 2.9 Hz, 2 H), 4.37 (d, *J* = 12.0 Hz, 1 H), 4.19 (d, *J* = 11.9 Hz, 1 H), 3.50 (d, *J* = 15.3 Hz, 1 H), 3.35 (d, *J* = 15.7 Hz, 1 H), 3.16 (d, *J* = 15.3 Hz, 1 H), 3.08 (ddd, *J* = 10.4, 7.7, 4.0 Hz, 1 H), 2.87 – 2.80 (m, 2 H), 2.74 (ddd, *J* = 10.3, 8.5, 6.8 Hz, 1 H), 2.67 (dd, *J* = 11.8, 2.6 Hz, 1 H), 2.53 (d, *J* = 14.1 Hz, 1 H), 1.92 (tdd, *J* = 15.9, 6.8, 4.1 Hz, 1 H), 1.82 – 1.72 (m, 1 H), 1.36 (s, 1 H).

^{13}C-NMR (126 MHz, C_6D_6) δ 142.7, 139.5, 139.0, 135.6, 135.6, 133.9, 130.7, 129.7, 128.8, 128.7, 128.5, 128.4, 128.2, 128.0, 126.9, 126.8, 126.2, 126.2, 99.5, 77.5, 60.8, 50.8, 44.4, 34.6, 32.6, 32.1.

IR (neat): 3027, 2923, 2358, 1749, 1601, 1494, 1454, 1029, 910, 701.

HR-MS: Calculated for $C_{34}H_{32}NaO_2$ $[M+Na]^+$: 497.2451, found: 497.2449.

3-Benzoyl-4,5-dibenzylfuran-2(5H)-one (4.27)



To a solution of 3-oxo-3-phenylpropanoic acid (**4.26**, 1.10 eq., 3.48 mmol, 571 mg) and 3-hydroxy-1,4-diphenylbutan-2-one (**2.30**, 1.00 eq., 3.16 mmol, 759 mg) in CH_2Cl_2 (40 ml) were added 4-dimethylaminopyridine (0.12 eq., 0.38 mmol, 46 mg) and pentafluorophenol (1.10 eq., 3.48 mmol, 640 mg). Subsequently, a solution of *N*,*N*'-dicyclohexylcarbodiimide (1.30 eq., 4.11 mmol, 848 mg) in CH_2Cl_2 (5 ml) was added in one minute. After stirring for 20 hours at room temperature, the finished reaction was quenched with water and filtrated. The filter cake was washed with CH_2Cl_2. The filtrate was mixed with a sat. aq. $NaHCO_3$ solution before the layers were separated. The aq. layer was extracted twice with CH_2Cl_2. The org. layers were washed with a sat. aq. NH_4Cl solution, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (1:6)) to give the already cyclized product **4.27** as a brownish solid. The solid was recrystallized from MeOH and water to give the title compound **4.27** (304 mg, 0.83 mmol, 26%) as grey solid. An X-ray diffraction analysis was performed after recrystallization.

Rf (SiO_2, pentane/EtOAc (6:1)): 0.36.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.54 (tt, *J* = 7.6, 1.3 Hz, 1 H), 7.41 – 7.37 (m, 3 H), 7.35 – 7.22 (m, 11 H), 5.14 (t, *J* = 4.5 Hz, 1 H), 4.06 (d, *J* = 15.0 Hz, 1 H), 3.54 (d, *J* = 15.0 Hz, 1 H), 3.45 (dd, *J* = 14.5, 4.5 Hz, 1 H), 3.08 (dd, *J* = 14.5, 4.6 Hz, 1 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 190.0, 170.2, 169.4, 136.0, 135.2, 134.2, 133.9, 130.1, 129.8, 129.5, 129.4, 129.2, 129.1, 128.7, 127.8, 127.7, 81.5, 37.5, 34.2.

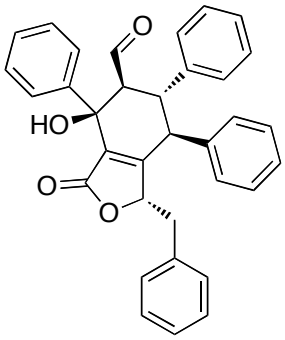
IR (neat): 2930, 1761, 1662, 1599, 1493, 1451, 1322, 1262, 1040, 998, 895, 766, 699.

EI-MS (70 eV) m/z (%): 369 (12), 368 (44, $[M]^+$), 277 (24), 259 (14), 105 (100), 91 (53), 77 (24).

HR-MS: Calculated for $C_{25}H_{20}NaO_3$ $[M+Na]^+$: 391.1305, found: 391.1301.

Mp: 109 – 111 °C.

1-Benzyl-4-hydroxy-3-oxo-4,6,7-triphenyl-1,3,4,5,6,7-hexahydroisobenzofuran-5-carbaldehyde (4.28)



A solution of 3-benzoyl-4,5-dibenzylfuran-2(5H)-one (**4.27**, 1.0 eq., 0.070 mmol, 26 mg), *trans*-cinnamaldehyde (1.2 eq., 0.0840 mmol, 10.7 µl) and cinchona alkaloid catalyst (**2.12**, 0.05 eq., 4 µmol, 2 mg) in CH_2Cl_2 (2 ml) was cooled to -40 °C. Subsequently, a 50% aq. KOH solution (20 eq., 1.40 mmol, 104 µl) was added over five minutes. The reaction was vigorously stirred for four days at -40 °C before some SiO_2 was added. After stirring for another 30 minutes, the reaction was filtrated over SiO_2. The filter cake was washed with EtOAc and TBME. The filtrate was concentrated and the crude product was purified by preparative TLC (SiO_2, pentane/EtOAc (2:1)) to give the title compound **4.28** (11 mg, 0.022 mmol, 31%) as colorless solids. An X-ray diffraction analysis was performed after recrystallization.

Rf (SiO_2, pentane/EtOAc (2:1)): 0.57.

^{1}H-NMR (400 MHz, $CDCl_3$): 9.33 (d, *J* = 3.8 Hz, 1 H), 7.50 – 7.41 (m, 3 H), 7.33 – 7.07 (m, 13 H), 6.92 – 6.86 (m, 2 H), 6.53 – 6.48 (m, 2 H), 5.05 (t, *J* = 4.0 Hz, 1 H), 3.85 – 3.78 (m, 2 H), 3.25 (dd, *J* = 14.6, 4.4 Hz, 2 H), 2.93 – 2.83 (m, 1 H), 2.68 (dd, *J* = 14.6, 3.7 Hz, 1 H).

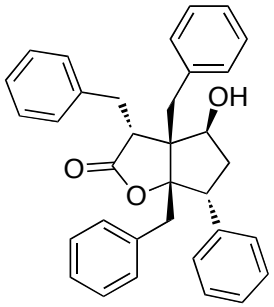
^{13}C-NMR (101 MHz, $CDCl_3$) δ 201.4, 169.7, 166.1, 141.8, 138.1, 137.5, 133.9, 132.4, 130.1, 129.3, 129.1, 128.9, 128.7, 128.3, 128.2, 127.9, 127.7, 127.7, 124.7, 80.4, 73.1, 63.3, 50.9, 47.6, 36.7.

IR (neat): 3029, 2929, 2849, 1749, 1494, 1454, 1336, 1069, 1008, 910, 756, 732, 699, 637.

HR-MS: Calculated for $C_{34}H_{28}NaO_4$ $[M+Na]^+$: 523.1880, found: 523.1879.

Mp: polymerization.

3,3a,6a-Tribenzyl-4-hydroxy-6-phenylhexahydro-2H-cyclopenta[b]furan-2-one (4.31)



To a solution of 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**4.07**, 1.0 eq., 0.062 mmol, 30mg) in dry THF (distilled from sodium, 6 ml) was added anhydrous EtOH (1.2 eq., 0.074 mmol, 4.4 µl). This was followed by the addition of samarium iodine (0.1 M solution in THF, 4.0 eq., 0.025 mmol, 2.5 ml) over 15 minutes at room temperature. The samarium iodine solution was prepared as described in literature.[20] After stirring the reaction mixture for 20 minutes, it was quenched with a half saturated aq. NH_4Cl solution. The resulting mixture was extracted three times with EtOAc. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (6:1)) to give the title compound **4.31** (18 mg, 0.037 mmol, 59%) as colorless oil.

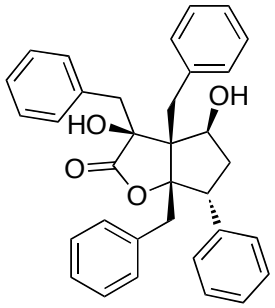
Rf (SiO_2, pentane/EtOAc (3:1)): 0.50.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.38 (dt, *J* = 5.1, 3.0 Hz, 2 H), 7.30 – 7.18 (m, 15 H), 7.17 – 7.09 (m, 3 H), 6.83 – 6.78 (m, 2 H), 4.51 (dt, *J* = 6.2, 3.3 Hz, 1 H), 3.47 – 3.38 (m, 2 H), 3.20 (d, *J* = 15.0 Hz, 1 H), 3.10 (d, *J* = 15.0 Hz, 1 H), 3.06 (d, *J* = 13.4 Hz, 1 H), 2.64 (dd, *J* = 14.2, 9.2 Hz, 1 H), 2.51 (dd, *J* = 9.2, 3.7 Hz, 1 H), 2.30 (ddd, *J* = 13.9, 11.7, 6.0 Hz, 1 H), 2.24 (dd, *J* = 14.2, 3.6 Hz, 1 H), 2.07 (ddd, *J* = 14.0, 7.8, 3.2 Hz, 1 H), 1.75 (d, *J* = 3.5 Hz, 1 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 177.3, 139.2, 137.9, 137.9, 136.4, 135.7, 131.1, 131.1, 131.0, 130.2, 129.0, 128.7, 128.5, 128.2, 128.1, 127.2, 127.1, 126.3, 95.5, 73.5, 60.7, 52.2, 50.2, 40.5, 40.1, 36.2.

HR-MS: Calculated for $C_{34}H_{32}NaO_3$ $[M+Na]^+$: 511.2244, found: 511.2242.

3,3a,6a-Tribenzyl-3,4-dihydroxy-6-phenylhexahydro-2H-cyclopenta[b]furan-2-one (4.32)



To a solution of 3,3a,6a-tribenzyl-4-hydroxy-6-phenylhexahydro-2H-cyclopenta[b]furan-2-one (**4.31**, 1.00 eq., 0.050 mmol, 24 mg) in dry THF (5 ml) at -78 °C was added NaHMDS (0.6 M solution in toluene, 3.00 eq., 0.150 mmol, 250 µl) in ten minutes. The slightly yellowish mixture was stirred for one hour at -78 °C and then heated to 0 °C. First, triethyl phosphite (distilled from sodium, 1.2 eq., 0.060 mmol, 10.7 µl) was added followed by the introduction of oxygen (dried over solid KOH) in the reaction atmosphere. The reaction was stirred under oxygen atmosphere at 0 °C for three hours. The yellowish reaction solution was quenched at 0 °C with a 1 M aq. HCl solution. The resulting mixture was extracted three times with EtOAc. The org. layers were washed with a mixture of brine and a 1 M aq. HCl solution (1:1 v/v), combined, dried with Na_2SO_4 and concentrated. The crude product was purified by preparative TLC (SiO_2, pentane/EtOAc (4:1)) to give the title compound **4.32** (16 mg, 0.032 mmol, 63%) as colorless oil.

Rf (SiO_2, pentane/EtOAc (4:1)): 0.56.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.77 (d, *J* = 7.1 Hz, 2 H), 7.42 – 7.27 (m, 8 H), 7.07 – 6.96 (m, 8 H), 6.86 (dd, *J* = 6.4, 3.2 Hz, 2 H), 4.62 (dd, *J* = 9.3, 5.6 Hz, 1 H), 3.63 (d, *J* = 14.6 Hz, 1 H), 3.53 (d, *J* = 13.8 Hz, 1 H), 3.31 (dd, *J* = 21.0, 11.5 Hz, 2 H), 3.21 (d, *J* = 14.6 Hz, 1 H), 3.16 (d, *J* = 14.0 Hz, 1 H), 3.06 (d, *J* = 14.0 Hz, 1 H), 2.16 (dd, *J* = 7.9, 5.5 Hz, 2 H), 1.94 (d, *J* = 4.4 Hz, 1 H).

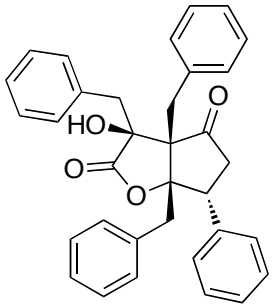
^{13}C-NMR (126 MHz, $CDCl_3$, as measured by HMBC and HMQC, no aromatic carbons): 176.0, 96.3, 77.9, 74.0, 63.6, 50.4, 41.8, 41.6, 38.3, 30.8.

IR (neat): 3526, 2927, 2361, 2343, 1742, 1496, 1455, 1198, 955, 751.

HR-MS: Calculated for $C_{34}H_{32}NaO_4$ $[M+Na]^+$: 527.2193, found: 527.2191.

$[\alpha]_D$ (c = 0.06, $CHCl_3$, 25% *ee*): -12.1°.

3,3a,6a-Tribenzyl-3-hydroxy-6-phenyltetrahydro-2H-cyclopenta[b]furan-2,4(5H)-dione (4.33)



To a solution of 3,3a,6a-tribenzyl-3,4-dihydroxy-6-phenylhexahydro-2H-cyclopenta[b]furan-2-one (**4.32**, 1.0 eq., 0.030 mmol, 15 mg) in dry CH_2Cl_2 (1.5 ml) was added Dess-Martin periodinane (2.0 eq., 0.060 mmol, 25 mg). After stirring for 1.5 hours at room temperature, the reaction was quenched with a 1 M aq. NaOH solution. The resulting mixture was extracted three times with TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was filtrated over SiO_2 using pentane/EtOAc (1:1). The filtrate was concentrated to give the title compound **4.33** (15 mg, 0.030 mmol, quantitative) as colorless oil.

Rf (SiO_2, pentane/EtOAc (6:1)): 0.65.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.60 – 7.55 (m, 2 H), 7.43 – 7.31 (m, 8 H), 7.09 – 7.02 (m, 3 H), 6.98 – 6.86 (m, 5 H), 6.73 (dd, *J* = 8.1, 1.3 Hz, 2 H), 3.87 (d, *J* = 14.3 Hz, 1 H), 3.45 (d, *J* = 14.6 Hz, 1 H), 3.40 (d, *J* = 14.1 Hz, 1 H), 3.32 (d, *J* = 14.1 Hz, 1 H), 3.20 (d, *J* = 14.3 Hz, 1 H), 3.08 (d, *J* = 14.6 Hz, 1 H), 2.64 (dd, *J* = 16.9, 12.2 Hz, 1 H), 2.57 – 2.49 (m, 1 H), 2.49 – 2.40 (m, 1 H), 2.31 (s, 1 H).

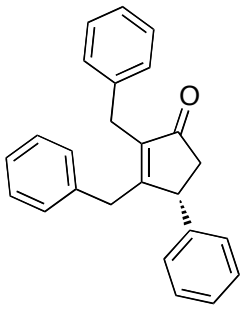
^{13}C-NMR (101 MHz, $CDCl_3$): 215.5, 174.9, 136.7, 135.6, 134.7, 133.3, 132.4, 131.1, 130.9, 129.8, 128.9, 128.8, 128.2, 127.9, 127.8, 127.7, 127.4, 126.4, 94.3, 75.7, 68.5, 49.1, 46.2, 40.2, 38.5, 33.3.

IR (neat): 3520, 3031, 2924, 2854, 1778, 1741, 1497, 1455, 1246, 1171, 1081, 991, 699.

HR-MS: Calculated for $C_{34}H_{29}Na_2O_4$ $[M-H+2Na]^+$: 547.1856, found: 547.1865.

$[\alpha]_D$ (c = 0.09, $CHCl_3$, 25% *ee*): +11.2°.

2,3-Dibenzyl-4-phenylcyclopent-2-enone (4.34)



Under various reaction conditions with 3,3a,6a-tribenzyl-3-hydroxy-6-phenyltetrahydro-2H-cyclopenta[b]furan-2,4(5H)-dione (**4.33**) as starting material or product, 2,3-dibenzyl-4-phenylcyclopent-2-enone (**4.34**) was observed as side product.

Rf (SiO_2, pentane/EtOAc (4:1)): 0.75.

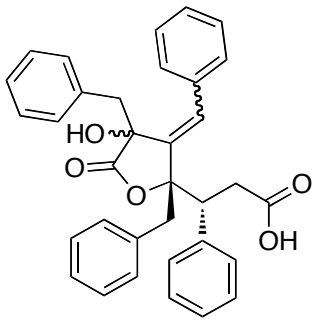
^{1}H-NMR (500 MHz, $CDCl_3$): 7.33 – 7.19 (m, 11 H), 6.99 – 6.94 (m, 2 H), 6.82 (dd, *J* = 6.6, 2.8 Hz, 2 H), 3.96 (d, *J* = 14.6 Hz, 1 H), 3.81 – 3.71 (m, 3 H), 3.11 (d, *J* = 14.6 Hz, 1 H), 2.87 (dd, *J* = 18.9, 7.2 Hz, 1 H), 2.38 (dd, *J* = 19.1, 2.1 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 208.8, 174.3, 140.8, 129.2, 129.1, 129.1, 128.8, 128.8, 128.7, 127.8, 127.3, 126.9, 126.9, 126.4, 126.4, 46.3, 44.8, 35.4, 29.9.

IR (neat): 3028, 2924, 2853, 1703, 1639, 1495, 1455, 1352, 1241, 1078, 759, 700.

HR-MS: Calculated for $C_{25}H_{22}NaO$ $[M+Na]^+$: 361.1563, found: 361.1565.

3-(2,4-Dibenzyl-3-benzylidene-4-hydroxy-5-oxotetrahydrofuran-2-yl)-3-phenylpropanoic acid (4.35)



To a solution of 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanoic acid (**4.18**, 1.0 eq., 0.030 mmol, 15 mg) in dry THF (5 ml) at -78 °C was added NaHMDS (0.6 M solution in toluene, 4.00 eq., 0.120 mmol, 200 µl) over five minutes. The slightly yellowish solution was stirred for one hour. This was followed by the addition of triethyl phosphite (distilled from sodium, 1.5 eq., 0.045 mmol, 7.9 µl) and the gas phase was flushed with oxygen (dried over solid KOH) at -78 °C. After stirring for another three hours at -78 °C, the reaction was quenched with a 1 M aq. HCl solution

and subsequently heated to room temperature. The resulting mixture was extracted three times with EtOAc. The org. layers were combined, dried with Na_2SO_4 and concentrated. The crude product was purified twice by preparative TLC (SiO_2, pentane/EtOAc (1:2) and pentane/EtOAc (2:3)) to obtain the title compound **4.35** (6 mg) as clear oil, containing still small amounts of impurities.

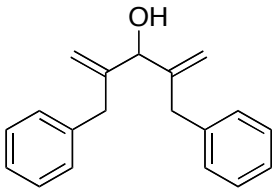
Rf (SiO_2, pentane/EtOAc (2:3)): 0.72.

^{1}H-NMR (400 MHz, $CDCl_3$): 9.22 (s, 1 H), 7.85 (d, *J* = 7.4 Hz, 2 H), 7.51 – 7.41 (m, 4 H), 7.41 – 7.28 (m, 4 H), 7.25 – 7.06 (m, 8 H), 6.93 (s, 1 H), 6.79 (dd, *J* = 6.4, 3.0 Hz, 2 H), 3.54 (dd, *J* = 11.2, 3.1 Hz, 1 H), 3.15 (dd, *J* = 16.2, 2.8 Hz, 1 H), 2.91 – 2.78 (m, 2 H), 2.74 (d, *J* = 14.1 Hz, 1 H), 2.53 (s, 1 H), 2.45 (d, *J* = 14.3 Hz, 1 H).

HR-MS: Calculated for $C_{34}H_{34}NO_5$ $[M+NH_4]^+$: 536.2434, found: 536.2431.

8.5 Studies on a Linear Approach Towards Ophiodilactone A and B

2,4-Dibenzylpenta-1,4-dien-3-ol (5.13)



Method A: To a solution of (2-bromoallyl)benzene (**5.11**, 1.00 eq., 1.00 mmol, 197 mg) in dry THF (4 ml) at -78 °C was added *t*BuLi (1.6 M solution in hexanes, 2.00 eq., 2.00 mmol, 1.25 ml). This mixture was stirred at that temperature for 30 minutes while the reaction turned dark yellow. Then, a solution of 2-benzylacrylaldehyde (**2.16**, 1.00 eq., 1.00 mmol, 146 mg) in THF (2 ml) was added dropwise. In doing so, the reaction turned colorless. Subsequently, the reaction mixture was stirred for one hour at -78 °C and was then allowed to warm to room temperature. The resulting colorless solution was quenched with water and stirred for 20 minutes. The mixture was extracted three times with EtOAc. The org. layers were washed with water and brine, combined, dried with Na_2SO_4 and concentrated. The colorless oil was purified by column chromatography (SiO_2, pentane/EtOAc (19:1)) to give the title compound **5.13** (205 mg, 0.78 mmol, 78%) as colorless oil.

Method B: A published procedure[21] was modified as follows: Pre-dried magnesium turnings (4.40 eq., 5.06 mmol, 132 mg) were mixed with dry THF (5 ml). Then diisobutylaluminium hydride (1 M solution in hexane, 0.002 eq., 2 µmol, 2 µl) was added and the solution was stirred for 10 minutes. This was followed by the addition of (2-bromoally)benzene (**5.11**, 2.22 eq., 2.53 mmol, 499 mg) at once. The mixture was stirred for 10 minutes at room temperature and heated for two hours to reflux. Then, the reaction mixture was cooled to 0 °C while it became turbid. The precipitate was filtered off and washed with dry THF (1 ml) using Schlock technique. To the clear brownish solution at 0 °C, freshly distilled ethyl formate (1.00 eq., 1.14 mmol, 92.1 µl) was added, while the Grignard solution losses its color immediately. After 10 minutes, the mixture was allowed to warm to room temperature and was stirred for one hour. The reaction was quenched with a sat. aq. NH_4Cl solution and stirred for another 40 minutes. The mixture was filtrated over Celite and the solids were washed

alternating with TBME and water. The layers of the filtrate were separated and the aq. layer was extracted twice with TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated to 259 mg. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (20:1)) to give the title compound **5.13** (81 mg, 0.31 mmol, 27%) as colorless oil and a 58:42 mixture (^{1}H-NMR) of the two side products **5.21** (52 mg, 0.10 mmol, 9%) and **5.20** (52 mg, 0.083 mmol, 7%). Side product **5.21** was isolated as colorless oil by column chromatography (SiO_2, pentane/EtOAc (20:1) and characterized. The ^{1}H-NMR of compound **5.21** reveals the depicted structure.

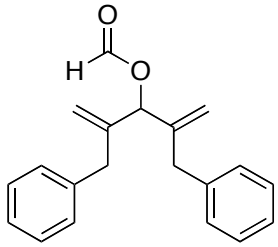
Method C: The side product **5.21** (1.00 eq., 3.36 mmol, 982 mg) was dissolved in dry toluene (20 ml) and cooled to -78 °C. Diisopropylaluminium hydride (1 M solution in hexane, 1.1 eq., 3.7 mmol, 3.7 ml) was slowly added and the reaction was stirred for three hours at -78 °C. Then the reaction was quenched with water and the mixture was heated to room temperature. Some Celite was added and the mixture was stirred for 15 minutes before the solids were filtered off. The filtrate was extracted three times with TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated to give the title compound **5.13** (885 mg, 3.4 mmol, quantitative) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.32 – 7.24 (m, 4 H), 7.24 – 7.17 (m, 2 H), 7.14 (d, J = 7.3 Hz, 4 H), 5.24 (s, 2 H), 4.89 (s, 2 H), 4.54 (d, J = 3.1 Hz, 1 H), 3.39 (d, J = 15.6 Hz, 2 H), 3.23 (d, J = 15.6 Hz, 2 H), 1.62 (d, J = 3.9 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 148.8, 139.4, 129.5, 128.5, 126.3, 113.8, 77.3, 38.6.

The analytical data of product **5.13** correspond to those reported in the literature.[21]

Side product **5.21** was identified as 2,4-dibenzylpenta-1,4-dien-3-yl formate.



Rf (SiO_2, pentane/EtOAc (10:1)): 0.87.

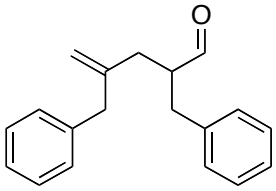
^{1}H-NMR (500 MHz, $CDCl_3$): 8.02 (d, J = 0.9 Hz, 1 H), 7.31 – 7.24 (m, 4 H), 7.24 – 7.19 (m, 2 H), 7.12 (d, J = 7.0 Hz, 4 H), 5.71 (s, 1 H), 5.25 (s, 2 H), 4.92 (d, J = 1.0 Hz, 2 H), 3.35 (d, J = 15.9 Hz, 2 H), 3.28 (d, J = 15.9 Hz, 2 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 159.8, 144.5, 138.5, 129.5, 128.5, 126.5, 115.8, 78.0, 38.6.

IR (neat): 3028, 2917, 2331, 1729, 1646, 1495, 1454, 1163, 915, 701.

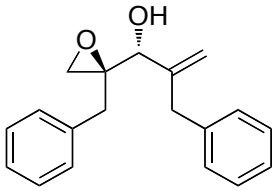
HR-MS: Calculated for $C_{20}H_{20}NaO_2$ $[M+Na]^+$: 247.1480, found: 247.1481.

Side product **5.20** was rationalized as the 1,4-addition product 2,4-dibenzylpent-4-enal.



^{1}H-NMR (500 MHz, $CDCl_3$): 9.59 (d, *J* = 2.5 Hz, 1 H), 7.26 (t, *J* = 7.5 Hz, 4 H), 7.20 (t, *J* = 7.2 Hz, 2 H), 7.11 (q, *J* = 6.8 Hz, 4 H), 4.88 (d, *J* = 5.7 Hz, 2 H), 3.34 (d, *J* = 15.0 Hz, 1 H), 3.29 (d, *J* = 15.0 Hz, 1 H), 2.91 (dd, *J* = 13.5, 7.5 Hz, 1 H), 2.87 – 2.75 (m, 1 H), 2.69 (dd, *J* = 13.6, 6.3 Hz, 1 H), 2.35 (dd, *J* = 15.1, 8.2 Hz, 1 H), 2.10 (dd, *J* = 15.1, 6.0 Hz, 1 H).

(*R*)-2-Benzyl-1-((*S*)-2-benzyloxiran-2-yl)prop-2-en-1-ol (5.14)



Method A (giving a high enantiomeric excess): A published procedure[22] was modified as follows: A mixture of pulverized 4 Å molecular sieve (25 mg) in dry CH_2Cl_2 (4 ml) was cooled to -20 °C. Titanium(IV) isopropoxide (1.10 eq., 0.627 mmol, 193 µl) and (+)-diisopropyl L-tartrate (1.30 eq., 0.741 mmol, 156 µl) were added at -20 °C. This mixture was stirred for 20 minutes. Subsequently, a solution of 2,4-dibenzylpenta-1,4-dien-3-ol (**5.13**, 1.00 eq., 0.570 mmol, 151 mg) in dry CH_2Cl_2 (1 ml) was added, followed by the addition of *tert*-butyl hydroperoxide (5.5 M solution in decane, 2.00 eq., 1.14 mmol, 207 µl). The reaction was stirred for 22 hours at -20 °C. Water, CH_2Cl_2 and Celite were added to the mixture and it was stirred for further 1.5 hours at -20 °C. The reaction mixture was brought to room temperature and filtrated over SiO_2. The solid were washed with CH_2Cl_2. The layers of the filtrate were separated and the aq. layer was extracted four times with CH_2Cl_2. The org. layers were washed with half concentrated brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (5:1)) to give

the title compound **5.14** (108 mg, 0.39 mmol, 68%) as clear oil with an enantiomeric excess of 87%.

Method B (giving a high yield): A mixture of pulverized 4 Å molecular sieve (25 mg) in dry CH_2Cl_2 (4 ml) was cooled to -20 °C. Titanium(IV) isopropoxide (1.10 eq., 0.627 mmol, 193 µl) and (+)-diethyl L-tartrate (1.30 eq., 0.741 mmol, 127 µl) were added at -20 °C. This mixture was stirred for 20 minutes. Subsequently, a solution of 2,4-dibenzylpenta-1,4-dien-3-ol (**5.13**, 1.00 eq., 0.570 mmol, 151 mg) in dry CH_2Cl_2 (1 ml) was added, followed by the addition of *tert*-butyl hydroperoxide (5.5 M solution in decane, 2.00 eq., 1.14 mmol, 0.207 ml). The reaction was stirred for 44 hours at -20 °C. To the cold mixture was added a sat. aq. Na_2SO_4 solution and the reaction was allowed to reach room temperature in three hours. After the addition of CH_2Cl_2 and Celite, the mixture was stirred for another 30 minutes, before the solids were filtered off and washed with CH_2Cl_2. The layers of the filtrate were separated and the aq. layer was extracted four times with CH_2Cl_2. The org. layers were subsequently washed with half sat. brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (19:1)) to give the title compound **5.14** (119 mg, 0.42 mmol, 75%) as clear oil with an enantiomeric excess of 71%.

Method C: This method was used to yield the racemic product. A published procedure[22] was modified as follows: To a mixture of pulverized 4 Å molecular sieve (100 mg) and vanadyl(IV) acetylacetonate (0.06 eq., 0.02mmol, 5mg) in dry CH_2Cl_2 (2 ml) at 0 °C was added a solution of 2,4-dibenzylpenta-1,4-dien-3-ol (**5.13**, 1.0 eq., 0.33 mmol, 87 mg) in dry CH_2Cl_2 (1.8 ml). By the addition, the color of the solution turned from blue to brown. After stirring for 10 minutes, *tert*-butyl hydroperoxide (5.5 M solution in decane, 1.0 eq., 0.33 mmol, 60 µl) was added dropwise. The reaction was stirred for one hour at 0 °C and anther 28 hours at room temperature. The reaction was quenched with a sat. aq. NH_4Cl solution. The layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (10:1)) to give the racemic title compound **5.14** (34 mg, 0.121 mmol, 37%) as clear oil.

Rf (SiO_2, pentane/EtOAc (5:1)): 0.38.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.34 – 7.18 (m, 8 H), 7.12 – 7.07 (m, 2 H), 5.24 (s, 1 H), 4.96 (dd, *J* = 2.7, 1.4 Hz, 1 H), 4.24 (d, *J* = 1.6 Hz, 1 H), 3.51 (d, *J* = 15.7 Hz,

1 H), 3.35 (d, *J* = 15.7 Hz, 1 H), 3.00 – 2.82 (m, 3 H), 2.38 (d, *J* = 4.7 Hz, 1 H), 2.16 (d, *J* = 2.0 Hz, 1 H).

^{1}H-NMR (400 MHz, DMSO-d_6): 7.32 – 7.15 (m, 8 H), 7.13 – 7.08 (m, 2 H), 5.26 (d, *J* = 4.3 Hz, 1 H), 5.16 (d, *J* = 0.7 Hz, 1 H), 4.78 (d, *J* = 1.3 Hz, 1 H), 3.82 (d, *J* = 3.3 Hz, 1 H), 3.43 (d, *J* = 15.4 Hz, 1 H), 3.30 (d, *J* = 15.4 Hz, 1 H), 2.95 (d, *J* = 14.4 Hz, 1 H), 2.80 (d, *J* = 14.5 Hz, 1 H), 2.60 (d, *J* = 5.2 Hz, 1 H), 2.17 (d, *J* = 5.1 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 147.1, 139.0, 135.7, 130.2, 129.5, 128.6, 128.4, 126.9, 126.4, 116.9, 73.8, 60.6, 48.7, 38.4, 37.1.

IR (neat): 3463, 3029, 2914, 1495, 1454, 1058, 910, 702, 632.

EI-MS (70 eV) m/z (%): 280 (0.59, $[M]^+$), 249 (13), 189 (18), 171 (34), 145 (17), 143 (15), 129 (37), 128 (10), 117 (25), 116 (30), 115 (23), 105 (17), 92 (18), 91 (100), 65 (11).

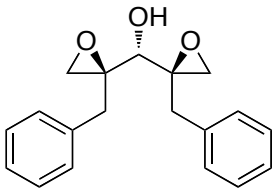
EA: Calculated for $C_{19}H_{20}O_2$: C 81.40% H 7.19% , found: C 80.70% H 7.02%.

$[\alpha]_D$ (c = 0.57, $CHCl_3$, 84% *ee*): +21.5°.

Chiral HPLC (Chiralpak IC column from Daicel, heptan/*i*PrOH (95:5 or 97:3), 0.5 ml/min, 20 °C, 258 nm) Rt: 17.7 and 19.0 or 23.7 and 25.6 minutes.

The analytical data of product **5.14** correspond to those reported in the literature.[22]

A observed side product is (*S*)-((*R*)-2-benzyloxiran-2-yl)((*S*)-2-benzyloxiran-2-yl)methanol originating from the double epoxidation.

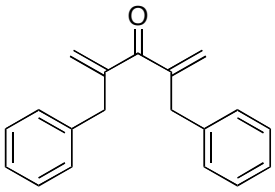


^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.19 (m, 10 H), 3.48 (s, 1 H), 3.13 (d, *J* = 14.7 Hz, 2 H), 3.06 (d, *J* = 14.6 Hz, 2 H), 2.81 (d, *J* = 4.7 Hz, 2 H), 2.43 (d, *J* = 4.7 Hz, 2 H), 2.26 (s, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 135.6, 130.5, 128.3, 126.9, 73.4, 59.3, 49.6, 36.0.

The analytical data of the product correspond to those reported in the literature.[22]

2,4-Dibenzylpenta-1,4-dien-3-one (5.25)



To a solution of 1,5-diphenylpentan-3-one (**5.23**, 1.00 eq., 1.05 mmol, 250 mg) in acetic acid (3 ml) was added formaldehyde (37% solution in water, 3.00 eq., 3.15 mmol, 234 µl) and morpholine (1.0 eq., 1.1 mmol, 91 µl). The mixture was heated in a microwave to 150 °C for one hour. Then additional morpholine (2.00 eq., 2.10 mmol, 181 µl) was added and the mixture was heated another hour to 150 °C. The reaction mixture was cooled down and neutralized with a 1 M aq. NaOH solution. This mixture was extracted three times with EtOAc. The org. layers were subsequently washed with a sat. aq. $NaHCO_3$ solution and brine, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (19:1)) to give the title compound **5.25** (80 mg, 0.30 mmol, 29%) as colorless oil.

Rf (SiO_2, pentane/EtOAc (20:1)): 0.61.

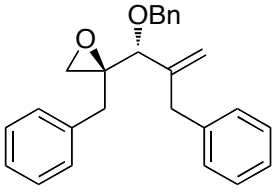
^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 – 7.24 (m, 4 H), 7.22 – 7.13 (m, 6 H), 5.67 (d, J = 0.9 Hz, 2 H), 5.54 (dd, J = 2.5, 1.4 Hz, 2 H), 3.65 (s, 4 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 198.6, 147.7, 138.8, 129.3, 128.6, 126.5, 125.7, 38.3.

IR (neat): 3030, 2920, 2854, 1712, 1602, 1496, 1454, 1076, 1029, 802, 739, 699.

HR-MS: Calculated for $C_{19}H_{18}NaO$ $[M+Na]^+$: 285.1250, found: 285.1250.

(*S*)-2-Benzyl-2-((*R*)-2-benzyl-1-(benzyloxy)allyl)oxirane (5.27)



To a solution of (*R*)-2-benzyl-1-((*S*)-2-benzyloxiran-2-yl)prop-2-en-1-ol (**5.14**, 1.0 eq., 0.071 mmol, 20 mg), benzyl bromide (1.2 eq., 0.085mmol, 10 µl) and tetrabutylammonium iodide (0.1 eq., 7 µmol, 3 mg) in dry THF (0.5 ml) at -20 °C was added half a micro spatula of sodium hydride (60%). The mixture was stirred for two hours at -20 °C and for 20 hours at room temperature. After complete consumption of the starting material, the reaction was quenched with a sat. aq. NH_4Cl solution and TBME was added. The layers were separated and the aq. layer was extracted twice with

TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by prep. TLC (SiO_2, pentane/EtOAc (9:1)) to give the title compound **5.27** (10 mg, 0.027 mmol, 38%) as pale yellow oil.

Rf (SiO_2, pentane/EtOAc (9:1)): 0.67.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.20 (m, 9 H), 7.16 (dd, *J* = 7.4, 1.9 Hz, 2 H), 7.13 – 7.09 (m, 2 H), 7.07 – 7.02 (m, 2 H), 5.21 (s, 1 H), 5.01 (d, *J* = 1.4 Hz, 1 H), 4.50 (d, *J* = 11.9 Hz, 1 H), 4.21 (d, *J* = 11.9 Hz, 1 H), 3.76 (s, 1 H), 3.45 (d, *J* = 15.5 Hz, 1 H), 3.30 (d, *J* = 15.4 Hz, 1 H), 3.06 (d, *J* = 14.5 Hz, 1 H), 2.87 (d, *J* = 14.5 Hz, 1 H), 2.68 (d, *J* = 5.1 Hz, 1 H), 2.39 (d, *J* = 5.1 Hz, 1 H).

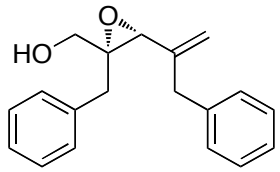
^{13}C-NMR (126 MHz, $CDCl_3$): 145.4, 139.1, 138.3, 136.4, 130.2, 129.7, 128.5, 128.4, 128.3, 128.1, 127.7, 126.6, 126.3, 116.0, 80.7, 71.0, 59.8, 49.5, 39.4, 37.0.

IR (neat): 3029, 2923, 2853, 1725, 1496, 1454, 1269, 1072, 1029, 913, 740, 699.

HR-MS: Calculated for $C_{26}H_{30}NO_2$ $[M+NH_4]^+$: 388.2271, found: 388.2271.

$[\alpha]_D$ (c = 0.41, $CHCl_3$): -2.3°.

((2*R*,3*R*)-2-Benzyl-3-(3-phenylprop-1-en-2-yl)oxiran-2-yl)methanol (5.28)



To a solution of (*R*)-2-benzyl-1-((*S*)-2-benzyloxiran-2-yl)prop-2-en-1-ol (**5.14**, 1.00 eq., 4.80 mmol, 1.35 g) in EtOH (40 ml) at 0 °C was added sodium ethoxide (1.50 eq., 7.20 mmol, 490 mg). The color of the solution turns immediately to orange and later to red. The reaction mixture is heated to room temperature and stirred for 8.5 hours, cooled to 0 °C and quenched with ice. The EtOH is removed from the mixture under vacuum before water and CH_2Cl_2 is added. The layers were separated and the aq. layer was extracted twice with CH_2Cl_2. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude mixture was purified by column chromatography (SiO_2, pentane/EtOAc (10:1)) to give the title compound **5.28** (1.01 g, 3.6 mmol, 75%) as colorless oil.

Rf (SiO_2, pentane/EtOAc (8:1)): 0.16.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.34 – 7.29 (m, 2 H), 7.28 – 7.18 (m, 6 H), 7.12 (d, *J* = 7.0 Hz, 2 H), 5.20 (s, 1 H), 5.17 (d, *J* = 1.2 Hz, 1 H), 3.59 (s, 1 H), 3.53 – 3.41 (m, 4 H), 2.64 (d, *J* = 14.6 Hz, 1 H), 2.22 (d, *J* = 14.6 Hz, 1 H), 1.46 (s, 1 H).

^{1}H-NMR (500 MHz, C_6D_6): 7.18 – 7.02 (m, 8 H), 7.01 – 6.97 (m, 2 H), 5.31 (dd, *J* = 1.2, 0.7 Hz, 1 H), 5.00 – 4.98 (m, 1 H), 3.50 (s, 1 H), 3.37 – 3.27 (m, 2 H), 3.20 (d, *J* = 14.6 Hz, 1 H), 3.15 (d, *J* = 14.6 Hz, 1 H), 2.62 (d, *J* = 14.5 Hz, 1 H), 2.17 (d, *J* = 14.5 Hz, 1 H), 0.93 (dd, *J* = 8.9, 4.2 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 142.4, 138.4, 137.1, 129.7, 129.2, 128.7, 128.5, 126.8, 126.7, 113.3, 65.8, 62.2, 60.8, 41.5, 33.1.

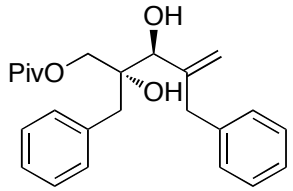
IR (neat): 3452, 3028, 2921, 1650, 1603, 1494, 1453, 1076, 908, 829, 750, 632.

EI-MS (70 eV) m/z (%): 280 (1.5, $[M]^+$), 189 (15), 159 (14), 129 (22), 128 (12), 115 (16), 92 (21), 91 (100), 81 (16).

EA: Calculated for $C_{19}H_{20}O_2$: C 81.40% H 7.19%, found: C 80.92% H 7.08%.

$[\alpha]_D$ (c = 0.76, $CHCl_3$, 84% *ee*): +119.9°.

(2*R*,3*S*)-2,4-Dibenzyl-2,3-dihydroxypent-4-en-1-yl pivalate (5.30)



Method A: A solution of (*S*)-2-benzyl-2-((*R*)-2-benzyl-1-(benzyloxy)allyl)oxirane (**5.28**, 1.00 eq., 0.360 mmol, 101 mg) in dry CH_2Cl_2 (1.5 ml) was cooled to -18 °C before pivalic acid (3.00 eq., 1.08 mmol, 110 mg) followed by titanium(IV) isopropoxide (2.00 eq., 0.720 mmol, 222 µl) were added. By the addition of titanium(IV) isopropoxide, the reaction turned dark red. The mixture was stirred for three hours at -15 °C and one hour at 0 °C before it was quenched with a 10% aq. tartric acid solution at 0 °C and stirred for another two hours. The precipitate was filtered off and washed with water and TBME. The layers of the filtrate were separated and the aq. layer was extracted twice with TBME. The org. layers were combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (8:1)) to give the title compound **5.30** (101 mg, 0.26 mmol, 73%) as white powder and the not rearranged (3*S*,4*R*)-2,4-dibenzyl-4,5-dihydroxypent-1-en-3-yl pivalate (**5.29**, 48 mg, 0.10 mmol, 27%) as clear oil.

Method B: This method was used to rearrange the undesired product **5.29** to the desired **5.30**. To a solution of (3*S*,4*R*)-2,4-dibenzyl-4,5-dihydroxypent-1-en-3-yl pivalate (**5.29**, 1.00 eq., 1.04mmol, 497 mg) in dry CH_2Cl_2 (5 ml) was first added pivalic acid (1.00 eq., 1.04 mmol, 106 mg) followed by the addition of

p-toluenesulfonic acid monohydrate (0.10 eq., 0.10 mmol, 20 mg). The reaction turns immediately yellowish. After stirring for three days at room temperature, the reaction was quenched at 0 °C with a sat. aq. $NaHCO_3$ solution. The layers were separated and the aq. layer was extracted twice with CH_2Cl_2. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (10:1)) to give the title compound **5.30** (292 mg, 0.76 mmol, 73%) as a white powder.

Rf (SiO_2, pentane/EtOAc (5:1)): 0.51.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.34 – 7.18 (m, 10 H), 5.16 (s, 1 H), 4.91 (dd, *J* = 1.4, 1.4 Hz, 1 H), 4.15 – 4.09 (m, 2 H), 3.77 (d, *J* = 11.6 Hz, 1 H), 3.61 (d, *J* = 15.8 Hz, 1 H), 3.52 (d, *J* = 15.8 Hz, 1 H), 3.07 (d, *J* = 13.7 Hz, 1 H), 2.98 (d, *J* = 13.7 Hz, 1 H), 2.39 (s, 1 H), 2.31 (d, *J* = 5.8 Hz, 1 H), 1.21 (s, 9 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 178.8, 148.3, 139.6, 136.2, 130.6, 129.5, 128.7, 128.6, 127.0, 126.4, 116.3, 76.0, 75.6, 66.3, 40.2, 39.9, 39.0, 27.4.

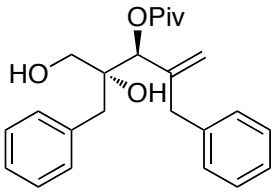
IR (neat): 3453, 3401, 1723, 1464, 1283, 1158, 1032, 920, 700.

EI-MS (70 eV) m/z (%): 235 (55), 151 (15), 133 (22), 91 (40), 85 (53), 57 (100).

EA: Calculated for $C_{24}H_{30}O_4$: C 75.36% H 7.91%, found: C 75.24% H 7.81%.

$[\alpha]_D$ (c = 0.47, $CHCl_3$, 84% *ee*): -21.5°.

Mp: 124 – 125 °C.

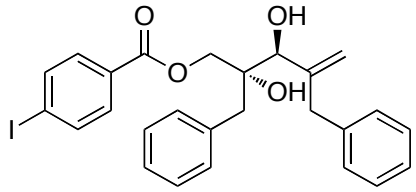


Product **5.29** could not be completely characterized, due to the low stability and the tendency to rearrange to compound **5.30**. If the remaining hydroxyl groups are protected, the compound is stable for analysis, see synthesis of (*S*)-2-benzyl-1-((*R*)-4-benzyl-2,2-dimethyl-1,3-dioxolan-4-yl)allyl pivalate (**5.45**). However, the following spectra's of **5.29** could be recorded.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.34 – 7.17 (m, 10 H), 5.31 (s, 1 H), 5.25 (s, 1 H), 4.89 (s, 1 H), 3.63 (s, 2 H), 3.38 (dd, *J* = 11.8, 4.3 Hz, 1 H), 3.26 (dd, *J* = 11.7, 7.2 Hz, 1 H), 3.08 (d, *J* = 13.9 Hz, 1 H), 2.75 (d, *J* = 13.9 Hz, 1 H), 2.51 (s, 1 H), 2.09 (t, *J* = 6.3 Hz, 1 H), 1.25 (s, 9 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 177.7, 145.6, 139.1, 136.3, 130.6, 129.7, 128.5, 128.5, 126.9, 126.4, 116.1, 76.1, 76.0, 64.8, 41.2, 39.2, 39.1, 27.3.

(2*R*,3*S*)-2,4-Dibenzyl-2,3-dihydroxypent-4-en-1-yl 4-iodobenzoate (5.34)



To a solution of (*S*)-2-benzyl-2-((*R*)-2-benzyl-1-(benzyloxy)allyl)oxirane (**5.28**, 1.0 eq., 0.18 mmol, 50 mg) in dry toluene (6 ml) was added titanium(IV) isopropoxide (1.5 eq., 0.27 mmol, 82 µl) at room temperature. Ten minutes later, 4-iodobenzoic acid (1.5 eq., 0.27 mmol, 68 mg) was added and the mixture was stirred for 44 hours at room temperature. The finished reaction was poured on a mixture of TBME and a 5% aq. H_2SO_4 solution. After stirring for two hours, the mixture was first made basic with a sat. aq. $NaHCO_3$ solution and then filtrated over Celite. The layers of the filtrate were separated and the aq. layer was extracted twice with TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (1:10)) to give the title compound **5.34** (24 mg, 0.045 mmol, 26%) as white crystals. For X-ray analysis, the solid was twice recrystallized from EtOH/water (2:1).

Rf (SiO_2, pentane/EtOAc (5:1)): 0.36.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.83 – 7.78 (m, 2 H), 7.66 – 7.60 (m, 2 H), 7.34 – 7.14 (m, 10 H), 5.18 (s, 1 H), 4.94 (d, *J* = 1.2 Hz, 1 H), 4.31 (d, *J* = 11.5 Hz, 1 H), 4.26 (d, *J* = 5.2 Hz, 1 H), 4.07 (d, *J* = 11.6 Hz, 1 H), 3.63 (d, *J* = 15.7 Hz, 1 H), 3.52 (d, *J* = 15.7 Hz, 1 H), 3.14 (d, *J* = 13.7 Hz, 1 H), 3.07 (d, *J* = 13.7 Hz, 1 H), 2.45 (s, 1 H), 2.16 (d, *J* = 5.3 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 166.1, 148.4, 139.5, 138.0, 136.2, 131.2, 130.6, 129.4, 129.3, 128.8, 128.7, 128.7, 127.1, 126.4, 116.5, 101.3, 75.8, 67.1, 40.6, 40.3.

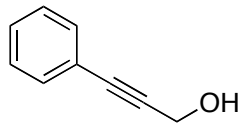
IR (neat): 3378, 3028, 2922, 2853, 1717, 1586, 1361, 1275, 1106, 1038, 925, 842, 743, 700.

EI-MS (70 eV) m/z (%): 381 (30), 231 (100), 91 (17).

HR-MS: Calculated for $C_{26}H_{26}IO_4$ $[M+H]^+$: 529.0870, found: 529.0867.

$[\alpha]_D$ (c = 0.10, $CHCl_3$): -1.9°.

3-Phenylprop-2-yn-1-ol (5.35)



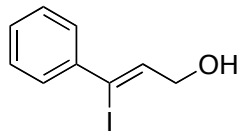
To a stirred solution of copper(I) iodide (0.015 eq., 0.15 mmol, 29 mg) and tetra is(triphenylphosphine)palladium(0) (0.010 eq., 0.100 mmol, 116 mg) in freshly distilled triethylamine (18 ml) at room temperature was added iodobenzene (1.00 eq., 10.0 mmol, 1.13 ml). After stirring for 30 minutes, propargyl alcohol (1.10 eq., 11.0 mmol, 650 µl) was added. The mixture was stirred for 20 hours at 60 °C. The finished reaction mixture was cooled down, diluted with Et_2O, filtered over Celite and concentrated. The crude product was purified by a filtration over SiO_2 using pentane/EtOAc (5:1) as solvent. The filtrate was concentrated and extensively dried in high vacuum to receive the title compound **5.35** (1.26 g, 9.5 mmol, 95%) as brownish liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.44 (dd, *J* = 6.6, 3.1 Hz, 2 H), 7.35 – 7.27 (m, 3 H), 4.50 (d, *J* = 6.0 Hz, 2 H), 1.71 (t, *J* = 6.1 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 131.8, 128.6, 128.5, 122.7, 87.3, 85.9, 51.8.

The analytical data of product **5.35** correspond to those reported in the literature.[23]

(*Z*)-3-Iodo-3-phenylprop-2-en-1-ol (5.36)



A published procedure[24] was modified as follows: To a solution of sodium bis(2-methoxyethoxy)aluminiumhydride (70% solution in toluene, 2.00 eq., 2.00 mmol, 558 µl) in dry Et_2O (5 ml) at 0 °C was slowly added a solution of 3-phenylprop-2-yn-1-ol (**5.35**, 1.00 eq., 1.00 mmol, 132 mg) in dry Et_2O (3 ml). The mixture was stirred for 10 minutes at 0 °C and for four hours at room temperature. Subsequently, the mixture was again cooled to 0 °C and dry EtOAc (1.0 eq., 1.0 mmol, 98 µl) was added to quench the excess of sodium bis(2-methoxyethoxy)aluminiumhydride. After stirring for 15 minutes, the reaction was cooled to -78 °C and a solution of iodine (1.50 eq., 1.50 mmol, 381 mg) in dry Et_2O (3 ml) was added in one portion. The mixture was allowed to warm to room temperature overnight. The finished reaction was quenched with a sat. aq. $Na_2S_2O_3$ solution and diluted with TBME and water. The layers were separated and the aq. layer was

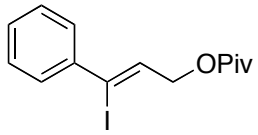
extracted three times with TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O (17:3)) to give the title compound **5.36** (193 mg, 0.74 mmol, 74%) as pale brownish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.51 – 7.43 (m, 2 H), 7.35 – 7.26 (m, 3 H), 6.26 (t, J = 5.7 Hz, 1 H), 4.40 (t, J = 5.8 Hz, 2 H), 1.73 (t, J = 5.9 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 142.3, 137.1, 128.9, 128.6, 128.5, 105.3, 68.4.

The analytical data of product **5.36** correspond to those reported in the literature.[24]

(*Z*)-3-Iodo-3-phenylallyl pivalate (5.37)



To a solution of (*Z*)-3-iodo-3-phenylprop-2-en-1-ol (**5.36**, 1.00 eq., 0.940 mmol, 244 mg), 4-dimethylaminopyridine (0.10 eq., 0.094 mmol, 12 mg) and pyridine (3.00 eq., 2.82 mmol, 227 µl) in CH_2Cl_2 (10 ml) was added pivaloyl chloride (1.20 eq., 1.13 mmol, 140 µl) at room temperature. After stirring for five hours, a TLC showed incomplete conversion. Therefore, additional pivaloyl chloride (0.50 eq., 0.47 mmol, 58 µl) was added. After stirring for another 18 hours, the reaction was quenched with a sat. aq. $NaHCO_3$ solution. The layers were separated and the aq. layer was washed with CH_2Cl_2. The org. layers were combined and subsequently washed with a 1 M aq. HCl solution, a 10% aq. NaOH solution and brine. The org. layer was dried with Na_2SO_4, concentrated and extensively dried in high vacuum to give the title compound **5.37** (240 mg, 0.70 mmol, 74%) as brown liquid.

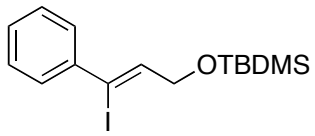
^{1}H-NMR (400 MHz, $CDCl_3$): 7.53 – 7.45 (m, 2 H), 7.34 – 7.28 (m, 3 H), 6.18 (t, J = 5.7 Hz, 1 H), 4.78 (d, J = 5.7 Hz, 2 H), 1.23 (s, 9 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 178.4, 142.3, 133.0, 129.0, 128.6, 128.5, 106.7, 69.5, 39.0, 27.4.

IR (neat): 2971, 1728, 1479, 1443, 1280, 1141, 1033, 985, 750, 692.

HR-MS: Calculated for $C_{14}H_{17}INaO_2$ $[M+Na]^+$: 367.0165, found: 367.0168.

(*Z*)-*tert*-Butyl((3-iodo-3-phenylallyl)oxy)dimethylsilane (5.38)



To a solution of (*Z*)-3-iodo-3-phenylprop-2-en-1-ol (**5.36**, 1.00 eq., 0.940 mmol, 244 mg) in dry CH_2Cl_2 (2 ml) at 0 °C was added triethylamine (2.00 eq., 1.88 mmol, 264 µl). The color of the solution changes from violet to yellow. After five minutes, *tert*-butylchlorodimethylsilane (1.40 eq., 1.32 mmol, 198 mg) was added. The mixture was stirred overnight at room temperature. The reaction was quenched with a sat. aq. NH_4Cl solution. The formed layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were combined, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (60:1)) to give the title compound **5.38** (308 mg, 0.823 mmol, 88%) as brownish liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.49 – 7.44 (m, 2 H), 7.34 – 7.24 (m, 4 H), 6.19 (t, J = 5.0 Hz, 1 H), 4.39 (d, J = 5.0 Hz, 2 H), 0.93 (s, 9 H), 0.13 (s, 6 H).

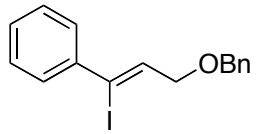
^{13}C-NMR (101 MHz, $CDCl_3$): 142.4, 138.8, 128.6, 128.6, 128.4, 102.1, 69.7, 26.1, 18.5, -4.9.

IR (neat): 2954, 2857, 1469, 1365, 1254, 1106, 834, 778, 693.

EI-MS (70 eV) m/z (%): 318 (17), 317 (100, $[M\text{-}t\text{Bu}]^+$), 215 (75), 189 (38), 185 (30), 116 (12), 115 (22), 73 (17).

EA: Calculated for $C_{15}H_{23}IOSi$: C 48.13% H 6.19%, found: C 48.32% H 6.12%.

(*Z*)-(3-(Benzyloxy)-1-iodoprop-1-en-1-yl)benzene (5.39)



A solution of (*Z*)-3-iodo-3-phenylprop-2-en-1-ol (**5.36**, 1.00 eq., 0.770 mmol, 200 mg) in toluene (0.5 ml) was cooled to 0 °C before a cold solution (0 °C) of sodium hydroxide (5.00 eq., 3.85 mmol, 154 mg) and tetrabutylammonium hydrogen sulfate (0.050 eq., 0.038 mmol, 13 mg) in water (1 ml) was added. After five minutes, benzyl bromide (1.50 eq., 1.16 mmol, 138 µl) was added and the reaction was allowed to warm to room temperature overnight. The finished reaction mixture was diluted with water and extracted three times with TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by Kugelrohr distillation (0.35 mbar, 150 to 190 °C) to give the title compound **5.39** (240 mg, 0.65 mmol, 85%) as brownish oil.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.50 – 7.44 (m, 2 H), 7.41 – 7.34 (m, 4 H), 7.34 – 7.27 (m, 4 H), 6.27 (t, *J* = 5.4 Hz, 1 H), 4.61 (s, 2 H), 4.29 (d, *J* = 5.4 Hz, 2 H).

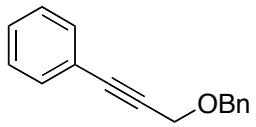
^{13}C-NMR (101 MHz, $CDCl_3$): 142.4, 138.1, 135.6, 128.8, 128.6, 128.6, 128.4, 128.0, 128.0, 105.2, 75.7, 73.0.

GC-MS (70 eV): 350 (0.39, $[M]^+$), 259 (40), 223 (33), 117 (23), 115 (39), 103 (58), 91 (100).

IR (neat): 2921, 2852, 1489, 1454, 1354, 1213, 1087, 1028, 751, 694.

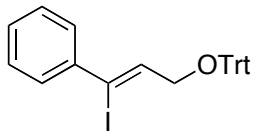
HR-MS: Calculated for $C_{16}H_{15}INaO$ $[M+Na]^+$: 373.0060, found: 373.0061.

The impurity was identified as the benzylated elimination product (3-(benzyloxy)prop-1-yn-1-yl)benzene.



The found ^{1}H-MNR shifts at ((400 MHz, $CDCl_3$): 4.69 (s, 2 H), 4.41 (s, 2 H)) correspond to those reported in the literature.[25]

(*Z*)-(((3-Iodo-3-phenylallyl)oxy)methanetriyl)tribenzene (5.40)



A solution of pyridine (1.0 eq., 0.70 mmol, 57 µl) and triphenylmethyl chloride (1.00 eq., 0.700 mmol, 195 mg) in CH_2Cl_2 (1 ml) was cooled to 0 °C. (*Z*)-3-iodo-3-phenylprop-2-en-1-ol (**5.36**, 1.00 eq., 0.700 mmol, 182 mg) was added and the reaction was stirred for 30 minutes at 0 °C and 24 hours at room temperature. Since the reaction was not completed, additional pyridine (0.1 eq., 0.07 mmol, 6 µl) and triphenylmethyl chloride (0.10 eq., 0.070 mmol, 20 mg) were added and the reaction was stirred for another 24 hours. The finished reaction was quenched with a 0.25 M aq. HCl solution. The layers were separated and the aq. layer was extracted two times with CH_2Cl_2. The org. layers were subsequently washed with a sat. aq. $NaHCO_3$ solution, combined, dried with Na_2SO_4 and concentrated. The residue was mixed with cyclohexane and filtrated over SiO_2. The filtrate was concentrated and twice recentralized from hot cyclohexane to give the title compound **5.40** (228 mg, 0.45 mmol, 65%) as white crystals. An X-ray diffraction analysis was performed after recrystallization.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.51 – 7.48 (m, 6 H), 7.44 – 7.41 (m, 2 H), 7.35 – 7.23 (m, 12 H), 6.26 (t, *J* = 5.1 Hz, 1 H), 3.93 (d, *J* = 5.1 Hz, 2 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 144.0, 142.4, 136.2, 128.8, 128.6, 128.5, 128.3, 128.1, 127.3, 103.5, 87.3, 70.5.

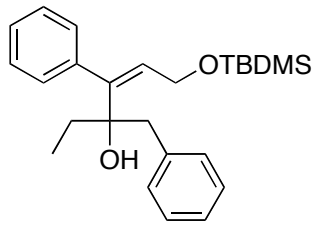
EI-MS (70 eV): 244 (46), 243 (100, $[M\text{-}Trt]^+$), 165 (21).

IR (neat): 3060, 3026, 2930, 2879, 1625, 1597, 1488, 1444, 1371, 1225, 1050, 995, 899, 846, 745, 691.

EA: Calculated for $C_{28}H_{23}IO$: C 66.94% H 4.61%, found: C 66.82% H 4.75%.

Mp: 101 – 102 °C.

(*Z*)-3-Benzyl-6-((*tert*-butyldimethylsilyl)oxy)-4-phenylhex-4-en-3-ol (5.41)



To a solution of (*Z*)-*tert*-butyl((3-iodo-3-phenylallyl)oxy)dimethylsilane (**5.38**, 1.1 eq., 0.098 mmol, 37 mg) in dry Et_2O (0.5 ml) at -78 °C was added *t*BuLi (1.6 M solution in hexanes, 2.2 eq., 0.196 mmol, 122 µl) over two minutes. After stirring for 15 minutes at -78 °C, 1-phenyl-2-butanone (1.0 eq., 0.089 mmol, 14 µl) was added neat. The reaction was stirred for 1.5 hours at -78 °C and one hour at 0 °C. The reaction was quenched with a sat. aq. NH_4Cl solution and water. The resulting mixture was extracted three times with TBME. The org. layers were combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (100:1)) to give the title compound **5.41** (6 mg, 0.015 mmol, 17%) as clear oil. Side products are the protonated lithium intermediate *tert*-butyl(cinnamyloxy)dimethylsilane[26] and the Brook rearrangement product **5.42**.

Rf (SiO_2, pentane/EtOAc (10:1)): 0.27.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.30 – 7.20 (m, 8 H), 7.06 – 7.02 (m, 2 H), 5.58 (t, *J* = 6.1 Hz, 1 H), 4.43 (dd, *J* = 13.6, 6.3 Hz, 1 H), 4.33 (dd, *J* = 13.6, 5.8 Hz, 1 H), 3.05 (d, *J* = 13.6 Hz, 1 H), 2.87 (d, *J* = 13.6 Hz, 1 H), 2.48 (s, 1 H), 1.77 (dq, *J* = 14.6, 7.3 Hz, 1 H), 1.55 (dq, *J* = 14.6, 7.3 Hz, 1 H), 0.98 (t, *J* = 7.4 Hz, 3 H), 0.91 (s, 9 H), 0.08 (s, 6 H).

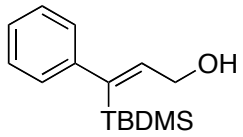
^{13}C-NMR (101 MHz, $CDCl_3$): 146.2, 143.5, 137.2, 133.3, 131.2, 128.8, 128.1, 127.9, 126.8, 126.6, 78.9, 60.7, 47.5, 33.2, 26.1, 18.5, 8.3, -5.0, -5.0.

IR (neat): 3453, 2929, 2856, 1463, 1254, 1073, 835, 703, 633.

EI-MS (70 eV) m/z (%): 305 (5, $[M-Ph]^+$), 247 (23), 174 (13), 173 (100), 145 (16), 117 (11), 91 (57), 75 (32), 73 (20), 57 (46).

HR-MS: Calculated for $C_{25}H_{36}NaO_2Si$ $[M+Na]^+$: 419.2377, found: 419.2376.

Side product **5.42** was identified as the Brook rearrangement product (*Z*)-3-(*tert*-butyldimethylsilyl)-3-phenylprop-2-en-1-ol.



Rf (SiO_2, pentane/EtOAc (10:1)): 0.34.

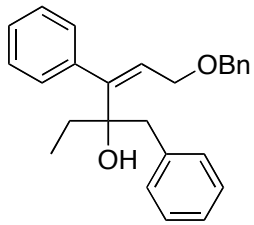
^{1}H-NMR (400 MHz, $CDCl_3$): 7.26 (ddd, *J* = 7.6, 4.5, 1.2 Hz, 2 H), 7.18 (ddd, *J* = 7.3, 3.8, 1.3 Hz, 1 H), 7.05 (dt, *J* = 3.3, 1.8 Hz, 2 H), 6.30 (t, *J* = 6.9 Hz, 1 H), 4.34 (d, *J* = 6.9 Hz, 2 H), 0.92 (s, 9 H), 0.10 (s, 6 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 147.1, 146.0, 145.0, 128.0, 127.8, 125.8, 63.0, 27.5, 18.3, -2.6.

IR (neat): 3308, 2955, 2857, 1597, 1253, 1013, 820, 774, 701.

HR-MS: Calculated for $C_{30}H_{48}NaO_2Si_2$ $[2M+Na]^+$: 519.3085, found: 519.3083.

(*Z*)-3-Benzyl-6-(benzyloxy)-4-phenylhex-4-en-3-ol (5.43)



To a solution of (*Z*)-(3-(benzyloxy)-1-iodoprop-1-en-1-yl)benzene (**5.39**, 1.40 eq., 0.092 mmol, 35 mg) in dry Et_2O (1 ml) at -78 °C was added *t*BuLi (1.6 M solution in pentane, 2.8 eq., 0.185 mmol, 116 µl) over two minutes. The mixture turned immediately yellow and slightly turbid. After stirring for 20 minutes at -78 °C, a solution of 1-phenyl-2-butanone (1.00 eq., 0.0660 mmol, 10.4 µg) in dry Et_2O (0.5 ml) was added. After stirring for another two hours at -78 °C, the reaction mixture was quenched with a half saturated aq. NH_4Cl solution and heated to room temperature. The resulting mixture was extracted three times with TBME. The org. layers were combined, dried with Na_2SO_4, concentrated and purified by preparative TLC (SiO_2, pentane/EtOAc (20:1)) to give the title compound **5.43** (10 mg, 0.027 mmol, 41%) as colorless honey.

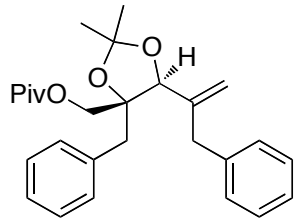
^{1}H-NMR (400 MHz, $CDCl_3$): 7.28 – 7.25 (m, 3 H), 7.24 – 7.10 (m, 10 H), 7.01 – 6.97 (m, 2 H), 5.57 (t, *J* = 6.1 Hz, 1 H), 4.43 (d, *J* = 1.4 Hz, 2 H), 4.22 (dd, *J* = 12.9, 6.3 Hz, 1 H), 4.13 (dd, *J* = 12.9, 5.9 Hz, 1 H), 2.95 (d, *J* = 13.5 Hz, 1 H), 2.77 (d, *J* = 13.6 Hz, 1 H), 2.23 (s, 1 H), 1.68 (dt, *J* = 14.7, 7.3 Hz, 1 H), 1.46 (dt, *J* = 14.3, 7.3 Hz, 1 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 147.8, 143.3, 138.3, 137.1, 131.2, 130.4, 128.8, 128.6, 128.2, 128.0, 127.9, 127.8, 126.9, 126.7, 78.9, 72.7, 67.7, 47.5, 33.1, 8.2.

IR (neat): 3570, 3062, 3029, 2966, 2932, 1494, 1454, 1363, 1074, 737, 701.

HR-MS: Calculated for $C_{26}H_{28}NaO_2$ $[M+Na]^+$: 395.1982, found: 395.1982.

((4*R*,5*S*)-4-Benzyl-2,2-dimethyl-5-(3-phenylprop-1-en-2-yl)-1,3-dioxolan-4-yl)methyl pivalate (5.44)



To a solution of (2*R*,3*S*)-2,4-dibenzyl-2,3-dihydroxypent-4-en-1-yl pivalate (**5.30**, 1.00 eq., 0.445 mmol, 171 mg) in THF (6 ml) was added *p*-toluenesulfonic acid monohydrate (0.1 eq., 0.05 mmol, 8 mg), followed by the addition of 2-methoxypropene (10.0 eq., 4.46 mmol, 427 µl). The reaction was stirred for five hours at room temperature. The reaction mixture was diluted with TBME and a sat. aq. $NaHCO_3$ solution. The layers were separated and the aq. layer was extracted twice with TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (30:1)) to give the title compound **5.44** (202 mg, 0.445 mmol, quantitative) as colorless oil.

Rf (SiO_2, pentane/EtOAc (30:1)): 0.44.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.36 – 7.31 (m, 2 H), 7.27 – 7.17 (m, 8 H), 5.49 (s, 1 H), 4.97 (s, 1 H), 4.33 (s, 1 H), 3.98 – 3.89 (m, 2 H), 3.63 (d, *J* = 15.8 Hz, 1 H), 3.44 (d, *J* = 15.8 Hz, 1 H), 3.25 (d, *J* = 14.1 Hz, 1 H), 2.87 (d, *J* = 14.1 Hz, 1 H), 1.43 (s, 3 H), 1.27 (s, 9 H), 0.98 (s, 3 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 178.1, 141.8, 138.6, 135.9, 131.4, 129.2, 128.7, 128.0, 126.8, 126.6, 114.9, 107.7, 82.5, 80.1, 65.0, 41.0, 40.6, 38.9, 28.5, 27.4, 26.4.

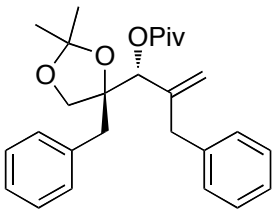
IR (neat): 2981, 1730, 1379, 1249, 1145, 1068, 995, 914, 856, 740, 700, 654.

EI-MS (70 eV) m/z (%): 422 (0.1, $[M]^+$), 273 (26), 188 (82), 171 (23), 132 (33), 91 (100), 57 (50).

EA: Calculated for $C_{27}H_{34}O_4$: C 76.75% H 8.11%, found: C 76.37% H 8.07%.

$[\alpha]_D$ (c = 0.28, $CHCl_3$, 84% *ee*): -17.9°.

(*R*)-2-Benzyl-1-((*S*)-4-benzyl-2,2-dimethyl-1,3-dioxolan-4-yl)allyl pivalate (5.45)



To a solution of (3*R*,4*S*)-2,4-dibenzyl-4,5-dihydroxypent-1-en-3-yl pivalate (**5.29**, 1.0 eq., 0.068 mmol, 26 mg) in THF, *p*-toluenesulfonic acid monohydrate (0.1 eq., 7 µmol, 1 mg) and 2-methoxypropene (10 eq., 0.68 mmol, 65 µl) were added. The reaction was stirred for four hours at room temperature. The finished reaction mixture was diluted with TBME and a sat. aq. $NaHCO_3$ solution. After stirring for 45 minutes, the layers were separated and the aq. layer was extracted twice with TBME. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by preparative TLC (SiO_2, pentane/EtOAc (20:1)) to give the title compound **5.45** (25 mg, 0.060 mmol, 87%) as colorless solid. An X-ray diffraction analysis was performed after recrystallization.

Rf (SiO_2, pentane/EtOAc (20:1)): 0.55.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.34 – 7.27 (m, 4 H), 7.27 – 7.20 (m, 6 H), 5.27 (s, 1 H), 5.13 – 5.11 (m, 1 H), 4.79 (d, *J* = 1.2 Hz, 1 H), 3.86 – 3.78 (m, 2 H), 3.72 (d, *J* = 16.6 Hz, 1 H), 3.58 (d, *J* = 16.6 Hz, 1 H), 3.14 (d, *J* = 14.2 Hz, 1 H), 2.81 (d, *J* = 14.2 Hz, 1 H), 1.33 (s, 3 H), 1.25 (s, 9 H), 0.86 (s, 3 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 176.6, 145.6, 139.1, 136.5, 131.7, 129.8, 128.4, 128.0, 126.7, 126.3, 114.7, 110.6, 84.0, 77.7, 69.3, 41.2, 39.0, 37.7, 27.3, 27.2, 26.1.

IR (neat): 3029, 2986, 3930, 1736, 1494, 1454, 1373, 1276, 1254, 1136, 1067, 1004, 908, 842, 755, 701.

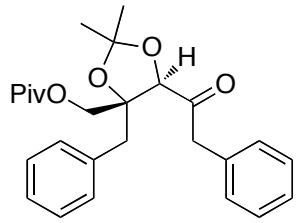
FAB-MS (8 kV Xe) m/z (%): 423 (13, $[M+H]^+$), 321 (15), 263 (19), 191 (69), 133 (26), 129 (17), 117 (17), 91 (100), 85 (15), 57 (88).

EA: Calculated for $C_{27}H_{34}O_4$: C 76.75% H 8.11%, found: C 76.05% H 8.19%.

$[\alpha]_D$ (c = 0.51, $CHCl_3$): -20.7°.

Mp: < 60 °C.

((4*R*,5*R*)-4-Benzyl-2,2-dimethyl-5-(2-phenylacetyl)-1,3-dioxolan-4-yl)methyl pivalate (5.46)



Some crystals of Sudan III were added to a solution of ((4*R*,5*S*)-4-benzyl-2,2-dimethyl-5-(3-phenylprop-1-en-2-yl)-1,3-dioxolan-4-yl)methyl pivalate (**5.44**, 1.0 eq., 0.040 mmol, 17 mg) in dry CH_2Cl_2 (2 ml) and the mixture was cooled to -78 °C. Ozone was passed through the solution until the red color disappeared. Subsequently, the reaction was flushed with oxygen. After stirring for five minutes, dimethyl sulfide (3.0 eq., 0.12 mmol, 9.8 µl) was added at -78 °C. The mixture was stirred for two hours at -78 °C and then heated to room temperature. The crude product was purified by preparative TLC (SiO_2, pentane/EtOAc (10:1)) to give the title compound **5.46** (10 mg, 0.022 mmol, 56%) as clear honey.

Rf (SiO_2, pentane/EtOAc (10:1)): 0.68.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.35 – 7.17 (m, 10 H), 4.30 (s, 1 H), 4.13 – 4.05 (m, 2 H), 4.00 (d, *J* = 11.5 Hz, 1 H), 3.87 (d, *J* = 16.7 Hz, 1 H), 3.16 (d, *J* = 14.2 Hz, 1 H), 3.00 (d, *J* = 14.2 Hz, 1 H), 1.53 (s, 3 H), 1.19 (s, 9 H), 0.92 (s, 3 H).

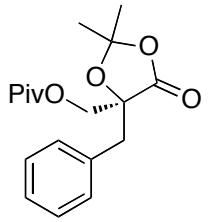
^{13}C-NMR (101 MHz, $CDCl_3$) δ 205.5, 178.1, 135.5, 133.1, 131.7, 130.1, 128.6, 128.1, 127.2, 127.0, 109.4, 83.7, 82.6, 65.4, 46.7, 40.1, 38.9, 28.2, 27.3, 26.3.

IR (neat): 2980, 1730, 1455, 1375, 1281, 1220, 1141, 1087, 1033, 992, 903, 853, 757, 700.

HR-MS: Calculated for $C_{26}H_{32}NaO_5$ $[M+Na]^+$: 447.2142, found: 447.2141.

$[\alpha]_D$ (c = 0.37, $CHCl_3$, 84% *ee*): +3.8°.

Surprisingly **5.46** showed to be instable and to decompose by standing at room temperature for longer periods. The decomposition product was isolated from a batch of the (4*S*,5*S*)-enantiomer by preparative TLC (SiO_2, pentane/EtOAc (20:1)) in 72% yield and identified as (*S*)-(4-benzyl-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)methyl pivalate (**5.47**).



Rf (SiO_2, pentane/EtOAc (20:1)): 0.29.

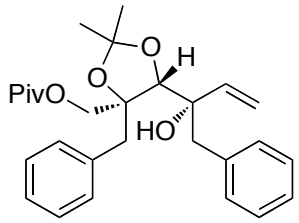
^{1}H-NMR (500 MHz, $CDCl_3$): 7.33 – 7.24 (m, 3 H), 7.24 – 7.20 (m, 2 H), 4.37 (d, *J* = 11.9 Hz, 1 H), 4.07 (d, *J* = 11.9 Hz, 1 H), 3.17 (d, *J* = 14.0 Hz, 1 H), 2.98 (d, *J* = 14.0 Hz, 1 H), 1.60 (d, *J* = 0.4 Hz, 3 H), 1.22 (s, 9 H), 0.96 (d, *J* = 0.4 Hz, 3 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 177.9, 171.8, 134.2, 130.9, 128.6, 127.7, 110.9, 83.2, 67.0, 40.7, 38.9, 28.3, 27.8, 27.3.

IR (neat): 2976, 1791, 1737, 1481, 1456, 1387, 1280, 1234, 1137, 1053, 1001, 926, 770, 700.

HR-MS: Calculated for $C_{18}H_{24}NaO_5$ $[M+Na]^+$: 343.1516, found: 343.1517.

((4*S*,5*R*)-4-Benzyl-5-((*S*)-2-hydroxy-1-phenylbut-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl pivalate (5.48)



To a solution of ((4*S*,5*S*)-4-benzyl-2,2-dimethyl-5-(2-phenylacetyl)-1,3-dioxolan-4-yl)methyl pivalate (*ent*-**5.46**, 1.0 eq., 0.059 mmol, 25 mg) in dry THF (0.5 ml) at -10 °C was added vinylmagnesium bromide (0.7 M solution in THF, 1.8 eq., 0.106 mmol, 151 µl). After stirring for 30 minutes at -10 °C, the reaction was warmed to 0 °C. As TLC showed after three hours only partial conversion, additional vinylmagnesium bromide (0.7 M solution in THF, 0.84 eq., 0.050 mmol, 71 µl) was added. After stirring for another hour, the reaction was still not finished. As the color started to get darker, it was quenched with a sat. aq. NH_4Cl solution. The mixture was extracted three times with EtOAc. The org. layers were combined, dried with Na_2SO_4 and concentrated. The crude product was purified by preparative TLC (SiO_2, pentane/EtOAc (25:1)) to give the title compound **5.48** (16 mg, 0.035 mmol, 60%) as a white solid. For X-ray analysis, the solid was recrystallized from MeOH.

Rf (SiO_2, pentane/EtOAc (25:1)): 0.48.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.33 – 7.24 (m, 3 H), 7.18 (dd, *J* = 6.5, 3.0 Hz, 2 H), 7.15 – 7.03 (m, 3 H), 6.91 (dd, *J* = 7.9, 1.4 Hz, 2 H), 6.51 – 6.36 (m, 1 H), 5.28 (dd, *J* = 17.6, 1.3 Hz, 1 H), 5.16 (dd, *J* = 11.0, 0.8 Hz, 1 H), 4.10 (d, *J* = 11.5 Hz, 1 H), 4.02 (d, *J* = 11.5 Hz, 1 H), 3.80 (s, 1 H), 3.04 – 2.94 (m, 2 H), 2.80 (d, *J* = 14.0 Hz, 1 H), 2.73 (d, *J* = 13.6 Hz, 1 H), 2.24 (s, 1 H), 1.40 (s, 3 H), 1.25 (s, 9 H), 0.79 (s, 3 H).

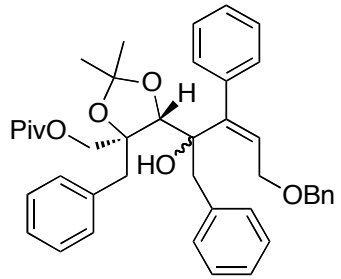
^{13}C-NMR (101 MHz, $CDCl_3$): 177.8, 140.7, 136.1, 135.9, 131.7, 131.2, 128.3, 127.8, 127.0, 126.2, 113.4, 107.5, 82.9, 79.6, 75.0, 66.4, 47.9, 40.8, 39.0, 28.4, 27.5, 26.1.

IR (neat): 3561, 2985, 2931, 1727, 1454, 1374, 1260, 1211, 1152, 1070, 989, 927, 853, 707.

HR-MS: Calculated for $C_{28}H_{36}NaO_5$ $[M+Na]^+$: 475.2455, found: 475.2453.

$[\alpha]_D$ (c = 0.13, $CHCl_3$): -32.8°.

((4*S*,5*R*)-4-Benzyl-5-((*Z*)-5-(benzyloxy)-2-hydroxy-1,3-diphenylpent-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl pivalate (5.49)



To a solution of (*Z*)-(3-(benzyloxy)-1-iodoprop-1-en-1-yl)benzene (**5.39**, 1.1 eq., 0.073 mmol, 28 mg) in Et_2O (0.5 ml) at -78°C was added *t*BuLi (1.6 M solution in pentane, 2.2 eq., 0.15 mmol, 90 µl) in two minutes and the mixture was stirred for 15 minutes. Subsequently, a solution of ((4*S*,5*S*)-4-benzyl-2,2-dimethyl-5-(2-phenylacetyl)-1,3-dioxolan-4-yl)methyl pivalate (*ent*-**5.46**, 1.0 eq., 0.066 mmol, 28 mg) in dry Et_2O (0.8 ml) was added and the reaction was stirred for 1.5 hours at -78 °C. Then, the mixture was heated to room temperature, stirred for another 30 minutes and quenched with a half sat. aq. NH_4Cl solution. The resulting mixture was extracted three times with TBME. The org. layers were washed with brine, combined, dried at Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (1:50 to 1:30)) to give the title compound **5.49** (10 mg, 0.015 mmol, 23%) as clear oil.

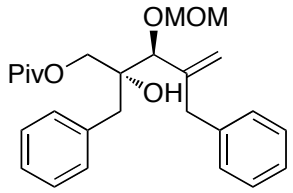
Rf (SiO_2, pentane/EtOAc (10:1)): 0.71.

^{1}H-NMR (600 MHz, toluene-D_8, 343 K): 7.30 (d, *J* = 6.7 Hz, 2 H), 7.21 (d, *J* = 7.6 Hz, 2 H), 7.17 – 7.03 (m, 10 H), 7.02 – 6.91 (m, 6 H), 5.68 (t, *J* = 6.2 Hz, 1 H), 4.97 (d, *J* = 11.3 Hz, 1 H), 4.45 (d, *J* = 11.2 Hz, 1 H), 4.29 – 4.20 (m, 2 H), 4.14 (s, 1 H), 4.11 (dd, *J* = 13.1, 6.3 Hz, 1 H), 3.71 (dd, *J* = 13.0, 5.9 Hz, 1 H), 3.39 (d, *J* = 14.2 Hz, 1 H), 3.25 (dd, *J* = 14.2, 2.2 Hz, 2 H), 3.13 (s, 1 H), 2.78 (d, *J* = 14.1 Hz, 1 H), 1.38 (s, 3 H), 1.22 (s, 9 H), 0.70 (s, 3 H).

^{13}C-NMR (151 MHz, toluene-D_8, 343 K): 177.5, 146.6, 142.8, 139.1, 137.7, 137.6, 137.4, 137.2, 132.3, 132.2, 129.7, 128.6, 128.1, 128.1, 128.0, 127.8, 127.3, 127.0, 126.6, 107.3, 85.4, 83.5, 79.2, 73.1, 68.2, 66.8, 43.9, 40.8, 39.2, 28.4, 27.6, 26.4.

ESI-MS m/z: 671 ($[M+Na]^+$).

(2*R*,3*S*)-2,4-Dibenzyl-2-hydroxy-3-(methoxymethoxy)pent-4-en-1-yl pivalate (5.50)



A solution of chloromethyl methyl ether (4.0 eq., 1.1 mmol, 84 mg) and sodium iodide (4.50 eq., 1.18 mmol, 177 mg) in dioxane (2 ml) was stirred for 20 minutes before a solution of freshly distilled diisopropylethylamine (4.50 eq., 1.18 mol, 195 µl) and (2*R*,3*S*)-2,4-dibenzyl-2,3-dihydroxypent-4-en-1-yl pivalate (**5.30**, 1.00 eq., 0.262 mmol, 100 mg) in dioxane (1.5 ml) was added. As after three hours at room temperature only little conversion could be observed, the reaction was heated to 60 °C for one hour. The reaction did still not proceed as expected and was heated to 100 °C for 20 hours. As only little conversion to the double protected product could be observed, the reaction mixture was heated to reflux for 24 hours, but no further conversion could be observed. Therefore, the reaction was cooled to room temperature and water and CH_2Cl_2 were added. The layers were separated and the aq. layer was extracted twice with CH_2Cl_2. The org. layers were combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (20:1)) to give the title compound **5.50** (67 mg, 0.157 mmol, 60%) as yellowish oil.

Rf (SiO_2, pentane/EtOAc (20:1)): 0.24.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.33 – 7.15 (m, 10 H), 5.15 (d, *J* = 0.6 Hz, 1 H), 4.96 (dd, *J* = 1.6, 1.6 Hz, 1 H), 4.56 (d, *J* = 6.6 Hz, 1 H), 4.50 (d, *J* = 6.6 Hz, 1 H), 4.22 (s,

1 H), 3.94 (d, *J* = 11.4 Hz, 1 H), 3.83 (d, *J* = 11.4 Hz, 1 H), 3.59 – 3.49 (m, 2 H), 3.39 (s, 3 H), 3.18 (d, *J* = 13.8 Hz, 1 H), 2.91 (d, *J* = 13.8 Hz, 1 H), 2.40 (s, 1 H), 1.20 (s, 9 H).

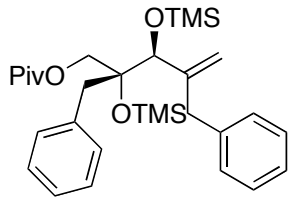
^{13}C-NMR (126 MHz, $CDCl_3$): 178.3, 145.7, 139.4, 136.4, 130.7, 129.7, 128.5, 128.5, 126.9, 126.3, 117.9, 94.6, 80.1, 75.7, 65.9, 56.6, 40.2, 40.2, 38.9, 27.4.

IR (neat): 2959, 1730, 1454, 1282, 1151, 1098, 1026, 989, 917, 740, 700.

HR-MS: Calculated for $C_{26}H_{34}KO_5$ $[M+K]^+$: 465.2038, found: 465.2036.

$[\alpha]_D$ (c = 0.62, $CHCl_3$, 84% *ee*): +53.6°.

(2*R*,3*S*)-2,4-Dibenzyl-2,3-bis((trimethylsilyl)oxy)pent-4-en-1-yl pivalate (5.52)



To a solution of (2*R*,3*S*)-2,4-dibenzyl-2,3-dihydroxypent-4-en-1-yl pivalate (**5.30**, 1.0 eq., 0.13 mmol, 50 mg) in CH_2Cl_2 (2 ml) was added imidazole (15.5 eq., 2.02 mmol, 133 mg) and the resulting solution was cooled to 0 °C. This was followed by the addition of chlorotimethylsilane (10.3 eq., 1.34 mmol, 173 µl) at 0 °C. The reaction was allowed to reach room temperature and was stirred for two days. The reaction mixture was mixed with some silica before it was concentrated. The formed solid was directly used for purification by column chromatography (SiO_2, pentane/EtOAc (50:1)) to give the title compound **5.52** (67 mg, 0.127 mmol, 98%) as colorless oil.

Rf (SiO_2, pentane/EtOAc (50:1)): 0.33.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.32 – 7.25 (m, 4 H), 7.24 – 7.19 (m, 6 H), 5.03 (s, 1 H), 4.72 (d, *J* = 1.4 Hz, 1 H), 4.23 (s, 1 H), 4.18 (d, *J* = 11.8 Hz, 1 H), 3.77 (d, *J* = 11.8 Hz, 1 H), 3.54 (s, 2 H), 3.10 (d, *J* = 13.3 Hz, 1 H), 3.02 (d, *J* = 13.3 Hz, 1 H), 1.28 (s, 9 H), 0.08 (s, 9 H), 0.05 (s, 9 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 178.4, 149.7, 139.9, 137.4, 131.07, 130.1, 128.4, 128.2, 126.6, 126.1, 115.9, 80.4, 76.2, 67.1, 40.8, 40.0, 39.1, 27.6, 3.0, 0.6.

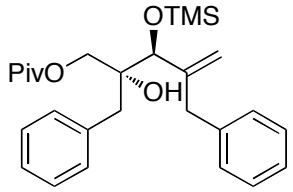
IR (neat): 2960, 1731, 1250, 1132, 1099, 1030, 839, 748, 702, 631.

EI-MS (70 eV) m/z (%): 333 (10), 307 (40), 206 (19), 205 (100), 73 (47), 57 (18).

EA: Calculated for $C_{30}H_{46}O_4Si_2$: C 68.39% H 8.80%, found: C 68.60% H 8.36%.

$[\alpha]_D$ (c = 0.62, $CHCl_3$, 84% *ee*): -34.3°.

A later experiment with lower concentrations and a shorter reaction time gave additionally significant amounts of the mono silylated product (2*R*,3*S*)-2,4-dibenzyl-2-hydroxy-3-((trimethylsilyl)oxy)pent-4-en-1-yl pivalate (**5.51**).



Rf (SiO_2, pentane/EtOAc (10:1)): 0.81.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.32 – 7.26 (m, 4 H), 7.26 – 7.16 (m, 6 H), 5.08 (s, 1 H), 4.77 (d, *J* = 1.6 Hz, 1 H), 4.27 (s, 1 H), 3.93 – 3.83 (m, 2 H), 3.62 – 3.50 (m, 2 H), 3.05 (d, *J* = 13.8 Hz, 1 H), 2.83 (d, *J* = 13.8 Hz, 1 H), 2.53 (s, 1 H), 1.21 (s, 9 H), 0.10 (s, 9 H).

^{13}C-NMR (126 MHz, $CDCl_3$) δ 178.2, 148.9, 139.6, 136.8, 130.7, 130.0, 128.4, 128.4, 126.7, 126.2, 115.8, 77.4, 76.0, 65.6, 40.2, 39.7, 38.9, 27.4, 0.3.

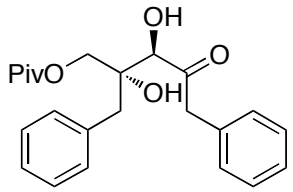
IR (neat): 2960, 1731, 1252, 1156, 1087, 884, 841, 703, 631.

EI-MS (70 eV) m/z (%): 235 (49), 221 (21), 220 (100), 219 (41), 205 (31), 151 (14), 133 (14), 129 (13), 91 (29), 85 (53), 75 (12), 73 (53), 57 (82).

HR-MS: Calculated for $C_{27}H_{39}O_4Si$ $[M+H]^+$: 455.2612, found: 455.2610.

$[\alpha]_D$ (c = 0.62, $CHCl_3$, 84% *ee*): -16.0°.

(2*R*,3*R*)-2-Benzyl-2,3-dihydroxy-4-oxo-5-phenylpentyl pivalate (5.53)



Some crystals of Sudan III were added to a solution of (2*R*,3*S*)-2,4-dibenzyl-2,3-dihydroxypent-4-en-1-yl pivalate (**5.30**, 1.0 eq., 0.066 mmol, 25 mg) in dry CH_2Cl_2 (5 ml) and the mixture was cooled to -78 °C. Ozone was passed through the solution until the red color disappeared. After flushing the reaction mixture with oxygen for five minutes, dimethyl sulfide (3.0 eq., 0.20 mmol, 15 µl) was added and the solution was stirred for two hours at -78 °C. Then, the mixture was warmed to room temperature and concentrated. The crude product was purified by preparative TLC (SiO_2, pentane/EtOAc (4:1)) to give the title compound **5.53** (17 mg, 0.044 mmol, 67%) as white solid.

Rf (SiO_2, pentane/EtOAc (4:1)): 0.60.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.36 – 7.18 (m, 10 H), 4.28 – 4.22 (m, 2 H), 4.07 (s, 2 H), 4.01 (d, *J* = 11.8 Hz, 1 H), 3.84 (d, *J* = 5.5 Hz, 1 H), 3.20 (s, 1 H), 2.84 (d, *J* = 13.9 Hz, 1 H), 2.62 (d, *J* = 13.9 Hz, 1 H), 1.17 (s, 9 H).

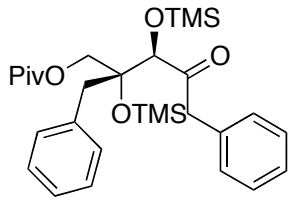
^{13}C-NMR (101 MHz, $CDCl_3$): 210.7, 180.0, 135.0, 133.7, 130.8, 129.9, 128.8, 128.6, 127.3, 127.2, 76.9, 76.5, 67.9, 48.0, 39.1, 38.8, 27.3.

IR (neat): 3407, 2979, 2911, 1710, 1293, 1150, 1083, 1037, 700, 665.

HR-MS: Calculated for $C_{23}H_{28}NaO_5$ $[M+Na]^+$: 407.1829, found: 407.1830.

$[\alpha]_D$ (c = 0.74, $CHCl_3$, 84% *ee*): -116.9°.

(2*R*,3*R*)-2-Benzyl-4-oxo-5-phenyl-2,3-bis((trimethylsilyl)oxy)pentyl pivalate (5.55)



Some crystals of Sudan III were added to a solution of (2*R*,3*S*)-2,4-dibenzyl-2,3-bis((trimethylsilyl)oxy)pent-4-en-1-yl pivalate (**5.52**, 1.00 eq., 0.200 mmol, 105 mg) in dry CH_2Cl_2 (10 ml) and the mixture was cooled to -78 °C. Ozone was passed through the solution until the red color disappeared. Subsequently, the reaction was flushed with oxygen and after stirring for five minutes, dimethyl sulfide (3.0 eq., 0.60mmol, 44 µl) was added at -78 °C. The reaction was allowed to reach room temperature within two hours before it was concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (50:1)) to give the title compound **5.55** (66 mg, 0.13 mmol, 62%) as clear oil.

Rf (SiO_2, pentane/EtOAc (30:1)): 0.41.

^{1}H-NMR (500 MHz, C_6D_6): 7.36 – 7.33 (m, 2 H), 7.20 – 7.15 (m, 4 H), 7.11 – 7.03 (m, 4 H), 4.73 (s, 1 H), 4.60 (d, *J* = 11.8 Hz, 1 H), 4.17 (d, *J* = 11.8 Hz, 1 H), 4.03 (d, *J* = 15.5 Hz, 1 H), 3.94 (d, *J* = 15.5 Hz, 1 H), 3.20 (d, *J* = 13.8 Hz, 1 H), 3.01 (d, *J* = 13.8 Hz, 1 H), 1.24 (s, 9 H), 0.07 (s, 9 H), 0.02 (s, 9 H).

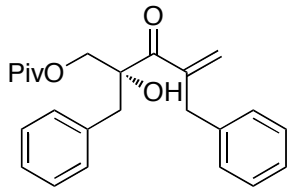
^{13}C-NMR (126 MHz, C_6D_6): 207.7, 177.2, 136.5, 134.8, 131.7, 130.3, 128.8, 128.4, 127.2, 126.9, 80.4, 79.1, 66.3, 49.2, 41.1, 39.0, 27.5, 2.6, 0.2.

IR (neat): 2960, 1730, 1455, 1251, 1132, 839, 750, 720.

EI-MS (70 eV) m/z (%): 308 (13), 307 (52), 295 (13), 294 (50), 218 (11), 217 (55), 206 (20), 205 (100), 147 (11), 91 (28), 73 (65), 57 (32).

EA: Calculated for $C_{29}H_{44}O_5Si_2$: C 65.87% H 8.39%, found: C 66.12% H 8.33%.

(*R*)-2,4-Dibenzyl-2-hydroxy-3-oxopent-4-en-1-yl pivalate (5.56)



To a solution of (2*R*,3*S*)-2,4-dibenzyl-2,3-dihydroxypent-4-en-1-yl pivalate (**5.30**, 1.00 eq., 0.300 mmol, 115 mg) in CH_2Cl_2 (5 ml) and DMSO (5 ml) was added 2-iodoxybenzoic acid (6.00 eq., 1.80 mmol, 504 mg). This mixture was stirred for 20 hours at room temperature before it was quenched with a sat. aq. $NaHCO_3$ solution. After the addition of further water, the layers were separated and the aq. layer was extracted three times with CH_2Cl_2. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (1:20)) to give the title compound **5.56** (83 mg, 0.22 mmol, 73%) as pale yellow honey.

Rf (SiO_2, pentane/EtOAc (10:1)): 0.42.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.30 – 7.26 (m, 2 H), 7.24 – 7.20 (m, 4 H), 7.14 – 7.09 (m, 4 H), 6.25 (s, 1 H), 5.73 (t, *J* = 1.5 Hz, 1 H), 4.52 (d, *J* = 11.6 Hz, 1 H), 4.30 (d, *J* = 11.5 Hz, 1 H), 3.94 (s, 1 H), 3.51 (s, 2 H), 3.14 – 3.05 (m, 2 H), 1.11 (s, 9 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 201.8, 178.3, 145.5, 138.3, 134.6, 130.5, 129.5, 128.7, 128.4, 127.4, 127.3, 126.6, 81.7, 69.8, 43.1, 39.0, 38.9, 27.2.

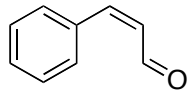
IR (neat): 3460, 2976, 2920, 1728, 1685, 1455, 1398, 1364, 1288, 1156, 1050, 1006, 940, 782, 744, 652.

HR-MS: Calculated for $C_{24}H_{28}KO_4$ $[M+K]^+$: 419.1619, found: 419.1619.

$[\alpha]_D$ (c = 0.62, $CHCl_3$, 84% *ee*): -30°.

8.6 Towards Maculalactone F, L and M

cis-Cinnamaldehyde (6.04)



A published procedure[27] was modified as follows: In a quartz glass tube, a solution of *trans*-cinnamaldehyde (1.00eq., 11.8 mmol, 1.57 g) in benzene (12 ml) was irradiated (λ = 302 nm, 100 W) without stirring until the *cis*/*trans*-equilibrium (determine by NMR) was reached. The solution was concentrated and the yellowish oil was purified by column chromatography (SiO_2, pentane/EtOAc (8:1)) to give the title compound **6.04** (668 mg, 5.1 mmol, 43%) as yellow oil.

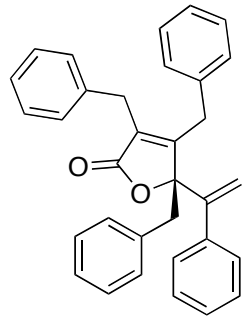
Rf (SiO_2, pentane/EtOAc (8:1)): 0.34.

^{1}H-NMR (400 MHz, $CDCl_3$): 9.88 (d, *J* = 8.0 Hz, 1 H), 7.00 – 6.84 (m, 5 H), 6.81 (d, *J* = 11.6, Hz, 1 H), 5.93 (dd, *J* = 11.6, 8.0 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 191.0, 147.2, 134.6, 130.8, 129.9, 129.4, 128.6.

The analytical data of product **6.04** correspond to those reported in the literature.[27]

3,4,5-Tribenzyl-5-(1-phenylvinyl)furan-2(5H)-one (6.09)



To a suspension of 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**4.07**, 1.0 eq., 0.01 mmol, 5 mg) and $NaHCO_3$ (1.2 eq., 0.01 mmol, 1 mg) in THF (0.3 ml) was added palladium acetate (traces) and allyl diethyl phosphate (1.0 eq., 0.010 mmol, 1.9 µl). The reaction was stirred at 90 °C. After 24 hours, additional allyl diethyl phosphate (3.0 eq., 0.030 mmol, 5.7 µl), palladium acetate (traces) and $NaHCO_3$ (3.6 eq., 0.03 mmol, 3 mg) were added. After another 20 hours at 90 °C, palladium acetate (1.3 eq., 0.01 mmol, 3 mg) and $NaHCO_3$ (2.4 eq., 0.02 mmol, 2 mg) were added. After another 24 hours at 90 °C, the reaction mixture was filtrated over SiO_2. The filtrate was mixed with water and the layers were separated. The aq. layer was extracted three times with EtOAc. The org. layers were combined, dried with Na_2SO_4 and

concentrated. The crude product was isolated by preparative TLC (SiO_2, pentane/EtOAc (5:1)) to give the title compound **6.09** (3.2 mg, 7.0 µmol, 68%) as yellow oil.

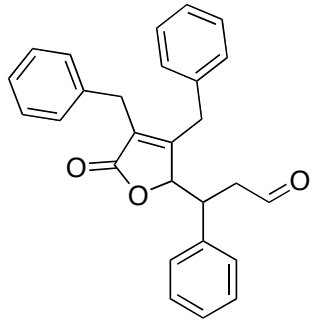
Rf (SiO_2, pentane/EtOAc (5:1)): 0.70.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30 – 6.99 (m, 16 H), 6.99 – 6.93 (m, 2 H), 6.88 – 6.84 (m, 2 H), 6.22 (d, *J* = 7.0 Hz, 2 H), 5.70 (s, 1 H), 5.45 (s, 1 H), 3.70 (d, *J* = 16.6 Hz, 1 H), 3.61 – 3.55 (m, 2 H), 3.29 (d, *J* = 14.3 Hz, 1 H), 3.14 (d, *J* = 15.7 Hz, 1 H), 3.02 (d, *J* = 15.6 Hz, 1 H).

IR (neat): 3029, 2919, 2850, 1754, 1495, 1454, 1079, 925, 754, 701.

HR-MS: Calculated for $C_{33}H_{28}NaO_2$ $[M+Na]^+$: 479.1982, found: 479.1988.

3-(3,4-Dibenzyl-5-oxo-2,5-dihydrofuran-2-yl)-3-phenylpropanal (6.11)



A solution of 3,4-dibenzylfuran-2(5H)-one (**2.06**, 1.0 eq., 0.23 mmol, 60 mg), *trans*-cinnamaldehyde (1.2 eq., 0.272 mmol, 34.6 µl) and cinchona alkaloid catalyst (**2.12**, 0.05 eq., 0.01 mmol, 7 mg) in toluene (5.6 ml) was cooled to -10 °C before a 50% aq. KOH solution (6.5 eq., 1.48 mmol, 110 µl) was added over five minutes. The reaction was vigorously stirred for 1 day at -10 °C before it was filtrated cold over SiO_2. The filter cake was rinsed with CH_2Cl_2. The filtrate was concentrated and purified by column chromatography (SiO_2, pentane/Et_2O (2:1)) to give the title compound **6.11** as two separated diastereomers (26 mg, 0.058 mmol, 25% and 36 mg, 0.082 mmol, 36%) as yellowish oils. A diastereomeric ration of 42:58 could be determined by ^{1}H-NMR of the crude mixture.

First diastereomer:

Rf (SiO_2, pentane/Et_2O (5:1)): 0.16.

^{1}H-NMR (400 MHz, $CDCl_3$): 9.43 (s, 1 H), 7.34 – 7.11 (m, 13 H), 7.03 – 6.97 (m, 2 H), 4.84 (d, *J* = 2.3 Hz, 1 H), 3.99 (d, *J* = 15.7 Hz, 1 H), 3.73 (s, 2 H), 3.68 (ddd, *J* = 7.9, 5.0, 2.9 Hz, 1 H), 3.50 (d, *J* = 15.7 Hz, 1 H), 2.73 (ddd, *J* = 18.2, 8.0, 0.9 Hz, 1 H), 2.49 (dd, *J* = 18.1, 5.1 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 199.6, 173.5, 161.2, 140.7, 138.2, 135.8, 129.9, 129.2, 129.0, 129.0, 128.9, 128.6, 128.2, 127.7, 127.5, 126.9, 84.5, 42.9, 40.5, 33.4, 29.9.

IR (neat): 3029, 2920, 1750 ,1724, 1494, 1453, 1045, 751, 698.

HR-MS: Calculated for $C_{27}H_{25}O_3$ $[M+H]^+$: 397.1798, found: 397.1802.

Second diastereomer:

Rf (SiO_2, pentane/Et_2O (5:1)): 0.10.

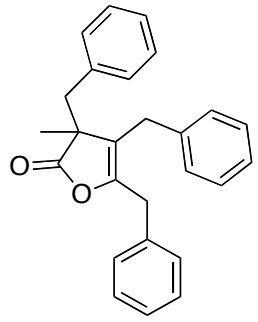
^{1}H-NMR (400 MHz, $CDCl_3$): 9.72 (s, 1 H), 7.37 – 7.17 (m, 9 H), 7.17 – 7.02 (m, 6 H), 6.47 (d, *J* = 6.8 Hz, 2 H), 5.01 (s, 1 H), 3.82 – 3.70 (m, 2 H), 3.45 (dt, *J* = 19.0, 15.7 Hz, 3 H), 3.27 – 3.17 (m, 1 H), 3.09 (d, *J* = 6.7 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 200.0, 173.6, 161.7, 137.3, 136.5, 136.0, 129.3, 129.1, 128.9, 128.8, 128.6, 128.6, 128.1, 128.0, 127.5, 126.2, 82.9, 47.3, 40.5, 33.4, 29.2.

IR (neat): 3029, 2919, 1749, 1721, 1494, 1453, 1053, 731, 702.

HR-MS: Calculated for $C_{27}H_{25}O_3$ $[M+H]^+$: 397.1798, found: 397.1804.

3,4,5-Tribenzyl-3-methylfuran-2(3H)-one (6.12)



To a solution of diisopropylamine (1.4 eq., 0.028 mmol, 4.0 µl) in dry THF (0.2 ml) at -78 °C was added dropwise BuLi (1.6 M solution in hexane, 1.3 eq., 0.0260 mmol, 16.3 µl). After stirring for 15 minutes at -78 °C, the mixture was heated to room temperature for 15 minutes and cooled again to -78 °C. Subsequently, a solution of maculalactone A (**1.34**, 1.0 eq., 0.02 mmol, 7 mg) in dry THF (0.2 ml) was added over ten minutes. The color of the reaction turns to violet. The mixture was stirred for five minutes at -78 °C before methyl iodide (1.8 eq., 0.036 mmol, 2.2 µl) was added. The reaction was allowed to reach room temperature overnight. The reaction mixture was concentrated and dried in high vacuum. The crude product was purified by preparative TLC (SiO_2, pentane/EtOAc (20:1)) to give the title compound **6.12** (2 mg, 5.4 µmol, 27%) as yellow oil.

Rf (SiO_2, pentane/EtOAc (20:1)): 0.31.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.32 – 7.07 (m, 18 H), 6.62 – 6.58 (m, 2 H), 3.67 (d, *J* = 16.1 Hz, 1 H), 3.48 (d, *J* = 16.0 Hz, 1 H), 3.44 – 3.35 (m, 2 H), 3.12 (d, *J* = 13.7 Hz, 1 H), 2.88 (d, *J* = 13.7 Hz, 1 H), 1.17 (s, 3 H).

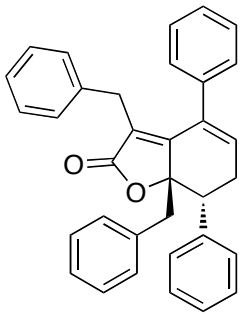
^{1}H-NMR (400 MHz, C_6D_6) δ 7.13 – 7.06 (m, 5 H), 7.06 – 6.98 (m, 6 H), 6.92 (d, *J* = 6.7 Hz, 2 H), 6.53 (dd, *J* = 6.4, 3.1 Hz, 2 H), 3.27 (d, *J* = 16.1 Hz, 1 H), 3.17 (d, *J* = 15.9 Hz, 1 H), 3.08 (d, *J* = 16.0 Hz, 1 H), 3.04 – 2.98 (m, 2 H), 2.49 (d, *J* = 13.6 Hz, 1 H), 0.95 (s, 3 H).

^{13}C-NMR (101 MHz, C_6D_6) δ 180.6, 148.6, 139.1, 136.9, 136.1, 129.8, 128.9, 128.8, 128.7, 128.6, 127.9, 127.2, 126.8, 126.6, 118.3, 52.8, 43.1, 31.9, 30.3, 23.7.

IR (neat): 3065, 3029, 2920, 2854, 1789, 1496, 1454, 1096, 1048, 739, 700.

HR-MS: Calculated for $C_{26}H_{25}O_2$ $[M+H]^+$: 369.1849, found: 369.1847.

3,7a-Dibenzyl-4,7-diphenyl-7,7a-dihydrobenzofuran-2(6H)-one (4.14)



Method A: This direct method leads to a racemic product. To a solution of maculalactone A (**1.34**, 1.0 eq., 0.080 mmol, 29 mg) in toluene (2 ml) was added *trans*-cinnamaldehyde (3.0 eq., 0.24 mmol, 31 µl) and tetrabutylammonium bromide (1.0 eq., 0.080 mmol, 26 mg). To this vigorously stirred mixture was added a 1 M aq. NaOH solution (2.5 eq., 0.201 mmol, 201 µl) at 0 °C. The mixture was allowed to reach room temperature and was stirred for two days. The finished reaction mixture was filtrated over SiO_2. The solid was extensively washed with EtOAc. The filtrate was concentrated. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc (7:1)) to give the title compound **4.14** (20 mg, 0.043 mmol, 53%) as colorless crystals. An X-ray diffraction analysis was performed.

Method B: This indirect approach results in an enantiomeric enriched product. To a solution of 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (**4.07**, 1.0 eq., 0.029 mmol, 14 mg) in toluene (0.5 ml) was added tetrabutylammonium bromide (0.3 eq., 9 µmol, 3 mg) before it was cooled to 0 °C. Subsequently, a 1 M aq.

NaOH solution (2.5 eq., 0.0732 mmol, 73.2 µl) was added to the vigorously stirred solution. The reaction was let warm to room temperature over a hour. After two days, additional tetrabutylammonium bromide (0.7 eq., 0.02 mmol, 7 mg) was added. After stirring for another day, the finished reaction was diluted with EtOAc and filtrated over SiO_2. The filtrate was concentrated and purified by preparative TLC (SiO_2, pentane/EtOAc (6:1)) to give the title compound **4.14** (8 mg, 0.017 mmol, 58%) as colorless solid.

Rf (SiO_2, pentane/EtOAc (5:1)): 0.46.

^{1}H-NMR (400 MHz, $CDCl_3$): 7.28 – 7.14 (m, 8 H), 7.06 – 6.98 (m, 3 H), 6.97 – 6.88 (m, 5 H), 6.88 – 6.80 (m, 2 H), 6.33 (dd, *J* = 4.4, 3.3 Hz, 1 H), 6.06 (d, *J* = 7.2 Hz, 2 H), 3.55 (d, *J* = 6.7 Hz, 1 H), 3.38 (d, *J* = 14.0 Hz, 1 H), 3.24 (d, *J* = 14.0 Hz, 1 H), 3.13 (ddd, *J* = 21.0, 6.8, 3.1 Hz, 1 H), 2.94 (d, *J* = 15.0 Hz, 1 H), 2.83 – 2.70 (m, 2 H).

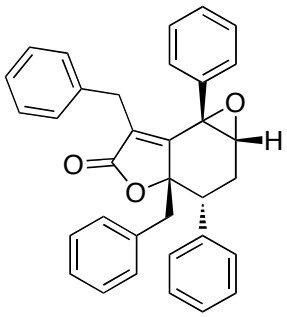
^{13}C-NMR (101 MHz, $CDCl_3$): 172.9, 154.3, 138.2, 137.7, 137.4, 135.6, 135.0, 133.5, 130.8, 128.8, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 128.0, 127.5, 127.3, 126.8, 125.6, 86.7, 46.2, 43.6, 32.0, 29.8.

IR (neat): 3029, 1744, 1494, 1453, 1060, 1033, 752, 697.

HR-MS: Calculated for $C_{34}H_{29}O_2$ $[M+H]^+$: 469.2162, found: 469.2164.

Mp: 64 – 65 °C.

3a,6-Dibenzyl-3,6b-diphenyl-1a,2,3,3a-tetrahydrooxireno[2,3-e]benzofuran-5(6bH)-one (6.13)



A solution of 3,7a-dibenzyl-4,7-diphenyl-7,7a-dihydrobenzofuran-2(6H)-one (**4.14**, 1.0 eq., 0.035 mmol, 16 mg) and Sudan Red III (traces) in CH_2Cl_2 (1.5 ml) was cooled to -78 °C before ozone was bubbled trough the solution. When the color of the reaction mixture changed from red to yellow, instead of ozone, pure oxygen was bubbled through the solution for 15 minutes. The reaction was quenched with dimethyl sulfide (0.1 ml), heated to room temperature and concentrated. The crude mixture was purified

by preparative TLC (SiO_2, pentane/EtOAc (5:1)) to give the title compound **6.13** (9 mg, 0.019 mmol, 53%) as clear oil.

Product **6.13** was also isolated as side product in the synthesis of **6.14** and **6.15**.

Rf (SiO_2, pentane/EtOAc (5:1)): 0.23.

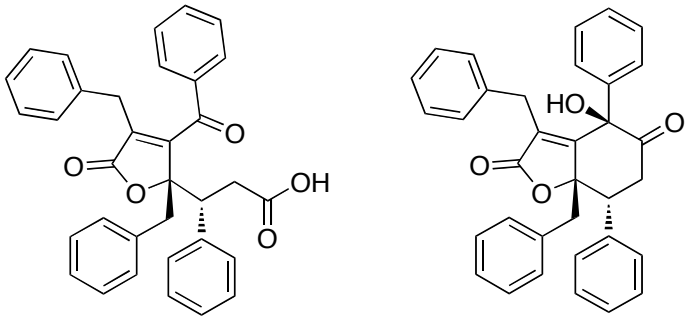
^{1}H-NMR (400 MHz, $CDCl_3$): 7.48 (dd, *J* = 7.8, 1.5 Hz, 2 H), 7.36 – 7.24 (m, 11 H), 7.19 (t, *J* = 7.4 Hz, 2 H), 6.94 (t, *J* = 7.3 Hz, 1 H), 6.85 (t, *J* = 7.5 Hz, 2 H), 5.83 (d, *J* = 7.2 Hz, 2 H), 3.97 (dd, *J* = 10.7, 9.3 Hz, 2 H), 3.70 (d, *J* = 7.4 Hz, 1 H), 3.39 (d, *J* = 13.4 Hz, 1 H), 3.00 (dd, *J* = 16.4, 7.5 Hz, 1 H), 2.71 (dd, *J* = 16.4, 4.1 Hz, 1 H), 2.60 (d, *J* = 15.7 Hz, 1 H), 2.42 (d, *J* = 15.7 Hz, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 171.3, 155.3, 138.5, 137.1, 136.1, 135.2, 133.9, 131.0, 129.2, 129.2, 128.7, 128.5, 128.2, 127.9, 127.9, 127.6, 127.4, 127.2, 125.5, 88.9, 63.4, 62.3, 48.8, 43.4, 28.6, 27.8.

IR (neat): 3032, 2922, 1750, 1495, 1452, 1056, 910, 879, 730, 696.

HR-MS: Calculated for $C_{34}H_{29}O_3$ $[M+H]^+$: 485.2111, found: 485.2116.

***epi*-Maculalactone M (6.14, left) and *epi*-maculalactone F (6.15, right)**



To a suspension of 3,7a-dibenzyl-4,7-diphenyl-7,7a-dihydrobenzofuran-2(6H)-one (**4.14**, 1.0 eq., 0.13 mmol, 62 mg) in CH_3CN (0.5 ml) and water (0.7 ml) at room temperature were added ruthenium(III) chloride (traces) and sodium periodate (4.1 eq., 0.540 mmol, 116 mg). The mixture was stirred for three hours at room temperature before it was diluted with water and EtOAc. The layers were separated and the aq. layer was extracted five times with EtOAc. The org. layers were combined, washed with brine, dried with Na_2SO_4 and concentrated. The products were separated by column chromatography (SiO_2, pentane/EtOAc (8:1 to 1:1)) to give *epi*-maculalactone M (**6.14**, 21 mg, 0.041 mmol, 32%) as colorless solid, *epi*-maculalactone F (**6.15**, 8 mg, 0.016 mmol, 12%) as solid and product **6.13** (16 mg, 0.033 mmol, 25%) as clear oil.

epi-Maculalactone M (**6.14**)

Rf (SiO_2, pentane/EtOAc (1:1)): 0.31.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.49 – 7.44 (m, 1 H), 7.38 (d, *J* = 7.1 Hz, 2 H), 7.28 – 7.20 (m, 7 H), 7.12 – 7.08 (m, 1 H), 7.03 (t, *J* = 7.5 Hz, 2 H), 7.00 – 6.90 (m, 5 H), 6.39 – 6.32 (m, 2 H), 4.00 (dd, *J* = 11.3, 3.3 Hz, 1 H), 3.29 – 3.21 (m, 2 H), 2.98 (d, *J* = 14.6 Hz, 1 H), 2.86 (d, *J* = 14.6 Hz, 1 H), 2.55 (dd, *J* = 16.1, 11.3 Hz, 1 H), 2.34 (dd, *J* = 16.1, 3.3 Hz, 1 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 191.9, 176.1, 171.7, 154.3, 138.0, 138.0, 136.3, 136.2, 134.6, 134.4, 130.5, 130.2, 129.6, 128.8, 128.7, 128.7, 128.6, 128.3, 128.0, 127.4, 126.7, 92.9, 48.4, 41.6, 35.6, 31.6.

IR (neat): 3030, 2924, 2361, 2326, 1760, 1710, 1650, 1597, 1244, 731, 697.

HR-MS: Calculated for $C_{34}H_{29}O_5$ $[M+H]^+$: 517.2010, found: 517.2017.

Mp: 74 – 75 °C.

epi-Maculalactone F (**6.15**)

Rf (SiO_2, pentane/EtOAc (5:1)): 0.23.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.43 – 7.37 (m, 3 H), 7.33 – 7.27 (m, 3 H), 7.23 – 7.09 (m, 10 H), 7.04 – 6.97 (m, 2 H), 6.65 (dd, *J* = 8.2, 1.0 Hz, 2 H), 4.39 (s, 1 H), 4.09 (d, *J* = 13.6 Hz, 1 H), 3.97 (d, *J* = 13.6 Hz, 1 H), 3.56 (dd, *J* = 6.8, 1.7 Hz, 1 H), 3.18 (dd, *J* = 16.5, 6.8 Hz, 1 H), 3.06 (dd, *J* = 16.5, 1.9 Hz, 1 H), 2.68 – 2.56 (m, 2 H).

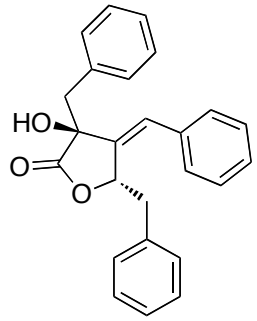
^{13}C-NMR (126 MHz, $CDCl_3$): 209.8, 171.8, 159.5, 139.5, 138.5, 135.9, 134.7, 132.3, 130.6, 130.0, 129.8, 129.3, 129.1, 128.8, 128.4, 128.2, 127.8, 127.7, 126.9, 126.3, 86.8, 84.3, 45.4, 45.2, 40.5, 30.2.

IR (neat): 3474, 3031, 2920, 1753, 1721, 1495, 1453, 1047, 696.

HR-MS: Calculated for $C_{34}H_{29}O_4$ $[M+H]^+$: 501.2060, found: 501.2064.

Mp: 83 – 85 °C.

***rac*-(*E*)-3,5-Dibenzyl-4-benzylidene-3-hydroxydihydrofuran-2(3H)-one (6.16)**



A solution of maculalactone A (**1.34**, 1.0 eq., 0.14 mmol, 50 mg) in dry THF (5 ml) was cooled to -78 °C before NaHMDS (0.6 M solution in toluene, 2.0 eq., 0.28 mmol, 470 µl) was added over five minutes. The resulting mixture was stirred for one hour

before dried triethyl phosphite (distilled from sodium, 1.5 eq., 0.210 mmol, 25.5 µl) was added. Then, the gas phase was flushed with oxygen (dried over solid KOH). The reaction was stirred for another hour at -78 °C and then heated to 0 °C. After stirring for 1.5 hours, the reaction was quenched with a 1 M aq. HCl solution. This mixture was extracted three times with EtOAc. The org. layers were washed with brine, combined, dried with Na_2SO_4 and concentrated. The crude reaction mixture was purified by column chromatography (SiO_2, pentane-EtOAc (9:1)) and by preparative TLC (SiO_2, CH_2Cl_2-Et_2O (9:1)) to give the title compound **6.16** (2.5 mg, 6.7 µmol, 5%) as clear oil.

Rf (SiO_2, CH_2Cl_2/Et_2O (9:1)): 0.75.

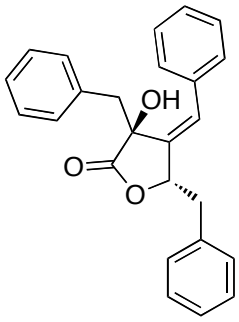
^{1}H-NMR (500 MHz, $CDCl_3$): 7.49 – 7.44 (m, 2 H), 7.40 – 7.35 (m, 1 H), 7.29 – 7.20 (m, 7 H), 7.18 – 7.15 (m, 2 H), 6.94 – 6.90 (m, 2 H), 6.80 (d, *J* = 2.6 Hz, 1 H), 5.15 (dt, *J* = 5.6, 3.0 Hz, 1 H), 3.26 (d, *J* = 12.6 Hz, 1 H), 3.02 (d, *J* = 12.6 Hz, 1 H), 2.98 (dd, *J* = 14.6, 3.2 Hz, 1 H), 2.68 (dd, *J* = 14.6, 5.4 Hz, 1 H), 1.62 (s, 1 H).

^{13}C-NMR (126 MHz, $CDCl_3$): 176.5, 138.8, 135.3, 135.3, 133.4, 130.7, 130.3, 129.2, 128.8, 128.8, 128.7, 128.6, 128.5, 127.6, 127.4, 81.0, 77.0, 47.1, 37.3.

IR (neat): 3060, 3030, 2927, 1766, 1496, 1454, 1353, 1150, 1030, 1003, 738, 699.

HR-MS: Calculated for $C_{25}H_{26}NO_3$ $[M+H]^+$: 388.1907, found: 388.1905.

***rac-epi*-Maculalactone L (6.17)**



A solution of maculalactone A (**1.34**, 1.0 eq., 0.085 mmol, 30 mg) in dry THF (2 ml) was cooled to -78 °C before NaHMDS (0.6 M solution in toluene, 2.0 eq., 0.17 mmol, 280 µl) was added over five minutes. The resulting mixture was stirred for one hour before triethyl phosphite (distilled from sodium, 1.5 eq., 0.128 mmol, 22.4 µl) was added followed by the exchange of the gas phase to oxygen (dried over solid KOH). The reaction was stirred for another 4.5 hours at -78 °C before it was quenched with a 1 M aq. HCl solution at this temperature. The mixture was heated to room temperature and extracted twice with EtOAc. The org. layers were washed with a 1 M aq. HCl solution, combined, dried with Na_2SO_4 and concentrated. The crude mixture was

purified by preparative TLC (SiO_2, pentane/EtOAc (4:1)) to give the title compound **6.17** (1 mg, 2.7 µmol, 3%) as colorless oil and the known compound **2.05** (8 mg, 0.022 mmol, 25%).

Rf (SiO_2, pentane/EtOAc (4:1)): 0.63.

^{1}H-NMR (500 MHz, $CDCl_3$): 7.76 – 7.71 (m, 2 H), 7.46 – 7.41 (m, 2 H), 7.40 – 7.35 (m, 1 H), 7.34 – 7.27 (m, 2 H), 7.21 – 7.18 (m, 2 H), 7.17 – 7.13 (m, 3 H), 6.89 – 6.85 (m, 2 H), 6.67 (d, *J* = 1.9 Hz, 1 H), 4.62 (ddd, *J* = 6.0, 4.1, 2.0 Hz, 1 H), 3.26 (d, *J* = 12.8 Hz, 1 H), 3.21 (dd, *J* = 14.3, 4.1 Hz, 1 H), 3.05 (d, *J* = 12.8 Hz, 1 H), 2.98 (dd, *J* = 14.3, 5.8 Hz, 1 H), 1.98 (s, 1 H).

^{13}C-NMR (101 MHz, $CDCl_3$): 177.4, 136.3, 135.2, 134.6, 133.8, 131.1, 130.6, 130.2, 130.1, 128.8, 128.7, 128.4, 127.5, 127.4, 82.2, 76.9, 42.3, 40.6.

IR (neat): 3442, 3062, 3030, 2923, 2853, 1763, 1495, 1454, 1345, 1240, 1148, 1081, 1040, 752, 699.

HR-MS: Calculated for $C_{25}H_{26}NO_3$ $[M+H]^+$: 388.1907, found: 388.1905.

8.7 References

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9 - APPENDIX

9.1 Abbreviations, Acronyms and Symbols

$[\alpha]_D$	specific rotation at the sodium D line
AADC	aromatic aminoacid decarboxylase
Ac	acetyl
acac	acetylacetone
AIBN	azobisisobutyronitrile
aq.	aqueous
BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Bu	butyl
c	concentrated
cat.	catalytic
COSY	correlation spectroscopy
C4H	cinnamate-4-hydroxylase
DC	circular dichroism
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMDO	3,3-dimethyldioxirane
DMPU	1,3-dimethyltetrahydropyrimidin-2(1*H*)-one
d	doublet
DBU	1,8-diazadicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DET	diethyl tartrate
DIBAL	diisopropylaluminium hydride
DIPA	diisopropylamine
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
DOPA	3,4-dihydroxyphenylalanine
dppf	1,1'-bis(diphenylphosphino)ferrocene
d.r.	diastereomeric ratio
ee	enantiomeric excess

EI	electron impact ionization
ent	enantiomeric
epi	epimeric
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple-quantum correlation spectroscopy
HPLC	high-performance liquid chromatography
i	iso
IBX	2-iodoxybenzoic acid
IC_{50}	50% inhibitory concentration
IR	infrared spectroscopy
J	coupling constant
LC_{50}	50% lethal concentration
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	mol/l
MAP	mussel adhesive protein
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute(s)
MOM	methoxymethyl
Mp	melting point
Ms	mesylate
MS	mass spectrometry / molecular sieves
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide

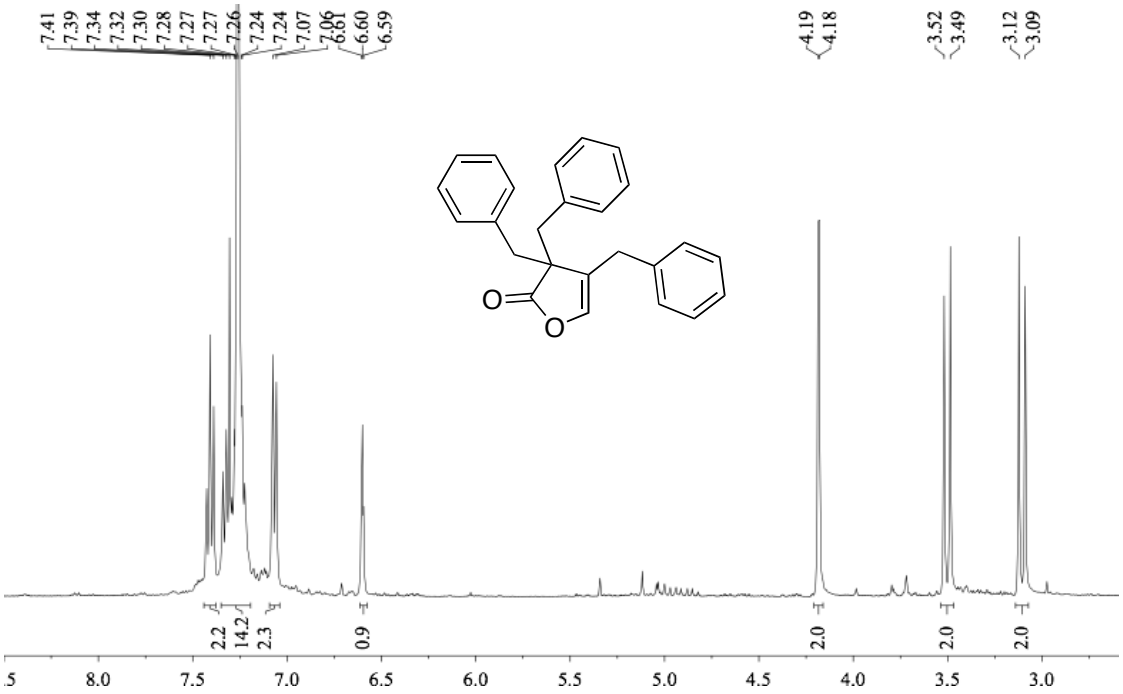
NMR	nuclear magnetic resonance spectroscopy
org.	organic
p	*para*
PAL	phenylalanine ammonia lyase
PCC	pyridinium chlorochromate
PEG	polyethylene glycol
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
PTC	phase transfer catalyst/catalysis
PTSA	*p*-toluenesulfonic acid
PVC	polyvinyl chloride
q	quartet
quant.	quantitative
rac	racemic
Red-Al	sodium bis(2-methoxyethoxy)aluminumhydride
Rf	retention factor
rf	reflux
Rt	retention time
rt	room temperature
s	singlet
SAR	structure activity relationsphip
sat.	saturated
SEM	standard error of the mean
t	triplet
t	*tert*
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAH	tetrabutylammonium hydroxide
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBME	*tert*-butyl methyl ether

TBT	tributyltin compound
TES	trimethylsilyl
Temp.	temperature
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TOF	time of flight
Trt	trityl
Ts	tosyl
UPLC	ultra pressure liquid chromatography
UV	ultraviolet (spectroscopy/light)
v/v	volume per volume

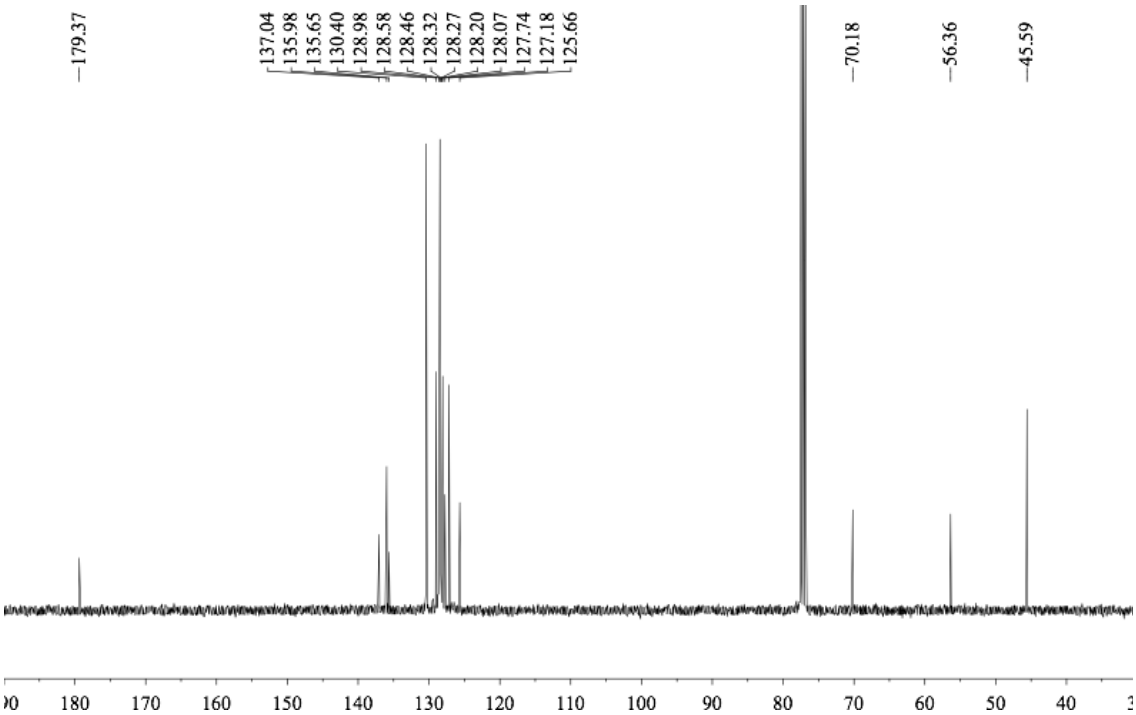
9.2 NMR Spectra

9.2.1 An Improved Synthesis of Maculalactone A

3,3,4-Tribenzylfuran-2(3H)-one (2.13)

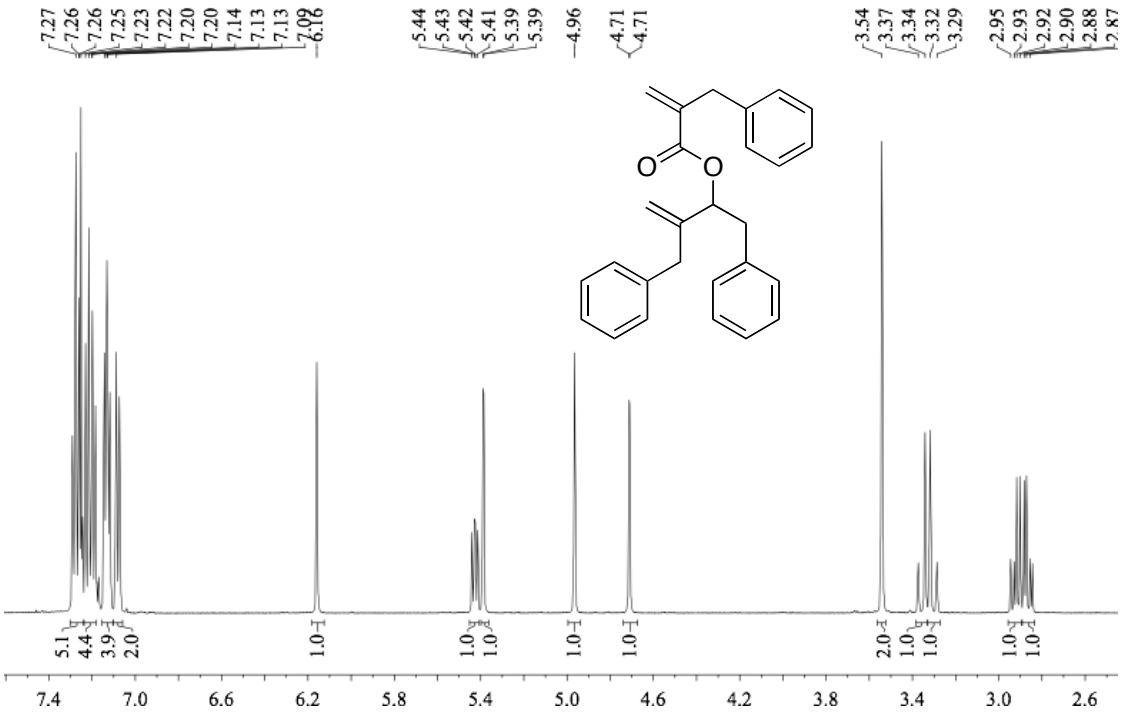


400 MHz ^{1}H-NMR in $CDCl_3$

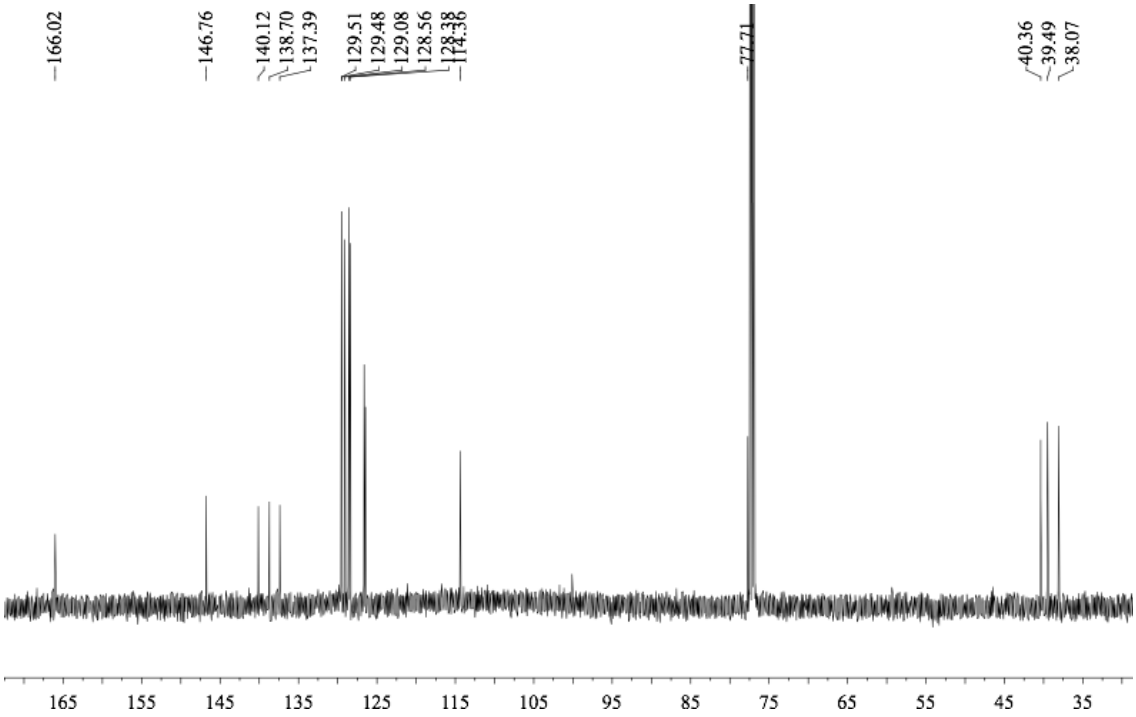


101 MHz ^{13}C-NMR in $CDCl_3$

3-Benzyl-1-phenylbut-3-en-2-yl 2-benzylacrylate (2.19)

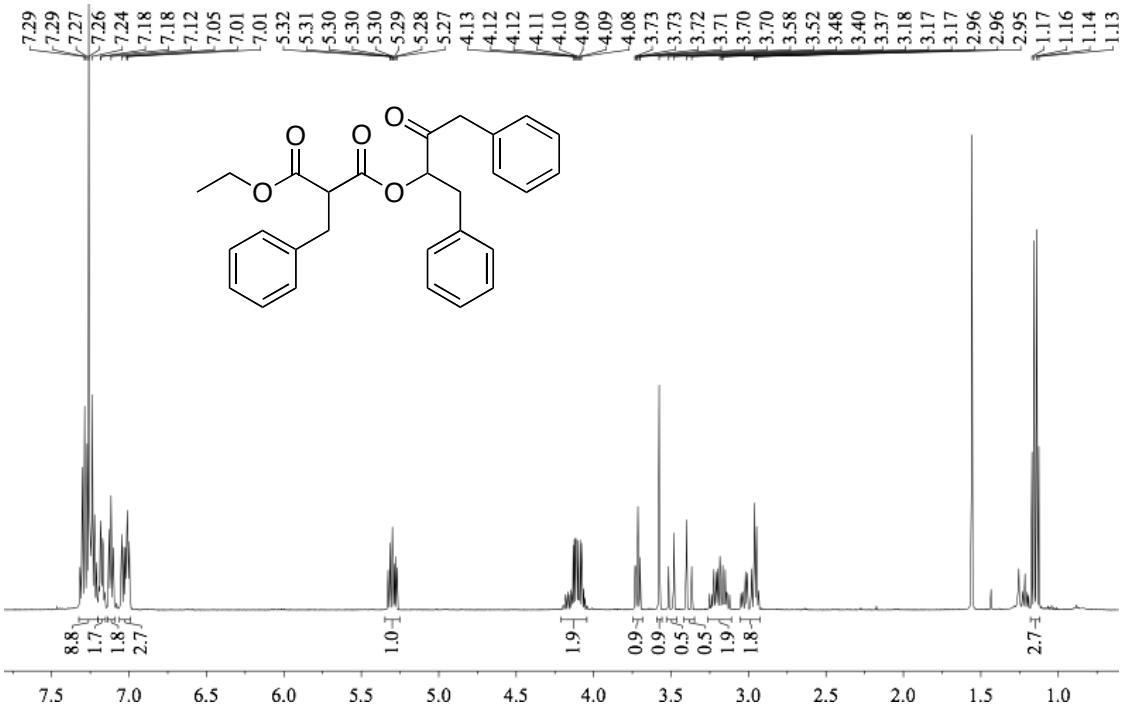


500 MHz ^{1}H-NMR in $CDCl_3$

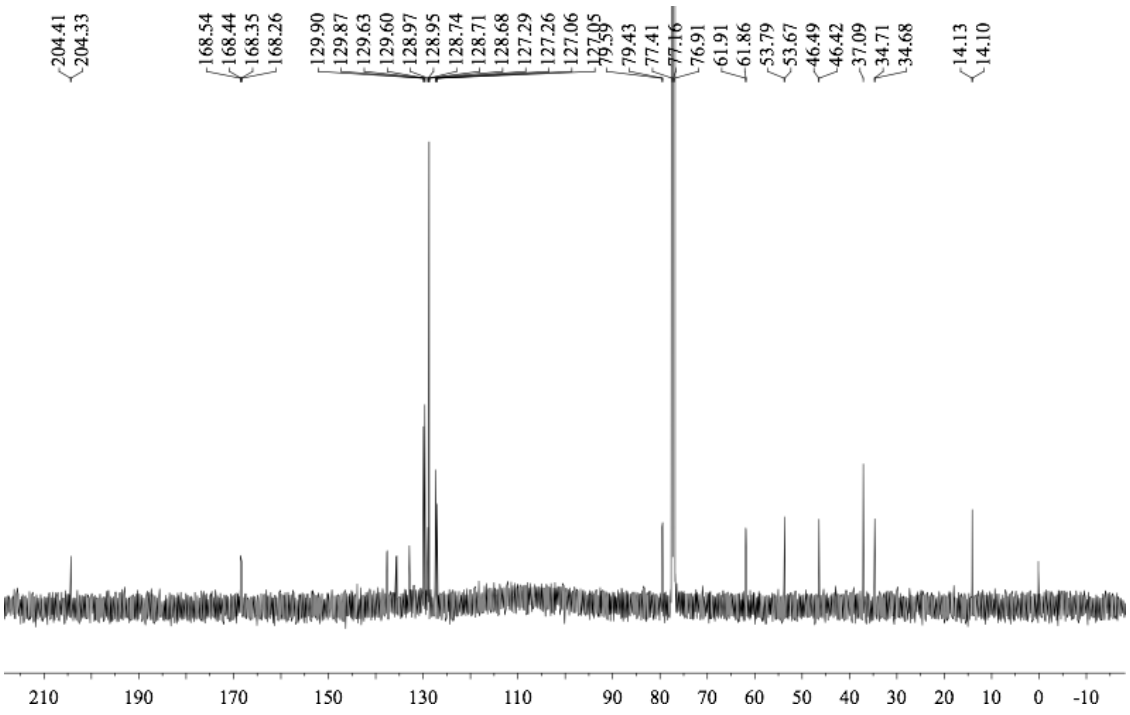


126 MHz ^{13}C-NMR in $CDCl_3$

1-Ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-benzylmalonate (2.31) as a mixture of diastereomers

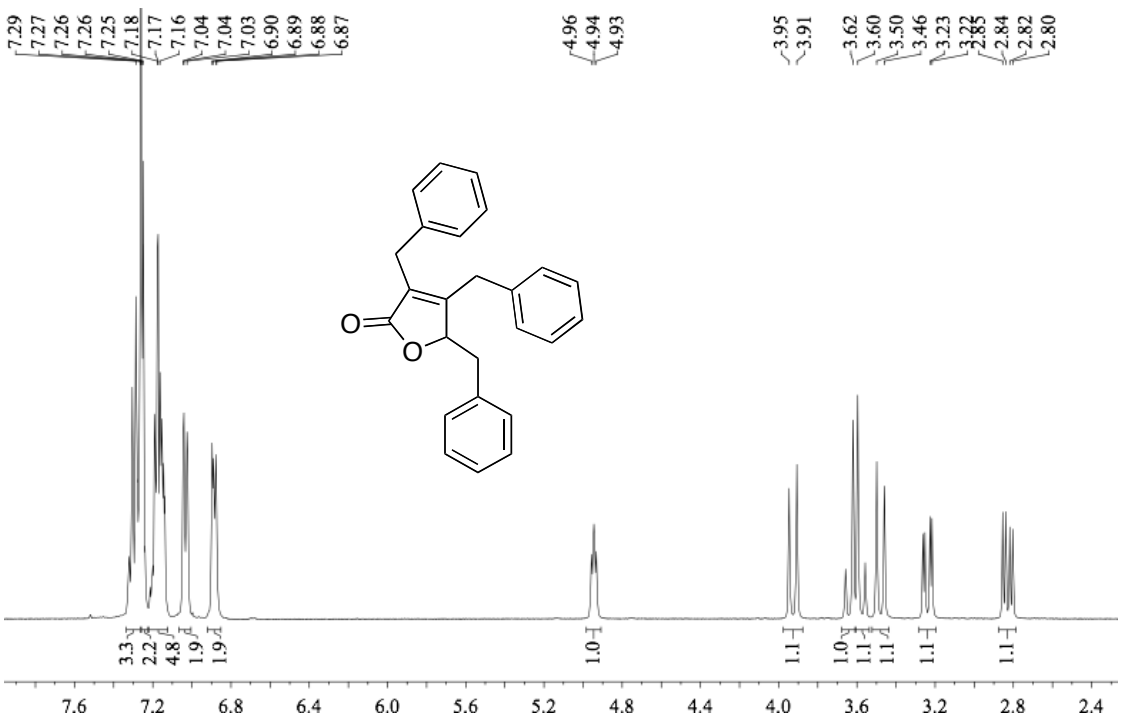


500 MHz ^{1}H-NMR in $CDCl_3$

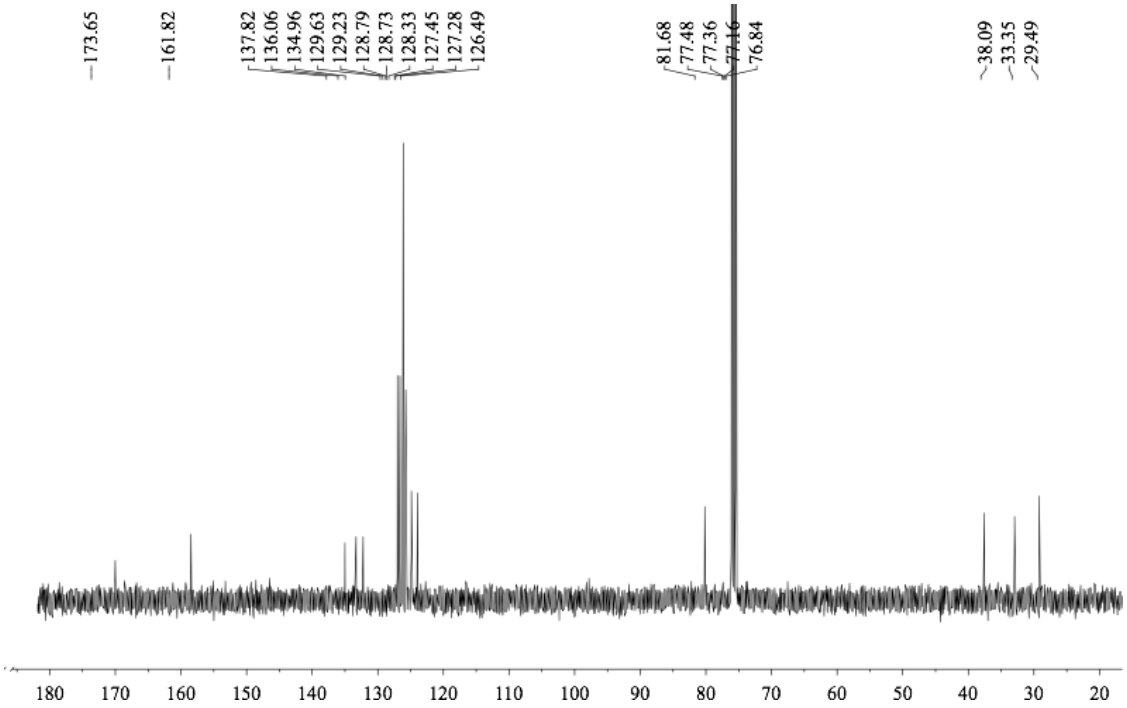


126 MHz ^{13}C-NMR in $CDCl_3$

Maculalactone A (1.34)



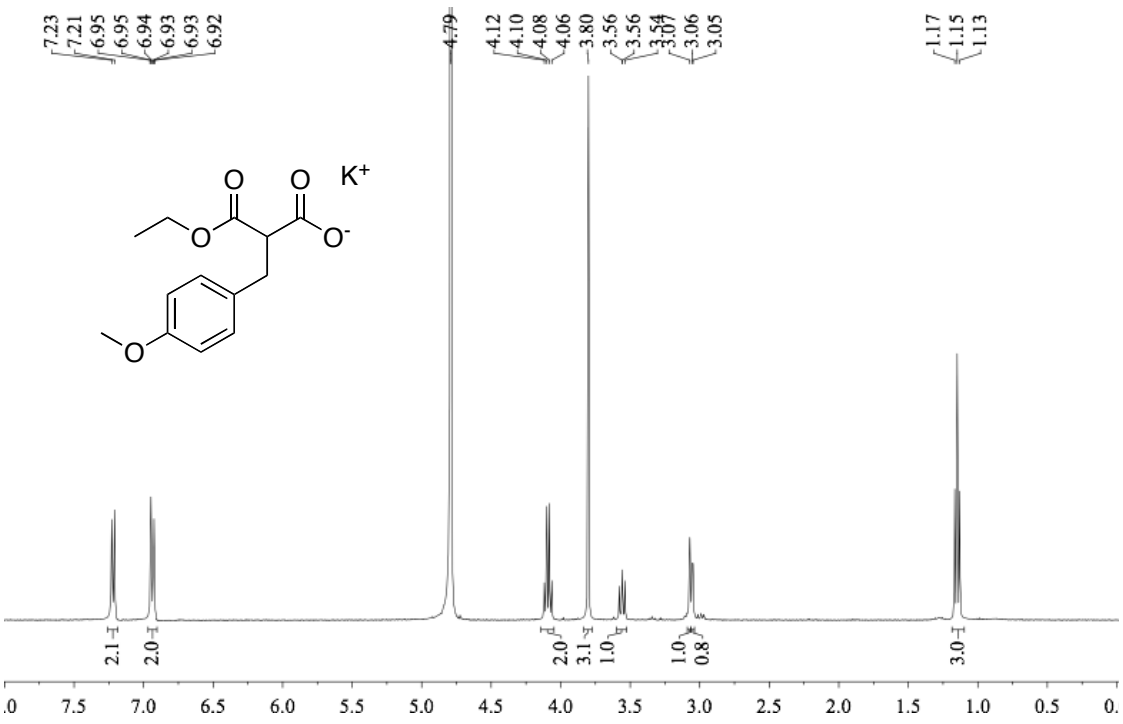
400 MHz ^{1}H-NMR in $CDCl_3$



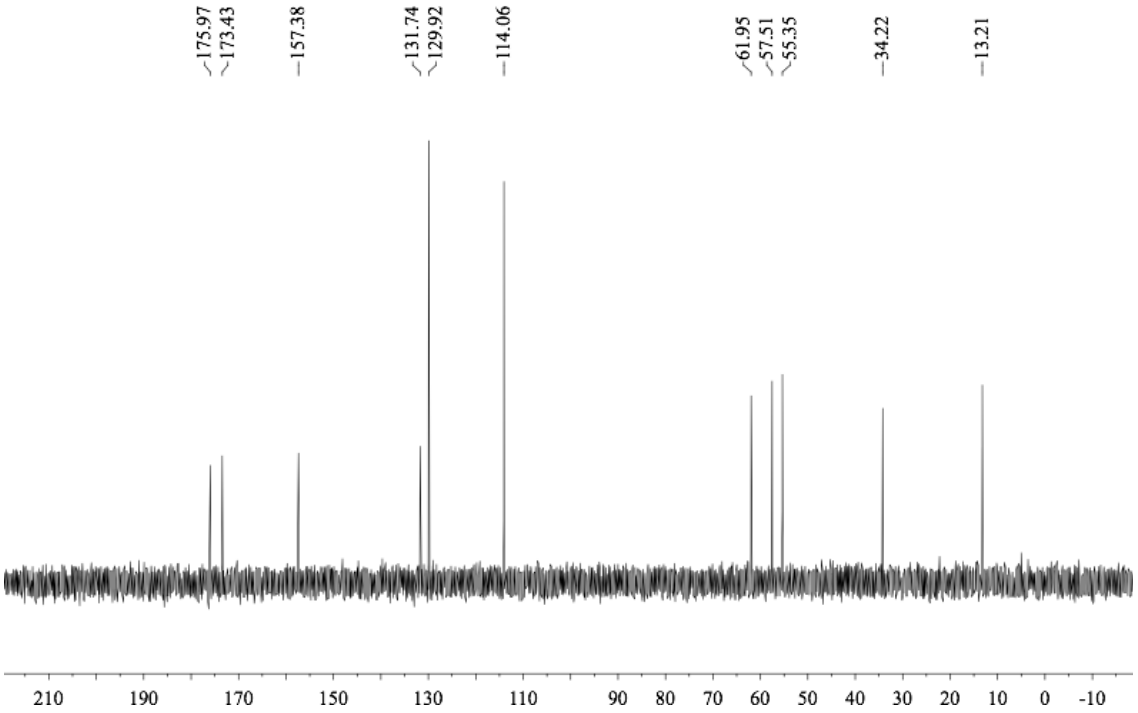
101 MHz ^{13}C-NMR in $CDCl_3$

9.2.2 From a Natural Product to a Functional Molecule

Potassium 3-ethoxy-2-(4-methoxybenzyl)-3-oxopropanoate (3.08)

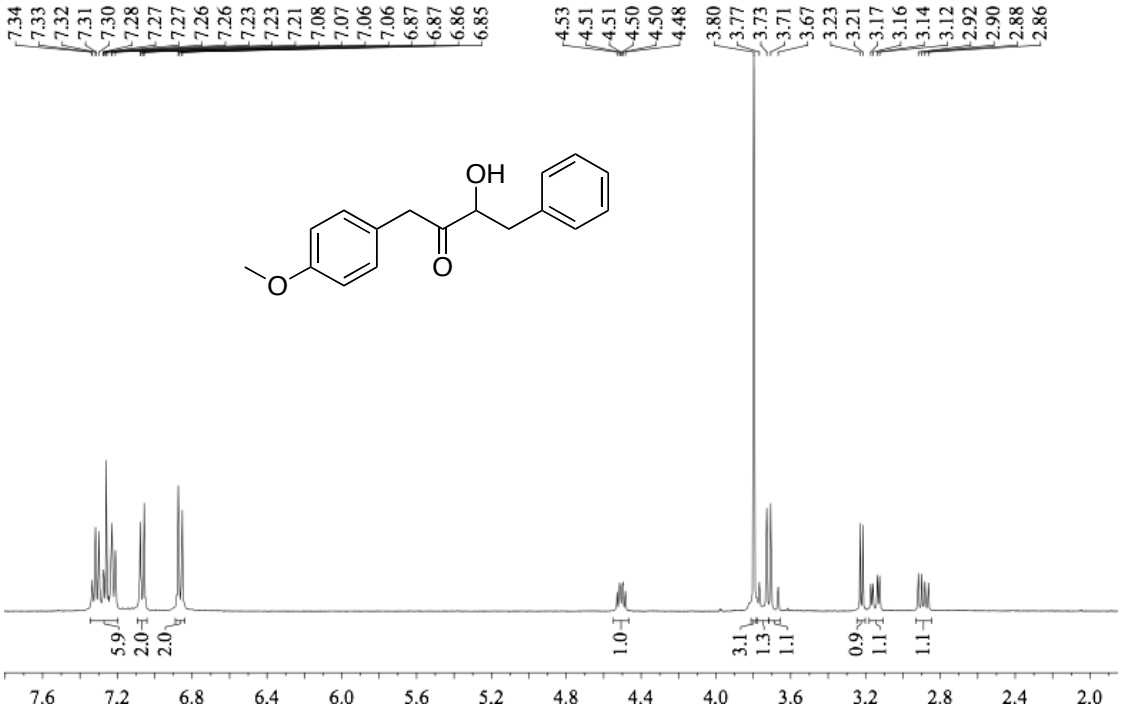


400 MHz ^{1}H-NMR in D_2O

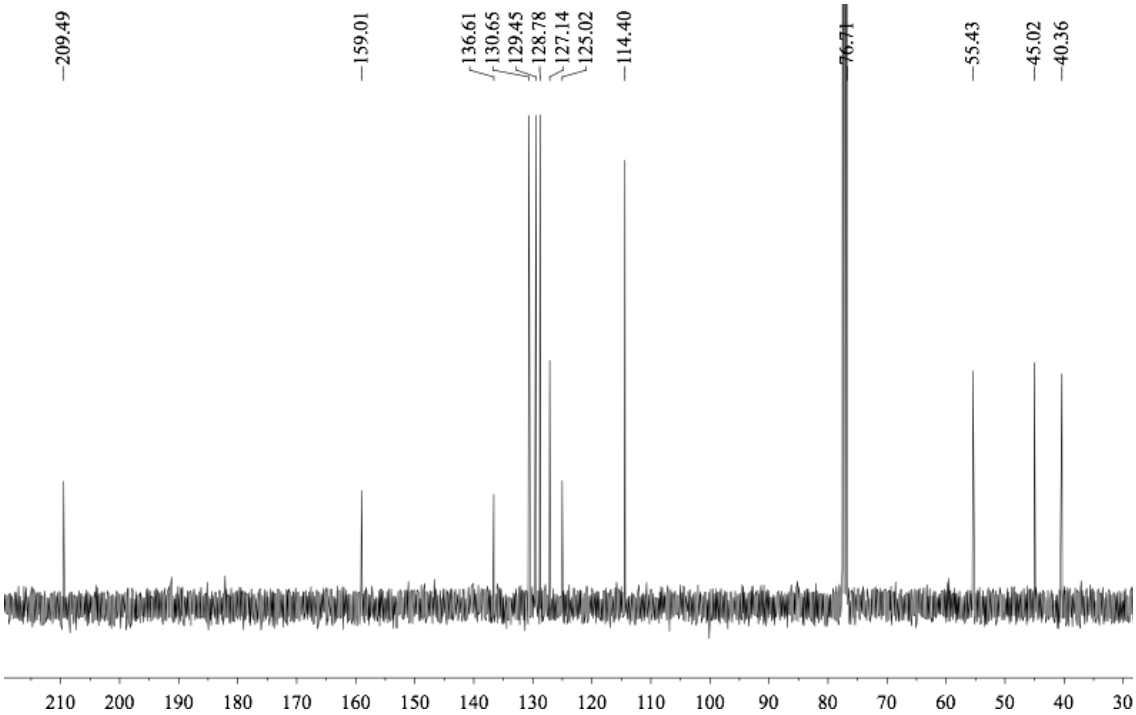


101 MHz ^{13}C-NMR in D_2O

3-Hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-2-one (3.10)

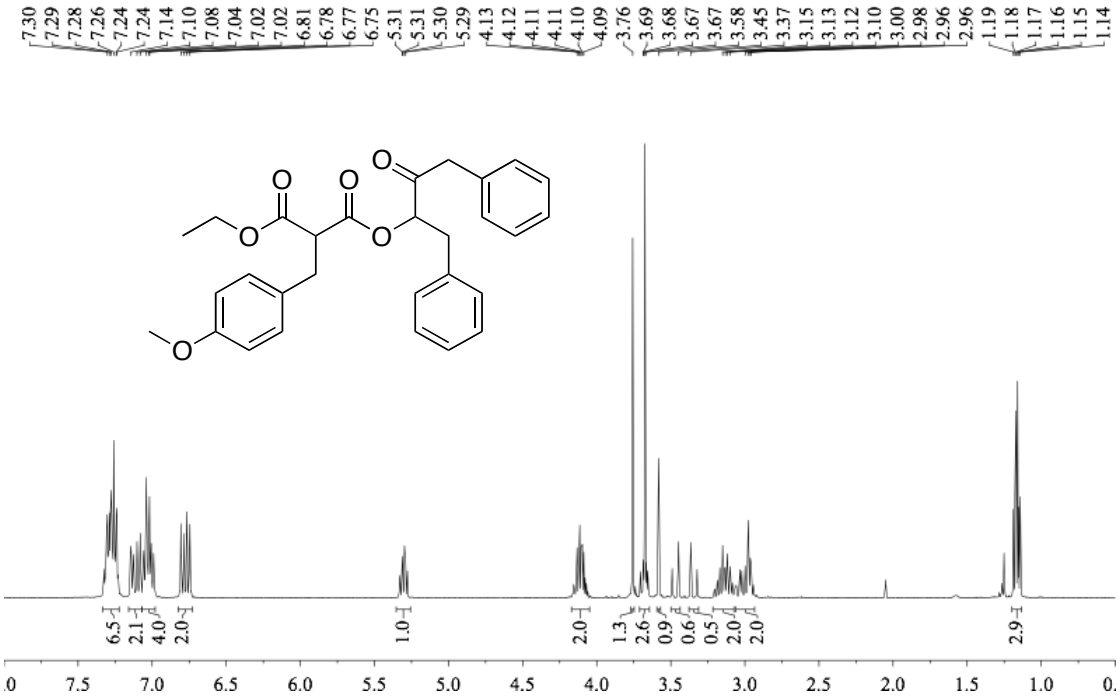


400 MHz ^{1}H-NMR in $CDCl_3$

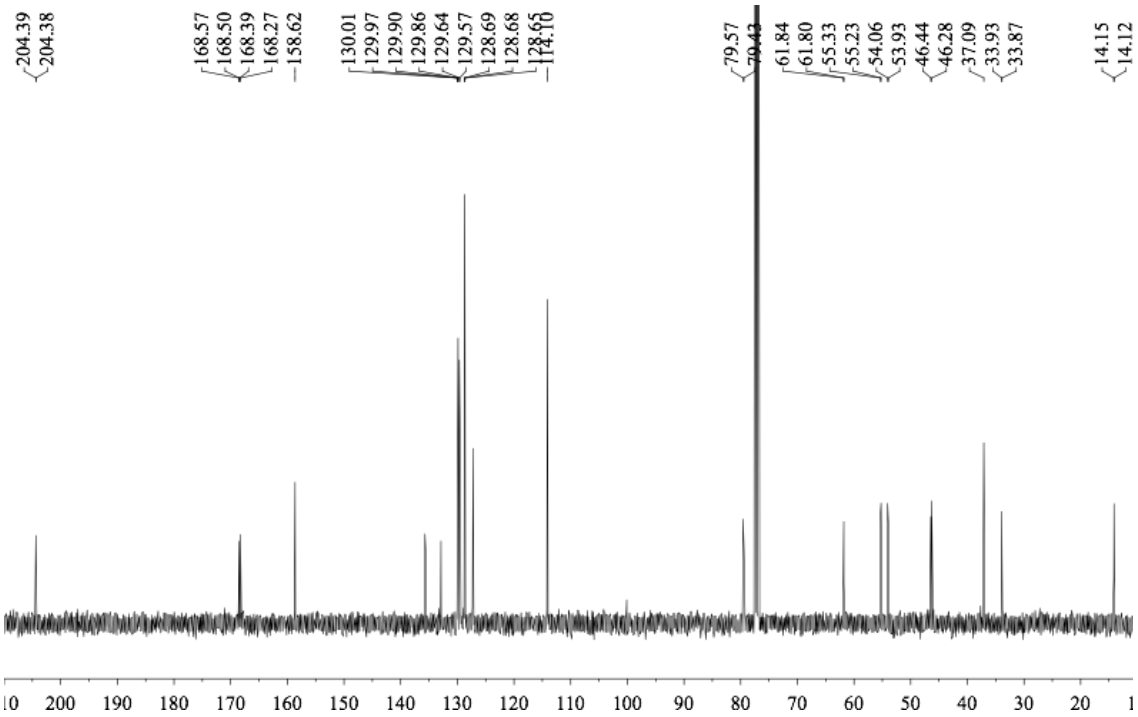


101 MHz ^{13}C-NMR in $CDCl_3$

1-Ethyl 3-(3-oxo-1,4-diphenylbutan-2-yl) 2-(4-methoxybenzyl)malonate (3.14) as a mixture of diastereomers

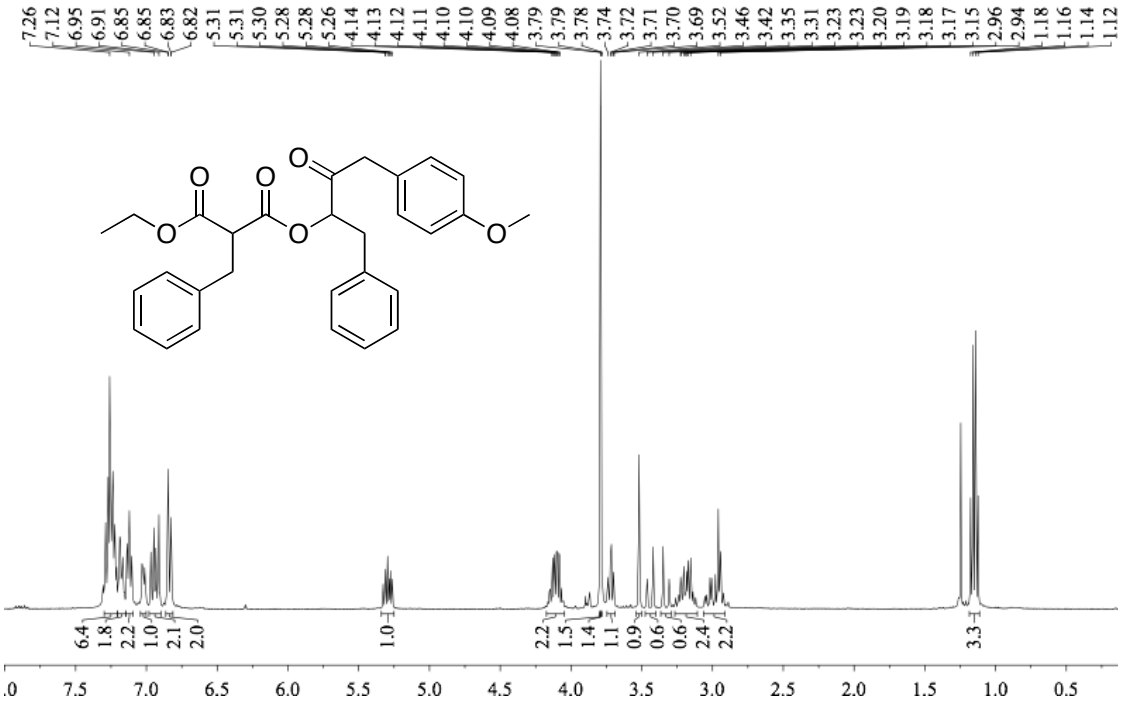


400 MHz ^{1}H-NMR in $CDCl_3$

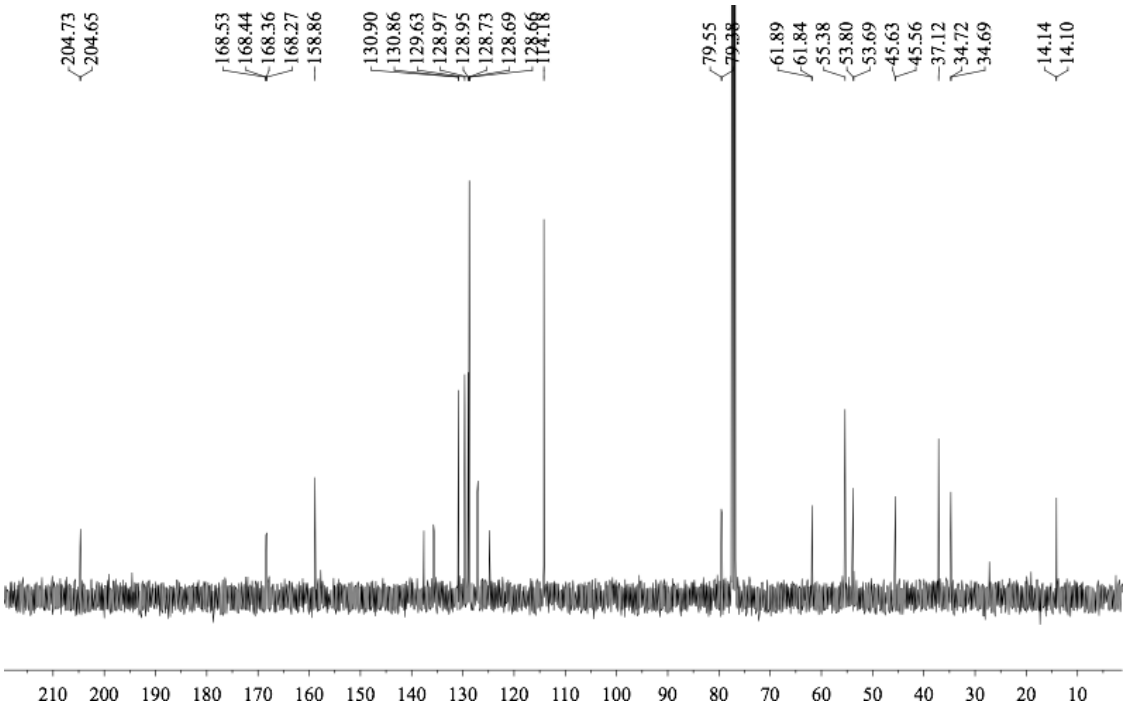


101 MHz ^{13}C-NMR in $CDCl_3$

1-Ethyl 3-(4-(4-methoxyphenyl)-3-oxo-1-phenylbutan-2-yl) 2-benzylmalonate (3.15) as a mixture of diastereomers

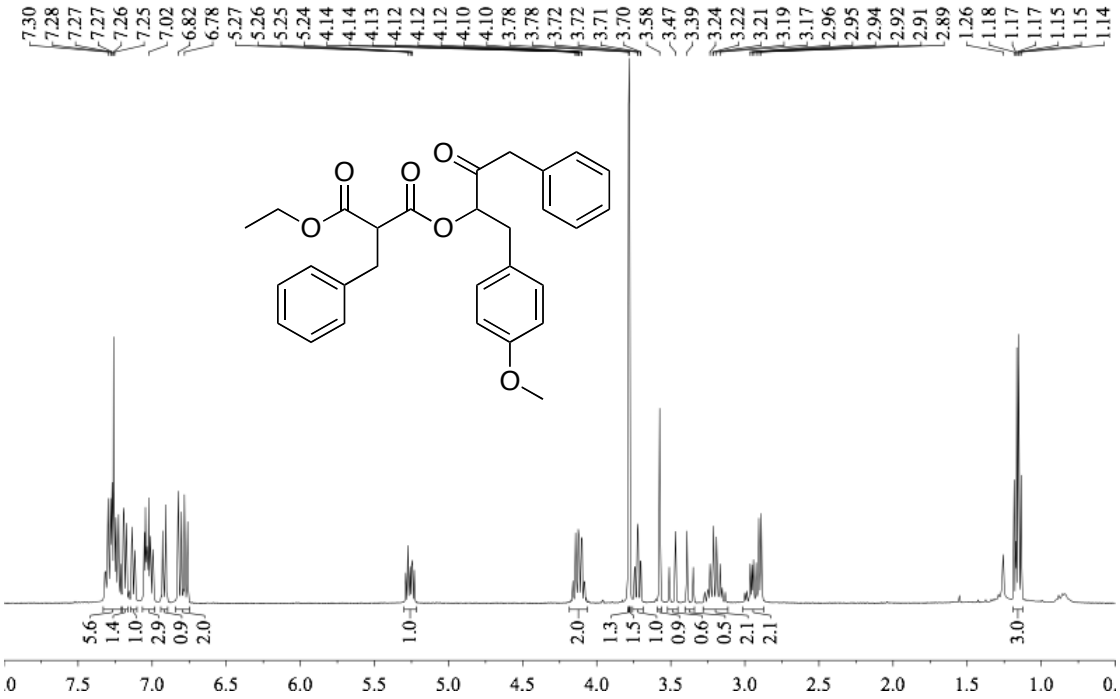


400 MHz ^{1}H-NMR in $CDCl_3$

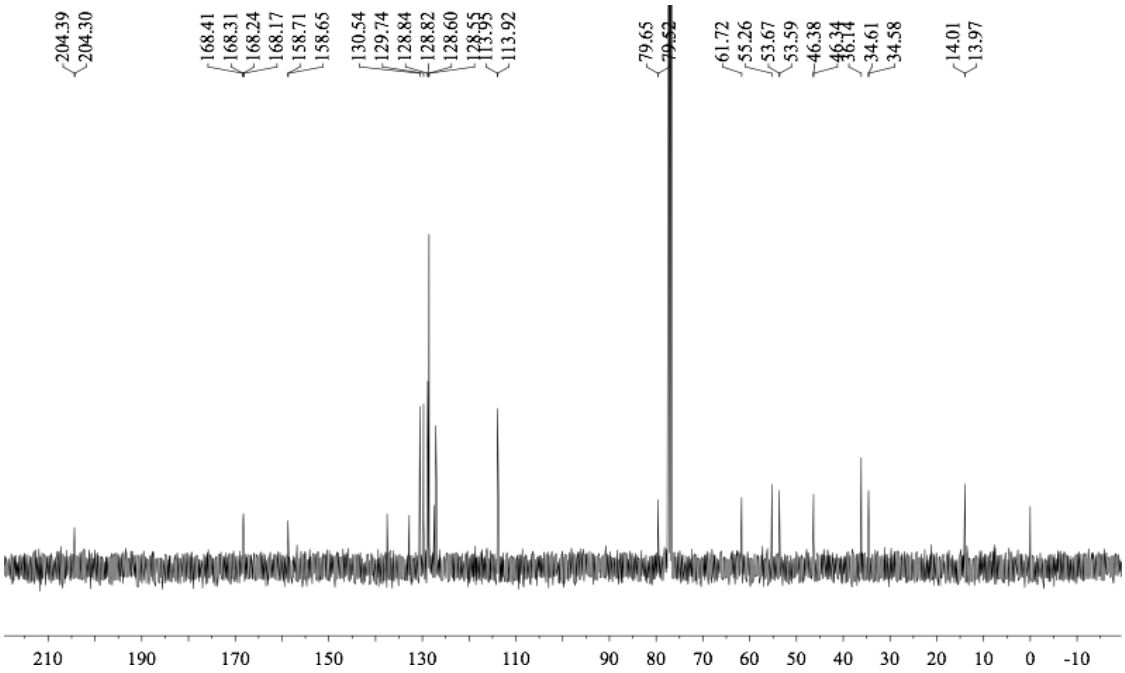


101 MHz ^{13}C-NMR in $CDCl_3$

1-Ethyl 3-(1-(4-methoxyphenyl)-3-oxo-4-phenylbutan-2-yl) 2-benzylmalonate (3.16) as a mixture of diastereomers

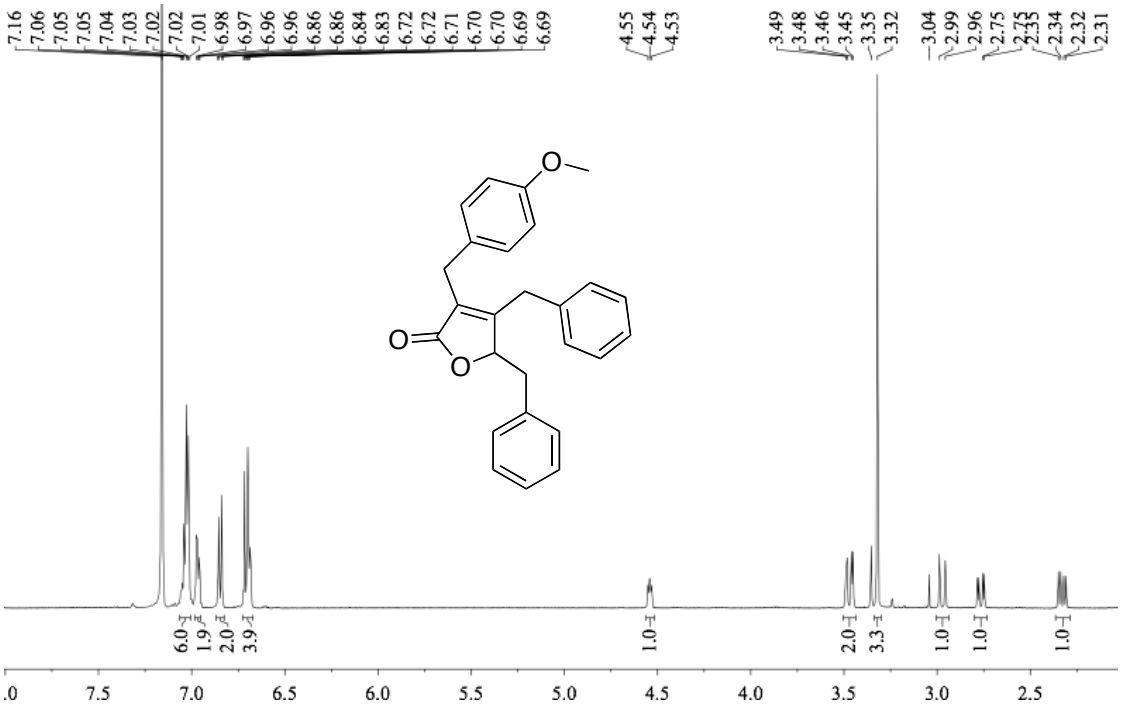


400 MHz ^{1}H-NMR in $CDCl_3$

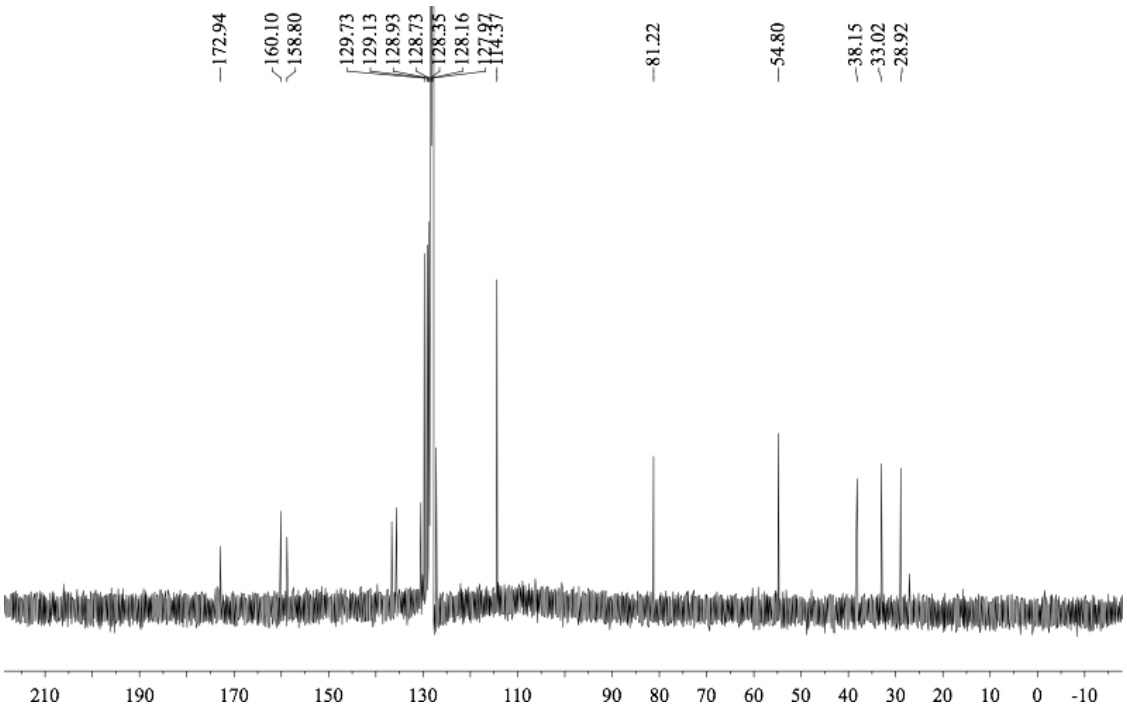


101 MHz ^{13}C-NMR in $CDCl_3$

4,5-Dibenzyl-3-(4-methoxybenzyl)furan-2(5H)-one (3.17)

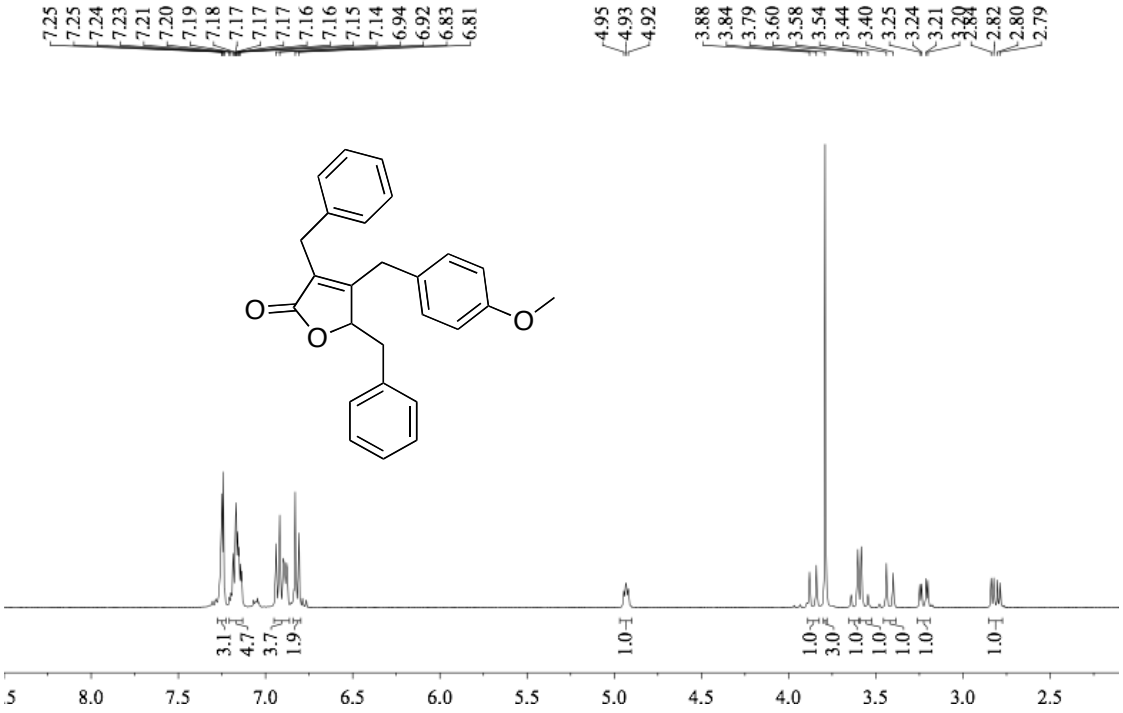


500 MHz ^{1}H-NMR in C_6D_6

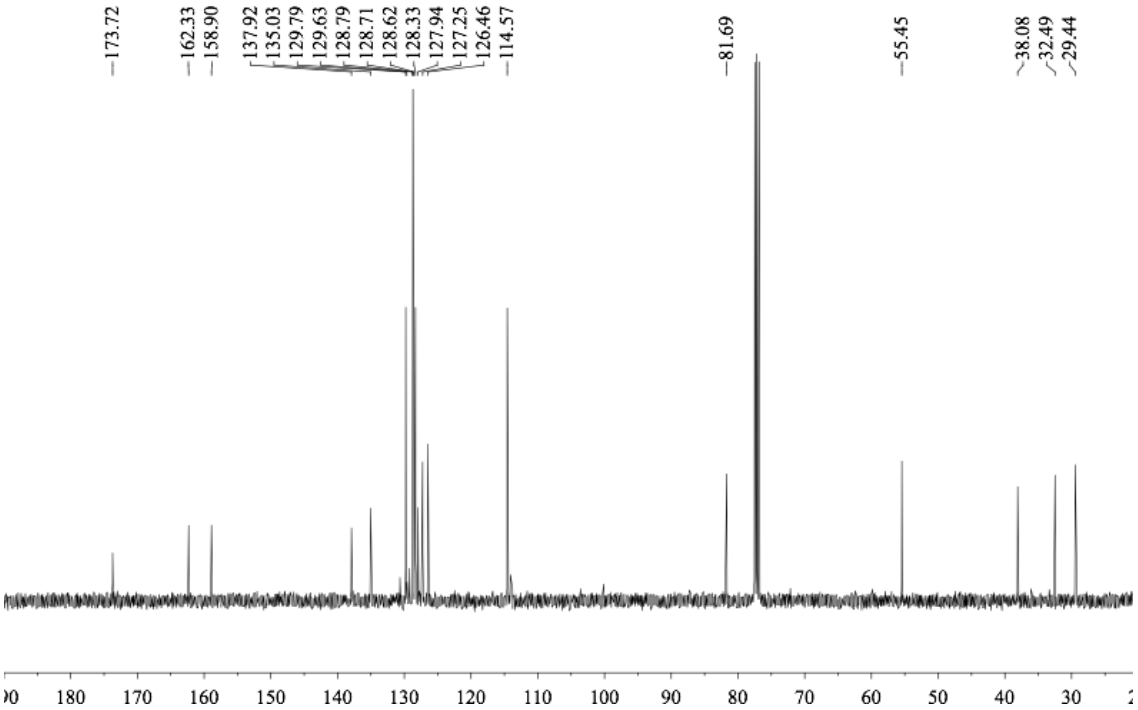


126 MHz ^{13}C-NMR in C_6D_6

3,5-Dibenzyl-4-(4-methoxybenzyl)furan-2(5H)-one (3.18)

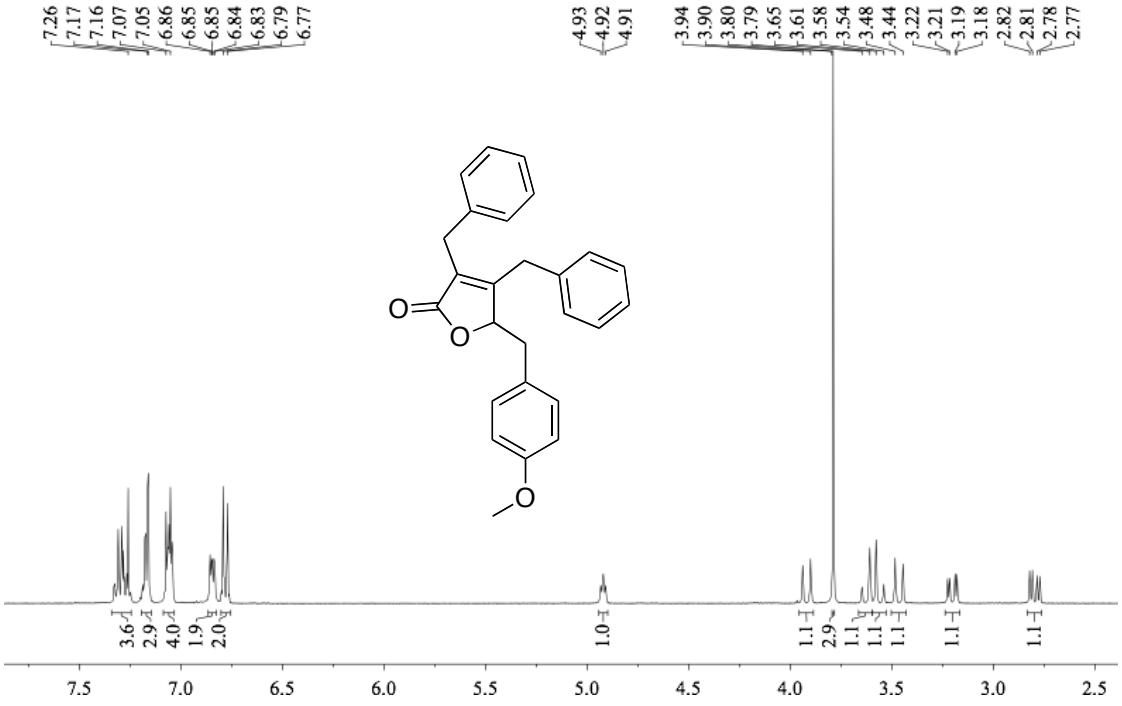


400 MHz ^{1}H-NMR in $CDCl_3$

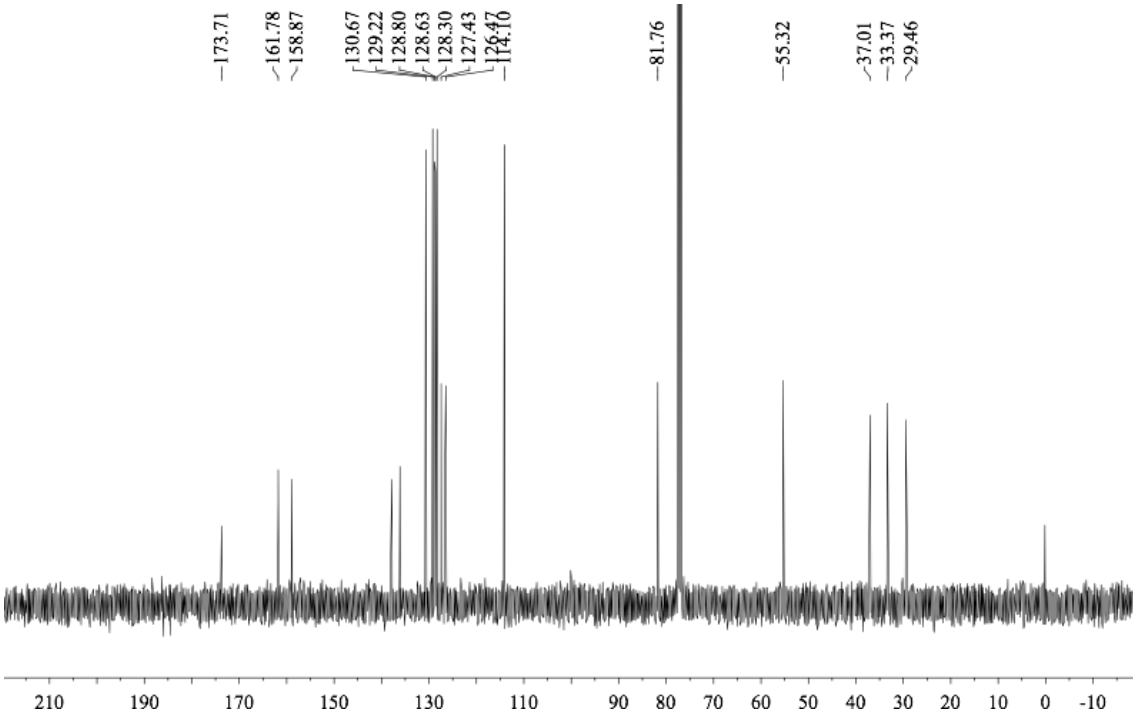


101 MHz ^{13}C-NMR in $CDCl_3$

3,4-Dibenzyl-5-(4-methoxybenzyl)furan-2(5H)-one (3.19)

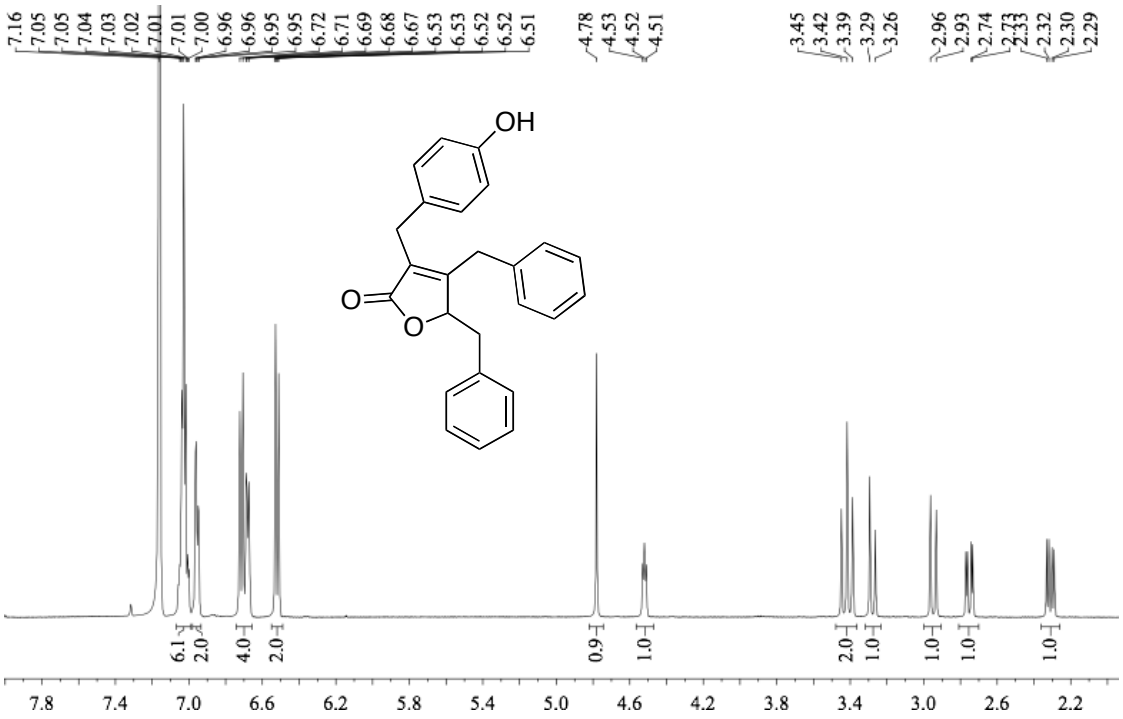


400 MHz ^{1}H-NMR in $CDCl_3$

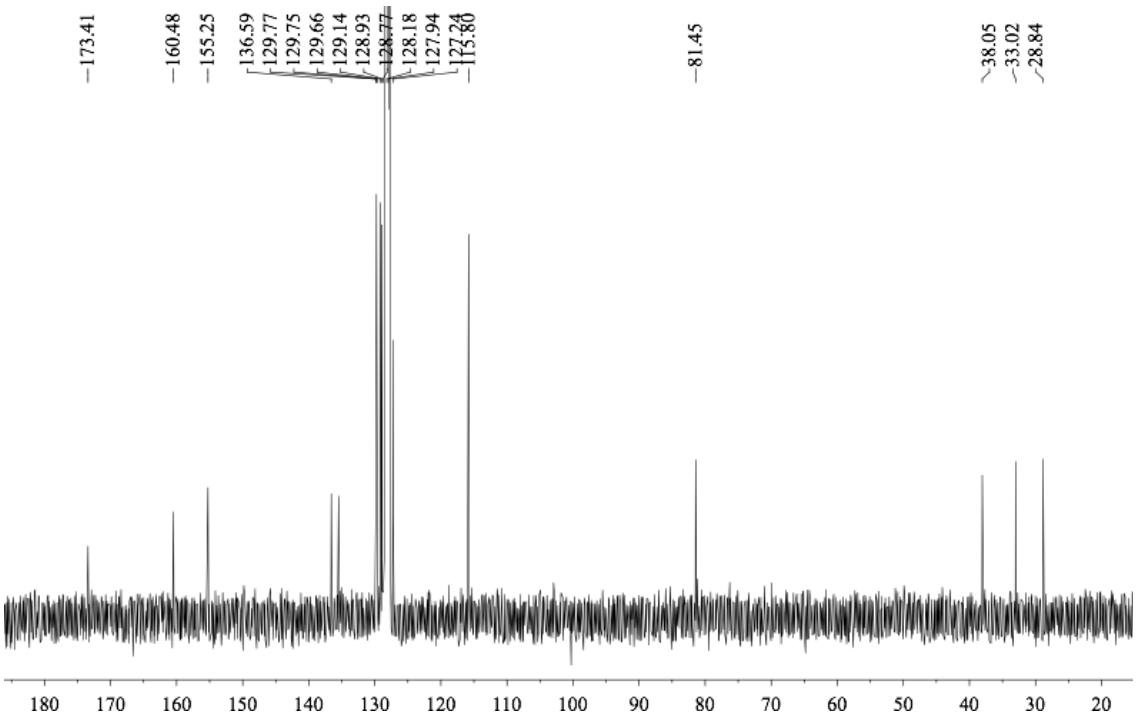


101 MHz ^{13}C-NMR in $CDCl_3$

4,5-Dibenzyl-3-(4-hydroxybenzyl)furan-2(5H)-one (3.20)

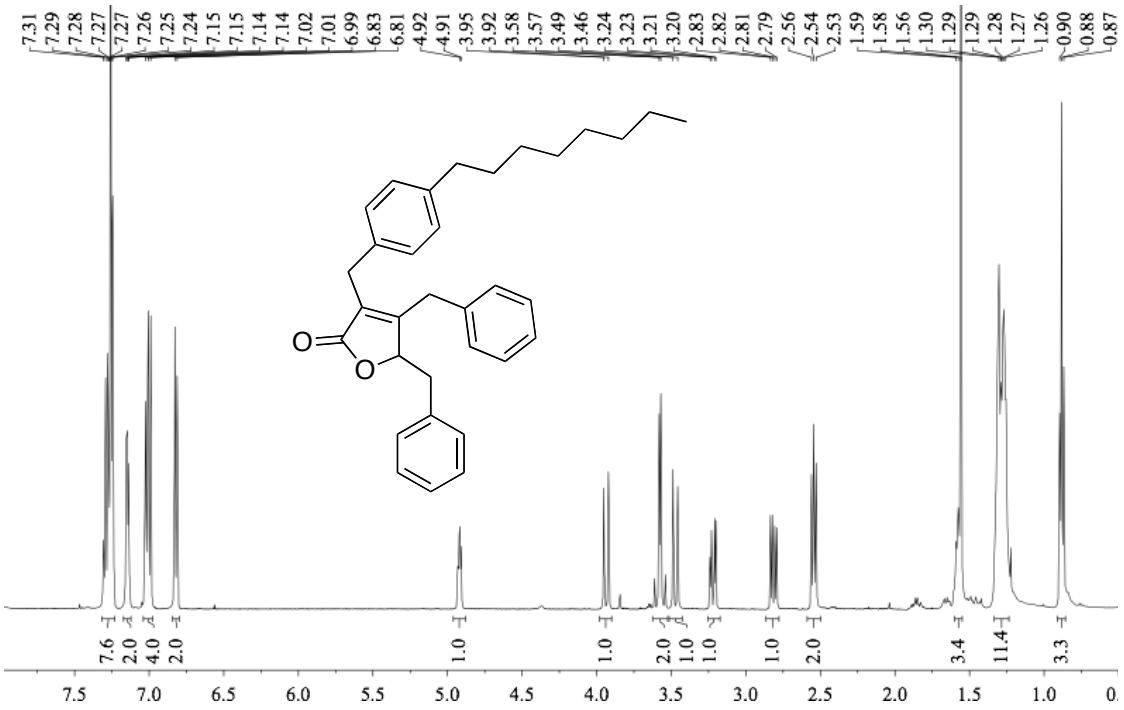


500 MHz ^{1}H-NMR in C_6D_6

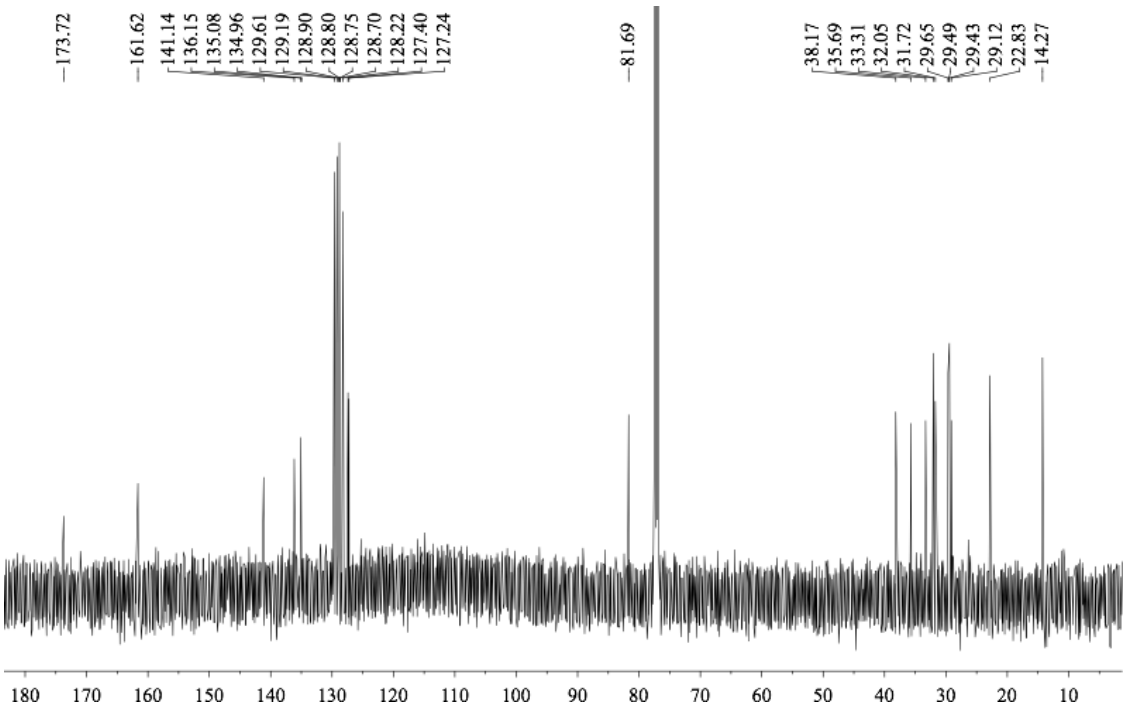


101 MHz ^{13}C-NMR in C_6D_6

4,5-Dibenzyl-3-(4-octylbenzyl)furan-2(5H)-one (3.21)

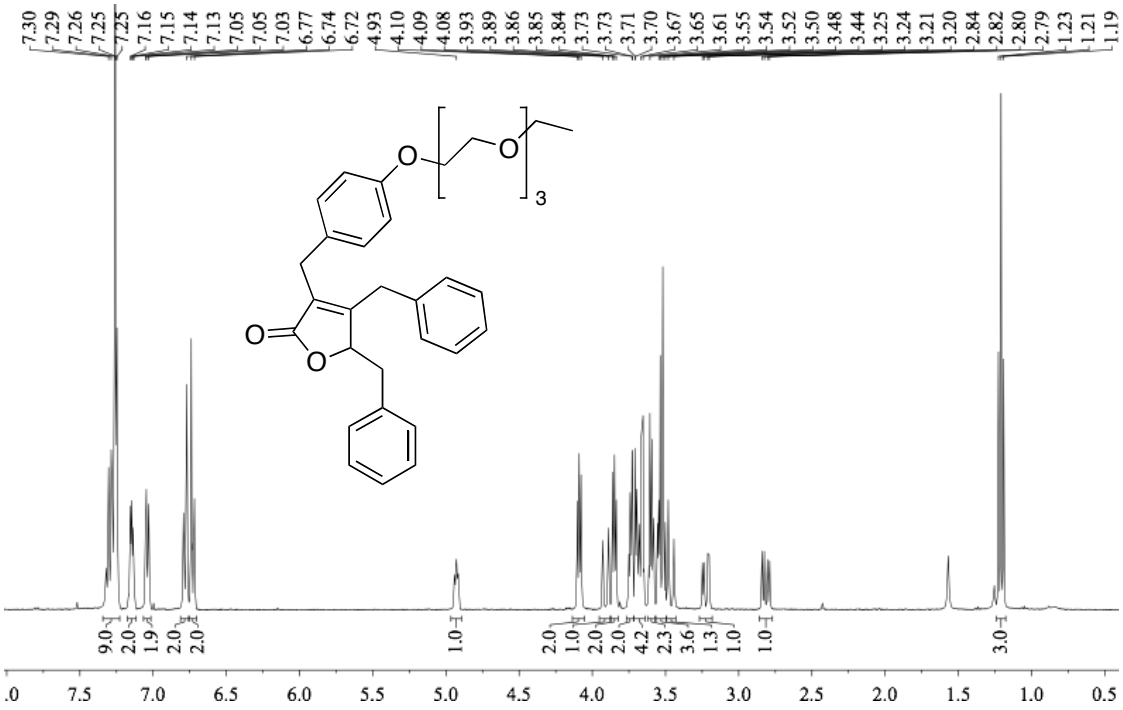


500 MHz ^{1}H-NMR in $CDCl_3$

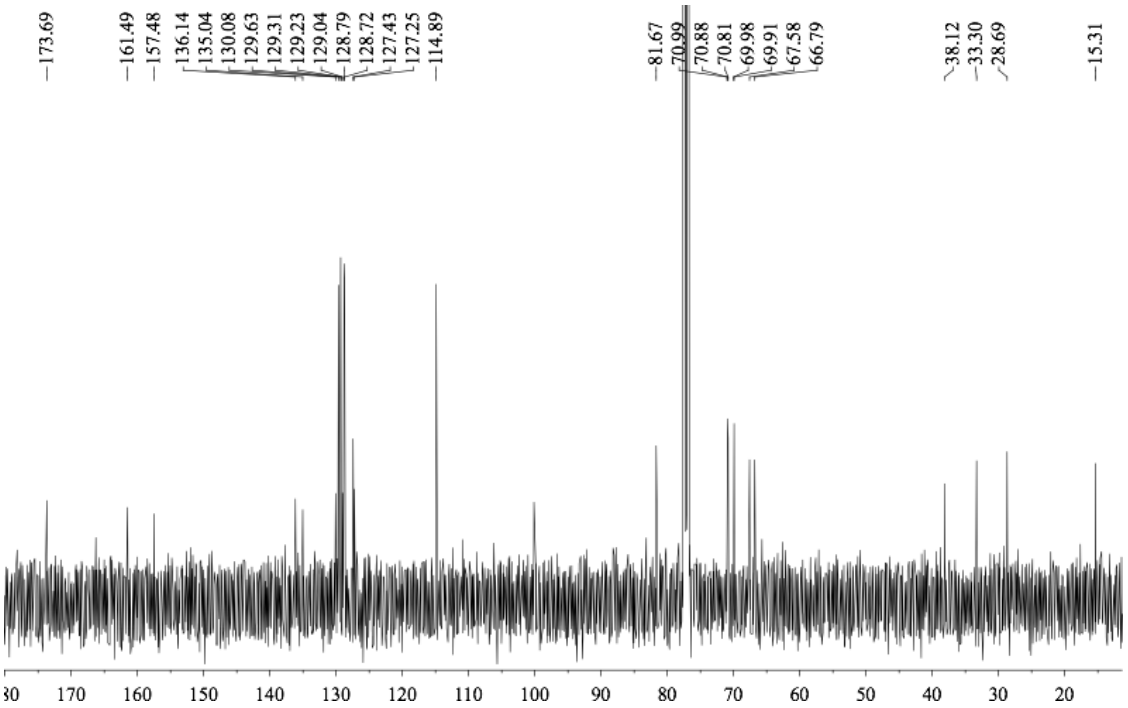


126 MHz ^{13}C-NMR in $CDCl_3$

4,5-Dibenzyl-3-(4-(2-(2-(2-ethoxyethoxy)ethoxy)ethoxy)benzyl)furan-2(5H)-one (3.23)

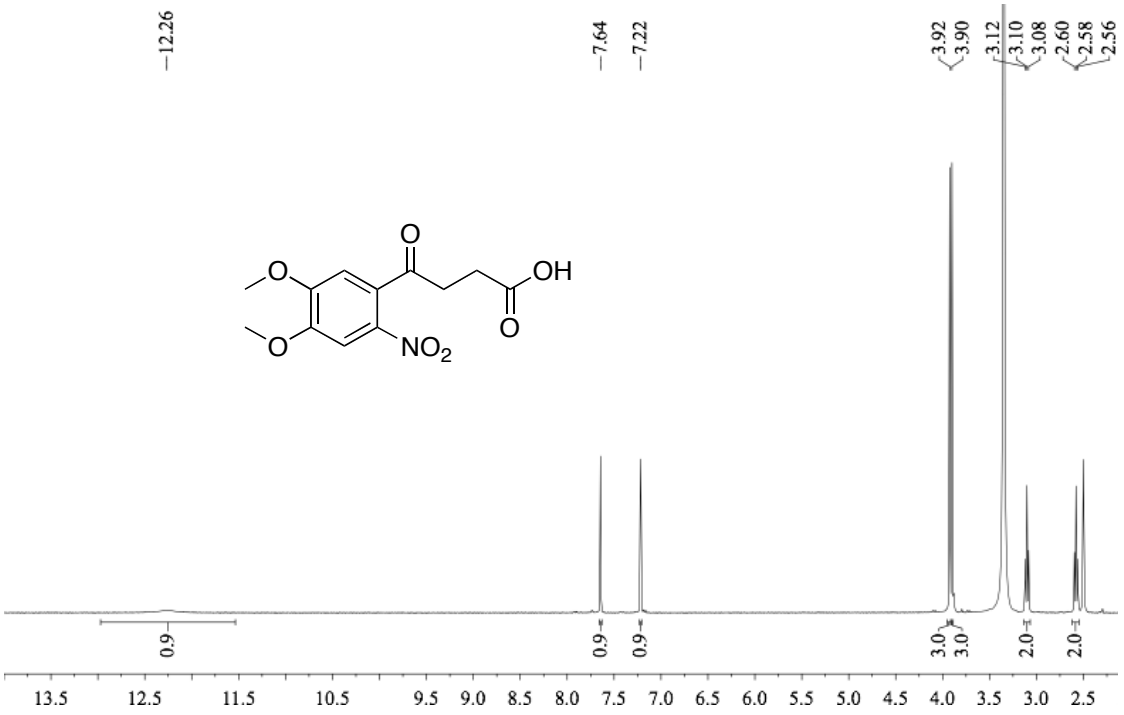


400 MHz ^{1}H-NMR in $CDCl_3$

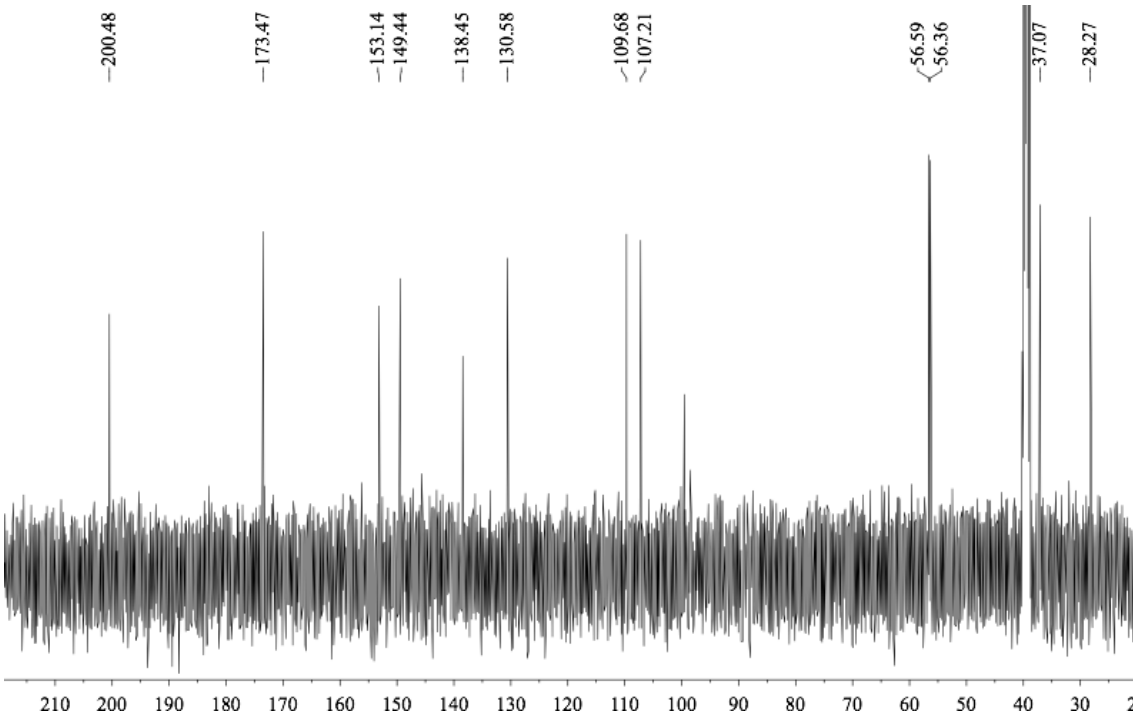


101 MHz ^{13}C-NMR in $CDCl_3$

4-(4,5-Dimethoxy-2-nitrophenyl)-4-oxobutanoic acid (3.29)

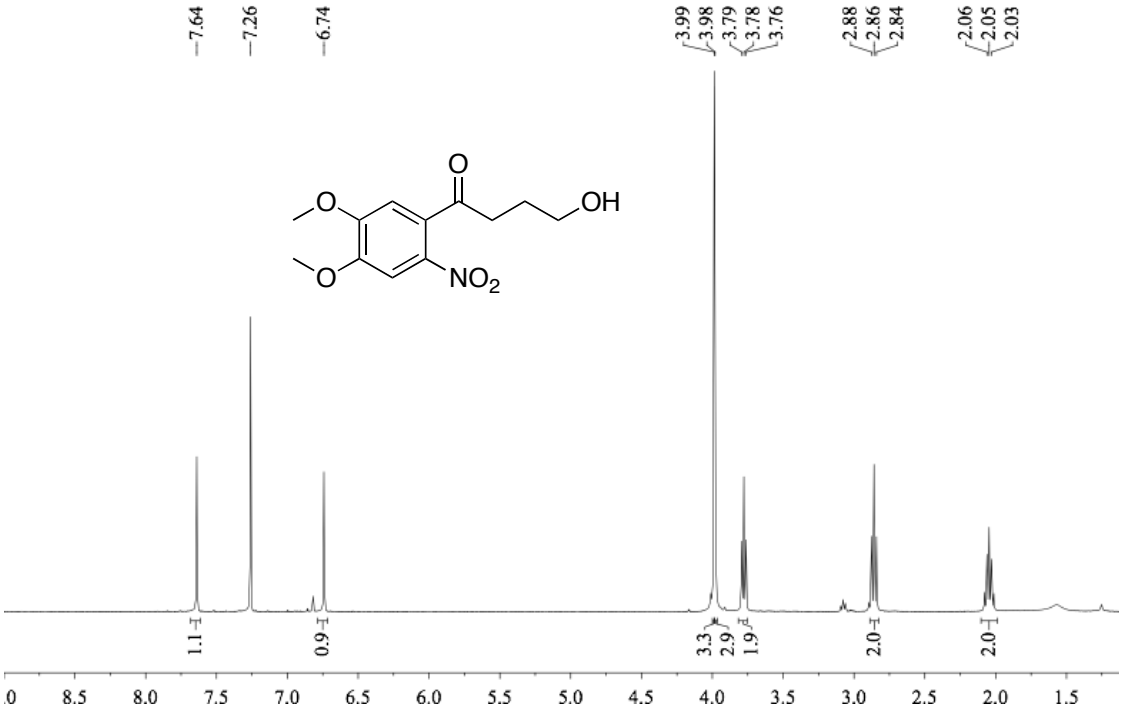


400 MHz ^{1}H-NMR in DMSO-d_6

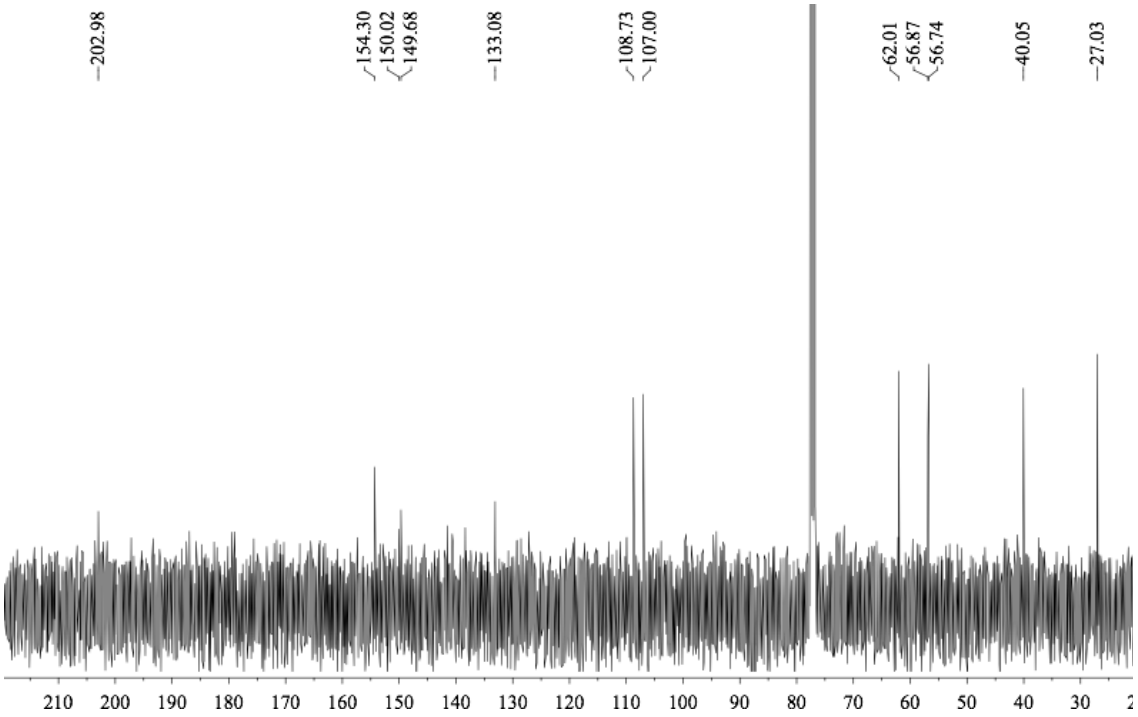


101 MHz ^{13}C-NMR in DMSO-d_6

1-(4,5-Dimethoxy-2-nitrophenyl)-4-hydroxybutan-1-one (3.30)

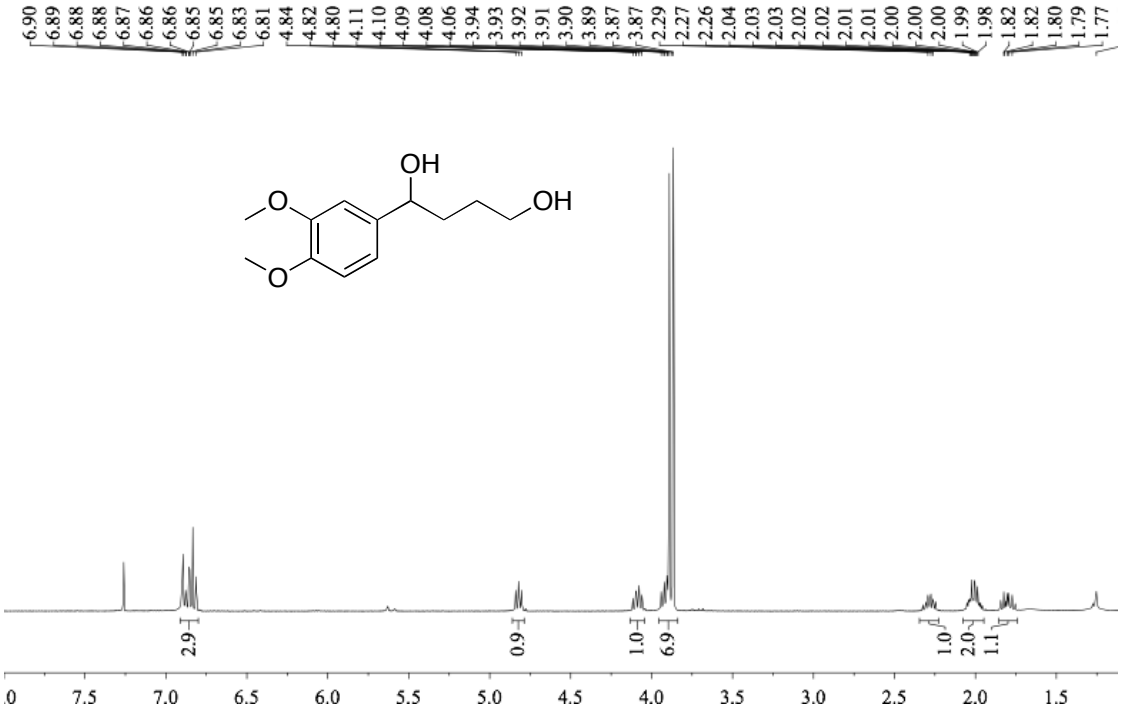


400 MHz ^{1}H-NMR in $CDCl_3$

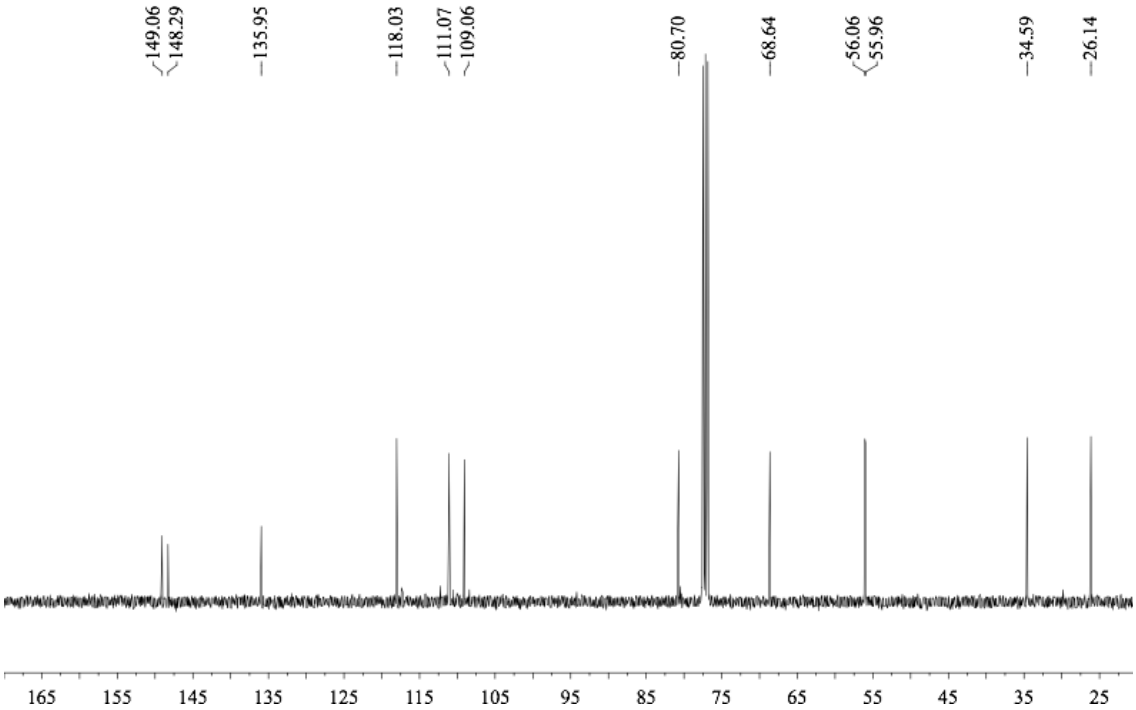


101 MHz ^{13}C-NMR in $CDCl_3$

1-(3,4-Dimethoxyphenyl)butane-1,4-diol (3.31)

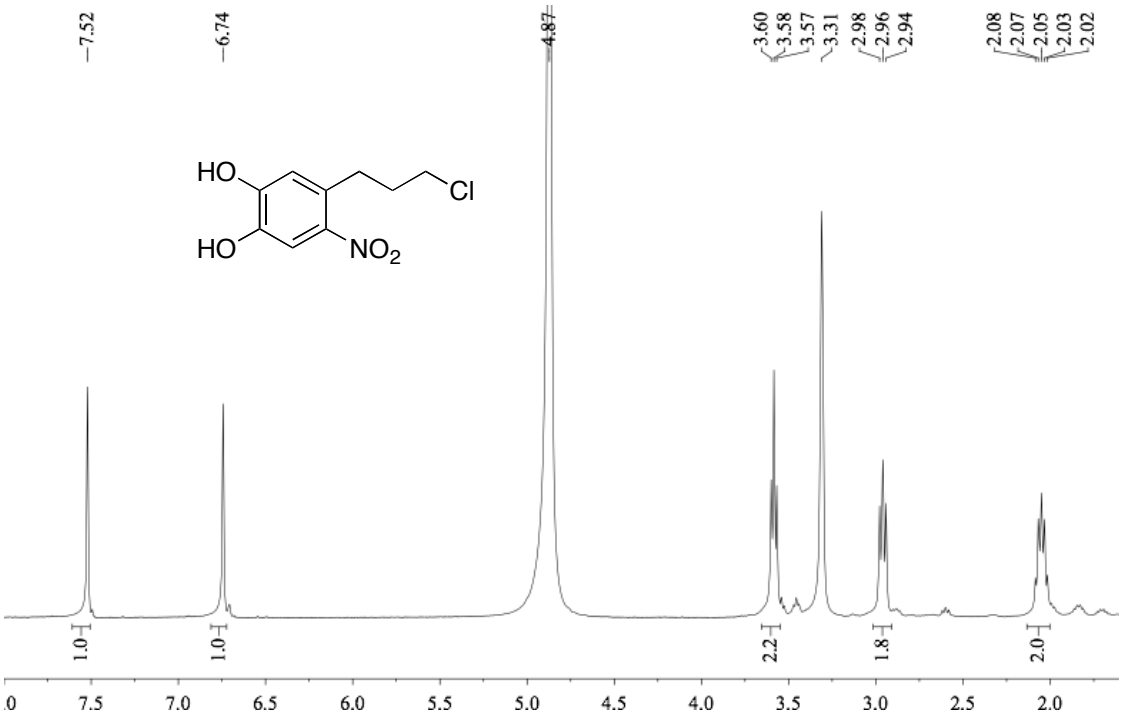


400 MHz ^{1}H-NMR in $CDCl_3$

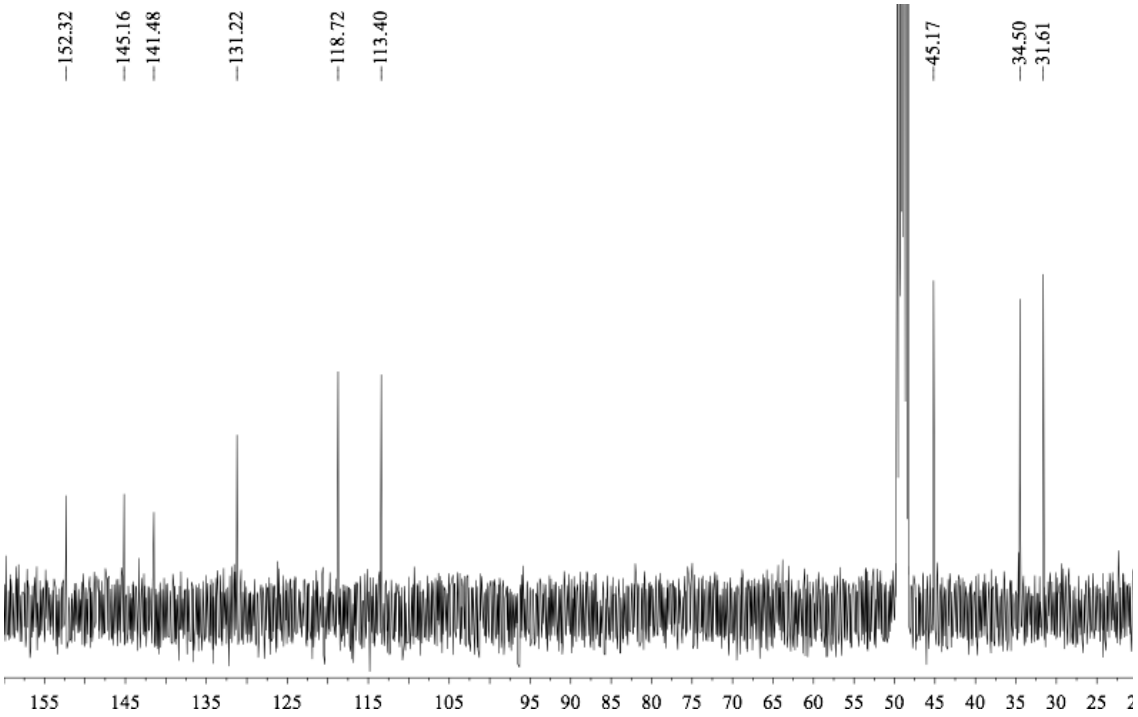


101 MHz ^{13}C-NMR in $CDCl_3$

4-(3-Chloropropyl)-5-nitrobenzene-1,2-diol (3.35)

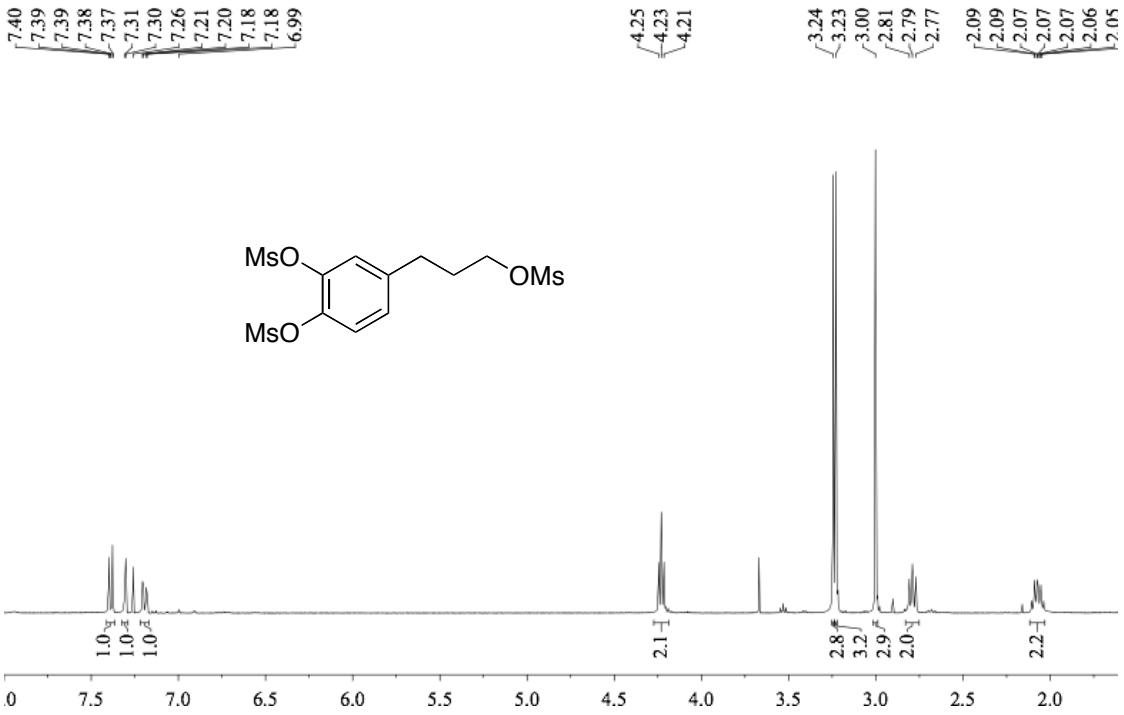


400 MHz ^{1}H-NMR in MeOD

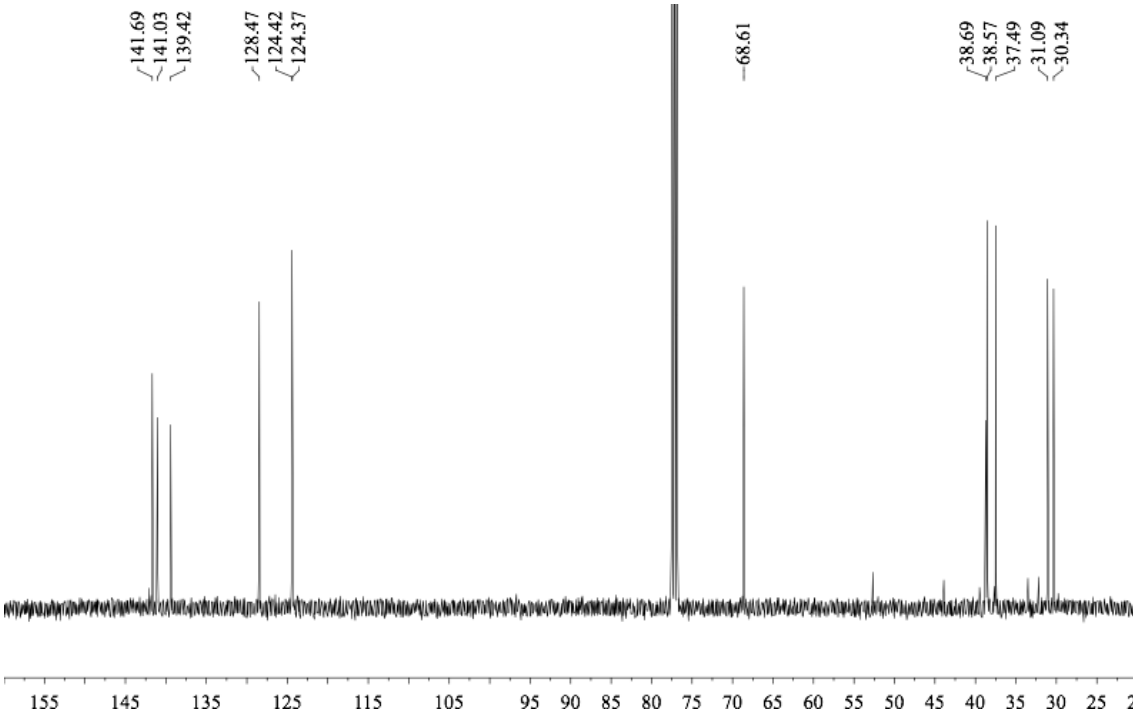


101 MHz ^{13}C-NMR in MeOD

4-(3-((Methylsulfonyl)oxy)propyl)-1,2-phenylene dimethanesulfonate (3.36)

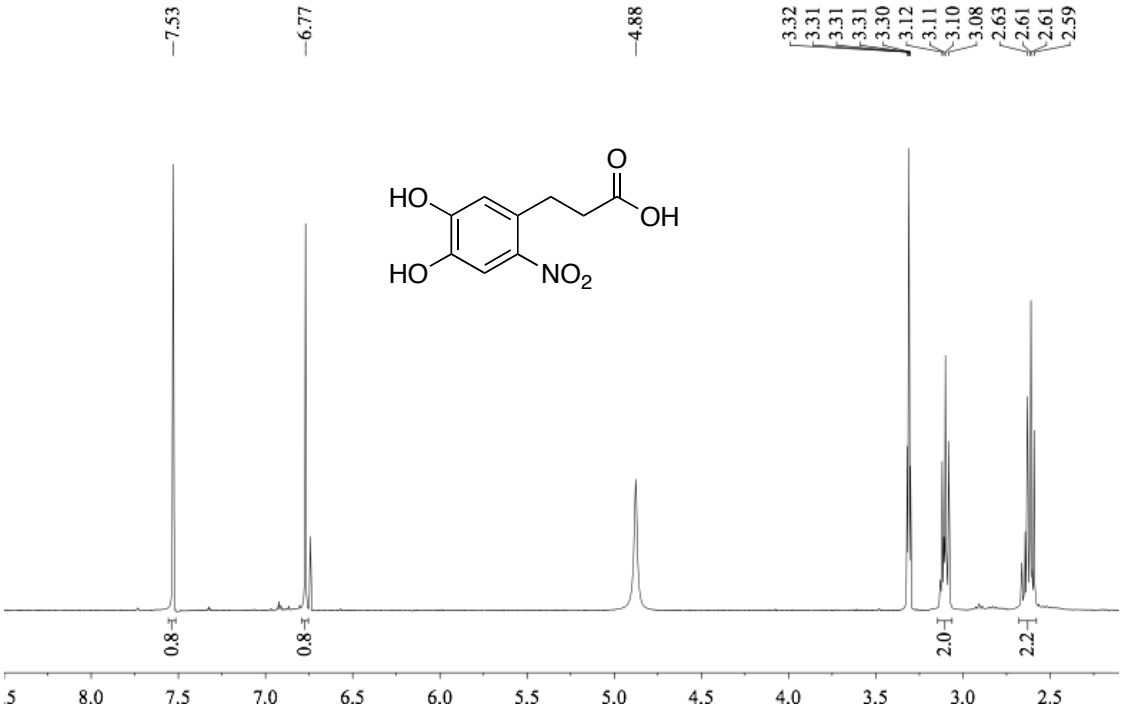


400 MHz ^{1}H-NMR in $CDCl_3$

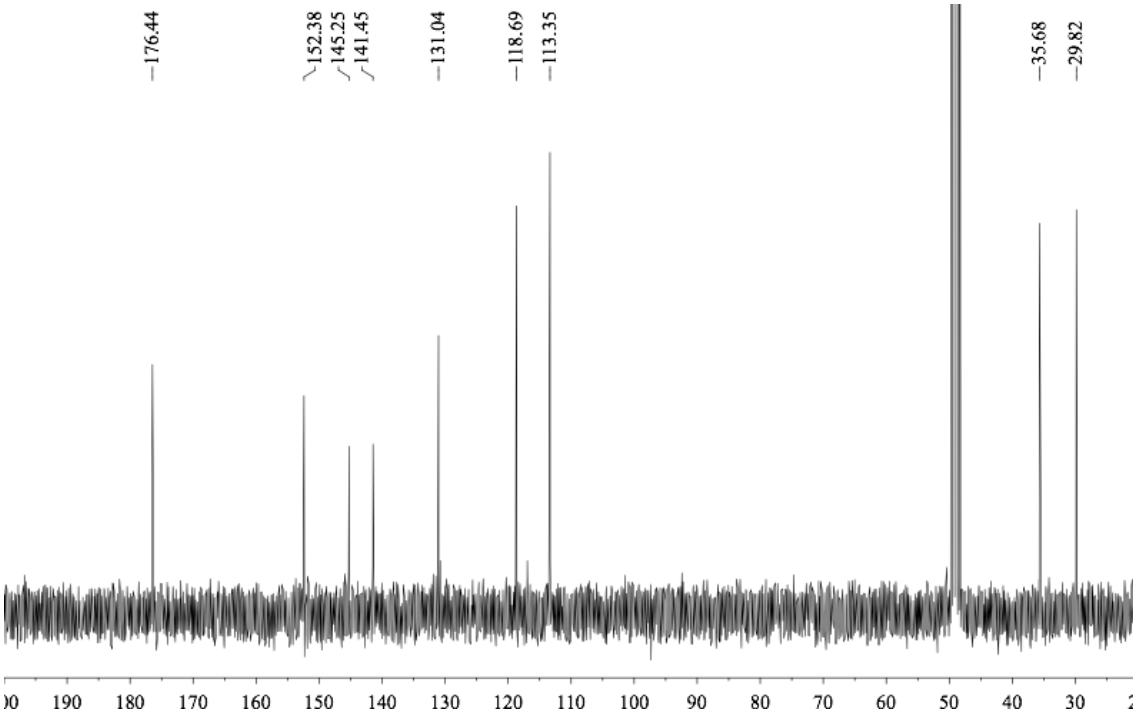


101 MHz ^{13}C-NMR in $CDCl_3$

3-(4,5-Dihydroxy-2-nitrophenyl)propanoic acid (3.37)

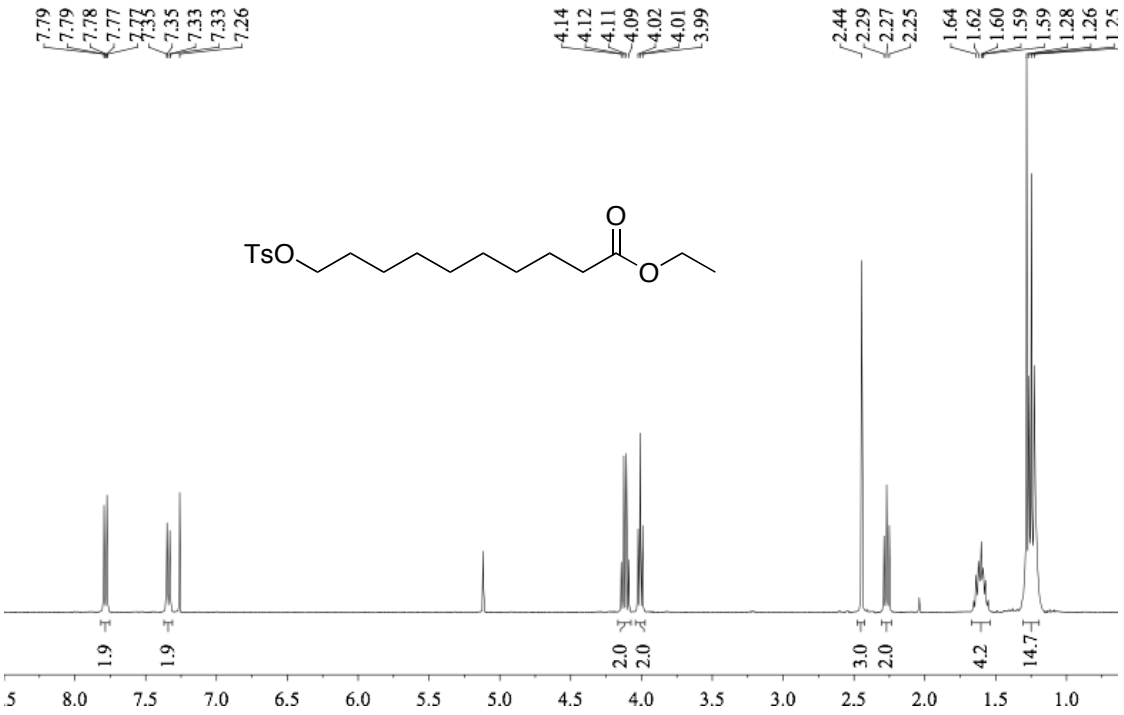


400 MHz ^{1}H-NMR in MeOD

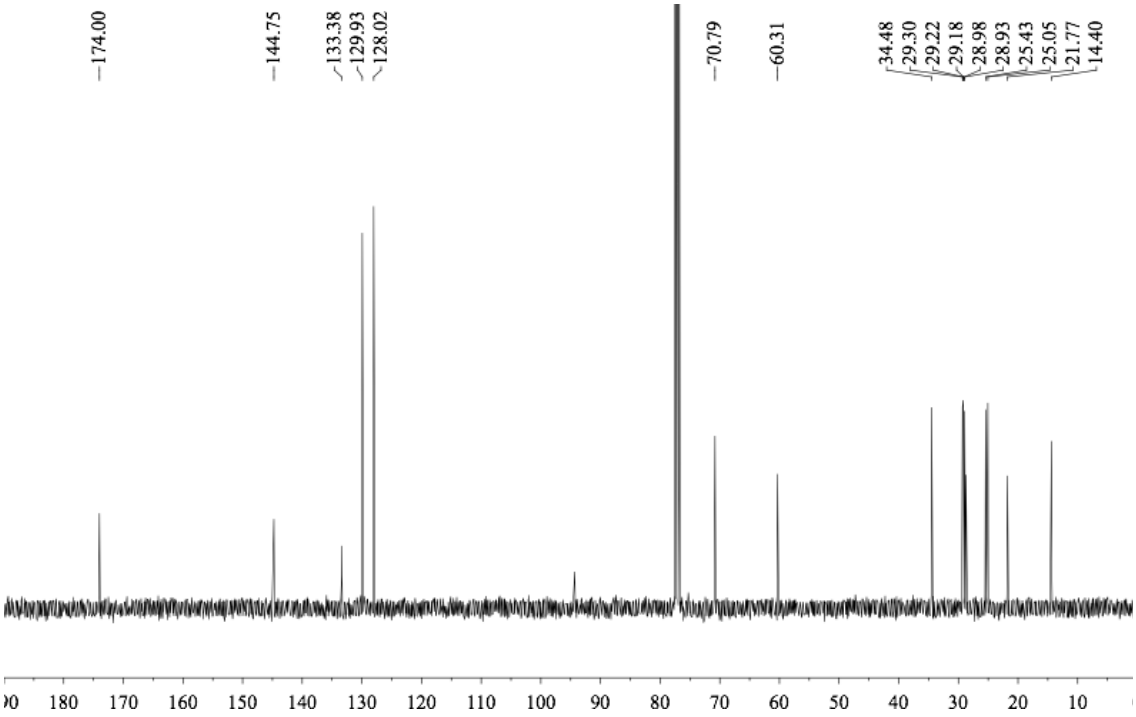


101 MHz ^{13}C-NMR in MeOD

Ethyl 10-(tosyloxy)decanoate (3.42)

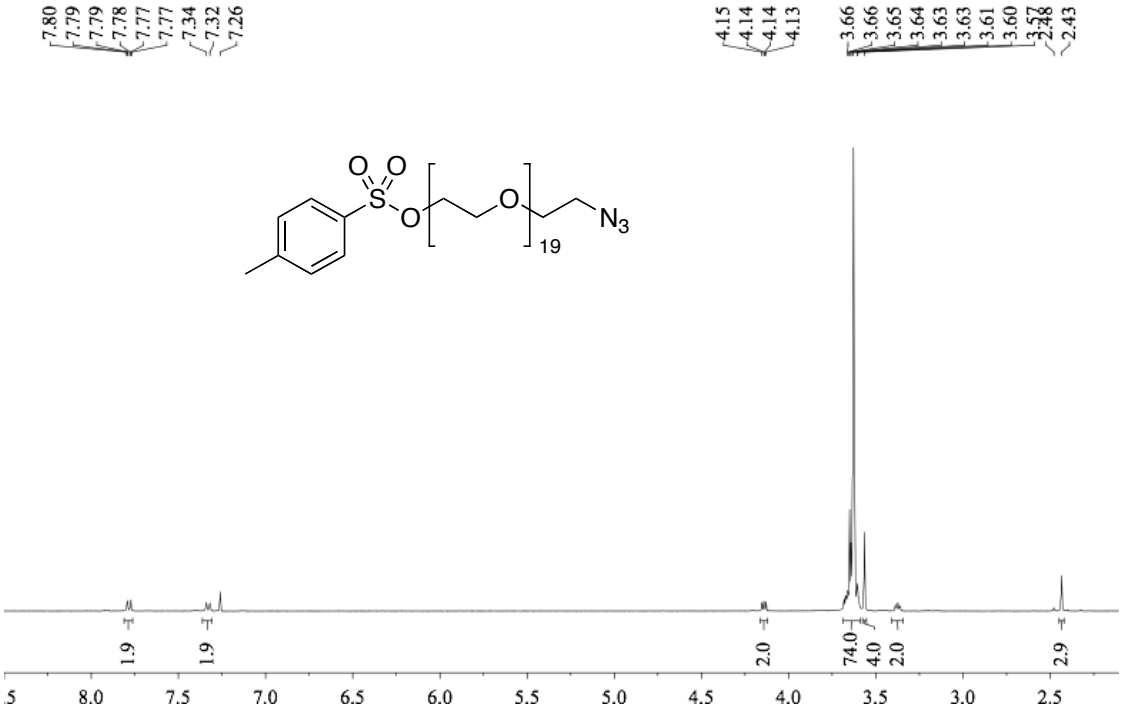


400 MHz ^{1}H-NMR in $CDCl_3$

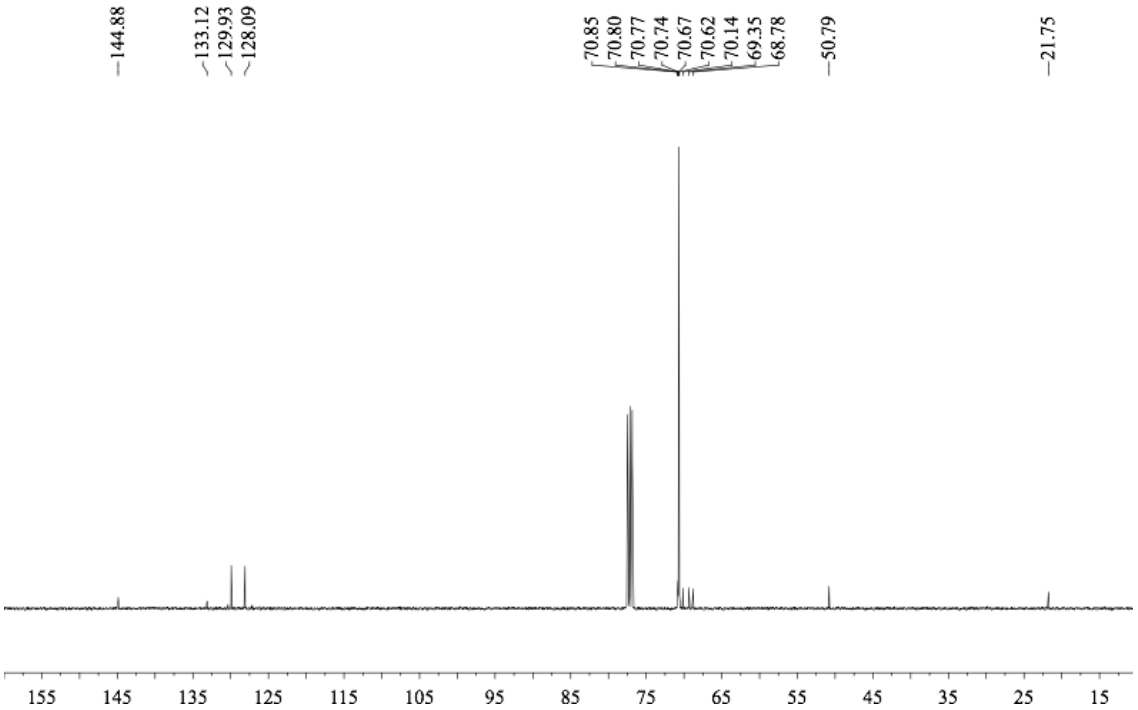


101 MHz ^{13}C-NMR in $CDCl_3$

***O*-(2-Azidoethyl)-*O*'-tosylnonadecaethylene glycol (3.45)**

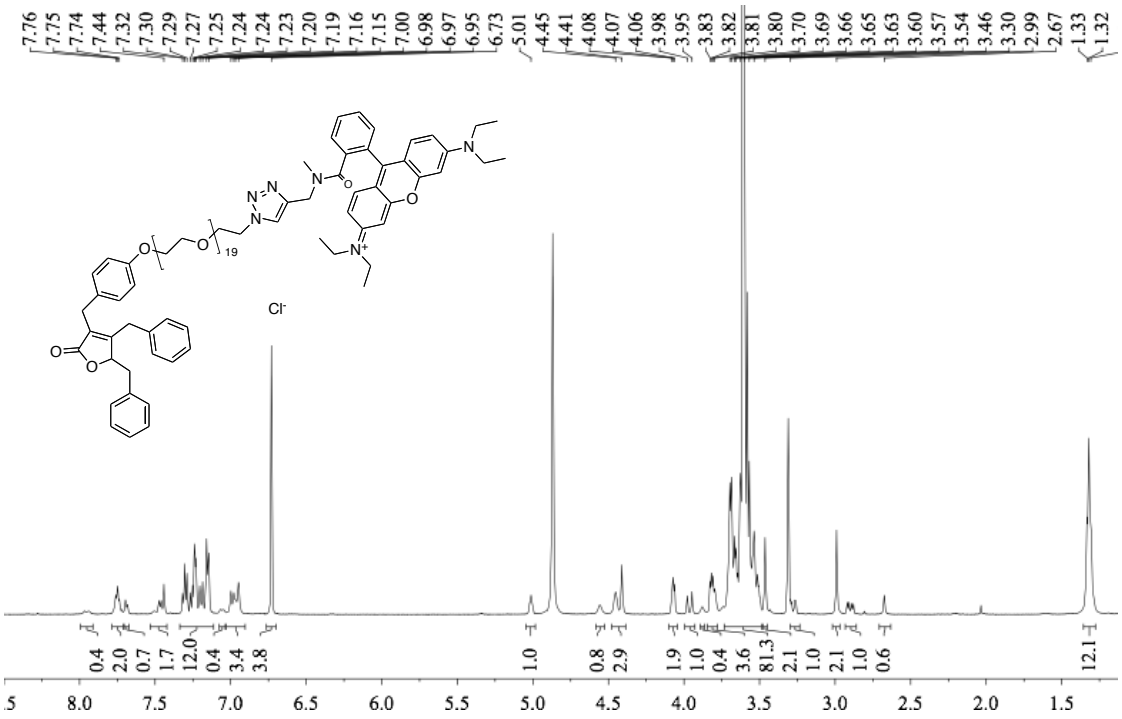


400 MHz ^{1}H-NMR in $CDCl_3$

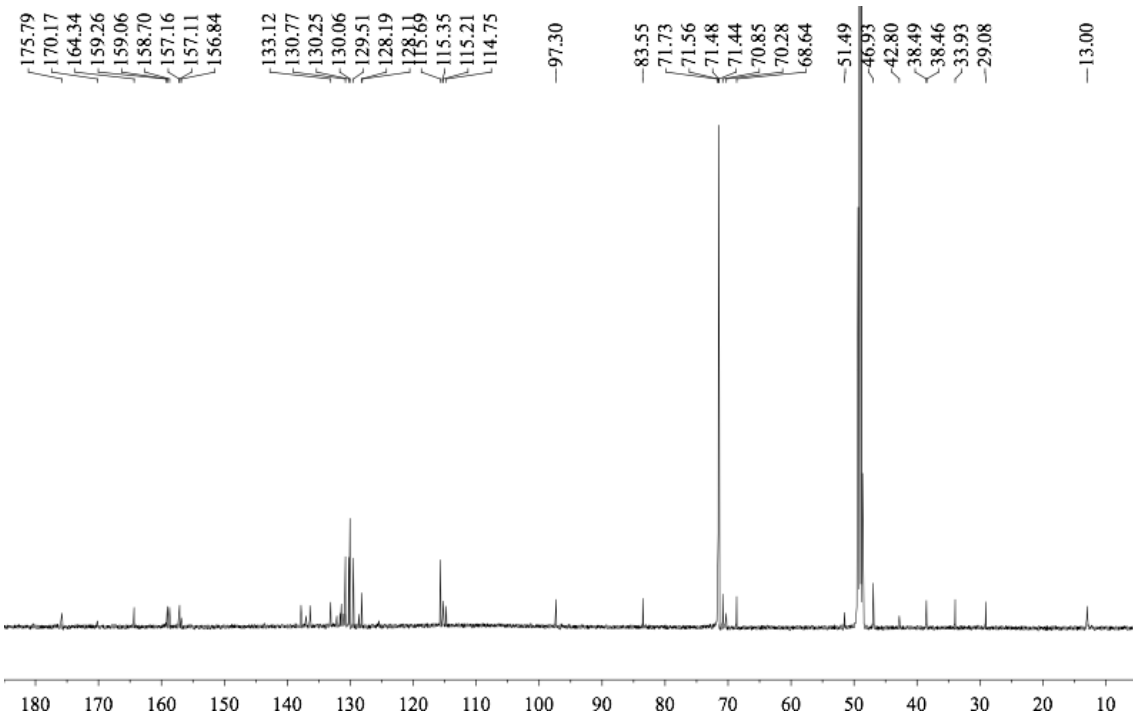


101 MHz ^{13}C-NMR in $CDCl_3$

Rhodamine B maculalactone A hybrid (3.47)

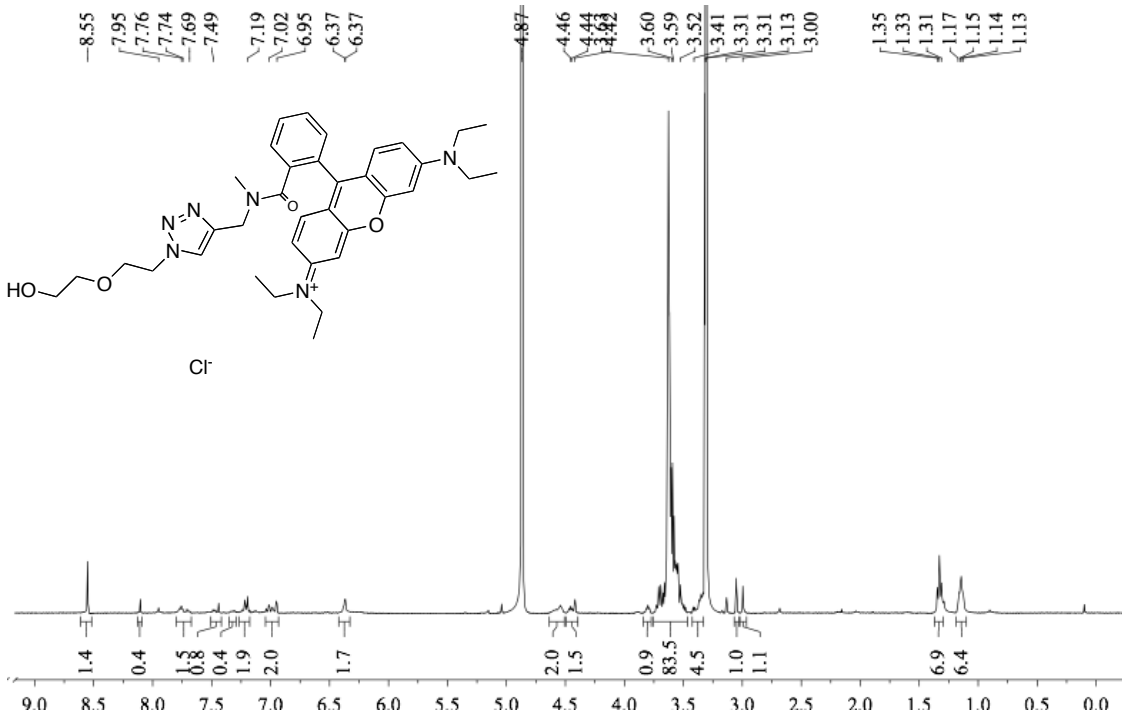


500 MHz ^{1}H-NMR in MeOD

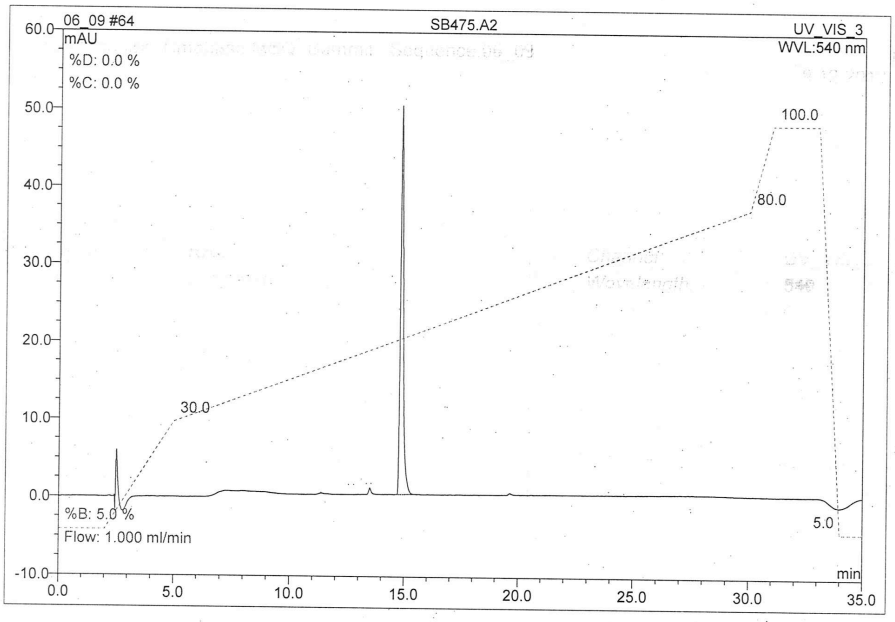


126 MHz ^{13}C-NMR in MeOD

Rhodamine B with linker (3.48)



400 MHz ^{1}H-NMR in MeOD

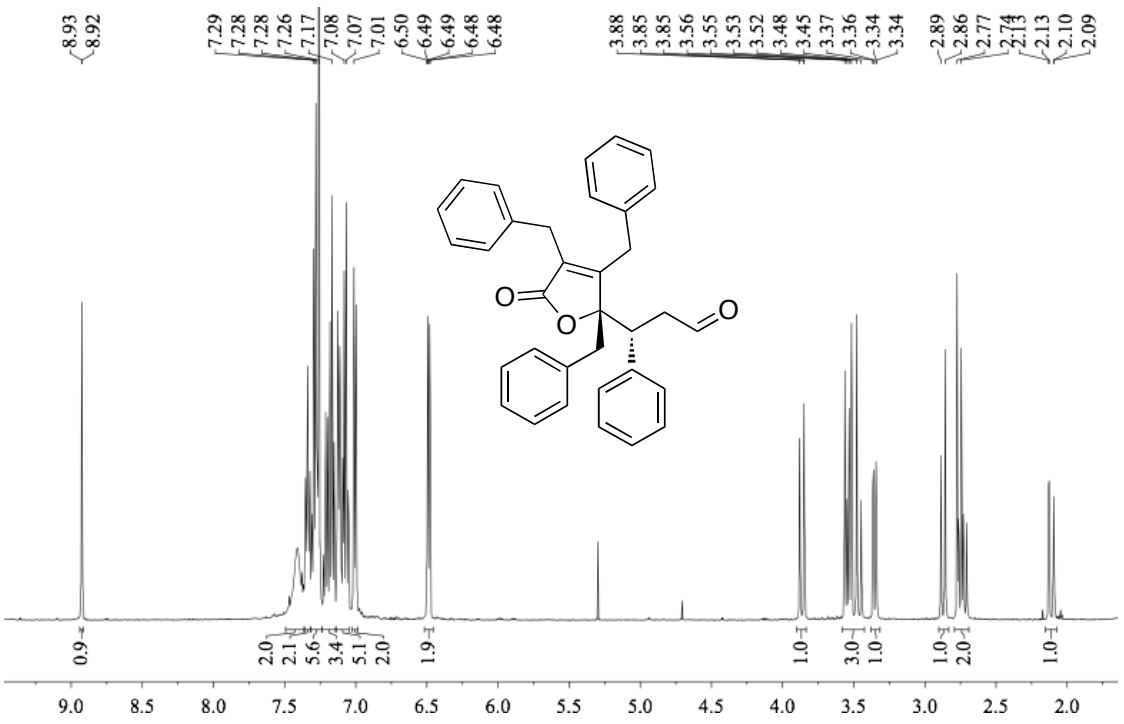


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.82	n.a.	50.153	7.663	100.00	n.a.	BMB
Total:			50.153	7.663	100.00	0.000	

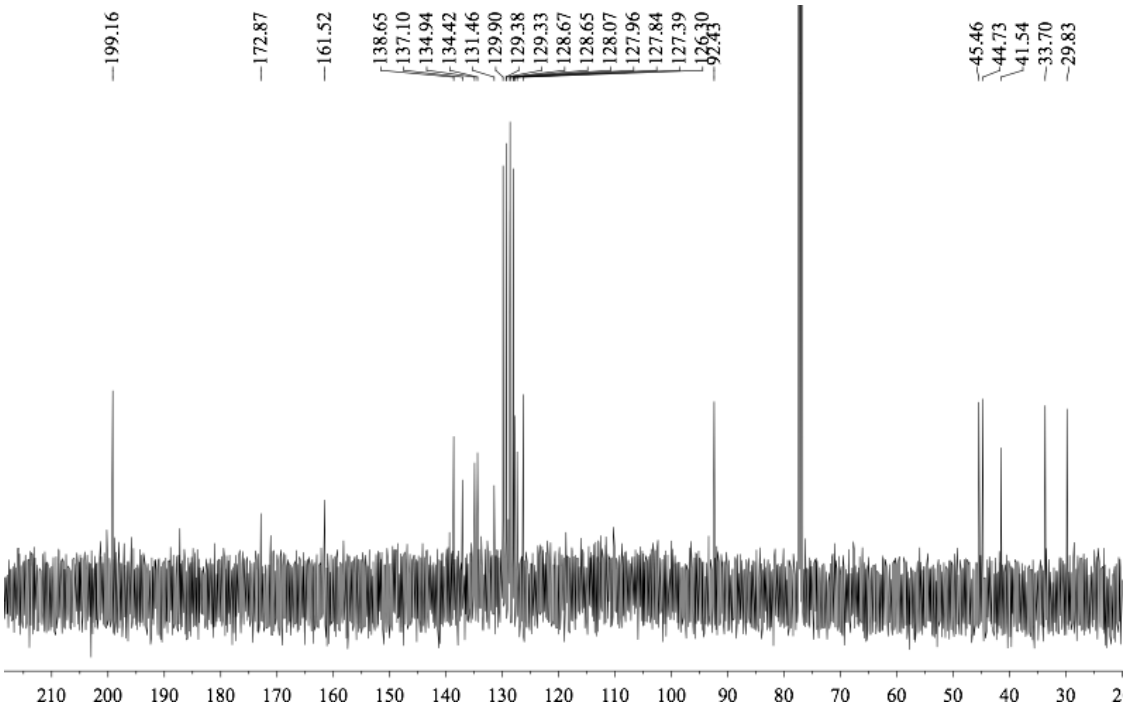
HPLC (Phenomenex Synergi Hydro-RP, AcN/water + 0.1% HCO_2H (2 min 1:19, in 3 min to 3:7, in 25 min to 4:1), 1 ml/min, 540 nm)

9.2.3 Synthetic Studies on Ophiodilactone A and B

3-Phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (4.07)

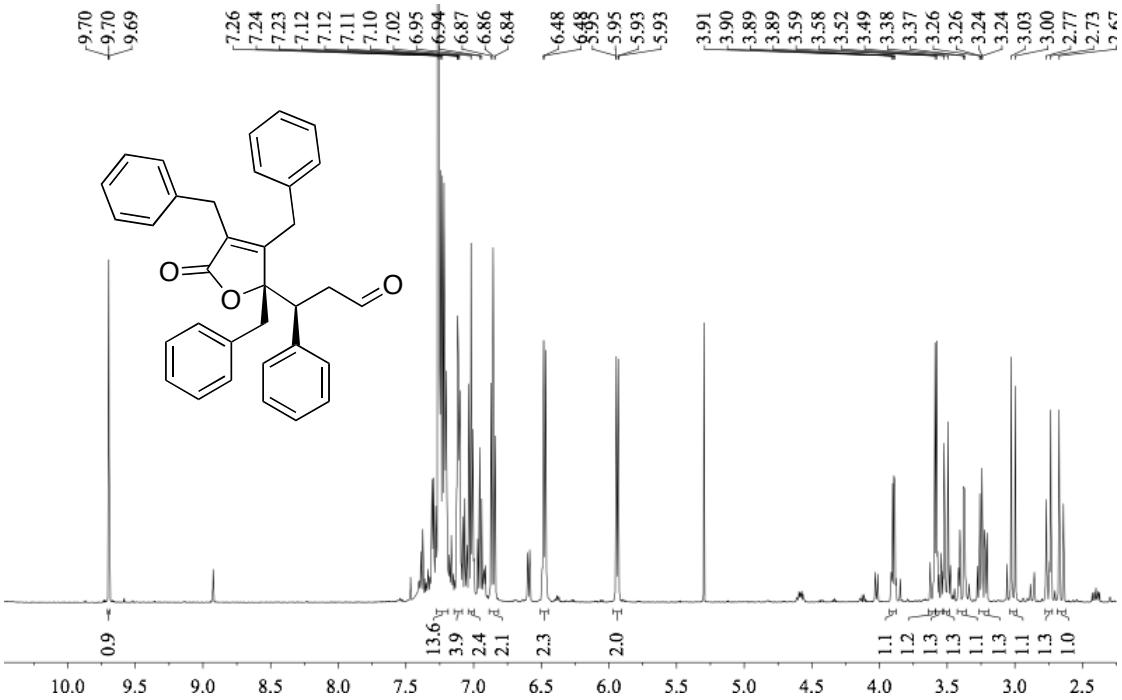


500 MHz ^{1}H-NMR in $CDCl_3$

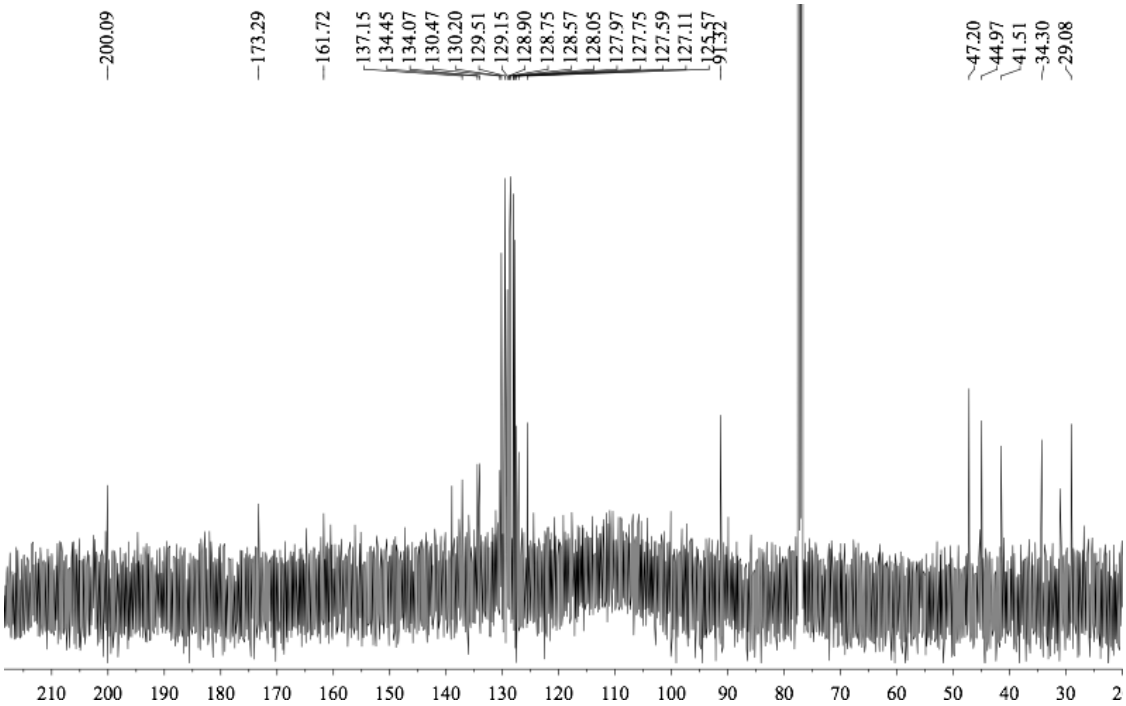


126 MHz ^{13}C-NMR in $CDCl_3$

3-Phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanal (6.02)

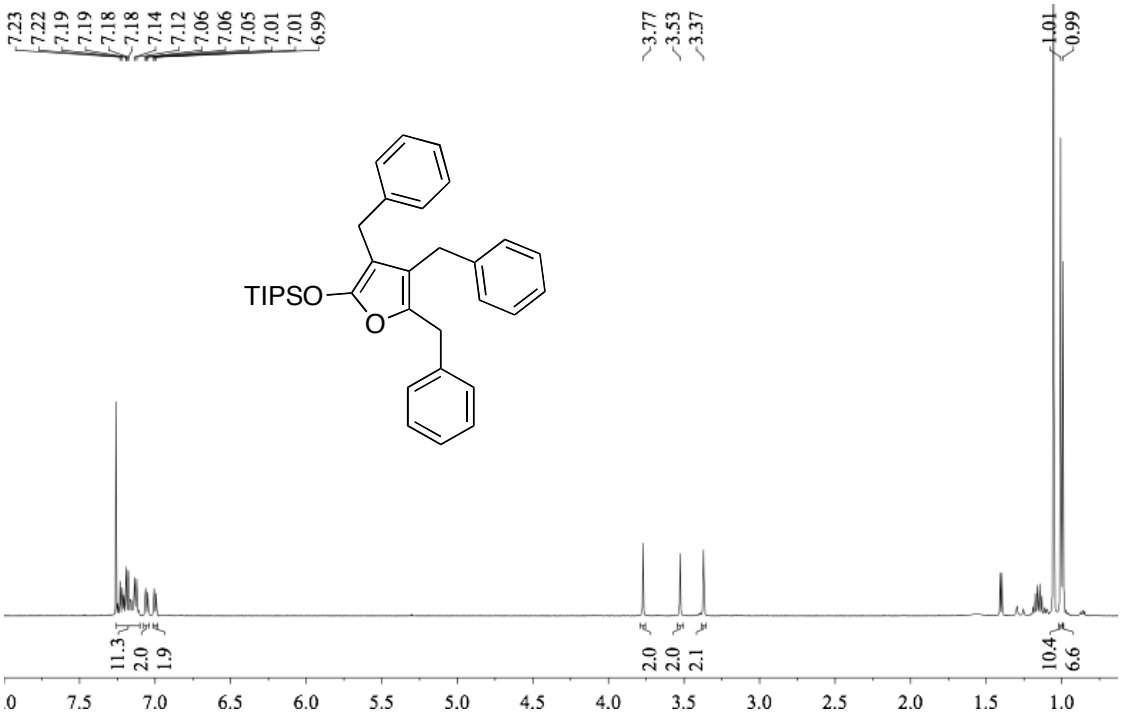


500 MHz ^{1}H-NMR in $CDCl_3$

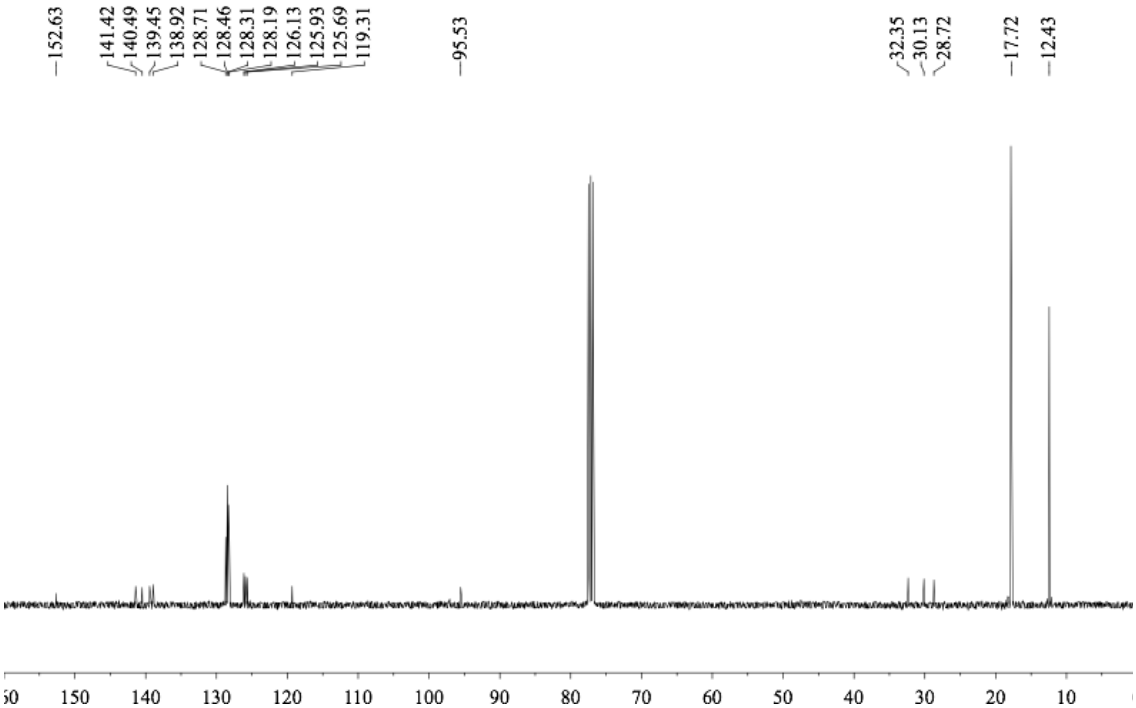


126 MHz ^{13}C-NMR in $CDCl_3$

Triisopropyl((3,4,5-tribenzylfuran-2-yl)oxy)silane (4.11)

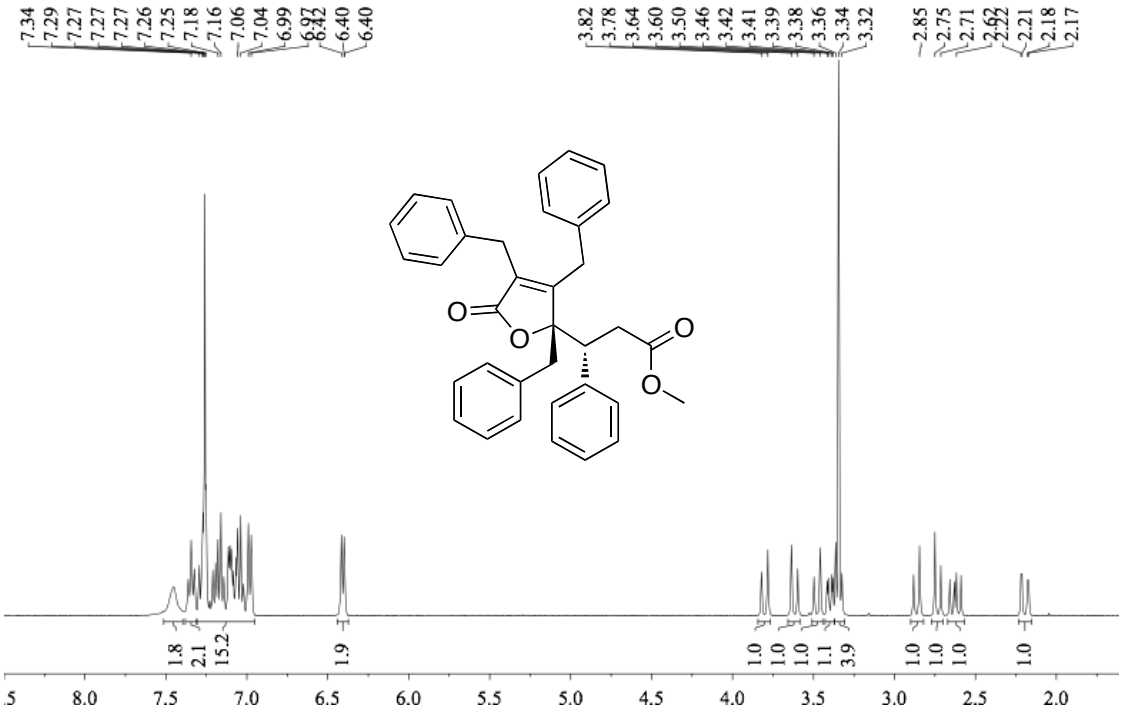


500 MHz ^{1}H-NMR in $CDCl_3$

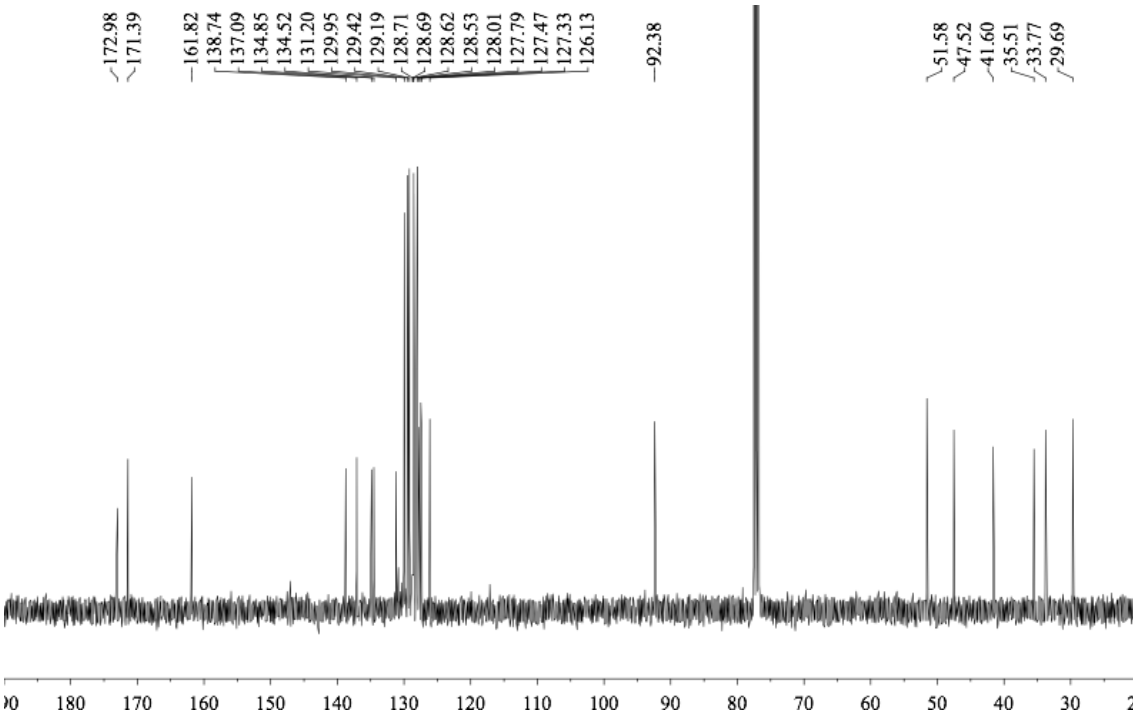


101 MHz ^{13}C-NMR in $CDCl_3$

***rac*-Methyl 3-phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanoate (4.13)**

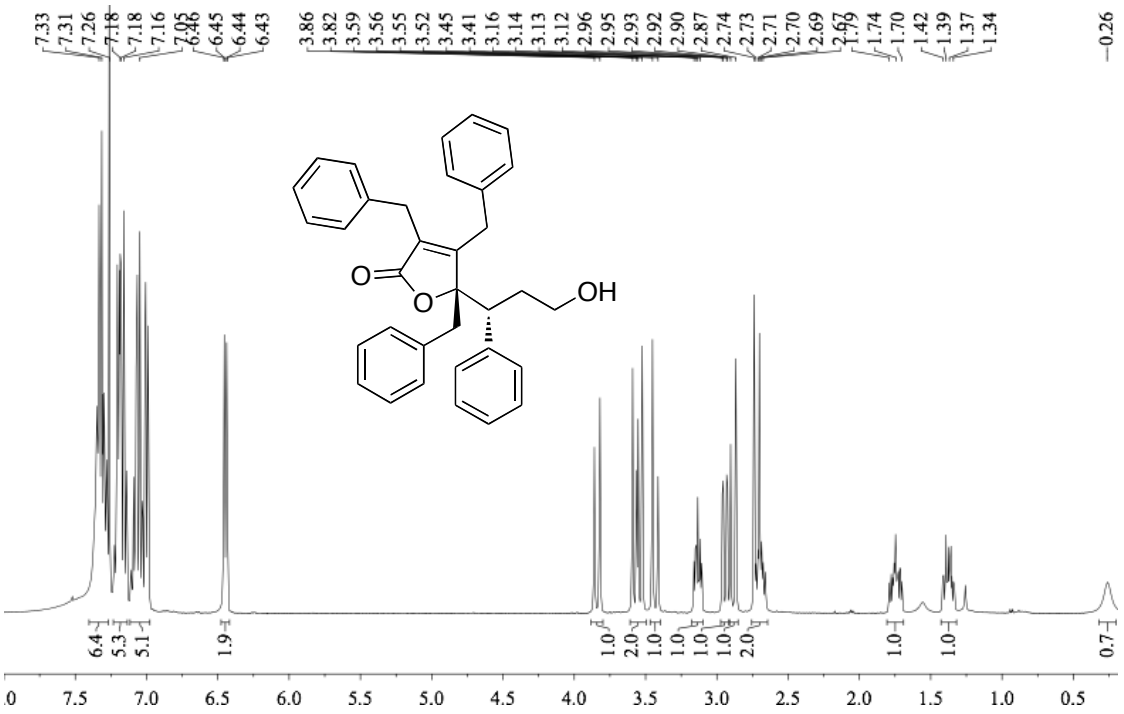


500 MHz ^{1}H-NMR in $CDCl_3$

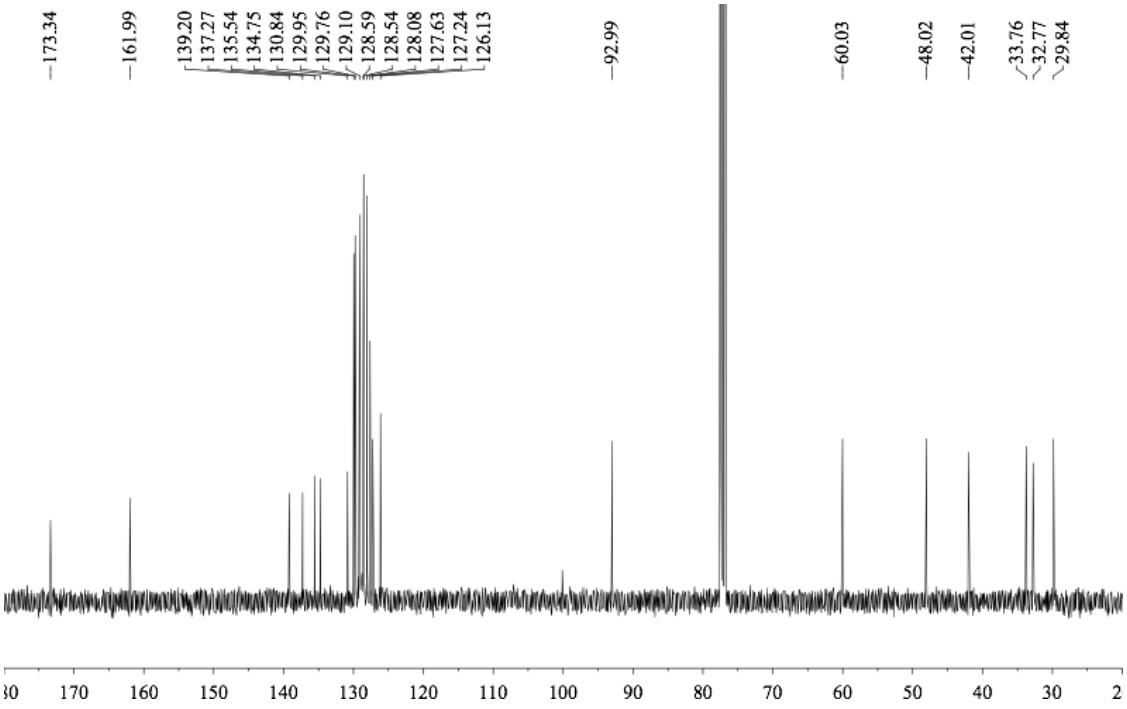


126 MHz ^{13}C-NMR in $CDCl_3$

3,4,5-Tribenzyl-5-(3-hydroxy-1-phenylpropyl)furan-2(5H)-one (4.17)

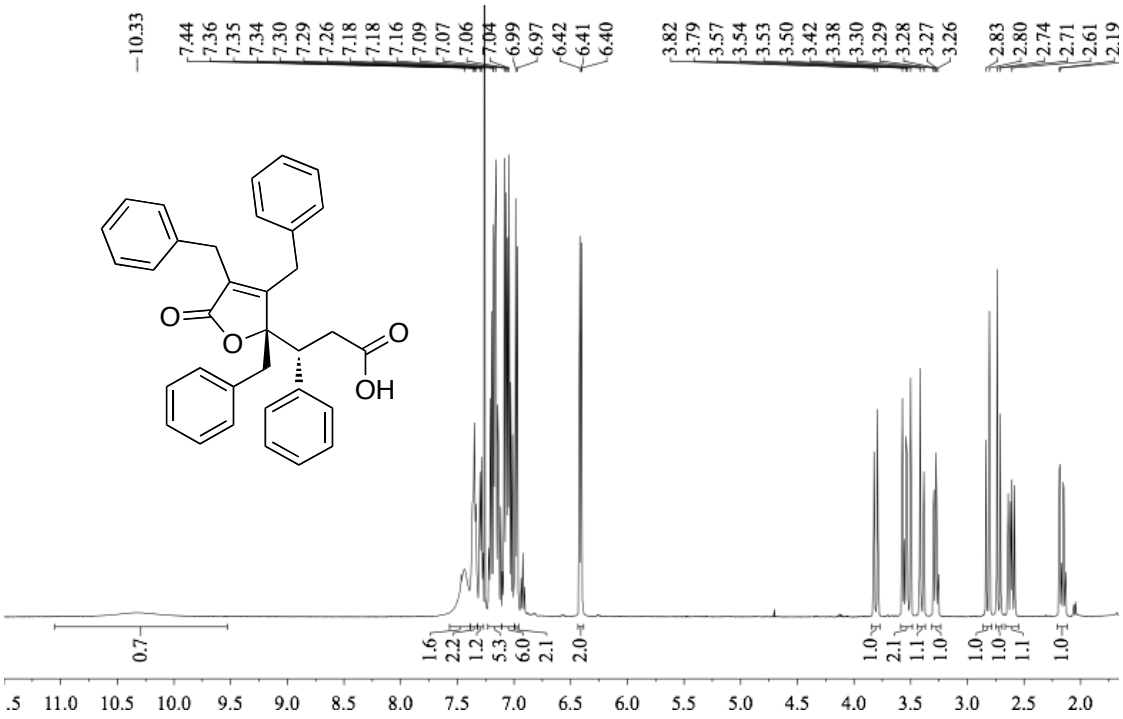


500 MHz ^{1}H-NMR in $CDCl_3$

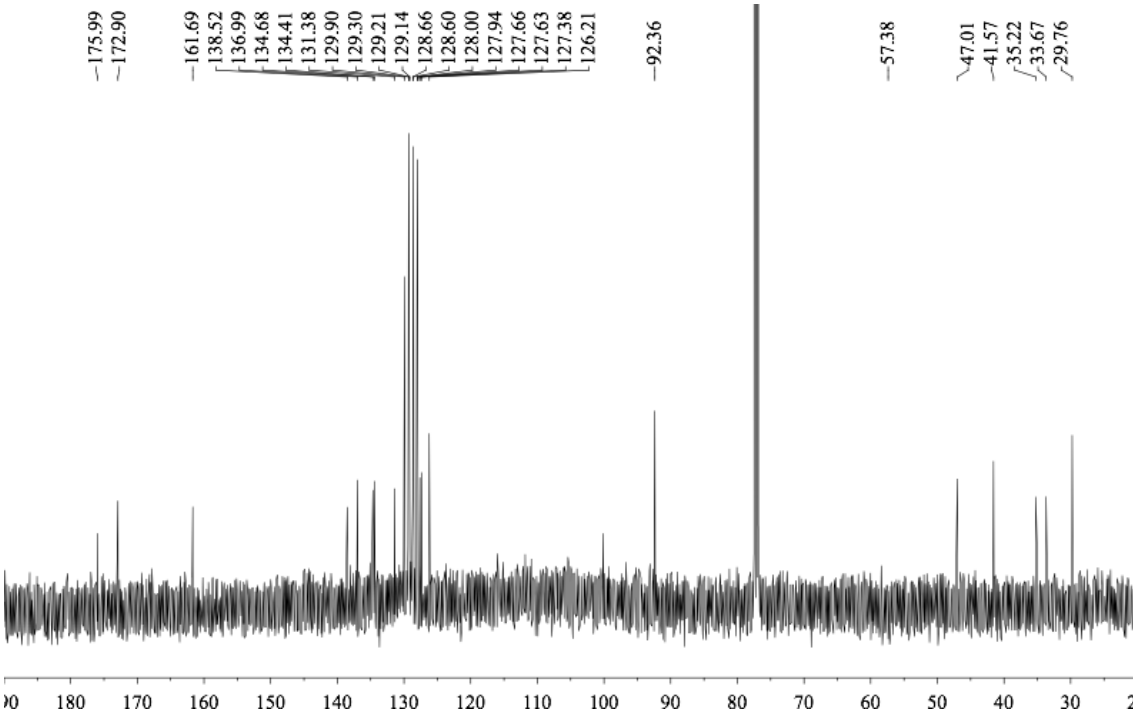


126 MHz ^{13}C-NMR in $CDCl_3$

3-Phenyl-3-(2,3,4-tribenzyl-5-oxo-2,5-dihydrofuran-2-yl)propanoic acid (4.18)

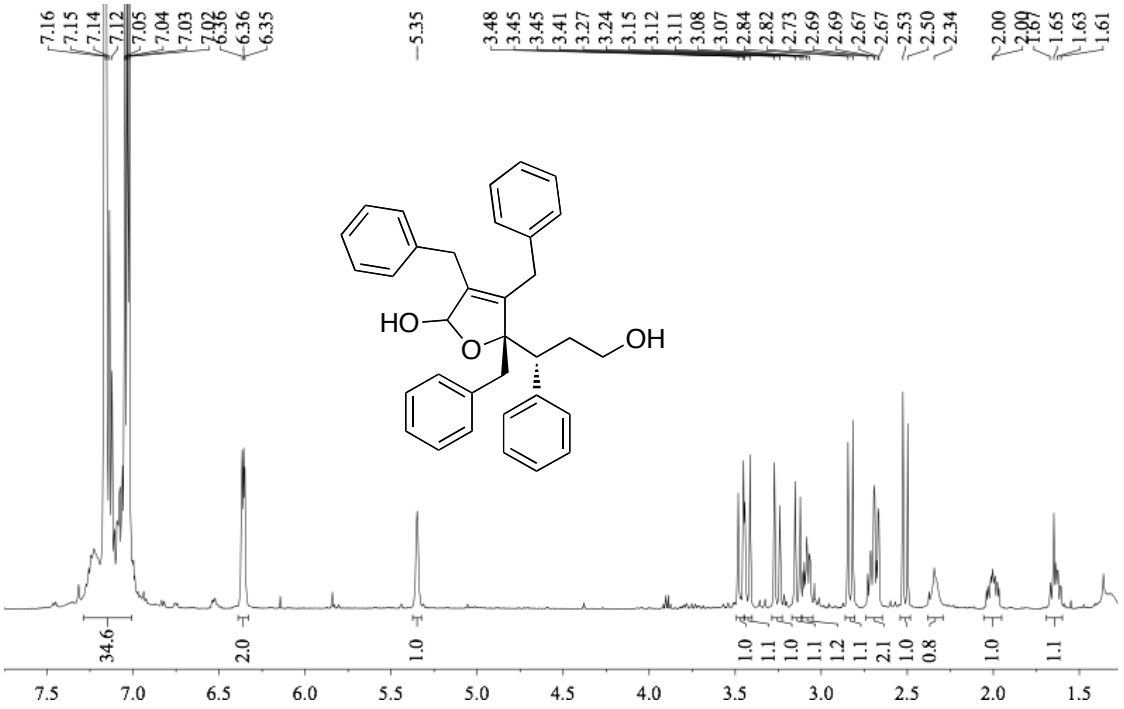


500 MHz ^{1}H-NMR in $CDCl_3$

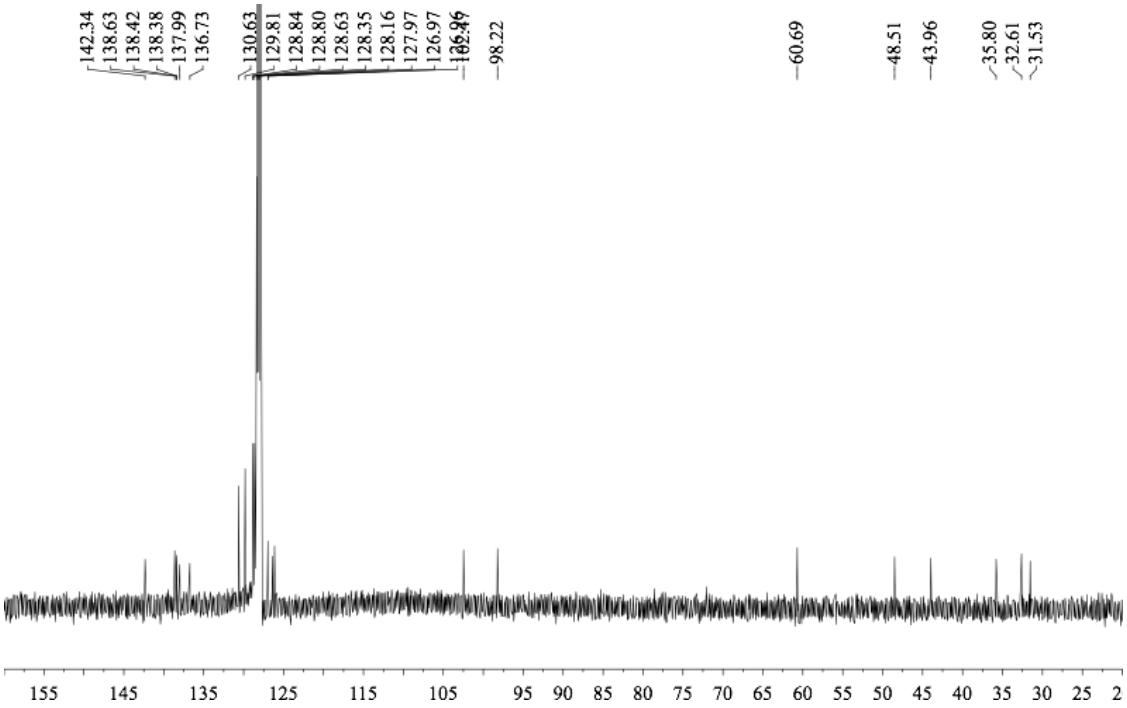


126 MHz ^{13}C-NMR in $CDCl_3$

3,4,5-Tribenzyl-5-(3-hydroxy-1-phenylpropyl)-2,5-dihydrofuran-2-ol (4.19)

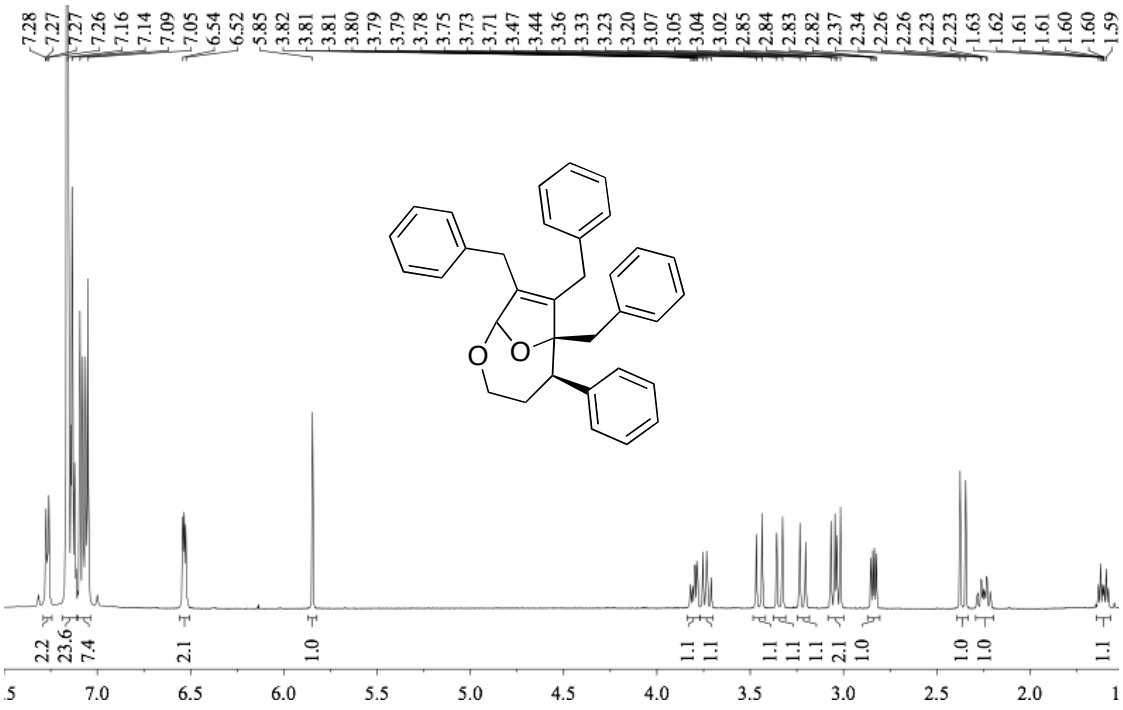


500 MHz ^{1}H-NMR in C_6D_6

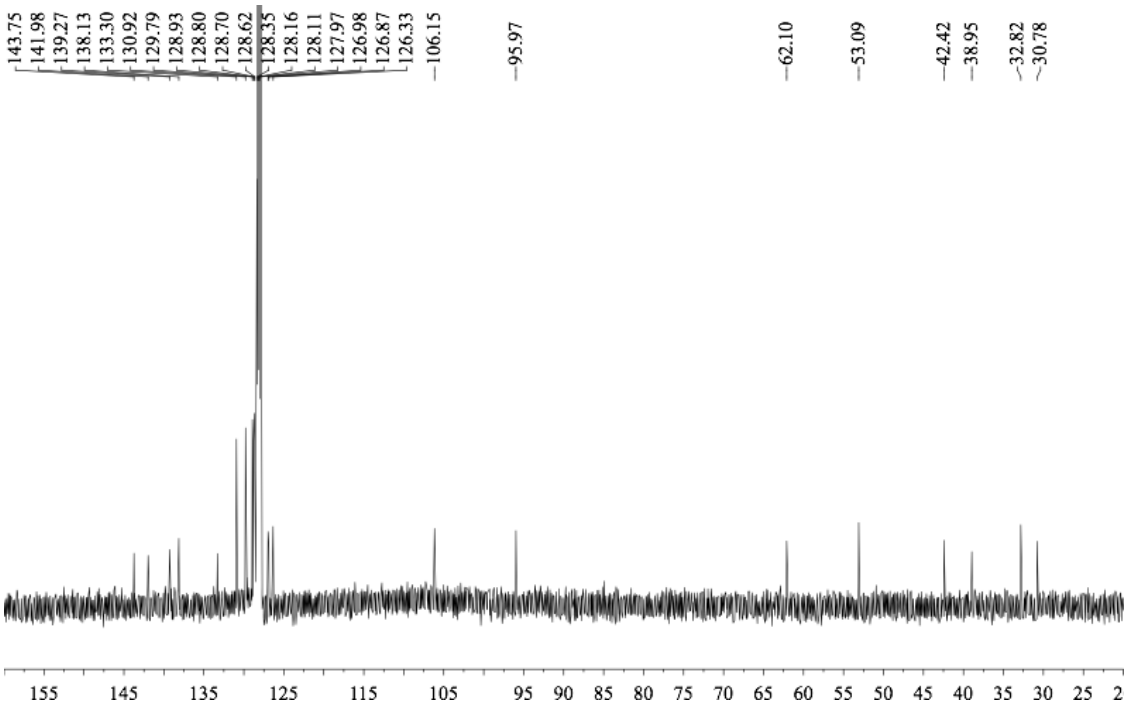


126 MHz ^{13}C-NMR in C_6D_6

6,7,8-Tribenzyl-5-phenyl-2,9-dioxabicyclo[4.2.1]non-7-ene (4.20)

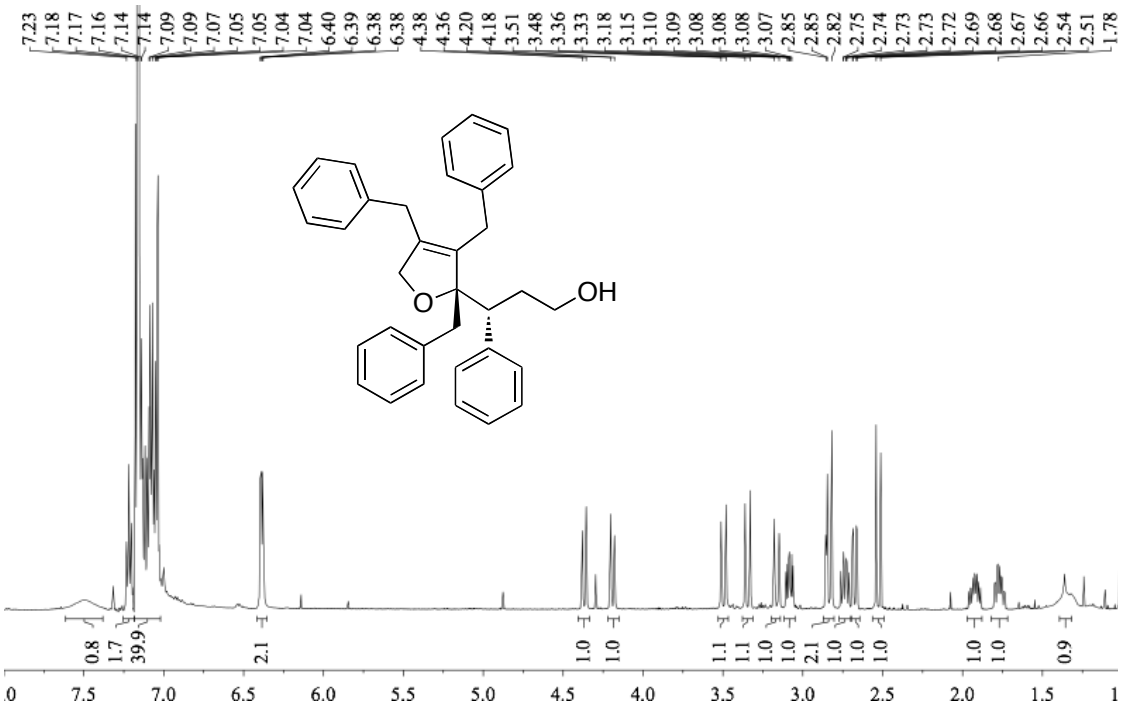


500 MHz ^{1}H-NMR in C_6D_6

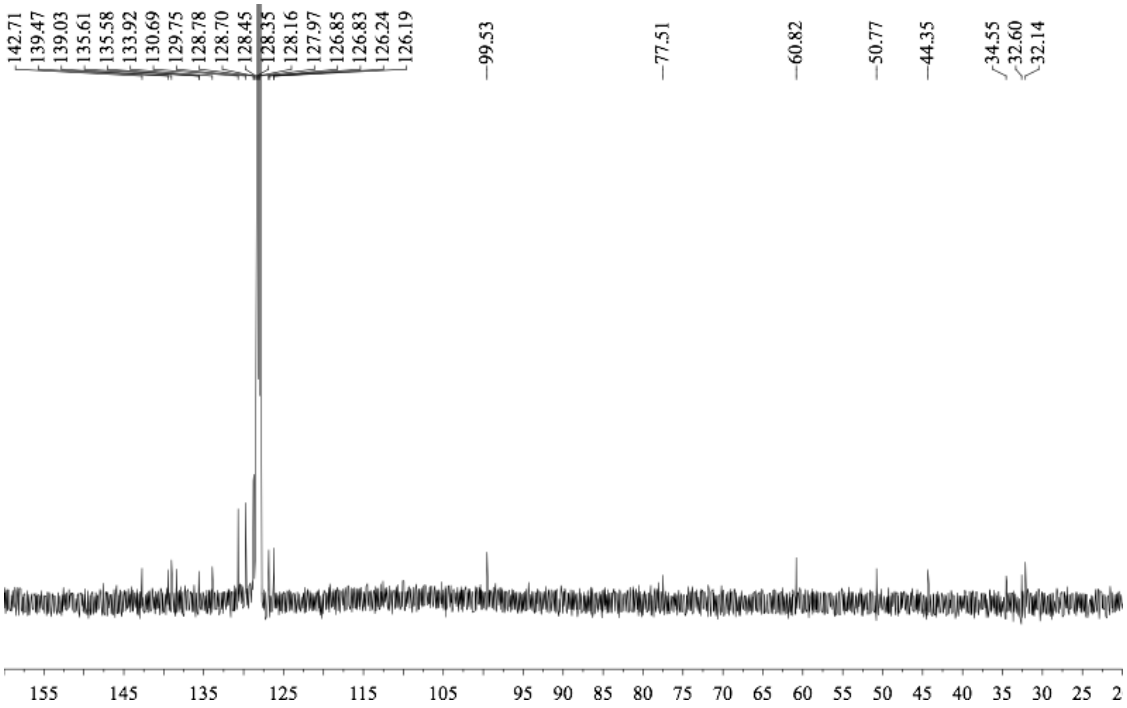


126 MHz ^{13}C-NMR in C_6D_6

3-Phenyl-3-(2,3,4-tribenzyl-2,5-dihydrofuran-2-yl)propan-1-ol (4.24)

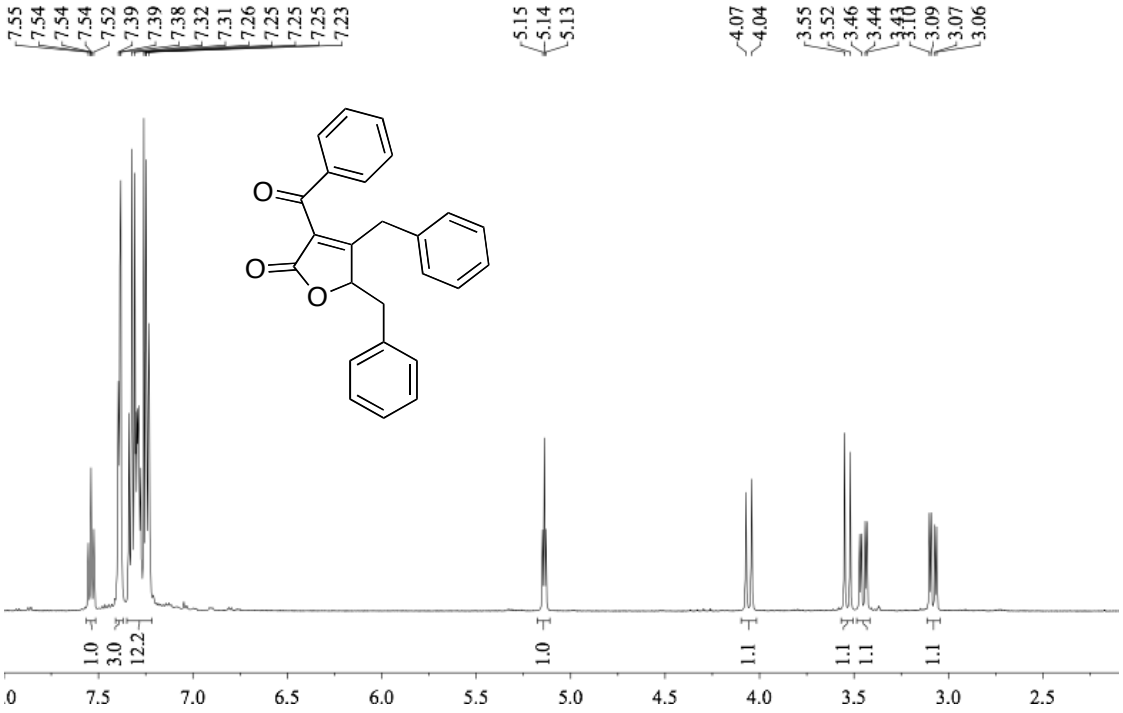


500 MHz ^{1}H-NMR in C_6D_6

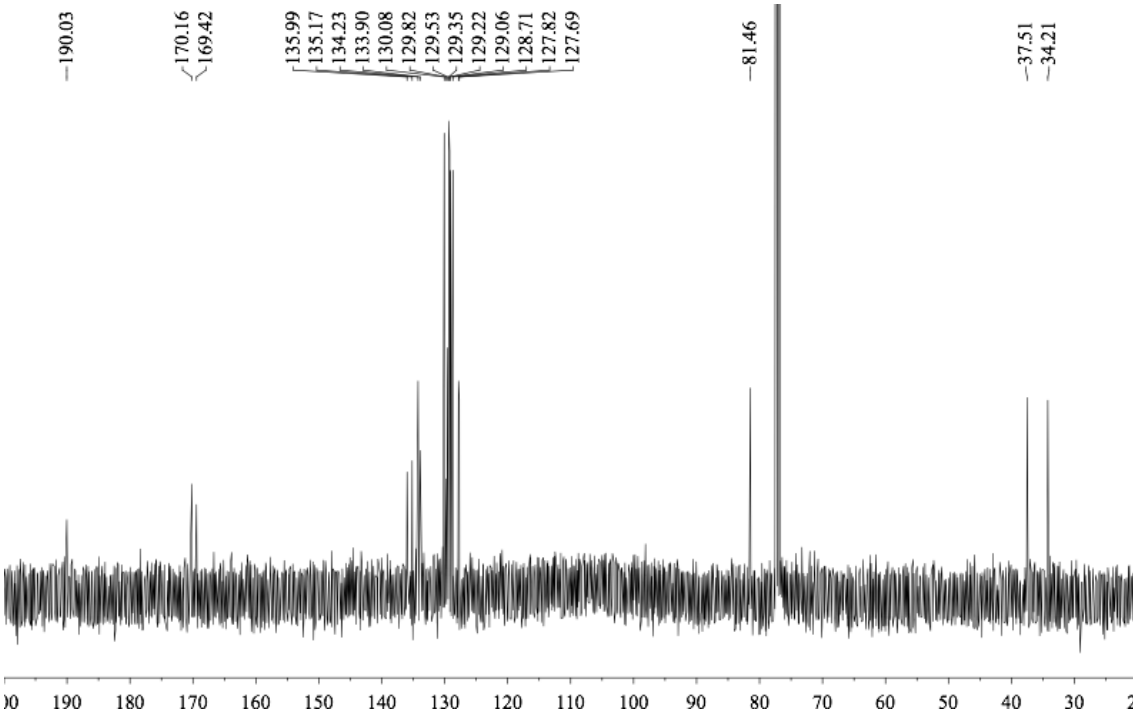


126 MHz ^{13}C-NMR in C_6D_6

3-Benzoyl-4,5-dibenzylfuran-2(5H)-one (4.27)

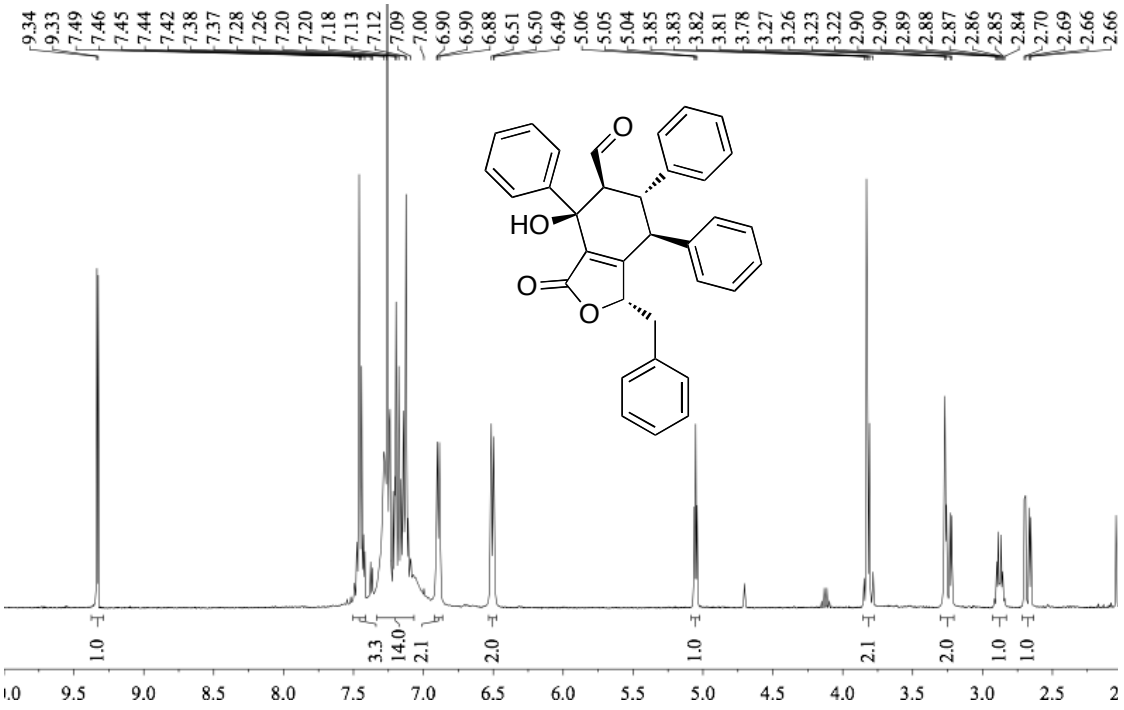


500 MHz ^{1}H-NMR in $CDCl_3$

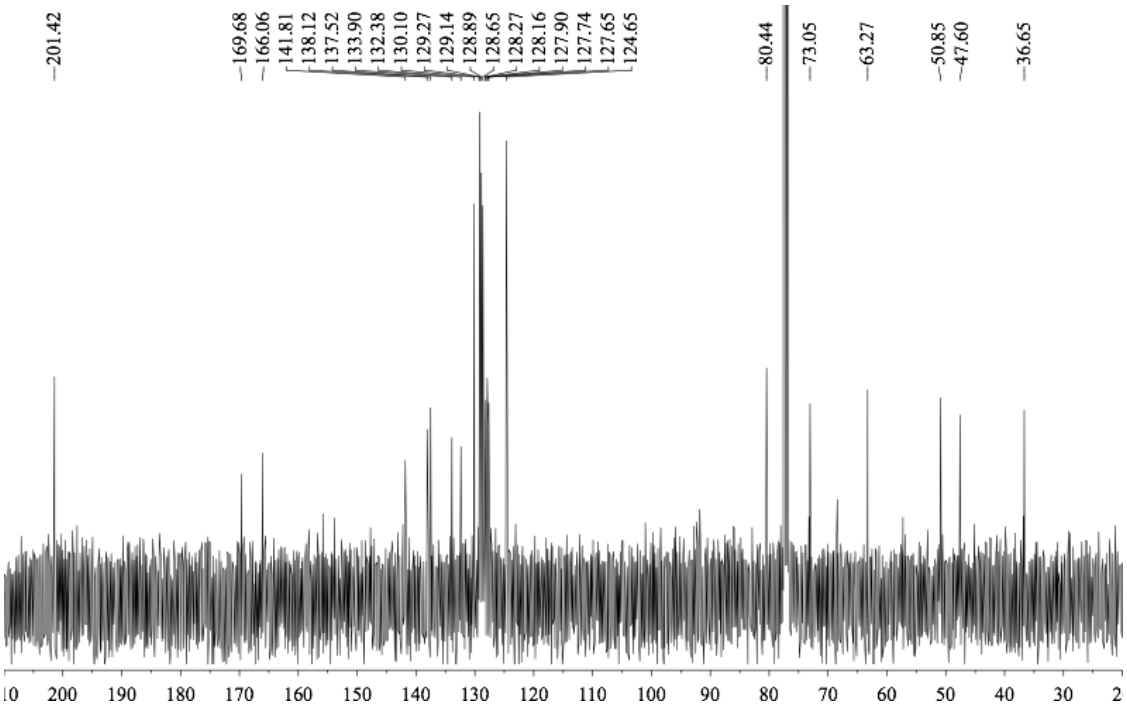


126 MHz ^{13}C-NMR in $CDCl_3$

1-Benzyl-4-hydroxy-3-oxo-4,6,7-triphenyl-1,3,4,5,6,7-hexahydroisobenzofuran-5-carbaldehyde (4.28)

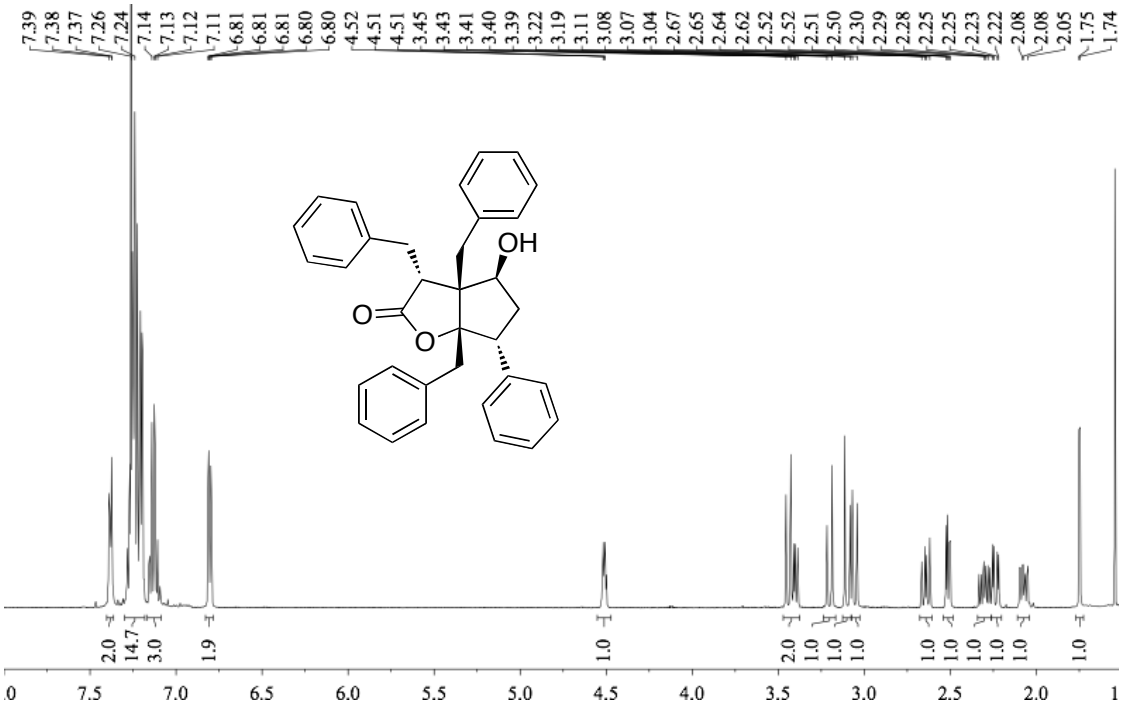


400 MHz ^{1}H-NMR in $CDCl_3$

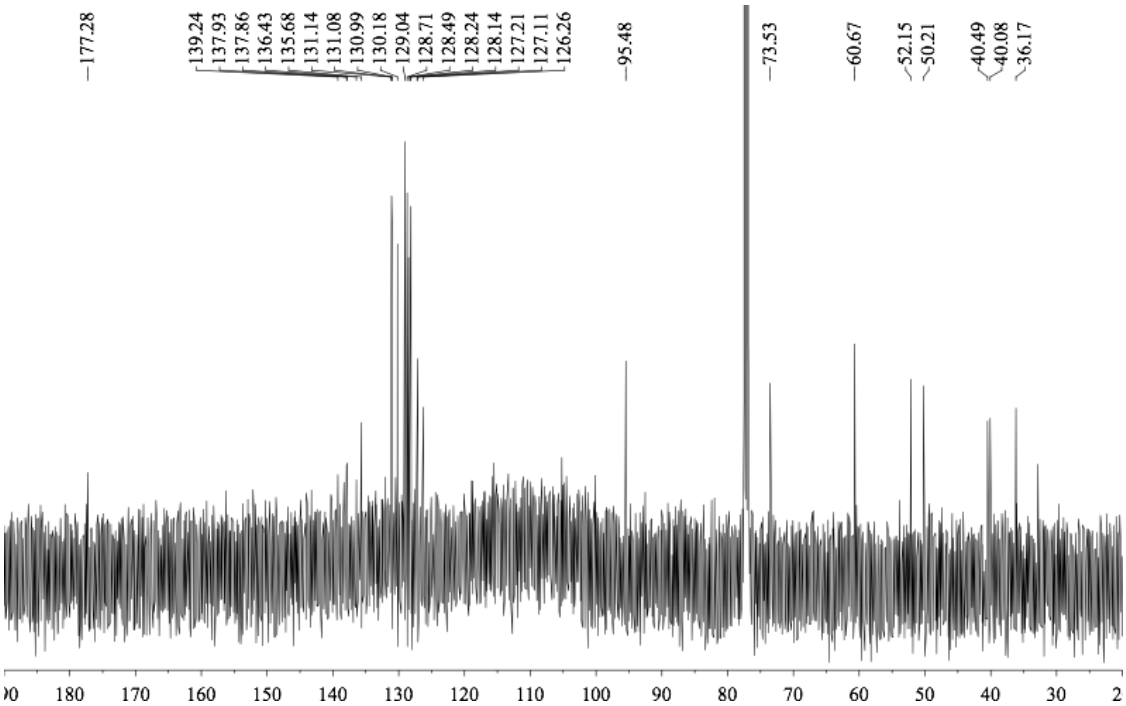


101 MHz ^{13}C-NMR in $CDCl_3$

3,3a,6a-Tribenzyl-4-hydroxy-6-phenylhexahydro-2H-cyclopenta[b]furan-2-one (4.31)

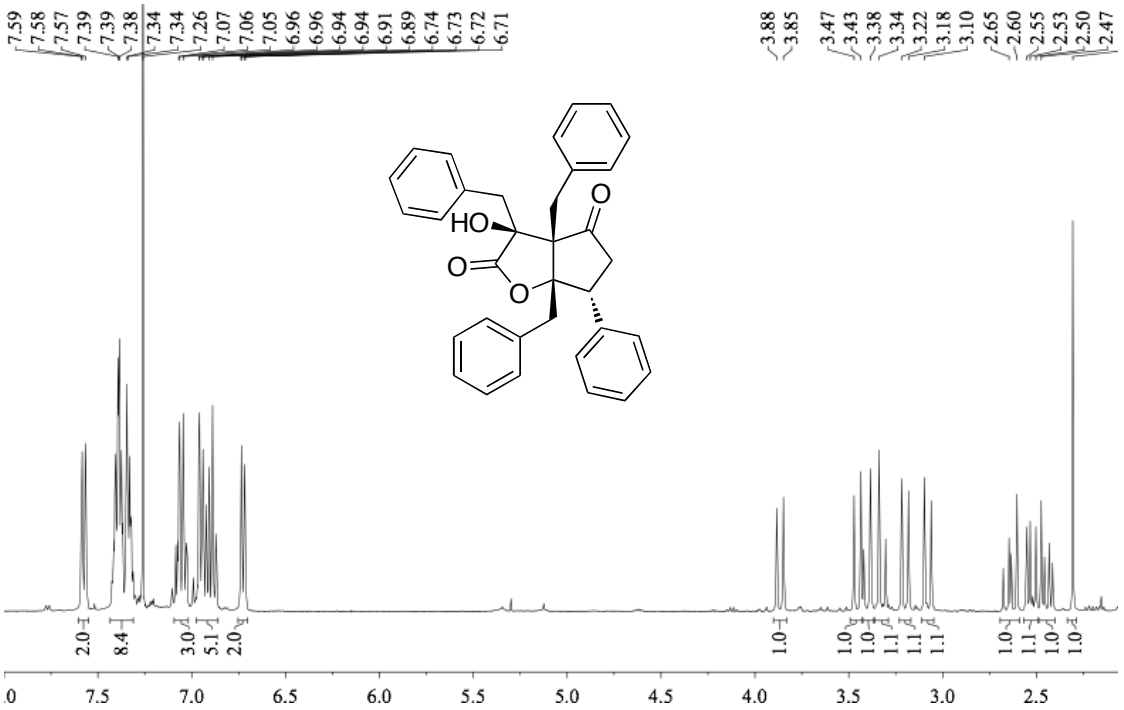


500 MHz ^{1}H-NMR in $CDCl_3$

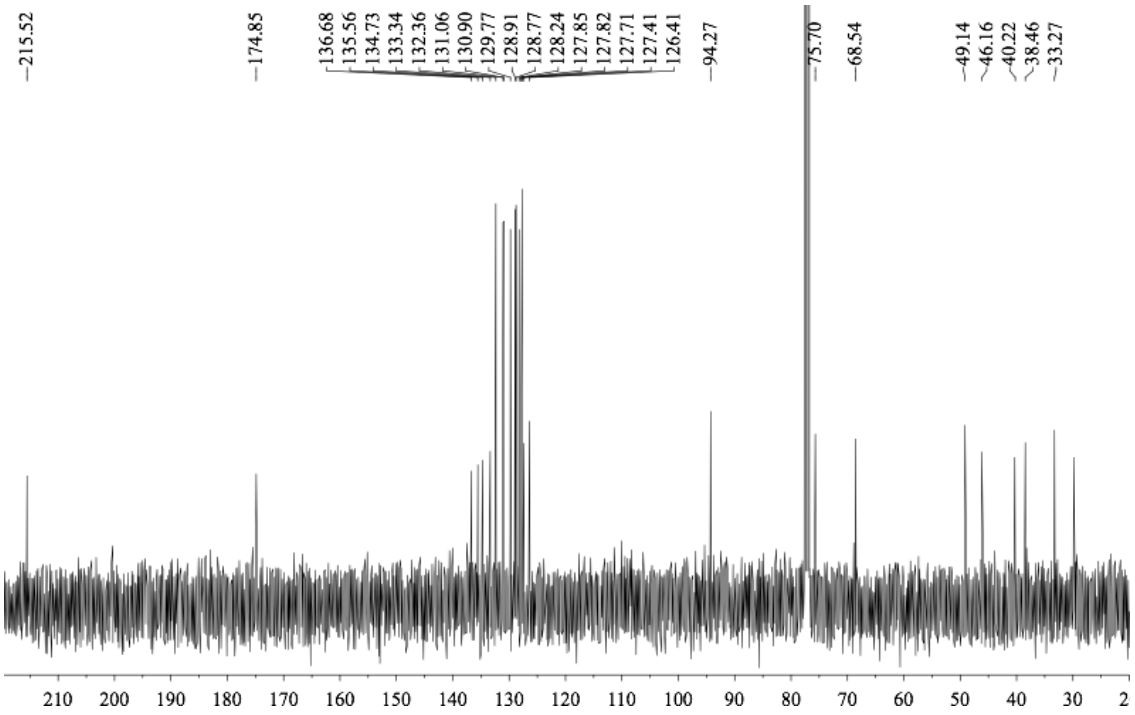


126 MHz ^{13}C-NMR in $CDCl_3$

3,3a,6a-Tribenzyl-3-hydroxy-6-phenyltetrahydro-2H-cyclopenta[b]furan-2,4(5H)-dione (4.33)

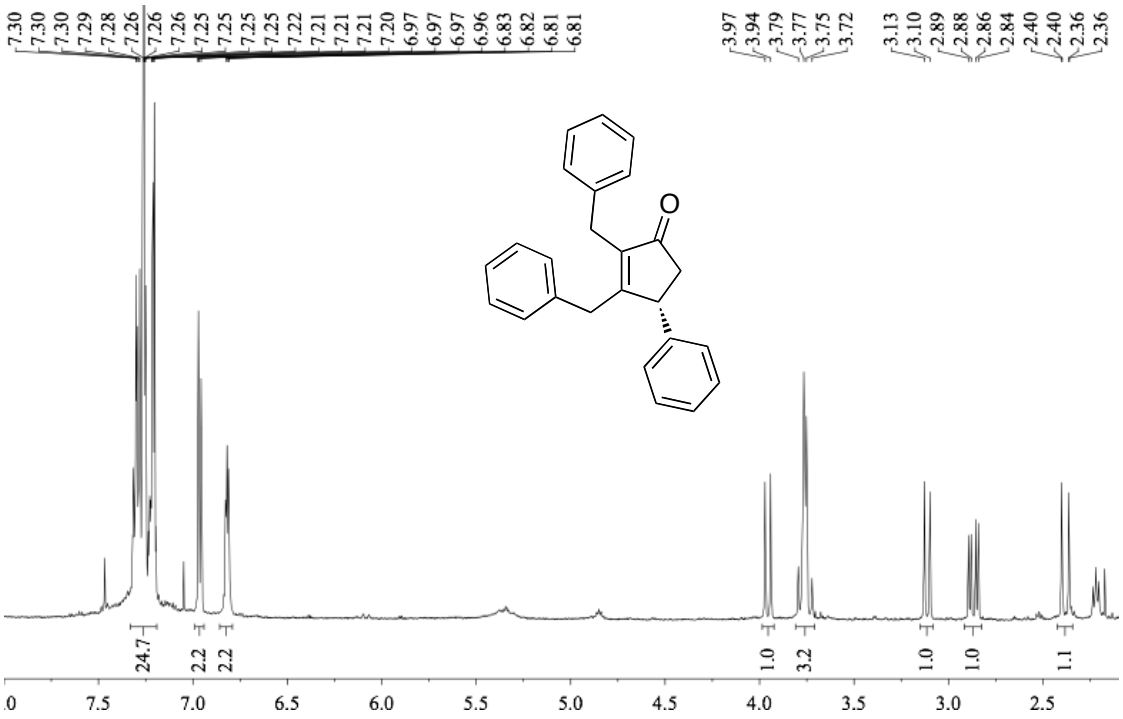


400 MHz ^{1}H-NMR in $CDCl_3$

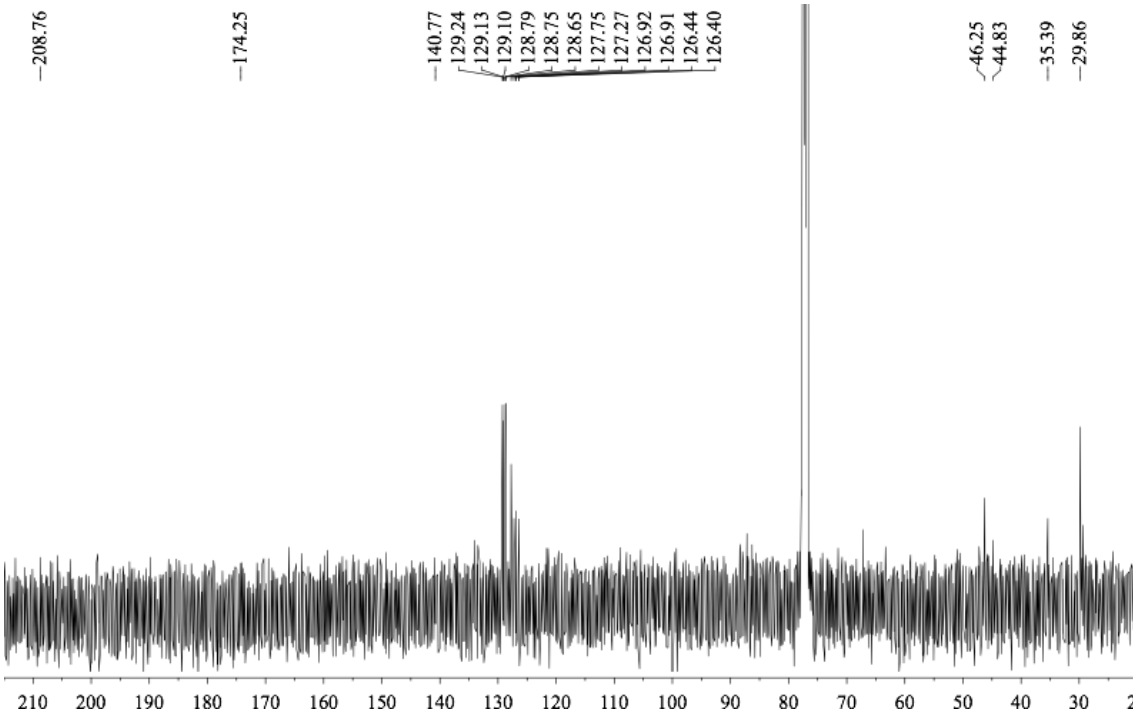


101 MHz ^{13}C-NMR in $CDCl_3$

2,3-Dibenzyl-4-phenylcyclopent-2-enone (4.34)

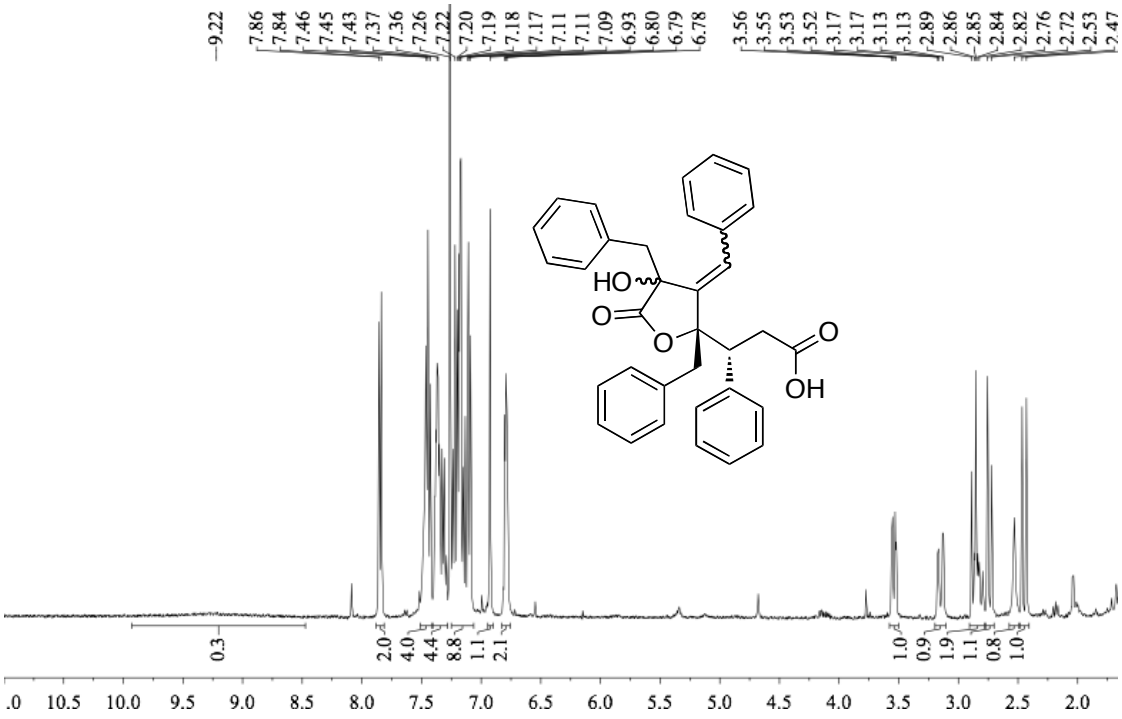


500 MHz ^{1}H-NMR in $CDCl_3$



101 MHz ^{13}C-NMR in $CDCl_3$

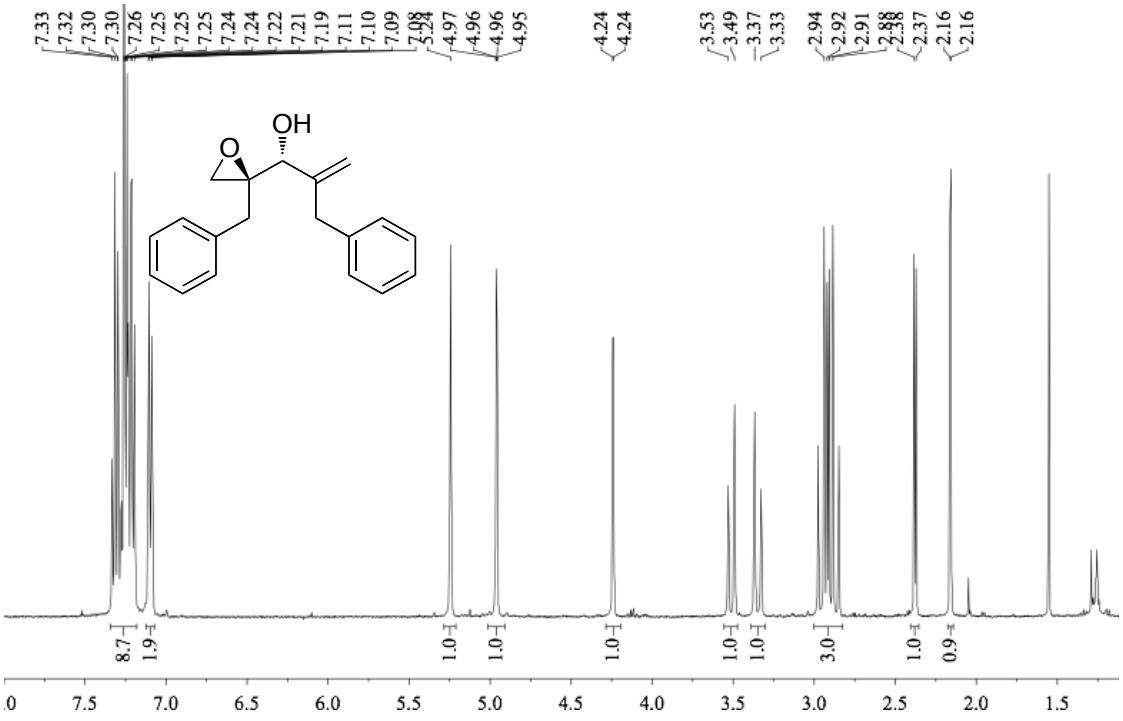
3-(2,4-Dibenzyl-3-benzylidene-4-hydroxy-5-oxotetrahydrofuran-2-yl)-3-phenylpropanoic acid (4.35)



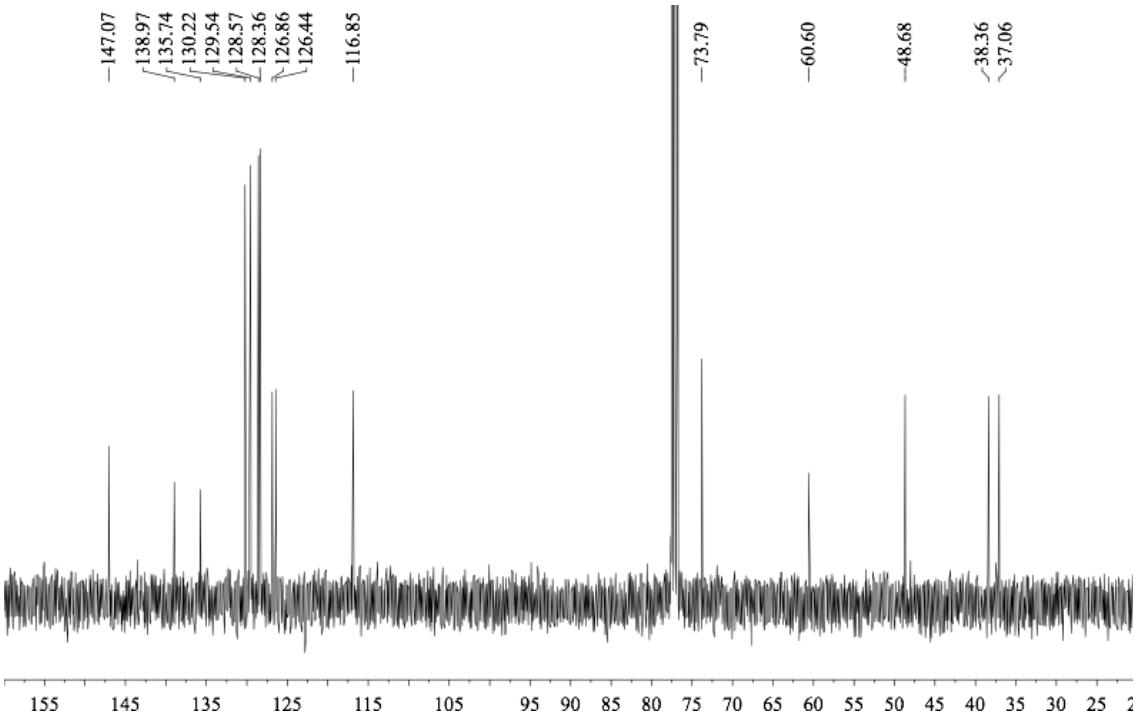
400 MHz ^{1}H-NMR in $CDCl_3$

9.2.4 Studies on a Linear Approach Towards Ophiodilactone A and B

(*R*)-2-Benzyl-1-((*S*)-2-benzyloxiran-2-yl)prop-2-en-1-ol (5.14)

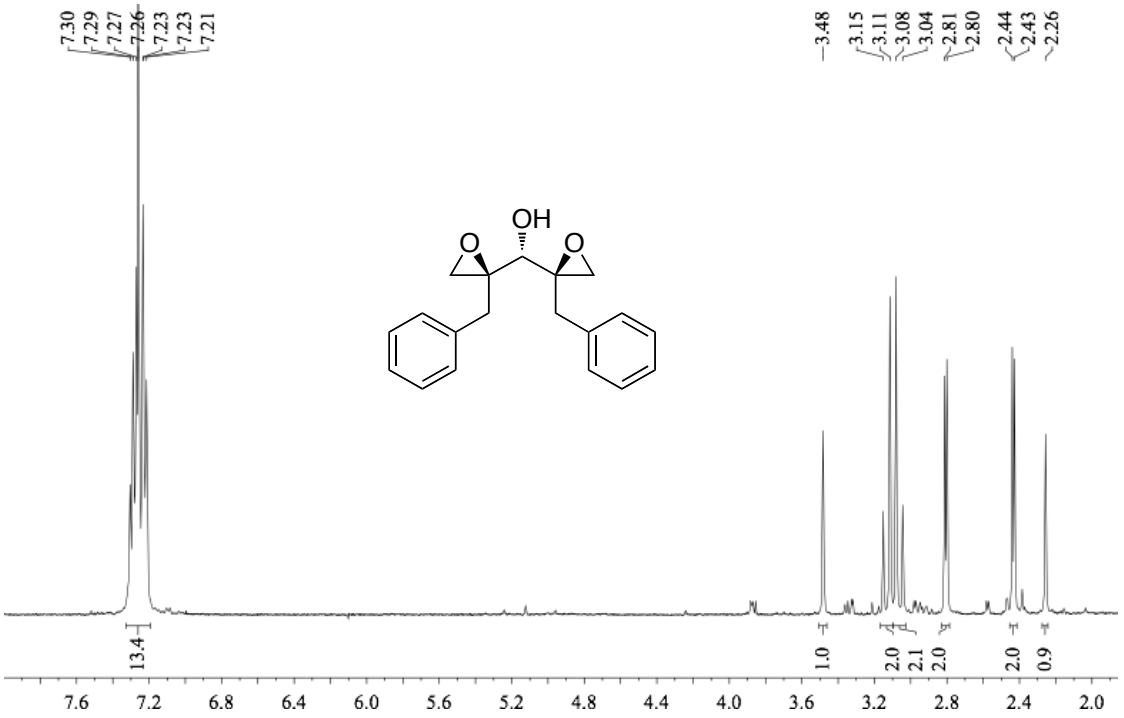


400 MHz ^{1}H-NMR in $CDCl_3$

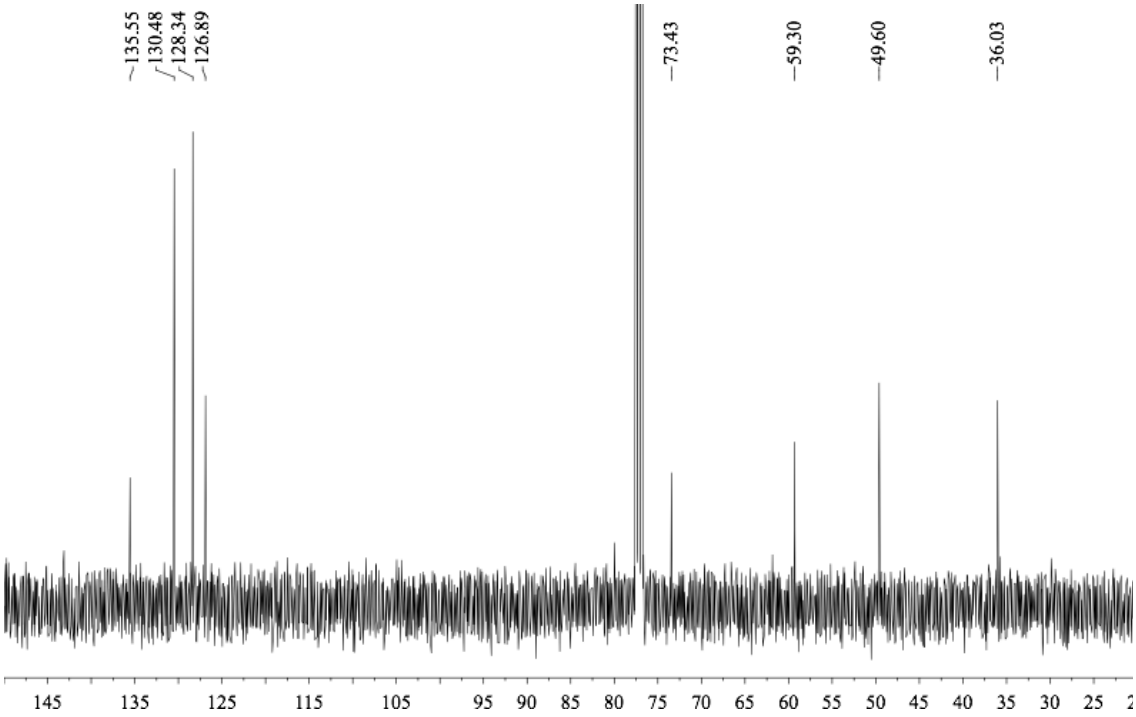


101 MHz ^{13}C-NMR in $CDCl_3$

(*S*)-((*R*)-2-Benzyloxiran-2-yl)((*S*)-2-benzyloxiran-2-yl)methanol

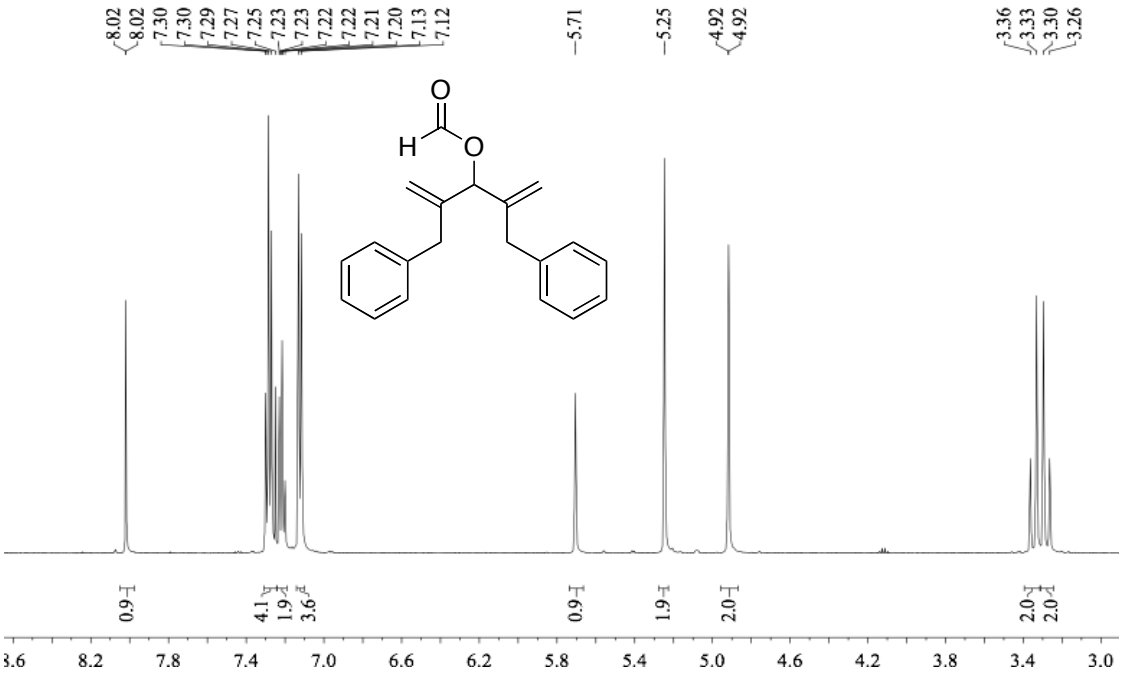


400 MHz ^{1}H-NMR in $CDCl_3$

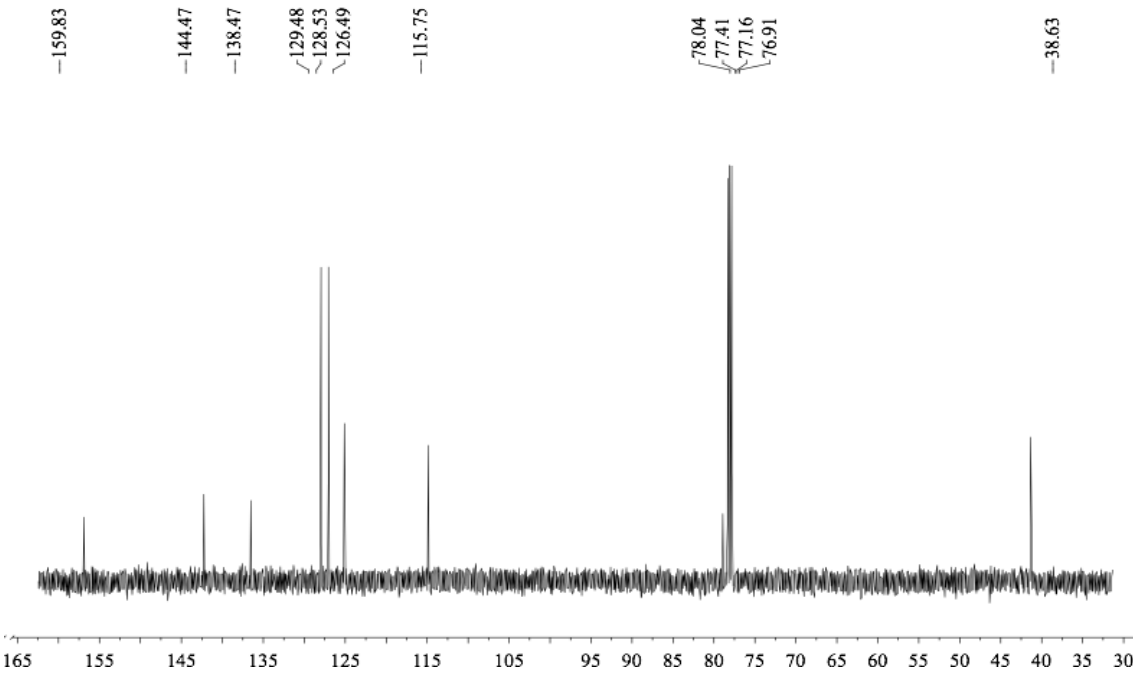


101 MHz ^{13}C-NMR in $CDCl_3$

2,4-Dibenzylpenta-1,4-dien-3-yl formate (5.21)



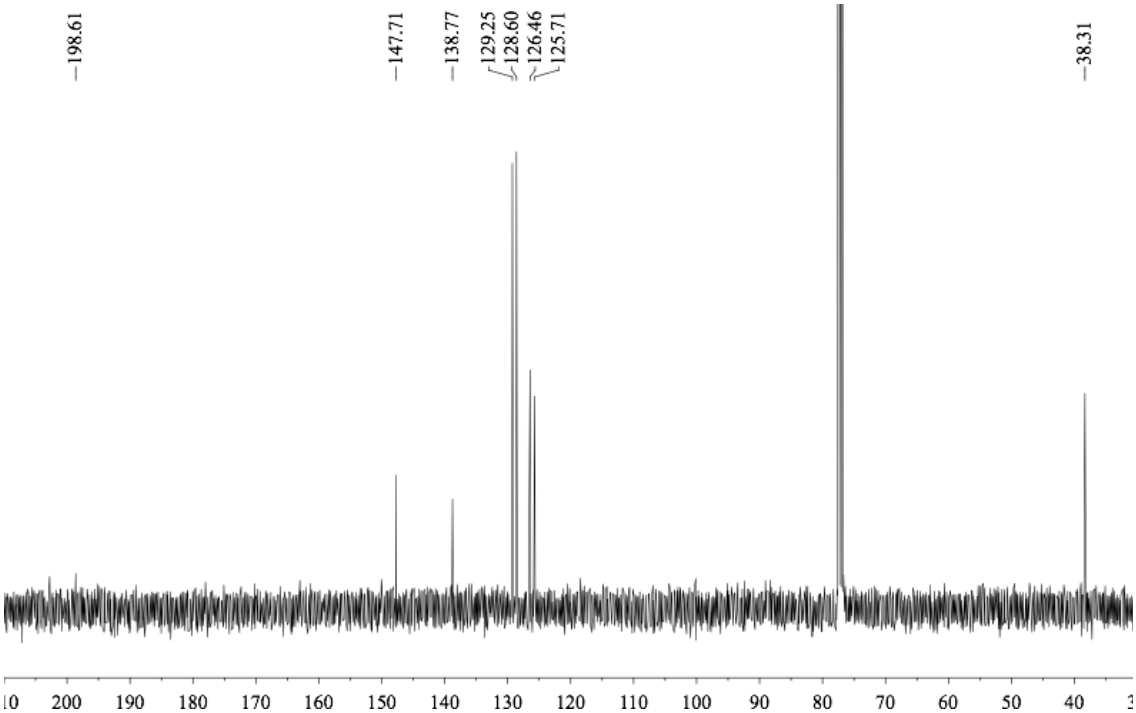
500 MHz ^{1}H-NMR in $CDCl_3$



126 MHz ^{13}C-NMR in $CDCl_3$

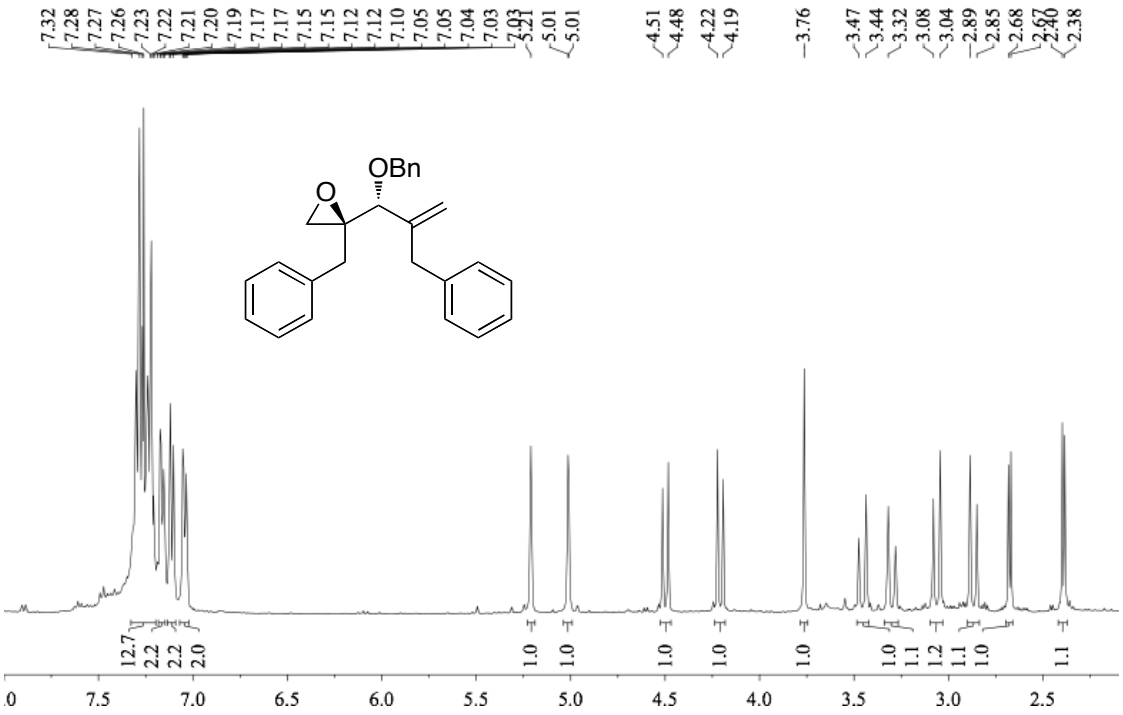
2,4-Dibenzylpenta-1,4-dien-3-one (5.25)

400 MHz ^{1}H-NMR in $CDCl_3$

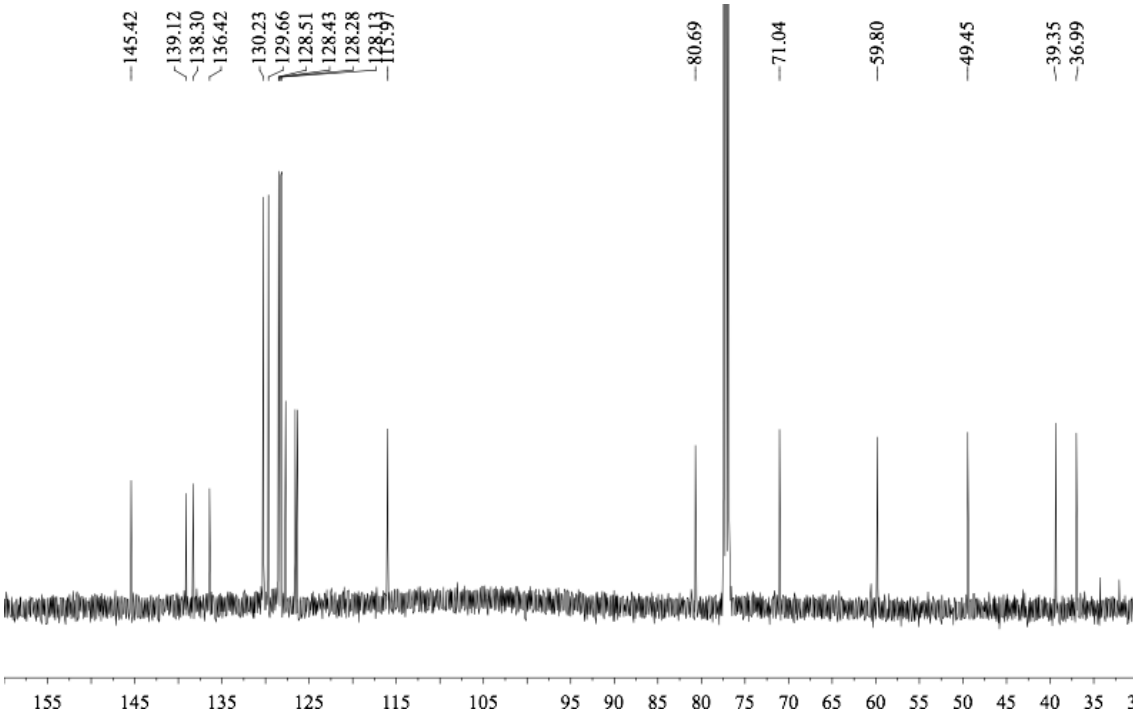


101 MHz ^{13}C-NMR in $CDCl_3$

(*S*)-2-Benzyl-2-((*R*)-2-benzyl-1-(benzyloxy)allyl)oxirane (5.27)

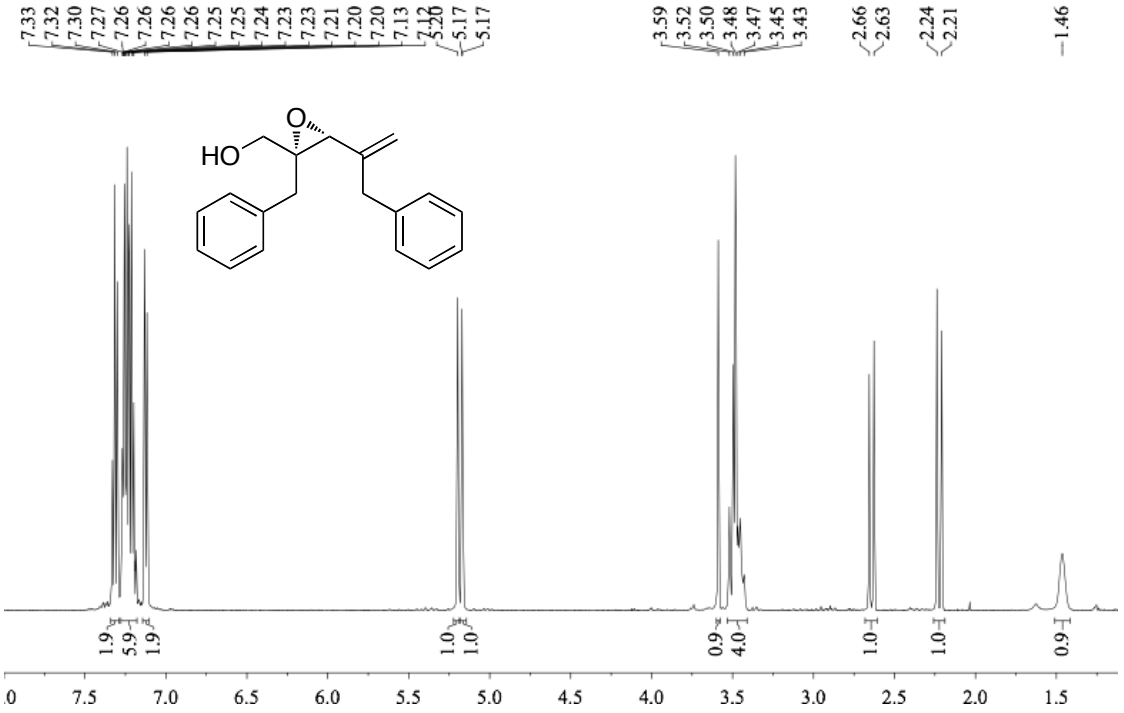


400 MHz ^{1}H-NMR in $CDCl_3$

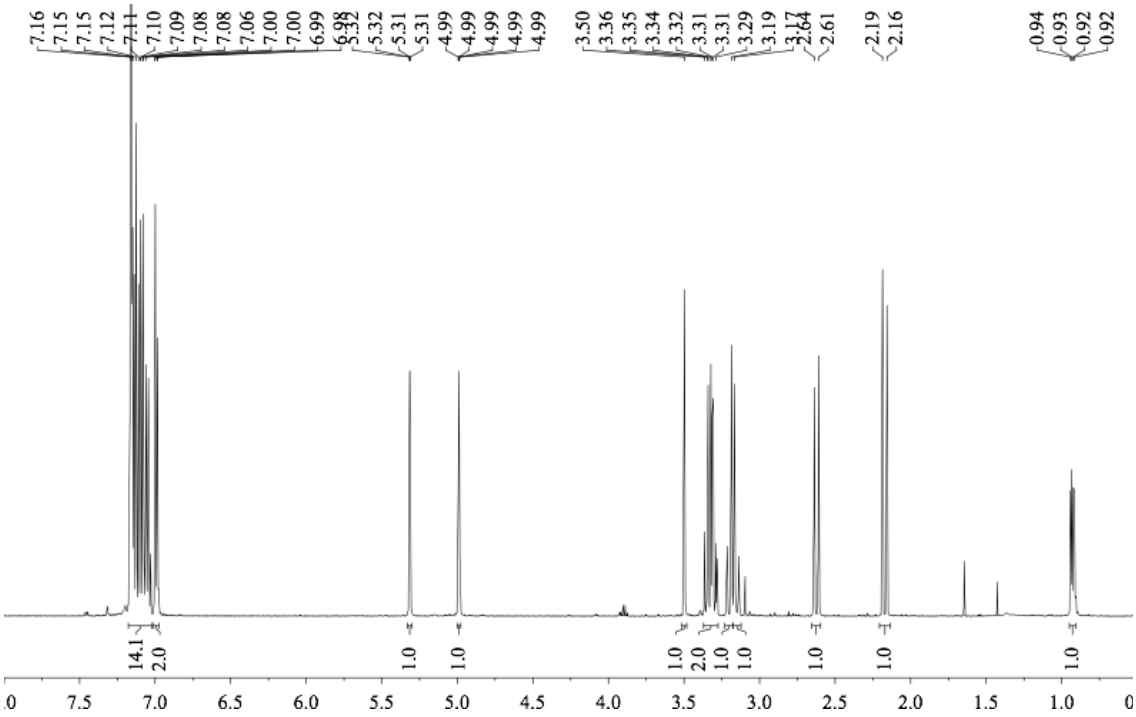


126 MHz ^{13}C-NMR in $CDCl_3$

((2*R*,3*R*)-2-Benzyl-3-(3-phenylprop-1-en-2-yl)oxiran-2-yl)methanol (5.28)

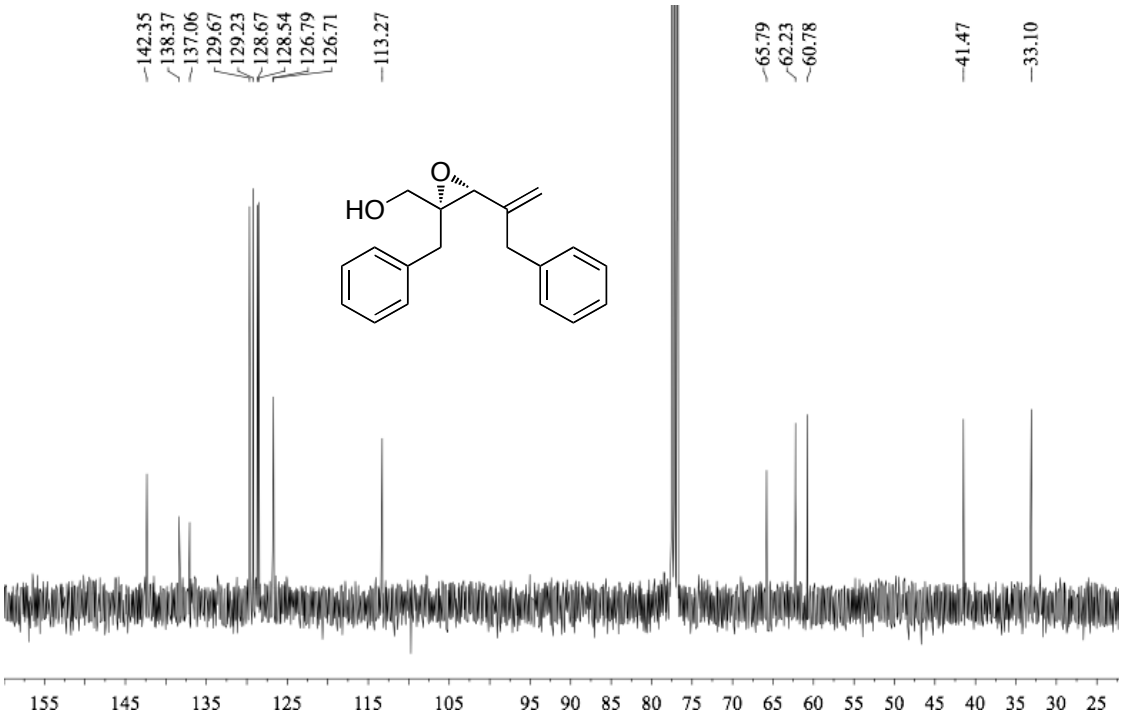


500 MHz ^{1}H-NMR in $CDCl_3$

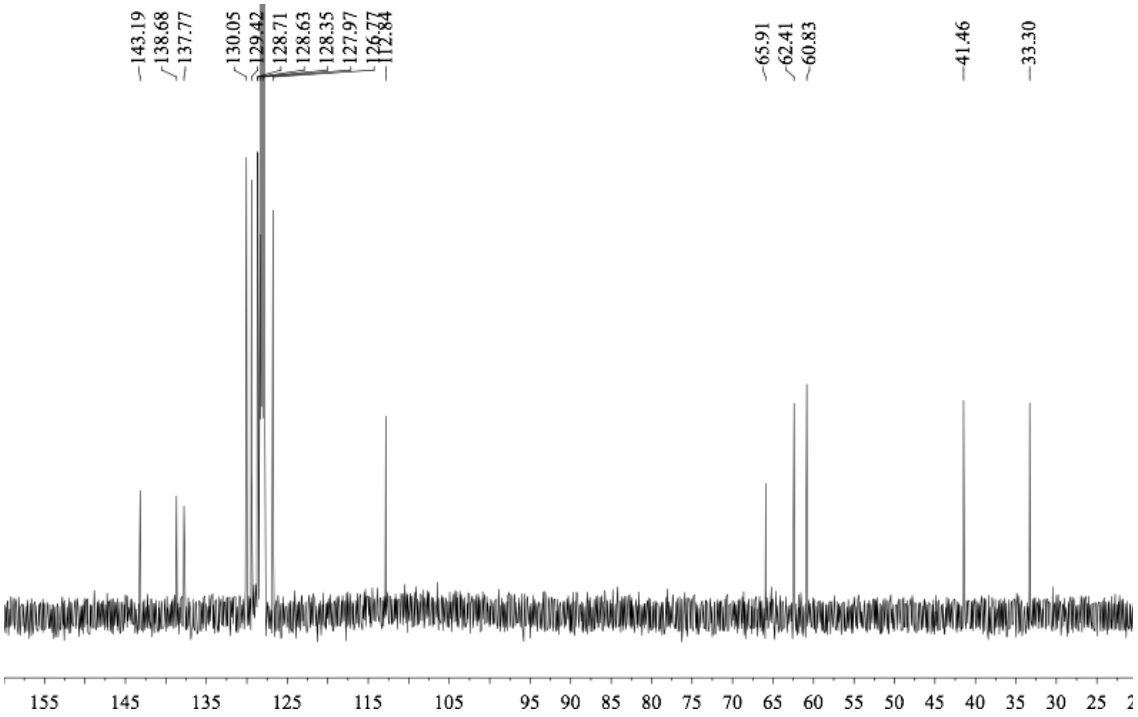


500 MHz ^{1}H-NMR in C_6D_6

((2*R*,3*R*)-2-Benzyl-3-(3-phenylprop-1-en-2-yl)oxiran-2-yl)methanol (5.28)

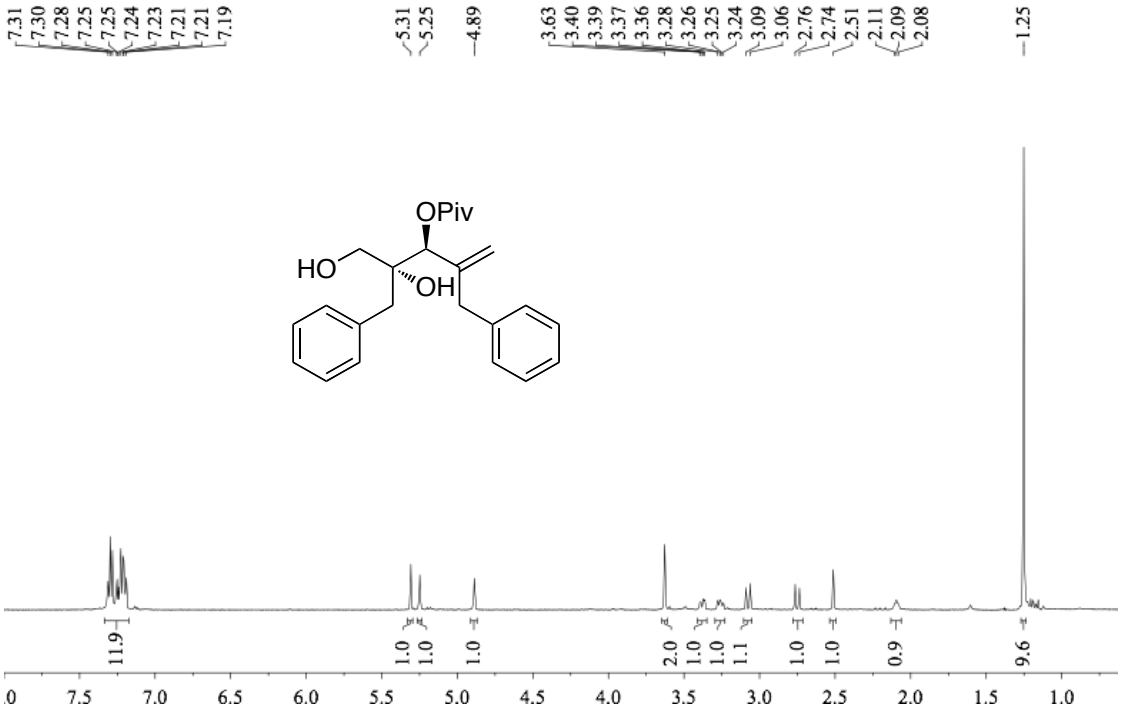


101 MHz ^{13}C-NMR in $CDCl_3$

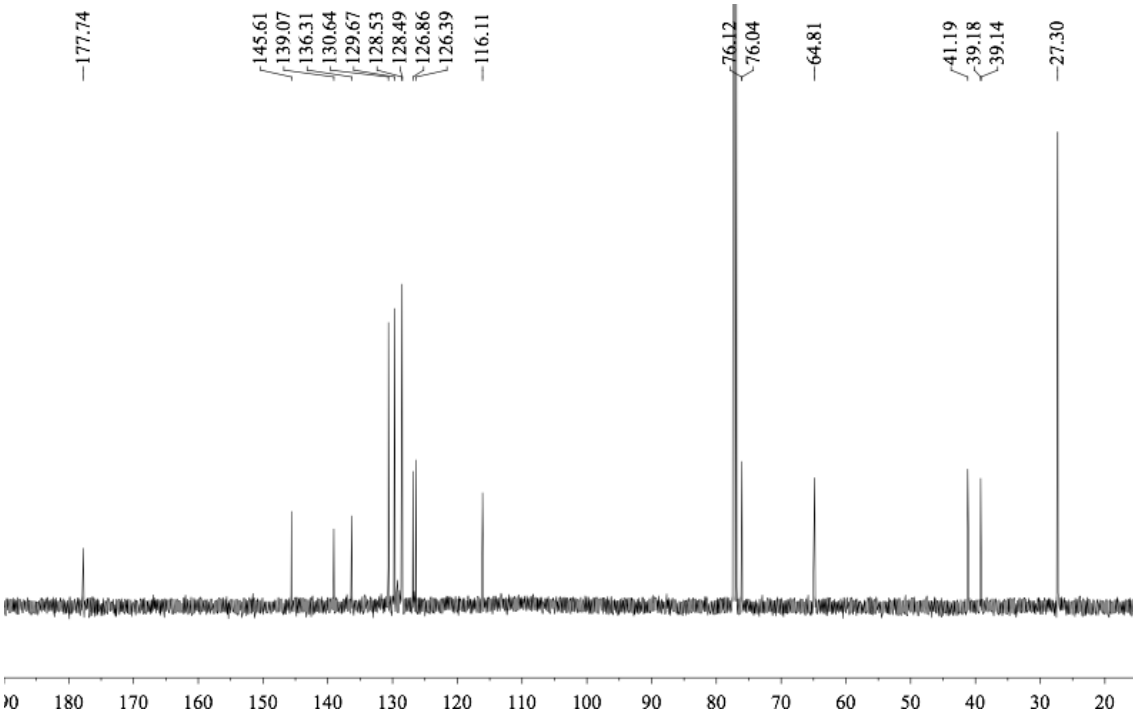


126 MHz ^{13}C-NMR in C_6D_6

(3*S*,4*R*)-2,4-Dibenzyl-4,5-dihydroxypent-1-en-3-yl pivalate (5.29)

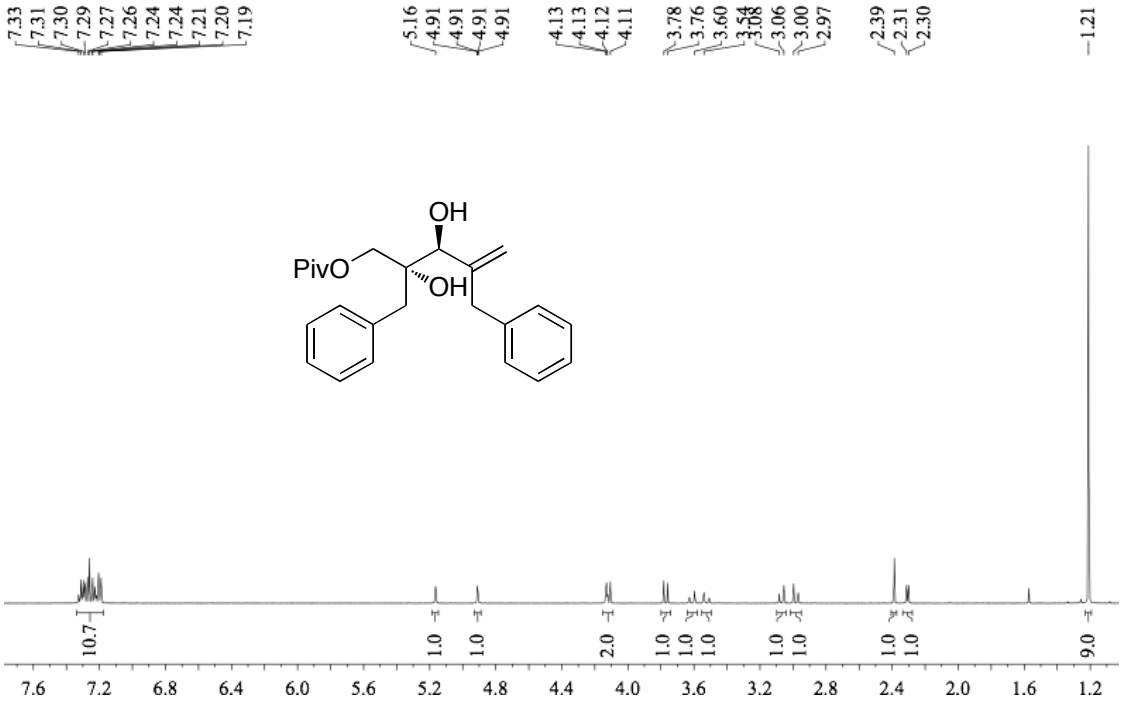


500 MHz ^{1}H-NMR in $CDCl_3$

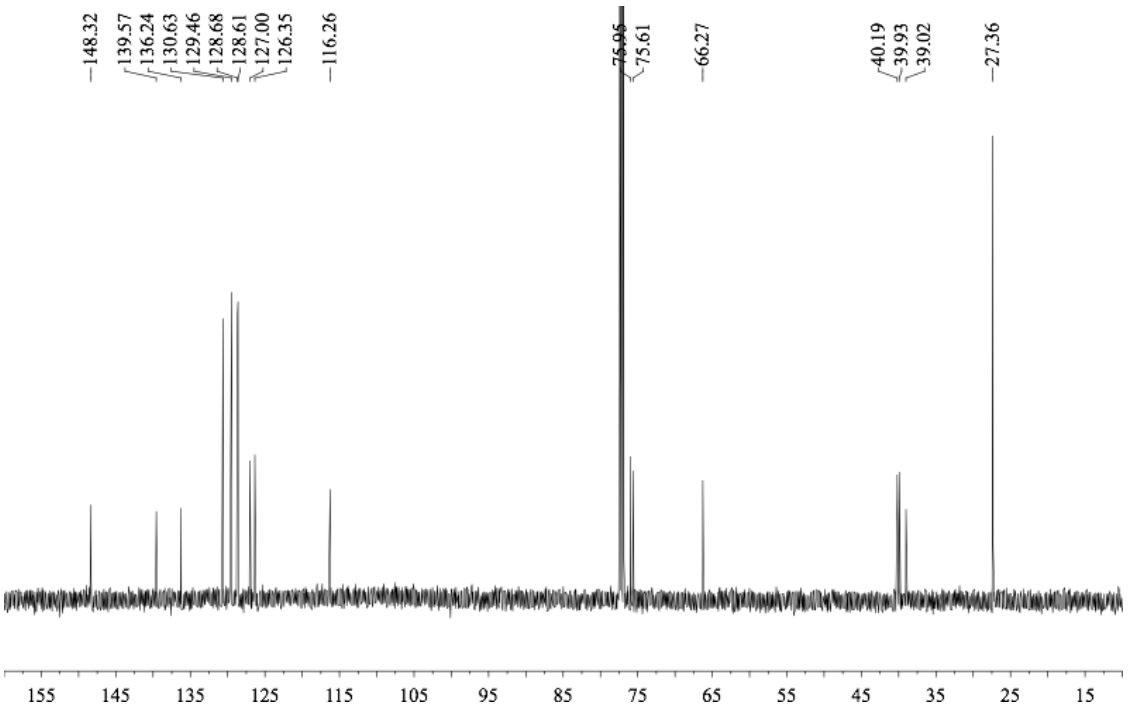


126 MHz ^{13}C-NMR in $CDCl_3$

((2*R*,3*S*)-2,4-Dibenzyl-2,3-dihydroxypent-4-en-1-yl pivalate (5.30)

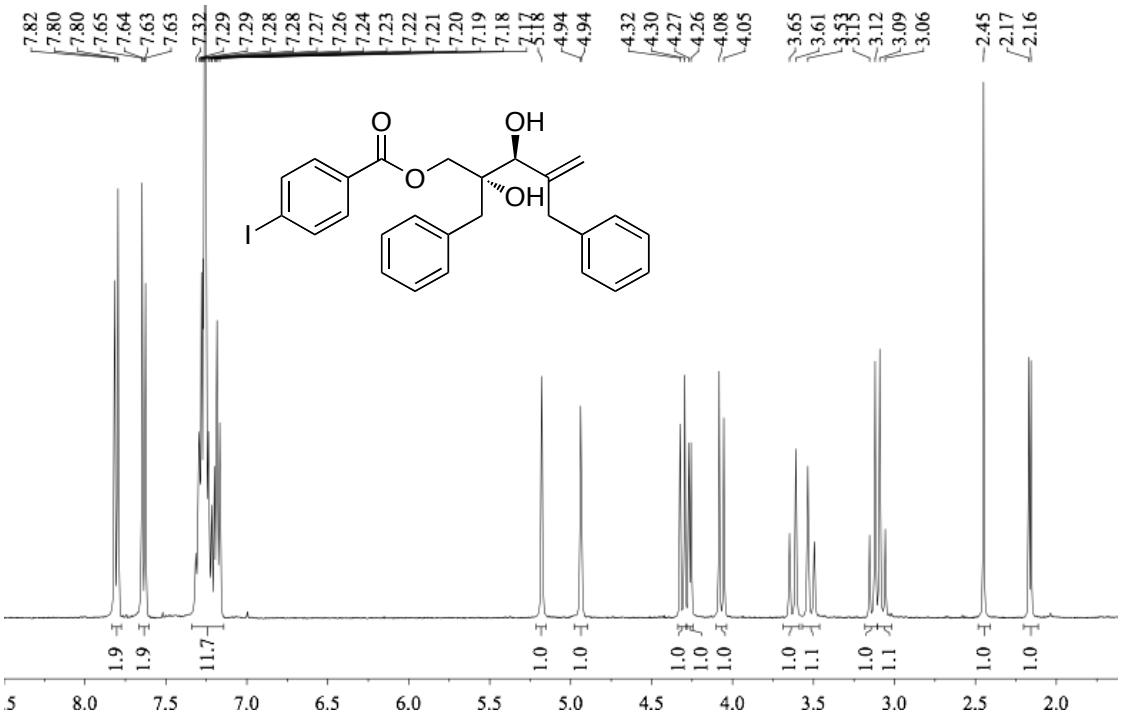


500 MHz ^{1}H-NMR in $CDCl_3$

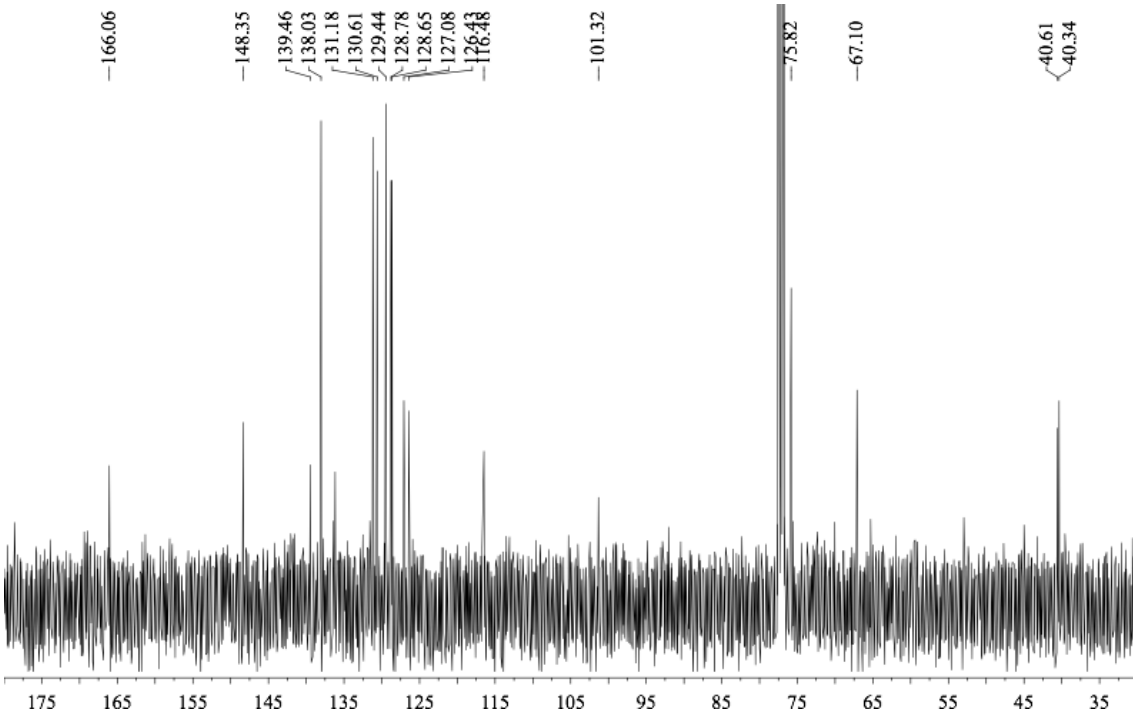


126 MHz ^{13}C-NMR in $CDCl_3$

(2*R*,3*S*)-2,4-Dibenzyl-2,3-dihydroxypent-4-en-1-yl 4-iodobenzoate (5.34)

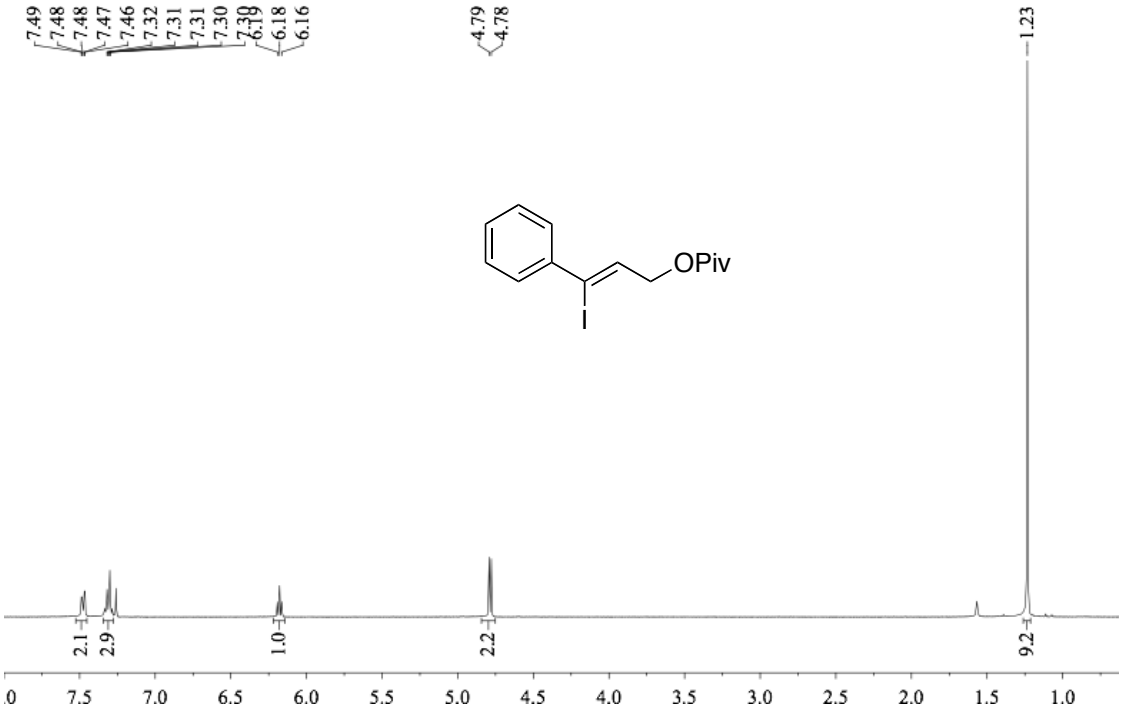


400 MHz ^{1}H-NMR in $CDCl_3$

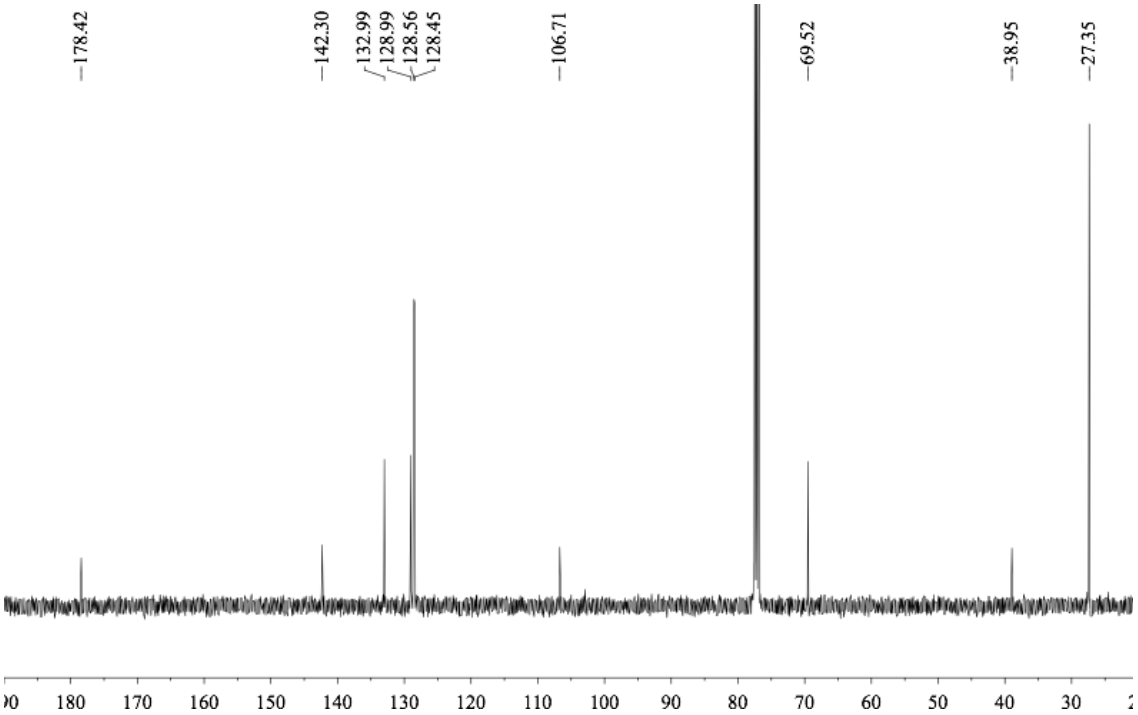


101 MHz ^{13}C-NMR in $CDCl_3$

(*Z*)-3-Iodo-3-phenylallyl pivalate (5.37)

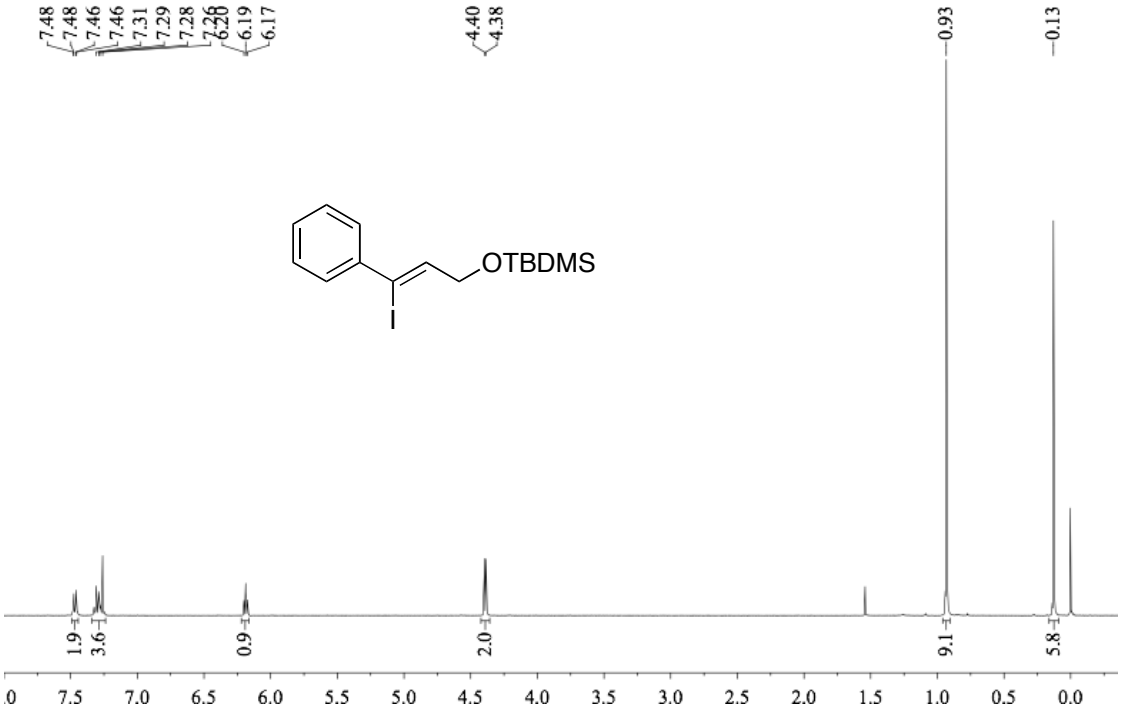


400 MHz ^{1}H-NMR in $CDCl_3$

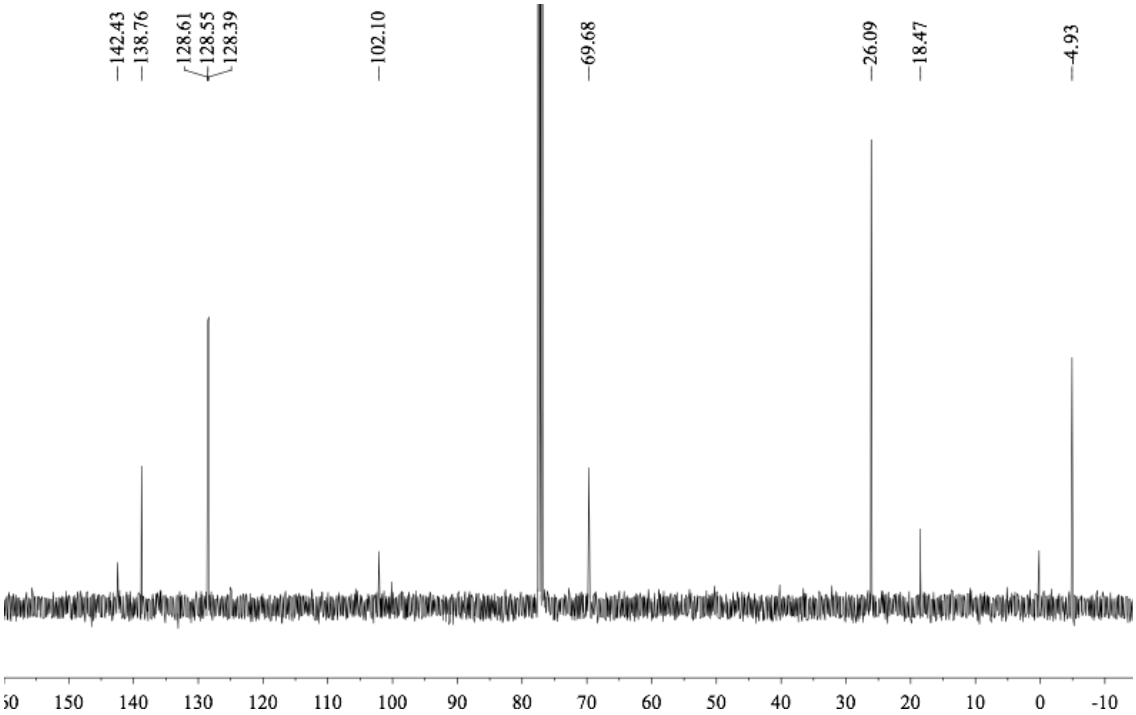


101 MHz ^{13}C-NMR in $CDCl_3$

(*Z*)-*tert*-Butyl((3-iodo-3-phenylallyl)oxy)dimethylsilane (5.38)

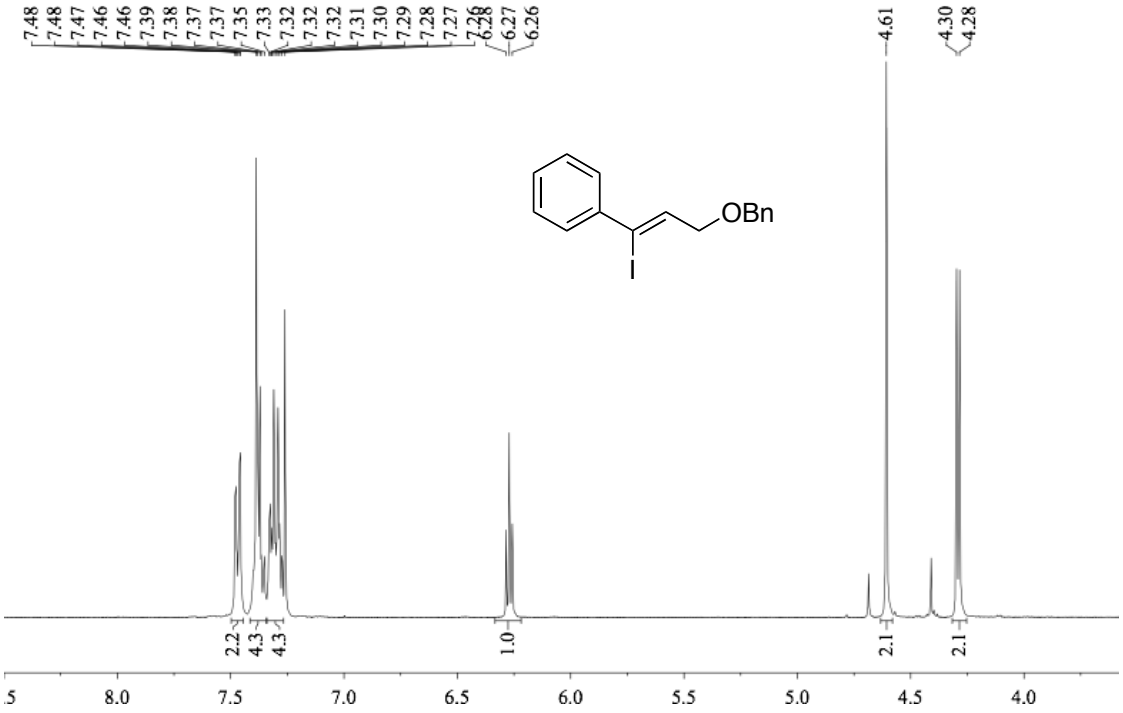


400 MHz ^{1}H-NMR in $CDCl_3$

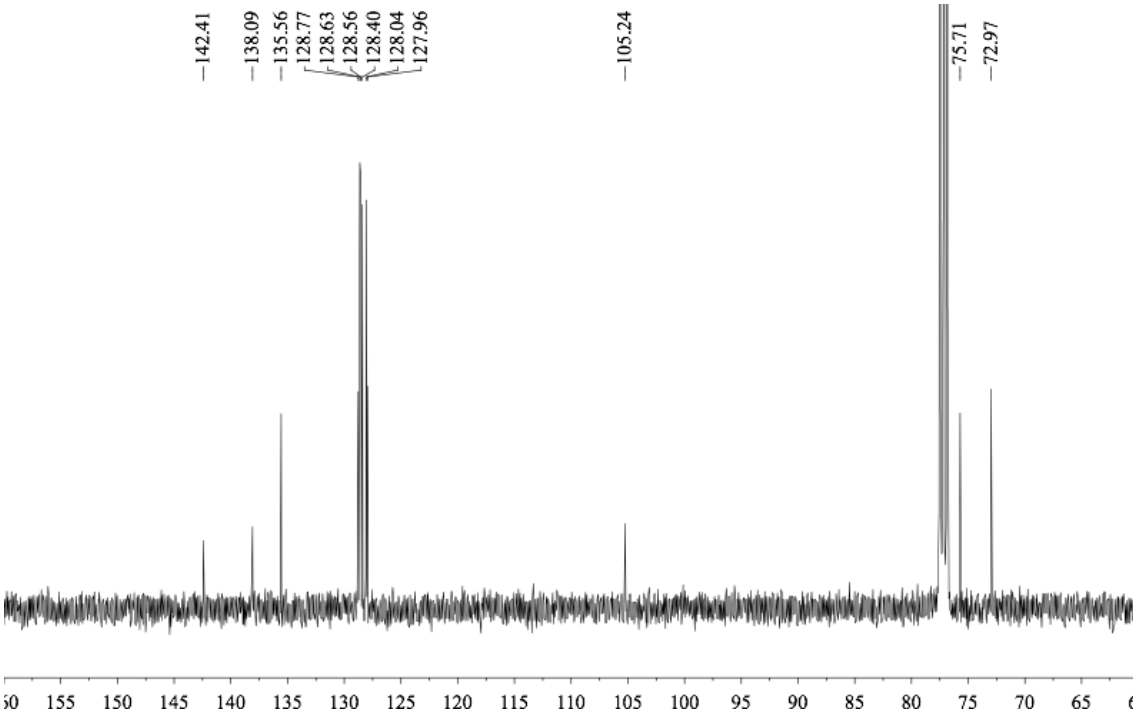


101 MHz ^{13}C-NMR in $CDCl_3$

(*Z*)-(3-(Benzyloxy)-1-iodoprop-1-en-1-yl)benzene (5.39)

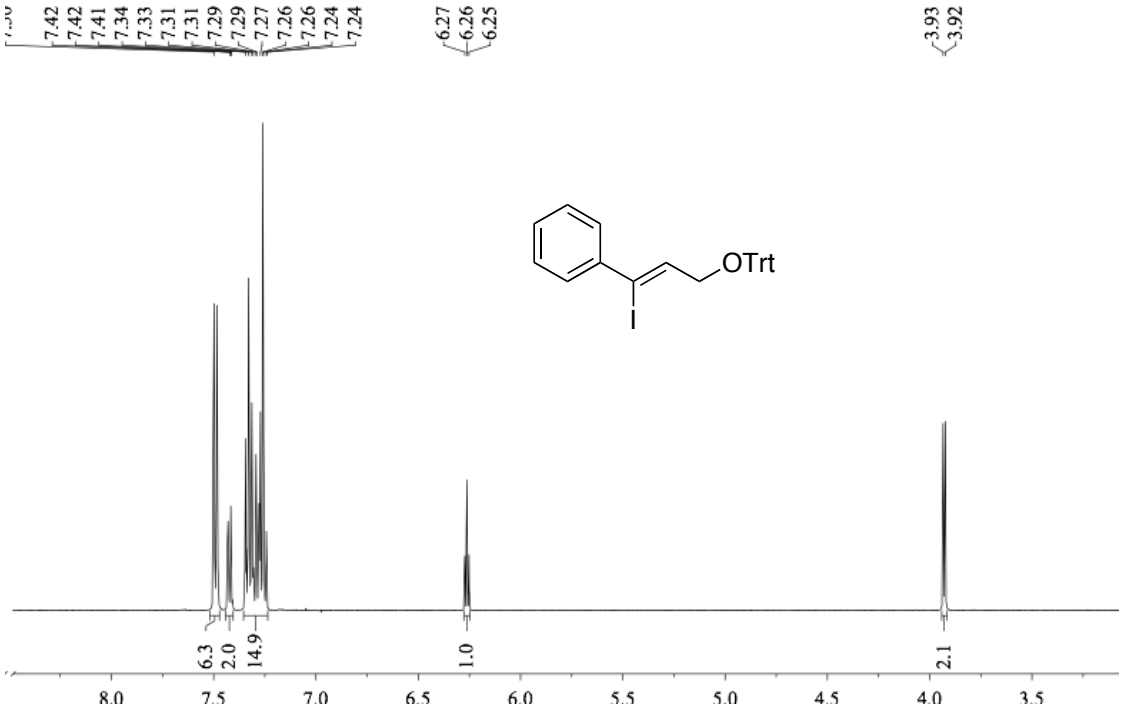


400 MHz ^{1}H-NMR in $CDCl_3$

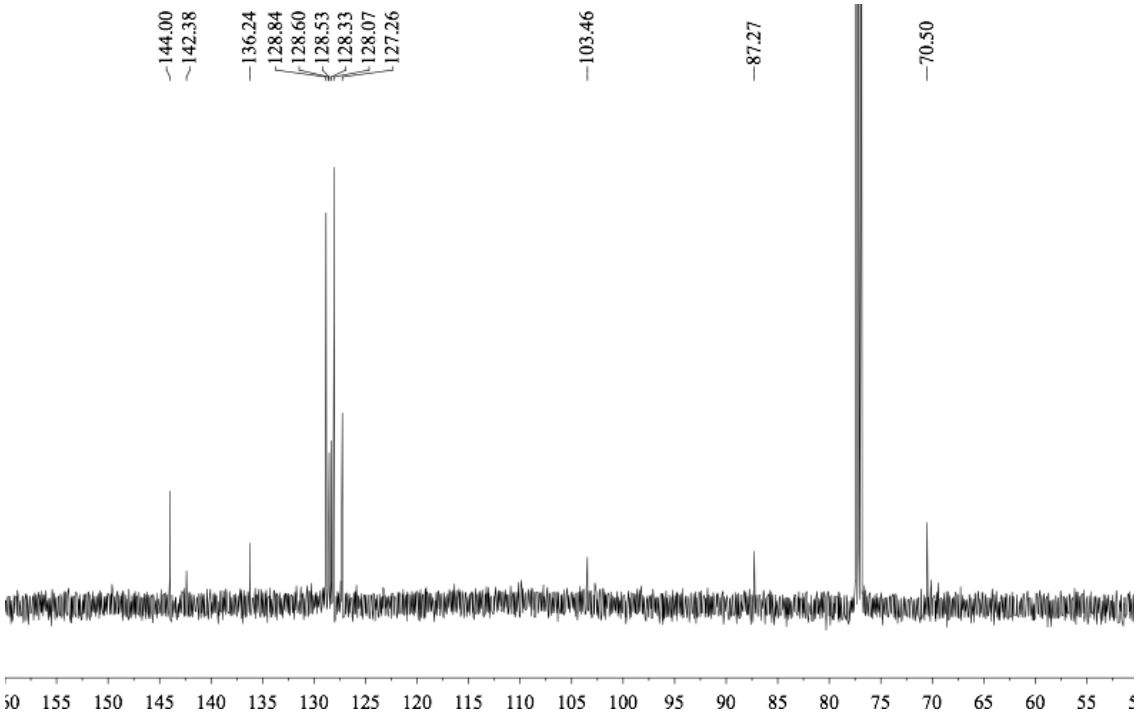


101 MHz ^{13}C-NMR in $CDCl_3$

(*Z*)-(((3-Iodo-3-phenylallyl)oxy)methanetriyl)tribenzene (5.40)

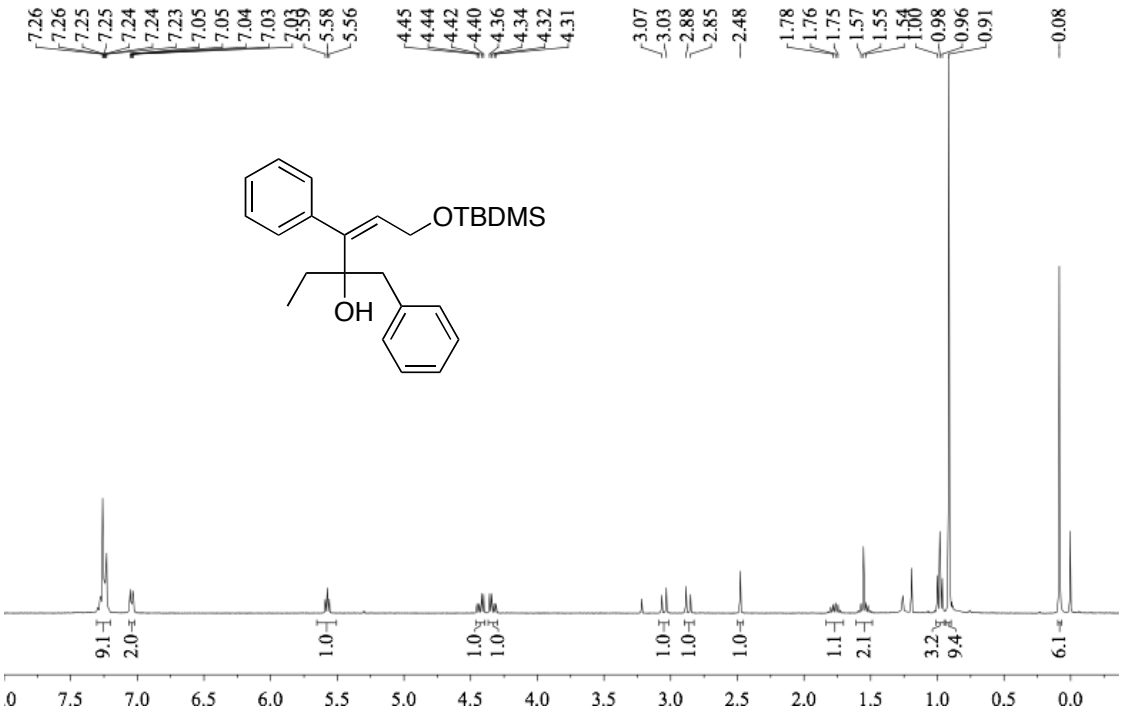


500 MHz ^{1}H-NMR in $CDCl_3$

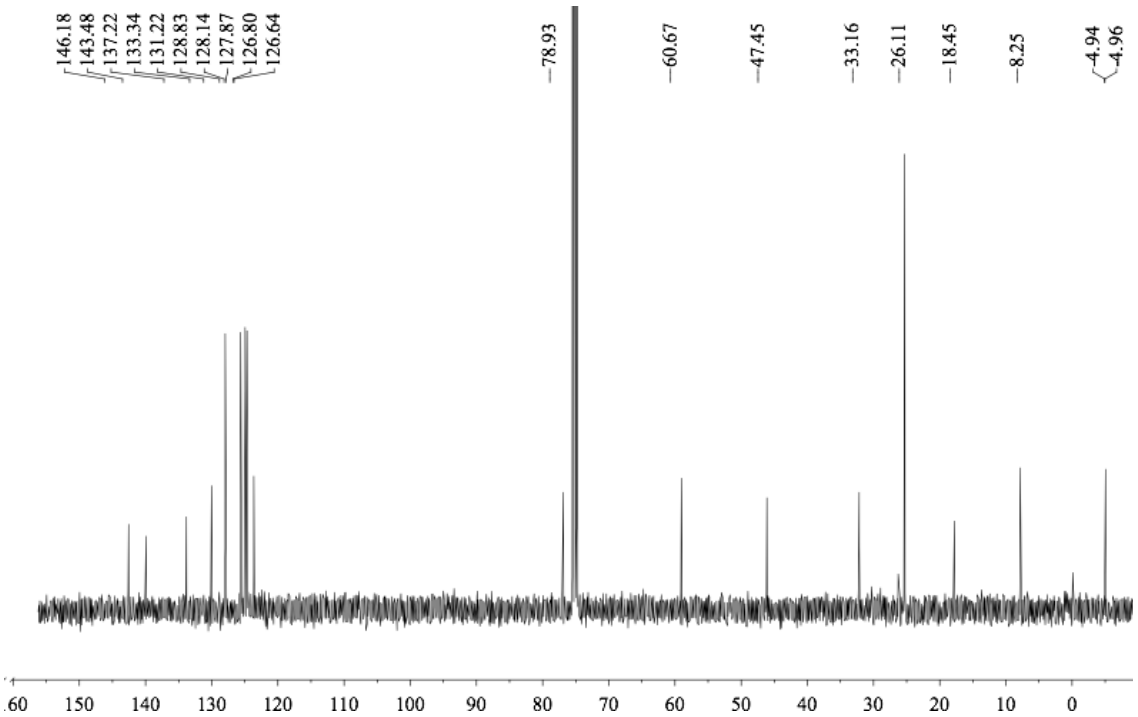


126 MHz ^{13}C-NMR in $CDCl_3$

(*Z*)-3-Benzyl-6-((*tert*-butyldimethylsilyl)oxy)-4-phenylhex-4-en-3-ol (5.41)

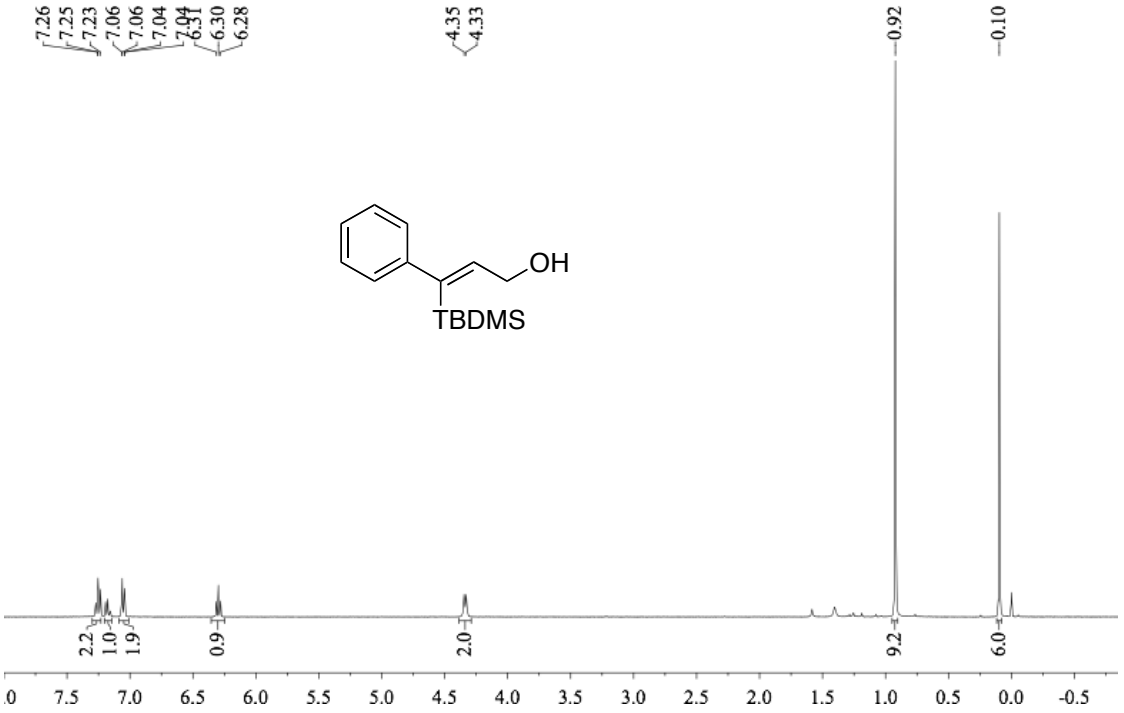


400 MHz ^{1}H-NMR in $CDCl_3$

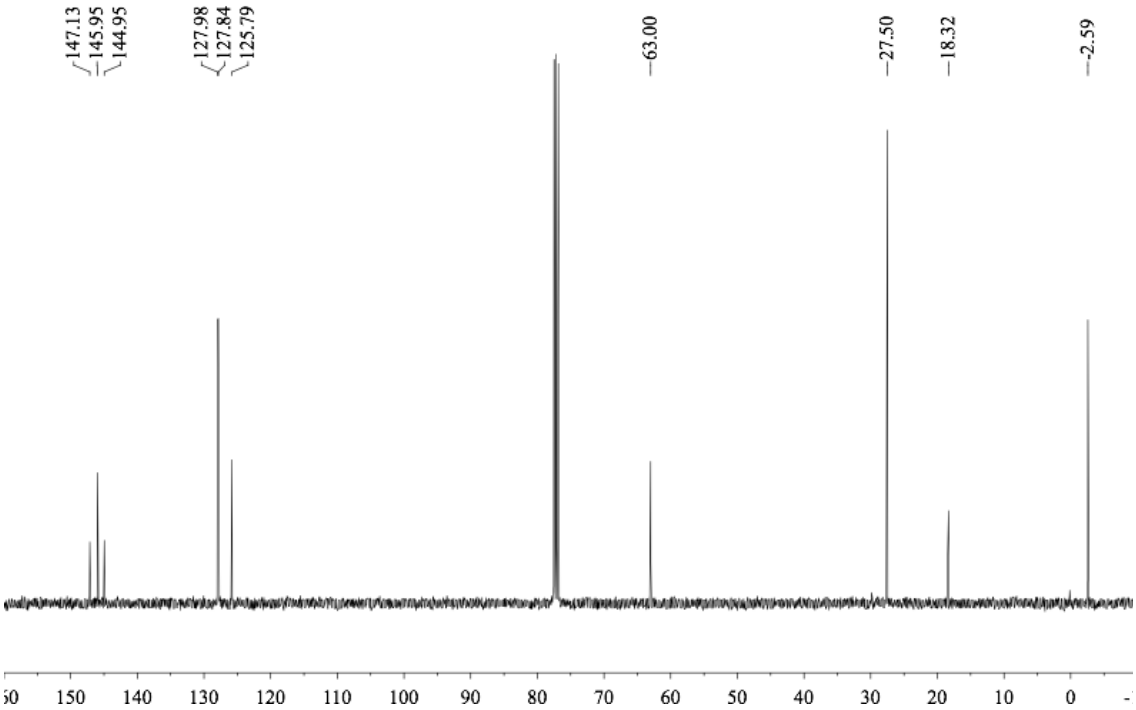


101 MHz ^{13}C-NMR in $CDCl_3$

(*Z*)-3-(*tert*-Butyldimethylsilyl)-3-phenylprop-2-en-1-ol (5.42)

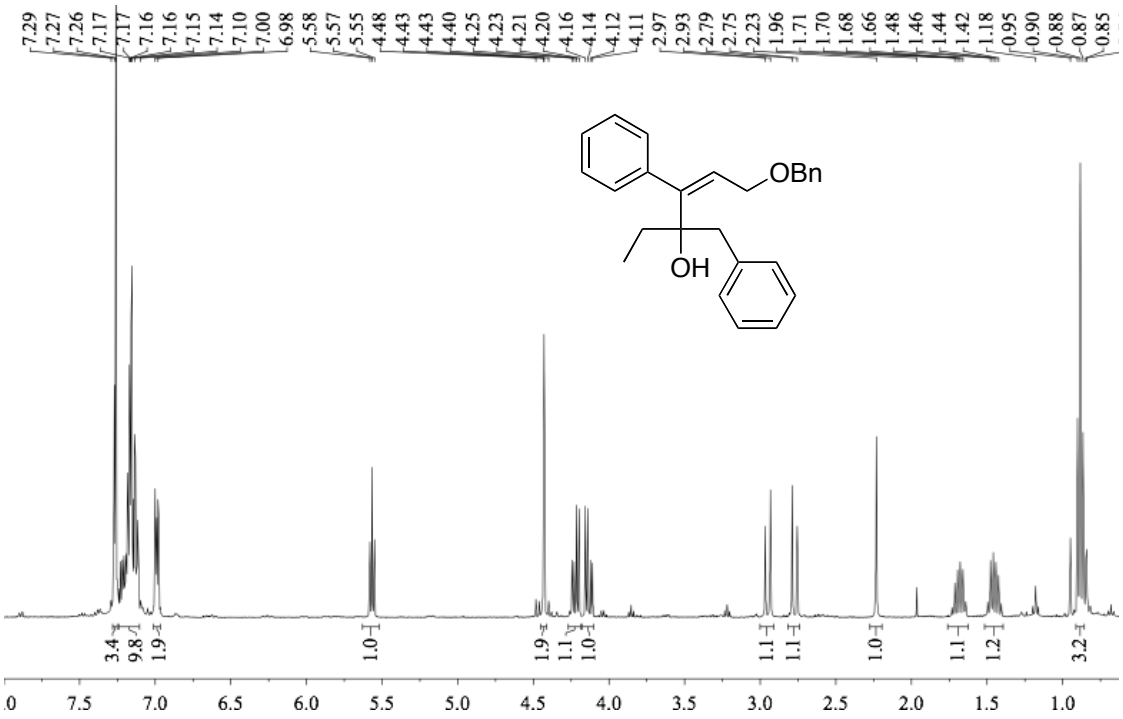


400 MHz ^{1}H-NMR in $CDCl_3$

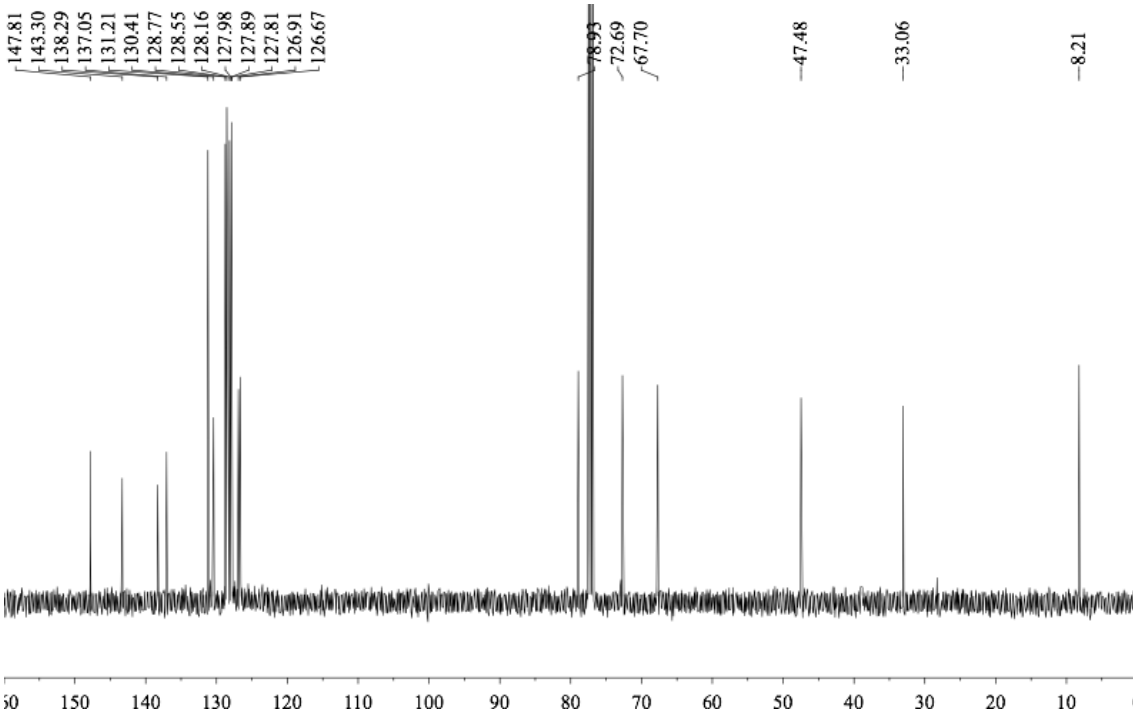


101 MHz ^{13}C-NMR in $CDCl_3$

(*Z*)-3-Benzyl-6-(benzyloxy)-4-phenylhex-4-en-3-ol (5.43)

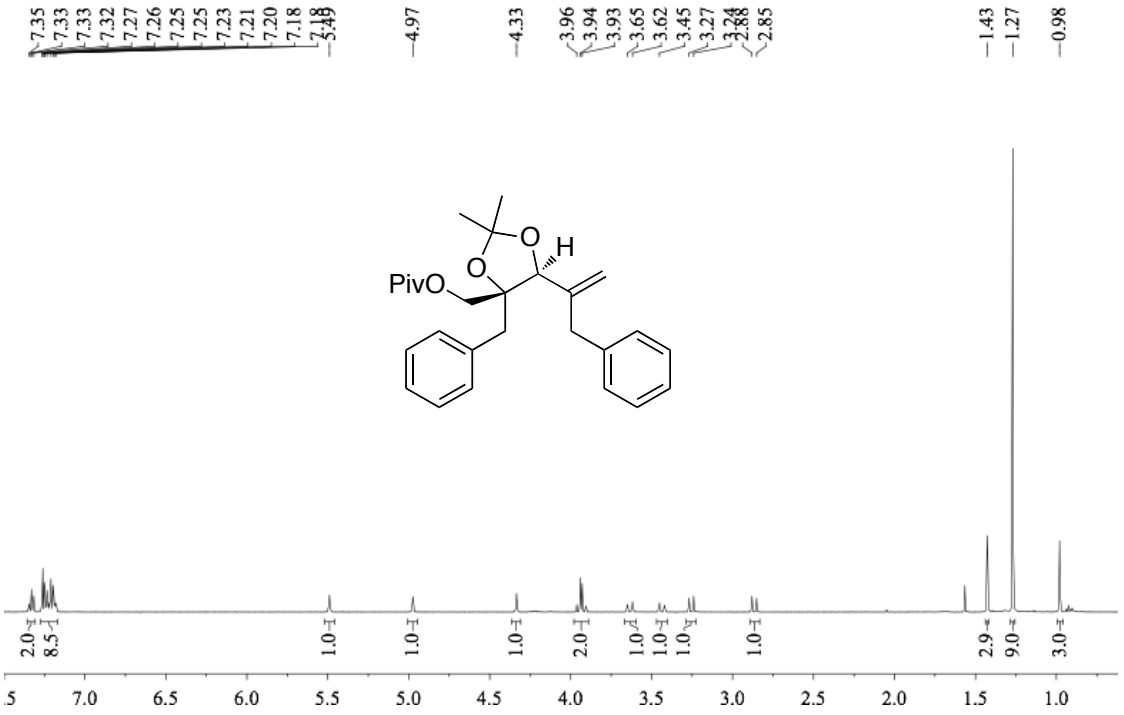


400 MHz ^{1}H-NMR in $CDCl_3$

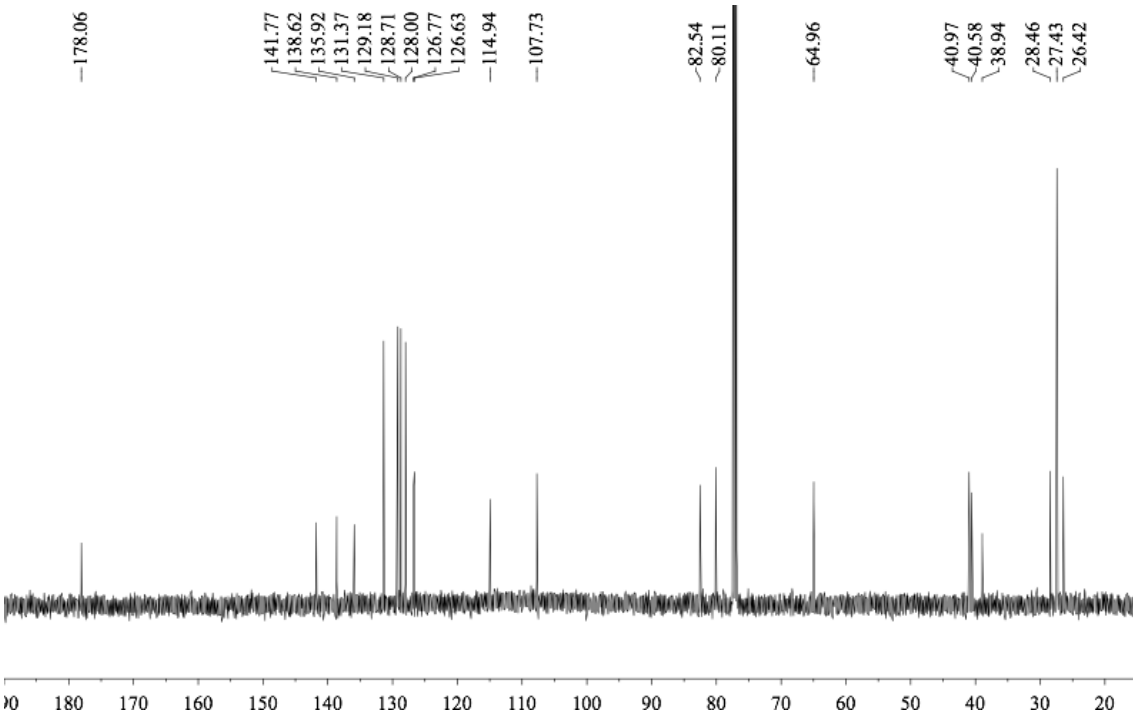


101 MHz ^{13}C-NMR in $CDCl_3$

((4*R*,5*S*)-4-Benzyl-2,2-dimethyl-5-(3-phenylprop-1-en-2-yl)-1,3-dioxolan-4-yl)methyl pivalate (5.44)

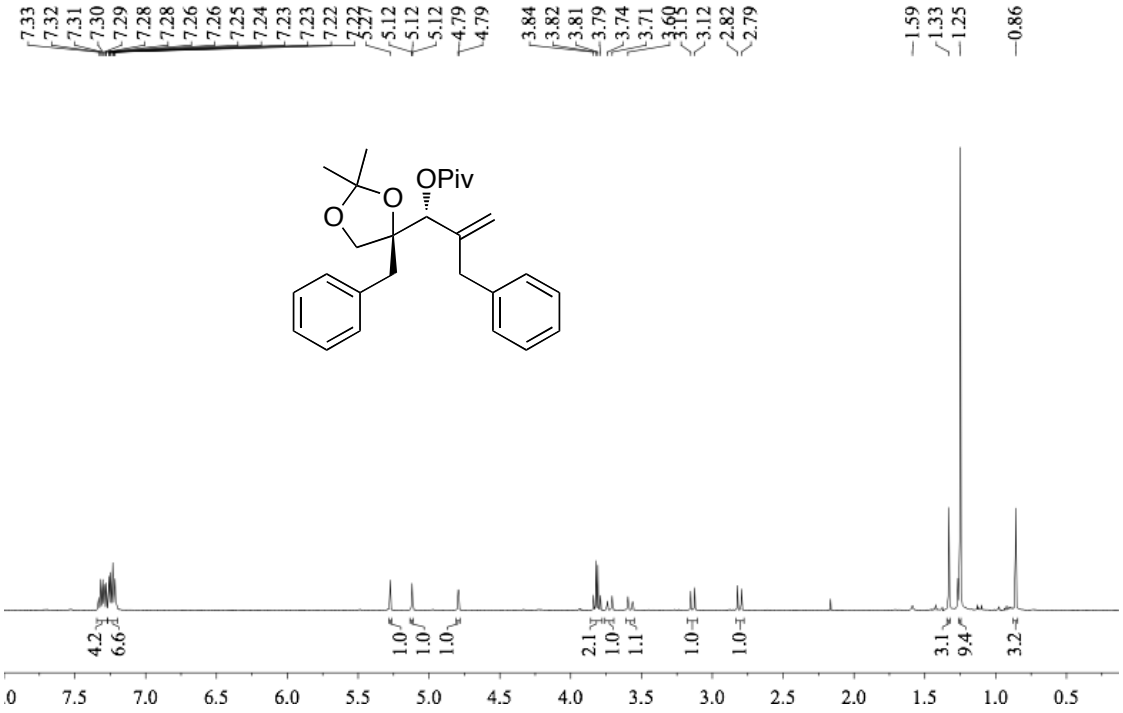


500 MHz ^{1}H-NMR in $CDCl_3$

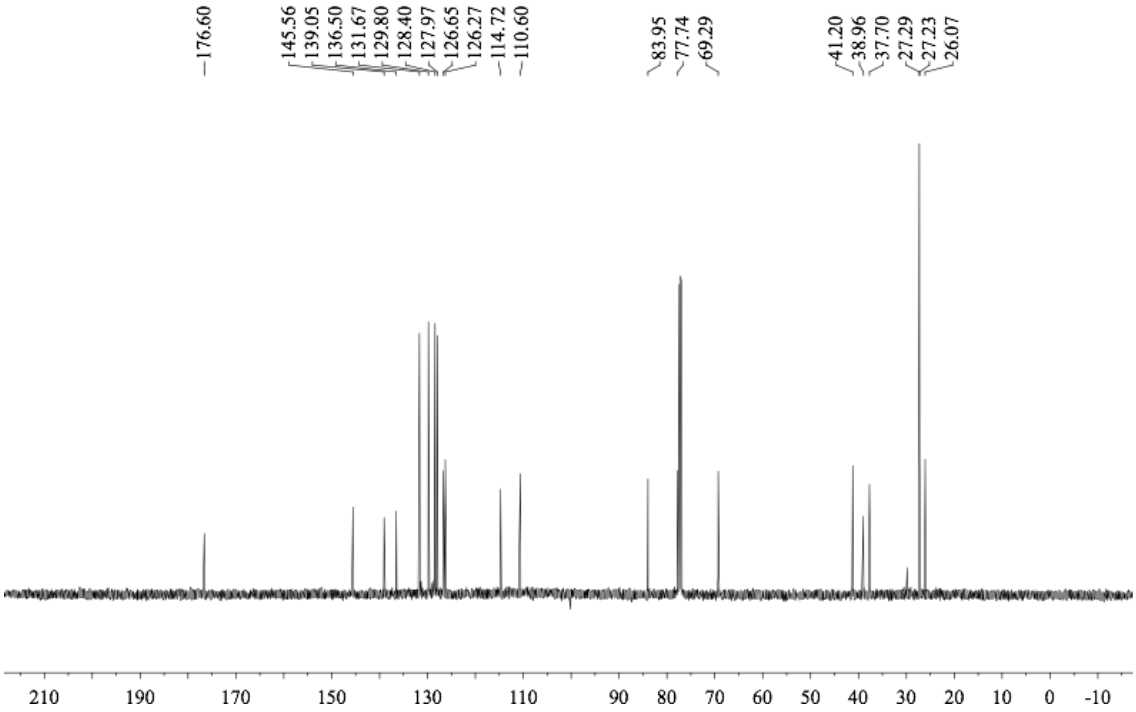


126 MHz ^{13}C-NMR in $CDCl_3$

(*R*)-2-Benzyl-1-((*S*)-4-benzyl-2,2-dimethyl-1,3-dioxolan-4-yl)allyl pivalate (5.45)

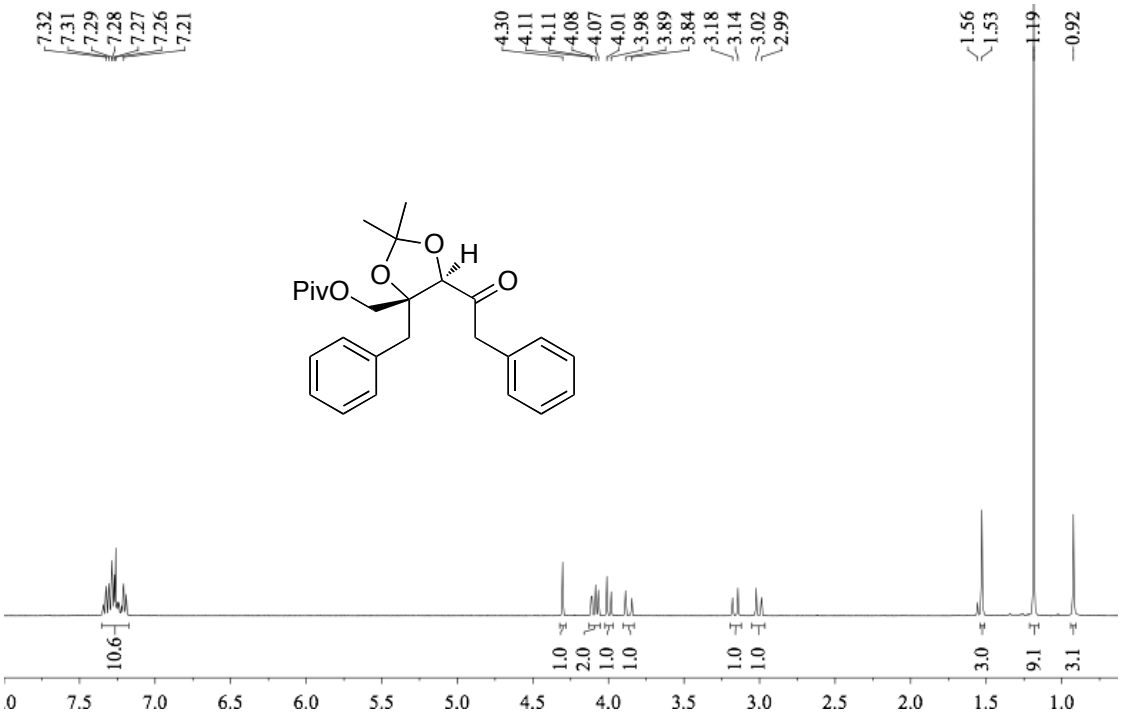


500 MHz ^{1}H-NMR in $CDCl_3$

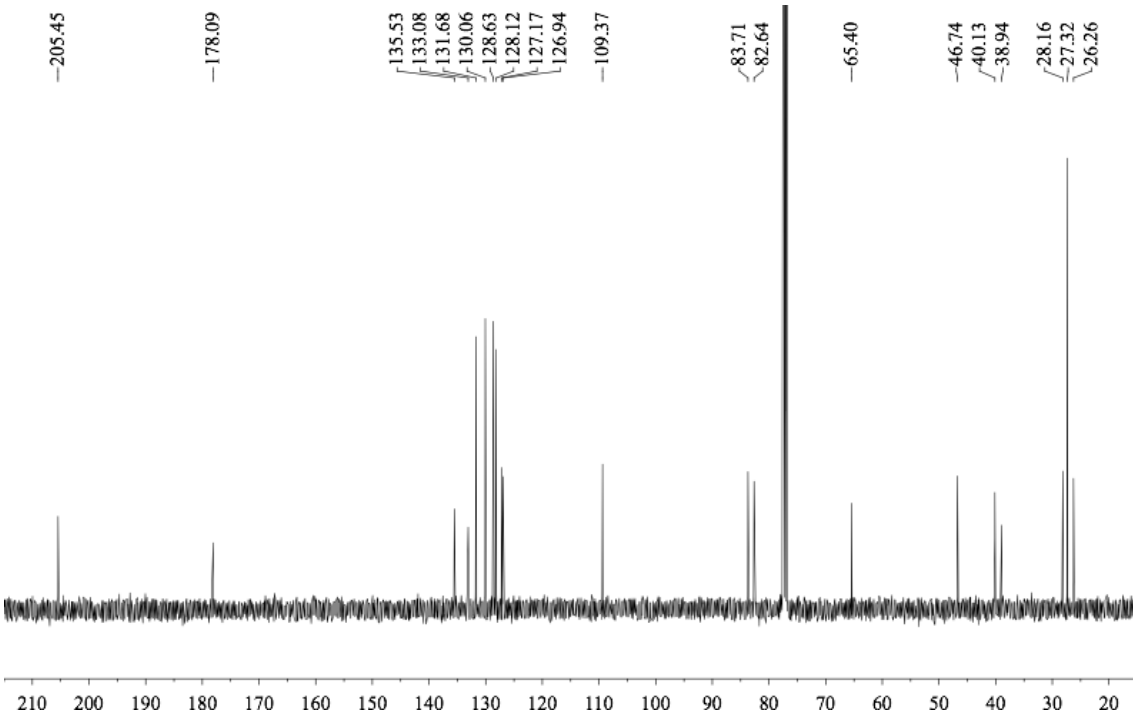


126 MHz ^{13}C-NMR in $CDCl_3$

((4*R*,5*R*)-4-Benzyl-2,2-dimethyl-5-(2-phenylacetyl)-1,3-dioxolan-4-yl)methyl pivalate (5.46)

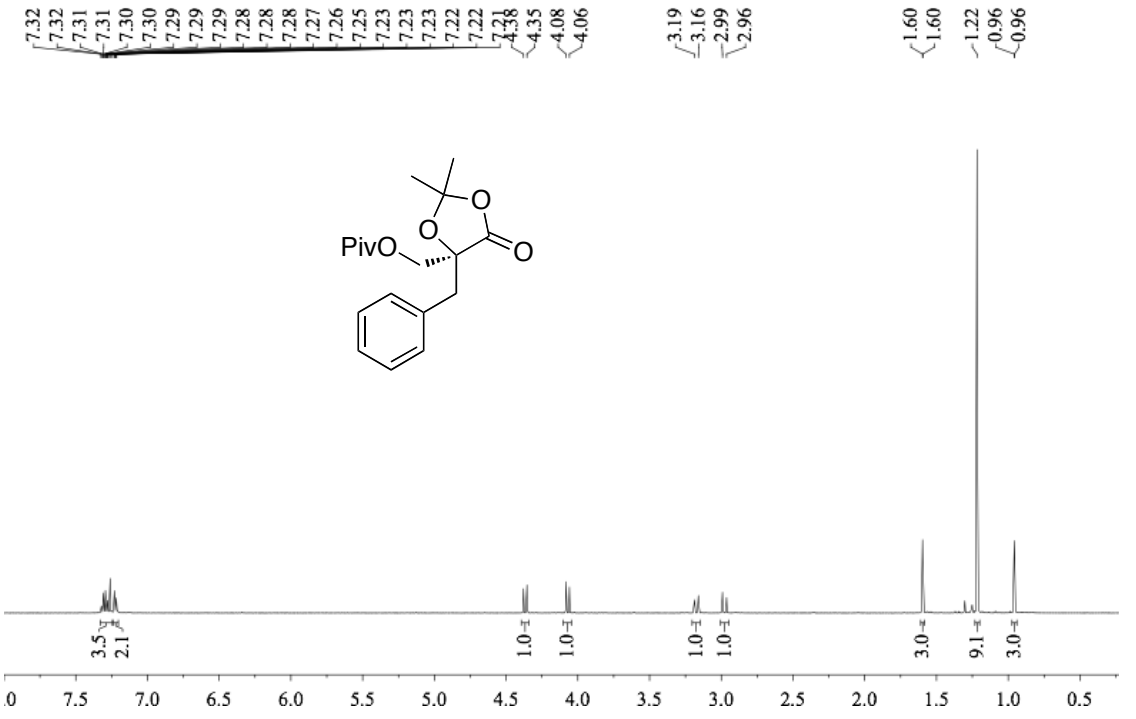


400 MHz ^{1}H-NMR in $CDCl_3$

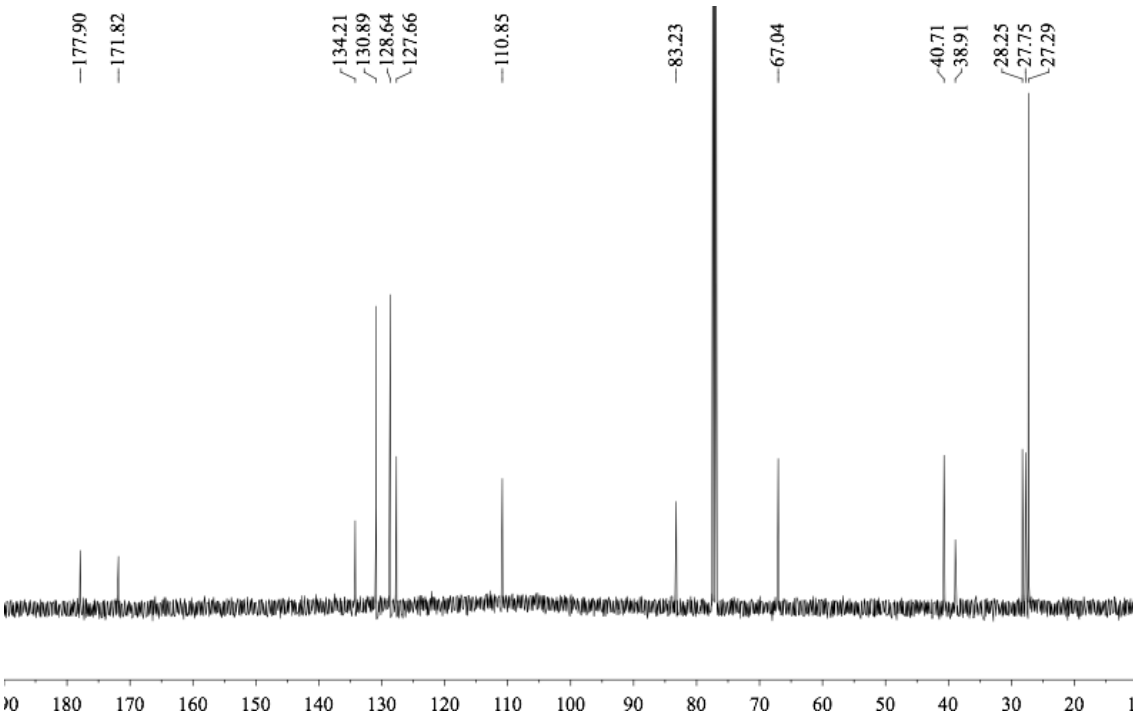


101 MHz ^{13}C-NMR in $CDCl_3$

(*S*)-(4-Benzyl-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)methyl pivalate (5.47)

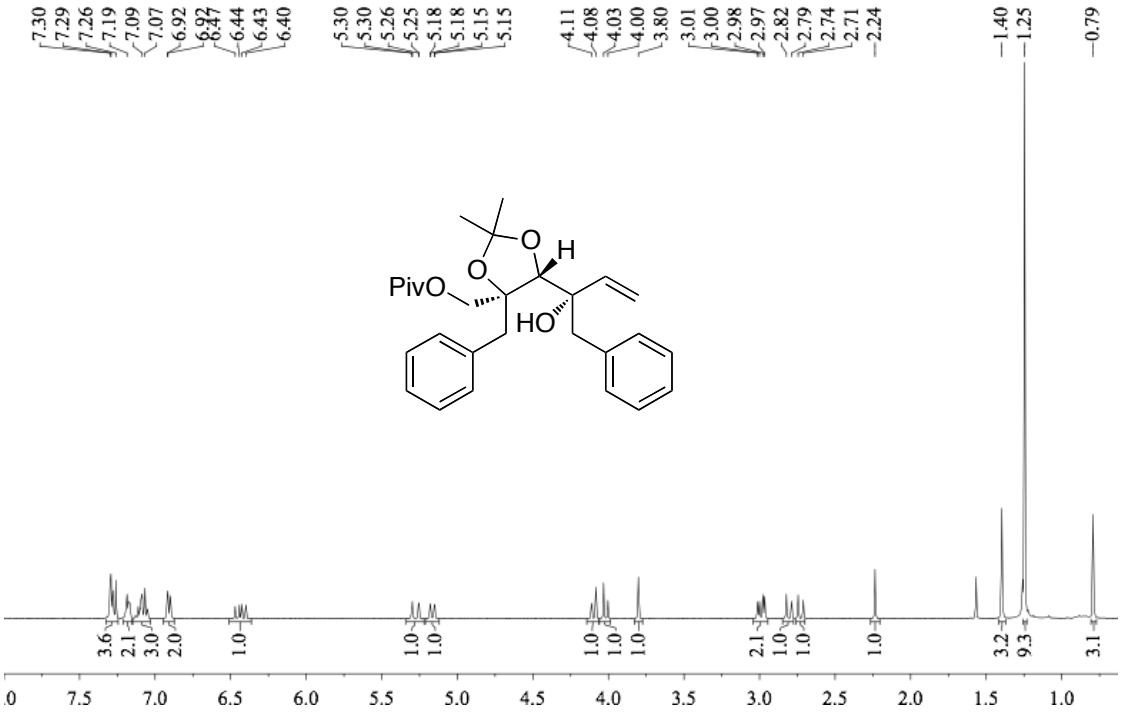


500 MHz ^{1}H-NMR in $CDCl_3$

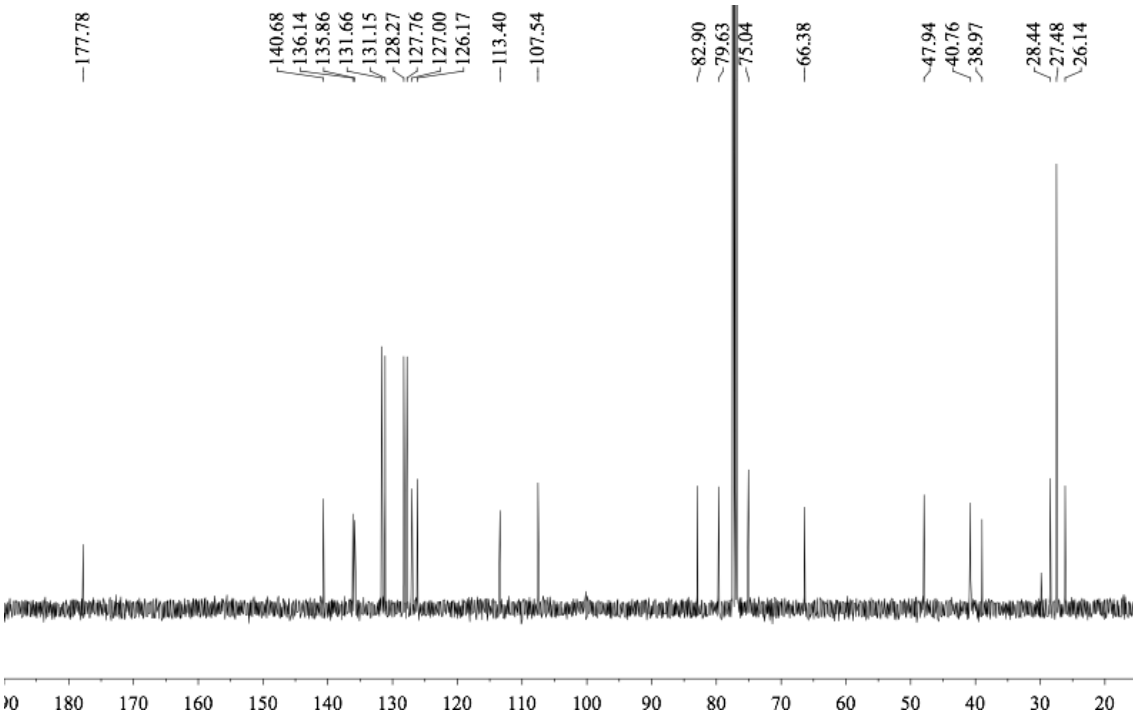


126 MHz ^{13}C-NMR in $CDCl_3$

((4*S*,5*R*)-4-Benzyl-5-((*S*)-2-hydroxy-1-phenylbut-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl pivalate (5.48)

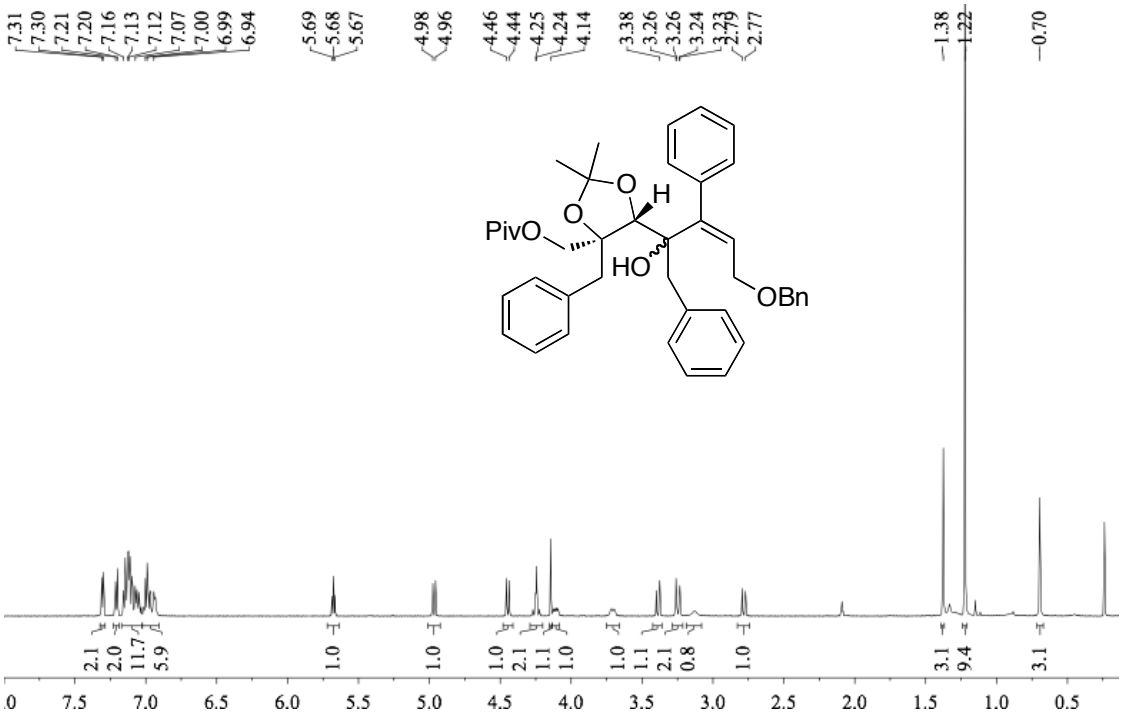


400 MHz ^{1}H-NMR in $CDCl_3$

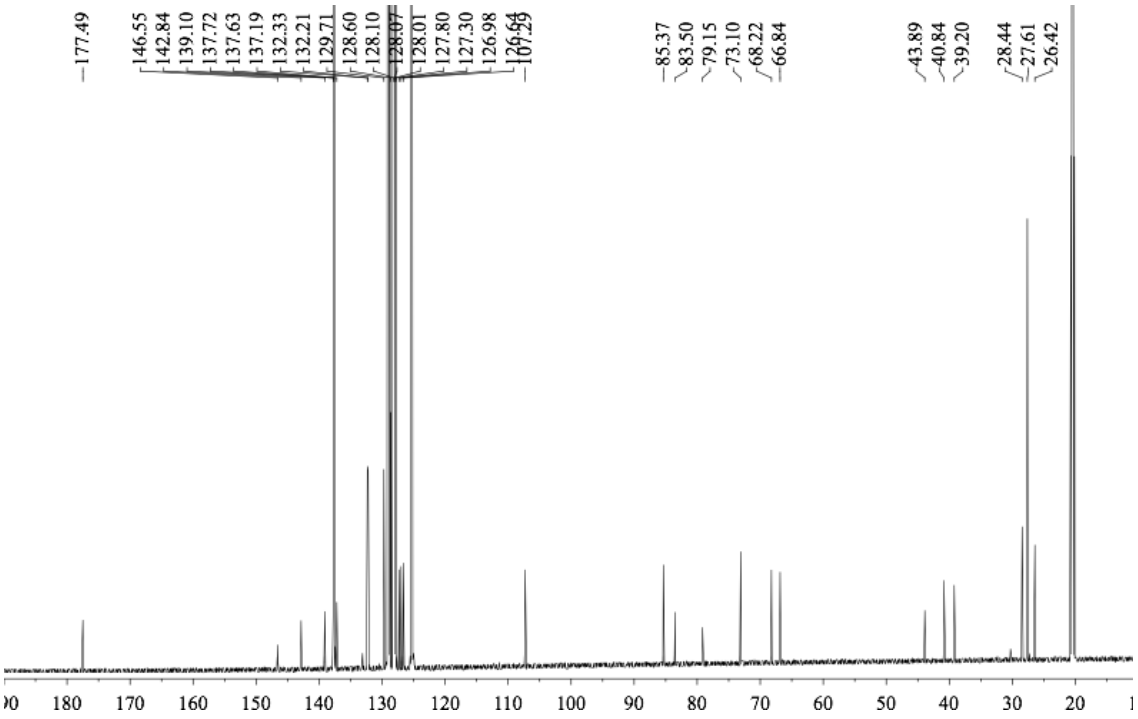


101 MHz ^{13}C-NMR in $CDCl_3$

((4*S*,5*R*)-4-Benzyl-5-((*Z*)-5-(benzyloxy)-2-hydroxy-1,3-diphenylpent-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl pivalate (5.49)

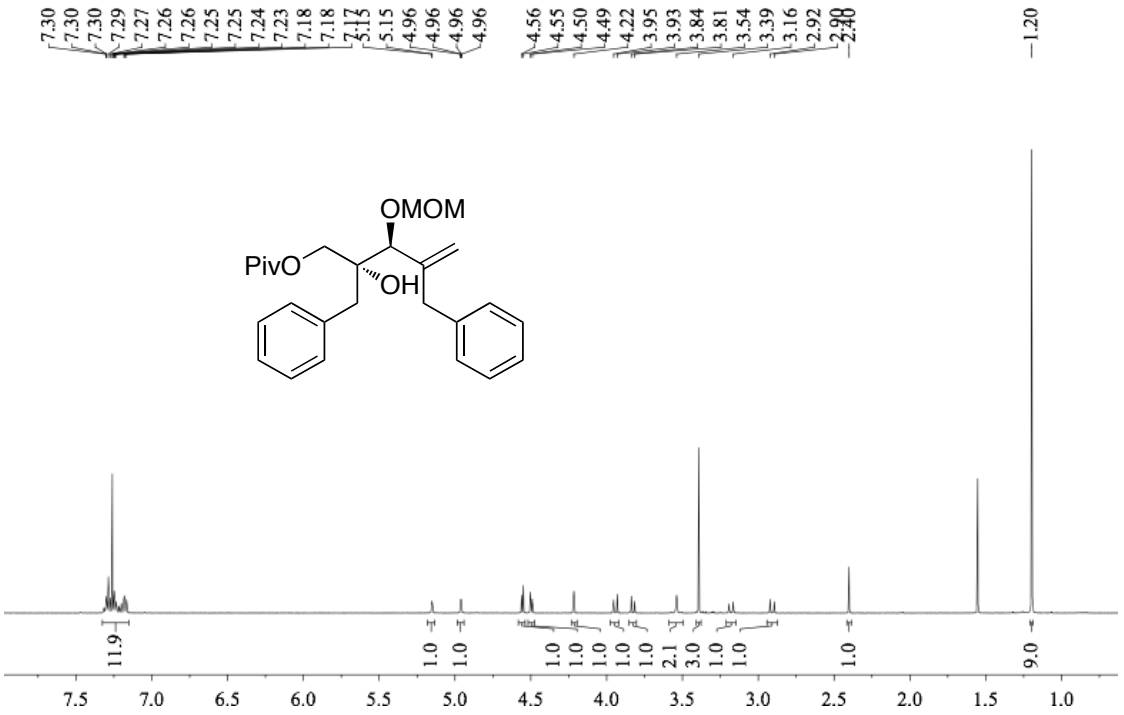


600 MHz ^{1}H-NMR in toluene-d_8 at 343 K

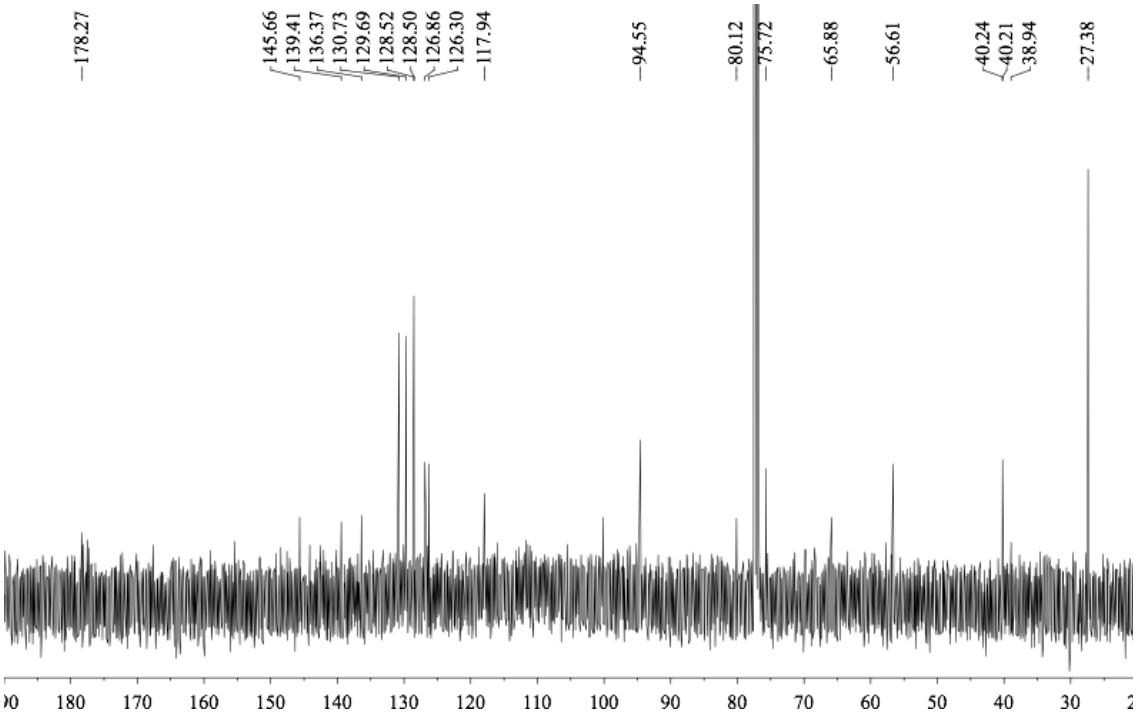


151 MHz ^{13}C-NMR in toluene-d_8 at 343 K

(2*R*,3*S*)-2,4-Dibenzyl-2-hydroxy-3-(methoxymethoxy)pent-4-en-1-yl pivalate (5.50)

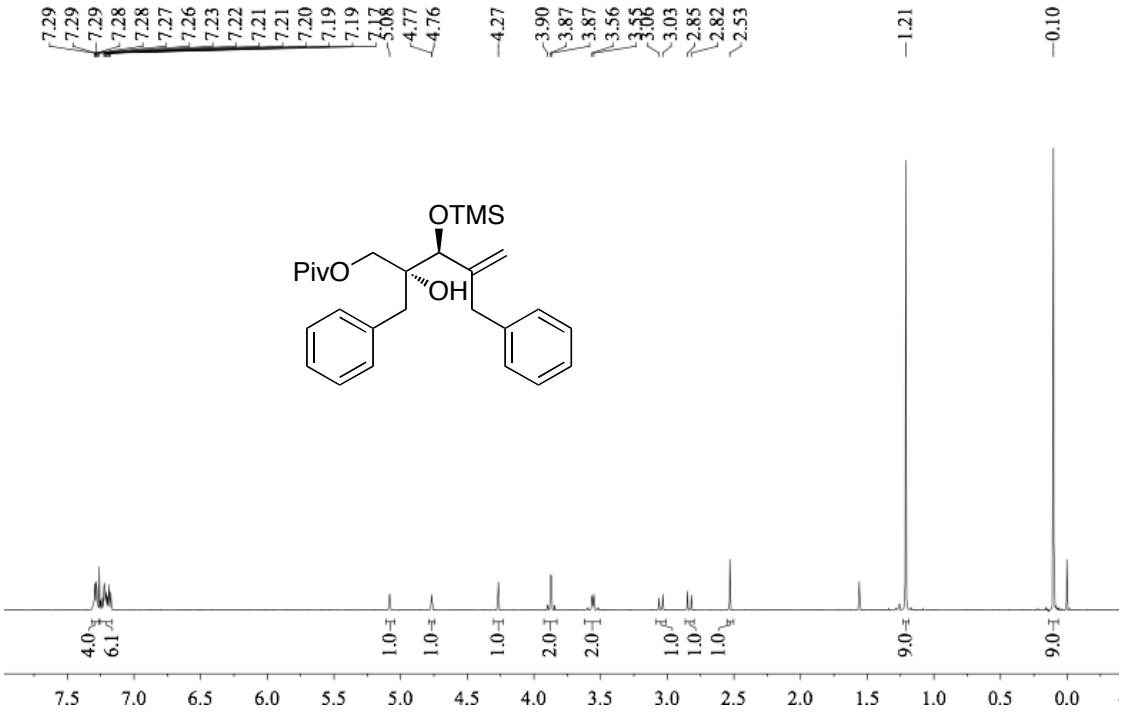


500 MHz ^{1}H-NMR in $CDCl_3$

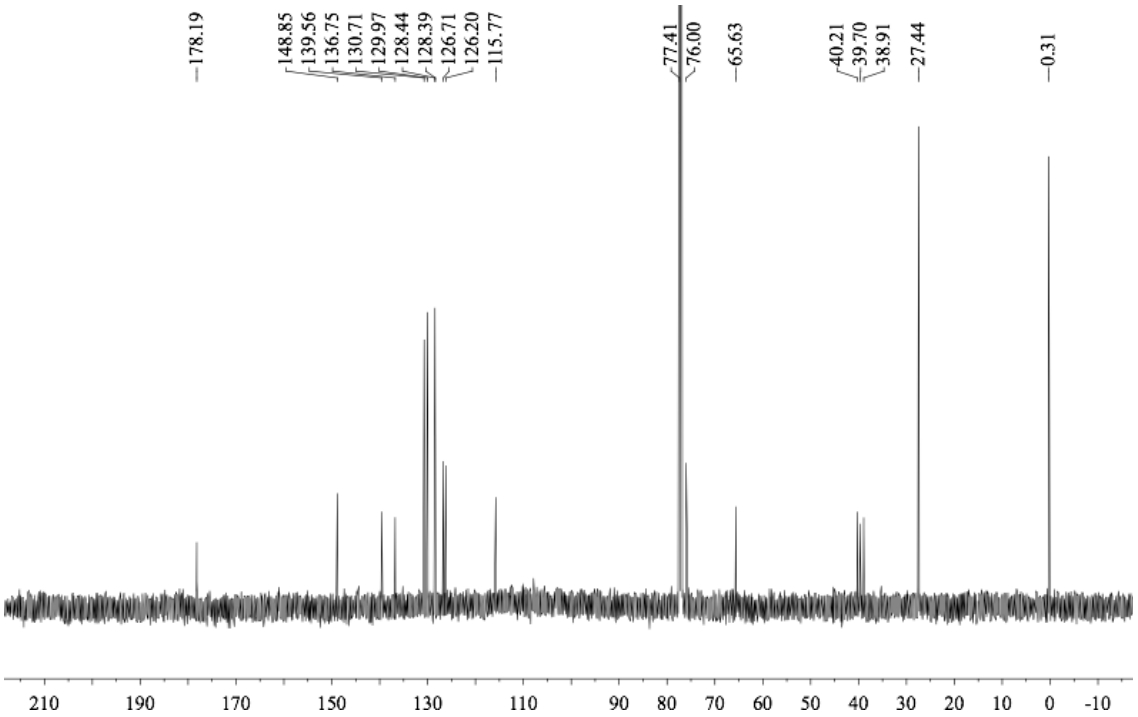


126 MHz ^{13}C-NMR in $CDCl_3$

(2*R*,3*S*)-2,4-Dibenzyl-2-hydroxy-3-((trimethylsilyl)oxy)pent-4-en-1-yl pivalate (5.51)

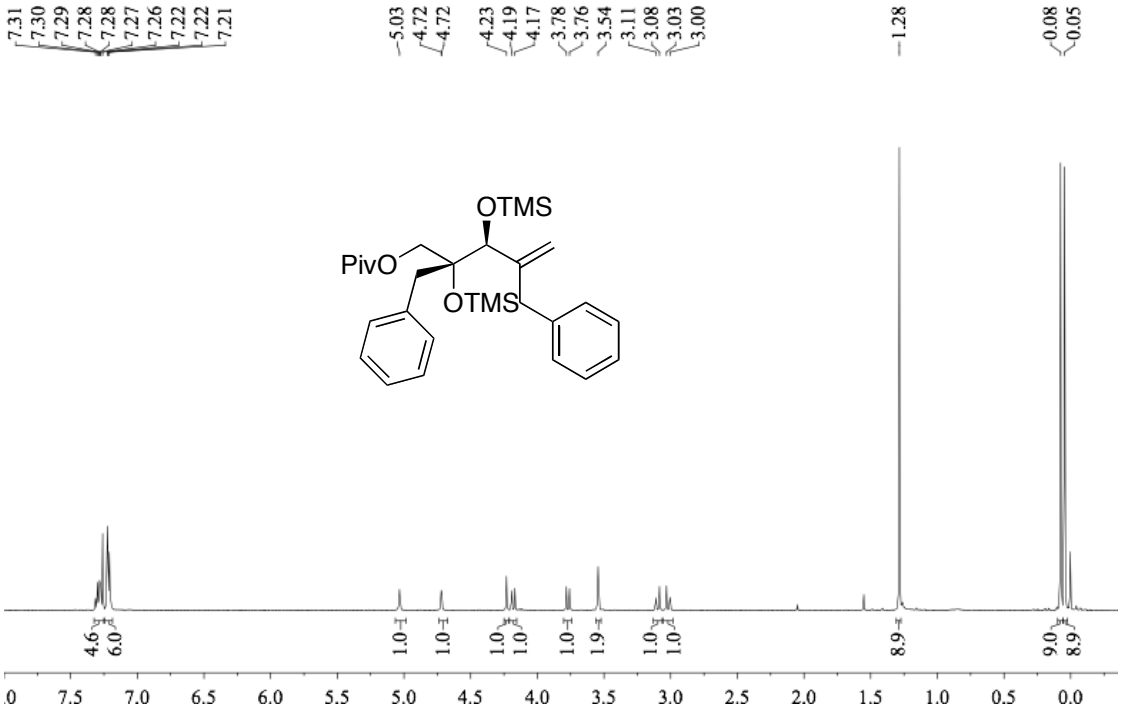


500 MHz ^{1}H-NMR in $CDCl_3$

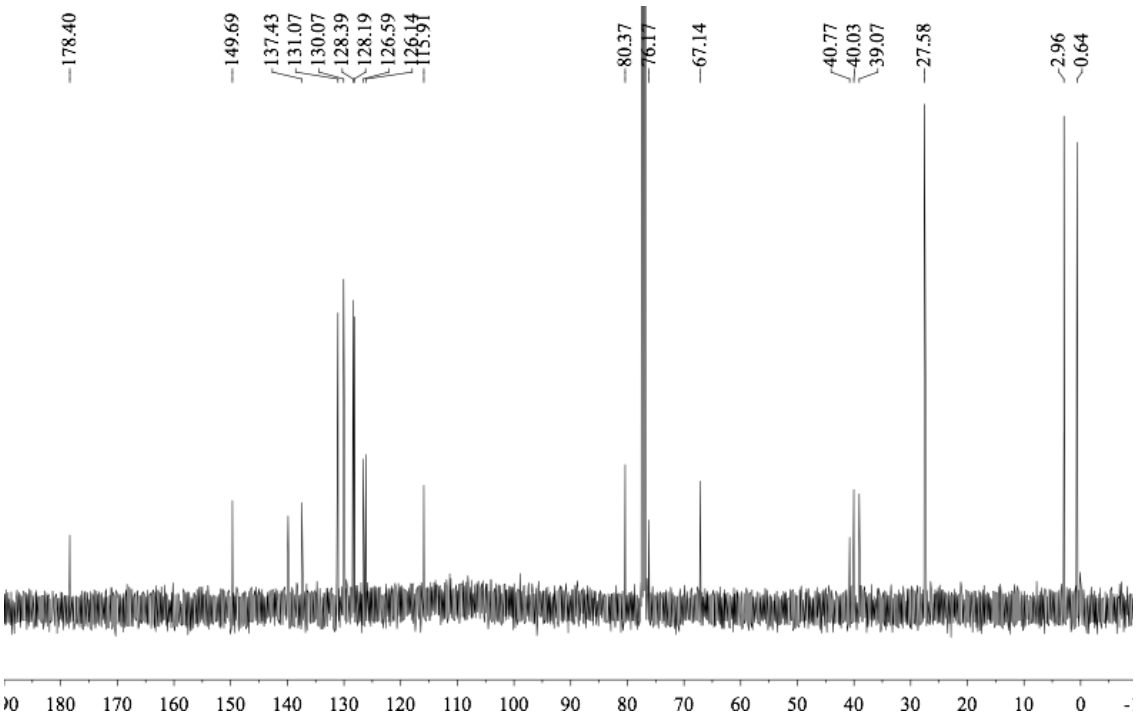


126 MHz ^{13}C-NMR in $CDCl_3$

(2*R*,3*S*)-2,4-Dibenzyl-2,3-bis((trimethylsilyl)oxy)pent-4-en-1-yl pivalate (5.52)

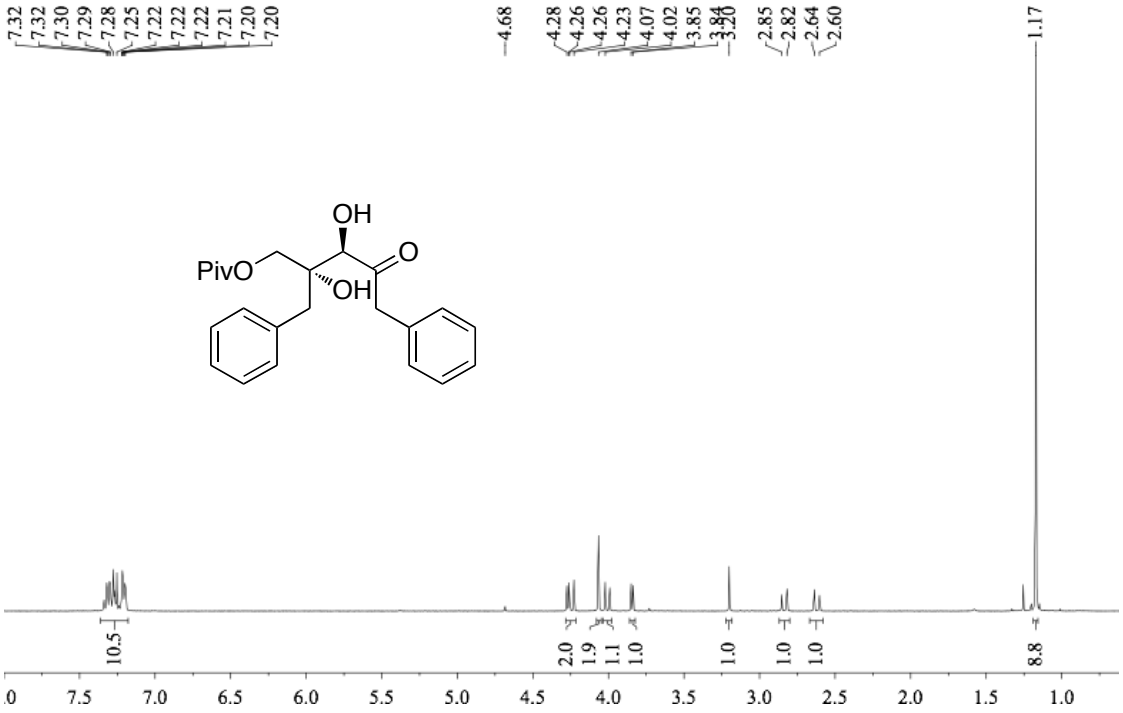


500 MHz ^{1}H-NMR in $CDCl_3$

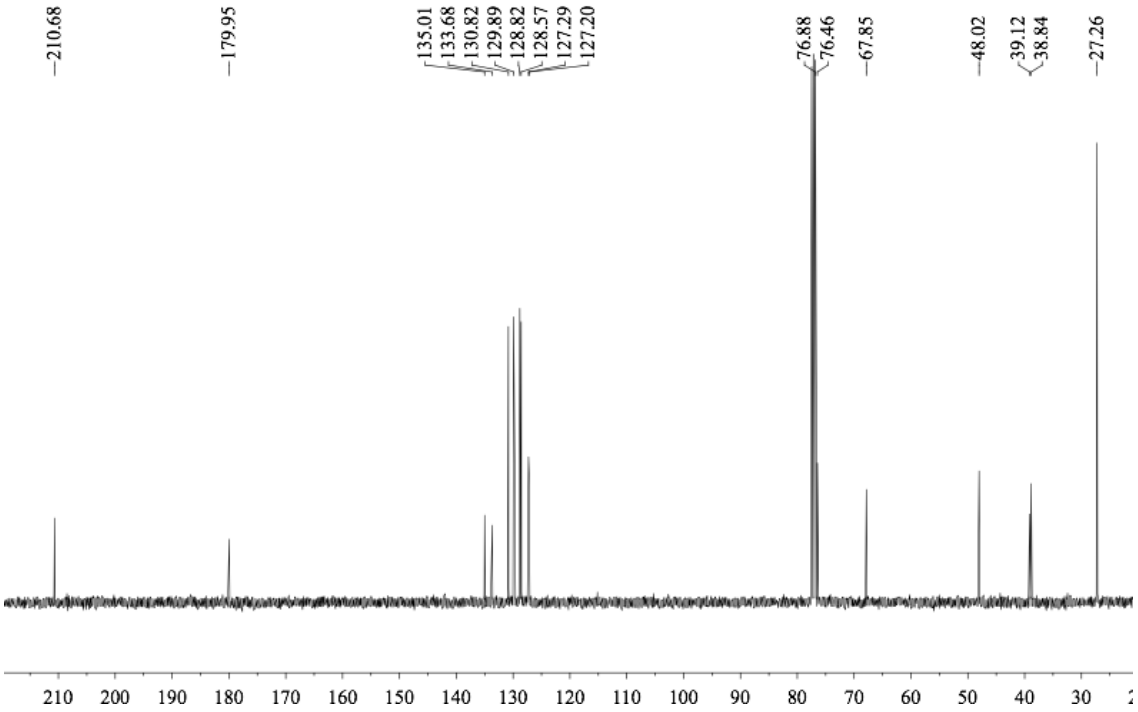


126 MHz ^{13}C-NMR in $CDCl_3$

(2*R*,3*R*)-2-Benzyl-2,3-dihydroxy-4-oxo-5-phenylpentyl pivalate (5.53)

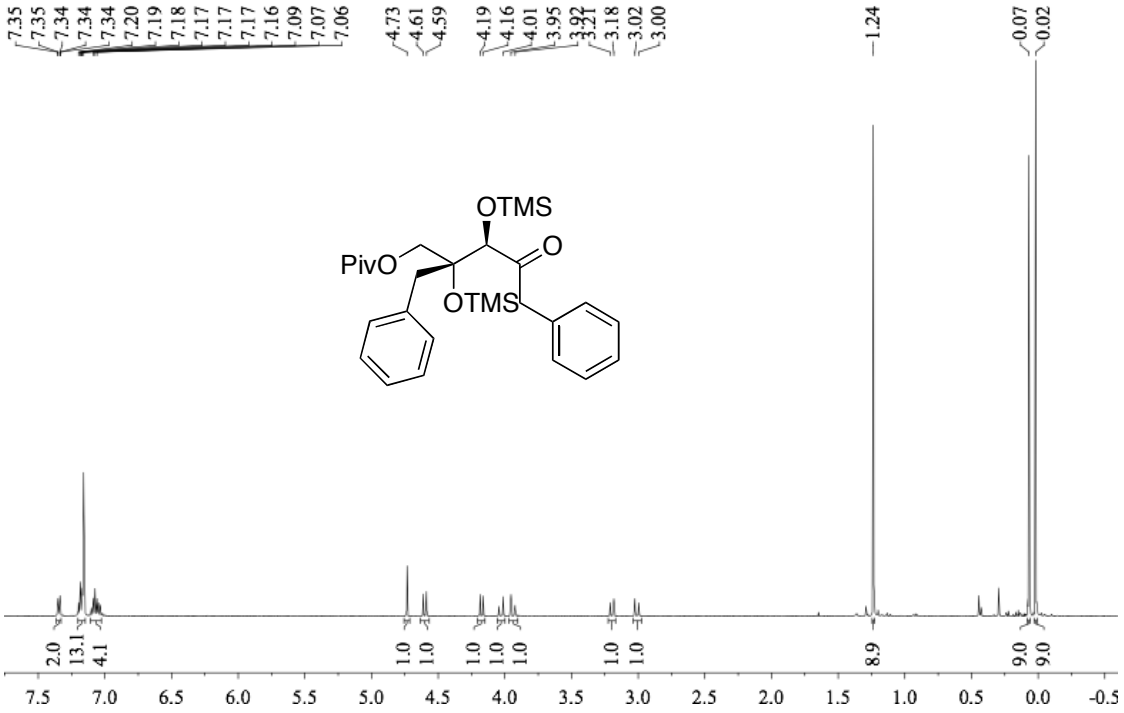


400 MHz ^{1}H-NMR in $CDCl_3$

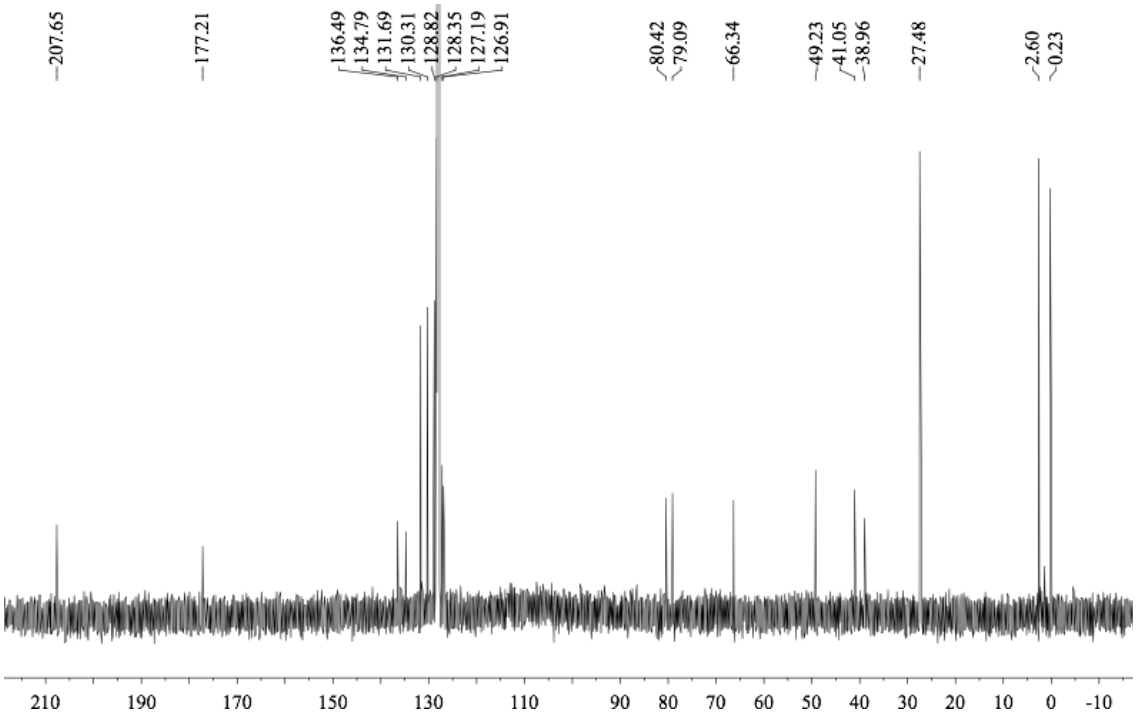


101 MHz ^{13}C-NMR in $CDCl_3$

(2*R*,3*R*)-2-Benzyl-4-oxo-5-phenyl-2,3-bis((trimethylsilyl)oxy)pentyl pivalate (5.55)

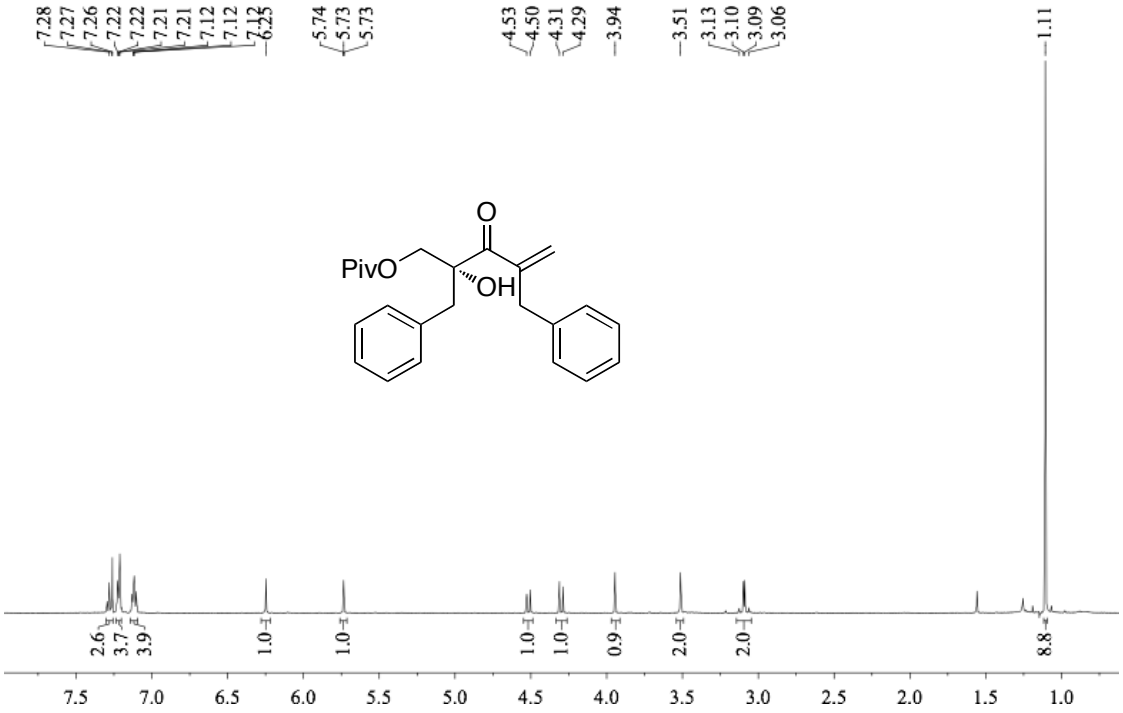


500 MHz ^{1}H-NMR in C_6D_6

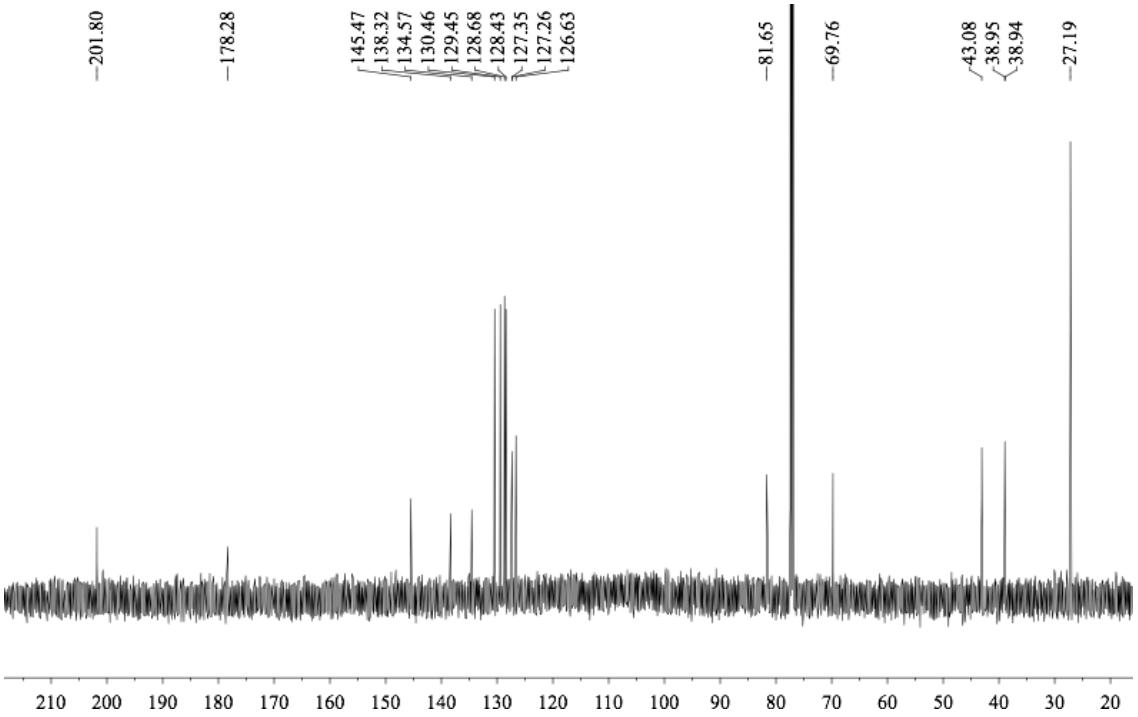


126 MHz ^{13}C-NMR in C_6D_6

(*R*)-2,4-Dibenzyl-2-hydroxy-3-oxopent-4-en-1-yl pivalate (5.56)



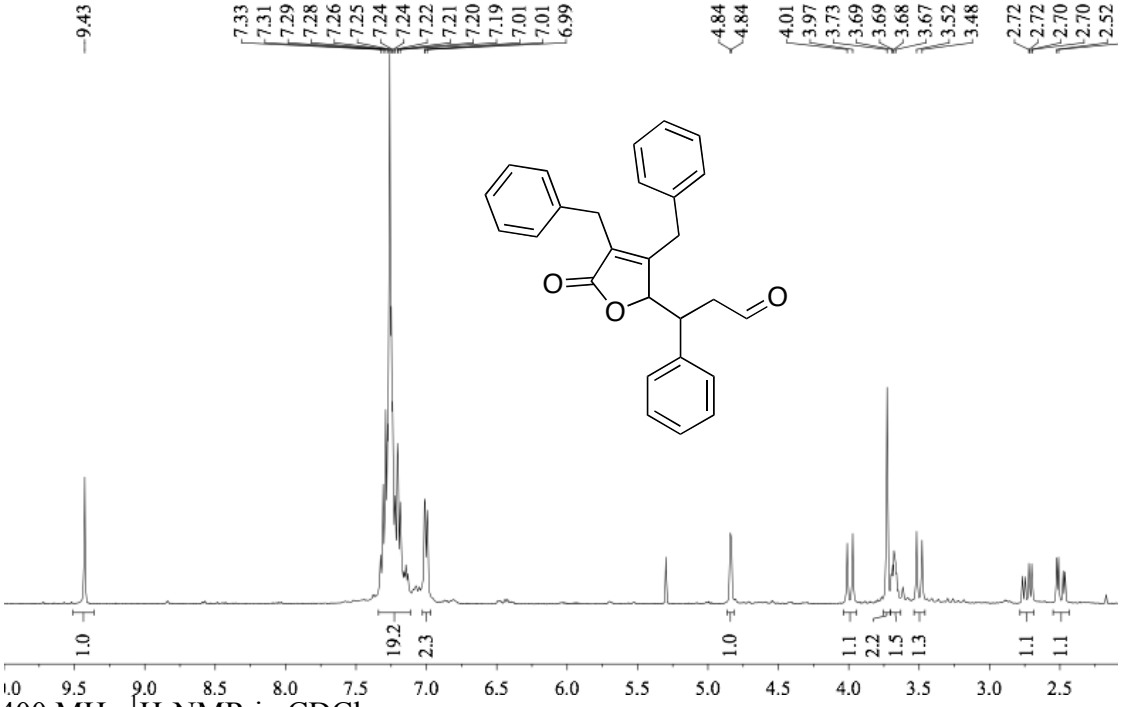
500 MHz ^{1}H-NMR in $CDCl_3$



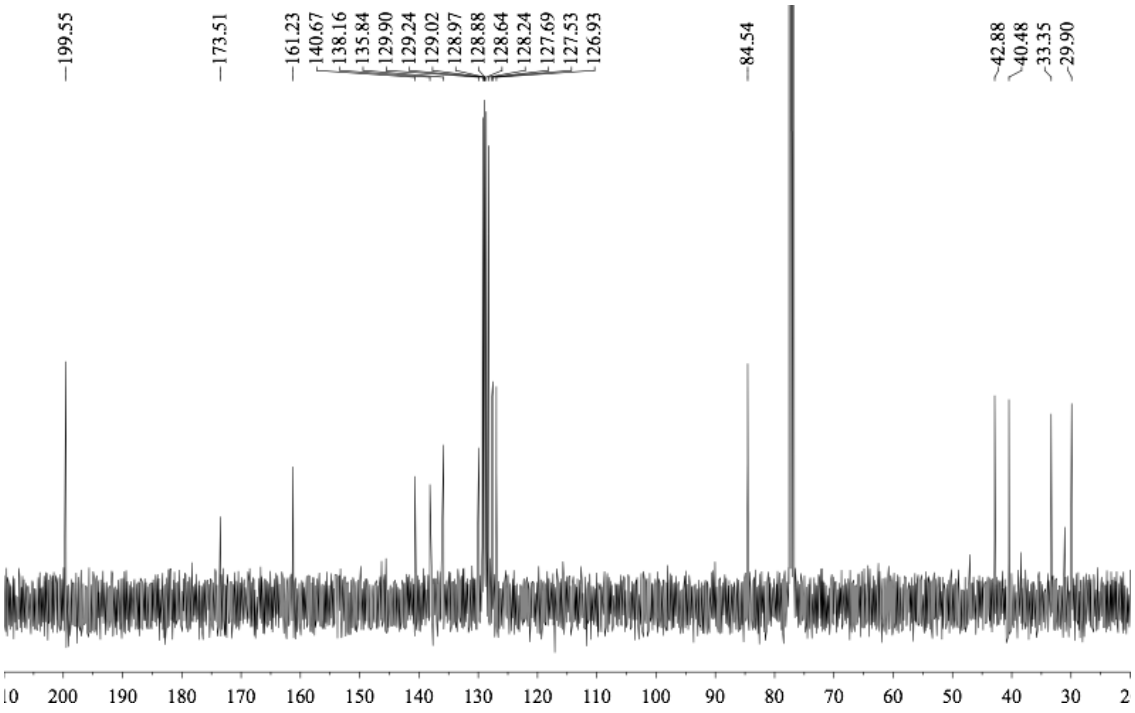
126 MHz ^{13}C-NMR in $CDCl_3$

9.2.5 Towards Maculalactone F, L and M

3-(3,4-Dibenzyl-5-oxo-2,5-dihydrofuran-2-yl)-3-phenylpropanal (6.11), first diastereomer

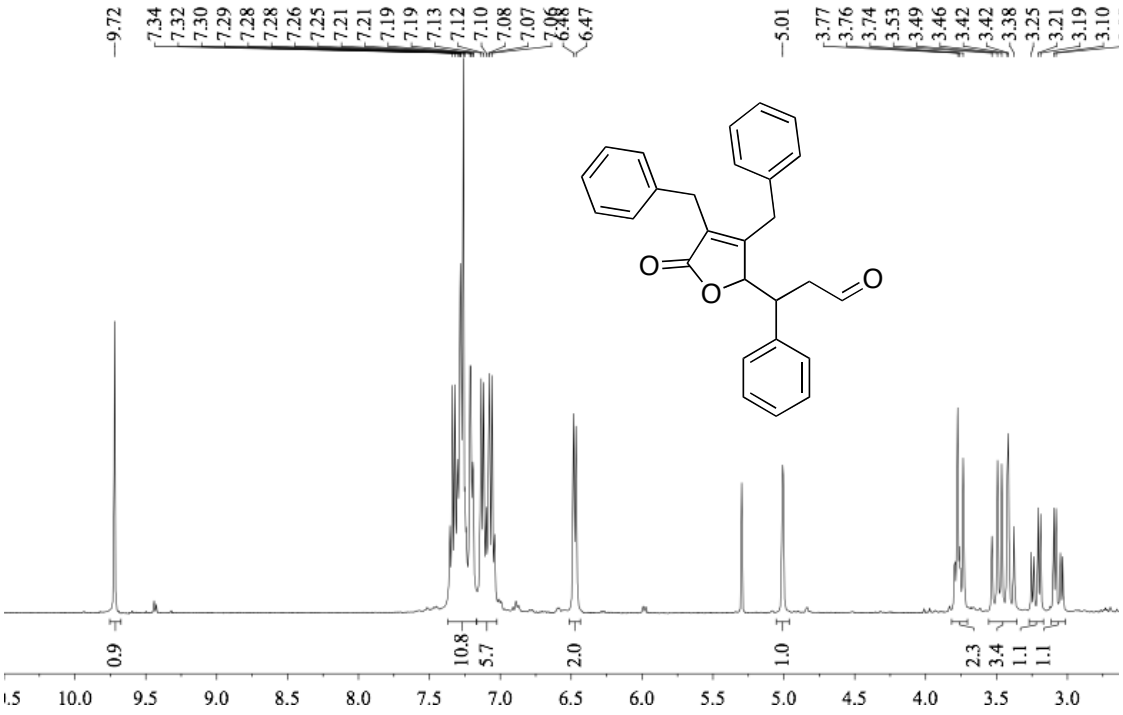


400 MHz ^{1}H-NMR in $CDCl_3$

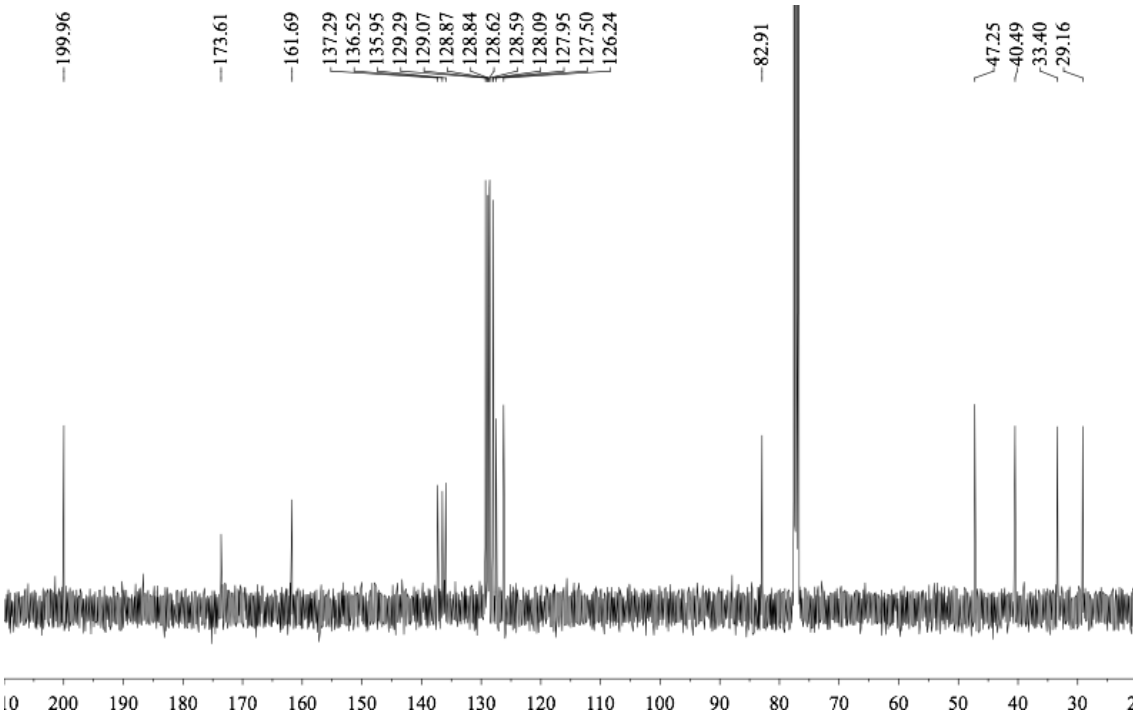


101 MHz ^{13}C-NMR in $CDCl_3$

3-(3,4-Dibenzyl-5-oxo-2,5-dihydrofuran-2-yl)-3-phenylpropanal (6.11), second diastereomer

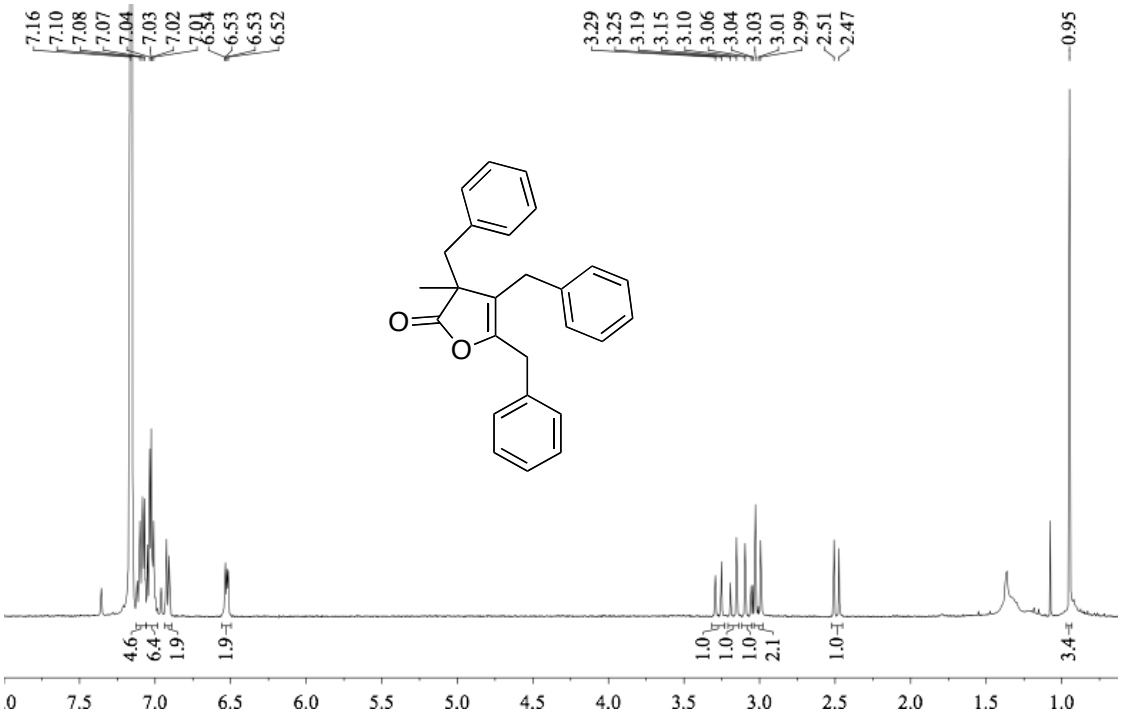


400 MHz ^{1}H-NMR in $CDCl_3$

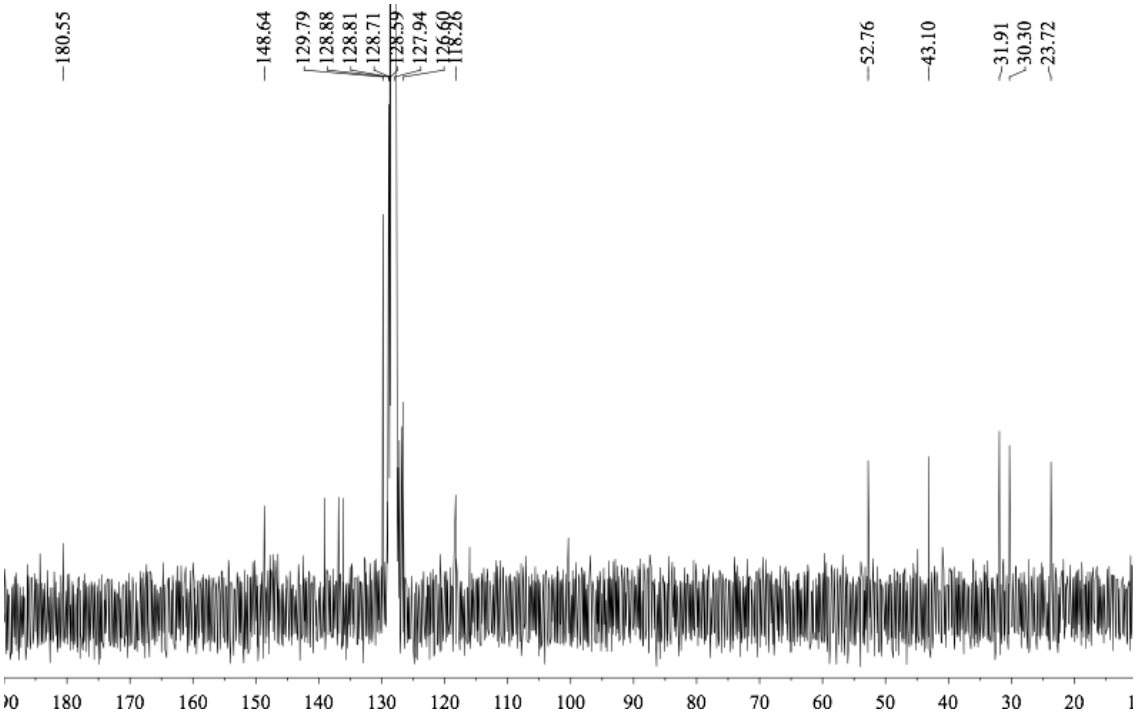


101 MHz ^{13}C-NMR in $CDCl_3$

3,4,5-Tribenzyl-3-methylfuran-2(3H)-one (6.12)

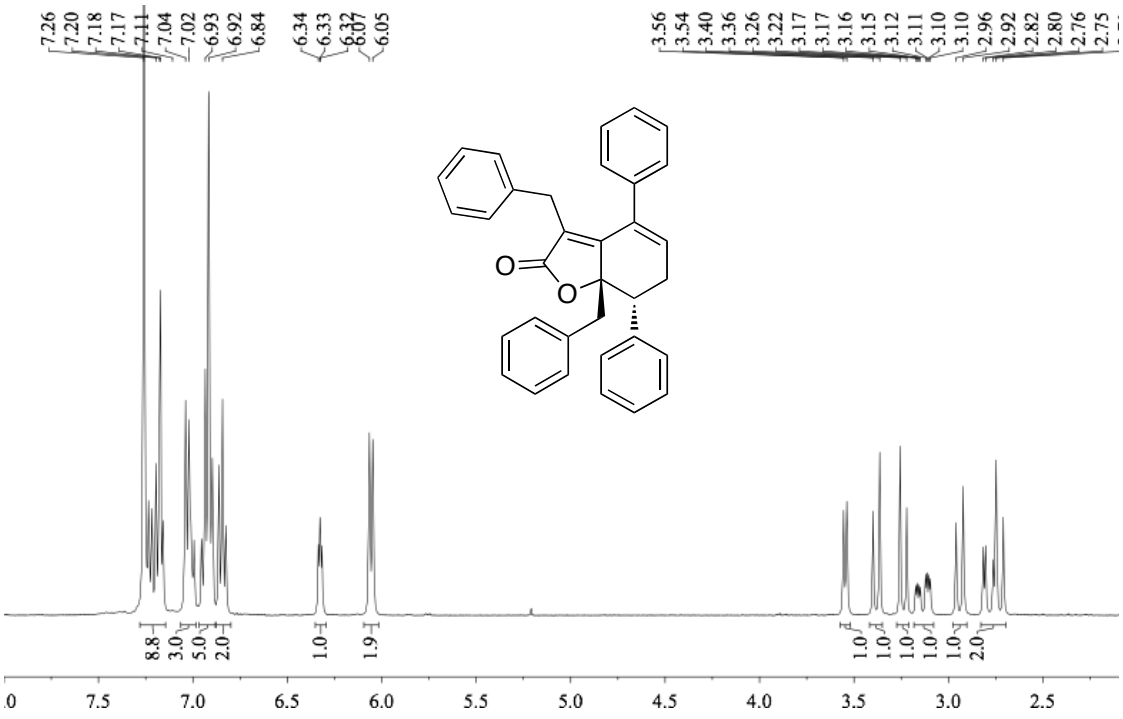


400 MHz ^{1}H-NMR in C_6D_6

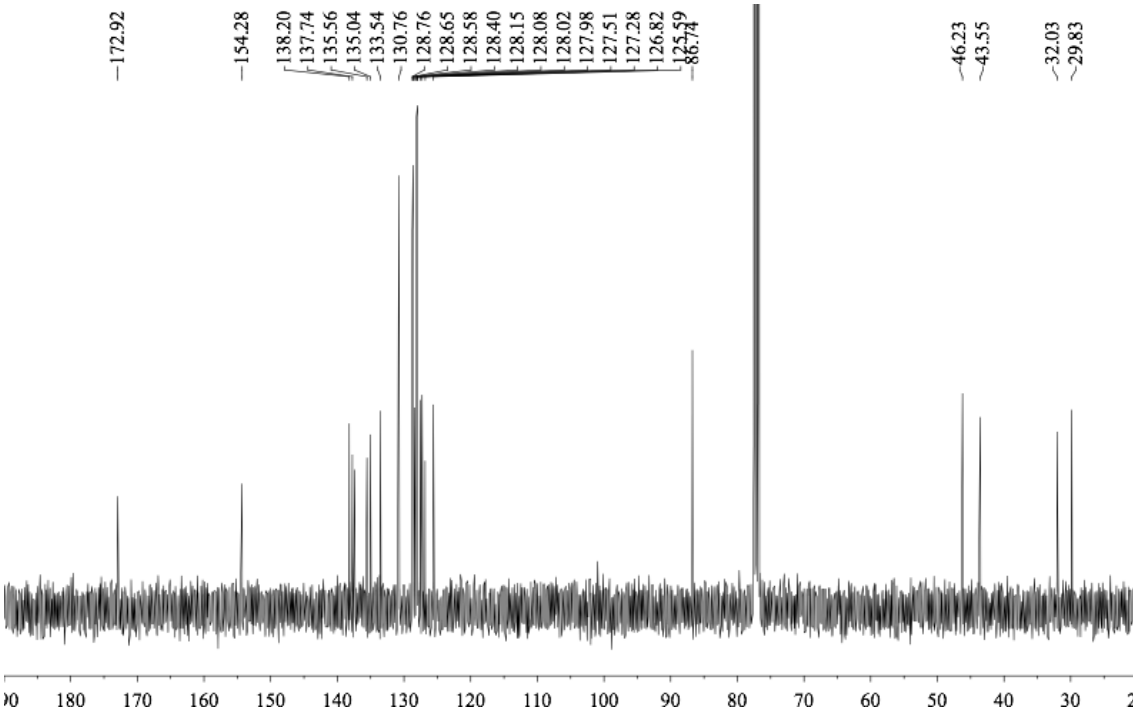


101 MHz ^{13}C-NMR in C_6D_6

3,7a-Dibenzyl-4,7-diphenyl-7,7a-dihydrobenzofuran-2(6H)-one (4.14)

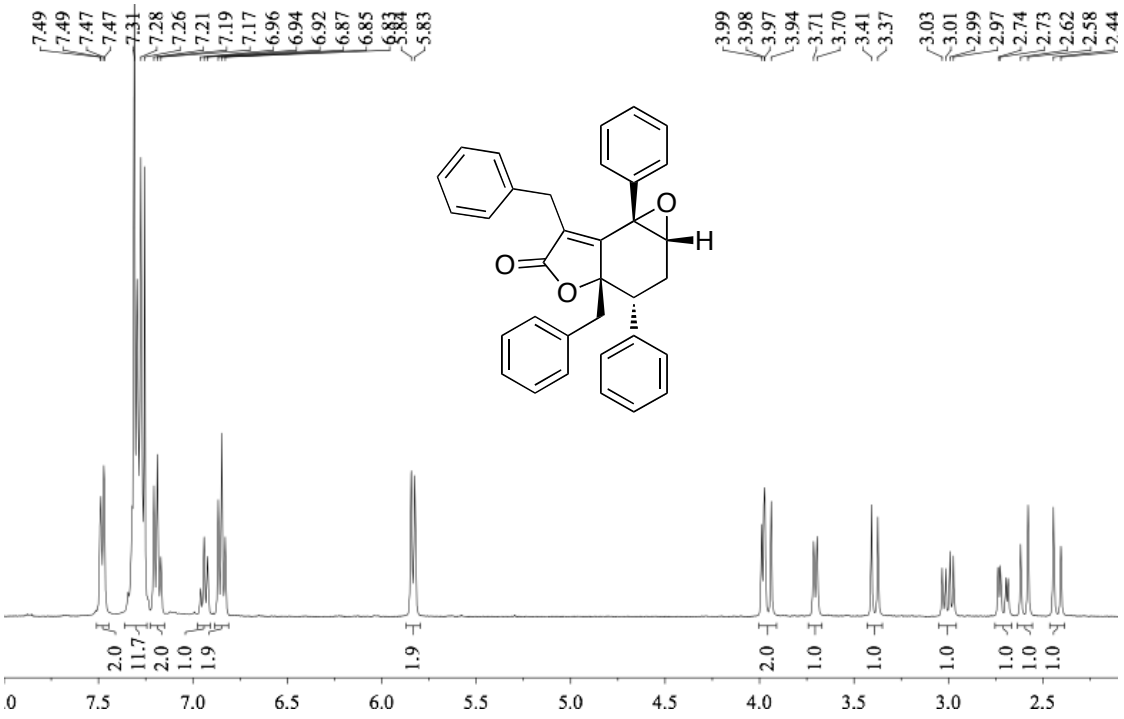


400 MHz ^{1}H-NMR in $CDCl_3$

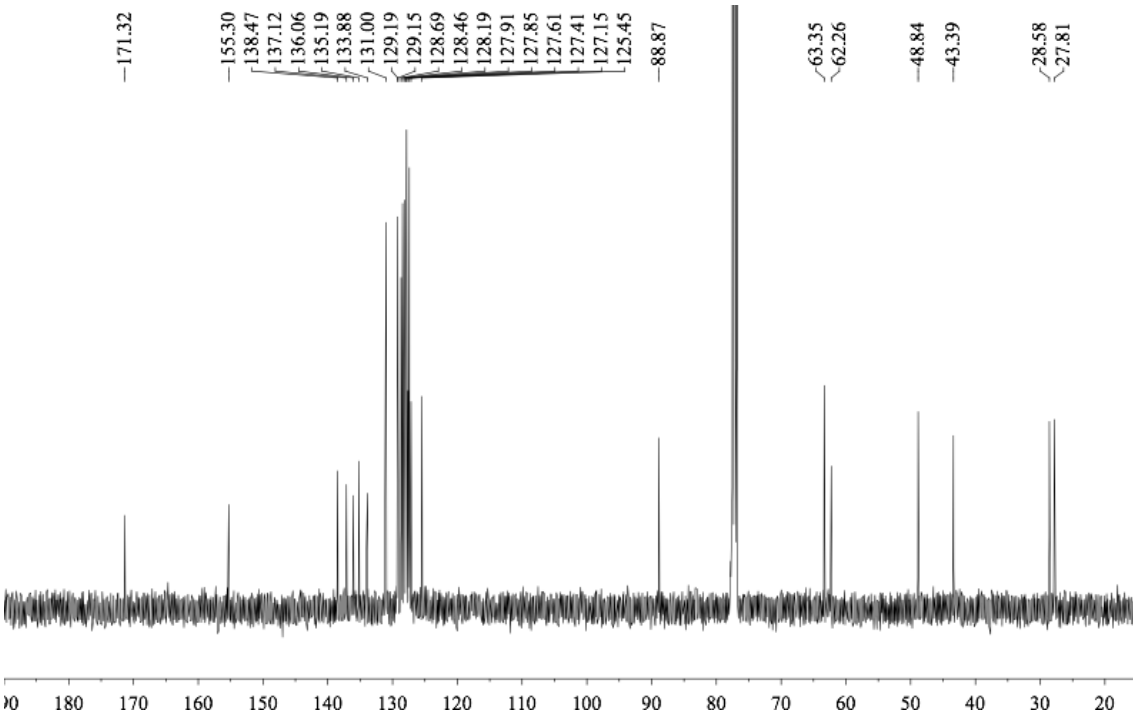


101 MHz ^{13}C-NMR in $CDCl_3$

3a,6-Dibenzyl-3,6b-diphenyl-1a,2,3,3a-tetrahydrooxireno[2,3-e]benzofuran-5(6bH)-one (6.13)

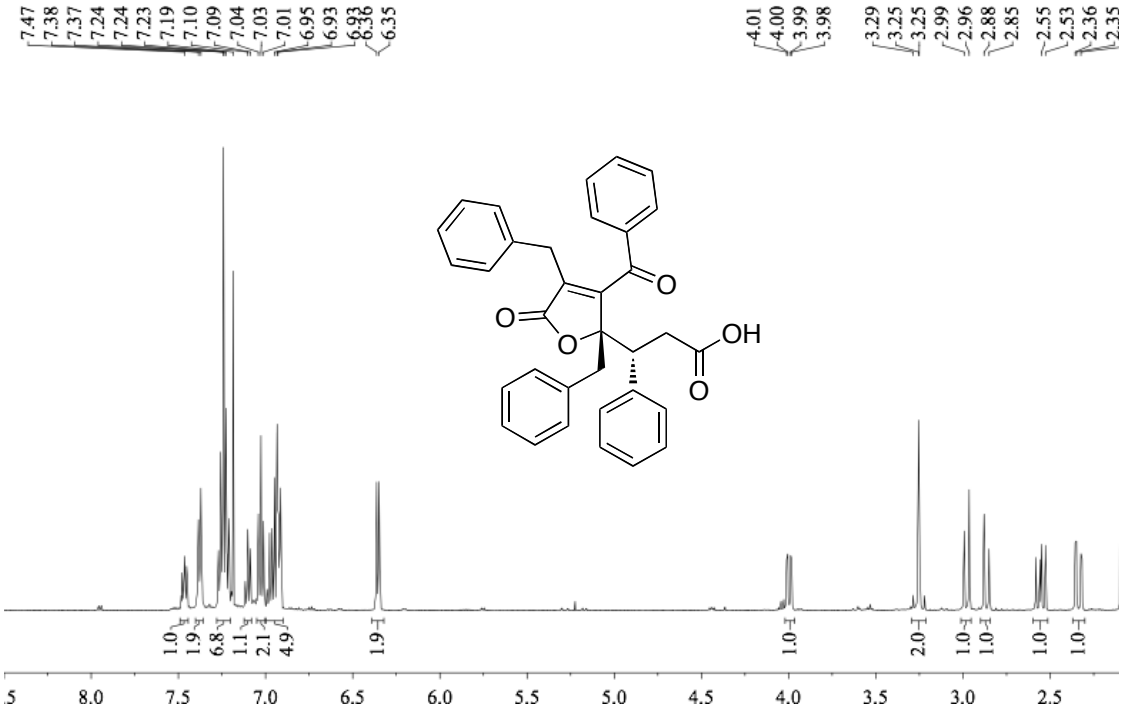


400 MHz ^{1}H-NMR in $CDCl_3$

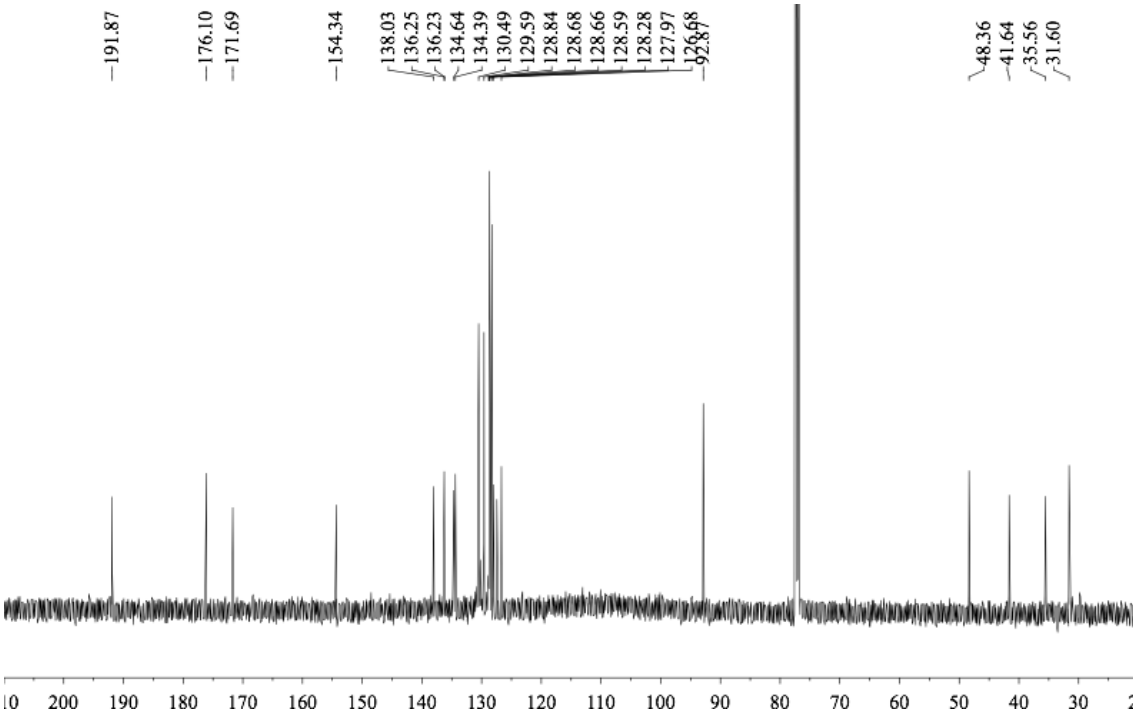


101 MHz ^{13}C-NMR in $CDCl_3$

***epi*-Maculalactone M (6.14)**

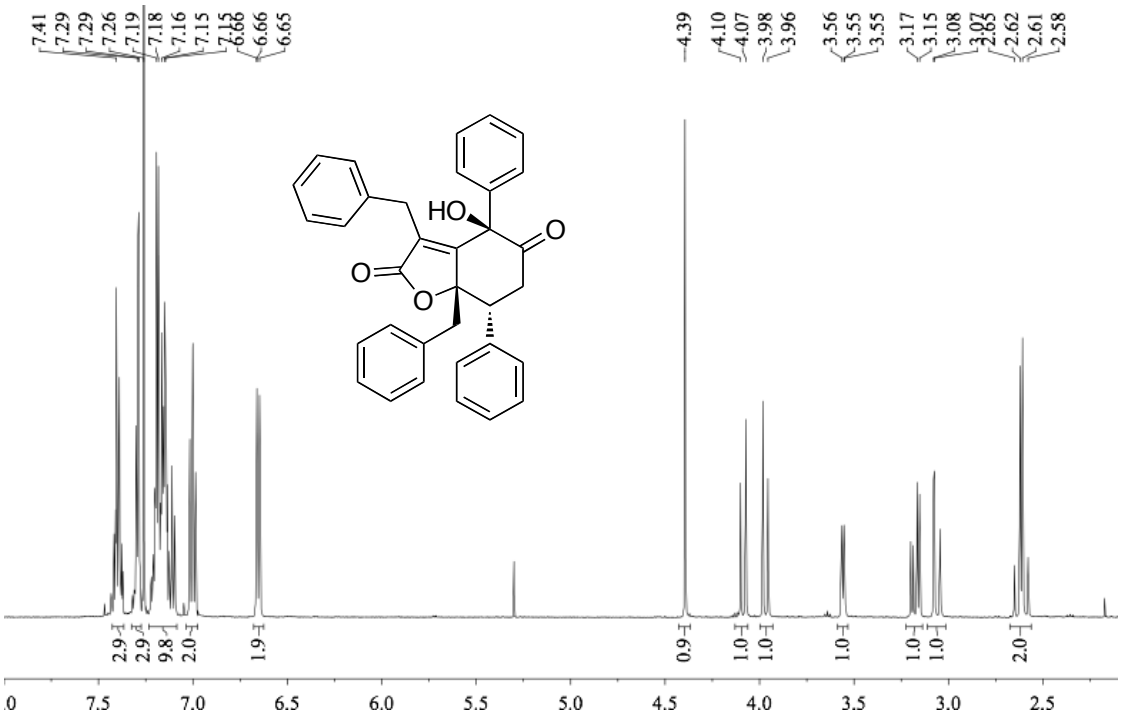


500 MHz ^{1}H-NMR in $CDCl_3$

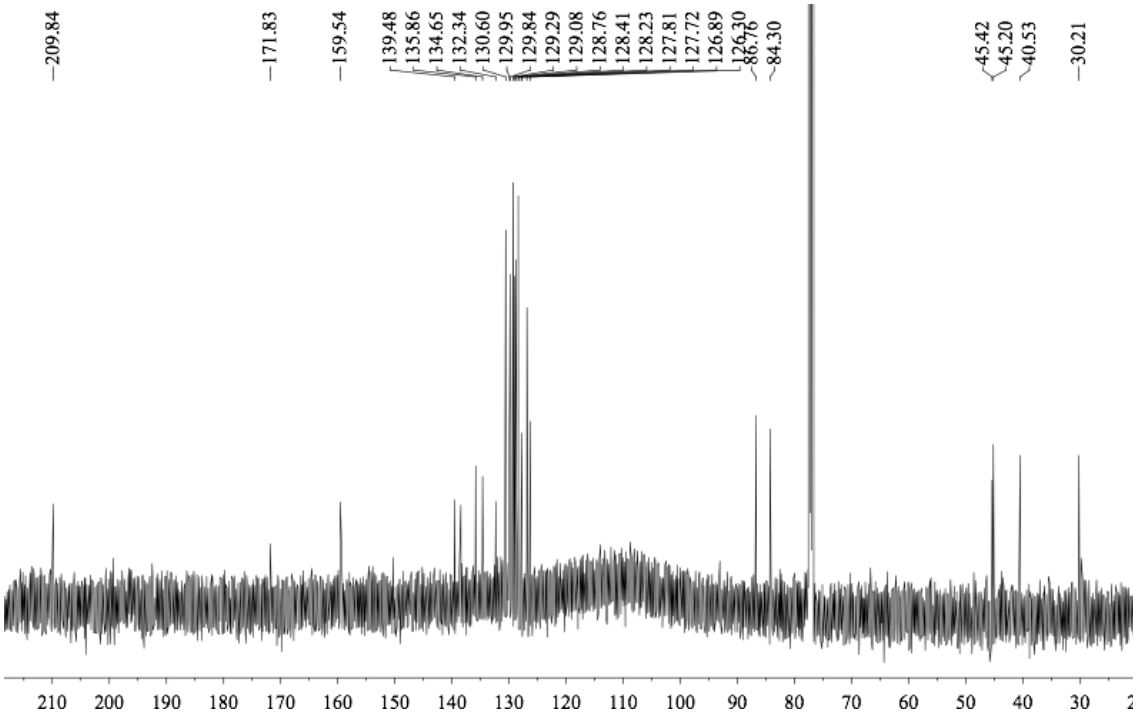


126 MHz ^{13}C-NMR in $CDCl_3$

***epi*-Maculalactone F (6.15)**

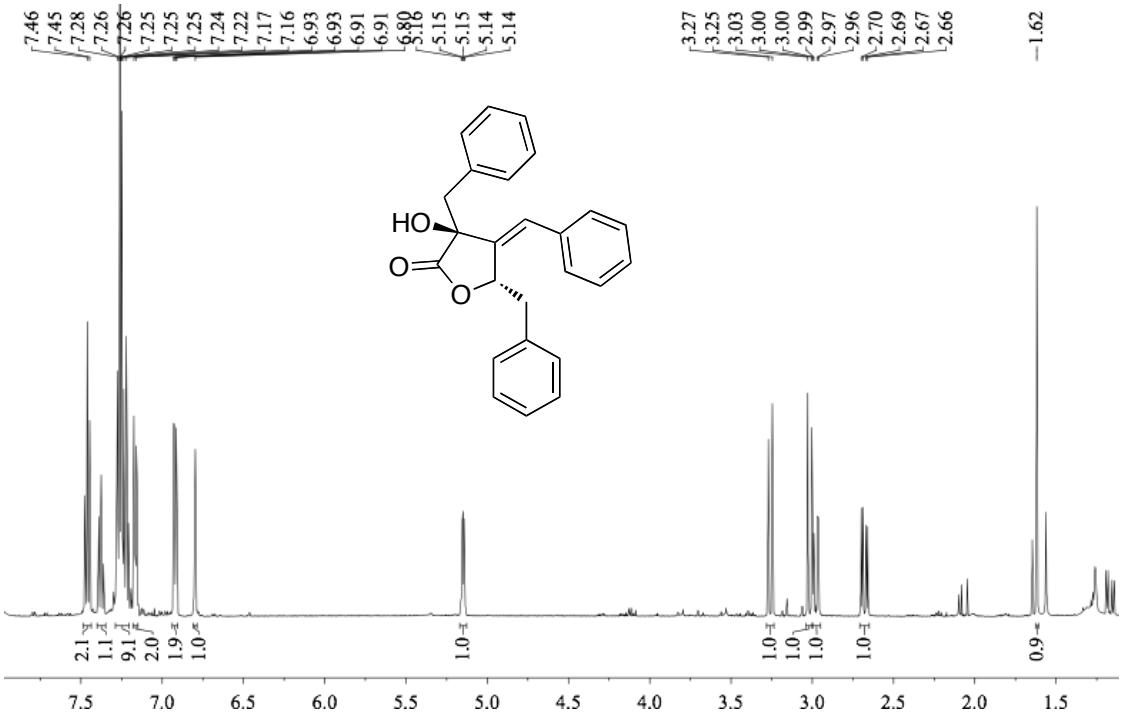


500 MHz ^{1}H-NMR in $CDCl_3$

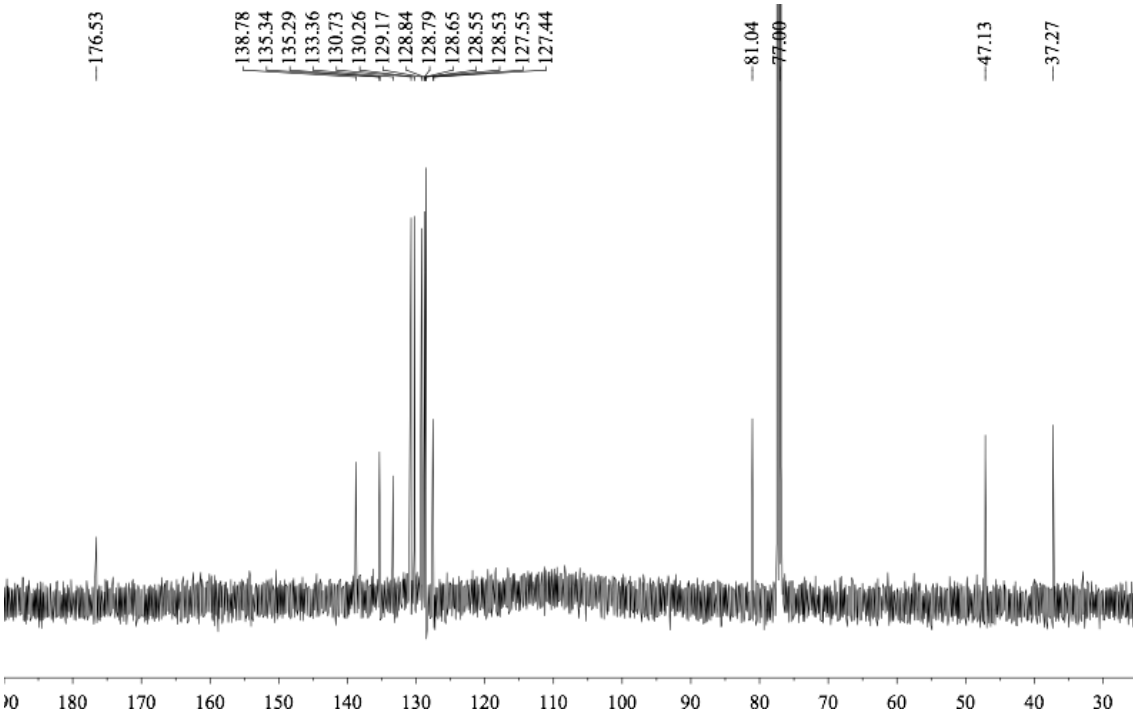


126 MHz ^{13}C-NMR in $CDCl_3$

***rac*-(*E*)-3,5-Dibenzyl-4-benzylidene-3-hydroxydihydrofuran-2(3H)-one (6.16)**

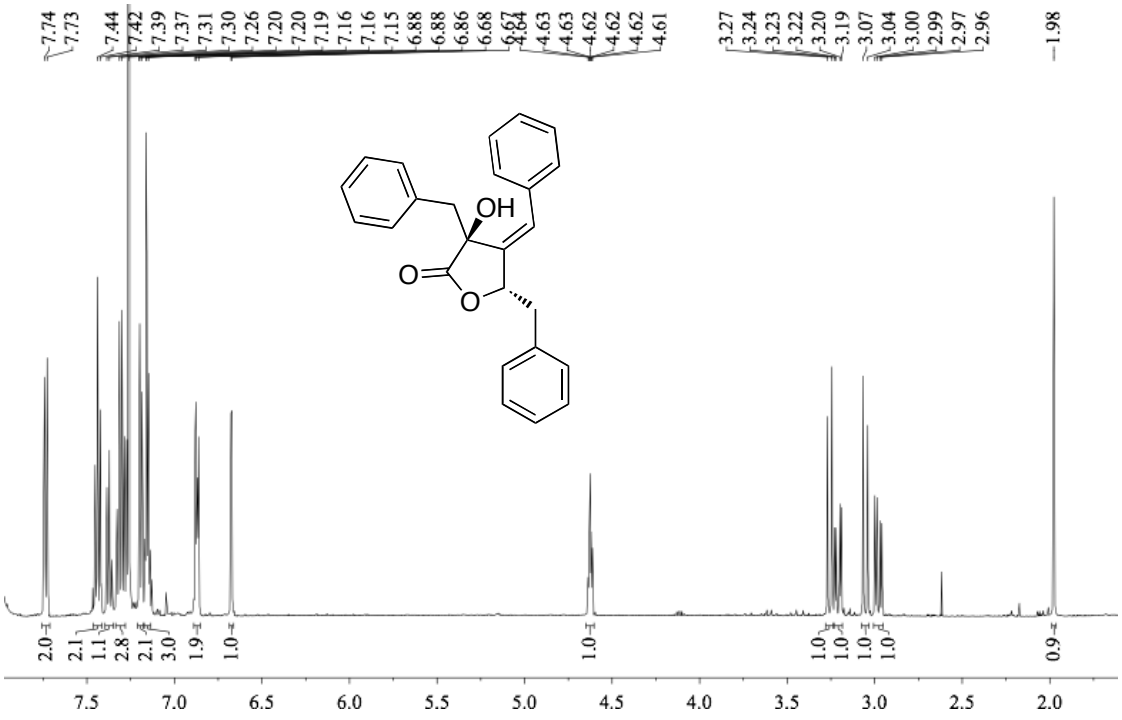


500 MHz ^{1}H-NMR in $CDCl_3$

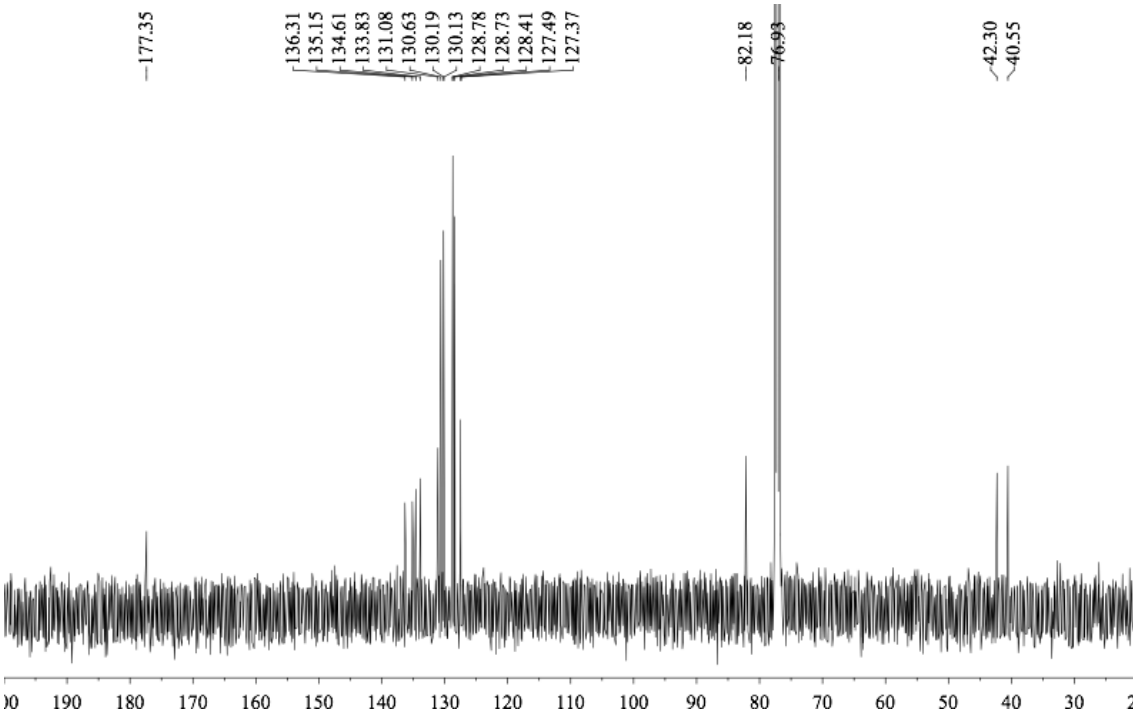


126 MHz ^{13}C-NMR in $CDCl_3$

***rac-epi*-Maculalactone L (6.17)**



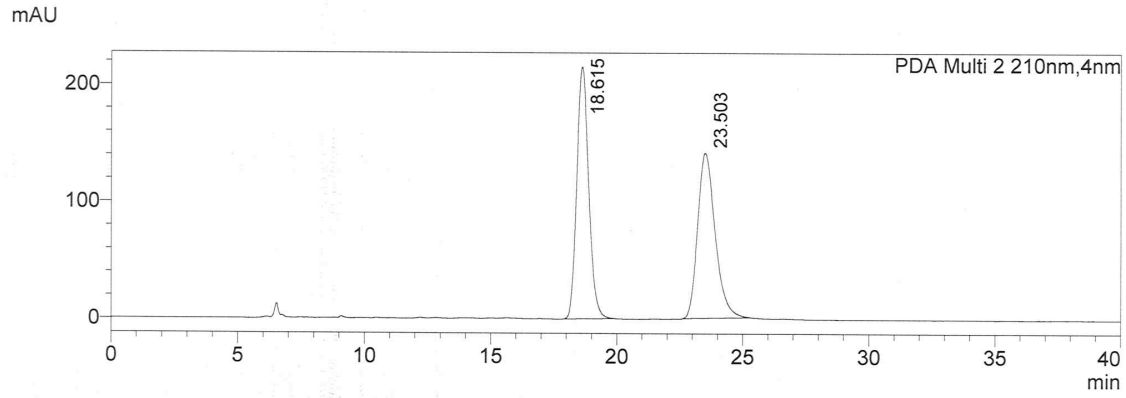
500 MHz ^{1}H-NMR in $CDCl_3$



101 MHz ^{13}C-NMR in $CDCl_3$

9.3 Chiral HPLC

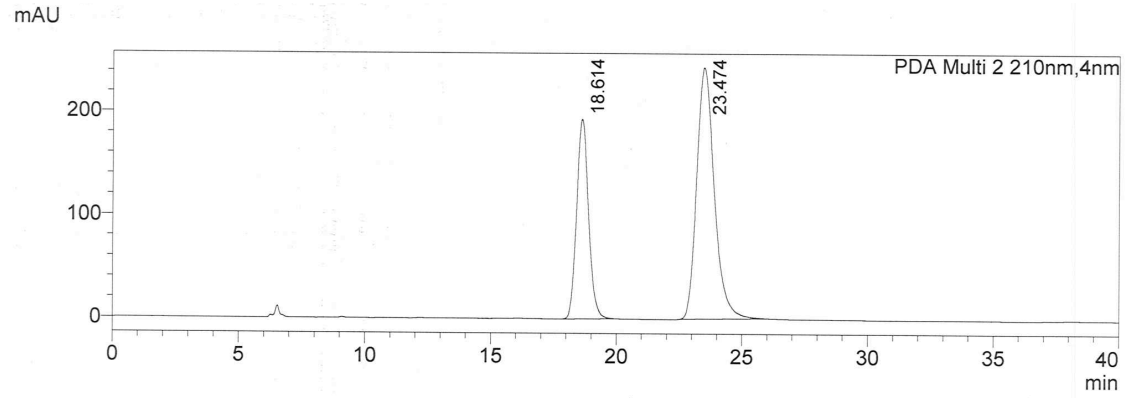
9.3.1 3,4,5-Tribenzyl-5-(3-hydroxy-1-phenylpropyl)furan-2(5H)-one (4.17)



PDA Ch2 210nm

Peak#	Ret. Time	Height	Area	Area%
1	18.615	215268	7107396	50.927
2	23.503	141028	6848653	49.073
Total		356296	13956049	100.000

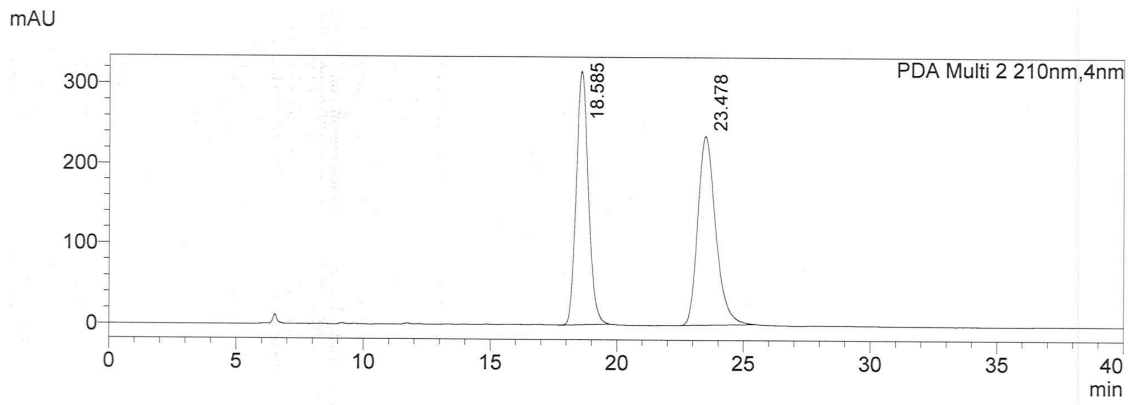
Racemic sample, LOT: Mul136B, (Chiralpak IC column from Daicel, heptane/*i*PrOH (80:20), 0.5 ml/min, 25 °C, 210nm)



PDA Ch2 210nm

Peak#	Ret. Time	Height	Area	Area%
1	18.614	193476	6395469	34.911
2	23.474	244093	11923650	65.089
Total		437569	18319119	100.000

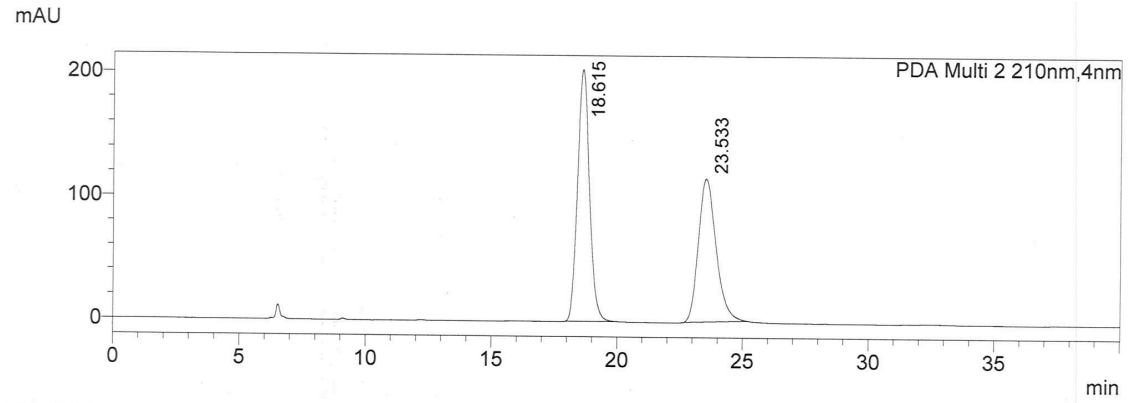
Vinylogous Michael addition with PTC **2.12** at 0 to 5 °C, LOT: Mul134B, (Chiralpak IC column from Daicel, heptane/*i*PrOH (80:20), 0.5 ml/min, 25 °C, 210nm)



PDA Ch2 210nm

Peak#	Ret. Time	Height	Area	Area%
1	18.585	315712	10546715	47.602
2	23.478	235602	11609108	52.398
Total		551314	22155823	100.000

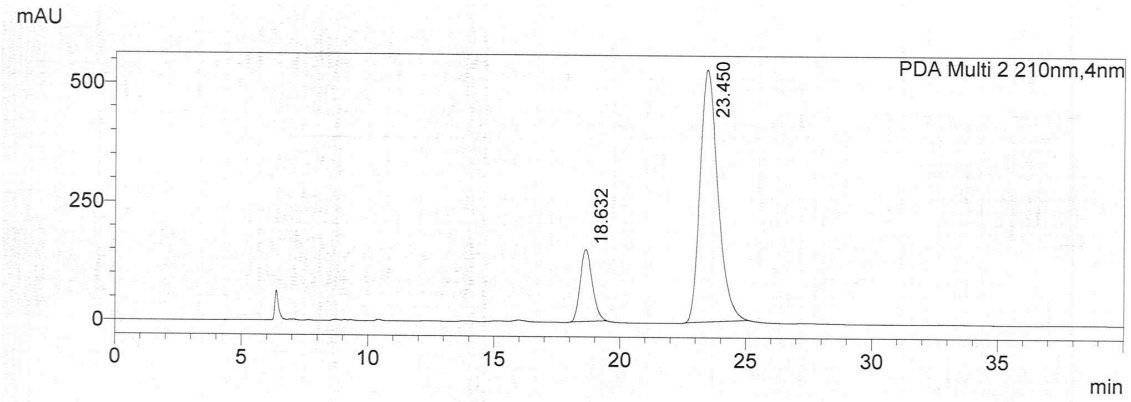
Vinylogous Michael addition with PTC **4.15** at 0 to 5 °C, LOT: Mul135B, (Chiralpak IC column from Daicel, heptane/*i*PrOH (80:20), 0.5 ml/min, 25 °C, 210nm)



PDA Ch2 210nm

Peak#	Ret. Time	Height	Area	Area%
1	18.615	203372	6721876	54.163
2	23.533	115933	5688567	45.837
Total		319305	12410443	100.000

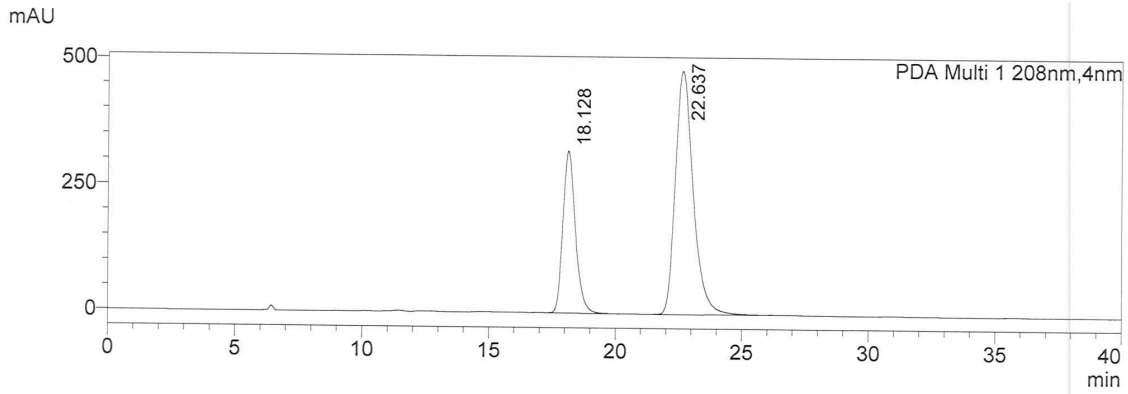
Vinylogous Michael addition with PTC **4.16** at 0 to 5 °C, LOT: Mul133B, (Chiralpak IC column from Daicel, heptane/*i*PrOH (80:20), 0.5 ml/min, 25 °C, 210nm)



PDA Ch2 210nm

Peak#	Ret. Time	Height	Area	Area%
1	18.632	151574	5039779	16.117
2	23.450	530277	26230391	83.883
Total		681851	31270171	100.000

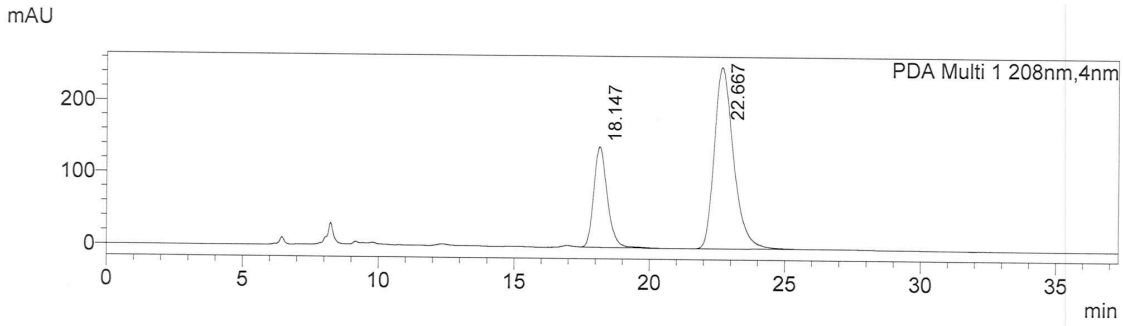
Vinylogous Michael addition with PTC **2.12** at -15 °C, LOT: Sb229.2, (Chiralpak IC column from Daicel, heptane/*i*PrOH (80:20), 0.5 ml/min, 25 °C, 210nm)



PDA Ch1 208nm

Peak#	Ret. Time	Height	Area	Area%
1	18.128	321705	11117212	31.828
2	22.637	482391	23812075	68.172
Total		804096	34929288	100.000

Vinylogous Michael addition with PTC **2.12** at -15 °C, scale-up to 0.76 mmol with mechanical stirring, LOT: Sb323.2, (Chiralpak IC column from Daicel, heptane/*i*PrOH (80:20), 0.5 ml/min, 25 °C, 208nm)



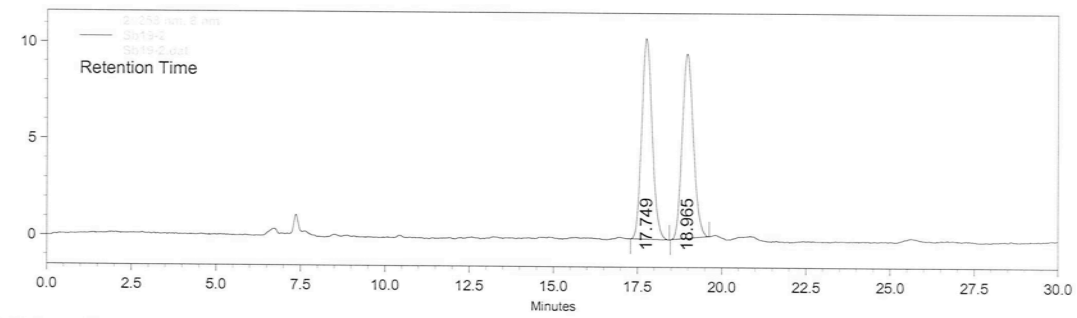
Peak Table

PDA Ch1 208nm

Peak#	Ret. Time	Height	Area	Area%
1	18.147	139273	4837041	27.936
2	22.667	251440	12477426	72.064
Total		390714	17314467	100.000

Vinylogous Michael addition with PTC **2.12** at -15 °C, scale-up to 0.76 mmol with mechanical stirring, LOT: Sb458.2, (Chiralpak IC column from Daicel, heptane/*i*PrOH (80:20), 0.5 ml/min, 25 °C, 208nm)

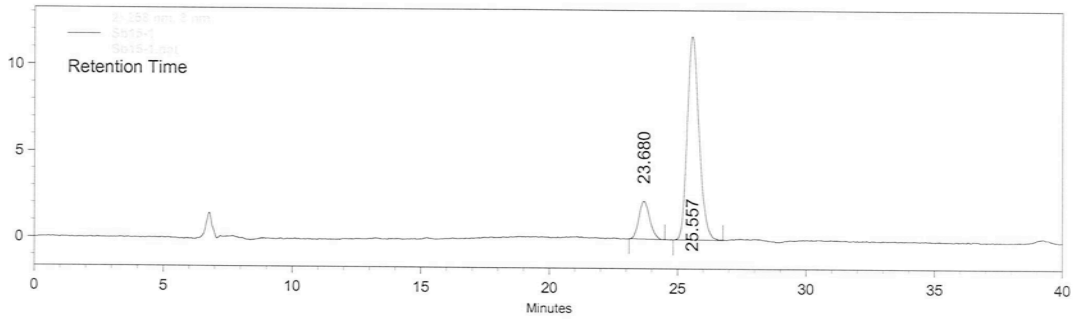
9.3.2 (*R*)-2-Benzyl-1-((*S*)-2-benzyloxiran-2-yl)prop-2-en-1-ol (5.14)



2: 258 nm, 8 nm

Retention Time	Area	Area Percent
17.749	224513	50.46
18.965	220444	49.54
Totals	444957	100.00

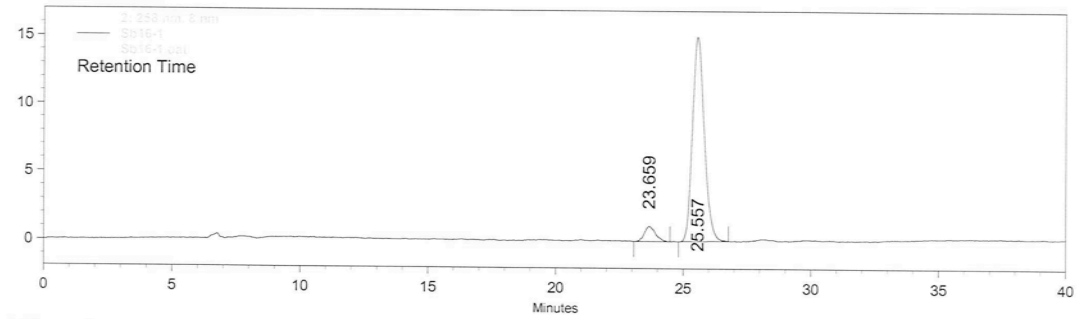
Racemic sample, LOT: Sb19.2, (Chiralpak IC column from Daicel, heptane/*i*PrOH (95:5), 0.5 ml/min, 20 °C, 258nm)



2: 258 nm, 8 nm

Retention Time	Area	Area Percent
23.680	64462	14.62
25.557	376486	85.38
Totals	440948	100.00

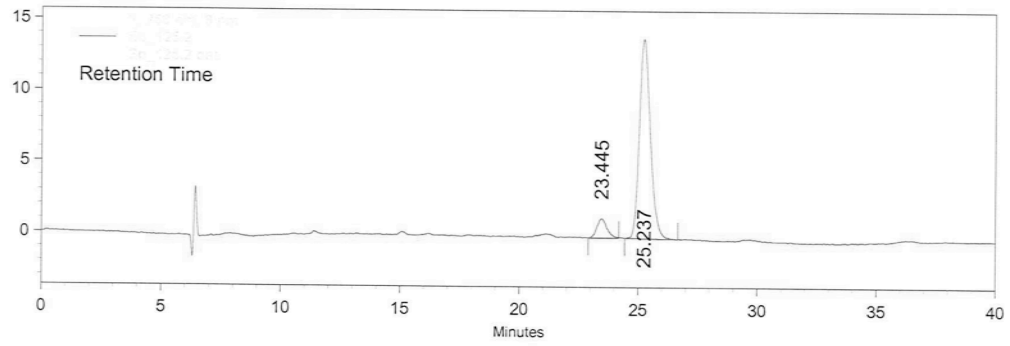
Sharpless with DET, LOT: Sb15.1, (Chiralpak IC column from Daicel, heptane/*i*PrOH (97:3), 0.5 ml/min, 20 °C, 258nm)



2: 258 nm, 8 nm

Retention Time	Area	Area Percent
23.659	33112	6.40
25.557	484616	93.60
Totals	517728	100.00

Sharpless with DIPT, LOT: Sb16.1, (Chiralpak IC column from Daicel, heptane/*i*PrOH (95:5), 0.5 ml/min, 20 °C, 258nm)



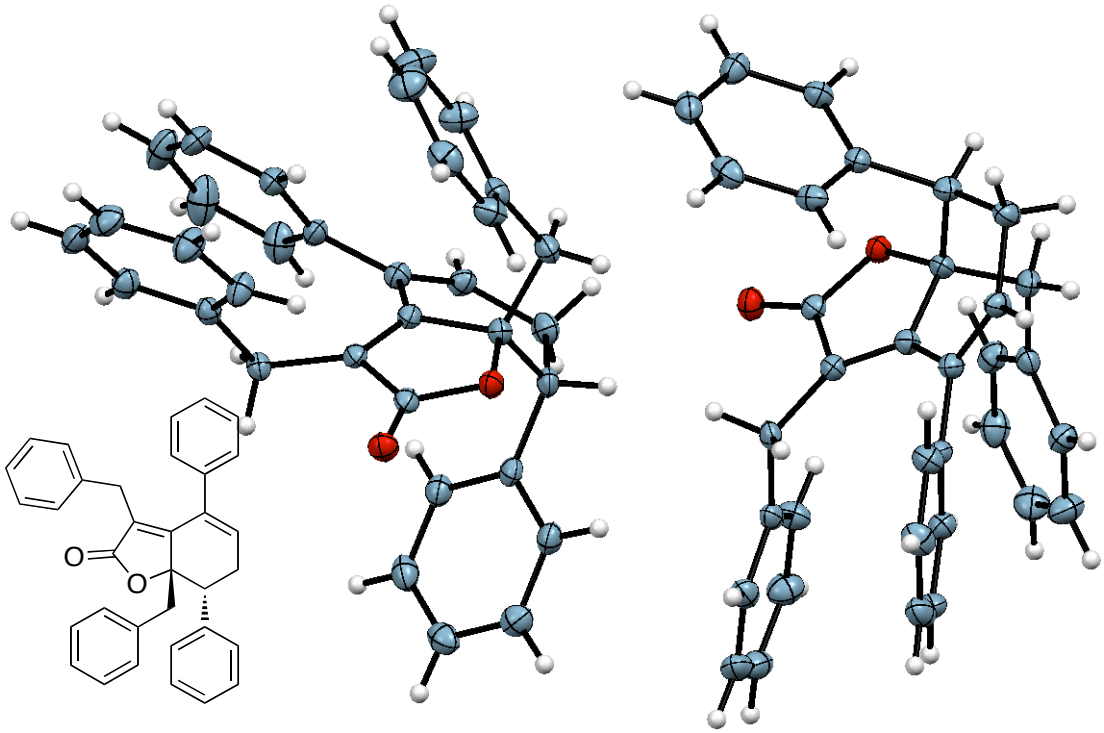
2: 258 nm, 8 nm

Retention Time	Area	Area Percent
23.445	38773	7.93
25.237	450305	92.07
Totals	489078	100.00

Sharpless with DIPT, LOT: Sb125.2, (Chiralpak IC column from Daicel, heptane/*i*PrOH (97:3), 0.5 ml/min, 20 °C, 258nm)

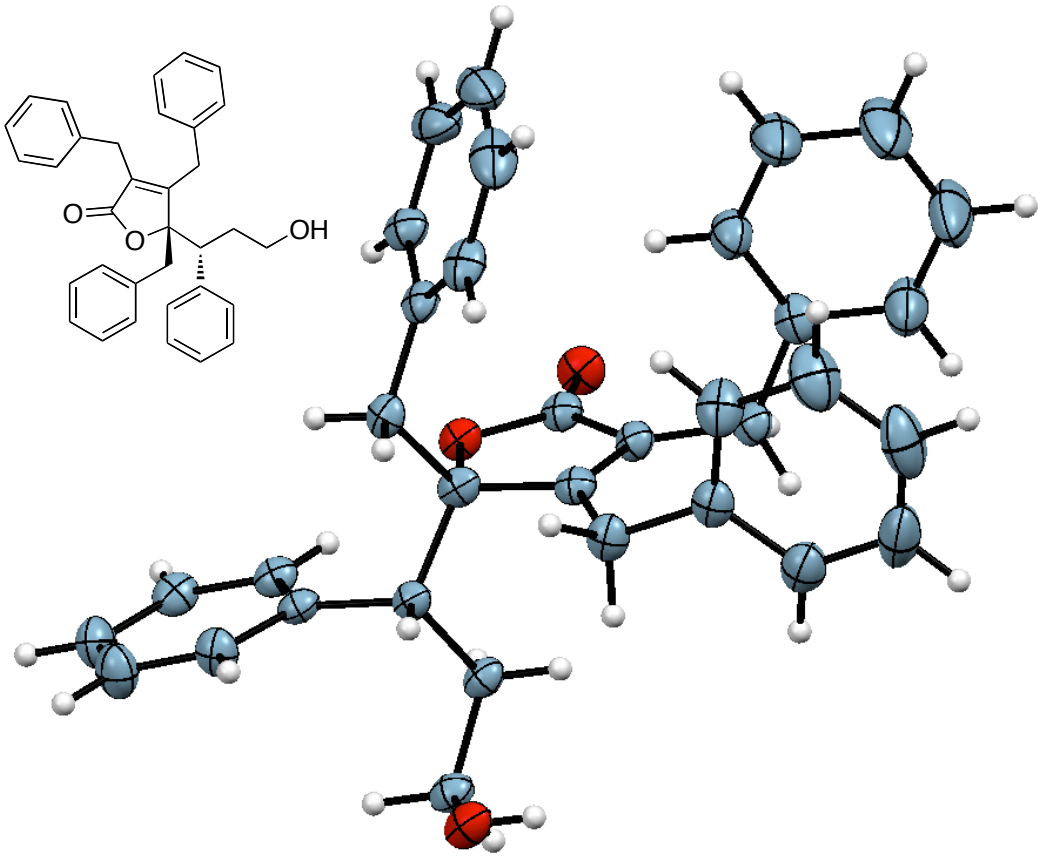
9.4 X-Ray Diffraction Analysis

3,7a-Dibenzyl-4,7-diphenyl-7,7a-dihydrobenzofuran-2(6H)-one (4.14)



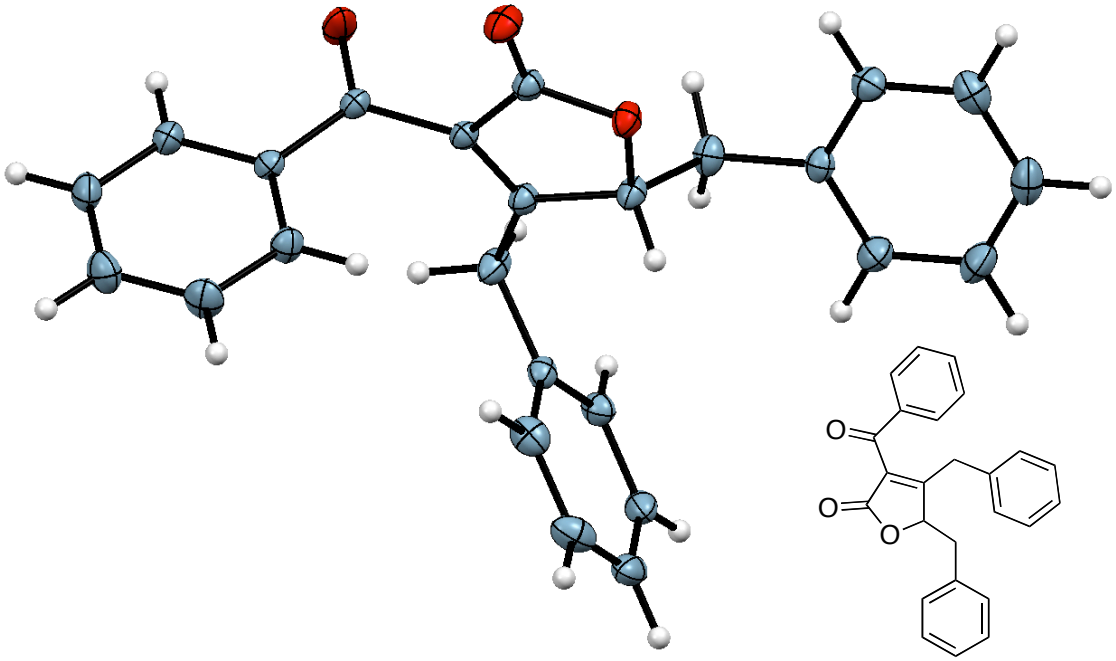
formula	$C_{34}H_{28}O_2$
formula weight	468.59
Z, calculated density	8, 1.258 Mg · m^{-3}
F(000)	1984
description and size of crystal	colourless plate, 0.040 · 0.170 · 0.260 mm^3
absorption coefficient	0.077 mm^{-1}
min/max transmission	0.99 / 1.00
temperature	123K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, C c
a	26.6904(15) Å
b	14.6073(8) Å
c	13.0650(7) Å
α	90°
β	103.804(3)°
γ	90°
V	4946.6(5) $Å^3$
min/max Θ	1.600° / 30.133°
number of collected reflections	30954
number of independent refections	7274 (merging r = 0.042)
number of observed reflections	6564 (I>2.0σ(I))
number of refined parameters	649
r	0.0633
rW	0.0853
goodness of fit	1.0603

3,4,5-Tribenzyl-5-(3-hydroxy-1-phenylpropyl)furan-2(5H)-one (4.17)



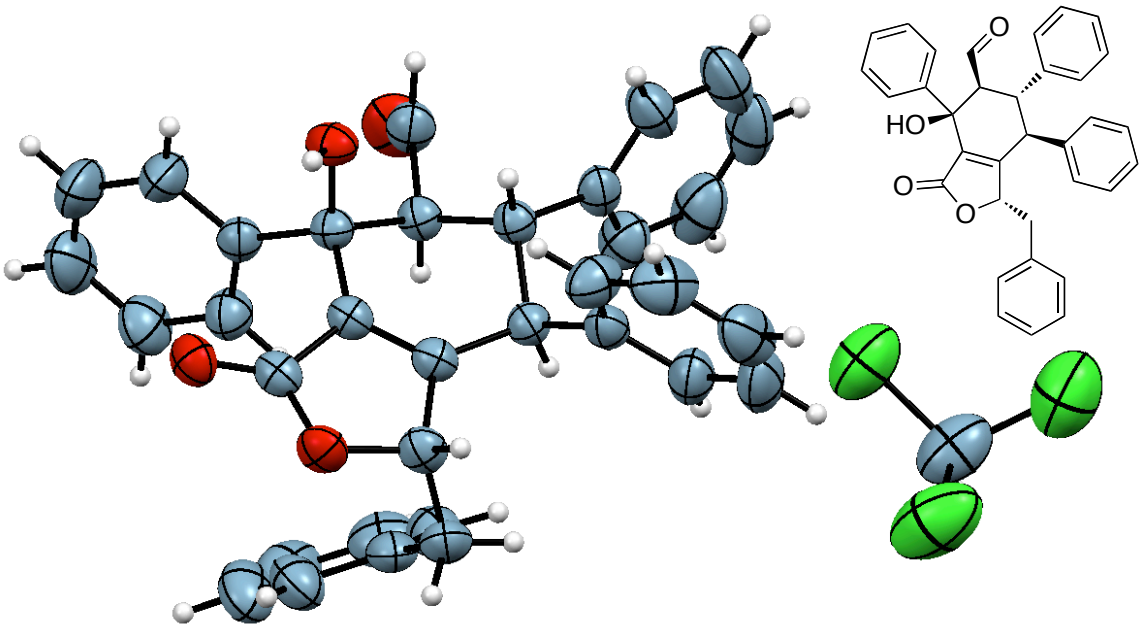
formula	$C_{34}H_{32}O_3$
formula weight	488.63 Z,
calculated density	4, 1.236 Mg · m^{-3}
F(000)	1040
description and size of crystal	colourless plate, 0.040 · 0.170 · 0.210 mm^3
absorption coefficient	0.077 mm^{-1}
min/max transmission	0.99 / 1.00
temperature	123K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, P $2_1/c$
a	14.658(2) Å
b	13.7997(18) Å
c	13.2307(17) Å
α	90°
β	101.228(9)°
γ	90°
V	2625.0(6) $Å^3$
min/max Θ	2.046° / 27.497°
number of collected reflections	32367
number of independent refections	6010 (merging r = 0.112)
number of observed reflections	3362 (I>2.0σ(I))
number of refined parameters	334
r	0.0518
rW	0.0944
goodness of fit	1.1262

3-Benzoyl-4,5-dibenzylfuran-2(5H)-one (4.27)



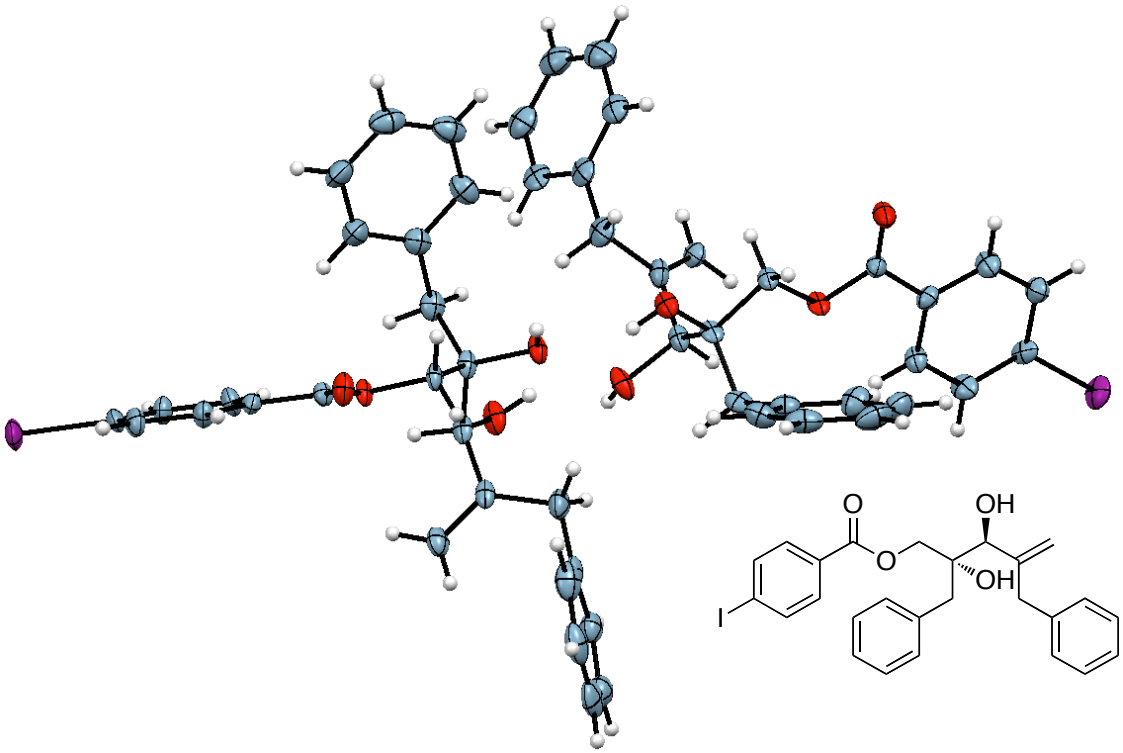
formula	$C_{25}H_{20}O_3$
formula weight	368.43 Z,
calculated density	4, 1.271 Mg · m^{-3}
F(000)	776
description and size of crystal	colourless plate, 0.040 · 0.130 · 0.210 mm^3
absorption coefficient	0.083 mm^{-1}
min/max transmission	0.99 / 1.00
temperature	123K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, P $2_1/c$
a	11.8690(10) Å
b	16.8261(13) Å
c	10.4258(9) Å
α	90°
β	112.399(4)°
γ	90°
V	1925.0(3) $Å^3$
min/max Θ	1.856° / 32.580°
number of collected reflections	32920
number of independent refections	6985 (merging r = 0.039)
number of observed reflections	4482 (I>2.0σ(I))
number of refined parameters	253
r	0.0429
rW	0.0829
goodness of fit	1.1121

1-Benzyl-4-hydroxy-3-oxo-4,6,7-triphenyl-1,3,4,5,6,7-hexahydroisobenzofuran-5-carbaldehyde (4.28)



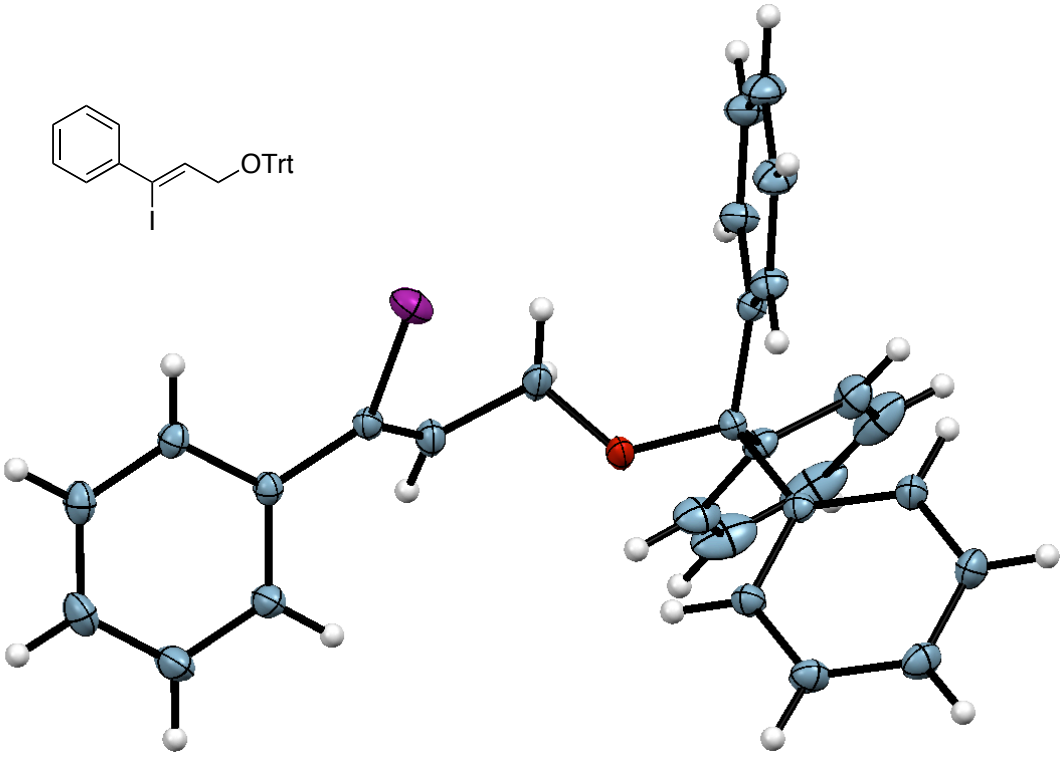
formula	$C_{35}H_{29}Cl_3O_4$
formula weight	619.97 Z,
calculated density	2, 1.314 Mg · m^{-3}
F(000)	644
description and size of crystal	colourless block, 0.070 · 0.180 · 0.270 mm^3
absorption coefficient	2.948 mm^{-1}
min/max transmission	0.59 / 0.81
temperature	123K
radiation(wavelength)	Cu K_α (λ = 1.54180 Å)
Crystal system, space group	triclinic, P -1
a	9.2387(5) Å
b	10.1306(6) Å
c	17.4005(10) Å
α	104.717(2)°
β	94.407(2)°
γ	92.523(3)°
V	1567.08(16) $Å^3$
min/max Θ	2.636° / 68.241°
number of collected reflections	15196
number of independent refections	5488 (merging r = 0.032)
number of observed reflections	4843 (I>2.0σ(I))
number of refined parameters	379
r	0.0669
rW	0.0790
goodness of fit	1.0806

(2*R*,3*S*)-2,4-Dibenzyl-2,3-dihydroxypent-4-en-1-yl 4-iodobenzoate (5.34)



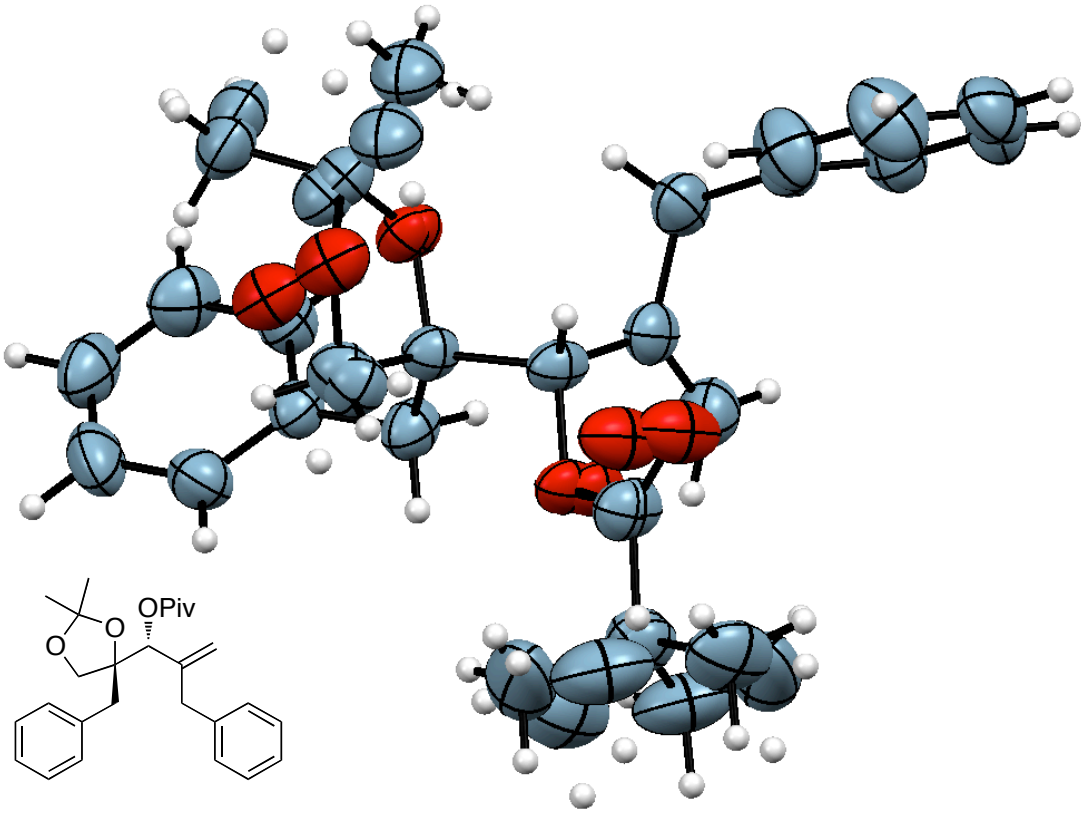
formula	$C_{26}H_{25}I_1O_4$
formula weight	528.39 Z,
calculated density	2, 1.544 Mg · m^{-3}
F(000)	532
description and size of crystal	colourless needle, 0.030 · 0.040 · 0.310 mm^3
absorption coefficient	1.439 mm^{-1}
min/max transmission	0.94 / 0.96
temperature	123K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	triclinic, P 1
a	5.6359(7) Å
b	13.7031(17) Å
c	15.0995(17) Å
α	82.314(8)°
β	79.604(5)°
γ	89.600(6)°
V	1136.5(2) $Å^3$
min/max Θ	1.899° / 27.484°
number of collected reflections	19016
number of independent refections	10123 (merging r = 0.036)
number of observed reflections	7325 (I>2.0σ(I))
number of refined parameters	560
r	0.0441
rW	0.0501
goodness of fit	1.1145

(*Z*)-(((3-Iodo-3-phenylallyl)oxy)methanetriyl)tribenzene (5.40)



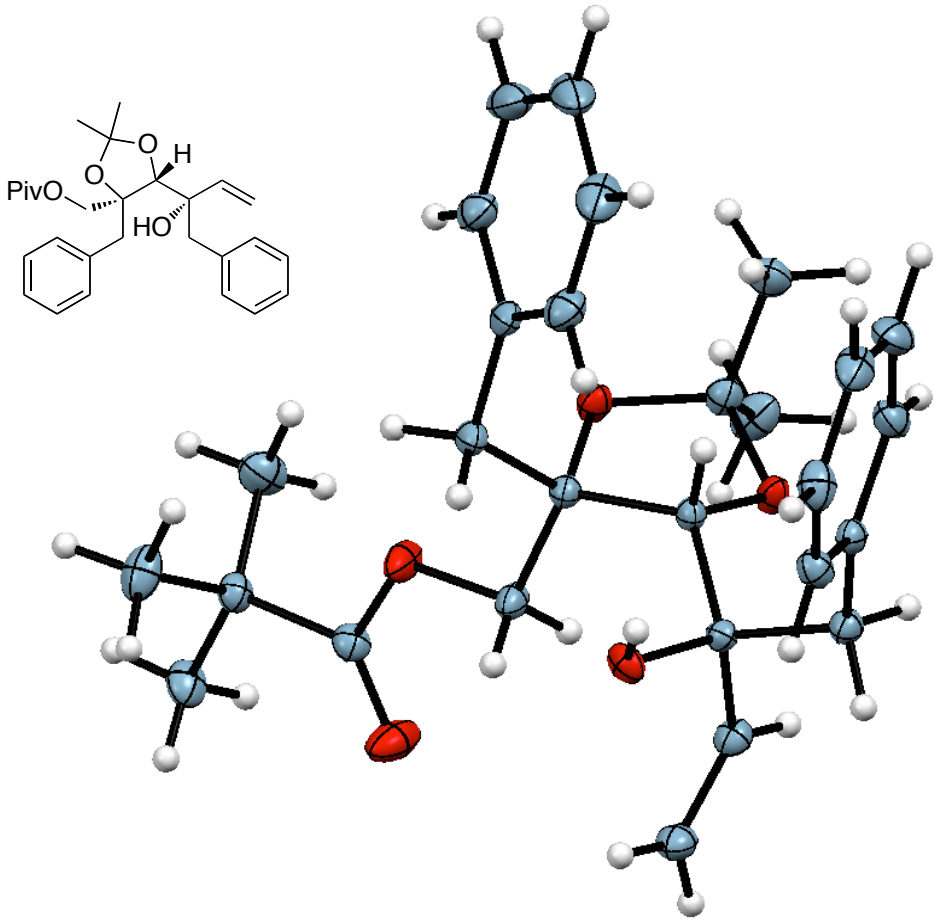
formula	$C_{28}H_{23}I_1O_1$
formula weight	502.39 Z,
calculated density	2, 1.495 Mg · m^{-3}
F(000)	504
description and size of crystal	colourless block, 0.110 · 0.180 · 0.320 mm^3
absorption coefficient	1.452 mm^{-1}
min/max transmission	0.77 / 0.85
temperature	123K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	triclinic, P -1
a	9.7741(3) Å
b	11.3226(3) Å
c	11.3299(3) Å
α	73.3990(10)°
β	83.8660(10)°
γ	68.1930(10)°
V	1115.61(5) $Å^3$
min/max Θ	1.876° / 36.318°
number of collected reflections	38378
number of independent refections	10736 (merging r = 0.025)
number of observed reflections	9077 (I>2.0σ(I))
number of refined parameters	271
r	0.0224
rW	0.0279
goodness of fit	1.0839

(*R*)-2-Benzyl-1-((*S*)-4-benzyl-2,2-dimethyl-1,3-dioxolan-4-yl)allyl pivalate (5.45)



formula	$C_{27}H_{34}O_4$
formula weight	422.56 Z,
calculated density	2, 1.170 Mg · m^{-3}
F(000)	456
description and size of crystal	colourless needle, 0.050 · 0.070 · 0.270 mm^3
absorption coefficient	0.611 mm^{-1}
min/max transmission	0.96 / 0.97
temperature	293K
radiation(wavelength)	Cu K_α (λ = 1.54178 Å)
Crystal system, space group	triclinic, P -1
a	9.2792(4) Å
b	10.3290(4) Å
c	14.0397(6) Å
α	90.580(2)°
β	108.348(2)°
γ	108.790(2)°
V	1199.81(9) $Å^3$
min/max Θ	4.557° / 69.427°
number of collected reflections	14130
number of independent refections	4331 (merging r = 0.030)
number of observed reflections	4031 (I>2.0σ(I))
number of refined parameters	399
r	0.0474
rW	0.0590
goodness of fit	1.1328

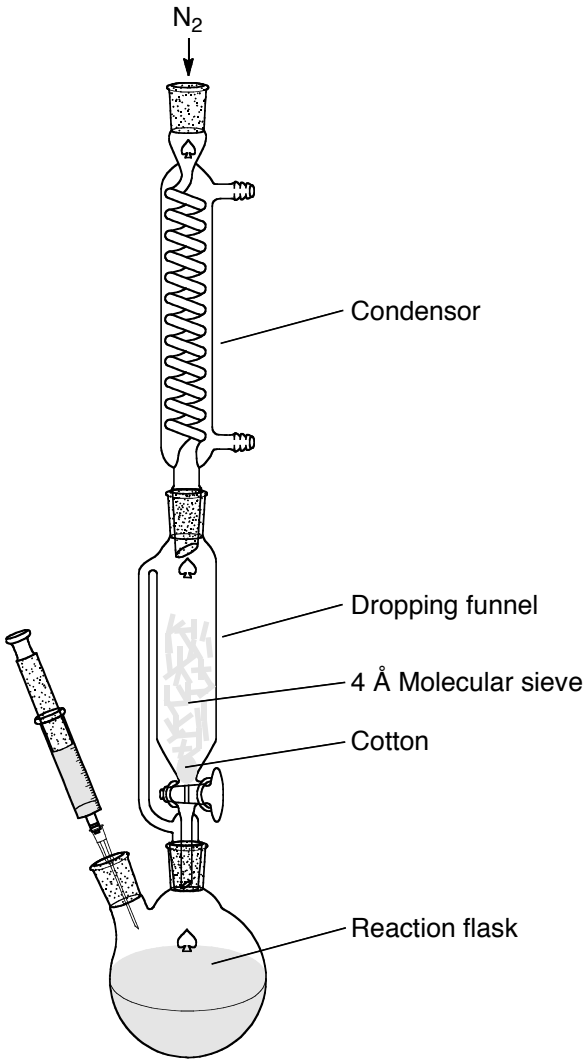
((4*S*,5*R*)-4-Benzyl-5-((*S*)-2-hydroxy-1-phenylbut-3-en-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl pivalate (5.48)



formula	$C_{28}H_{36}O_5$
formula weight	452.59 Z,
calculated density	4, 1.208 Mg · m^{-3}
F(000)	976
description and size of crystal	colourless block, 0.050 · 0.130 · 0.190 mm^3
absorption coefficient	0.081 mm^{-1}
min/max transmission	0.99 / 1.00
temperature	123K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	orthorhombic, P 2_1 2_1 2_1
a	7.4755(2) Å
b	12.1299(3) Å
c	27.4449(6) Å
α	90°
β	90°
γ	90°
V	2488.62(11) $Å^3$
min/max Θ	1.836° / 31.506°
number of collected reflections	58760
number of independent refections	4646 (merging r = 0.047)
number of observed reflections	3766 (I>2.0σ(I))
number of refined parameters	298
r	0.0341
rW	0.0503
goodness of fit	1.1242

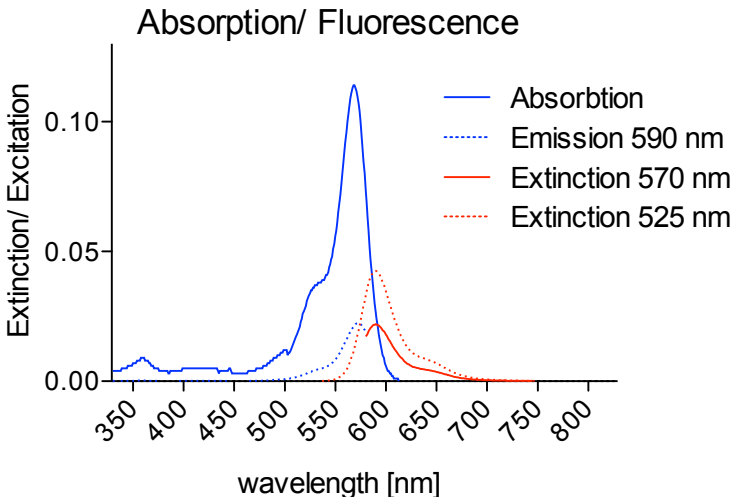
9.5 Various

9.5.1 Apparatus for Maculalactone A Synthesis

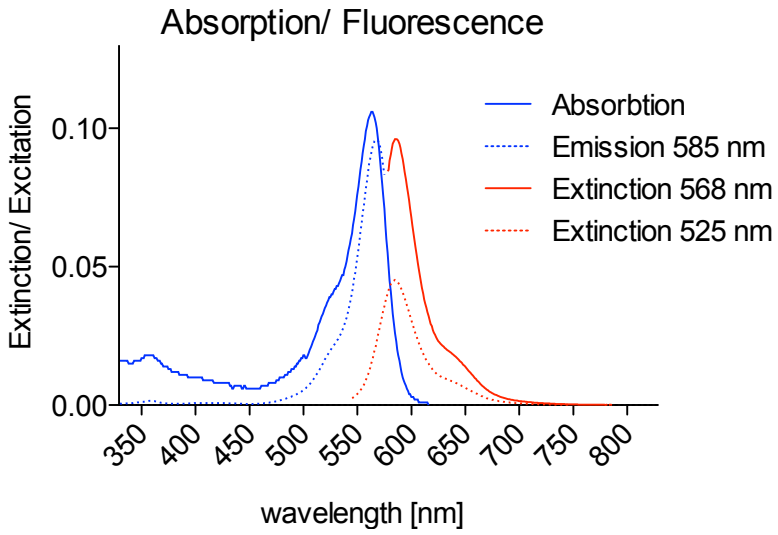


Apparatus for the cyclization of ester **2.31** as described in chapter 2.

9.5.2 Absorption and Fluorescence Spectra



Spectra of compound **3.47** with emission at 590 nm under varying extinction and extinction at 525 and 570 nm and varying emission. The absolute values vary due to differences in the extinction energy. λ_{max} = 568 nm.



Spectra of compound **3.48** with emission at 585 nm under varying extinction and extinction at 525 and 568 nm and varying emission. The absolute values vary due to differences in the extinction energy: λ_{max} = 563 nm.

9.6 Curriculum Vitae

Name: Samuel Bader

Date of birth: January 28, 1982

Place of origin Lauperswil BE, Switzerland

Education

2014	Ph.D., Organic Chemistry, University of Basel. Thesis Titel: "Higher Marine Phenylpropanoids: Synthesis and Biology of Maculalactones and Ophiodilactones" Prof. Dr. K. Gademann.
2010	M.Sc., Organic Chemistry, University of Basel. Thesis Title: "Synthesis and Properties of Bidentate Boron Lewis Acids and Their Potential as Catalysts in Organic Chemistry." Prof. Dr. H. A. Wegner.
2006	Diploma, Process Chemistry, University of Applied Sciences and Art Northwestern Switzerland. Thesis Title: "Yield Optimization on the Hydroxenin Stage in the Vitamine A Process." Prof. Dr. M. Barblan.
2002	Baccalaureate, School for Professionals, Basel.
2001	Chemielaborant (laboratory technician), F. Hoffmann-La Roche AG, Basel.

Work Experience

2006 - 2008	Laboratory Development Expert, DSM Nutritional Products AG, Sisseln. Vitamin A and E process development and support.
2001	Laboratory Technician, F. Hoffmann-La Roche AG, Basel. Combinatorial and high throughput chemistry.

Award

2012 Clariant CleanTech Award, first place awarded for the project entitled: "Development of a new Antifouling Agent: The Protection of Metal Surfaces with (±)-Maculalactone A."

Publications

2013 Bader, S. L.; Kessler, S. N.; Zampese, J. A.; Wegner, H. A. "Exploration of 1,2-phenylenediboronic esters as potential bidentate catalysts for organic synthesis," *Monatsh. Chem.* **2013**, *144*, 531–537.

2010 Bader, S. L.; Kessler, S. N.; Wegner, H. A. "A Convenient Iron-Catalyzed Method for the Preparation of 1,2-Bis(trimethylsilyl)benzenes," *Synthesis* **2010**, *16*, 2759–2762.

Internships

2009 "Au-Catalyzed Domino Cyclization and Oxidative Coupling Reaction," Prof. Dr. H. A. Wegner, University of Basel.

2005 "Identification of Key Performance Indicators (KPI's) in a biological process with *E. coli*," Prof. Dr. M. Barblan, University of Applied Sciences and Art Northwestern Switzerland.

2004 "Development of a Personalized Biology-Based Security Marker," Prof. Dr. D. Gygax, University of Applied Sciences and Art Northwestern Switzerland.

2003 Biotechnological Development, Novartis Pharma AG, Basel.

2000 Process Research, F. Hoffmann-La Roche AG, Basel.

Further Training

2008 Six-Sigma Green Belt, Celerant Consulting GmbH, Sisseln.

Basic Leadership Seminar, DSM Nutritional Products AG, Sisseln.

2007 Berufsbildner (apprentice training certificate), Aprentas, Muttenz.

Organic Chemistry for Professionals from Research and Development, Gesellschaft Deutscher Chemiker (GDCh), Berlin, Germany.

Quality Improvements and Cost Reductions by Experimental Design (DoE), Gesellschaft Deutscher Chemiker (GDCh), Frankfurt, Germany.

Teaching Experience

2013 Laboratory Course Assistant, Organic Chemistry for Pharmacy Students, University of Basel.

2012 Laboratory Course Assistant, Advanced Organic Chemistry, University of Basel.

2011 Lecture Assistant, Organic Chemistry I, University of Basel.

Laboratory Course Assistant, Advanced Organic Chemistry, University of Basel.

Presentations

2013 "Studies Towards the Synthesis of Ophiodilactones A and B," poster presentation, REGIO-Symposium, Mittelwihr, France.

"Studies Towards the Synthesis of Ophiodilactones A and B," poster presentation, SCS Fall Meeting, Lausanne.

"(±)-Maculalactone A: Potential as new Antifouling Agent," poster presentation, Prof. Schönbein Symposium, Basel.

"Studies Towards the Total Synthesis of Ophiodilactones A and B," poster presentation, Komppa symposium, Aalto, Finland.

"Towards the Synthesis of Ophiodilactones A and B," poster presentation, Swiss Snow Symposium, Saas Fee.

2012	"Development of a new Antifouling Agent: The Protection of Metal Surfaces with (±)-Maculalactone A," oral presentation, Clariant Chemistry Day, Basel.
	"Development of Antifouling Agents: A Straight forward Synthesis of (±)-Maculalactone A," poster presentation, Clariant Chemistry Day, Basel.
	"Towards the Synthesis of Ophiodilactone A and B," poster presentation, SCS Fall Meeting, Zürich.
	"Towards the Total Synthesis of Ophiodilactone A and B," poster presentation, Belgian organic synthesis symposium, Leuven, Belgium.
2011	"Towards the Total Synthesis of Ophiodilactone A and B," poster presentation, REGIO-Symposium, Sornetan.
	"Towards the Total Synthesis of Ophiodilactone A and B," poster presentation, SCS Fall Meeting, Lausanne.

Activities

2013	Founding member of the Ph.D. Chemistry Community (PCC) of the University of Basel.
2006	Member of the Swiss Chemical Society (SCS).
	Member of the Division of Industrial and Applied Chemistry of SCS.