Reductive Deoxygenation of Alcohols
&
Synthesis of Novel Natural Products isolated from *Ruscus aculeatus* L.

Dissertation

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gewidmet

Meiner geliebten Frau Veronika

&

Meinen Eltern

“Hoffentlich hat mein Schaden

kein Gehirn genommen!”

Homer Simpson

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Chapter 1

Reductive Deoxygenation of Alcohols – Catalytic Methods beyond Barton McCombie Deoxygenation

This chapter was submitted to the *European Journal of Organic Chemistry* as Microreview.

1 Reductive Deoxygenation of Alcohols – Catalytic Methods beyond Barton McCombie Deoxygenation

The deoxygenation is an extensively studied field in organic chemistry and over the last decades many methods like the Barton McCombie deoxygenation or the deoxygenation with alkali metals in liquid ammonia were established. Within this review we discuss different strategies for the chemoselective catalytic deoxygenation of alcohols with special attention to their scope and limitations. The deoxygenation of derivatives of alcohols and their direct deoxygenation as step-economic alternative are covered with current examples. Catalytic methods can serve as convenient and economic alternatives for established methods in the reduction of carbon oxygen single bonds.

1.1 Introduction

The deoxygenation of alcohols is an important and rather broad area of research in modern organic chemistry. The scope includes the conversion of organic feedstock to biofuel just as the removal of hydroxyl groups in the synthesis of natural products. While for the production of biofuel only non-selective methods are used to convert a mixture of carbohydrates derived from natural resources,[1-4] organic chemists need chemoselective methods for the synthesis of specific molecules. Specific deoxygenation methods should be applicable to various substrates and tolerate a variety of functional groups.

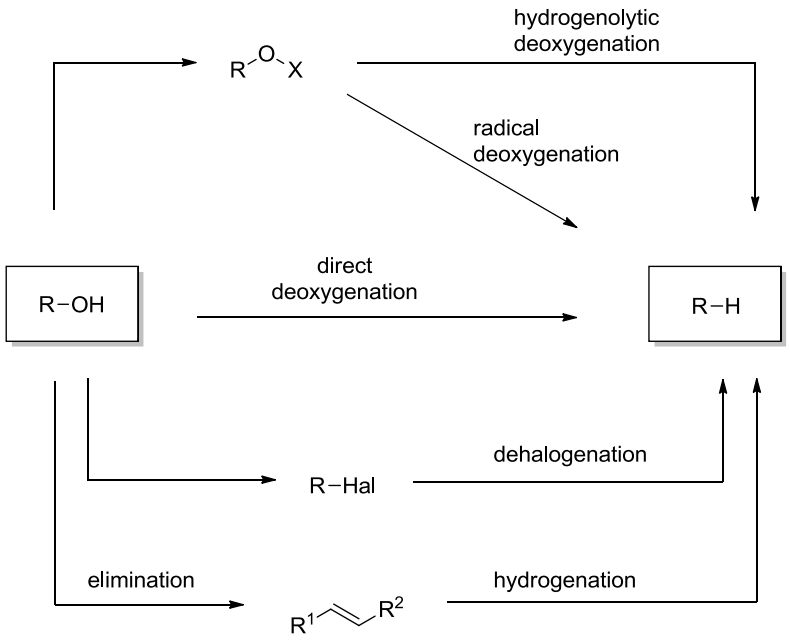


Figure 1.1. Reaction pathways for the deoxygenation of alcohols.

Taking a closer look at the principles of deoxygenation, several pathways should be considered (Figure 1.1). Most methods for the deoxygenation of alcohols employ a two-step procedure. A commonly used two-step deoxygenation of alcohols is the elimination followed by hydrogenation of the resulting carbon-carbon double bond. This principle of dehydration and hydrogenation is the most important method for the conversion of biomass-derived carbohydrates into alkanes.[5] Another possibility is the conversion of the hydroxyl group into a suitable leaving group, which is removed in the second step. The conversion to a halide followed by dehalogenation is a widely used strategy.[6,7] Also, the conversion to ethers or esters is very common with O-thiocarbonyls as typical derivatives. They can be reduced by electron transfer using alkali metals in the so called “dissolving metal reduction”, or with stannanes in the Barton-McCombie-Deoxygenation.[8,9] The use of stannanes as hydride source for the deoxygenation entails disadvantages as they are toxic and hardly to remove from the reaction mixture. Therefore stannanes cannot be used in the synthesis of pharmaceuticals. Several improvements like the catalytic use of stannanes or the use of other hydride sources like silanes have been made.[10] However, undesired radical side reactions and the two step procedure render this approach still disadvantageous. The direct deoxygenation and the use of catalysts are far more desirable.

The aim of this review is to give the reader an overview of catalytic deoxygenation methods, show their substrate scope and the tolerated functional groups. We only discuss catalytic deoxygenation methods for alcohols or their derivatives, with typical examples, as a comprehensive coverage would exceed the scope of this review. Moreover, we exclude the known catalytic Barton McCombie deoxygenation, because it was already reviewed extensively.[10] These catalytic methods may serve synthetic organic chemists as tools for the selective removal of hydroxyl groups and disclose alternatives for the established methods, like the Barton McCombie reaction.

1.2 Deoxygenations employing a two-step procedure

1.2.1 Deoxygenation of alcohol derivatives (ethers, esters)

The removal of a hydroxyl group under mild reaction conditions is challenging, because of the high C-O bond strength, which can be diminished by the conversion of the alcohol into an appropriate derivative, like an ether or ester. In this first part we discuss catalytic deoxygenation methods for such substrates.

1.2.1.1 Transition metal catalysts for the deoxygenation of ethers and esters

Palladium catalyzed deoxygenations

Palladium is one of the most powerful catalysts for the deoxygenation of phenolic hydroxyl groups. The most convenient catalytic approach is the transfer hydrogenation with palladium on charcoal (Pd/C), which is an easy to handle and active reducing system. Before this reductive cleavage can be applied, the hydroxyl group must be converted into a suitable leaving group. Very typical is the transformation into the corresponding aryl sulfonates[11-13], like triflates, tosylates or mesylates. But also isourea derivatives[14,15], thiocarbamates[15], aryl ethers and heteroaromatic ethers[16,17] were successfully reduced by Pd/C with hydrogen (Figure 1.2). Undesired side reactions, like the reduction of

carbon-carbon double bonds, benzyl ethers, nitro groups and chloro arenes, are limiting this method to substrates without reducible functional groups.

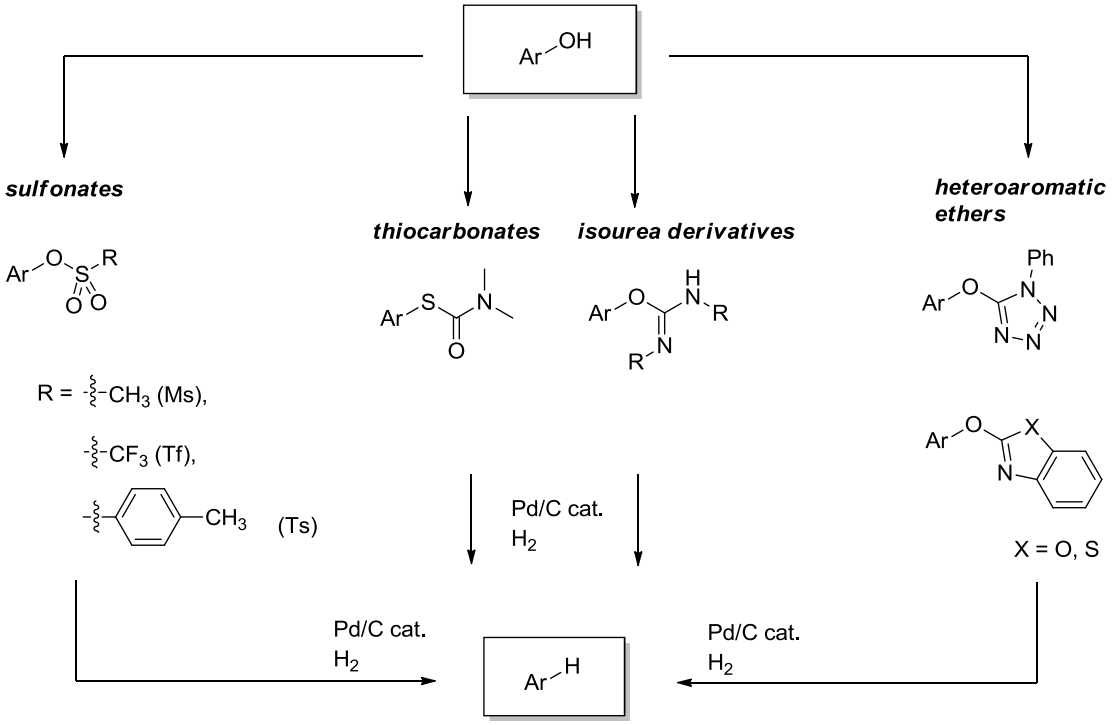
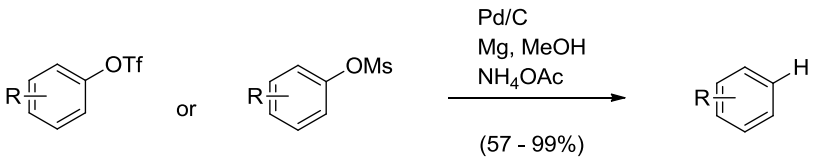


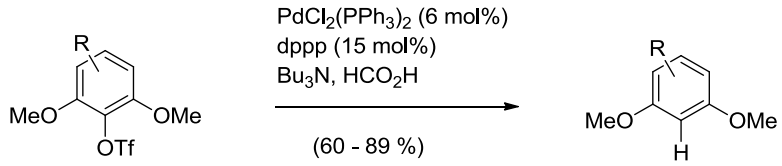
Figure 1.2. Substrates for the deoxygenation by palladium on charcoal catalyzed transfer hydrogenation.

Another mild reducing system was described by Sajiki *et al.*, using Pd/C in combination with Mg/MeOH/NH_4OAc[18] or Et_2NH/MeOH/H_2[19], for the reduction of aryl triflates and mesylates (Scheme 1.1). They describe a mechanism involving a single electron transfer from the ammonium/amine to the aromatic system followed by the cleavage of ¯OTf/¯OMs.[20]



Scheme 1.1. Reductive deoxygenation of aryl triflates and mesylates using Pd/C as catalyst.

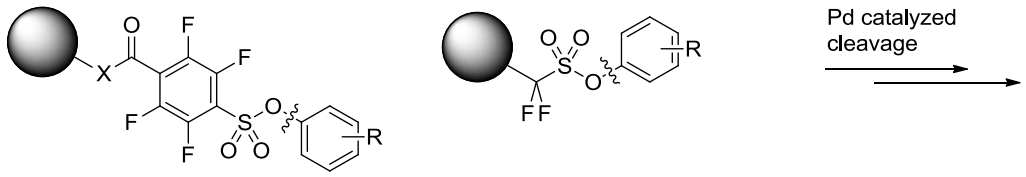
Cacchi *et al.* described a chemoselective homogeneous reduction system using $Pd(OAc)_2$, a phosphine ligand and ammonium formate as hydrogen donor. This method tolerates the presence of carbon–carbon double bonds, nitro groups and ketones in the substrate.[21] Not only a chemoselective deoxygenation is possible, also the deoxygenation of highly sterically hindered phenyl triflates, using $PdCl_2(PPh_3)_2$ with dppp (1,3-bis(diphenylphosphino)propane) as bidentate ligand, was achieved (Scheme 1.2).[22]



Scheme 1.2. Chemoselective deoxygenation of hindered phenols using homogeneous palladium catalysis.[22]

A method, invented by Lipshutz *et al.*, tolerates reducible functional groups, like chloro and bromo groups or olefins, during deoxygenation of perfluoroalkyl sulfonates (OTf, ONf).[23] $Pd(PPh_3)_4$ as homogeneous catalyst, was found to be most effective in combination with $Me_2NH{\bullet}BH_3$, as reductant, and K_2CO_3 in acetonitrile. The presence of potassium carbonate as base was essential in the reduction of substrates containing an olefin; otherwise the hydroboration of the olefin occurred.

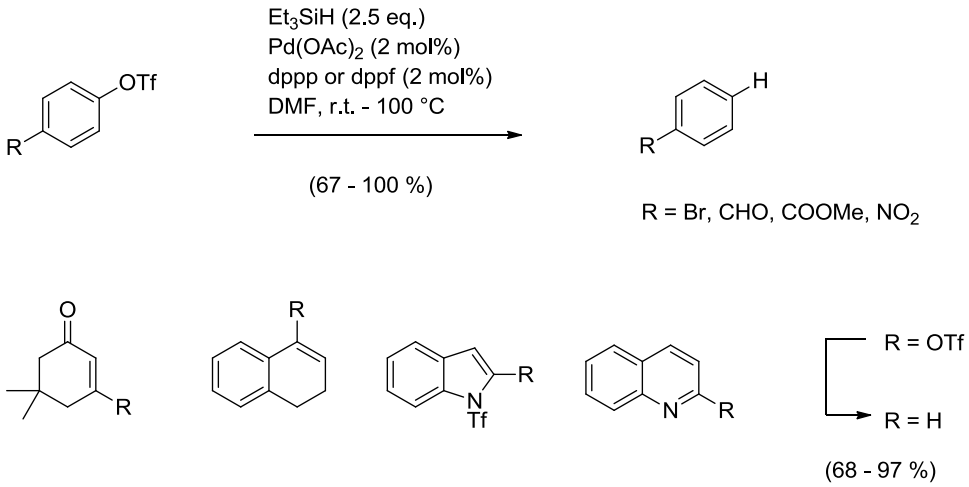
An interesting application of this palladium catalyzed deoxygenation is the cleavage from a solid support. With perfluoroalkylsulfonyl esters as the linker to the resin, the cleavage can be performed by palladium catalyzed deoxygenation.[24-26]



Scheme 1.3. Perflouroalkylsulfonates as linker to a solid phase cleavable by palladium catalyzed deoxygenation.[24-26]

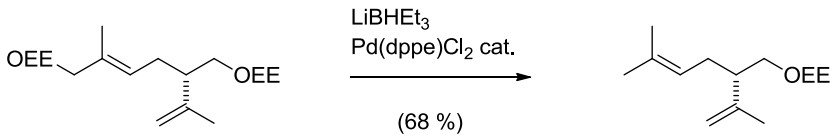
Closely associated to the deoxygenation of phenolic hydroxyl groups is the deoxygenation of enols, which proceeds effectively with vinyl triflates and homogeneous palladium catalysis using $Pd(OAc)_2$ in combination with dppp (1,3-bis(diphenyl-

phosphino)propane) or dppf (1,3-bis(diphenylphosphino)ferrocene) as ligand and Et_3SiH as hydride source.[27] This procedure was found to deoxygenate even stabilized triflates while other reducible functional groups like esters, aldehydes, nitro or bromo groups and olefins were unaffected (Scheme 1.4). A similar method with $Pd(PPh_3)_4$, $NaBH_4$ and NEt_3 was used to deoxygenate vinyl triflates of nucleotides.[28]



Scheme 1.4. Aryl and vinyl triflates deoxygenated by homogeneous palladium catalysis.[27]

Beside phenolic hydroxyl groups also allyl alcohols can be deoxygenated catalytically with palladium.[29-31] Their alkoxyalkyl ethers (methoxymethyl MOM or ethoxyethyl EE) can be deoxygenated selectively in the presence of other ethers, shown exemplary in the synthesis of lavendulol (Scheme 1.5).[32] The ethoxy ethyl ether of the allyl alcohol was removed selectively.



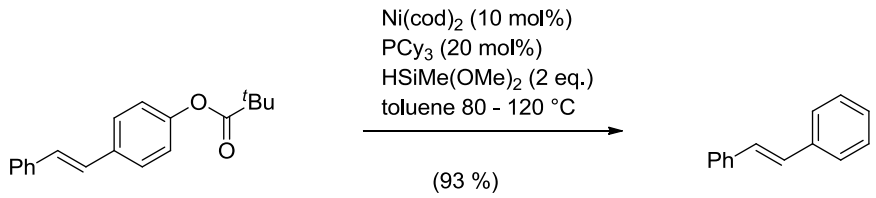
Scheme 1.5. Chemoselective deoxygenation of allyl alcohol in the synthesis of lavendulol.[32]

This reduction proceeds *via* a π-allyl-palladium intermediate by hydride transfer. The deoxygenation method was also successfully applied in the synthesis of desoxyribose derivatives of pyrimidine nucleosides.[33]

Nickel catalyzed deoxygenations

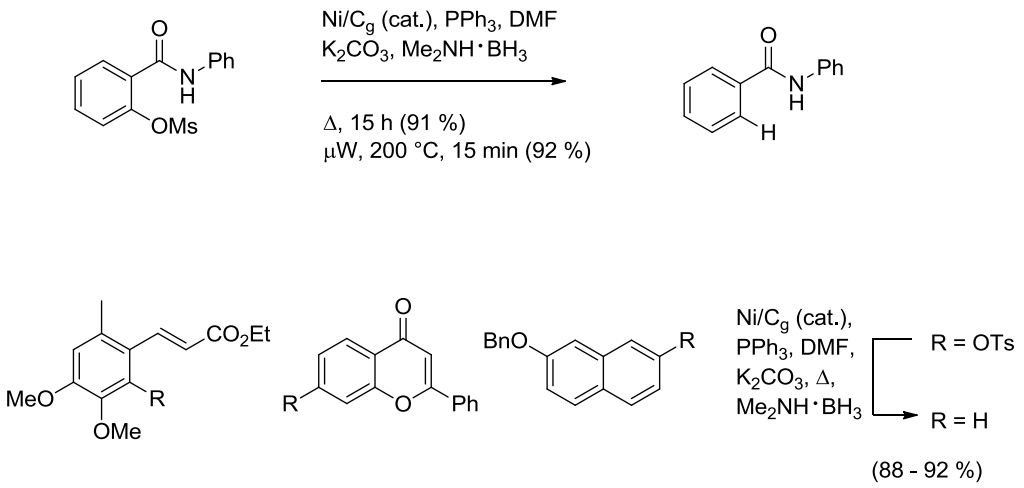
Nickel is becoming more popular in recent years as a cheap and more available alternative for palladium catalysts.[34] Nickel(0) has d^{10} configuration that is often found to be highly active in catalysis. And, like palladium, it is used as catalyst for carbon-carbon bond coupling reactions.[35,36]

Already 1975, Lonsky *et al.* reported the use of Raney nickel for the deoxygenation of potassium aryl sulfates.[37] Later, the use of Raney nickel as catalyst for the transfer hydrogenation of aryl and vinyl perfluoroalkyl sulfonates was compared with palladium and PtO_2 catalysts and a very high potential of this catalyst for the deoxygenation was found.[38] However, the substrates and the reductants for the deoxygenation with nickel are similar to the substrates for deoxygenations with palladium. Sasaki *et al.* have shown the deoxygenation of aryl triflates[39] and mesylates[40] with $NiBr_2(PPh_3)_3$/dppp catalyst, zinc as reductant and methanol as hydrogen donor. Another commonly used homogeneous catalyst for the deoxygenation is $Ni(cod)_2$; it was used for the effective hydrogenolysis of alkyl aryl ethers and benzyl ethers using hydrogen,[41,42] but this is a very unselective protocol. More interesting is the use of a different reductant resulting in enhanced chemoselectivity. With silane hydride as reductant, alkoxy aryl ethers and, more easily, aryl pivaloates are effectually deoxygenated without reduction of olefins (Scheme 1.6).[43]



Scheme 1.6. Homogeneous catalyst for the chemoselective deoxygenation of aryl ethers and esters.[43]

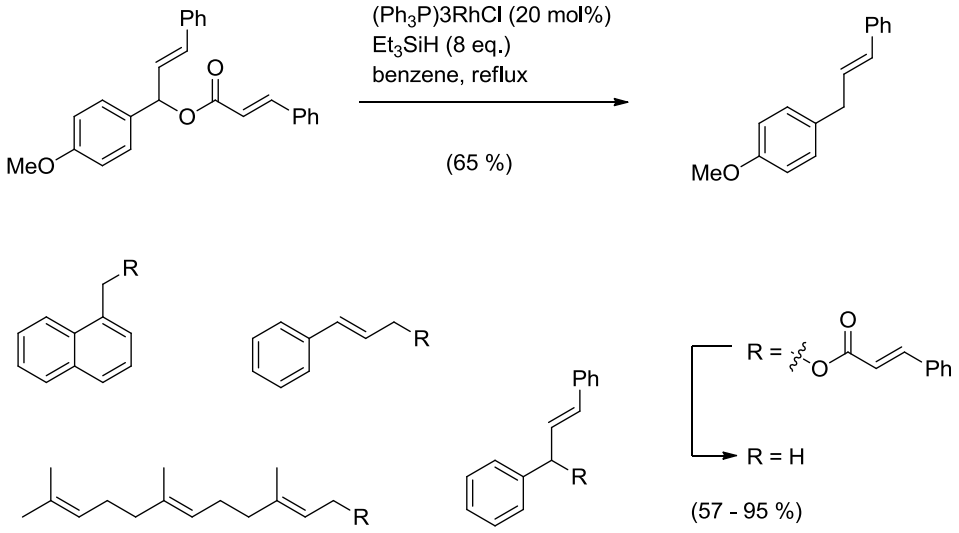
Nickel on graphite was found to have several advantages like lower costs and higher thermal conductivity, which is important for microwave assisted reactions, and compable with nickel on charcoal.[44] In combination with $Me_2NH{\bullet}BH_3$ as reducing agent and PPh_3, K_2CO_3 in DMF, it catalyzes the deoxygenation of aryl tosylates and mesylates in high yields, while benzyl protecting groups and conjugated carbon-carbon double bonds were not removed (Scheme 1.7).[45]



Scheme 1.7. Deoxygenation of aryl tosylates and mesylates catalyzed by Ni/C_g.[45]

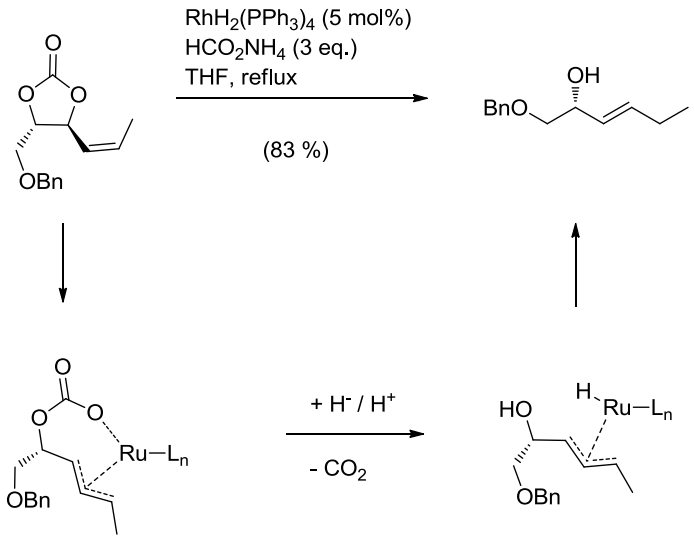
Rhodium and Ruthenium catalyzed deoxygenations

While palladium and nickel catalysts are used for C_{aryl}–O cleavage, rhodium, by contrast, is mostly used for deoxygenations of allylic and benzylic alcohols. The well-known Wilkinson catalyst, $RhCl(PPh_3)_3$, catalyzes the deoxygenation of allylic and benzylic alcohols (Scheme 1.8). However, the use of α,β–unsaturated esters as substrates is essential, otherwise no deoxygenation was observed.[46]



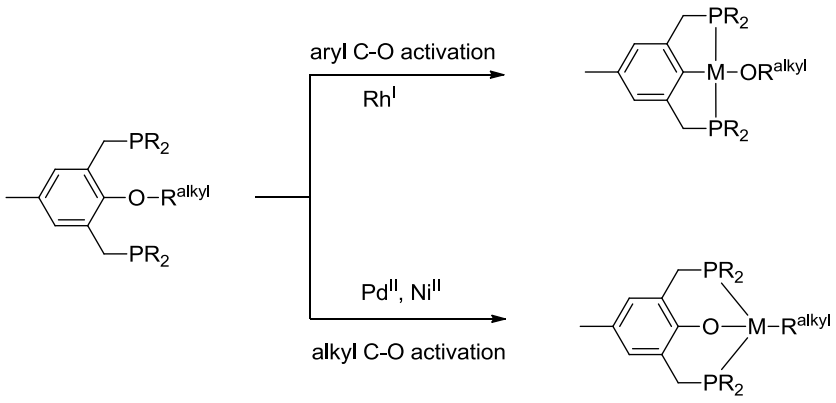
Scheme 1.8. Deoxygenation of allylic and benzylic alcohols with Wilkinson´s catalyst.[46]

Rh(cod)(cot) catalyzes the deoxygenation of allyl acetates with HCO_2H and NEt_3.[47] Furthermore, $RhH_2(PPh_3)_4$ with ammonium formate was used for the deoxygenation of allyl and propargyl carboxylates and carbonates.[48] Due to the π-allyl ruthenium complex that is formed during this reaction a shift of the double bond can occur (Scheme 1.9).



Scheme 1.9. Rhodium catalyzed deoxygenation of allyl carbonates.[48]

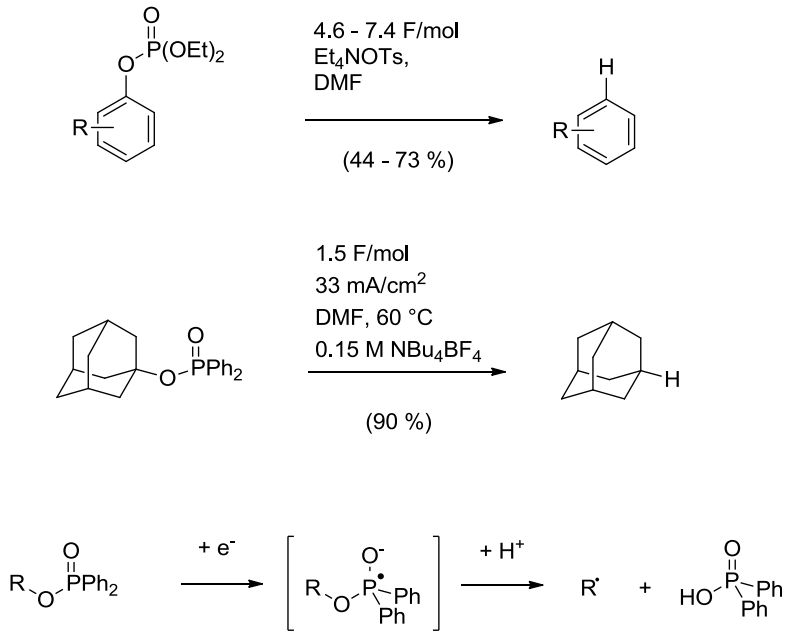
Rhodium(I), like palladium(II) and nickel(II), were found suitable homogeneous catalyst for deoxygenation, their d^8 configuration makes an oxidative addition of C–O bonds to the metal center *via* a d^6 octahedral intermediate possible. Van de Boom *et al.* studied the tendency for the C–O insertion of these three catalysts. For their model system they could demonstrated insertion into $C(sp^2)$–O bonds for the nucleophilic rhodium(I) catalyst while electrophilic palladium(II) and nickel(II) preferably inserted into $C(sp^3)$–O bonds (Scheme 1.10).[49] Nevertheless, all deoxygenations with palladium and nickel catalyst led to the cleavage of the C_{aryl}–O and not the C_{alkyl}–O bond. Consequently, the observed tendency of insertion of the C–O bond seems to be dependent on the model system, and may not be involved in the deoxygenation mechanism.



Scheme 1.10. Model system for the study of C-O activation by transition metal catalysts.[49]

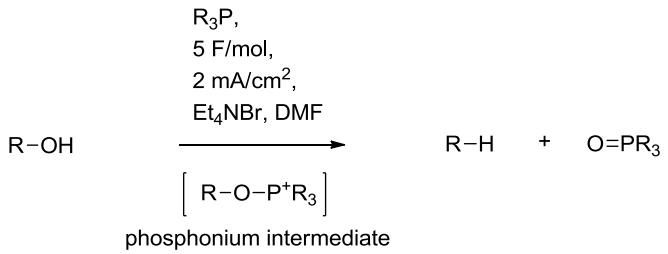
1.2.1.2 Electrochemical deoxygenation

Using electrons as reductant is a very elegant possibility for reductive deoxygenation of alcohols. Such electroreductive deoxygenations of alcohols can be achieved after conversion into the corresponding phosphates or phosphinates. In 1979, Shono *et al.* reported the deoxygenation of aryl diethylphosphates in a divided cell, equipped with a platinum anode and lead cathode, with a cathode potential of -2.6 to -2.7 V vs. SCE. They could apply this method successfully in the synthesis of olivetol.[50] A similar electroreductive deoxygenation was applied for the deoxygenation of diphenylphosphinate esters of aliphatic alcohols. The mechanism of this deoxygenation consists of an initial single electron transfer followed by decomposition of the resulting radical anion into the diphenylphosphonic acid and the alkyl radical (Scheme 1.11).[51]



Scheme 1.11. Electrochemical deoxygenation of diethylphosphates and diphenylphosphinates.[50,51]

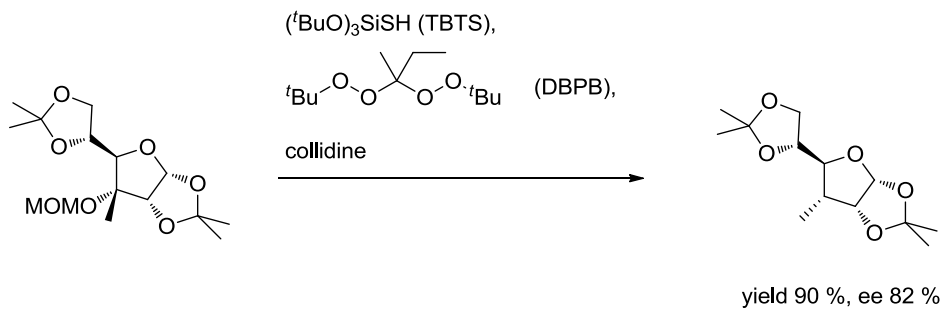
Ohmori *et al.* demonstrated the possibility of one-step electroreductive deoxygenation without initial transformation by so-called "double electrolysis". They used phosphines, which undergo initially anodic oxidation, to form a phosphonium ion with the alcohol. The phosphonium ion intermediates are subsequently reduced to the phosphinoxide and the deoxygenation product (Scheme 1.12).[52]



Scheme 1.12. Direct electroreductive deoxygenation *via* "double electrolysis". [52]

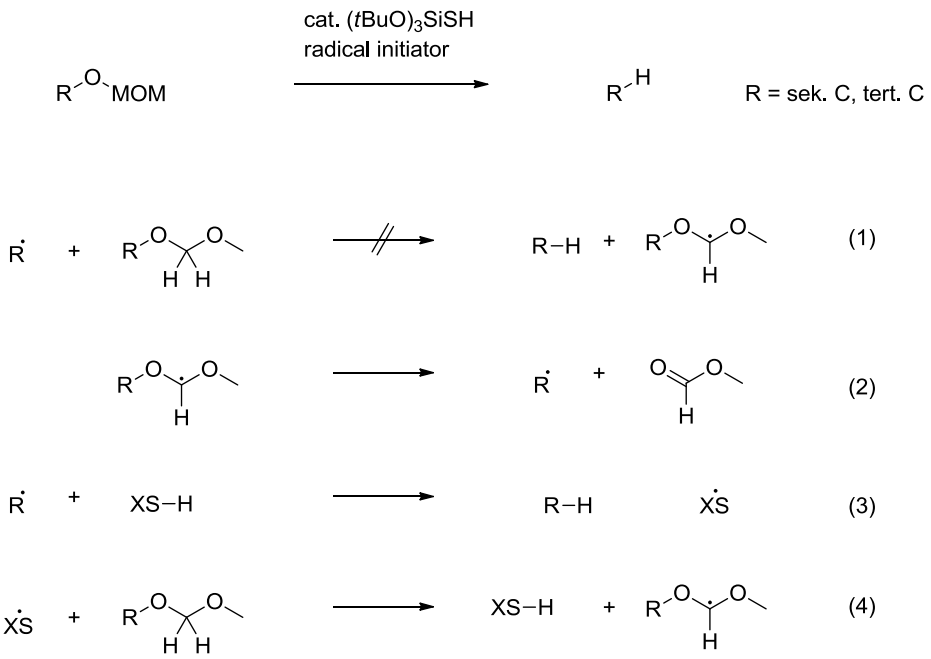
1.2.1.3 Thiol-catalyzed radical-chain redox decomposition

A very interesting catalytic deoxygenation is the so called thiol catalyzed radical-chain redox decomposition. With this method methoxymethyl ethers of secondary and tertiary aliphatic alcohols can be deoxygenated. Dang *et al.* reported the use of tri-*tert*-butoxysilanethiol (TBST) as polarity-reversal catalyst for the deoxygenation of several secondary and tertiary alcohols even in more complex systems (Scheme 1.13).[53,54] 2,2-Di-*tert*butylperoxybutane (DBPB) was used as initiator for the radical chain mechanism.



Scheme 1.13. Thiol catalyzed radical-chain redox decomposition.[53,54]

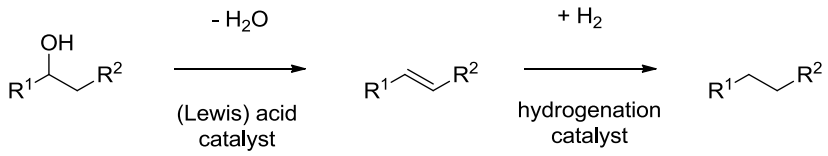
The polarity reversal catalyst enables this radical chain reaction by replacing the unfavored hydrogen abstraction of the nucleophilic radical $R^{\bullet}$ from $ROCH_2OMe$ (Scheme 1.14, Equation 1) by a stepwise hydrogen transfer (Scheme 1.14, Equation 3,4). This stepwise hydrogen transfer is more favored due to polar effects.[55]



Scheme 1.14. Mechanism of the thiol catalyzed radical-chain redox decomposition.[53-55]

1.2.2 Deoxygenation of alcohols *via* elimination-hydrogenation sequence

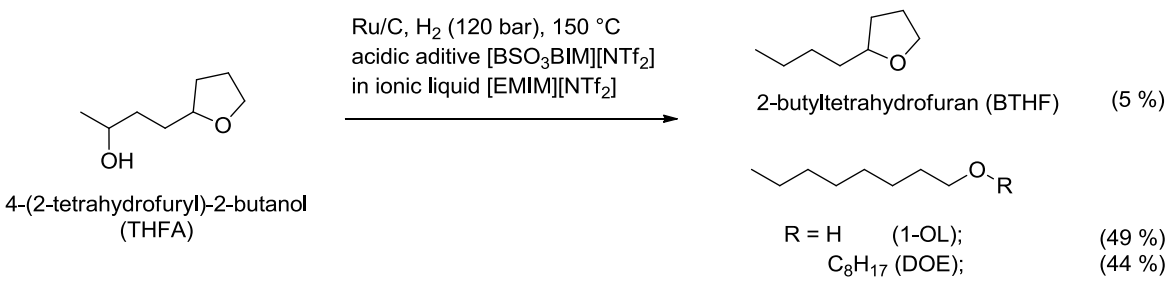
Dehydration followed by hydrogenation is a classical two-step procedure for the deoxygenation of alcohols. Both, the elimination of hydroxyl groups (dehydration) and the hydrogenation of carbon-carbon double bonds are well studied reactions and excellent reviews exist.[56-63] We therefore will only discuss very few selected examples.



Scheme 1.15. Atom-economic two-step deoxygenation of alcohols employing a dehydration-hydrogenation sequence.

In theory, the generation of waste can be limited to water when catalytic reactions are used, while only hydrogen is needed as reactant (Scheme 1.15). Hence, this method is desirable for industrial applications and frequently employed for the synthesis of platform chemicals or biofuel from carbohydrates derived from biomass.[1-4] The catalysts for the

industrial hydrodeoxygenation (HDO), i.e. CoMo/γ-Al_2O_3 and NiMo/γ-Al_2O_3, remove hydroxyl groups unselectively from biomass derived carbohydrates.[64-66] But also the selective conversion of biomass derived platform chemicals by dehydration-hydrogenation is possible. Leitner *et al.* showed the conversion of 4-(2-tetrahydrofuryl)-2-butanol (THFA) into 1-octanol (1-OL) and 1,1-dioctylether (DOE) employing a ruthenium hydrogenation catalyst under acidic conditions(Scheme 1.16).[67]

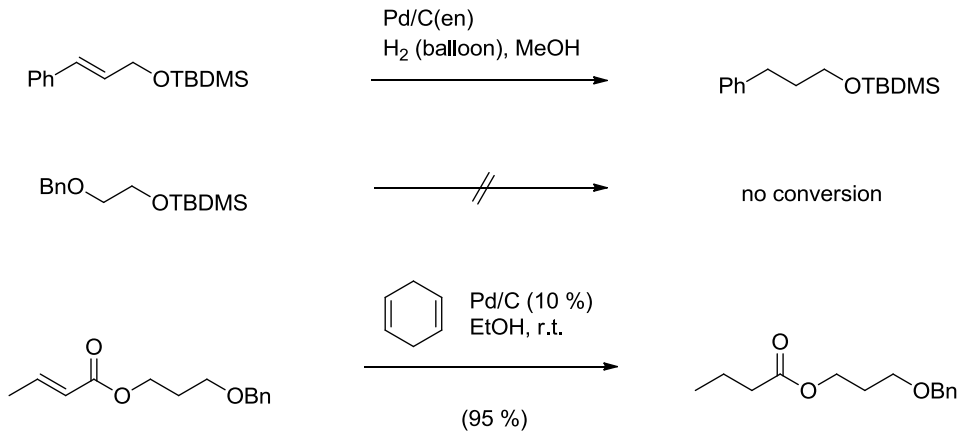


Scheme 1.16. Selective HDO of 4-(2-tetrahydrofuryl)-2-butanol (THFA) with Ru/C in ionic liquid.

For chemoselective organic synthesis the catalytic processes must be chosen with care, as the acidic conditions for the dehydrogenation as well as the catalytic hydrogenation can cause undesirable side reactions. The acidic conditions for the dehydration can lead to the generation of ethers or the cleavage of acid sensitive protecting groups. Hydrogenation is problematic, if other reducible functional groups are present in the molecule, but choosing the appropriate conditions these problems can be solved.

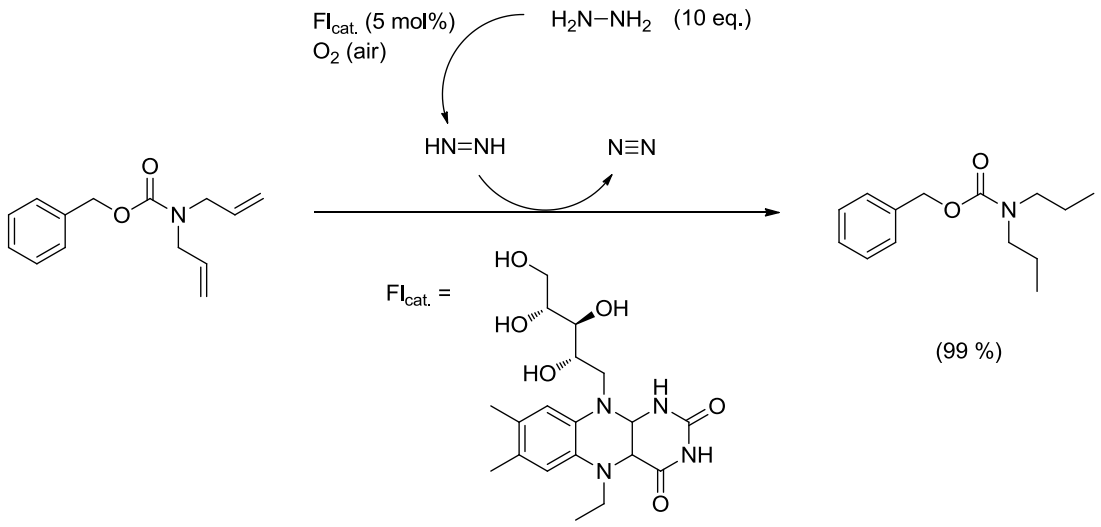
The dehydration is usually achieved under acidic conditions, i.e. with para-toluenesuflonic acid, but also solid acid catalysts, like heteropoly acids, or acid ion exchange resins (Amberlyst-18, Nafion-H), and basic catalysts can be applied.[68,69] For the hydrogenation of carbon-carbon double bonds a variety of catalyst is available, including palladium, nickel, ruthenium, iridium, rhenium and platinum metal catalysts.[70] Palladium, as for the deoxygenation of ethers and esters, is the outstanding catalyst for the hydrogenation of carbon-carbon double bonds. Either homogenous or heterogeneous catalysts can be used, but the functional groups within the molecule have to be considered.[71,72] For example, the deoxygenation with Pd/C under hydrogen atmosphere is not applicable for molecules containing benzyl or allyl ether moieties. Therefore, either the catalyst or the hydrogen source must be changed. Using the palladium catalyst Pd/C(en), poisoned with ethylenediamine, carbon-carbon double bonds can be hydrogenated

selectively while benzylethers, Cbz protection groups and TBDMS ethers are unaffected.[73,74] With 1,4-cyclohexydiene as hydrogen-source, even Pd/C can be used for the hydrogenation of carbon-carbon double bonds without the cleavage of benzylethers.[75]



Scheme 1.17. Chemoselective hydrogenation of carbon-carbon double bonds with transfer hydrogenation catalysts.

A metal-free hydrogenation method for non-polarized multiple bond employs diimide as hydrogen source. As diimide is very unstable, it has to be generated *in situ* from hydrazine hydrate or its derivatives.[76] For example riboflavin catalysts are able to oxidize hydrazine catalytically to diimide in the presence of air-oxygen and promote the chemoselective reduction of non-polarized carbon-carbon double bonds (Scheme 1.18).[77]

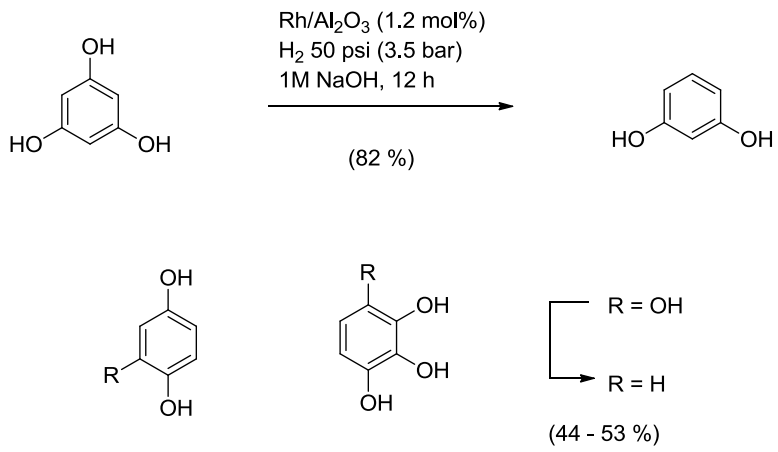


Scheme 1.18. Reduction of nonpolarized carbon-carbon double bonds with organocatalytically generated diimide.

1.3 Direct reductive deoxygenation of alcohols

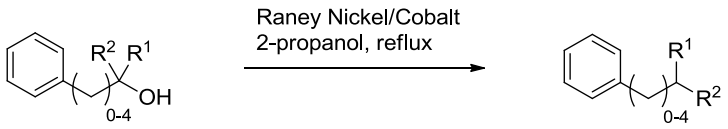
1.3.1 Direct deoxygenation with hydrogenation catalysts

In the second part of this review we discuss direct deoxygenation methods of alcohols. Being a one-step procedure the direct deoxygenation saves time, chemicals and consequently money and is therefore of great interest. While in the first part the C-O bonds of the alcohols were activated by derivatization for the catalytic cleavage, the catalyst has to achieve this activation for the direct deoxygenation. Indeed, the hydrogenation catalysts, mentioned in the first part, are able to deoxygenate phenols as the study of Frost *et al.* demonstrates.[78] They studied the deoxygenation of polyhydroxybenzenes (Scheme 1.19), derived from glucose, by hydrogenation with supported rhenium, platinum and palladium catalysts. But these special substrates cannot serve as general examples for the chemoselective deoxygenation of phenols with these catalysts.



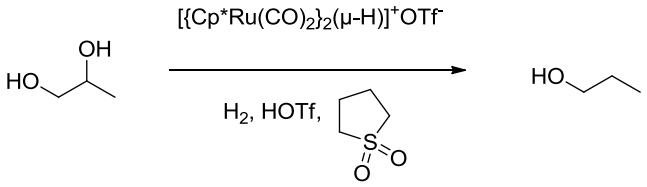
Scheme 1.19. Direct deoxygenation of polyhydroxybenzenes.[78]

Raney nickel and Raney cobalt in refluxing 2-propanol were applied for the direct deoxygenation of aliphatic alcohols substituted in α, β, γ, δ or ε position with an aromatic ring (Scheme 1.20). Raney nickel gave very high yields in short reaction times of a few hours while Raney cobalt suffered from low conversions even after 24 hours.[79]



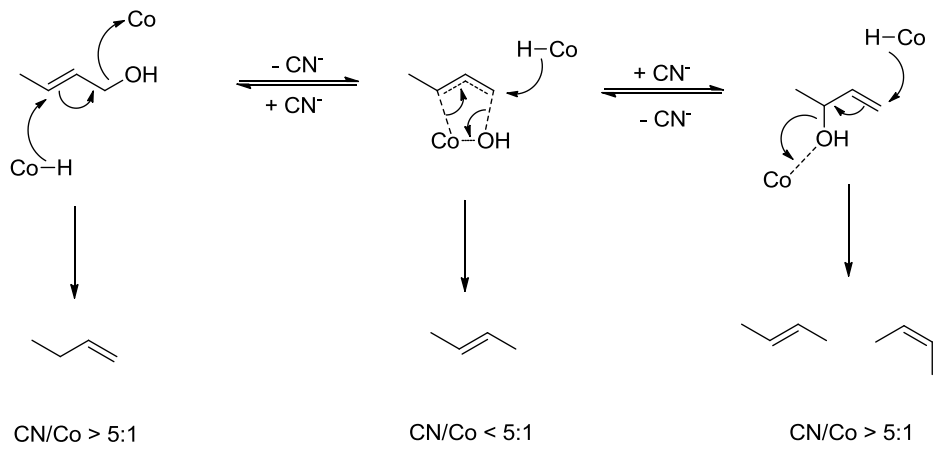
Scheme 1.20. Direct deoxygenation of aliphatic alcohols catalyzed by Raney nickel or cobalt.[79]

The ruthenium catalyst $[\{Cp^*Ru(CO)_2\}_2(\mu\text{-}H)]^+OTf^-$ was found to deoxygenate terminal diols partially by hydrogenation (Scheme 1.21). The secondary alcohol was removed selectively due to the higher stability of the carbenium ion intermediate.[80] Other ruthenium and iridium catalysts have been investigated to catalyze this reaction.[81,82]



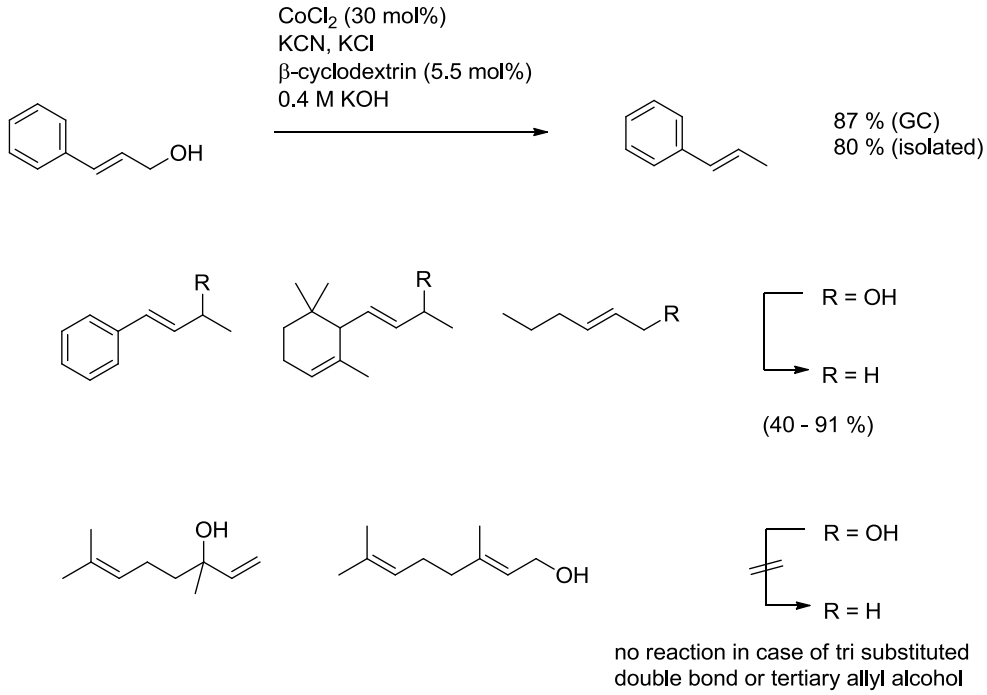
Scheme 1.21. Partial direct deoxygenation of a terminal diol using a ruthenium catalyst.[80]

The hydrido cobalt complex $HCo(CN)_5^{-3}$ was identified as catalyst for the deoxygenation of allyl alcohols.[83] The complex is formed *in situ* from cobalt(II)chloride and potassium cyanide under hydrogen atmosphere. In a first study the hydridopentacyano-cobaltate anion was found to deoxygenate allyl alcohols by hydrogenation of the C-C double bond followed by an elimination of the hydroxyl group. This leads to the overall deoxygenation of the allylic alcohol, but a 1,2-shift of the double bond occurs, dependent on the ratio of cyanide to cobalt, and yields a mixture of products (Scheme 1.22).



Scheme 1.22. Direct deoxygenation of allyl alcohols with *in situ* formed $HCo(CN)_5^{-3}$.[83]

Lee *et al.* used the hydridopentacyanocobaltate anion $HCo(CN)_5^{-3}$ for the deoxygenation of allyl alcohols. Their improved protocol deoxygenates allyl alcohols directly by 1,2-reduction applying β-cyclodextrin as phase transfer catalyst.[84] No hydrogenation and no shift of the double bond was observed and catalytic deoxygenation of several allylic alcohols was accomplished in high yields at room temperature (Scheme 1.23).

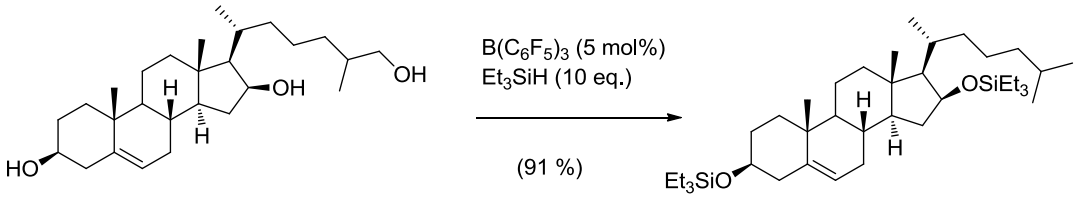


Scheme 1.23. Direct catalytic deoxygenation of allyl alcohols by *in situ* formed $HCo(CN)_5^{-3}$.[84]

1.3.2 (Lewis) Acid catalyzed direct deoxygenations

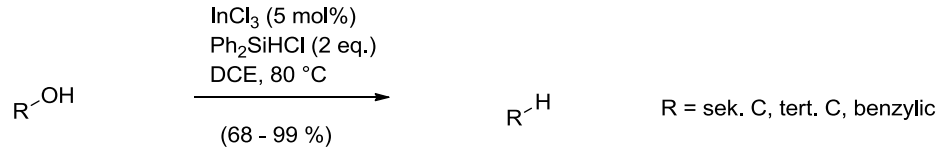
1.3.2.1 Direct deoxygenation by activation of the C-O bonds with Lewis acids

Lewis acids are known to activate C-O bonds for the deoxygenation with a hydride source.[85] They are used in stoichiometric amounts and reveal selectivity for alcohols following the trend tertiary > secondary >> primary. Gevorgyan *et al.* demonstrated convincingly that the use of $B(C_6F_5)_3$ in catalytical amounts and $HSiEt_3$ as hydrid source changes this order of reactivity completely to primary >> secondary > tertiary.[86] Even the chemoselective deoxygenation of a primary alcohol in the presence of a secondary alcohol is possible (Scheme 1.24).[87]



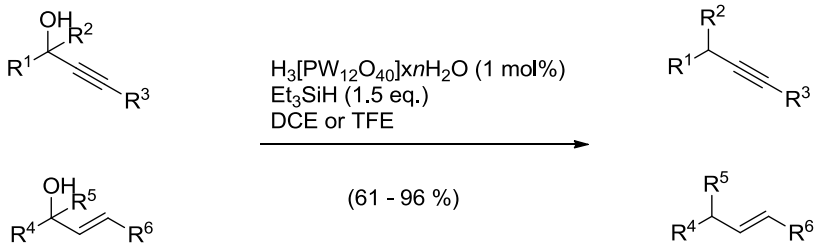
Scheme 1.24. Chemoselective deoxygenation of a primary alcohol in the presence of a secondary alcohol.[87]

Indium(III) catalysts are used for carbon-carbon bond formations and as Lewis acids.[88,89] In combination with silanes as a hydride source trivalent indium halides are good catalysts for the mild deoxygenation of secondary, tertiary and benzylic alcohols. Baba *et al.* studied the deoxygenation of ketones using $InCl_3$ (5 mol%) and Me_2SiClH and discovered that their protocol was applicable for alcohols.[90] Later they refined this protocol for the direct catalytic deoxygenation of alcohols. The use of an $InCl_3$ catalyst in dichloroethane with Ph_2SiClH as hydride source gave the best results for the deoxygenation of secondary, tertiary and benzylic alcohols.[91] The mechanism involves an initial formation of the silylether followed by the deoxygenation by hydride transfer. Without catalyst the reaction yields the silylether.



Scheme 1.25. Indium(III) chloride catalyzed direct deoxygenation.[91]

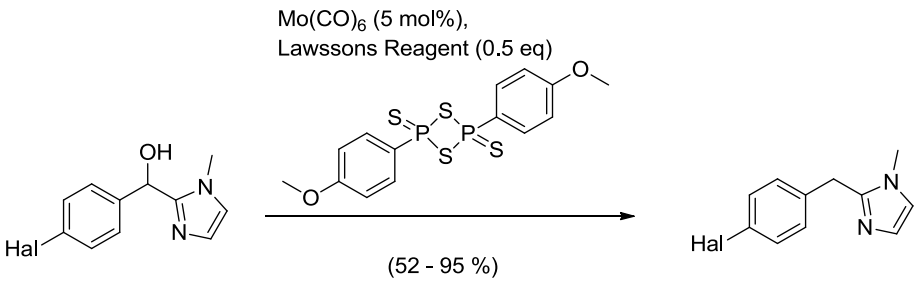
Recent examples also demonstrate the acid catalyzed chemoselective deoxygenation of allylic and propargylic alcohols with silane as reductant. The heteropolyacid $H_3[PW_{12}O_{40}]\times nH_2O$ deoxygenates allylic and propargylic alcohols under mild conditions in high yields with Et_3SiH as reducing agent (Scheme 1.26).[92]



Scheme 1.26. Direct deoxygenation of propargylic and allylic alcohols with the heteropolyacid catalyst $H_3[PW_{12}O_{40}]\times nH_2O$.[92]

The Lewis acids $Ca(NTf_2)_2$ and $Bi(OTf)_3$ deoxygenate propargylic alcohols with Et_3SiH as hydride source. The $Ca(NTf_2)_2$ catalyzed reaction was enhanced by Bu_4NPF_6 as additive,[93] while the deoxygenation catalyzed by $Bi(OTf)_3$ was performed in the ionic liquid [BMIM][BF_4].[94] The latter study explored several Lewis acids and the bismute(II)triflate gave the best results. Furthermore, not only propargylic also allylic and benzylic alcohols were deoxygenated successfully.

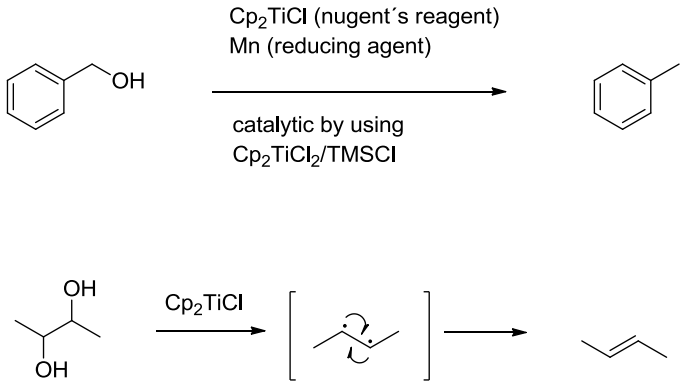
Molybdenum hexacarbonyl, known for the cleavage of C-S bonds, was also applied in the catalytic deoxygenation of alcohols. In combination with Lawesson´s reagent, normally used for the conversion of carbonyl compounds into thiocarbonyls, $Mo(CO)_6$ deoxygenates heterocyclic halo-benzyl alcohols in high yields (Scheme 1.27).[95]



Scheme 1.27. Molybdenum hexacarbonyl catalyzed deoxygenation of heterocyclic halo-benzyl alcohols.[95]

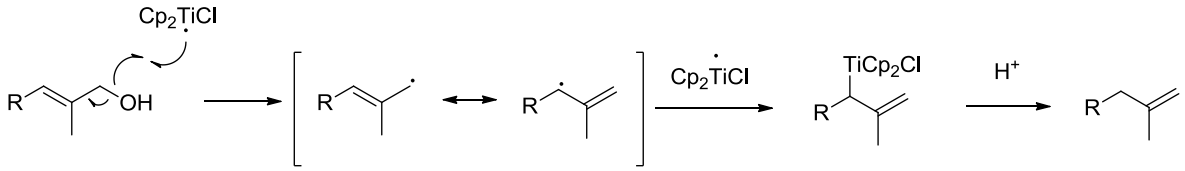
1.3.2.2 Radical deoxygenation catalyzed by low-valent titanium

Low-valent titanium is long known for the activation of C-O bonds, not only in McMurry reactions, but also for the deoxygenation of benzylic and allylic alcohols.[96] In 1980, Sato *et al.* described the catalytic deoxygenation of allyl and benzyl alcohols and allyl ethers. They used $LiAlH_4$ as reducing agent with catalytic amounts of $TiCl_4$ or titanocene dichloride, Cp_2TiCl_2.[97] Recently, Dieguez studied the mechanism of the deoxygenations of benzylic and allylic alcohols, diols and carbonyl compounds with Nugent´s Reagent, Cp_2TiCl.[98] The C-O bond is cleaved homolytically by single electron transfer, SET, from Cp_2TiCl and generates a radical. This radical can either react with a hydrogen donor under hydrogen abstraction, giving overall deoxygantion, or recombine with a second radical. In the case of 1,2-diols the recombination of the radical intermediate leads to the generation of a double bond (Scheme 1.28).



Scheme 1.28. Deoxygenation of benzylic alcohols with Cp_2TiCl_2 as catalyst. [97]

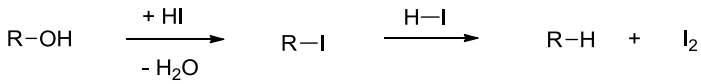
Deoxygenation of allyl alcohols sometimes gave a mixture of products with different positions of the double bond. Depending on the stability of the generated radical intermediate, the double bond shifts to generate the most stable radical (Scheme 1.29).



Scheme 1.29. Mechanism of the deoxygenation of allylic alcohols with Cp_2TiCl. [98]

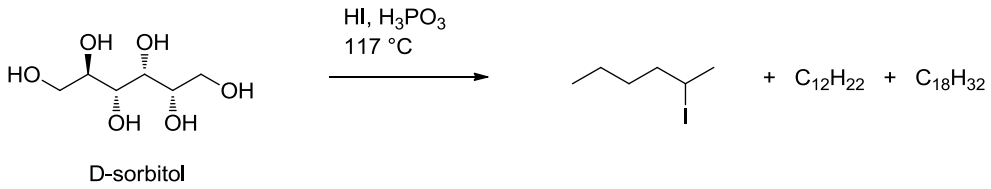
1.3.2.3 Iodine/HI catalyzed deoxygenations

The deoxygenation of alcohols using refluxing hydriodic acid and red phosphorous was invented by Kiliani *et al.* 140 years ago, is still used for industrial applications and was reinvestigated as catalytic reduction.[99] The mechanism of this reduction consists of two steps, first the hydroxyl group is converted into the corresponding alkyl iodide that is subsequently reduced by redox comproportionation with hydriodic acid (Scheme 1.30). While the nucleophilic substitution as the first step is widely accepted, the second step is controversially discussed in literature.[100-102] Already in 1939, Miescher *et al.* described the regeneration of HI from iodine by red phosphorous and the possibility of using iodine or iodide instead of hydriodic acid.[103]



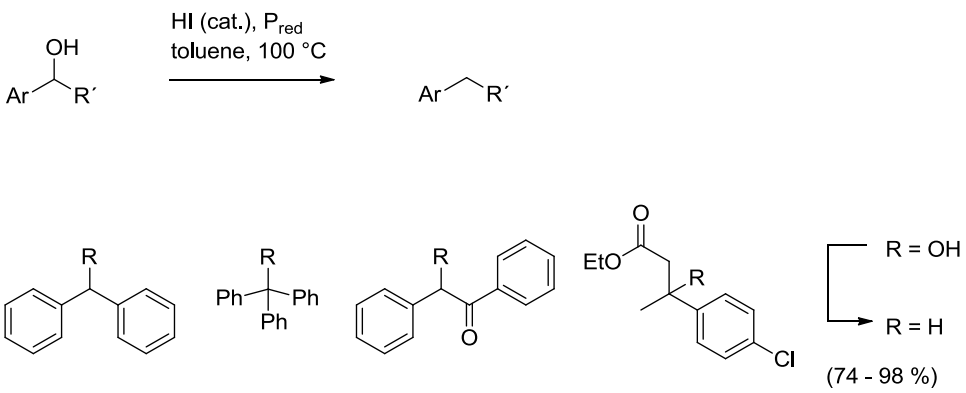
Scheme 1.30. Mechanism of the deoxygenation of alcohols with hydriodic acid.

Robinson *et al.* studied the deoxygenation of polyols, i.e. D-sorbitol, with hydriodic acid and the recycling of the acid for industrial application (Scheme 1.31). They regenerated hydriodic acid either by chemical reduction with H_3PO_3 or electrochemically.[104,105] But the harsh conditions of these methods are still problematic for the use in organic synthesis.



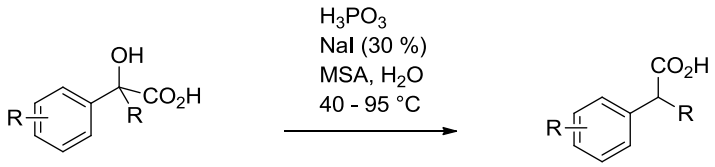
Scheme 1.31. Deoxygenation of D-sorbitol with catalytic amounts of hydriodic acid. [104]

König *et al.* described the use of red phosphorous and catalytic amounts of aqueous HI in a biphasic reaction media for the reduction of benzylic alcohols (Scheme 1.32).[106] The cleavage of methyl ethers or dehalogenation reactions were not observed with this protocol in contrast to the classic method.



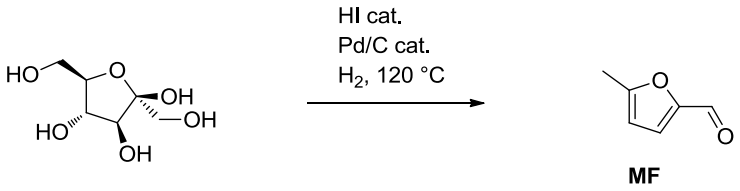
Scheme 1.32. Direct deoxygenation of benzylic alcohols with hydriodic acid and red phosphorous.[106]

Another possibility is the *in situ* generation of HI from another iodide source. Milne *et al.* used sodium iodide in combination with phosphorous acid as stoichiometric reductant. Under these conditions α-hydroxyphenylacetic acids could be deoxygenated successfully. Furthermore, bromo substituents and ethers were tolerated (Scheme 1.33).[107,108] Using hypophosphorous acid and catalytic amounts of iodine in acetic acid Gordon *et al.* could deoxygenate benzhydrols without the cleavage of chloro and bromo substituents.[102,109]



Scheme 1.33. *In situ* generation of HI from sodium iodide and phosphorous acid for the deoxygenation of α-hydroxyphenylacetic acids. [107,108]

Sen *et al.* also used HI in catalytic amounts for the deoxygenation of biomass derived fructose to generate 5-methylfurfural **MF**.[110] They applied a hydrogenation catalyst and hydrogen for the regeneration of HI from iodine. The reaction could not be achieved without hydriodic acid and provides another good opportunity for the catalytic use and the regeneration of hydriodic acid.



Scheme 1.34. Generation of **MF** from fructose with catalytic amounts of HI.[110]

1.4 Conclusion

The Barton McCombie deoxygenation has been studied and developed extensively over more than 35 years. It is the first method that comes to most chemists mind thinking about the chemoselective and mild removal of a hydroxyl group. In this review we have provided a short overview of catalytic alternatives for this method, including their scope and limitations.

For the deoxygenation of aryl alcohols the currently best methods employ a two-step procedure transferring the alcohol first into an appropriate ester or ether that can be reductively cleaved catalytically with a palladium or nickel catalyst. The deoxygenation of alkyl hydroxyl groups is more versatile; depending on the substrate even the direct deoxygenation is possible. Mostly activated alkyl alcohols, like benzyl, allyl or propargyl alcohols, are preferred for the direct deoxygenation. This substrates can stabilize a radical or ionic intermediate by delocalization *via* the neighbouring π-system, thus the C-O bond is cleaved more easily. But also without this activation, the direct deoxygenation is possible by activation of C-O bond with an appropriate Lewis acid. In the case of the radical chain deoxygenation an external reductant is not even needed, as the MOM ether serves as internal reducing agent.

The direct deoxygenation will be the preferred method when more catalytic procedures with improved chemoselectivity will become available. The increasing use of biomass derived compounds instead of fossil carbon for chemical synthesis will set a strong demand for efficient, selective and catalytic defunctionalization methods.

1.5 References

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Chapter 2

Reduction of benzylic alcohols and α-hydroxycarbonyl compounds by hydriodic acid in a biphasic reaction medium

This chapter was written in collaboration with Michael Dobmeier and published in the "Beilstein Journel of Organic Chemistry": Dobmeier, M.; Herrmann, J. M.; Lenoir, D.; König, B. *Beilstein Journal of Organic Chemistry* **2012**, *8*, 330. Michael Dobmeier and Josef Herrmann contributed equally to the written part of this chapter. Table entries based on experiments performed by Josef Herrmann are marked with *. The alcohols 1-(4-methoxyphenyl)-2-phenylpropan-1-ol, 2-methyl-1-(thiophen-3-yl)propan-1-ol, 4-methyl-2-phenyl-pentan-2-ol, 3-methyl-1-phenylbutan-1-ol, (E)-6-methyl-1-phenylhept-4-en-3-ol, 6,6-dimethyl-2-phenylhept-4-yn-3-ol, ethyl 3-(4-chlorophenyl)-3-hydroxybutanoate were synthesized by Josef Herrmann. Radical capture experiments with TEMPO were performed by Josef Herrmann.

2 Reduction of benzylic alcohols and α-hydroxycarbonyl compounds by hydriodic acid in a biphasic reaction medium

2.1 Introduction

The reduction of hydroxyl groups is a typical and important step in the synthesis of complex natural products or drugs.[1-4] Functional group tolerance during this reduction step is essential since various other groups are usually present. A number of synthetic procedures have been developed, which allow selective reduction, but only a few one-step transformations are known using either titanium-(III)[5-8] or different metal-complexes.[9-13] Most procedures require a sequence of steps, e.g. the conversion of hydroxyl groups into a chloride or bromide substituent and subsequent catalytic reduction with H_2/Pt or the conversion into a tosylate and reduction with $LiAlH_4$. The most commonly applied method is the Barton-McCombie reaction,[14] due to its versatility and its very high functional group tolerance.[15-18] Although very general, the reaction has some drawbacks: the involved organo tin hydrides are costly, highly toxic[19-21] and often difficult to separate from the reaction products. Furthermore, secondary alcohols give best results, while others may react less efficient.

We have reinvestigated the long known reduction of benzylic alcohols and α-hydroxy carbonyl compounds by hydriodic acid.[22-32] First described by Kiliani more than 140 years ago for the reduction of gluconic acid to hydrocarbons,[33] the method has been reported for a variety of alcohols, but typically proceeds in aqueous solution and requires an excess of HI or strong mineral acids like phosphoric or sulfuric acid.[34-36]

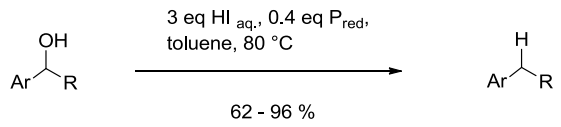
We describe a biphasic reaction medium consisting of toluene and aqueous hydriodic acid. The phase separation allows milder reaction conditions compared to the classic Kiliani protocol and is more applicable to organic synthesis.

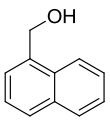
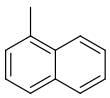
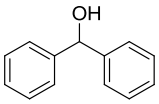
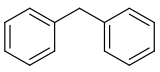
2.2 Results and Discussion

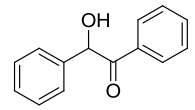
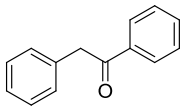
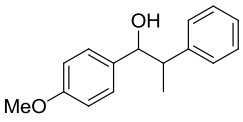
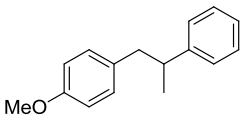
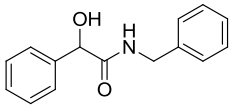
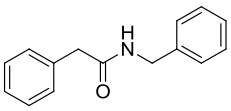
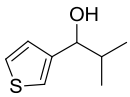
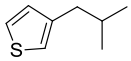
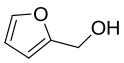
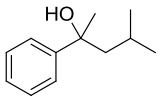
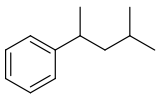
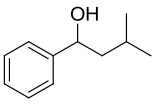
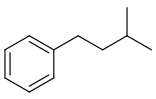
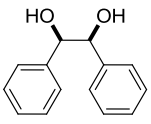
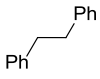
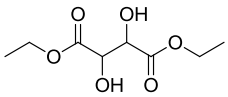
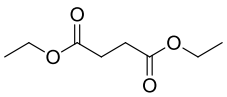
2.2.1 Deoxygenation of benzylic alcohols

Initial investigations focused on simple benzylic alcohols (Table 2.1, entry 1-3), which were converted in high to quantitative yields into the corresponding alkanes. Carbonyl groups or amides in benzylic position (Table 2.1, entries 4 and 6) and aromatic hydroxyl groups, (Table 2.2, entry 7) or aromatic ethers (Table 2.1, entry 5) are not affected. Moreover, heterocycles like thiophene (Table 2.1, entry 7) were stable under these conditions whereas furans (Table 2.1, entry 8) were decomposed due to ring opening. Benzylic alcohols were converted in good to high yields to alkanes with increasing reactivity in the order primary (2 h) < secondary (0.5-1 h) < tertiary alcohol (15 – 30 min); carbonyl groups and ethers are tolerated. Diethyl tartrate is converted into diethyl succinate under the reaction condition (Table 2.1, entry 12), but some of the material is lost due to ester hydrolysis.

Table 2.1. Reduction of benzylic alcohols to corresponding alkanes.



Entry	Alcohol	Product[a]	Yield [%]
1			70[b]
2			96
3			100

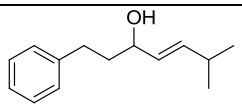
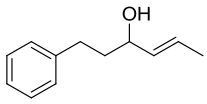
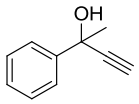
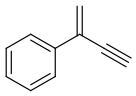
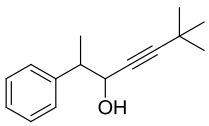
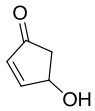
4			80
5*			92
6			82
7*			62[c]
8		decomposition	
9*			74[c]
10*			49[c]
11			78
12			65

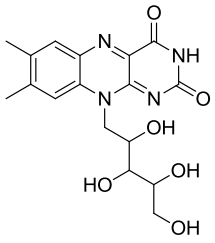
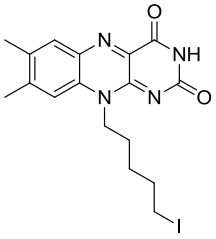
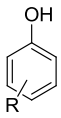
[a] All products are known compounds described in the literature. Identity has been proven by proton NMR and mass analysis, which match literature data. [b] The corresponding iodo compound was identified as byproduct; [c] the corresponding elimination product was obtained as byproduct.

2.2.2 Deoxygenation of allylic and propargylic alcohols

Allylic alcohols are completely consumed, but the corresponding alkenes could not be isolated as pure product (Table 2.2). Mixtures of eliminiation and deoxygenation products, in some cases also rearangement of the deoxygenated product into the higher substitued, thermodynamical more stable, alkene occurred. Propargylic alcohols (Table 2.2, entry 3,4) showed elimination or decomposed. In the case of flavin (Table 2.2, entry 6), three hydroxyl groups were reduced and one was converted into an iodo substituent.

Table 2.2. Alcohols showing incomplete or unselective reaction with hydriodic acid and red phosphorous (3.0 eq. HI, 0.4 eq. P_{red}).

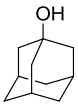
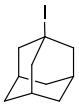
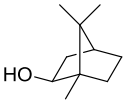
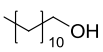
Entry	Alcohol	Product	Yield [%]
1*		mixture of several products	-
2*		mixture of several products	-
3			Traces
4*		Decomposition	-
5		Decomposition	-

6			21
7		no conversion	-

2.2.3 Conversion of aliphatic alcohols without π-system in α-position

Others alcohols than benzylic or α to carbonyl groups were not converted into the corresponding alkane and the reaction stopped at the iodo alkanes (Table 2.3). The reactivity follows the order of primary < secondary < tertiary alcohols, as expected for an S_N 1 reaction. The reduction potential of the non-benzylic iodo alkanes is not sufficient for reduction by hydriodic acid.

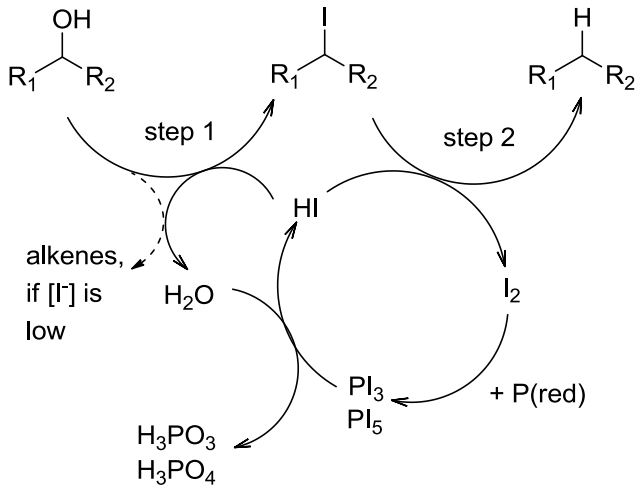
Table 2.3. Alcohols yielding alkyl iodides with hydriodic acid and red phosphorous[a]

Entry	Alcohol	Product	Yield [%]
1			98
2			83[b]
3*			81[c]

[a] 3 eq. HI, 0.6 eq. P_{red}; 8 h; [b] single isomer; [c] 20 h; products were analyzed by gas chromatography; chlorobenzene was used as internal standard.

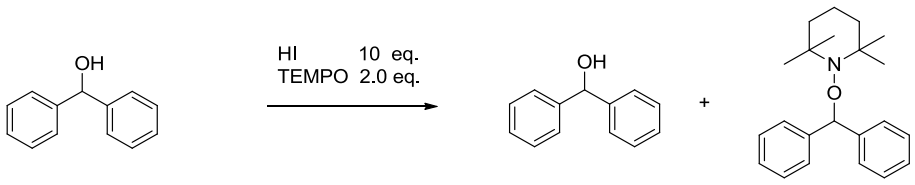
2.2.4 Mechanism of the deoxygenation with hydriodic acid

The mechanism of reduction by hydriodic acid consists of two steps (Scheme 2.1): The nucleophilic substitution of the hydroxyl group by iodide and the subsequent reduction of the alkyl iodide by hydriodic acid. The iodine, generated in the second step, is recycled by reduction with red phosphorous regenerating hydriodic acid.



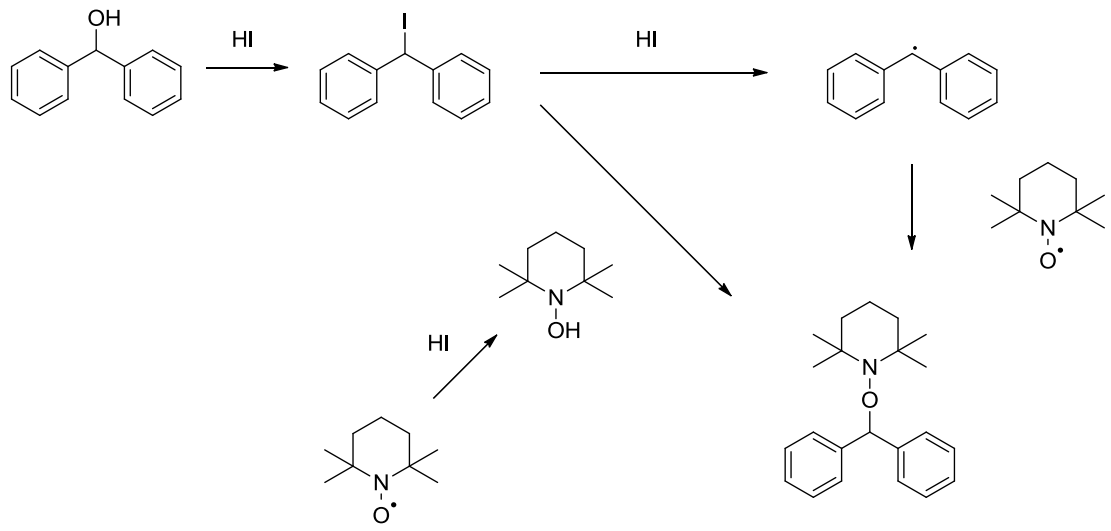
Scheme 2.1. Mechanism of the alcohol reduction and recycling of iodine

The mechanistic details of the redox comproportionation of alkyl iodides and H–I are controversially discussed in the literature.[37-39] However, the required benzylic or α-carbonyl position for the redox comproportionation indicates an intermediate with mesomeric stabilization by the adjacent π-system. In a trapping experiment, using HI without phosphorous, diphenylcarbinol as substrate and TEMPO as trapping agent for radical intermediates, the TEMPO adduct of diphenylcarbinol was detected by mass analysis (Scheme 2.2).



Scheme 2.2. Radical capture experiments with diphenylcarbinol and TEMPO.

This indicates a radical mechanism of the redox comproportionation. We suggest a stepwise reduction by single electron transfer (SET) accompanied by the oxidation of I^- to I_2. The iodine, generated in the second step, is recycled by reduction with red phosphorous, regenerating hydriodic acid. Admittedly, the above-mentioned TEMPO adduct could also be generated by nucleophilic substitution of the alkyl iodide with reduced TEMPO. At least this would be another proof for the first reaction step (Scheme 2.3).



Scheme 2.3. Possible reaction pathways for the generation of the TEMPO adduct.

2.2.5 Deoxygenation with catalytic amounts of hydriodic acid

According to the redox equations of the reaction between iodine and red phosphorous, each mol of red phosphorous is able to reduce at least 1.5 mol of iodine.

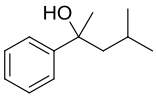
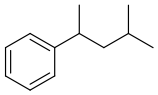
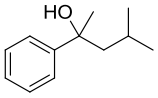
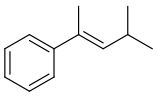
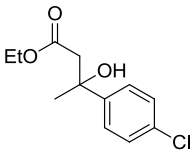
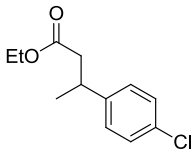
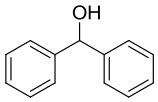
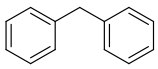
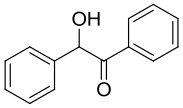
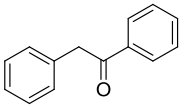
$$3\ I_2 + 2\ P + 6\ H_2O \rightarrow 6\ HI + 2\ H_3PO_3$$

$$5\ I_2 + 2\ P + 8\ H_2O \rightarrow 10\ HI + 2\ H_3PO_4$$

Catalytic amounts of hydriodic acid are therefore sufficient for the reduction of the hydroxy group, when excess red phosphorous is added as terminal reducing agent (Table 2.4, entry 1, 3-6). However, depending on the amount of added hydriodic acid the elimination of water may occur as an alternative reaction pathway (Table 2.4, entry 2). Low concentration of HI favors the elimination of water, while higher HI concentrations lead to

deoxygenation (Table 2.4, entry 1). But for substrates without a methyl, methylene of methine group in α-position (Table 2.4, entry 4 - 6), even low concentration of HI were sufficient for deoxygenation. In these cases dehydration could not take place as alternative reaction pathway.

Table 2.4. Reduction of alcohols with catalytic amounts of hydriodic acid.

Entry	Alcohol	Product	Yield [%]
1*			74[a]
2*			67[b]
3*			82[a]
4			92[b]
5			98[b]
6			74[b]

[a] 0.6 eq. HI, 0.4 eq. P_{red}; [b] 0.1 eq. HI, 0.7 eq. P_{red}.

2.3 Conclusions

Toluene and aqueous hydriodic acid are a suitable biphasic reaction mixture for the reduction of a range of benzylic alcohols. The two-phase system makes the Kiliani protocol easier applicable to organic synthesis, as organic substrates and products dissolve in the organic phase and are separated from the mineral acids. The procedure allows the use of catalytic amounts of hydriodic acid and red phosphorous as the terminal reductant. In the case of alcohols having no activation by adjacent benzylic or carbonyl groups the reaction stops at the corresponding alkyl iodide. A quantitative mass efficiency analysis[40] of the reaction in comparison to tosylation/LAH, Ti(III)-mediated and Barton-McCombie reduction revealed a better atom economy and mass efficiency.

2.4 Experimental

General: All reagents and solvents used were of analytical grade, purchased from commercial sources and used without further purification. Unless stated otherwise, purification and drying of the solvents used was performed according to accepted general procedures. All reactions were performed under an inert atmosphere of N_2 by using standard Schlenk techniques, if not otherwise stated. TLC analyses were performed on silica-gel-coated alumina plates (F254 silica gel, layer thickness 0.2 mm). Visualization was achieved by UV light at 254 nm/366 nm or through staining with ninhydrin dissolved in EtOH. For preparative column chromatography, silica gels (70–230 mesh and 230–400 mesh) were used. For chromatography commercially available solvents of standard quality were used without further purification.

Representative experimental procedure: The alcohol (1 mmol, 1 eq.) is dissolved in 4 mL of toluene. Red phosphorus (0.4 mmol), followed by concentrated hydriodic acid (57 wt.-%; 3.0 mmol, 3 eq.) is added and the reaction mixture is heated to 127 °C for the stated time, allowed to cool to room temperature and quenched with $Na_2S_2O_3$ (10 mL; 10 wt.-%) solution. The aqueous phase is extracted with dichloromethane (3 x 10 mL), the combined organic phases are dried over $MgSO_4$, filtered and the solvent is removed. The crude product is purified by chromatography and spectroscopically characterized.

For catalytic reactions of 1 mmol of the respective alcohol the following amounts of hydriodic acid and $P_{(red)}$ were used: (a) 0.6 mmol HI / 0.4 mmol $P_{(red)}$, (b) 0.2 mmol HI / 0.6 mmol $P_{(red)}$, (c) 0.1 mmol HI / 0.7 mmol $P_{(red)}$.

E-6-Methyl-1-phenylhept-4-en-3-ol: The reaction was carried out under dry nitrogen atmosphere using standard Schlenk techniques. To a slurry of Mg powder (0.67 g, 28 mmol) in dry THF (4 mL), 2 mL of a solution of 2-phenyl-1-bromethane (3.0 mL, 28 mmol) in dry THF (10 mL) were added. The Grignard reaction was initiated by addition of iodine and sonication for several minutes. When the exothermic reaction had started the rest of the 2-phenyl-1-bromethane solution was added through a septum via syringe over

15 minutes. After addition the reaction solution was heated to reflux for 1 hour to complete the reaction. The reaction solution was allowed to cool to room temperature before 4-methyl-2-pentenal (2.3 mL, 20 mmol) was added dropwise. To complete the reaction the solution was again heated to reflux for 1 hour. The reaction was quenched by addition of HCl (2 M, 25 mL). The aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with saturated $NaHCO_3$ (15 mL), H_2O (2 × 10 mL) and dried with $MgSO_4$. The solvent was removed with a rotary evaporator. The crude product was purified by flash chromatography (PE/EtOAc 4:1, R_f = 0.32, staining with vanillin solution gave a blue spot). *E*-6-Methyl-1-phenylhept-4-en-3-ol was isolated as yellow oil in 74 % yield (3.05 g, 14.9 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.14 (m, 5H), 5.63 (ddd, *J* = 15.5, 6.4, 0.7 Hz, 1H), 5.44 (ddd, *J* = 15.5, 7.0, 1.2 Hz, 1H), 4.13 – 4.01 (m, 1H), 2.79 – 2.59 (m, 2H), 2.39 – 2.21 (m, 1H), 1.97 – 1.72 (m, 2H), 1.58 (d, *J* = 2.7 Hz, 0.3H), 1.46 (d, *J* = 1.8 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 129.7, 128.5, 128.4, 125.8, 72.6, 38.8, 31.8, 30.7, 22.4, 21.3. EI-MS: m/z (%) = 91.1 (100) $[C_7H_7]^+$, 161.1 (81) $[M–C_3H_7]^+$, 186.1 (5) $[M-H_2O]^+$, 204.2 $[M]^{+\cdot}$. HR-MS: calcd. for $C_{14}H_{20}O$ $[M]^{+\cdot}$ 204.1514; found 204.1511.

E- 1-Phenylhex-4-en-3-ol: The reaction was carried out under dry nitrogen atmosphere using standard Schlenk techniques. A solution (1 mL) of 2-phenyl-1-bromethane (1.35 mL, 10.0 mmol) in dry THF (10 mL) was added to Mg-powder (0.25 g, 10 mmol). The Grignard reaction was initiated by addition of iodine and sonication for several minutes. When the exothermic reaction had started the rest of the 2-phenyl-1-bromethane solution was added through a septum via syringe over 15 minutes. After addition the reaction solution was heated to reflux for 1 hour to complete the reaction. The reaction solution was allowed to cool to room temperature before crotonaldehyde (0.74 mL, 9.0 mmol) was added dropwise. To complete the reaction the solution was again heated to reflux for 2.5 hours. The reaction was quenched by addition of HCl (2 M, 10 mL). The aqueous phase was extracted with diethyl ether (2 × 15 mL). The combined organic phases were washed with saturated $NaHCO_3$ (5 mL), H_2O (2 × 5 mL) and dried with $MgSO_4$. The solvent was removed with a rotary evaporator. *E*-1-Phenylhex-4-en-3-ol was obtained in 96 % yield (1.53 g, 8.69 mmol). Analytical data were identical with the literature.[41] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.06 (m, 5H), 5.63 (dq, J = 15.3, 6.2 Hz, 1H), 5.48 (ddd, J = 15.3,

7.0, 1.4 Hz, 1H), 4.02 (q, J = 6.7 Hz, 1H), 2.73 – 2.56 (m, 2H), 1.67 (dd, J = 6.3, 0.7 Hz, 3H) , 1.52 (s, 0.3H), 1.40 (s, 0.7H). EI-MS: m/z (%) = 71.1 (100) $[C_4H_7O]^+$, 91.1 (67) $[C_7H_7]^+$, 105.1 (19) $[M– C_4H_7O]^+$, 176.1 (50) $[M]^{+\cdot}$.

1-(4-Methoxyphenyl)-2-phenylpropan-1-ol: The reaction was carried out under dry nitrogen atmosphere using standard Schlenk techniques. 1 mL of a solution of 4-bromo-1-methoxy-benzene (0.62 mL, 5.0 mmol) in dry THF (10 mL) was added to Mg-powder (0.12 g, 5.0 mmol). The Grignard reaction was initiated by addition of iodine and sonication for several minutes. When the exothermic reaction had started the rest of the 4-bromo-1-methoxy-benzene solution was added through a septum via syringe over 15 minutes. After addition the reaction solution was heated to reflux for 1 hour to complete the reaction. The reaction solution was allowed to cool to room temperature before 2-phenylpropionaldehyde (0.60 mL, 4.5 mmol) was added dropwise. To complete the reaction the solution was again heated to reflux for 2 hour. The reaction was quenched by addition of HCl (2 M, 5 mL). The aqueous phase was extracted with diethyl ether (2 × 5 mL). The combined organic phases were washed with saturated $NaHCO_3$ (3 mL), H_2O (2 × 2.5 mL) and dried with $MgSO_4$. The solvent was removed with a rotary evaporator. The crude product was purified by flash chromatography (PE/EtOAc 4:1, R_f = 0.3, staining with vanillin solution gave a blue spot). 1-(4-Methoxyphenyl)-2-phenylpropan-1-ol was isolated as yellow oil in 57 % yield (0.62 g, 2.6 mmol). Analytical data are identical with literature.[42] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.05 (m, 7H), 6.85 – 6.74 (m, 2H), 4.76 (d, *J* = 6.1 Hz, 1H), 3.78 (s, 3H), 3.09 (p, *J* = 6.9 Hz, 1H), 1.34 (d, *J* = 7.0 Hz, 3H). EI-MS: m/z (%) = 137.1 (53) $[M–C_8H_9]^+$, 224.1 (2) $[M\text{-}H_2O]^+$, 242.1 (1) $[M]^{+\cdot}$.

6,6-Dimethyl-2-phenylhept-4-yn-3-ol: The reaction was carried out under dry nitrogen atmosphere using standard Schlenk techniques. The solution of 3,3-dimethyl-1-butyne (0.62 mL, 5 mmol) in dry THF (10 mL) was cooled to –78 °C. n-BuLi (1.6 M in hexane, 3.5 mL, 5.6 mmol) was added dropwise through a septum via syringe. The reaction mixture was allowed to warm to room temperature before the solution of 2-propionaldehyde (0.68 mL, 5 mmol) in dry THF (5 mL) was added dropwise through a

septum via syringe. This solution was stirred for 4.5 hours. The reaction was stopped by addition of H_2O (10 mL). The aqueous phase was extracted with diethyl ether (3 × 15 mL) and the combined organic layers were dried with $MgSO_4$. The solvent was removed with a rotary evaporator. The crude product was purified by flash chromatography (PE/EtOAc 4:1, R_f = 0.42, staining with vanillin solution gave a blue spot). 6,6-dimethyl-2-phenylhept-4-yn-3-ol was isolated as colorless oil in 46 % yield (0.50 g, 2.3 mmol). ^{1}H NMR (300 MHz, CDCl3) δ 7.40 – 7.19 (m, 5H), 4.44 (dd, J = 7.4, 5.4 Hz, 1H), 3.03 (dd, J = 7.1, 5.4 Hz, 1H), 1.67 (d, J = 5.4 Hz, 1H), 1.64 (d, J = 7.4 Hz, 1H), 1.39 (d, J = 7.1 Hz, 3H), 1.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 128.8, 128.2, 127.0, 95.5, 78.1, 67.8, 67.5, 55.0, 46.1, 31.0, 30.0, 16.3. EI-MS: m/z (%) = 57.1 (36) $[C_4H_9]^+$, 99.1 (100), 105.1 (20) $[C_8H_{10}]^+$, 216.2 (7) $[M]^{+\cdot}$.

2.5 References

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Chapter 3

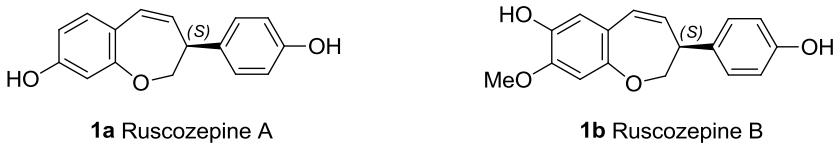
Synthesis of novel natural products isolated from butchers broom

The compounds ruscozepine A and B were isolated from Rusci rhizoma in the working group of Prof. Dr. Jörg Heilmann at the University of Regensburg by Martej Barbič. The synthetic approach was performed by Josef Herrmann. Pharmaceutical testing was performed by Monika Untergehrer and Gabriele Brunner, coworkers of Prof. Dr. Jörg Heilmann.

3 Synthesis of novel natural products isolated from butchers broom

3.1 Benzoxepines isolated from butchers broom

Ruscus aculeatus L. (Figure 3.2), also known as butchers broom, is a low evergreen shrub native to South- and West-Central Europe, Asia Minor, Northern Africa and Caucasus. The use of the plant for medical applications is long known, ancient Greek physicians applied it as laxative or diuretic and in Europe it was added to wine as diuretic to remove kidney stones.[1] In a study on the in vitro active compounds of the Rusci rhizoma, the novel phenyl-1-benzoxepinols ruscozepine A **1a** and ruscozepine B **1b** (Figure 3.1) were isolated from the methanolic extract of the Rusci rhizoma.[2]



1a Ruscozepine A **1b** Ruscozepine B

Figure 3.1. Phenyl-1-benzoxepinols isolated from the Rusci rhizoma.

The plant and its constituents are of special interest as the Rusci rhizoma extract is already used for the preparation of commercially available drugs.[3] Main application of the Rusci rhizoma preparations is the treatment of varicose veins and hemorrhoids, but the anti-inflammatory and vasoconstrictive activity is also of interest in recent studies, e.g. for the treatment of venous insufficiency.[4,5] Furthermore, a clinical trial indicated that the use of Rusci rhizoma extract may prevent diabetic retinopathy.[6]

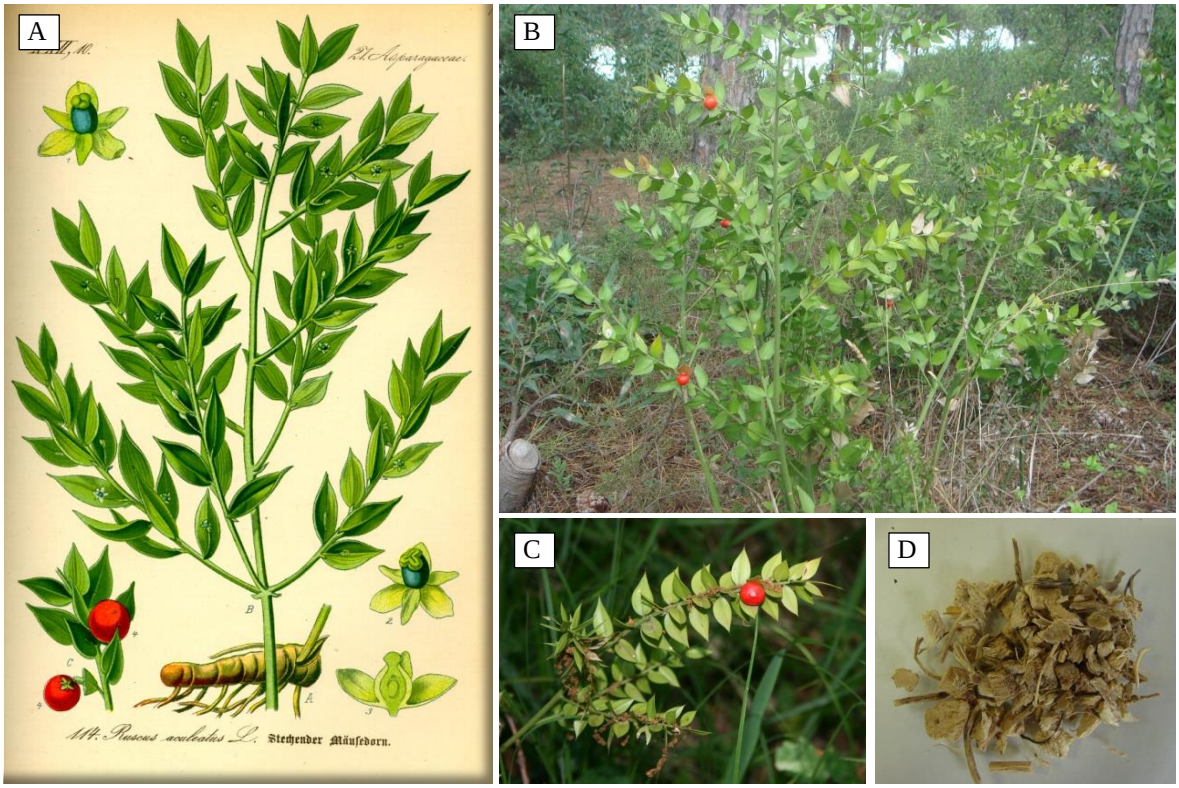


Figure 3.2., A: Illustration of *Ruscus aculeatus* L., B: *Ruscus aculeatus* plant, C: *Ruscus aculeatus* twig, D: Rusci rhizoma.[7]

All these effects are mostly ascribed to the steroidal saponins and ruscinogens (Figure 3.3) being the main constituents of the Rusci rhizoma extract. However, nothing is known about the influence on the pharmacological effects of the newly found ruscozepines. Due to the limited availability of these substances by isolation a synthetic approach is needed to provide enough material for pharmacological testing.

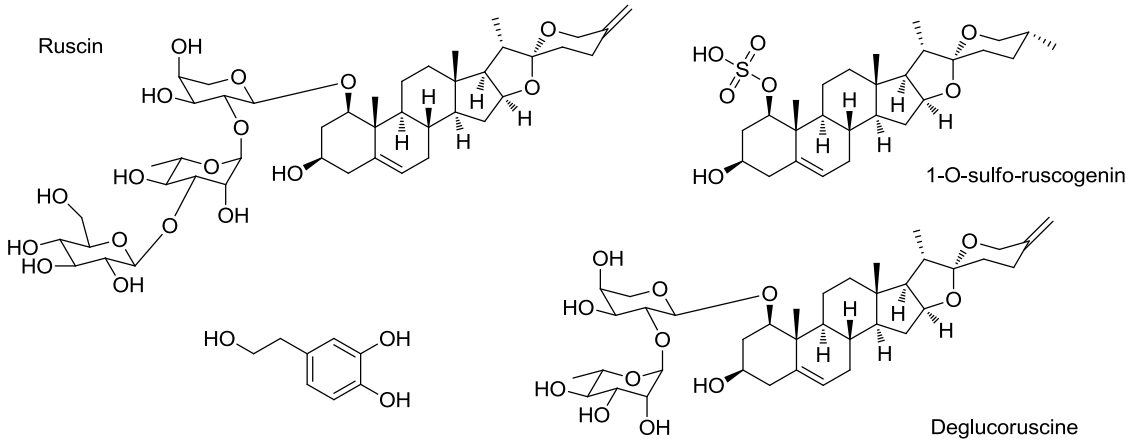
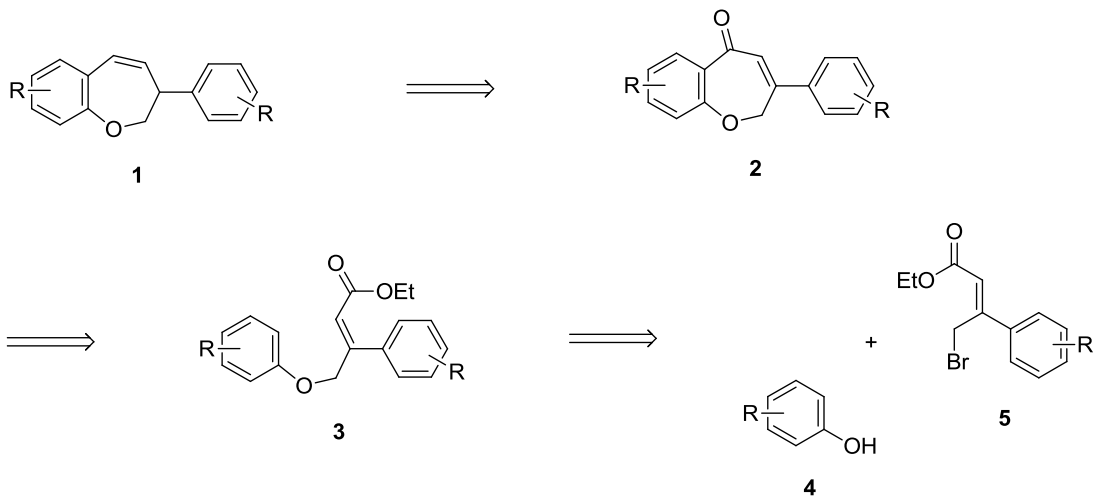


Figure 3.3. Constituents of Rusci rhizoma isolated besides ruscozepine A and B.[2]

3.2 Synthesis of the ruscozepines and analogous benzoxepines

The syntheses of the desired benzoxepines follows a known synthetic pathway,[8] which was improved for the ruscozepines. The carbon-carbon double bond of the 2,3-dihydro-benzo[b]oxepins **1** is generated by a reduction and elimination sequence from the α,β-unsaturated ester of the 3-aryl-benzo[b]oxepin-5(2H)-ones **2**. The 7-membered ring is closed by Friedel-Crafts acylation of the compounds **3**, which are generated by coupling of a phenol derivative **4** with an allyl bromide **5**. For the synthesis of the benzoxepines containing methoxy ether beside a phenol hydroxyl group, it was essential to apply an appropriate protection group strategy.



Scheme 3.1. Retro synthetic analysis of the 2,3-dihydrobenzo[b]oxepins.

In addition to the two isolated benzoxepines further analogous substances were synthesized (Figure 3.4). The planned synthesis of a benzazepine analog was not possible with the established synthetic protocol of the benzoxepines. The synthesized compounds differ in the substitution pattern of the aromatic rings and the functional groups present in the molecule and should help to broaden the knowledge of the pharmacological effects of this substance class.

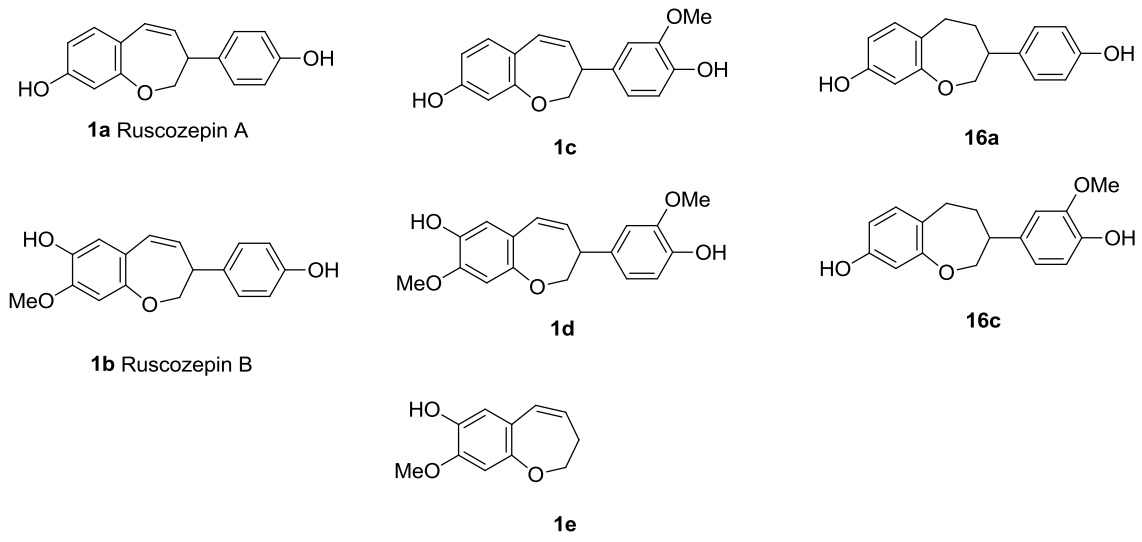
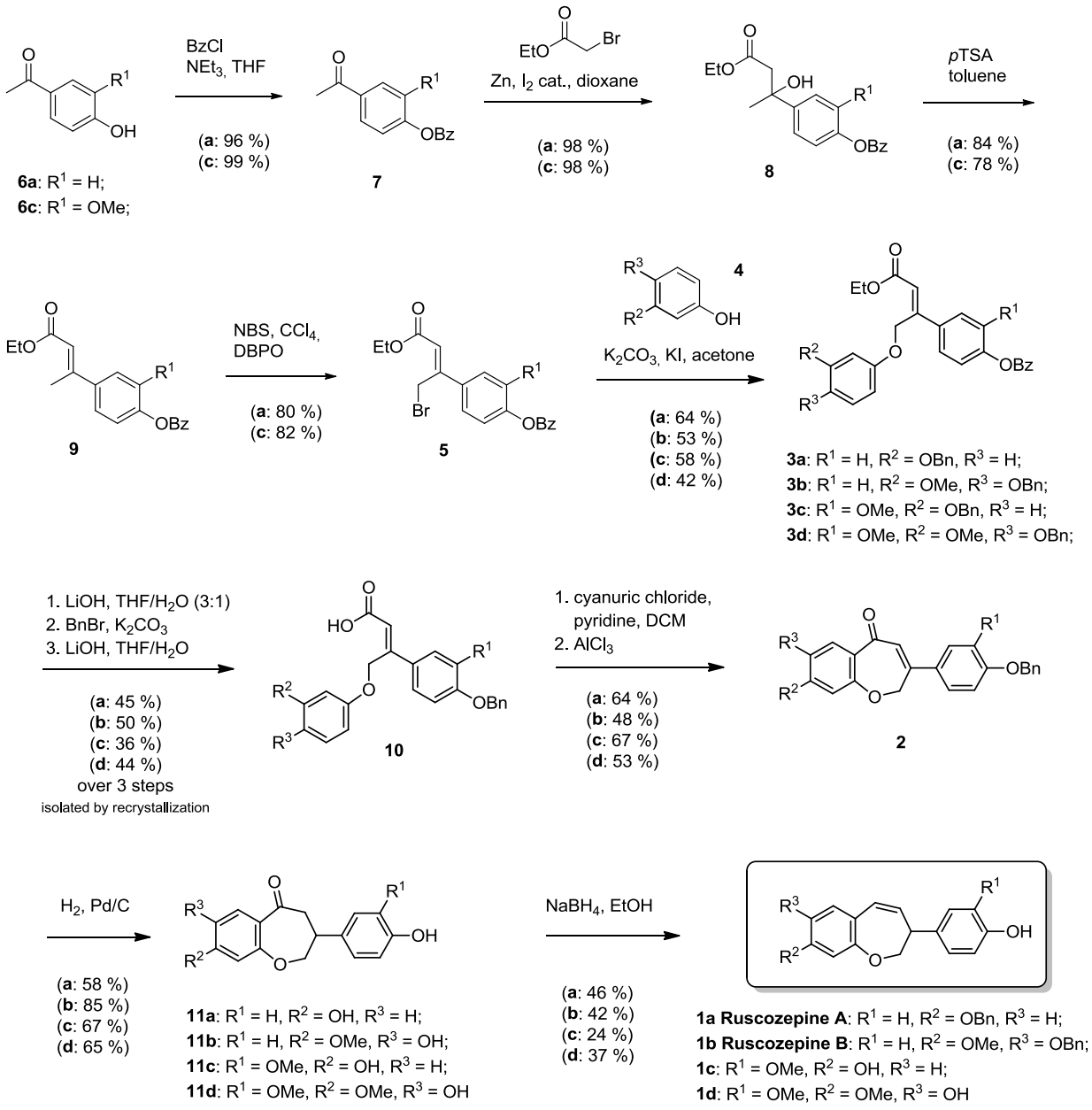


Figure 3.4. Synthesized compounds.

Aim of the study was the synthesis of the novel isolated phenyl-1-benzoxepinols ruscozepine A **1a** and ruscozepine B **1b** to elucidate their pharmacological effects and their role in the overall activity of the Rusci rhizoma extract. The synthesis was inevitable due to the limited availability of these compounds by isolation. In addition to the isolated substances further analogs were synthesized to broaden the knowledge on the pharmacological effects of this substance class.

3.2.1 Ruscozepine A, B and analogous benzoxepines

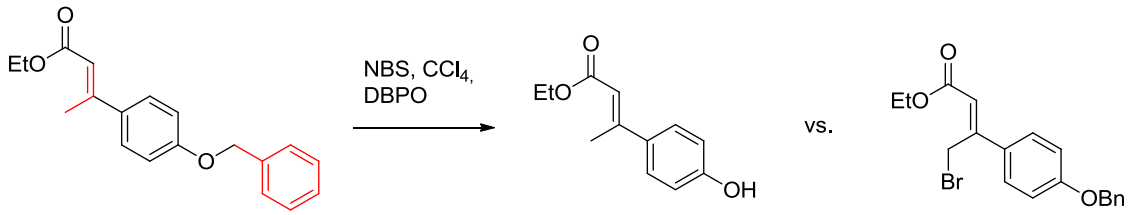
The Syntheses of the isolated ruscozepines A **1a** and B **1b** and the related benzoxepines **1c** and **1d** are shown in Scheme 3.2. The 11 steps proceeded with yields ranging from moderate to very good and provided the desired benzoxepines **1a-d** in overall yields from 1.5 % to 3.1 %, which means an average yield of 68 % to 73 % per step. A detailed description of the synthetic approach including encountered difficulties is provided in the following chapter.



Scheme 3.2. Syntheses of ruscozepine A and B and analogous benzoxepines.

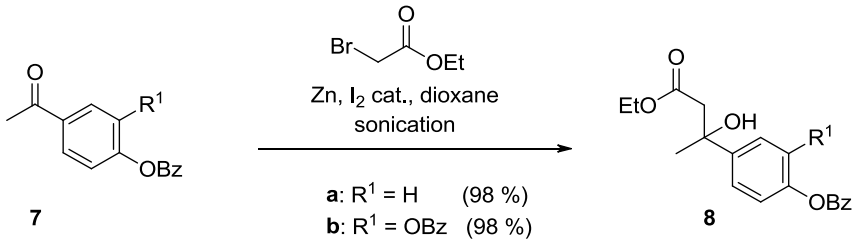
3.2.1.1 Synthesis of the 4-bromo-but-2-enoic acid esters 5a and 5c

In a first attempt benzyl was used as protection group for the aromatic hydroxyl groups as it was considered to be stable towards the conditions throughout the whole synthesis. Unfortunately, the benzyl group turned out is to be unstable during the allylic bromination. This reaction not only brominates in allylic, but also in benzylic position (Scheme 3.3). As a similar method is already used for the cleavage of benzyl groups using NBS in CCl_4 and additional $CsCO_3$ as base,[9,10] it is not appropriate for the synthesis of the 4-bromo-but-2-enoic acid esters.



Scheme 3.3. Side reaction of the radical bromination.

Consequently, benzoyl was chosen as alternative protection group, which is stable for the first part of the synthesis. The benzoyl protection of the commercial available acetophenones **6a/c** proceeded with excellent yields.[11] The following Reformatsky reaction of ethylbromo acetate with the benzoyl protected acetophenone derivatives **7a/c** was accelerated in an ultrasonic bath and afforded the corresponding alcohols **8a/c** in high yields (Scheme 3.4).[12]

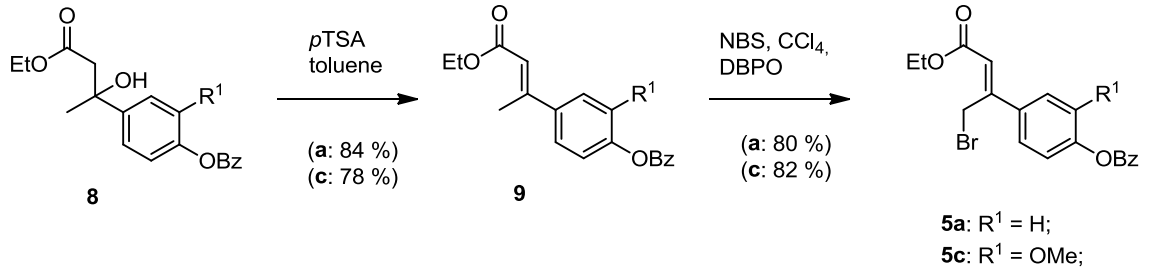


Scheme 3.4. Reformatsky reaction with commercial available zinc powder accelerated by sonication.

The Reformatsky reaction, being the classical reaction for the synthesis of β-hydroxy esters, proceeds *via* a nucleophilic addition of an organo zinc reagent to a ketone or aldehyde. The advantage of the Reformatsky reaction, in contrast to the Grignard

approach, is the toleration of esters, which would be attacked by Grignard reagents. In typical procedures activated zinc is prepared by reduction of zinc(II) chloride with potassium.[13-16] Using such a procedure,[15] only a unsatisfactory yield of 43 % was obtained. Therefore a simpler and faster procedure, accelerated by ultrasound, was chosen that could even be performed with commercially available zinc powder activated with catalytic amounts of iodine.

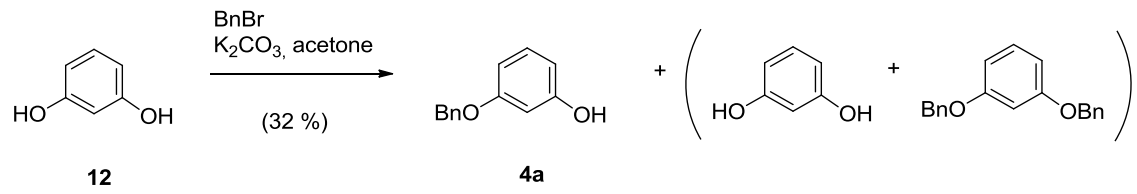
The alcohols **8a/c** were dehydrated with catalytic amounts of *p*-toluenesulfonic acid by continuous azeotropic removal of water in a Dean-Stark-apparatus.[17] Allylic bromination of the compounds **9a/c** with N-bromosuccinimide and dibenzoylperoxide as radical starter gave the 4-bromo-but-2-enoic acid esters **5a/c** in good yields (Scheme 3.5).[18]



Scheme 3.5. Synthesis of ethyl 4-bromobut-2-enoate derivatives.

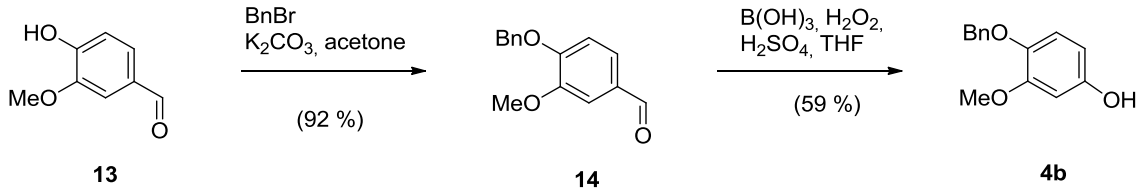
3.2.1.2 Synthesis of selectively protected phenol derivatives

The phenol derivatives were protected with benzyl groups, to guarantee the regioselective coupling with the allyl bromides **5a/c**.[11] The protection of resorcinol **12** with one equivalent of benzyl bromide gave the mono-protected resorcinol **13** in 32 % yield in a 1:1:1 mixture with the double- und unprotected resorcinol, which could be easily separated by flash chromatography (Scheme 3.6).



Scheme 3.6. Synthesis of 3-(benzyloxy)phenol.

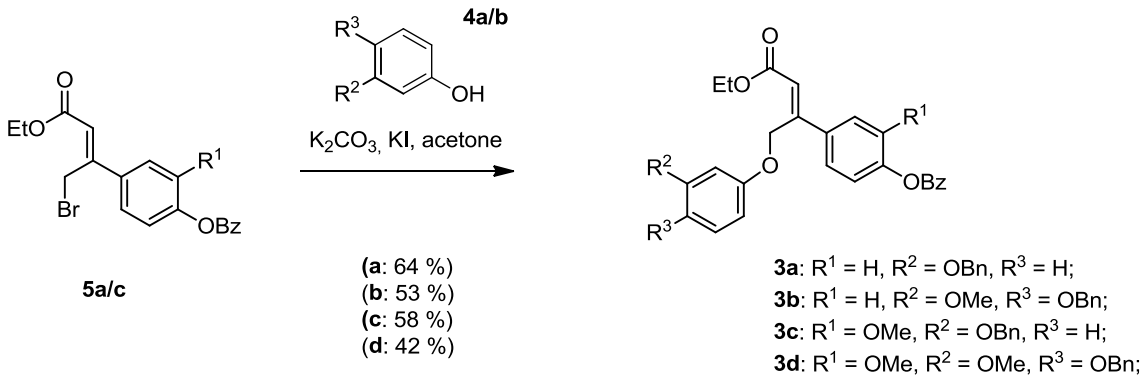
The selectively protected phenyl derivative **4b** was generated by a two-step procedure starting from vanillin **13**. The selective benzyl protection of 2-methoxybenzene-1,4-diol would not have been possible to our knowledge. First, the hydroxyl group was protected with benzyl bromide followed by conversion of the aldehyde **14** to the hydroxyl group by a Dakin reaction using boric acid and hydrogen peroxide (Scheme 3.7).[19,20]



Scheme 3.7. Synthesis of 4-(benzyloxy)-3-methoxyphenol.

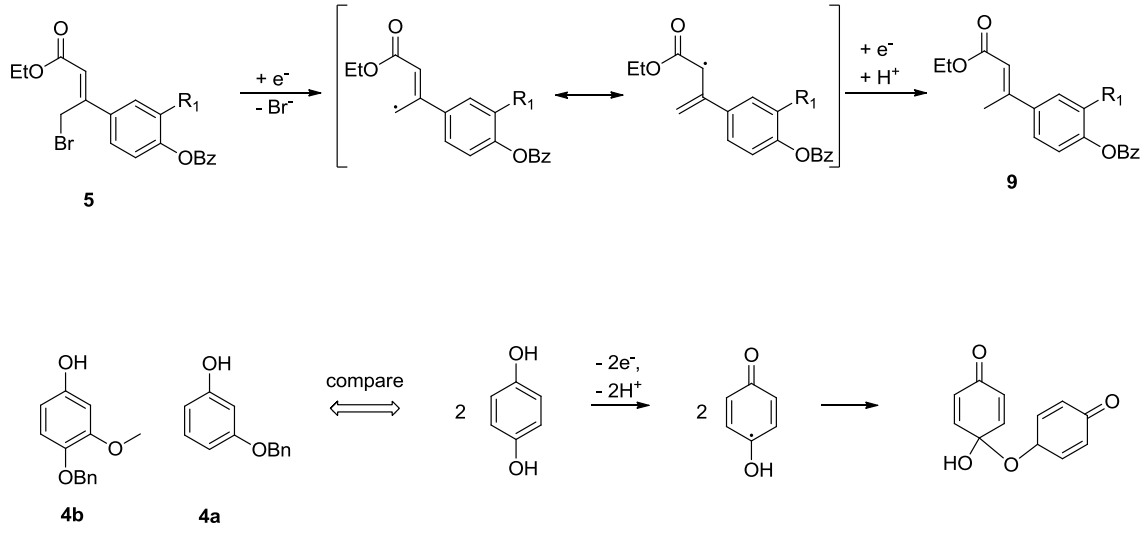
3.2.1.3 Intramolecular Friedel-Crafts acylation

For the synthesis of the 4-phenoxy-3-phenylbut-2-enoic acids **10a-d** the 4-bromo-but-2-enoic acid esters **5a/c** were coupled with the phenol derivatives **4a/b** under standard conditions for the nucleophilic substitution. With potassium carbonate as base and additional potassium iodide in refluxing acetone, the ethyl 4-phenoxy-3-phenylbut-2-enoates **3a-d** could be obtained in moderate yields from 42 % to 64 % (Scheme 3.8). The replacement of the base or the solvent with cesium carbonate or DMF, respectively, did not show any improvement of the yields.



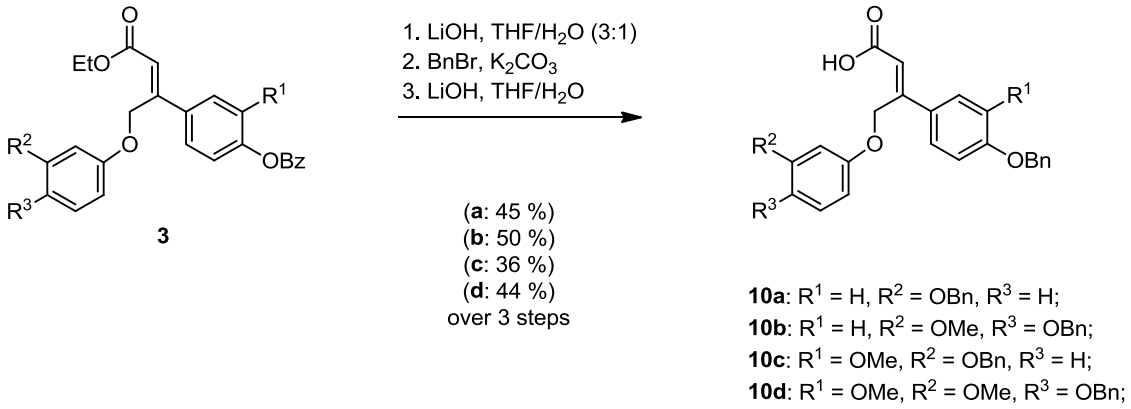
Scheme 3.8. Nucleophilic substitution of the 4-bromo-but-2-enoic acid esters **5a/c** with the phenol derivatives **4a/b**.

One possible explanation for these moderate yields might be the debromination of the 4-bromo-but-2-enoic acid esters **5** by single electron transfer (SET) reduction (Scheme 3.9).[21] This theory is supported by the successful isolation of a significant amount of the debrominated α,β-unsaturated esters **9**. The phenyl derivatives **4a/b**, being structurally related to hydroquinone, might serve as electron donors in this debromination reaction.[22]



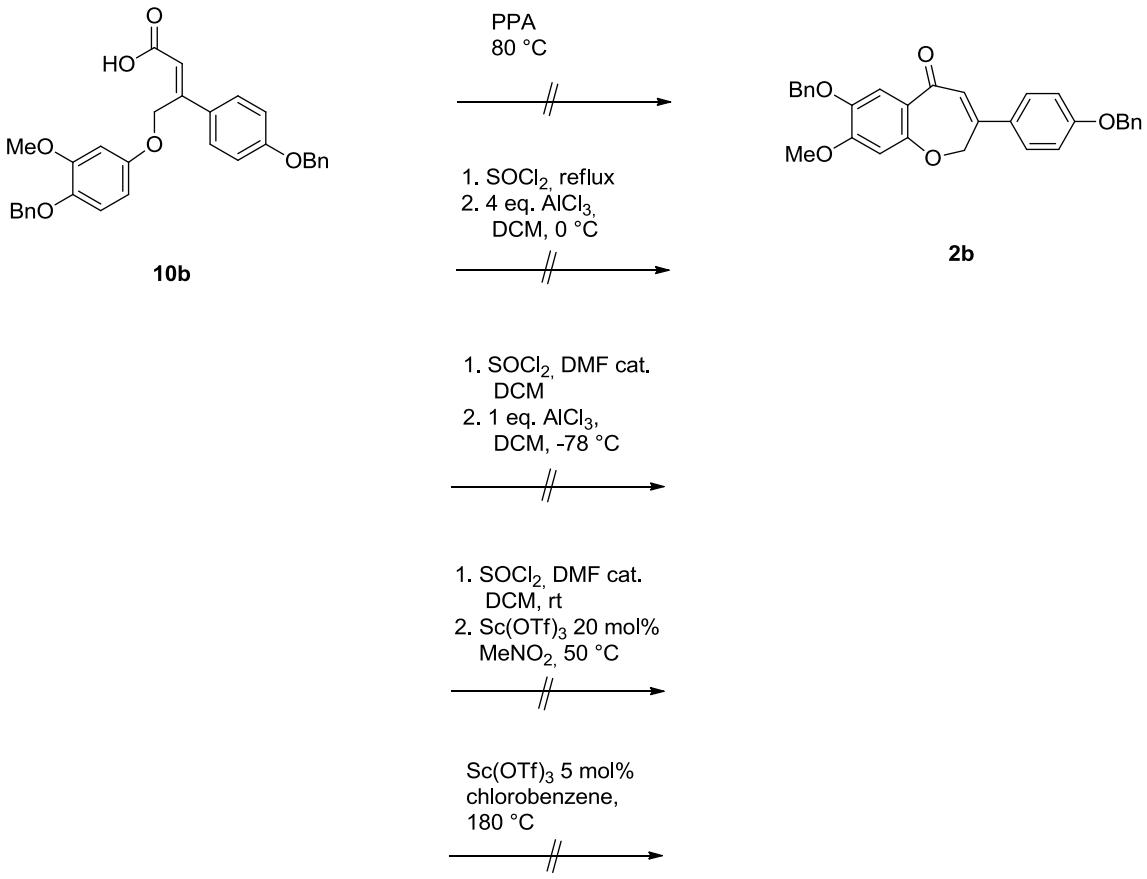
Scheme 3.9. Possible mechanism for the debromination of the allyl bromides **5a/c** by SET.[21,22]

Saponification of the esters **3a-d** was performed with lithium hydroxide in a THF/water solvent mixture at 50 °C. Under these conditions both, the ethyl and benzoyl esters were cleaved. Afterwards, the phenol hydroxyl group was protected with benzyl bromide and potassium carbonate in refluxing acetone. The benzyl ether formation of the hydroxyl group was accompanied by the simultaneous formation of the benzyl ester of the acid. Hence, this ester has to be cleaved subsequently by saponification. These steps of deprotection and protection could have been avoided if the benzyl group could have been used from the beginning of the synthesis. The 4-phenoxy-3-phenylbut-2-enoic acids **10a-d** could be isolated by crystallization from ethyl acetate in 36 % to 50 % yield over three steps (Scheme 3.10).



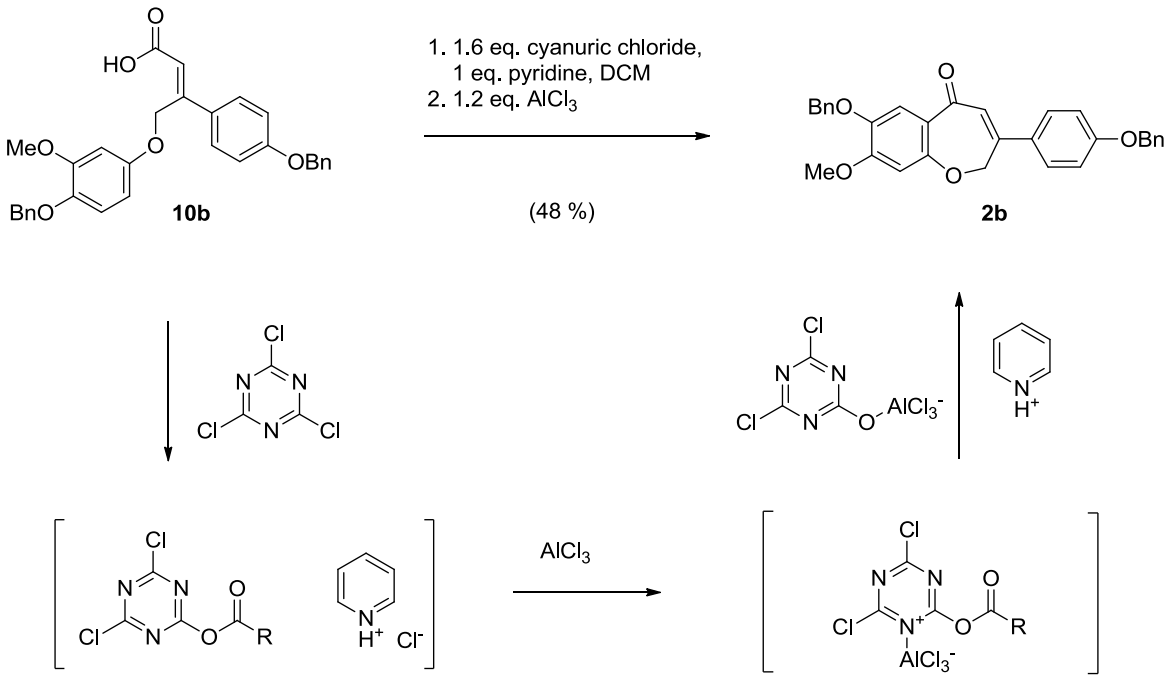
Scheme 3.10. Synthesis of the 4-phenoxy-3-phenylbut-2-enoic acids **10a-d**.

The 7-membered ring of the 3-phenyl-benzo[b]oxepin-5(2H)-ones **2a-d** was formed by intramolecular Friedel-Crafts acylation of the 4-phenoxy-3-phenylbut-2-enoic acids **10a-d**. Unfortunately, all attempts to perform this reaction under standard conditions failed. Applying polyphosphoric acid (PPA),[23-25] activation as acid chloride, with thionyl chloride (either in excess or stoichiometric with DMAP as catalyst) or oxalyl chloride,[26-28] followed by $AlCl_3$ or the use of $Sc(OTf)_3$ Lewis acid in catalytic amounts,[29-31] did not yield the desired 3-phenyl-benzo[b]oxepin-5(2H)-one **2b** (Scheme 3.11).



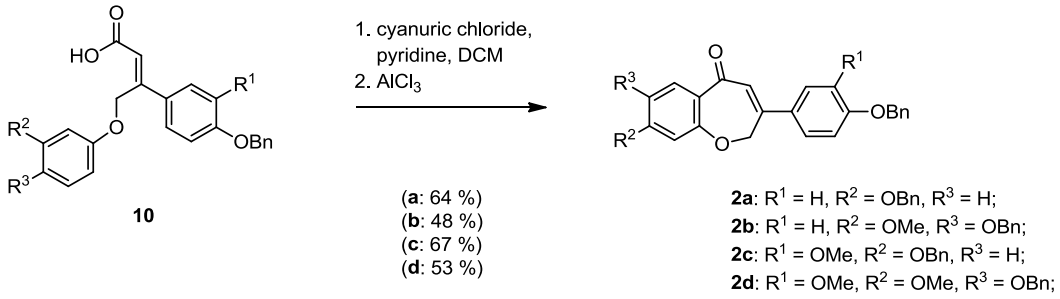
Scheme 3.11. Unsuccessful attempts for the intramolecular Friedel-Crafts acylation.

All of these procedures involve harsh acidic conditions, either Brønsted or Lewis acids are employed or released during the reaction. These strong acids are frequently used for the cleavage of ether groups and may lead to the cleavage of one or more of the ether groups in 4-(4-(benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid **10b**.[32,33] Consequently, a milder procedure for the Friedel-Crafts acylation invented by Kangani *et al.* was employed, activating the carboxylic acid with cyanuric chloride and pyridine (Scheme 3.12).[34] These reagents avoid the excessive release of HCl in combination with $AlCl_3$ and thus serve as mild alternative for the classical procedures.[35,36]



Scheme 3.12. Mild procedure for the Friedel-Crafts acylation invented by Kangani *et al.* employing cyanuric chloride.[34]

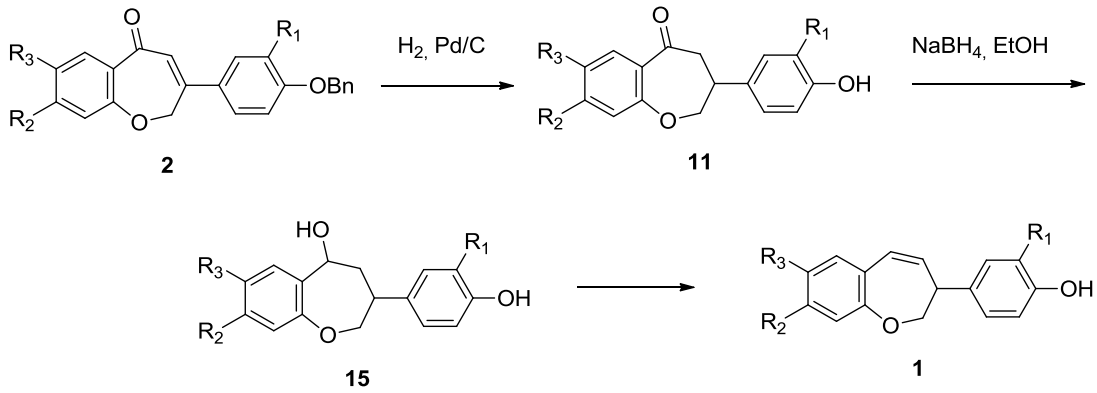
Thus, the 3-phenyl-benzo[b]oxepin-5(2H)-ones **2a-d** were obtained in 50 to 65 % yield. Moreover, no problems concerning the regioselectivity could be observed (Scheme 3.13).



Scheme 3.13. Synthesis of the 3-phenyl-benzo[b]oxepin-5(2H)-ones **2a-d**.

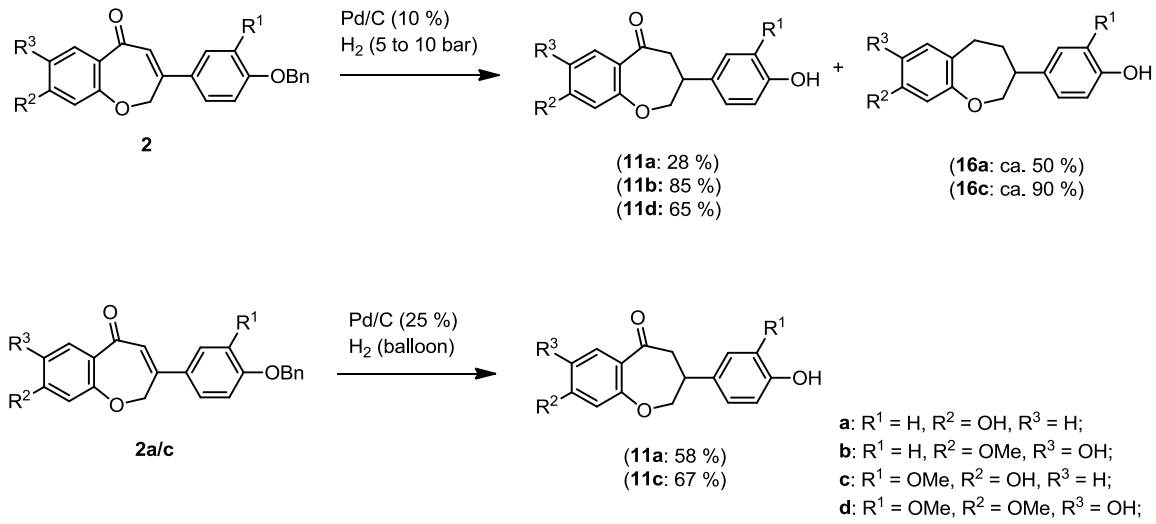
3.2.1.4 Reduction of the 3-phenyl-benzo[b]oxepin-5(2H)-ones 2a-d yielding the desired 3-phenyl-2,3-dihydrobenzo[b]oxepins 1a-d

The final three steps of the synthesis include the reduction of the carbon-carbon double bond of the α,β-unsaturated ketone **2a-d** and the simultaneous cleavage of the benzyl protection groups with hydrogen and palladium on charcoal, the reduction of the ketone **11** to the alcohol **15** and the subsequent elimination of this hydroxyl group (Scheme 3.14).



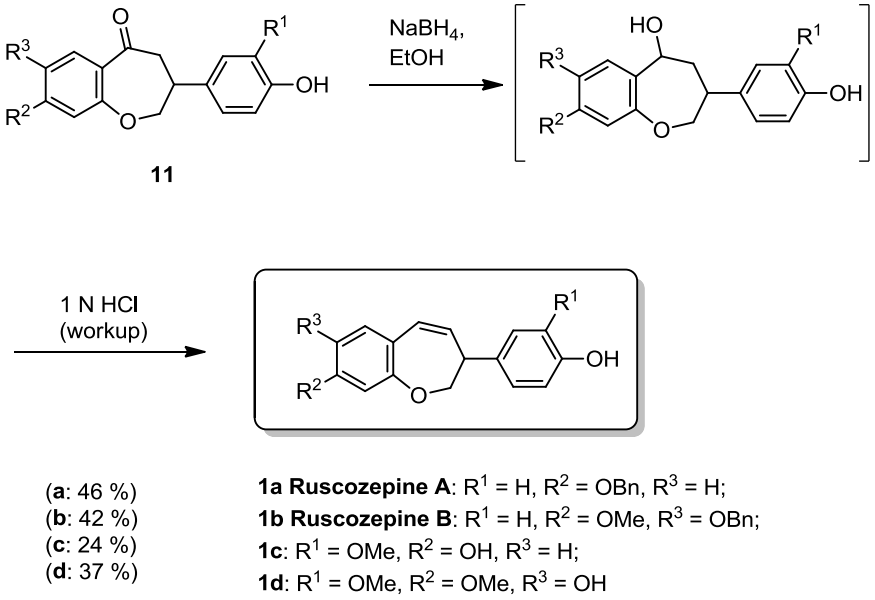
Scheme 3.14. Reduction and dehydration sequence yielding the 3-phenyl-2,3-dihydrobenzo[b]oxepins **1a-d**.

The reduction of the carbon-carbon double bond and the deprotection of the benzyl ethers in one step turned out to be problematic, because the complete reduction of the α,β-unsaturated ketones **2a/c** occurred as side reaction yielding the 3-phenyl-2,3,4,5-tetrahydrobenzo[b]oxepins **16a/c** (Scheme 3.15). High catalyst loading with 25 wt.-% of Pd/C and low hydrogen pressure could reduce this side reaction. The 3,4-dihydro-benzo[b]oxepin-5(2H)-ones **11a-d** could be isolated in 58 to 85 % yield.



Scheme 3.15. Transfer hydrogenation of the 3-phenyl-benzo[b]oxepin-5(2H)-ones **2a-d** with Pd/C and hydrogen.

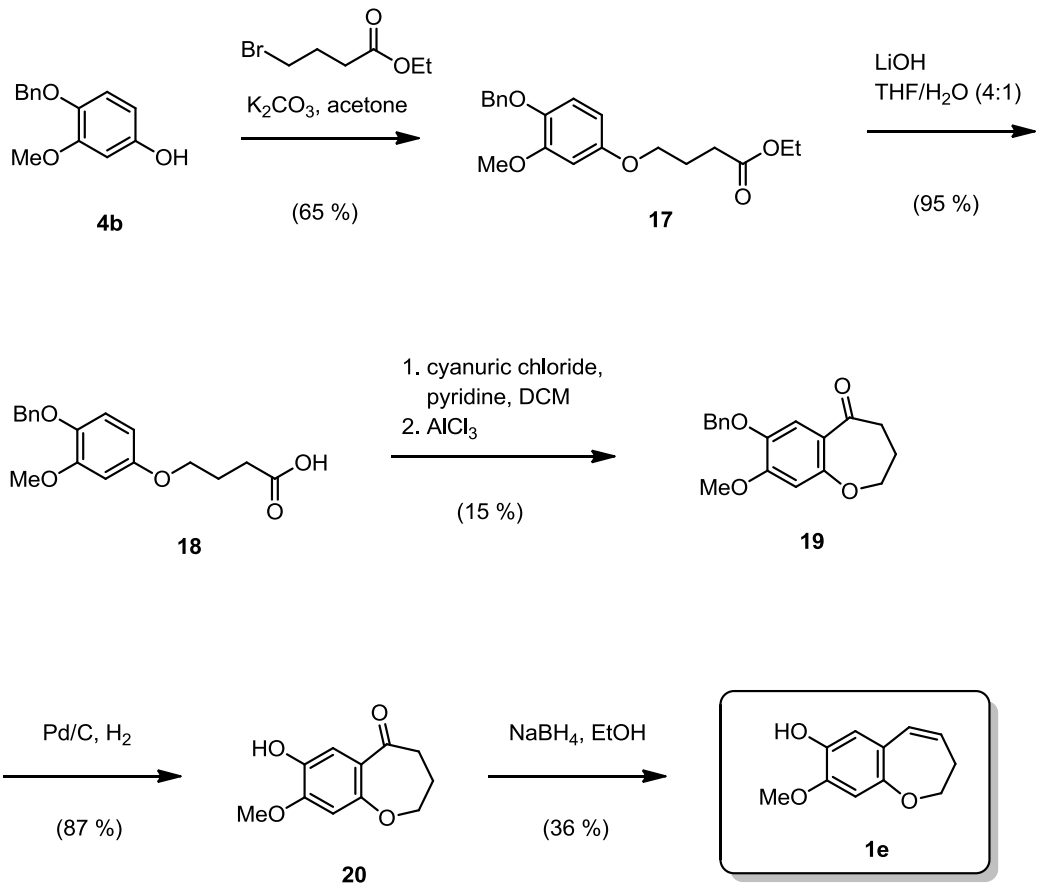
The following reduction of the ketone using sodium borohydride gave the 2,3-dihydro-benzo[b]oxepins **1a-d** as final products in about 40 % yield. The alcohols **15a-d** corresponding to the ketones **11a-d** could not be isolated, as the elimination to the desired product occurred by basic as well as acidic workup.



Scheme 3.16. Synthesis of the 2,3-dihydrobenzo[b]oxepins **1a-d**.

3.2.2 Synthesis of 8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol

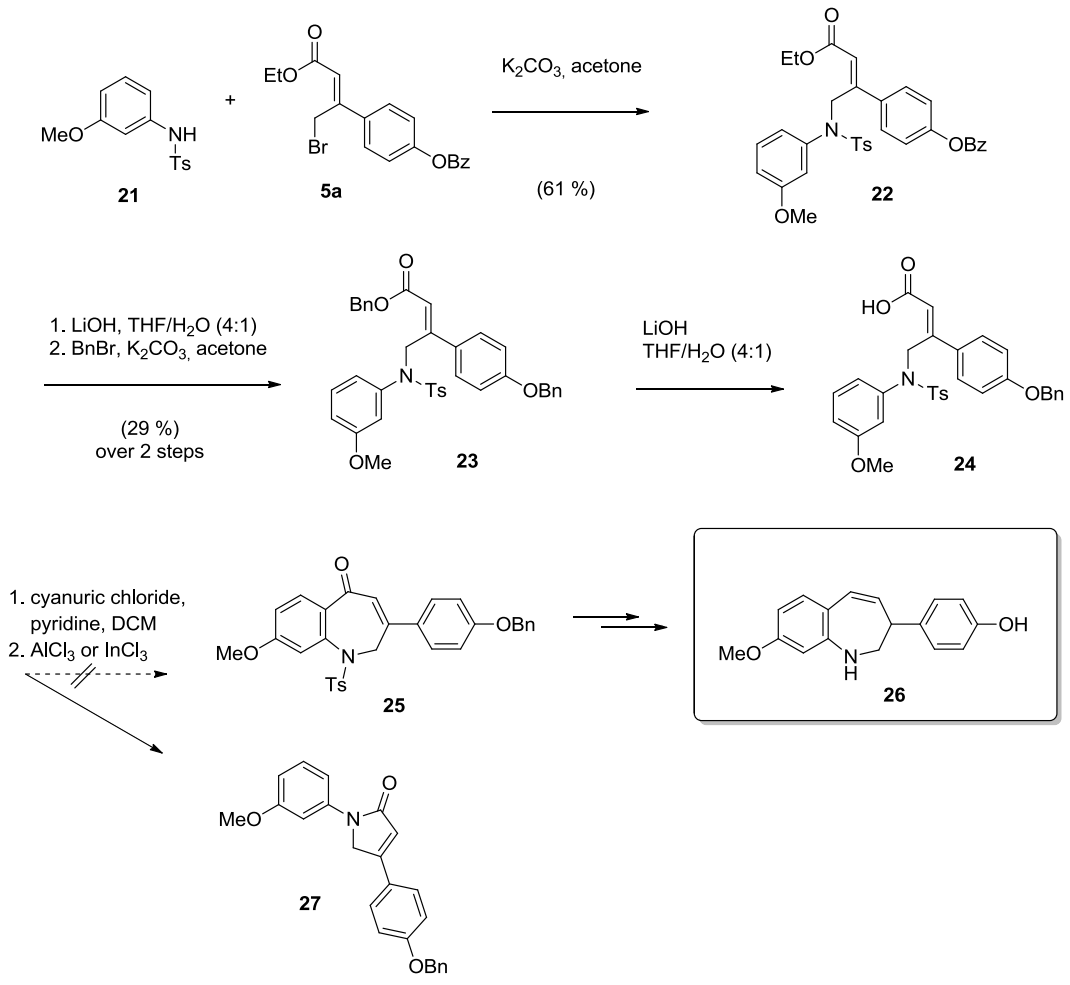
8-Methoxy-2,3-dihydrobenzo[b]oxepin-7-ol **1e** was synthesized *via* an analogous synthesis (Scheme 3.17), starting with the coupling of 4-(benzyloxy)-3-methoxyphenol **4b** with 4-bromo-butanoic acid ethyl ester under standard S_N reaction conditions. The closure of the 7-membered ring gave only a poor yield of 15 %, even the increase of temperature or reaction time couldn´t solve this problem. This poor yield of the ring closure might be ascribed to the higher rotational freedom of the 4-(4-(benzyloxy)-3-methoxy-phenoxy)butanoic acid **18** compared to the 4-phenoxy-3-phenylbut-2-enoic acids **10a-d** containing an E-configured carbon-carbon double bond. The following steps were performed similarly to the synthesis of previous benzoxepines.



Scheme 3.17. Synthesis of 8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol **1e**.

3.2.3 Nitrogen analog of ruscozepines - benzazepine

In addition to the benzoxepines the synthetic protocol was applied for the synthesis of a benzazepine **26** (Scheme 3.18), a nitrogen analog of the ruscozepines. Therefore the phenol derivative for the coupling with the allyl bromide was replaced by the aniline **21**. A tosyl group was used for the protection of the aniline to avoid the formation of an amide. The synthesis proceeded well till the Friedel-Crafts acylation step. The tosyl group was not stable towards the reaction conditions and was cleaved, resulting in the formation of the 5-memebered γ-lactam **27**. Even the use of a milder Lewis acid, i.e. indium(III) chloride that is known not to cleave the tosyl protection group,[37] did not avoid the formation of the lactam. For synthesis of the benzazepine a complete change of the synthetic plan would have been required exceeding the time frame of the project.



Scheme 3.18. Unsuccessful synthesis of the benzazepine **26**.

3.3 Pharmacology

3.3.1 Rhizoma extract of *Ruscus aculeatus* L.

Ruscus aculeatus L. is long known for its medical use. In present times the alcoholic extract of the Rusci rhizoma is mostly used for the treatment of chronic venous insufficiency (CVI) and hemorrhoids. As the anti-inflammatory activity of the extract is mostly subscribed to the saponins and ruscogenin,[38] the aim of this study was to elucidate the pharmacological effects of the ruscozepines A and B and if they contribute to the anti-inflammatory activity of the Rusci rhizoma extract. Therefore, the effect of the ruscozepines on the TNF-α-induced expression of ICAM-1 (intercellular adhesion molecule), besides cytotoxicity and antioxidant activity, was investigated. The pharmacological testing was done by the working group of Pharmaceutical Biology of Prof. Dr. Jörg Heilmann at the University of Regensburg.

3.3.2 MTT viability assay - cytotoxicity

The cytotoxicity of ruscozepine B was measured with the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) viability assay with HMEC-1 (human micro-vascular endothelial cells) that are used for the ICAM-1 expression inhibition assay. Ruscozepine B **1b** had no effect on the viability of HMEC-1 in the concentration range of 1-100 μM (Figure 3.5).

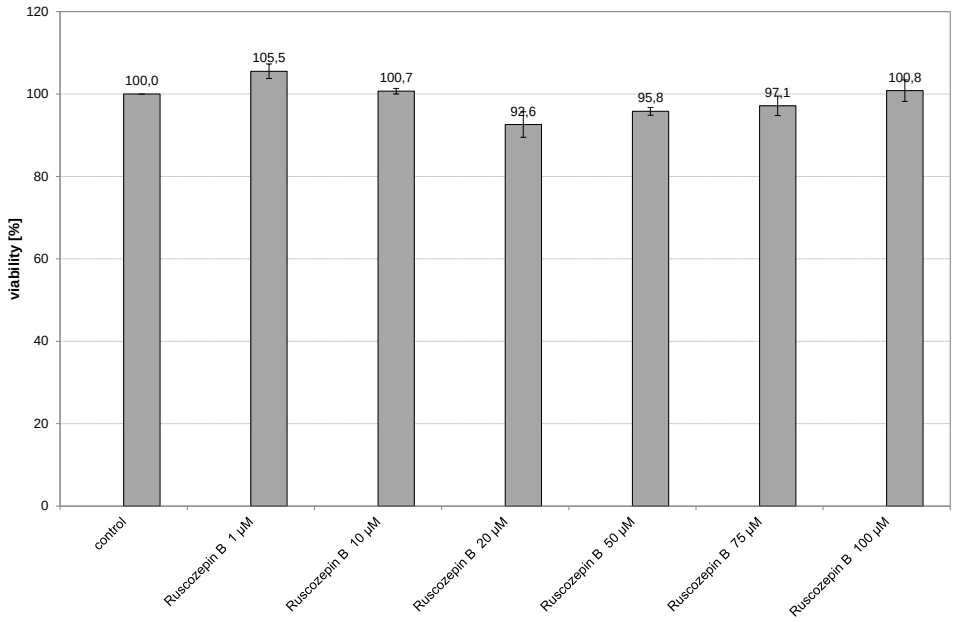


Figure 3.5. MTT viability assay after 24 h of ruscozepine B on HMEC #2-4; n=3; mean±SD.

3.3.3 ICAM-1 expression inhibition assay – anti-inflammatory activity

The ICAM-1 expression inhibition assay was used for the determination of the anti-inflammatory activity of ruscozepine B **1b**. For this assay, a HMEC-1 cell culture is treated with TNF-α (tumor necrosis factor) to induce ICAM-1 expression via the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B-cells) signal transduction pathway (Figure 3.6). The expression of ICAM-1 is a good indicator for the degree of inflammation in the endothelial cells and is determined by a fluorescence labeled antibody. An anti-inflammatory compound leads to a decrease of the TNF-α induced ICAM-1 expression, indicated by a reduced fluorescence compared with a control.

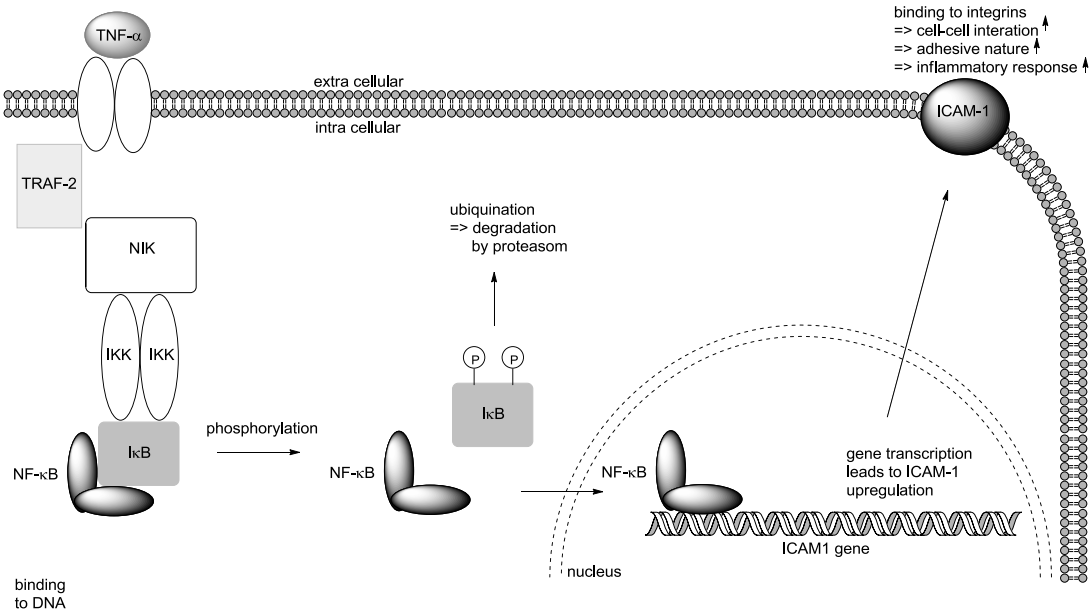


Figure 3.6. Simplified signal transduction pathway of the TNF-α induced ICAM-1 expression.

Ruscozepine B **1b** shows no significant inhibition of the ICAM-1 expression in the concentrations 1, 50 and 75 μM (Figure 3.7). The inhibition of 23 % at a concentration of 10 μM is not clear and might either be an outlier or an effect of the concentration or solubility.

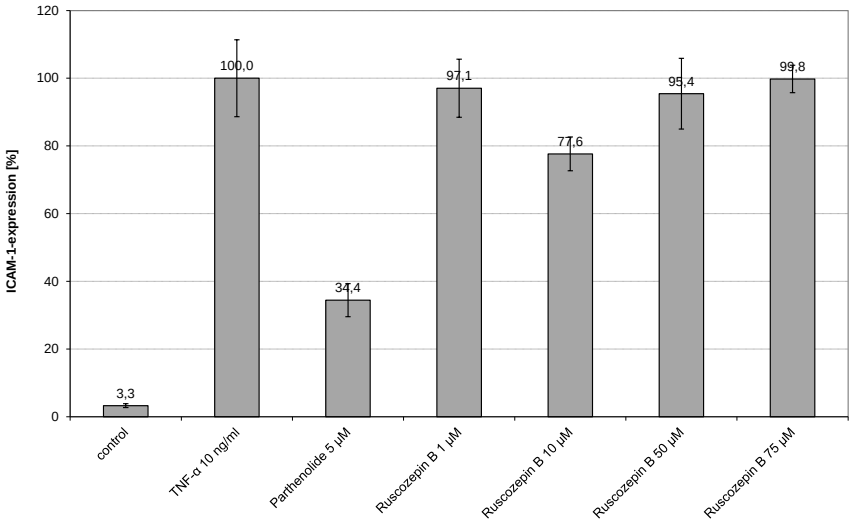


Figure 3.7. Inhibition of TNF-α induced ICAM-1-expression of ruscozepine B **1b** after 24 h; Parthenolide (5µM) is used as positive control; HMEC#2-10; n=3 in duplicates; mean±SD.

3.3.4 ORAC-Fluorescein assay – antioxidant activity

Antioxidants, especially phenolic antioxidants, are supposed to exhibit anti-inflammatory activity by the down regulation of the TNF-α expression by blocking the LPS (lipopolysaccharide) induced TNF-α production and the decrease of ROS (reactive oxygen species) in the cell, respectively.[39-41] Furthermore, a direct radical scavenging activity of various phenolics is discussed by a reaction with the ROS. Consequently, the antioxidant activity of the synthesized benzoxepines is of great interest and was measured with an ORAC-Fluorescein assay (oxygen radical absorbance capacity).[42,43] Therefore a fluorescent probe, containing fluorescein, is treated with an antioxidant to measure the decrease of the fluorescein decay (Figure 3.9), induced by addition of AAPH (2,2´-azobis-(2-methylpropionamide)-dihydrochloride, Figure 3.8). The antioxidant activity is referenced to Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, water-soluble derivative of vitamin E) equivalents, TEAC (trolox equivalent antioxidant capacity).

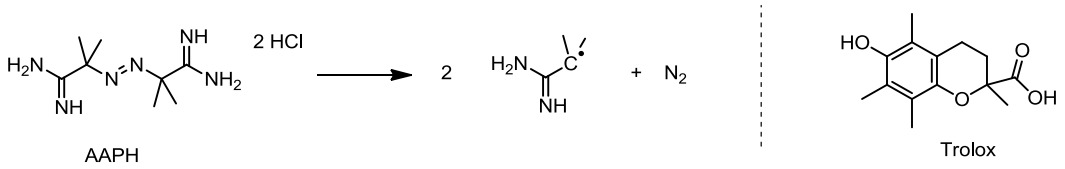


Figure 3.8. Radical generation reaction from AAPH; the water-soluble vitamin E derivative trolox.

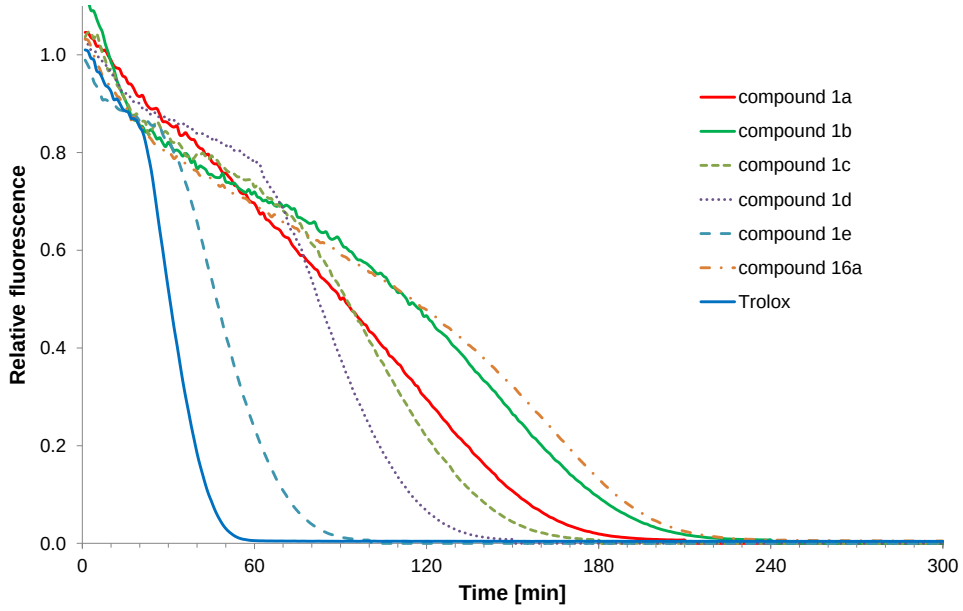
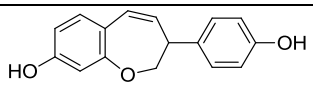
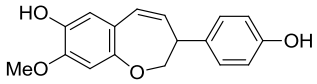
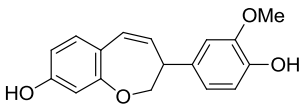
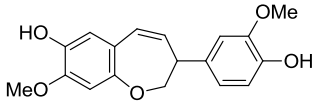
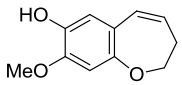
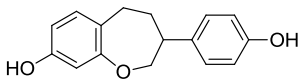
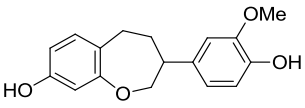


Figure 3.9. Fluorescence curves of compounds **1a-e**, **16a** and Trolox (concentration 5 μM, each) for the ORAC-assay.

Both isolated compounds, ruscozepine A **1a** and ruscozepine B **1b**, showed a high antioxidant activity of 3.7±0.2 and 4.2±0.3 TEAC (concentration range 1-5 μM), respectively (Table 3.1). These TEAC values are comparable with strong antioxidants like ferulic acid (4.5±0.2 TEAC, concentration range 0.4-1.3 μM) and *p*-coumaric acid (4.5±0.2 TEAC, concentration range 0.4-1.0 μM).[42] The analogous 2,3-dihydrobenzo[b]oxepins **1c/d** have also shown a good antioxidant activity, but the additional methoxy substitution of the second aromatic ring seems to decrease the activity. The big influence of the second aromatic ring becomes clear looking at the TEAC value of compound **1e**, where this second aromatic ring is not present. The TEAC value is lowered by 1.8 Trolox units compared to ruscozepine **1b**. Surprisingly, the compounds **16a/c**, having no carbon-carbon double bond that was expected to increase the TEAC value by being involved in the radical capture mechanism, show a 0.8/1.2 higher TEAC value compared with **1a/c**. Consequently, the antioxidant activity of the ruscozepines is mostly caused by the phenolic rings and influenced by the different substitution patterns.

Table 3.1. TEAC values of the compounds **1a-e** and **16a** in the concentration range of 1-5 μM.

compound		TEAC ± SD
1a		3.7 ± 0.2
1b		4.2 ±0.3
1c		3.2 ± 0.1
1d		3.2 ± 0.2
1e		2.4 ± 0.2
16a		4.5 ± 0.2
16c		4.4 ± 0.3

3.4 Conclusion

We developed the racemic synthesis of novel phenyl-1-benzoxepinols ruscozepine A **1a** and ruscozepine B **1b**, analogous benzoxepines **1c-e** and the 3-phenyl-2,3,4,5-tetrahydro-benzo[b]oxepins **16a/c**. For the crucial step, the formation of the 7-membered ring by Friedel-Crafts acylation, a mild procedure using cyanuric chloride for the activation of the carboxylic acid had to be applied, while standard methods for the Friedel-Crafts acylation failed, because of the harsh acidic conditions. Unfortunately, the synthetic protocol could not be applied for the synthesis of an analogous benzazepine.

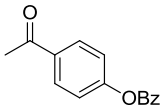
Pharmacological testing of ruscozepine B **1b** did not show an effect on the TNF-α induced expression of ICAM-1 on human microvascular endothelial cells (HMEC-1). Moreover, no cytotoxicity on the HMEC-1 could be detected in a MTT viability assay. However, the ORAC-Fluorescein assay revealed a high antioxidant activity for the compounds **1a-d** and **16a/c** that could influence the anti-inflammatory activity *via* a decreasing level of ROS in the cell, which play an important role in cell signaling, including inflammation.

Consequently, the anti-inflammatory effect of the Rusci rhizoma extract might at least partly be ascribed to the novel found phenyl-1-benzoxepinols. The overall activity might be a cooperative effect of the Rusci rhizoma constituents, as the amount of the ruscozepines in the Rusci rhizoma extract is very low these compounds will only contribute a minor part of the pharmacological activity. Further investigations are needed to provide clear evidence for the exact pharmacological effects of these compounds.

3.5 Experimental

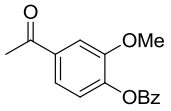
3.5.1 Preparation of compounds

General: Commercial reagents and starting materials were purchased from Acros Organics, Alpha-Aesar, Eurorad, Fluka, Merck or Sigma-Aldrich and used without further purification. 1,4-Dioxane was dried with sodium and stored over 4 Å molecular sieves according to common procedures.[44] Acetone, dichloromethane, dichloroethane and dimethylformamide were dried by storage over molecular sieves for at least 24 hours. Zinc dust was activated according to reports of Cava *et al.*.[45] Flash column chromatography was performed on Merck silica gel (Si 60 40-63 μm) either manually or on a Biotage® Isolera™ flash purification system. TLC was performed on aluminum plates coated with Merck silica gel (60 F_{254}, thickness 0.2 mm), compounds were detected by UV-light (λ = 254 nm) and staining with common vanillin or ninhydrin staining-solutions. Melting points were measured on a SRS melting point apparatus (MPA100 Opti Melt) and are uncorrected. NMR spectra were recorded on Bruker Avance 300 (^{1}H 300.13 MHz, ^{13}C 75.47 MHz, T = 300 K), Bruker Avance 400 (^{1}H 400.13 MHz, ^{13}C 100.61 MHz, T = 300 K), Bruker Avance 600 (^{1}H 600.13 MHz, ^{13}C 150.92 MHz, T = 300 K) and Bruker Avance III 600 Kryo (^{1}H 600.25 MHz, ^{13}C 150.95 MHz, T = 300 K) instruments. Chemical shifts are reported in δ [ppm] relative to external standards and coupling constants *J* are given in Hz. Abbreviations for the multiplet signals: s = singlet, d = doublet, t = triplet, q = quartet, , qunit = quintet, m = multiplet, bs = broad singlet, dd = double doublet, dt = doublet of triplets. The relative number of protons was determined by integration. Error of reported values: chemical shift 0.01 ppm (^{1}H NMR) and 0.1 ppm (^{13}C NMR), coupling constant 0.1 Hz. The solvents used for the measurements are reported for each spectrum. IR spectra were recorded with a Bio-Rad FT-IR-FTS 155 spectrometer and UV/Vis spectra with a Cary BIO 50 UV/Vis/NIR spectrometer (Varian). Mass spectra were recorded on Finnigan MAT95 (EI-MS), Agilent Q-TOF 6540 UHD (ESI-MS, APCI-MS), Finnigan MAT SSQ 710 A (EI-MS, CI-MS) or ThermoQuest Finnigan TSQ 7000 (ES-MS, APCI-MS) spectrometer.



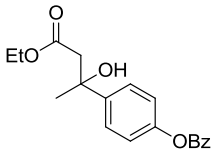
*4-Acetylphenyl benzoate (**7a**)*

NEt_3 (3.8 mL, 28 mmol) was added to a solution of p-hydroxyacetophenone **6a** (3.40 g, 25.0 mmol) in THF (200 mL). The stirring solution was cooled with an ice-water bath while benzoyl chloride (3.1 mL, 27 mmol) was added *via* syringe over 30 minutes. After 2 hours the cooling bath was removed and the solution stirred at room temperature for additional 2 hours. The reaction solution was evaporated and the residue dissolved in dichloromethane (150 mL). The organic layer was washed with 1 N HCl (50 mL), saturated sodium chloride solution (50 mL) and water (50 mL). Afterwards the organic layer was dried with $MgSO_4$ before the solvent was removed under reduced pressure. The product, 4-acetylphenyl benzoate **7a**, was obtained as pale white solid in 96 % yield (5.80 g, 24.1 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (dt, *J* = 8.5, 1.6 Hz, 2H), 8.09 – 8.03 (m, 2H), 7.70 – 7.63 (m, 1H), 7.58 – 7.49 (m, 2H), 7.37 – 7.30 (m, 2H), 2.63 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0, 154.7, 134.8, 134.0, 130.3, 130.0, 129.1, 128.7, 122.0, 26.7 ppm. EI-MS: m/z (%) = 77.1 (69), 105.0 (100), 240.1 (11) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{15}H_{12}O_3$ $[M]^{+\bullet}$ 240.0786; found 240.0792. (Ref. [46])



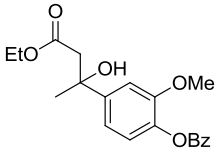
*4-Acetyl-2-methoxyphenyl benzoate (**7c**)*

NEt_3 (14.7 mL, 105 mmol) was added to a solution of acetovanillone **6c** (16.6 g, 100 mmol) in THF (700 mL). The stirring solution was cooled with an ice-water bath while benzoyl chloride (12.1 mL, 105 mmol) was added *via* syringe over 30 minutes. After 2 hours the cooling bath was removed and the solution stirred at room temperature for additional 2 hours. The reaction solution was evaporated and the residue dissolved in dichloromethane (500 mL). The organic layer was washed with 1 N HCl (100 mL), saturated sodium chloride solution (150 mL) and water (150 mL). Afterwards the organic layer was dried with $MgSO_4$ before the solvent was removed under reduced pressure. 4-Acetyl-2-methoxyphenyl benzoate **7c** was obtained as pale white solid in 99 % yield (27.3 g, 99 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (dt, *J* = 8.5, 1.7 Hz, 2H), 7.69 – 7.58 (m, 3H), 7.57 – 7.48 (m, 2H), 7.25 (d, *J* = 8.1 Hz, 1H), 3.88 (s, 3H), 2.63 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.0, 164.3, 151.7, 144.1, 136.0, 133.8, 130.4, 129.0, 128.6, 123.0, 122.0, 111.5, 56.1, 26.6 ppm. (Ref. [47,48])



*4-(4-Ethoxy-2-hydroxy-4-oxobutan-2-yl)phenyl benzoate (**8a**)*

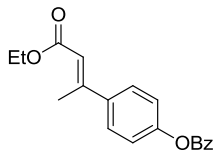
The reaction was performed under inert nitrogen atmosphere using standard Schlenk techniques. 4-Acetylphenyl benzoate **7a** (5.13 g, 21.4 mmol) and ethylbromoacetate (2.8 mL, 26 mmol) were dissolved in dry dioxane (45 mL) and zinc dust (2.52 g, 38.5 mmol) was added. Stirring of the solution was stopped before iodine (0.28 g, 1.1 mmol) was added. The reaction solution was then sonicated for 3 hours. Afterwards the reaction mixture was cooled with an ice-water bath and quenched adding 1 N HCl (50 mL). To remove remaining iodine from the organic layer, potassium iodide (0.4 g) was added. The aqueous layer was extracted with dichloromethane (3×100 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (PE/EtOAc 4:1, R_f 0.22). 4-(4-Ethoxy-2-hydroxy-4-oxobutan-2-yl)phenyl benzoate **8a** was obtained as white crystalline needles in 98 % yield (6.88 g, 20.9 mmol). Mp 72 – 76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 – 8.15 (m, 2H), 7.69 – 7.59 (m, 1H), 7.58 – 7.46 (m, 4H), 7.23 – 7.15 (m, 2H), 4.47 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 2.98 (d, *J* = 15.9 Hz, 1H), 2.80 (d, *J* = 15.9 Hz, 1H), 1.56 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 165.2, 149.8, 144.5, 133.7, 133.6, 130.2, 129.6, 128.6, 125.8, 121.4, 72.6, 60.9, 46.4, 30.7, 14.0 ppm. FT-IR: ν (cm^{-1}) = 707, 1024, 1062, 1171, 1205, 1244, 1267, 1708, 1731, 2903, 2959, 2984, 3071, 3543. ESI-MS: m/z (%) = 311.0 (18), 329.0 (36) $[M+H]^+$, 346.1 (100) $[M+NH_4]^+$, 370.1 (92) $[M+H+MeCN]^+$, 388.1 (32). HR-MS: calcd. for $C_{19}H_{20}NaO_5$ $[M+Na]^+$ 351.1203; found 351.1205.



*4-(4-Ethoxy-2-hydroxy-4-oxobutan-2-yl)-2-methoxyphenyl benzoate (**8c**)*

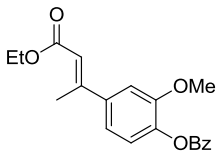
The reaction was performed under inert nitrogen atmosphere using standard Schlenk techniques. 4-Acetyl-2-methoxyphenyl benzoate **7c** (27.3 g, 100 mmol) and ethylbromoacetate (13.3 mL, 120 mmol) were dissolved in dry dioxane (250 mL) and zinc dust (11.8 g, 180 mmol) was added. Stirring of the solution was stopped before iodine (1.27 g, 5.00 mmol) was added. The reaction solution was then sonicated for 20 hours. Afterwards the reaction mixture was cooled with an ice-water bath and quenched adding 1 N HCl (300 mL). To remove remaining iodine from the organic layer, potassium iodide

(1.5 g) was added. The aqueous layer was extracted with dichloromethane (3×250 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. 4-(4-Ethoxy-2-hydroxy-4-oxobutan-2-yl)-2-methoxyphenyl benzoate **8c** was obtained as yellowish white solid in 98 % yield (35.2 g, 98.0 mmol). The crude product was used without further purification. Mp 95 – 101 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 – 8.17 (m, 2H), 7.67 – 7.59 (m, 1H), 7.55 – 7.45 (m, 2H), 7.24 (d, *J* = 2.1 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.96 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.53 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.99 (d, *J* = 15.9 Hz, 1H), 2.80 (d, *J* = 15.9 Hz, 1H), 1.56 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 164.8, 151.1, 146.1, 138.7, 133.5, 130.3, 129.5, 128.5, 122.5, 116.7, 109.4, 72.8, 60.9, 56.0, 46.3, 30.8, 14.1 ppm. FT-IR: ν (cm^{-1}) = 708, 1022, 1065, 1172, 1268, 1714, 2968, 2986, 3080, 3508. ESI-MS: m/z (%) = 341.1 (35) $[M+H-H_2O]^+$, 376.2 (100) $[M+NH_4]^+$. HR-MS: calcd. for $C_{20}H_{26}NO_6$ $[M+NH_4]^+$ 376.1755; found 376.1752.



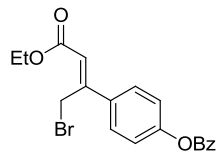
*4-(4-Ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate (**9a**)*

4-(4-Ethoxy-2-hydroxy-4-oxobutan-2-yl)phenyl benzoate **8a** (6.9 g, 21 mmol), toluene (40 mL) and p-toluenesulfonic acid (0.20 g, 1.1 mmol) were placed in a Dean-Stark apparatus and heated to reflux for 4 hours. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (PE/EtOAc 4:1 R_f 0.4). 4-(4-Ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate **9a** was obtained as white crystals in 84 % yield (5.46 g, 17.6 mmol). Mp 77 – 80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 – 8.15 (m, 2H), 7.69 – 7.61 (m, 1H), 7.60 – 7.47 (m, 4H), 7.24 (dt, *J* = 9.5, 2.6 Hz, 2H), 6.15 (q, *J* = 1.2 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.59 (d, *J* = 1.3 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 165.0, 154.5, 151.5, 139.9, 133.8, 130.2, 129.3, 128.6, 127.6, 121.8, 117.4, 59.9, 18.0, 14.4 ppm. FT-IR: ν (cm^{-1}) = 717, 1164, 1211, 1252, 1703, 1726, 2903, 2961, 2989, 3073. ESI-MS: m/z (%) = 328.0 (100) $[M+NH_4]^+$, 356.1 (40), 369.1 (33) $[M+NH_4+MeCN]^+$, 638.2 (70) $[2M+NH_4]^+$. HR-MS: calcd. for $C_{19}H_{18}O_4$ $[M+H]^+$ 311.1278; found 311.1280.



*4-(4-Ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate (**9c**)*

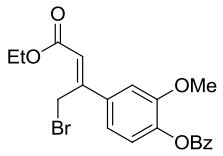
4-(4-Ethoxy-2-hydroxy-4-oxobutan-2-yl)-2-methoxyphenyl benzoate **8c** (34.8 g, 97.2 mmol), toluene (200 mL) and p-toluenesulfonic acid (0.95 g, 5.0 mmol) were placed in a Dean-Stark apparatus and heated to reflux for 4 hours. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (PE/EtOAc 4:1, R_f 0.3). 4-(4-Ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate **9c** was obtained as pale white solid in 78 % yield (26.4 g, 77.6 mmol). Mp 88 – 91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 – 8.15 (m, 2H), 7.71 – 7.60 (m, 1H), 7.57 – 7.45 (m, 2H), 7.19 – 7.07 (m, 3H), 6.14 (q, *J* = 1.2 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 2.59 (d, *J* = 1.3 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 164.7, 154.9, 151.2, 141.3, 140.6, 133.6, 130.4, 129.2, 128.6, 122.9, 119.0, 117.4, 110.6, 60.0, 56.0, 18.2, 14.4 ppm. FT-IR: ν (cm^{-1}) = 707, 1155, 1235, 1262, 1709, 1741, 2980, 3061. EI-MS: m/z (%) = 77.1 (26) $[C_6H_5]^{+\bullet}$, 84.0 (35), 105.1 (100) $[PhCO]^+$, 340.3 (9) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{20}H_{20}O_5$ $[M]^{+\bullet}$ 340.1311; found 340.1312.



*4-(1-Bromo-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate (**5a**)*

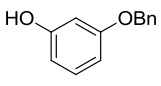
The reaction was performed under inert nitrogen atmosphere using standard Schlenk techniques. Dibenzoyl peroxide was dried on vacuum for 2 hours prior to use. 4-(4-Ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate **9a** (3.81 g, 12.3 mmol) was dissolved in dry tetrachloromethane (40 mL). This solution was degassed using the freeze-pump-thaw technique before NBS (2.58 g, 14.5 mmol) was added. The reaction mixture was then heated to reflux and when refluxing started the radical starter dibenzoyl peroxide (0.13 g, 0.53 mmol) was added. Heating was continued for 24 hours. After the reaction mixture has cooled down to room temperature, the succinimide was filtered off. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (PE/EtOAc 4:1, R_f 0.34). 4-(1-Bromo-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate **5a** was obtained as white solid in 80 % yield (3.81 g, 9.82 mmol). Mp 90 – 95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 – 8.16 (m, 2H), 7.70 – 7.59 (m, 3H), 7.58 – 7.48 (m, 2H), 7.33 – 7.23 (m, 2H), 6.23 (s, 1H), 4.98 (s, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 164.9, 152.3, 152.1, 136.1, 133.8, 130.3,

129.2, 128.7, 127.9, 122.2, 120.0, 60.6, 26.4, 14.2 ppm. FT-IR: ν (cm^{-1}) = 540, 709, 1166, 1269, 1715, 2902, 2939, 2978, 3072. EI-MS: m/z (%) = 77.1 (22) $[C_6H_5]^{+\bullet}$, 84.0 (35), 105.1 (100) $[PhCO]^+$, 388.1 (2) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{19}H_{17}BrO_4$ $[M]^{+\bullet}$ 388.0310; found 388.0315.



*4-(1-Bromo-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate (**5c**)*

The reaction was performed under inert nitrogen atmosphere using standard Schlenk techniques. Dibenzoyl peroxide was dried on vacuum for 2 hours prior to use. 4-(4-Ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate **9c** (24.0 g, 70.5 mmol) was dissolved in dry tetrachloromethane (250 mL). This solution was degassed using the freeze-pump-thaw technique before NBS (13.9 g, 78.3 mmol) was added. The reaction mixture was then heated to reflux and when refluxing started the radical starter dibenzoyl peroxide (0.59 g, 2.5 mmol) was added. Heating was continued for 48 hours. After the reaction mixture has cooled down to room temperature, the succinimide was filtered off. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (PE/EtOAc 4:1, R_f 0.32). 4-(1-Bromo-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate **5c** was obtained as pale white solid in 82 % yield (24.2g, 61.5 mmol). Mp 84 – 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 – 8.15 (m, 2H), 7.70 – 7.59 (m, 1H), 7.57 – 7.45 (m,2H), 7.19 (s, 3H), 6.21 (s, 1H), 4.96 (s, 2H), 4.28 (q, 7.1 Hz, 2H), 3.86 (s, 3H), 1.35 (t, 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 164.6, 152.7, 151.5, 141.2, 137.6, 133.7, 130.4, 129.1, 128.6, 123.2, 120.1, 119.3, 110.9, 60.7, 56.1, 26.7, 14.3 ppm. FT-IR: ν (cm^{-1}) = 669, 708, 1162, 1247, 1710, 1742, 2981, 3074. EI-MS: m/z (%) = 77.1 (13) $[C_6H_5]^{+\bullet}$, 105.1 (100) $[PhCO]^+$, 418.2 (4) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{20}H_{19}BrO_5$ $[M]^{+\bullet}$ 418.0416; found 418.0418.

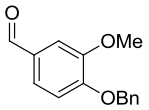


*3-(Benzyloxy)phenol (**4a**)*

Benzylbromide (120 mmol, 14.2 mL) was added over 15 minutes to a slurry of resorcinol (10.0 mmol, 1.10 g) and K_2CO_3 (20.0 mmol, 2.76 g) in acetone (18 mL). The slurry was heated to 60 °C for 4 hours. After completion of the reaction potassium carbonate was filtered off and washed with EtOAc. The organic layer was washed with HCl (1 N, 2×10 mL) and brine (10 mL). Afterward the organic layer was dried with

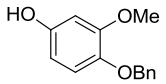
anhydrous $MgSO_4$ before the solvent was removed under reduced pressure with a rotary evaporator. The crude product was purified by flash chromatography (PE/EtOAc 4:1, R_f = 0.26). 3-(Benzyloxy)phenol **4a** was isolated as pale white solid in 32 % yield (7.68 g, 38.4 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.29 (m, 5H), 7.14 (t, *J* = 8.2 Hz, 1H), 6.57 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.49 (t, *J* = 2.3 Hz, 1H), 6.44 (dd, *J* = 7.9, 2.1 Hz, 1H), 5.04 (s, 2H) ppm. ESI-MS: m/z (%) = 91.1 (100), 200.1 (27.4) [$M^{+\cdot}$]. (Ref. [49])

*4-(Benzyloxy)-3-methoxybenzaldehyde (**14**)*



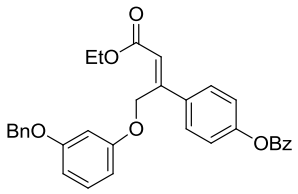
Vanillin **13** (3.8 g, 25 mmol) was dissolved in acetone (45 mL) and potassium carbonate (6.9 g, 50 mmol) and benzyl bromide (4.45 mL, 37.5 mmol) were added. This slurry was heated to 60 °C for 2 hours. Potassium carbonate was filtered off and washed with EtOAc (100 mL). The organic phase was washed with 1 N HCl (50 mL), brine (40 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure. 4-(Benzyloxy)-3-methoxybenzaldehyde **14** was obtained in 92 % yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.84 (s, 1H), 7.51 – 7.28 (m, 9H), 6.99 (d, *J* = 8.2 Hz, 1H), 5.25 (s, 2H), 4.50 (s, 1H), 3.95 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.0, 153.6, 150.1, 136.0, 128.8, 128.2, 127.2, 126.6, 112.4, 109.3, 70.9, 56.1, 33.6 ppm. ESI-MS: m/z (%) = 91.0 (100), 242.1 (38) $[M]^{+\bullet}$. (Ref. [50])

*4-(Benzyloxy)-3-methoxyphenol (**4b**)*



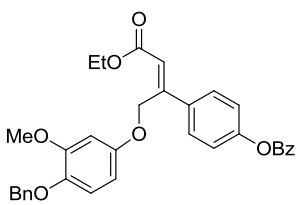
A solution of 4-(benzyloxy)-3-methoxybenzaldehyde **14** in THF (20 mL) was added to the slurry of boric acid (7.02 g, 114 mmol), 30 % aqueous H_2O_2 (7.5 mL,), H_2SO_4 (3.2 mL) and THF (65 mL). This slurry was stirred for 5 hours at room temperature. The mixture was neutralized with sat. $NaHCO_3$ solution (150 mL) and extracted with EtOAc (3×80 mL). The combined organic phases were dried with $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (PE/EtOAc 3:1). 4-(Benzyloxy)-3-methoxyphenol **4b** was obtained as brownish solid in 59 % yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 – 7.28 (m, 6H), 6.73 (d, *J* = 8.6 Hz, 1H), 6.47 (d, *J* = 2.8 Hz, 1H), 6.26 (dd, *J* = 8.6, 2.8 Hz, 1H), 5.06 (s, 2H), 4.67 (d, *J* = 1.6 Hz, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.7, 142.2, 137.5, 128.5, 127.8,

127.5, 127.0, 116.2, 105.9, 100.8, 72.3, 55.9 ppm. ESI-MS: m/z (%) = 91.1 (100), 139.1 (91), 230.1 (46) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{14}H_{14}O_3$ $[M]^+$ 230.0943; found 230.0945. (Ref. [50])



*4-(1-(3-(Benzyloxy)phenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate (**3a**)*

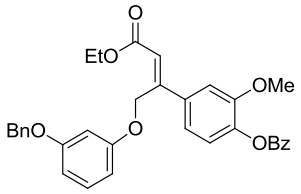
3-(Benzyloxy)phenol **4a** (4.0 g, 20 mmol) and 4-(1-bromo-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate **5a** (7.8 g, 20 mmol) were dissolved in dry acetone (90 mL) before K_2CO_3 (13.8 g, 100 mmol) and KI (0.16 g, 0.10 mmol) were added. The stirring reaction mixture was heated to 60 °C for 8 hours. Subsequently, H_2O (75 mL) was added and extracted with Et_2O (3×100 mL). The combined organic phases were washed with brine (25 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography on Biotage® Isolera™ flash purification system (PE/EtOAc 4:1, R_f 0.36). 4-(1-(3-(Benzyloxy)phenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate **3a** was obtained as slight yellow viscose oil in 64 % yield (6.52 g, 12.8 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 – 8.16 (m, 2H), 7.70 – 7.61 (m, 1H), 7.60 – 7.49 (m, 4H), 7.47 – 7.31 (m, 5H), 7.26 – 7.21 (m, 2H), 7.20 – 7.12 (m, 1H), 6.62 – 6.53 (m, 3H), 6.27 (s, 1H), 5.57 (d, *J* = 0.4 Hz, 2H), 5.02 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 165.0, 160.0, 159.6, 152.8, 151.7, 137.0, 136.0, 133.8, 130.2, 129.9, 129.3, 128.7, 128.6, 127.9, 127.5, 121.7, 120.5, 107.8, 107.4, 102.1, 70.0, 64.1, 60.6, 14.3 ppm. FT-IR: ν (cm^{-1}) = 695, 1025, 1169, 1266, 1590, 1695, 1726, 2933, 2985, 3036, 3063. ESI-MS: m/z (%) = 282.3 (100), 509.2 (93) $[M+H]^+$, 526.2 (69) $[M+NH_4]^+$, 531.2 (84) $[M+Na]^+$. HR-MS: calcd. for $C_{32}H_{29}O_6$ $[M+H]^+$ 509.1959; found 509.1962.



*4-(1-(4-(Benzyloxy)-3-methoxyphenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate (**3b**)*

4-(Benzyloxy)-3-methoxyphenol **4b** (1.15 g, 5.0 mmol) and 4-(1-bromo-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate **5a** (1.94 g, 5.0 mmol) were dissolved in dry acetone (20

mL) before K_2CO_3 (3.46 g, 25.0 mmol) and KI (0.08 g, 0.5 mmol) were added. The stirring reaction mixture was heated to 60 °C for 5 hours. Subsequently, H_2O (15 mL) was added and extracted with EtOAc (3×15 mL). The combined organic phases were washed with brine (10 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (PE/EtOAc 4:1, R_f 0.2). 4-(1-(4-(Benzyloxy)-3-methoxyphenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate **3b** was obtained as gum-like oil in 52 % yield (1.73 g, 2.60 mmol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.21 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.67 – 7.63 (m, 1H), 7.58 – 7.55 (m, 2H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.25 – 7.22 (m, 2H), 6.77 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.49 (d, *J* = 2.8 Hz, 1H), 6.40 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.26 (s, 1H), 5.53 (s, 2H), 5.07 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 165.8, 164.9, 153.5, 152.9, 151.7, 150.7, 142.7, 137.5, 136.0, 133.7, 130.2, 129.3, 128.6, 128.5, 128.4, 127.7, 127.4, 121.7, 120.4, 115.5, 104.7, 101.4, 72.0, 64.4, 60.5, 55.9, 14.2 ppm. FT-IR: ν (cm^{-1}) = 794, 1023, 1157, 1506, 1708, 1735, 2937, 2979, 3066. ESI-MS: m/z (%) = 539.1 (100) $[M+H]^+$, 556.1 (74) $[M+NH_4]^+$. HR-MS: calcd. for $C_{33}H_{31}O_7$ $[M+H]^+$ 539.2064; found 539.2063.

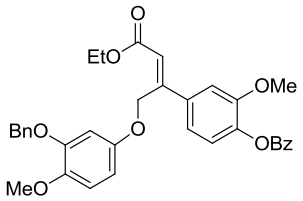


*4-(1-(3-(Benzyloxy)phenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate (**3c**)*

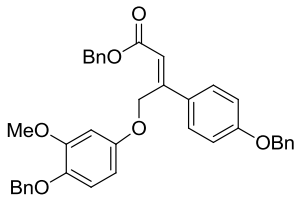
3-(Benzyloxy)phenol **4a** (1.53 g, 7.65 mmol) and 4-(1-bromo-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate **5c** (3.2 g, 7.7 mmol) were dissolved in dry acetone (50 mL) before K_2CO_3 (5.3 g, 39 mmol) and KI (0.12 g, 0.77 mmol) were added. The stirring reaction mixture was heated to 60 °C for 8 hours. Subsequently, H_2O (50 mL) was added and extracted with Et_2O (3×100 mL). The combined organic phases were washed with brine (25 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography on Biotage® Isolera™ flash purification system (PE/EtOAc 4:1, R_f 0.3). 4-(1-(3-(Benzyloxy)phenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate **3c** was obtained in 58 % yield (2.40 g, 4.46 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 – 8.18 (m, 2H), 7.68 – 7.60 (m, 1H), 7.56 – 7.48 (m, 2H), 7.46 – 7.31 (m, 5H), 7.18 – 7.09 (m, 4H), 6.62 – 6.54 (m, 3H), 6.27 (s, 1H),

5.55 (s, 2H), 5.02 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.79 (s, J = 8.2 Hz, 3H), 1.32 (dd, J = 9.2, 5.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 164.6, 160.0, 159.6, 153.0, 151.1, 140.8, 137.4, 137.0, 133.6, 130.4, 129.9, 129.2, 128.6, 128.0, 127.6, 122.9, 120.7, 120.0, 111.5, 107.8, 107.3, 102.1, 70.0, 64.3, 60.7, 56.0, 14.3 ppm. FT-IR: ν (cm^{-1}) = 706, 1022, 1146, 1251, 1590, 1708, 1741, 2873, 2937, 2980, 3031, 3062. ESI-MS: m/z (%) = 282.3 (50), 539.2 (100) $[M+H]^+$, 556.2 (90) $[M+NH_4]^+$, 561.2 (100) $[M+Na]^+$. HR-MS: calcd. for $C_{33}H_{31}O_7$ $[M+H]^+$ 539.2064; found 539.2068.

*4-(1-(3-(Benzyloxy)-4-methoxyphenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate (**3d**)*



4-(Benzyloxy)-3-methoxyphenol **4b** (4.60 g, 20.0 mmol) and 4-(1-bromo-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate **5c** (8.36 g, 20.0 mmol) were dissolved in dry acetone (100 mL) before K_2CO_3 (13.1 g, 100 mmol) and KI (0.32 g, 2.0 mmol) were added. The stirring reaction mixture was heated to 60 °C for 18 hours. Subsequently, H_2O (50 mL) was added and extracted with EtOAc (3×100 mL). The combined organic phases were washed with brine (50 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 4:1, R_f 0.22). 4-(1-(3-(Benzyloxy)-4-methoxyphenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate **3d** was obtained as yellow oil in 42 % yield (4.69 g, 8.46 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 – 8.18 (m, 2H), 7.69 – 7.60 (m, 1H), 7.56 – 7.47 (m, 2H), 7.46 – 7.40 (m, 2H), 7.39 – 7.32 (m, 2H), 7.32 – 7.28 (m, 1H), 7.16 – 7.10 (m, 3H), 6.78 (d, *J* = 8.7 Hz, 1H), 6.51 (d, *J* = 2.8 Hz, 1H), 6.41 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.26 (s, 1H), 5.51 (s, 2H), 5.07 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 164.6, 153.5, 153.2, 151.2, 150.7, 142.7, 140.9, 137.5, 137.5, 133.7, 130.4, 129.2, 128.6, 128.5, 127.8, 127.4, 122.9, 120.6, 120.0, 115.4, 111.5, 104.7, 101.4, 72.0, 64.7, 60.6, 56.0, 55.9, 14.3 ppm. FT-IR: ν (cm^{-1}) = 706, 1025, 1161, 1452, 1510, 1600, 1625, 1704, 1728, 2904, 2939, 2985, 3085. ESI-MS: m/z (%) = 568.2 (6) $[M]^{+\bullet}$, 569.2 (99) $[M+H]^+$, 586.2 (39) $[M+NH_4]^+$, 591.2 (100) $[M+Na]^+$. HR-MS: calcd. for $C_{34}H_{32}O_8$ $[M]^{+\bullet}$ 568.2097; found 568.2090.

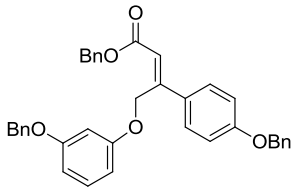


Benzyl 4-(4-(benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoate

4-(1-(4-(Benzyloxy)-3-methoxyphenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate (4.4 g, 8.1 mmol) was dissolved in THF/H_2O (3:1, 80 mL) and cooled with an ice-water-bath before LiOH (2.0 g, 82 mmol) was added. This slurry was stirred at 0 °C for 1 hour and heated to 50 °C for 24 hours. Afterwards the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (3 × 100 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was used without further purification in the subsequent reaction. 4-(4-(Benzyloxy)-3-methoxyphenoxy)-3-(4-hydroxyphenyl)but-2-enoic acid was recrystallized from PE/EtOAc (1:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.49 – 7.27 (m, 7H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 2.7 Hz, 1H), 6.41 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.18 (s, 1H), 5.48 (s, 2H), 4.97 (s, 2H), 3.71 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 167.1, 158.7, 153.1, 151.6, 150.0, 141.9, 137.4, 128.5, 128.2, 127.6, 118.0, 115.2, 114.9, 104.4, 100.9, 70.7, 63.1, 55.4 ppm.

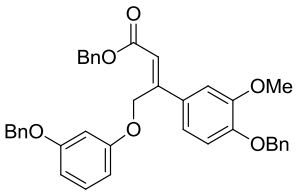
4-(4-(Benzyloxy)-3-methoxyphenoxy)-3-(4-hydroxyphenyl)but-2-enoic acid (4.05 g, 8.10 mmol) was dissolved in acetone (40 mL). Benzyl bromide (2.3 mL, 19.4 mmol), K_2CO_3 (2.24 g, 16.2 mmol) and KI (0.13 g, 0.8 mmol) were added to the stirring solution before heating was initiated. The reaction mixture was heated to 60 °C for 24 h. After K_2CO_3 was filtered off, H_2O (20 mL) was added. The mixture was extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine (20 mL) and dried with $MgSO_4$. The crude product was purified by flash chromatography (PE/EtOAc 5:1). Benzyl 4-(4-(benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoate was obtained as colorless oil in 79 % yield (3.78 g, 6.45 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 – 7.27 (m, 17H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.49 (d, *J* = 2.8 Hz, 1H), 6.37 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.28 (s, 1H), 5.51 (s, 2H), 5.20 (s, 2H), 5.08 (s, 2H), 5.07 (s, 2H), 3.78 (s, *J* = 3.5 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 160.0, 153.8, 153.7, 150.8, 142.8, 137.7, 136.7, 136.0, 130.8, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 127.6, 127.5, 118.1, 115.6, 114.9, 104.9, 101.5, 72.1, 70.2, 66.4, 64.4, 56.0 ppm. FT-IR: ν (cm^{-1}) = 695, 734, 794, 829, 1015, 1149, 1508, 1600, 1707, 2875, 2936, 3033,

3062. ESI-MS: m/z (%) = 586.2 (15) $[M]^{+\bullet}$, 587.2 (100) $[M+H]^+$, 1195.5 (74) $[2M+Na]^+$. HR-MS: calcd. for $C_{38}H_{35}O_6$ $[M+H]^+$ 587.2428; found 587.2429.



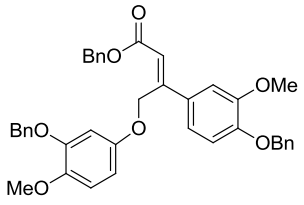
Benzyl 4-(3-(benzyloxy)phenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoate

4-(1-(3-(Benzyloxy)phenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate (1.2 g, 2.5 mmol) was dissolved in THF/H_2O (3:1, 30 mL) and cooled with an ice-water-bath before LiOH (0.60 g, 25 mmol) was added. This slurry was stirred at 0 °C for 1 hour and heated to 50 °C for 18 hours. The completion of the reaction was monitored by TLC. Afterwards the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (3×50 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was used without further purification in the subsequent reaction and dissolved in acetone (15 mL). Benzyl bromide (0.57 mL, 4.8 mmol), K_2CO_3 (0.55 g, 4.0 mmol) and KI (0.03 g, 0.2 mmol) were added to the stirring solution before heating was initiated. The reaction mixture was heated to 60 °C for 20 h. After K_2CO_3 was filtered off, H_2O (10 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (10 mL) and dried with $MgSO_4$. The crude product was purified by flash chromatography (PE/EtOAc 4:1, R_f 0.34). Benzyl 4-(3-(benzyloxy)phenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoate was obtained as colorless oil in 73 % yield (1.02 g, 1.83 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 – 7.28 (m, 17H), 7.20 – 7.11 (m, 1H), 7.00 – 6.91 (m, 2H), 6.62 – 6.52 (m, 2H), 6.29 (s, 1H), 5.55 (s, 2H), 5.21 (s, *J* = 5.5 Hz, 2H), 5.08 (s, 2H), 5.00 (s, 2H) ppm. FT-IR: ν (cm^{-1}) = 694, 733, 829, 1015, 1144, 1248, 1599, 1707, 2872, 2934, 3032, 3061. ESI-MS: m/z (%) = 557.2 (98) $[M+H]^+$, 1135.4 (74) $[2M+Na]^+$. HR-MS: calcd. for $C_{37}H_{33}O_5$ $[M+H]^+$ 557.2323; found 557.2327.



Benzyl 3-(4-(benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)phenoxy)but-2-enoate

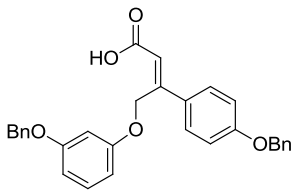
4-(1-(3-(Benzyloxy)phenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate (2.40 g, 4.46 mmol) was dissolved in THF/H_2O (3:1, 50 mL) and cooled with an ice-water-bath before LiOH (1.07 g, 44.6 mmol) was added. This slurry was stirred at 0 °C for 1 hour and heated to 50 °C for 20 hours. The completion of the reaction was monitored by TLC. Afterwards the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (3 × 75 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was used without further purification in the subsequent reaction and dissolved in acetone (50 mL). Benzyl bromide (1.85 mL, 15.6 mmol), K_2CO_3 (1.2 g, 9.0 mmol) and KI (0.07 g, 0.44 mmol) were added to the stirring solution before heating was initiated. The reaction mixture was heated to 60 °C for 24 h. After K_2CO_3 was filtered off, H_2O (20 mL) was added. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (20 mL) and dried with $MgSO_4$. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 4:1, R_f 0.23). Benzyl 3-(4-(benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)phenoxy)but-2-enoate was obtained as yellow oil in 84 % yield (2.20 g, 3.75 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 – 7.28 (m, 15H), 7.18 – 7.11 (m, 1H), 7.04 (td, *J* = 4.5, 2.1 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 1H), 6.61 – 6.50 (m, 3H), 6.28 (s, 1H), 5.53 (s, 2H), 5.20 (s, 2H), 5.17 (s, 2H), 5.00 (s, 2H), 3.85 (s, 3H) ppm. FT-IR: ν (cm^{-1}) = 695, 734, 1023, 1140, 1254, 1453, 1513, 1593, 1708, 2870, 2933, 3032, 3065. ESI-MS: m/z (%) = 587.2 (100) $[M+H]^+$, 604.3 (14) $[M+NH_4]^+$, 1195.5 (52) $[2M+Na]^+$. HR-MS: calcd. for $C_{38}H_{35}O_6$ $[M+H]^+$ 587.2428; found 587.2430.



Benzyl 3-(4-(benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)-4-methoxyphenoxy)but-2-enoate

4-(1-(3-(Benzyloxy)-4-methoxyphenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)-2-methoxyphenyl benzoate (2.75 g, 5.00 mmol) was dissolved in THF/H_2O (3:1, 50 mL) and cooled with an ice-water-bath before LiOH (1.20 g, 50.0 mmol) was added. This slurry was stirred

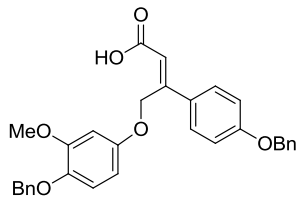
at 0 °C for 1 hour and heated to 45 °C for 48 hours. The completion of the reaction was monitored by TLC. Afterwards, the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was used without further purification in the subsequent reaction and dissolved in acetone (50 mL). Benzyl bromide (1.90 mL, 15.6 mmol), K_2CO_3 (1.38 g, 10.0 mmol) and KI (0.08 g, 0.50 mmol) were added to the stirring solution before heating was initiated. The reaction mixture was heated to 60 °C for 20 h. After K_2CO_3 was filtered off, 1 N HCl (50 mL) was added. The mixture was extracted with EtOAc (3 × 75 mL). The combined organic phases were washed with H_2O (50 mL) and dried with $MgSO_4$. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 4:1, R_f 0.13). Benzyl 3-(4-(benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)-4-methoxy-phenoxy)but-2-enoate was obtained as yellow oil in 78 % yield (2.39 g, 3.87 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 – 7.28 (m, 15H), 7.08 – 7.02 (m, 2H), 6.85 (d, *J* = 9.0 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 6.48 (d, *J* = 2.8 Hz, 1H), 6.37 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.27 (s, 1H), 5.49 (s, 2H), 5.20 (s, 2H), 5.17 (s, 2H), 5.07 (s, 2H), 3.86 (s, 3H), 3.78 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 153.8, 153.6, 150.6, 149.5, 149.3, 142.7, 137.5, 136.7, 135.8, 131.2, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.8, 127.6, 127.4, 127.3, 120.3, 118.3, 115.4, 113.2, 110.7, 104.7, 101.3, 72.0, 70.8, 66.4, 64.4, 56.1, 55.9 ppm. FT-IR: ν (cm^{-1}) = 695, 734, 1015, 1139, 1452, 1507, 1597, 1708, 2874, 2937, 3032, 3063. ESI-MS: m/z (%) = 282.3 (36), 616.2 (21) $[M]^{+\bullet}$, 617.3 (100) $[M+H]^+$, 634.3 (27) $[M+NH_4]^+$. HR-MS: calcd. for $C_{39}H_{37}O_7$ $[M+H]^+$ 617.2534; found 617.2526.



*4-(3-(Benzyloxy)phenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid (**10a**)*

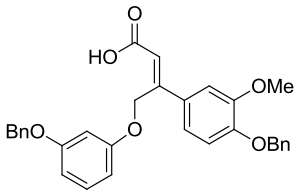
Benzyl 4-(3-(benzyloxy)phenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoate (1.4 g, 2.5 mmol) was dissolved in THF/H_2O (3:1, 30 mL) and cooled with an ice-water-bath before LiOH (1.3 g, 55 mmol) was added. This slurry was stirred at 0 °C for 1 hour and additional 24 hours at 45 °C. Afterwards the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (3×40 mL). The combined organic phases were dried with

$MgSO_4$ and the solvent was removed under reduced pressure. The residue was recrystallized from PE/EtOAc (1:2). 4-(3-(Benzyloxy)phenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid **10a** was obtained as white crystalline solid in 61 % yield (0.71 g, 1.5 mmol). Mp 131 – 133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 – 7.28 (m, 12H), 7.16 (t, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.63 – 6.51 (m, 3H), 6.25 (s, 1H), 5.55 (s, 2H), 5.09 (s, 2H), 5.01 (s, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 160.0, 159.6, 156.0, 136.9, 136.6, 130.4, 129.9, 129.0, 128.7, 128.6, 128.2, 128.0, 127.5, 117.2, 114.8, 107.8, 107.4, 102.1, 70.1, 70.0, 63.9 ppm. FT-IR: ν (cm^{-1}) = 505, 697, 741, 998, 1172, 1593, 1687, 1738, 2873, 3033. ESI-MS: m/z (%) = 449.2 (41), 467.2 (100) $[M+H]^+$. HR-MS: calcd. for $C_{30}H_{27}O_5$ $[M+H]^+$ 467.1853; found 467.1856.



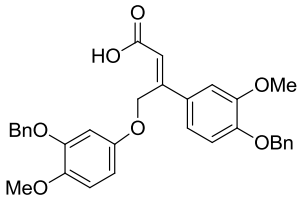
*4-(4-(Benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid (**10b**)*

Benzyl 4-(4-(benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoate (3.2 g, 5.5 mmol) was dissolved in THF/H_2O (3:1, 60 mL) and cooled with an ice-water-bath before LiOH (1.3 g, 55 mmol) was added. This slurry was stirred at 0 °C for 1 hour and additional 15 hours at 50 °C. Afterwards the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (3×75 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was recrystallized from PE/EtOAc (1:1). 4-(4-(Benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid **10b** was obtained as white crystalline solid in 63 % yield (1.77 g, 3.57 mmol). Mp 135 - 138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.8 Hz, 2H), 7.45 – 7.29 (m, 10H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.48 (d, *J* = 2.8 Hz, 1H), 6.39 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.25 (s, 1H), 5.51 (s, 2H), 5.09 (s, 2H), 5.07 (s, 2H), 3.79 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 156.1, 153.4, 150.6, 142.7, 137.5, 136.5, 130.4, 129.0, 128.7, 128.5, 128.2, 127.8, 127.5, 127.4, 117.2, 115.2, 114.8, 104.6, 101.4, 71.9, 70.1, 64.2, 55.9 ppm. FT-IR: ν (cm^{-1}) = 695, 746, 999, 1178, 1510, 1595, 1673, 1738, 2875, 2946, 3032. ESI-MS: m/z (%) = 496.2 (9) $[M]^{+\bullet}$, 497.2 (100) $[M+H]^+$. HR-MS: calcd. for $C_{31}H_{29}O_6$ $[M+H]^+$ 497.1959; found 497.1961.



3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)phenoxy)but-2-enoic acid (10c)

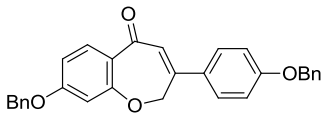
Benzyl 3-(4-(benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)phenoxy)but-2-enoate (2.00 g, 3.41 mmol) was dissolved in THF/H_2O (3:1, 60 mL) and cooled with an ice-water-bath before LiOH (0.41 g, 17 mmol) was added. This slurry was stirred at 0 °C for 1 hour and additional 20 hours at 50 °C. Afterwards the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (3×30 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was recrystallized from EtOAc (15 mL) covered with a layer of hexane. 3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)phenoxy)but-2-enoic acid **10c** was obtained as white crystalline solid in 62 % yield (1.05 g, 2.12 mmol). Mp 118 – 120 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 – 7.30 (m, 10H), 7.15 (t, *J* = 8.2 Hz, 1H), 7.08 – 7.02 (m, 2H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.62 – 6.50 (m, 3H), 6.24 (s, 1H), 5.52 (s, 2H), 5.18 (s, 2H), 5.00 (s, 2H), 3.86 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 160.0, 159.6, 155.9, 149.7, 149.3, 136.9, 136.7, 130.9, 129.9, 128.6, 128.6, 128.0, 128.0, 127.5, 127.3, 120.6, 117.5, 113.2, 110.9, 107.8, 107.4, 102.2, 70.9, 70.0, 64.0, 56.1 ppm. FT-IR: ν (cm^{-1}) = 681, 743, 1020, 1146, 1590, 1686, 1738, 2874, 2941, 3030. ESI-MS: m/z (%) = 496.2 (2) $[M]^{+\bullet}$, 497.2 (100) $[M+H]^+$. HR-MS: calcd. for $C_{31}H_{29}O_6$ $[M+H]^+$ 497.1959; found 497.1963.



*3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)-4-methoxyphenoxy)but-2-enoic acid (**10d**)*

Benzyl 3-(4-(benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)-4-methoxyphenoxy)but-2-enoate (2.35 g, 3.80 mmol) was dissolved in THF/H_2O (3:1, 55 mL) and cooled with an ice-water-bath before LiOH (0.46 g, 20 mmol) was added. This slurry was stirred at 0 °C for 1 hour and additional 20 hours at 40 °C. Afterwards the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (3×50 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The

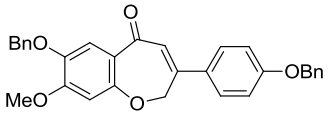
residue was recrystallized from EtOAc covered with a layer of hexane. 3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)-4-methoxyphenoxy)but-2-enoic acid **10d** was obtained as white crystalline solid in 57 % yield (1.14 g, 2.17 mmol). Mp 104 – 106 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 – 7.27 (m, 11H), 7.09 – 7.02 (m, 2H), 6.87 (d, *J* = 8.9 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 1H), 6.48 (d, *J* = 2.8 Hz, 1H), 6.38 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.24 (s, *J* = 7.0 Hz, 1H), 5.48 (s, 2H), 5.19 (s, 2H), 5.07 (s, 2H), 3.87 (s, 3H), 3.79 (s, *J* = 4.8 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 156.0, 153.5, 150.7, 149.7, 149.3, 142.8, 137.5, 136.7, 131.0, 128.7, 128.5, 128.0, 127.8, 127.4, 127.3, 120.6, 117.4, 115.3, 113.2, 110.8, 104.7, 101.4, 72.0, 70.8, 64.4, 56.1, 55.9 ppm. FT-IR: ν (cm^{-1}) = 698, 745, 1001, 1141, 1194, 1510, 1593, 1682, 1738, 2875, 2936, 3031. ESI-MS: m/z (%) = 526.2 (6) $[M]^{+\bullet}$, 527.2 (100) $[M+H]^+$, 544.2 (24) $[M+NH_4]^+$. HR-MS: calcd. for $C_{32}H_{31}O_7$ $[MH]^+$ 527.2064; found 527.2064.



*8-(Benzyloxy)-3-(4-(benzyloxy)phenyl)benzo[b]oxepin-5(2H)-one (**2a**)*

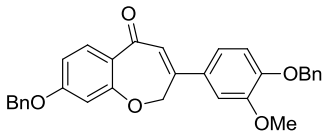
4-(3-(Benzyloxy)phenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid **10a** (0.23 g, 0.50 mmol) was dissolved in dry dichloromethane (10 mL). The solution was cooled with an ice-water-bath before pyridine (40 µL, 0.50 mmol) and cyanuric chloride (0.15 g, 0.80 mmol) were added. The reaction mixture was stirred at 0 °C for 0.5 hours, the cooling bath was then removed and the mixture stirred for additional 3 hours at room temperature. After cooling to -60 °C, $AlCl_3$ (80 mg, 0.60 mmol) was added in three portions. The mixture was allowed to warm slowly up to 0 °C over a period of 4 hours, before the reaction was quenched by adding ice/H_2O (5 mL). Phase separation could be enhanced by the addition of saturated $NaHCO_3$ solution (5 mL). The aqueous phase was exctracted with dichloromethane (3×10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 3:1, R_f 0.28). 8-(Benzyloxy)-3-(4-(benzyloxy)phenyl)benzo[b]oxepin-5(2H)-one **2a** was obtained as slightly yellow solid in 64 % yield (144 mg, 0.32 mmol). Mp 146 – 148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 9.0 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.45 – 7.31 (m, 11H), 7.07 – 6.99 (m, 2H), 6.81 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.66 (s, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 5.12 (s, 4H), 5.08 (s, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.5, 164.0, 162.3,

160.2, 150.0, 136.4, 136.0, 133.5, 130.8, 130.2, 128.7, 128.6, 128.3, 128.2, 127.5, 127.5, 121.5, 115.4, 111.6, 105.0, 71.7, 70.3, 70.1 ppm. FT-IR: ν (cm^{-1}) = 697, 827, 999, 1243, 1599, 1730, 2871, 2917, 2932, 3033, 3063. ESI-MS: m/z (%) = 449.2 (100) $[M+H]^+$, 919.3 (100) $[2M+Na]^+$. HR-MS: calcd. for $C_{30}H_{25}O_4$ $[M+H]^+$ 449.1747; found 449.1746.



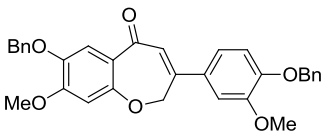
*7-(Benzyloxy)-3-(4-hydroxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one (**2b**)*

4-(4-(Benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid **10b** (0.50 g, 1.0 mmol) was dissolved in dry dichloromethane (20 mL). The solution was cooled with an ice-water-bath before pyridine (80 μL, 1.0 mmol) and cyanuric chloride (0.30 g, 1.6 mmol) were added. The reaction mixture was stirred at 0 °C for 0.5 hours, the cooling bath was then removed and the mixture stirred for additional 2 hours at room temperature. After cooling to -60 °C, $AlCl_3$ (0.16 g, 1.2 mmol) was added in three portions. The mixture was allowed to warm slowly up to -20 °C over a period of 2 hours, before the cooling bath was removed. The reaction mixture was stirred at room temperature for 2 hours and then quenched by adding H_2O (5 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by recrystallization from PE/EtOAc (1:2). 7-(Benzyloxy)-3-(4-hydroxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one **2b** was obtained as slightly yellow crystals in 48 % yield (0.22 g, 0.46 mmol). Mp 137 – 142 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.52 – 7.30 (m, 12H), 7.06 – 6.99 (m, 2H), 6.65 (s, 1H), 6.58 (s, 1H), 5.16 (s, 2H), 5.12 (s, 2H), 5.05 (s, 2H), 3.92 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.2, 160.3, 156.9, 155.4, 150.2, 144.7, 136.8, 136.6, 130.8, 130.4, 128.8, 128.7, 128.5, 128.3, 128.1, 127.8, 127.6, 120.0, 115.4, 113.9, 103.2, 72.0, 71.2, 70.2, 56.4 ppm. FT-IR: ν (cm^{-1}) = 695, 735, 830, 1001, 1220, 1450, 1605, 1691, 2937, 3032, 3061. ESI-MS: m/z (%) = 479.2 (100) $[M+H]^+$. HR-MS: calcd. for $C_{31}H_{27}O_5$ $[M+H]^+$ 479.1853; found 479.1849.



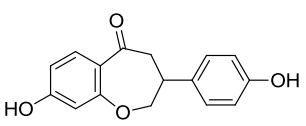
*8-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)benzo[b]oxepin-5(2H)-one (**2c**)*

3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)phenoxy)but-2-enoic acid **10c** (0.25 g, 0.50 mmol) was dissolved in dry dichloromethane (10 mL). The solution was cooled with an ice-water-bath before pyridine (40 µL, 0.50 mmol) and cyanuric chloride (0.15 g, 0.80 mmol) were added. The reaction mixture was stirred at 0 °C for 0.5 hours, the cooling bath was then removed and the mixture stirred for additional 4 hours at room temperature. After cooling to -60 °C, $AlCl_3$ (80 mg, 0.60 mmol) was added in three portions. The mixture was allowed to warm slowly up to -10 °C over a period of 3 hours, before the cooling bath was removed. The reaction mixture was stirred at room temperature for 2 hours and then quenched by adding H_2O (5 mL). Phase separation could be enhanced by the addition of saturated $NaHCO_3$ solution (5 mL). The aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 3:1, R_f 0.28). 8-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)-benzo[b]oxepin-5(2H)-one **2c** was obtained as pale white solid in 67 % yield (161 mg, 0.34 mmol). Mp 142 – 146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 9.0 Hz, 1H), 7.48 – 7.31 (m, 10H), 7.06 (dd, *J* = 7.2, 1.9 Hz, 2H), 6.95 – 6.89 (m, 1H), 6.81 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.67 (s, 1H), 6.63 (d, *J* = 2.5 Hz, 1H), 5.21 (s, 2H), 5.12 (s, 2H), 5.06 (s, 2H), 3.94 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.6, 164.2, 162.5, 150.4, 150.0, 149.9, 136.7, 136.1, 133.6, 131.0, 130.8, 128.9, 128.8, 128.5, 128.2, 127.7, 127.3, 121.5, 120.0, 113.6, 111.8, 110.3, 105.1, 71.8, 71.0, 70.5, 56.3 ppm. FT-IR: ν (cm^{-1}) = 697, 735, 1023, 1145, 1248, 1514, 1593, 1738, 2875, 2935, 3031, 3063. ESI-MS: m/z (%) = 280.3 (10), 479.2 (100) $[M+H]^+$. HR-MS: calcd. for $C_{31}H_{27}O_5$ $[M+H]^+$ 479.1853; found 479.1849.



*7-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one (**2d**)*

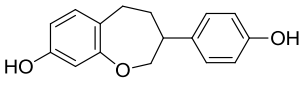
3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)-4-methoxyphenoxy)but-2-enoic acid **10d** (0.26 g, 0.50 mmol) was dissolved in dry dichloromethane (10 mL). The solution was cooled with an ice-water-bath before pyridine (40 μL, 0.50 mmol) and cyanuric chloride (0.15 g, 0.80 mmol) were added. The reaction mixture was stirred at 0 °C for 0.5 hours, the cooling bath was then removed and the mixture stirred for additional 4 hours at room temperature. After cooling to -60 °C, $AlCl_3$ (80 mg, 0.60 mmol) was added in three portions. The mixture was allowed to warm slowly up to -10 °C over a period of 3 hours, before the cooling bath was removed. The reaction mixture was stirred at room temperature for 1 hour and then quenched by adding H_2O (5 mL). The aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.32). 7-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one **2d** was obtained as pale white solid in 53 % yield (135 mg, 0.27 mmol). Mp 82 – 85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (s, 1H), 7.52 – 7.28 (m, 10H), 7.10 – 7.03 (m, 2H), 6.92 (d, *J* = 8.9 Hz, 1H), 6.66 (s, 1H), 6.57 (s, 1H), 5.21 (s, 2H), 5.16 (s, 2H), 5.05 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.1, 156.8, 155.4, 150.2, 149.8, 149.7, 144.6, 136.7, 136.6, 130.8, 130.7, 128.7, 128.6, 128.0, 127.7, 127.2, 119.9, 119.8, 113.7, 113.5, 110.2, 103.0, 71.9, 71.1, 70.9, 56.3, 56.2 ppm. FT-IR: ν (cm^{-1}) = 695, 736, 1006, 1140, 1206, 1505, 1596, 1738, 2341, 2359, 2871, 2939, 3033, 3063. ESI-MS: m/z (%) = 509.2 (100) $[M+H]^+$, 567.2 (5) $[M+NH_4+MeCN]^+$, 1039.4 (9) $[2M+Na]^+$. HR-MS: calcd. for $C_{32}H_{29}O_6$ $[M+H]^+$ 509.1959; found 509.1957.



*8-Hydroxy-3-(4-hydroxyphenyl)-3,4-dihydrobenzo[b]oxepin-5(2H)-one (**11a**)*

8-(Benzyloxy)-3-(4-(benzyloxy)phenyl)benzo[b]oxepin-5(2H)-one **2a** (0.14 g, 0.32 mmol) was dissolved in EtOAc/MeOH (2:1, 35 mL) and Pd/C (35 mg) was added. The reaction mixture was placed in flask equipped with a hydrogen filled balloon and stirred for 6 hours under a H_2 atmosphere. The mixture was filtered through celite and the solvent

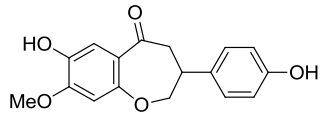
removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.14). 8-Hydroxy-3-(4-hydroxyphenyl)-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11a** was isolated in 58 % yield (50 mg, 0.11 mmol). ^{1}H NMR (300 MHz, MeOD): δ = 7.67 (d, *J* = 8.7 Hz, 1H), 7.22 – 7.13 (m, 2H), 6.77 – 6.69 (m, 2H), 6.56 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 4.35 (dd, *J* = 12.2, 6.3 Hz, 1H), 4.19 (dd, *J* = 12.2, 6.9 Hz, 1H), 3.56 – 3.43 (m, 1H), 3.08 (dd, *J* = 12.6, 7.7 Hz, 1H), 3.00 (dd, *J* = 12.6, 6.9 Hz, 1H) ppm. ^{13}C NMR (75 MHz, MeOD): δ = 200.2, 167.2, 164.8, 157.6, 134.5, 132.3, 129.5, 122.0, 116.5, 112.1, 107.5, 80.6, 45.1 ppm. FT-IR: ν (cm^{-1}) = 532, 737, 830, 1020, 1111, 1160, 1244, 1448, 1515, 1596, 1648, 2853, 2924, 3026, 3293. APCI-MS: m/z (%) = 271.1 (100) $[M+H]^+$. HR-MS: calcd. for $C_{16}H_{15}O_4$ $[M+H]^+$ 271.0965; found 271.0969.



*3-(4-Hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-8-ol (**16a**)*

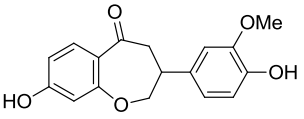
8-(Benzyloxy)-3-(4-(benzyloxy)phenyl)benzo[b]oxepin-5(2H)-one **2a** (54 mg, 0.12 mmol) was dissolved in EtOAc/MeOH (2:1, 35 mL) and Pd/C (14 mg) was added. The reaction mixture was placed in an autoclave under 5 bar H_2 pressure and stirred for 6 hours. The mixture was filtered through celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.32). 3-(4-Hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-8-ol **16a** was isolated in 50 % yield (18 mg, 0.07 mmol) (in addition 8-hydroxy-3-(4-hydroxyphenyl)-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11a** was isolated in 28 % yield (9 mg, 0.03 mmol)). ^{1}H NMR (600 MHz, MeOD): δ = 7.01 – 6.98 (m, 2H, H-2´/6´), 6.94 (d, *J* = 8.0 Hz, 1H, H-6), 6.72 – 6.67 (m, 2H, H-3´/5´), 6.43 (dd, *J* = 8.0, 2.5 Hz, 1H, H-7), 6.42 (d, *J* = 2.4 Hz, 1H, H-9), 4.21 (ddd, *J* = 12.0, 3.6, 1.7 Hz, 1H, H-2A), 3.55 (dd, *J* = 11.9, 10.5 Hz, 1H, H-2B), 3.03 (tt, *J* = 11.0, 3.5 Hz, 1H, H-3), 2.83 (t, *J* = 12.7 Hz, 1H, H-5B), 2.69 (ddd, *J* = 14.4, 6.3, 1.6 Hz, 1H, H-5A), 2.08 – 1.98 (m, 1H, H-4A), 1.65 (td, *J* = 13.5, 1.8 Hz, 1H, H-4B) ppm. ^{13}C NMR (151 MHz, MeOD): δ = 162.1 (C-10), 157.8 (C-8), 157.1 (C-4´), 135.1 (C-1´), 131.7 (C-6), 129.4 (C-2´/6´), 127.7 (C-11), 116.3 (C-3´/5´), 111.5 (C-7), 109.0 (C-9), 79.2 (C-2), 49.9 (C-3), 35.5 (C-4), 33.2 (C-5) ppm. FT-IR: ν (cm^{-1}) = 830, 1006, 1114, 1153, 1234, 1361, 1448, 1514, 1615, 2927,

3375. EI-MS: m/z (%) = 107.1 (19), 123.1 (21), 149.1 (100), 256.1 (24) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{16}H_{16}O_3$ $[M]^{+\bullet}$ 256.1099; found 256.1097.



*7-Hydroxy-3-(4-hydroxyphenyl)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one (**11b**)*

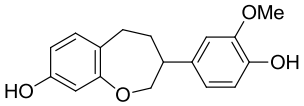
7-(Benzyloxy)-3-(4-hydroxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one **2b** (0.20 g, 0.42 mmol) was dissolved in MeOH/EtOAc (1:1, 20 mL) and Pd/C (0.05 g) was added. The reaction mixture was placed in an autoclave under 20 bar H_2 pressure and stirred for 10 hours. The mixture was filtered through celite and the solvent removed under reduced pressure. 7-Hydroxy-3-(4-hydroxyphenyl)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11b** was obtained as colorless oil in 85 % yield (0.11 g, 0.37 mmol). ^{1}H NMR (600 MHz, MeOD): δ = 7.20 (s, *J* = 4.6 Hz, 1H), 7.18 – 7.13 (m, 2H), 6.76 – 6.72 (m, 2H), 6.71 (s, 1H), 4.33 (dd, *J* = 12.1, 6.6 Hz, 1H), 4.17 (dd, *J* = 12.1, 7.2 Hz, 1H), 3.90 (s, *J* = 5.2 Hz, 3H), 3.50 – 3.44 (m, 1H), 3.12 (dd, *J* = 12.9, 8.2 Hz, 1H), 3.00 (dd, *J* = 12.9, 6.0 Hz, 1H) ppm. ^{13}C NMR (151 MHz, MeOD): δ = 200.4, 159.8, 157.6, 154.6, 143.6, 134.4, 129.4, 122.2, 116.5, 114.5, 104.8, 80.8, 56.6, 49.7, 44.9 ppm. FT-IR: ν (cm^{-1}) = 532, 834, 1209, 1267, 1445, 1515, 1613, 1699, 2963, 3087, 3216. ESI-MS: m/z (%) = 272.6 (35), 301.0 (100) $[M+H]^+$, 318.0 (60) $[M+NH_4]^+$, 342.0 (50) $[M+H+MeCN]^+$. HR-MS: calcd. for $C_{17}H_{17}O_5$ $[M+H]^+$ 301.1071; found 301.1070.



*8-Hydroxy-3-(4-hydroxy-3-methoxyphenyl)-3,4-dihydrobenzo[b]oxepin-5(2H)-one (**11c**)*

8-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)benzo[b]oxepin-5(2H)-one **2c** (0.15 g, 0.31 mmol) was dissolved in EtOAc/MeOH (2:1, 30 mL) and Pd/C (38 mg) was added. The reaction mixture was placed in flask equipped with a hydrogen filled balloon and stirred for 5 hours under a H_2 atmosphere. The mixture was filtered through celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/Et_2O 0:1, R_f 0.48). 8-Hydroxy-3-(4-hydroxy-3-methoxyphenyl)-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11c** was isolated in 67 % yield (63 mg, 0.21 mmol). ^{1}H NMR (300 MHz, MeOD): δ = 7.68 (d,

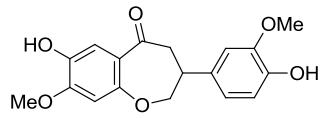
J = 8.7 Hz, 1H), 6.94 (d, *J* = 1.8 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.57 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.49 (d, *J* = 2.3 Hz, 1H), 4.37 (dd, *J* = 12.2, 6.4 Hz, 1H), 4.19 (dd, *J* = 12.2, 7.1 Hz, 1H), 3.84 (s, 3H), 3.58 – 3.43 (m, 1H), 3.15 – 2.99 (m, 2H) ppm. ^{13}C NMR (75 MHz, MeOD): δ = 200.3, 167.2, 164.8, 149.2, 146.7, 135.2, 132.3, 122.0, 120.9, 116.4, 112.2, 112.0, 107.5, 80.6, 56.4, 45.5 ppm. FT-IR: ν (cm^{-1}) = 539, 735, 794, 819, 856, 1024, 1109, 1157, 1212, 1238, 1268, 1449, 1467, 1517, 1576, 1598, 1651, 2844, 2938, 2966, 3062, 3345. ESI-MS: m/z (%) = 301.1 (100) $[M+H]^+$. HR-MS: calcd. for $C_{17}H_{17}O_5$ $[M+H]^+$ 301.1071; found 301.1069.



*3-(4-Hydroxy-3-methoxyphenyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-8-ol (**16c**)*

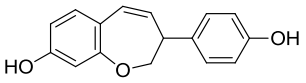
8-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)benzo[b]oxepin-5(2H)-one **2c** (0.16 g, 0.23 mmol) was dissolved in EtOAc/MeOH (2:1, 30 mL) and Pd/C (38 mg) was added. The reaction mixture was placed in an autoclave under 5 bar H_2 pressure and stirred for 6 hours. The mixture was filtered through celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/DCM/ACN 4:1:1, R_f 0.3). 3-(4-Hydroxy-3-methoxyphenyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-8-ol **16c** was isolated in 90 % yield (85 mg, 0.3 mmol). ^{1}H NMR (300 MHz, MeOD): δ = 6.95 (d, *J* = 7.8 Hz, 1H, H-6), 6.76 (d, *J* = 1.2 Hz, 1H, H-2´), 6.71 (d, *J* = 8.1 Hz, 1H, H-5´), 6.62 (d, *J* = 8.1 Hz, 1H, H-6´), 6.47 – 6.39 (m, 2H, overlapping signals H-7 and H-9), 4.24 (dd, *J* = 11.9, 2.2 Hz, 1H, H-2A), 3.80 (s, 3H, OCH_3), 3.59 (dd, *J* = 11.8, 10.6 Hz, 1H, H-2B),3.11 – 2.99 (m, 1H, H-3), 2.85 (t, *J* = 12.8 Hz, 1H, H-5B), 2.70 (dd, *J* = 13.8, 5.6 Hz, 1H, H-5A), 2.12 – 2.01 (m, 2H, H-4A), 1.68 (dd, *J* = 23.9, 11.9 Hz, 1H, H-4B) ppm. ^{13}C NMR (75 MHz, MeOD): δ = 162.2 (C-10), 157.9 (C-8), 149.0 (C-3´), 146.2 (C-4´), 135.9 (C-1´), 131.7 (C-6), 127.7 (C-11), 120.9 (C-6´), 116.3 (C-5´), 112.2 (C-2´), 111.5 (C-7), 109.1 (C-9), 79.3 (C-2), 56.4 (OCH_3), 50.5 (C-3), 35.6 (C-4), 33.3 (C-5) ppm. FT-IR: ν (cm^{-1}) = 734, 1023, 1112, 1150, 1228, 1267, 1515, 1614, 2853, 2927, 3029, 3383. ESI-MS: m/z (%) = 123.1 (15), 137.1 (22), 149.1 (100), 176.0 (26), 286.1 (24) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{17}H_{18}O_4$ $[M]^{+\bullet}$ 286.1205; found 286.1204.

*7-Hydroxy-3-(4-hydroxy-3-methoxyphenyl)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one (**11d**)*



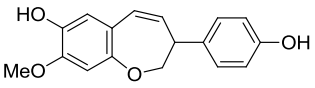
7-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one **2d** (0.10 g, 0.20 mmol) was dissolved in EtOAc/MeOH (2:1, 30 mL) and Pd/C (10 mg) was added. The reaction mixture was placed in an autoclave under 5 bar H_2 pressure and stirred for 10 hours. The mixture was filtered through celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.22). 7-Hydroxy-3-(4-hydroxy-3-methoxyphenyl)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11d** was isolated in 65 % yield (42 mg, 0.13 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (s, 1H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 1.8 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.62 (s, 1H), 5.60 (s, 1H), 5.45 (s, 1H), 4.35 (dd, *J* = 12.1, 6.5 Hz, 1H), 4.26 (dd, *J* = 12.1, 6.5 Hz, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.48 (p, *J* = 6.5 Hz, 1H), 3.19 (dd, *J* = 12.6, 8.2 Hz, 1H), 3.09 (dd, *J* = 12.6, 6.4 Hz, 1H) ppm. ^{13}C NMR (101 MHz, MeOD): δ = 200.4, 159.8, 154.6, 149.2, 146.7, 143.6, 135.1, 122.2, 121.0, 116.4, 114.5, 112.0, 104.8, 80.8, 56.6, 56.4, 45.3 ppm. FT-IR: ν (cm^{-1}) = 827, 1031, 1151, 1208, 1270, 1362, 1443, 1504, 1613, 1656, 2953, 3418. ESI-MS: m/z (%) = 331.1 (100) $[M+H]^+$. HR-MS: calcd. for $C_{18}H_{19}O_6$ $[M+H]^+$ 331.1176; found 331.1178.

*3-(4-Hydroxyphenyl)-2,3-dihydrobenzo[b]oxepin-8-ol (**1a**)*



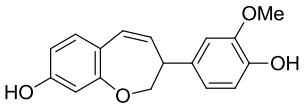
8-Hydroxy-3-(4-hydroxyphenyl)-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11a** (30 mg, 0.21 mmol) was dissolved in EtOH (15 mL). The solution was cooled to 0 °C before $NaBH_4$ (31 mg, 0.55 mmol) was added. The reaction mixture was stirred for 3 hour at 0 °C and additional 20 hours at room temperature. The progress of the reaction was monitored by TLC. After the consumption of the substrate the reaction was quenched by addition of 1 N HCl (2 mL) while cooling with an ice-water bath and stirring over night. EtOH was removed under reduced pressure before the rest of the reaction solution was extracted with Et_2O (4×10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.24). 3-(4-Hydroxyphenyl)-2,3-dihydrobenzo[b]oxepin-8-ol **1a** was obtained as white solid in 46 % yield (13 mg, 0.051 mmol). ^{1}H NMR (600 MHz, MeOD): δ = 7.10 – 7.03 (m,

3H), 6.76 – 6.71 (m, 2H), 6.48 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.41 – 6.34 (m, 2H), 5.78 (dd, *J* = 11.8, 4.1 Hz, 1H), 4.23 (ddd, *J* = 11.7, 3.2, 0.8 Hz, 1H), 4.07 (dd, *J* = 11.6, 6.7 Hz, 1H), 3.88 – 3.82 (m, 1H) ppm. ^{13}C NMR (151 MHz, MeOD): δ = 161.7, 158.8, 157.4, 134.8, 133.5, 131.1, 130.4, 128.9, 120.0, 116.2, 111.0, 107.3, 76.4, 50.7 ppm. FT-IR: ν (cm^{-1}) = 732, 820, 1115, 1161, 1248, 1511, 1611, 2923, 2957, 3066, 3376. ESI-MS: m/z (%) = 107.1 (49), 147.1 (100), 239.1 (24), 254.1 (41) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{16}H_{14}O_3$ $[M]^{+\bullet}$ 254.0943; found 254.0943. (Ref.[2])



*3-(4-Hydroxyphenyl)-8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol (**1b**)*

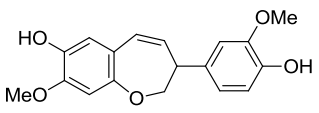
7-Hydroxy-3-(4-hydroxyphenyl)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11b** (0.11 g, 0.36 mmol) was dissolved in EtOH (15 mL) and $NaBH_4$ (0.07 g, 1.8 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature before aqueous NaOH (5 %, 15 mL) was added. Ater stirring for an additional hour, the mixture was extracted with EtOAc (3×20 mL), the combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (DCM/ACN/PE 1:1:1.5, R_f 0.44). 3-(4-Hydroxyphenyl)-8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol **1b** was obtained in 42 % yield (44 mg, 0.15 mmol). ^{1}H NMR (300 MHz, MeOD): δ = 7.07 – 7.01 (m, 2H), 6.74 – 6.69 (m, 2H), 6.66 (s, 1H), 6.52 (s, 1H), 6.28 (dd, *J* = 12.0, 1.9 Hz, 1H), 5.81 (dd, *J* = 11.8, 4.1 Hz, 1H), 4.19 (dd, *J* = 11.5, 3.1 Hz, 1H), 4.03 (dd, *J* = 11.6, 6.6 Hz, 1H), 3.87 – 3.82 (m, 1H), 3.80 (s, 3H) ppm. ^{13}C NMR (75 MHz, MeOD): δ = 157.4, 154.3, 148.7, 142.5, 133.5, 132.6, 130.5, 128.6, 120.3, 119.1, 116.2, 104.7, 76.7, 56.4, 51.0 ppm. APCI-MS: m/z (%) = 191.0 (20), 285.0 (100) $[M+H]^+$. EI-MS: m/z (%) = 177.1 (100), 284.1 (27) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{17}H_{16}O_4$ $[M]^{+\bullet}$ 284.1049; found 284.1048. (Ref.[2])



*3-(4-Hydroxy-3-methoxyphenyl)-2,3-dihydrobenzo[b]oxepin-8-ol (**1c**)*

8-Hydroxy-3-(4-hydroxy-3-methoxyphenyl)-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11c** (63 mg, 0.21 mmol) was dissolved in EtOH (15 mL). The solution was cooled to 0 °C

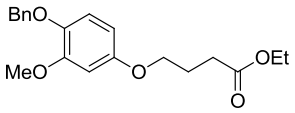
before $NaBH_4$ (40 mg, 1.05 mmol) was added. The reaction mixture was stirred for 2 hour at 0 °C and additional 20 hours at room temperature. The progress of the reaction was monitored by TLC. After the consumption of the substrate, the reaction was quenched by the addition of 1 N HCl (3 mL) while cooling with an ice-water bath. EtOH was removed under reduced pressure before the rest of the reaction solution was extracted with Et_2O (4×10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.2). 3-(4-Hydroxy-3-methoxyphenyl)-8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol **1c** was obtained in 15 % yield (9 mg, 0.014 mmol). The unconverted substrate 8-hydroxy-3-(4-hydroxy-3-methoxyphenyl)-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11c** (25 mg, 0.08 mmol) could be reisolated and reused; the corrected yield of **1c** is 24 %. ^{1}H NMR (600 MHz, MeOD): δ = 7.05 (d, *J* = 8.4 Hz, 1H, H-6), 6.79 (d, *J* = 1.9 Hz, 1H, H-2´), 6.73 (d, *J* = 8.1 Hz, 1H, H-5´), 6.67 (dd, *J* = 8.1, 1.9 Hz, 1H, H-6´), 6.45 (dd, *J* = 8.4, 2.5 Hz, 1H, H-7), 6.36 (dd, *J* = 11.8, 1.9 Hz, 1H, H-5), 6.34 (d, *J* = 2.5 Hz, 1H, H-9), 5.77 (dd, *J* = 11.8, 4.0 Hz, 1H, H-4), 4.22 (ddd, *J* = 11.7, 3.2, 0.6 Hz, 1H, H-2), 4.07 (dd, *J* = 11.6, 6.7 Hz, 1H, H-2), 3.84 (m, 1H, H-3), 3.79 (s, 3H, OCH_3) ppm. ^{13}C NMR (151 MHz, MeOD): δ = 161.7 (C-11), 158.8 (C-8), 148.9 (C-3´), 146.5 (C-4´), 134.9 (C-6), 134.3 (C-1´), 131.0 (C-4), 129.0 (C-5), 121.9 (C-6´), 120.0 (C-10), 116.2 (C-5´), 113.1 (C-2´), 111.1 (C-7), 107.3 (C-9), 76.4 (C-2), 56.3 (C-OMe), 51.1 (C-3) ppm. FT-IR: ν (cm^{-1}) = 540, 736, 819, 854, 1023, 1110, 1158, 1236, 1268, 1517, 1598, 1651, 2841, 2939, 2964, 3065, 3374. ESI-MS: m/z (%) = 161.1 (52), 182.5 (66), 284.1 (17) $[M]^{+\bullet}$, 285.1 (100) $[M+H]^+$. HR-MS: calcd. for $C_{17}H_{17}O_4$ $[M+H]^+$ 285.1121; found 285.1120.



*3-(4-Hydroxy-3-methoxyphenyl)-8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol (**1d**)*

7-Hydroxy-3-(4-hydroxy-3-methoxyphenyl)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one **11d** (56 mg, 0.17 mmol) was dissolved in EtOH (15 mL). The solution was cooled to 0 °C before $NaBH_4$ (32 mg, 0.85 mmol) was added. The reaction mixture was stirred for 1 hour at 0 °C and additional 6 hours at room temperature. The progress of the reaction was monitored by TLC. After the consumption of the substrate the reaction was quenched by the addition of 1 N HCl (3 mL) while cooling with an ice-water bath. EtOH

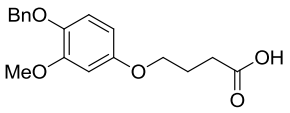
was removed under reduced pressure before the rest of the reaction solution was extracted with Et_2O (4 × 10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.3). 3-(4-Hydroxy-3-methoxyphenyl)-8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol **1d** was obtained in 37 % yield (20 mg, 0.063 mmol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.87 (d, *J* = 8.0 Hz, 1H, H-5´), 6.78 (s, 1H, H-6), 6.75 (dd, *J* = 8.0, 1.9 Hz, 1H, H-6´), 6.73 (d, *J* = 1.9 Hz, 1H, H-2´), 6.54 (s, 1H, H-9), 6.33 (dd, *J* = 11.9, 1.9 Hz, 1H, H-5), 5.89 (dd, *J* = 11.8, 4.1 Hz, 1H, H-4), 5.54 (s, 0.5H, OH), 5.25 (s, 0.5H, OH), 4.26 (dd, *J* = 11.7, 3.3 Hz, 1H, H-2), 4.13 (dd, *J* = 11.7, 6.6 Hz, 1H, H-2), 3.91 – 3.87 (m, 1H, H-3), 3.85 (s, 6H, OCH_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 153.0 (C-11), 146.5 (C-3´), 146.4, 146.0 (C-8), 145.9, 144.6 (C-4´), 144.5, 140.6 (C-7), 140.5, 133.0 (C-1´), 131.4 (C-4), 127.8 (C-5), 121.1 (C-6´), 119.1 (C-10), 117.0 (C-6), 116.9, 114.3 (C-5´), 114.3, 110.8 (C-2´), 103.2 (C-9), 75.5 (C-2), 56.0 (C-OMe), 55.9 (C-OMe), 49.9 (C-3) ppm. FT-IR: ν (cm^{-1}) = 736, 776, 816, 843, 876, 1030, 1123, 1167, 1203, 1260, 1430, 1444, 1507, 1612, 2846, 2938, 2963, 3008, 3425. EI-MS: m/z (%) = 177.1 (100), 314.2 (18) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{16}H_{14}O_3$ $[M]^{+\bullet}$ 314.1154; found 314.1150.



*Ethyl 4-(4-(benzyloxy)-3-methoxyphenoxy)butanoate (**17**)*

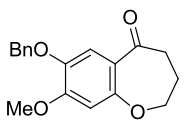
4-(Benzyloxy)-3-methoxyphenol **4b** (4.60 g, 20.0 mmol) and ethyl-4-bromo-butyrate (3.0 mL, 20 mmol) were dissolved in dry acetone (150 mL). Anhydrous K_2CO_3 (8.14 g, 60 mmol) and KI (0.16 g, 1.0 mmol) were added in one portion. This slurry was heated to 60 °C for 24 hours. K_2CO_3 was filtered off and washed with EtOAc (50 mL). The organic phase was washed with 1 N HCl (20 mL) and the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 4:1). Ethyl 4-(4-(benzyloxy)-3-methoxyphenoxy)butanoate **17** was isolated as yellow oil in 65 % yield (4.52 g, 13.1 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 – 7.40 (m, 2H), 7.40 – 7.28 (m, 3H), 6.78 (d, *J* = 8.7 Hz, 1H), 6.52 (t, *J* = 2.3 Hz, 1H), 6.32 (dd, *J* = 8.7, 2.8 Hz, 1H), 5.07 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.94 (t, *J* = 6.1 Hz, 2H), 3.86 (s, 3H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.14 – 2.02 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =

173.3, 154.1, 150.9, 142.5, 137.5, 128.7, 128.5, 128.2, 127.8, 127.6, 127.5, 115.7, 103.9, 101.0, 72.1, 67.1, 60.5, 55.9, 30.8, 24.7, 14.3 ppm. FT-IR: ν (cm^{-1}) = 696, 736, 791, 834, 1025, 1196, 1450, 1508, 1730, 2939, 3029. ESI-MS: m/z (%) = 345.2 (100) $[M+H]^+$, 362.2 (19) $[M+NH_4]^+$, 367.2 (25) $[M+Na]^+$. HR-MS: calcd. for $C_{20}H_{24}O_5$ $[M+H]^+$ 345.1697; found 345.1705.



*4-(4-(Benzyloxy)-3-methoxyphenoxy)butanoic acid (**18**)*

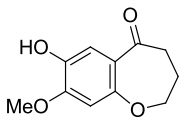
Ethyl 4-(4-(benzyloxy)-3-methoxyphenoxy)butanoate **17** (4.50 g, 13.0 mmol) was dissolved in THF/H_2O (3:1, 130 mL) and cooled with an ice-water-bath before LiOH (3.13 g, 130 mmol) was added. This slurry was stirred at 60 °C for 20 hours. Afterwards the reaction mixture was acidified with 1 N HCl to about pH 2 and extracted with EtOAc (3×100 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. 4-(4-(Benzyloxy)-3-methoxyphenoxy)butanoic acid **18** was obtained as white crystalline solid in 98 % yield (4.03 g, 12.7 mmol). Mp 111 – 113 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 – 7.28 (m, 6H), 6.78 (d, *J* = 8.8 Hz, 1H), 6.52 (d, *J* = 2.8 Hz, 1H), 6.31 (dd, *J* = 8.7, 2.8 Hz, 1H), 5.08 (s, 2H), 3.96 (t, *J* = 6.1 Hz, 2H), 3.86 (s, *J* = 8.3 Hz, 4H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.14 – 2.03 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 154.0, 150.9, 142.5, 137.5, 128.7, 128.5, 128.3, 127.8, 127.7, 127.5, 115.6, 103.9, 101.0, 72.1, 66.9, 55.9, 30.5, 24.4 ppm. FT-IR: ν (cm^{-1}) = 729, 1027, 1207, 1447, 1515, 1695, 1739, 2889, 2948, 2970, 3032. ESI-MS: m/z (%) = 317.1 (100) $[M+H]^+$, 334.2 (11) $[M+NH_4]^+$, 655.3 (12) $[2M+Na]^+$. HR-MS: calcd. for $C_{18}H_{20}O_5$ $[M+H]^+$ 317.1384; found 317.1390.



*7-(Benzyloxy)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one (**19**)*

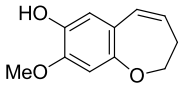
4-(4-(Benzyloxy)-3-methoxyphenoxy)butanoic acid **18** (0.32 g, 1.0 mmol) was dissolved in dry dichloromethane (10 mL). The solution was cooled with an ice-water-bath before pyridine (80 μL, 0.50 mmol) and cyanuric chloride (0.30 g, 1.6 mmol) were added. The reaction mixture was stirred at 0 °C for 0.5 hours, the cooling bath was then removed and the mixture stirred for additional 4 hours at room temperature. After cooling to -60 °C, $AlCl_3$ (0.16 g, 1.2 mmol) was added in three portions. The mixture was allowed to warm

slowly up to 0 °C over a period of 3 hours, before the cooling bath was removed. The reaction mixture was stirred at room temperature for 2 days and then quenched by addition of H_2O (5 mL). The aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.3). 7-(Benzyloxy)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one **19** was obtained as colorless oil in 15 % yield (45 mg, 0.15 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 – 7.29 (m, 6H), 6.59 (s, 1H), 5.12 (s, 2H), 4.21 (t, *J* = 6.8 Hz, 2H), 3.90 (s, 3H), 2.86 (t, *J* = 6.9 Hz, 2H), 2.16 (quint, *J* = 6.8 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1, 158.4, 154.5, 144.2, 136.7, 128.6, 128.0, 127.6, 120.9, 112.6, 104.2, 73.1, 71.2, 56.2, 40.5, 26.0 ppm. FT-IR: ν (cm^{-1}) = 697, 746, 1148, 1198, 1262, 1381, 1444, 1504, 1606, 1664, 1732, 2927, 2959, 3028. APCI-MS: m/z (%) = 299.1 (100) $[M+H]^+$. HR-MS: calcd. for $C_{18}H_{19}O_4$ $[M+H]^+$ 299.1278; found 299.1279.



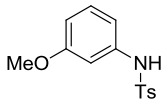
*7-Hydroxy-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one (**20**)*

7-(Benzyloxy)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one **19** (62 mg, 0.21 mmol) was dissolved in EtOAc (10 mL) and Pd/C (15 mg) was added. The reaction mixture was placed in an autoclave under 5 bar H_2 pressure and stirred for 5 hours. The mixture was filtered through celite and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.12). 7-Hydroxy-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one **20** was isolated in 64 % yield (28 mg, 0.13 mmol). ^{1}H NMR (300 MHz, MeOD): δ = 7.14 (s, *J* = 4.5 Hz, 1H), 6.64 (s, *J* = 10.3 Hz, 1H), 4.14 (t, *J* = 6.9 Hz, 2H), 3.87 (s, *J* = 4.1 Hz, 3H), 2.82 – 2.72 (m, 2H), 2.15 – 2.03 (m, 2H) ppm. ^{13}C NMR (75 MHz, MeOD): δ = 201.9, 158.4, 154.6, 143.7, 122.9, 114.6, 105.3, 73.7, 56.6, 41.3, 26.7 ppm. FT-IR: ν (cm^{-1}) = 885, 937, 1056, 1143, 1264, 1443, 1501, 1614, 1662, 2883, 2954, 3402. EI-MS: m/z (%) = 123.1 (38), 166.1 (47), 177.1 (27), 193.1 (11), 208.1 (100) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{11}H_{12}O_4$ $[M]^{+\bullet}$ 208.0736; found 208.0734.



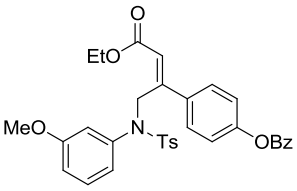
*8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol (**1e**)*

7-Hydroxy-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one **20** (27 mg, 0.13 mmol) was dissolved in EtOH (4 mL). The solution was cooled to 0 °C before $NaBH_4$ (25 mg, 0.65 mmol) was added. The reaction mixture was stirred for 5 hour at 0 °C and additional 3 hours at room temperature. The progress of the reaction was monitored by TLC. After the consumption of the substrate the reaction was quenched by the addition of 1 N HCl (1 mL) while cooling with an ice-water bath. EtOH was removed under reduced pressure before the rest of the reaction solution was extracted with Et_2O (4 × 10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.34). 8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol **1e** was obtained in 36 % yield (9.0 mg, 0.047 mmol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.70 (s, 1H, H-6), 6.52 (s, 1H, H-9), 6.18 (dt, *J* = 11.8, 1.7 Hz, 1H, H-5), 5.84 (dt, *J* = 11.7, 4.5 Hz, 1H, H-4), 5.19 (s, 0.8H, OH), 4.20 (t, *J* = 4.9 Hz, 1H, H-2), 3.85 (s, *J* = 5.6 Hz, 2H, OCH_3), 2.64 (ddd, *J* = 9.8, 4.7, 1.9 Hz, 1H, H-3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 152.7 (C-10), 145.8 (C-8), 140.4 (C-7), 128.3 (C-4), 128.0 (C-5), 119.5 (C-11), 117.0 (C-6), 103.1 (C-9), 69.9 (C-2), 56.0 (OCH_3), 34.4 (C-3) ppm. FT-IR: ν (cm^{-1}) = 800, 872, 1023, 1168, 1201, 1258, 1444, 1506, 1624, 2935, 3013, 3428. EI-MS: m/z (%) = 105.1 (13) $[PhCO]^+$, 162.1 (11), 177.1 (50), 192.1 (100) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{11}H_{12}O_3$ $[M]^{+\bullet}$ 192.0786; found 192.0785.



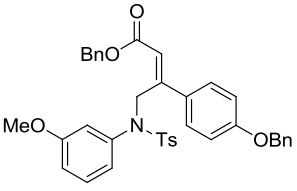
*N-(3-Methoxyphenyl)-4-methylbenzenesulfonamide (**21**)*

m-Anisidine (1.12 mL, 10.0 mmol) was dissolved in dry THF (15 mL). NEt_3 (1.66 mL, 12.0 mmol) and tosylchloride (1.90 g, 10.0 mmol) were added and the solution was stirred at room temperature for 28 hours. The reaction was quenched by adding water (5 mL). The aqueous phase was extracted with EtOAc (3×10 mL) and the combined organic phases were dried with $MgSO_4$. The solvent was removed under reduced pressure to obtain N-(3-methoxyphenyl)-4-methylbenzenesulfonamide **21** in 100 % yield (2.8 g, 10 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.71 (t, *J* = 2.2 Hz, 1H), 6.66 – 6.59 (m, 2H), 3.73 (d, *J* = 3.6 Hz, 3H), 2.37 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.3, 143.9, 137.8, 136.0, 130.0, 129.7, 127.3, 113.3, 110.8, 106.8, 55.3, 21.6 ppm. (Ref.[51])



*4-(4-Ethoxy-1-(N-(3-methoxyphenyl)-4-methylphenyl-sulfonamido)-4-oxobut-2-en-2-yl)phenyl benzoate (**22**)*

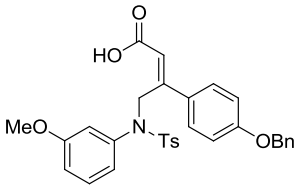
N-(3-Methoxyphenyl)-4-methylbenzenesulfonamide **21** (2.27 g, 8.20 mmol) was dissolved in acetone (50 mL) and cooled with ice-water-bath before 4-(1-bromo-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate **5a** (3.18 g, 8.20 mmol) and anhydrous K_2CO_3 (2.27 g, 16.4 mmol) were added. This slurry was stirred at 0 °C for 0.5 hours and afterwards heated to 50 °C for 40 hours. K_2CO_3 was filtered off and washed with EtOAc (50 mL). The organic phase was washed with 1 N HCl (10 mL) and water (10 mL). The aqueous phase was extracted with EtOAc (20 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was recrystallized from EtOAc. 4-(4-Ethoxy-1-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)-4-oxobut-2-en-2-yl)phenyl benzoate **22** was obtained as colorless crystals in 61 % yield (2.93 g, 5.00 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 – 8.18 (m, 2H), 7.70 – 7.63 (m, 1H), 7.58 – 7.50 (m, 2H), 7.50 – 7.43 (m, 4H), 7.29 – 7.21 (m, 4H), 7.01 (t, *J* = 8.1 Hz, 1H), 6.73 (ddd, *J* = 8.3, 2.5, 0.7 Hz, 1H), 6.29 (ddd, *J* = 7.9, 1.8, 0.8 Hz, 1H), 6.22 (t, *J* = 2.2 Hz, 1H), 5.97 (s, 1H), 5.41 (d, *J* = 0.8 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.58 (s, 3H), 2.43 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 164.9, 159.4, 152.9, 151.8, 143.6, 139.2, 135.7, 134.5, 133.7, 130.2, 129.5, 129.4, 128.8, 128.7, 127.9, 121.7, 121.2, 120.6, 114.7, 113.8, 60.3, 55.2, 47.0, 21.6, 14.2 ppm. FT-IR: ν (cm^{-1}) = 536, 579, 707, 816, 1053, 1154, 1248, 1348, 1599, 1705, 1737, 2937, 2972, 3004, 3065. ESI-MS: m/z (%) = 586.2 (91) $[M+H]^+$, 603.2 (81) $[M+NH_4]^+$, 608.2 (41) $[M+Na]^+$, 1193.4(100) $[2M+Na]^+$. HR-MS: calcd. for $C_{33}H_{32}NO_7S$ $[M+H]^+$ 586.1894; found 586.1899.



*(Benzyl 3-(4-(benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)but-2-enoate (**23**)*

4-(4-Ethoxy-1-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)-4-oxobut-2-en-2-yl)phenyl benzoate **22** (0.77 g, 1.32 mmol) was dissolved in THF/H_2O (4:1, 30 mL) and cooled with an ice-water-bath before LiOH (0.32 g, 13 mmol) was added. This slurry was stirred at 0 °C for 1 hour and heated to 55 °C for 44 hours. The completion of the reaction

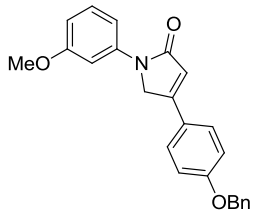
was monitored by TLC. Afterwards the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (3×50 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was used without further purification in the subsequent reaction and dissolved in acetone (10 mL). Benzyl bromide (0.77 mL, 6.5 mmol), K_2CO_3 (0.36 g, 2.6 mmol) and KI (20 mg, 0.13 mmol) were added to the stirring solution before heating was initiated. The reaction mixture was heated to 60 °C for 40 h. After K_2CO_3 was filtered off and acidified with 1 N HCl, the mixture was extracted with dichloromethane (3×40 mL). The combined organic phases were dried with $MgSO_4$. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 4:1, R_f 0.3). (Benzyl 3-(4-(benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)-but-2-enoate **23** was obtained as yellow oil in 29 % yield (0.24 g, 0.38 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 – 7.23 (m, 20H), 7.00 – 6.92 (m, 3H), 6.71 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.24 (d, *J* = 7.7 Hz, 1H), 6.19 (t, *J* = 2.1 Hz, 1H), 5.97 (s, 1H), 5.40 (s, 2H), 5.11 (s, 2H), 5.07 (s, *J* = 5.0 Hz, 2H), 3.50 (s, 3H), 2.44 (s, *J* = 5.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.8, 159.9, 159.2, 153.9, 143.6, 139.1, 136.7, 135.8, 134.6, 130.4, 129.5, 129.1, 128.8, 128.7, 128.6, 128.2, 128.1, 128.0, 127.9, 127.6, 127.0, 120.8, 118.9, 114.6, 113.8, 70.1, 65.9, 55.1, 46.7, 21.6 ppm. ESI-MS: m/z (%) =634.2 (100) $[M+H]^+$, 656.2 (33) $[M+Na]^+$, 1289.4 (63) $[2M+Na]^+$. HR-MS: calcd. for $C_{38}H_{36}NO_6S$ $[M+H]^+$ 634.2258; found 634.2256.



*3-(4-(Benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)but-2-enoic acid (**24**)*

(Benzyl 3-(4-(benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenyl-sulfonamide)but-2-enoate **23** (0.23 g, 0.36 mmol) was dissolved in THF/H_2O (4:1, 12 mL) and cooled with an ice-water-bath before LiOH (43 mg, 1.8 mmol) was added. This slurry was stirred at 0 °C for 1 hour and additional 30 hours at 60 °C. Afterwards the reaction mixture was acidified with 1 N HCl to pH 1 - 2 and extracted with EtOAc (3×10 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was recrystallized from MeOH/dichloromethane (4:1, 2.5 mL). 3-(4-(Benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenylsulfon-amido)but-2-enoic acid **24** was obtained as white crystalline solid in 23 % yield (44 mg,

0.08 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 – 7.34 (m, 9H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.03 – 6.95 (m, 3H), 6.72 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.27 – 6.19 (m, 1H), 6.16 (t, *J* = 2.2 Hz, 1H), 5.94 (d, 2H), 5.36 (s, 2H), 5.13 (s, 2H), 3.51 (s, 3H), 2.42 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 160.2, 159.3, 156.5, 143.7, 139.2, 136.6, 134.4, 130.2, 129.4, 129.2, 128.9, 128.7, 128.2, 127.9, 127.6, 120.8, 117.8, 114.7, 114.6, 113.9, 70.1, 55.1, 46.9, 21.6 ppm. ESI-MS: m/z (%) = 544.2 (100) $[M+H]^+$, 561.2 (20) $[M+NH_4]^+$. HR-MS: calcd. for $C_{31}H_{30}NO_6S$ $[M+H]^+$ 544.1788; found 544.1791.



*4-(4-(Benzyloxy)phenyl)-1-(3-methoxyphenyl)-1H-pyrrol-2(5H)-one (**27**)*

3-(4-(Benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)but-2-enoic acid **24** (26 mg, 0.05 mmol) was dissolved in dry dichloroethane (1 mL). The solution was cooled with an ice-water-bath before pyridine (4 μL, 0.05 mmol) and cyanuric chloride (13 mg, 0.08 mmol) were added. The reaction mixture was stirred at 0 °C for 0.5 hours, the cooling bath was then removed and the mixture stirred for additional 3 hours at room temperature. After cooling to -30 °C, $InCl_3$ (11 mg, 0.05 mmol) was added in three portions. The mixture was allowed to warm slowly up to 0 °C over a period of 2 hours and was stirred additional 10 hours at room temperature before the reaction was quenched by adding H_2O (0.5 mL). The aqueous phase was extracted with Et_2O (3×2 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on a Biotage® Isolera™ flash purification system (PE/EtOAc 2:1, R_f 0.3). 4-(4-(Benzyloxy)phenyl)-1-(3-methoxyphenyl)-1H-pyrrol-2(5H)-one **27** was obtained in 28 % yield (5 mg, 0.013 mmol) (when $AlCl_3$ was used as Lewis acid, 4-(4-(Benzyloxy)phenyl)-1-(3-methoxyphenyl)-1H-pyrrol-2(5H)-one **27** was obtained in 87 % yield (12 mg, 0.032 mmol) from 3-(4-(Benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)but-2-enoic acid **24** (20 mg, 0.037 mmol)). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 (t, *J* = 2.1 Hz, 1H), 7.53 – 7.50 (m, 2H), 7.46 – 7.42 (m, 2H), 7.42 – 7.39 (m, 2H), 7.37 – 7.33 (m, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.27 (t, *J* = 1.5 Hz, 1H), 7.06 – 7.02 (m, 2H), 6.69 (ddd, *J* = 7.8, 2.3, 1.3 Hz, 1H), 6.39 (s, 1H), 5.13 (s, 2H), 4.74 (d, *J* = 0.9 Hz, 2H), 3.85 (s, 3H) ppm. ^{13}C NMR

(151 MHz, $CDCl_3$): δ = 170.9, 160.8, 160.4, 153.3, 140.8, 136.5, 129.9, 128.9, 128.4, 127.7, 127.6, 124.4, 119.5, 115.6, 110.7, 109.6, 104.8, 70.3, 55.5, 53.0 ppm. FT-IR: ν (cm^{-1}) = 695, 765, 823, 1034, 1178, 1252, 1382, 1514, 1604, 1674, 2924, 3036. EI-MS: m/z (%) = 91.1 (100) $[C_7H_7]^+$, 280.2 (7) $[M\text{-}C_7H_7]^+$, 371.2 (11) $[M]^{+\bullet}$. HR-MS: calcd. for $C_{24}H_{21}NO_3$ $[M]^{+\bullet}$ 371.1521; found 371.1524.

3.5.2 Pharmacological testing

Cytotoxicity

The influence of ruscozepine B **1b** on the viability of HMEC-1 cells was determined after 24 hours of incubation using an MTT assay according to Mosman[52] (modified, n = 3 in sextuplicates).

ICAM-1

Confluent grown human microvascular endothelial cells (HMEC-1)[53] were pretreated either with ruscozepine B **1b**, parthenolide (Calbiochem, purity ≥ 97 %, 5 μM, positive control), or medium (ECGM, endothelial cell growth medium (Provitro) + 10 % FCS, + antibiotics, + supplements) as a negative control in 24-well plates. Thirty minutes later, 10 ng/mL TNF-α (Sigma-Aldrich) were added to stimulate the ICAM-1 expression. After 24 hours of incubation (New Brunswick Scientific, 37 °C, 5 % CO_2), cells were washed with PBS, removed from the plate with trypsin/EDTA and fixed with formalin. After incubating with a FITC-labelled mouse antibody against ICAM-1 (Biozol) for 20 min, the fluorescence intensity was measured by FACS analysis (Becton Dickinson Facscalibur™). ICAM-1 expression of cells treated with TNF-α only was set as 100 %.

ORAC-Fluorescein assay

The ORAC-Fl assay was performed according to Davalos *et al.* [42] and Vogel et al. [43] in 96-well plates with fluorescein (final concentration 300 nM) as fluorescent probe and 75 mM phosphate buffer (pH 7.4) for all dilution steps and as reaction milieu. The antioxidant (compounds **1a-e**, **16a/c** or Trolox, 20 μL) was incubated in different concentrations (compounds **1a-e**, **16a/c** 1.0-5.0 μM; Trolox, 1-8 μM) together with a fluorescein solution (120 μL) at 37 °C for 15 min. The reaction was started by the addition of 60 μL of AAPH (2,2′-azobis(2-methylpropionamide) dihydrochloride; final concentration, 12 mM), yielding a final volume of 200 μL. After the addition of AAPH, the fluorescence was recorded every minute in a Tecan 96-plate reader (λ_{ex} = 485 nm, λ_{em} = 536 nm, 37 °C) for 300 min. Samples were measured at five different concentrations (1.0-5.0 μM). Eight

calibration curves using 1-8 μM Trolox as antioxidant were also carried out in each assay. Controls were measured without antioxidant as well as without AAPH and antioxidant. ORAC values were expressed as Trolox equivalents (mean±SD) by using the standard curve calculated for each assay. The regression coefficient between AUC and antioxidant concentration was calculated for all samples ($r^2 > 0.93$). Further positive control measurements were performed with xanthohumol.

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4 Summary

The first part of this dissertation (chapter 1 and 2) deals with the deoxygenation of alcohols. Chapter 1 reviews catalytic deoxygenation methods currently used in organic synthesis. Recent examples are used to demonstrate the different deoxygenation strategies employing either a two-step procedure or the direct deoxygenation of alcohols. For the commonly used two-step procedures the alcohols are transferred into a corresponding ester or ether that can be cleaved reductively by common palladium, nickel or rhodium catalysts. The direct deoxygenation is the preferred method; while the catalyst activates the C-O bond a conversion into an appropriate leaving group is not necessary. Lewis acids are commonly used for this activation and silanes are typically used as reducing agents.

Chapter 2 reports the deoxygenation of benzylic alcohols with hydriodic acid in a biphasic media. This method, using boiling hydriodic acid and red phosphorous for the deoxygenation of gluconic acid to hydrocarbons, was reported the first time by Killiani 140 years ago. We reinvestigated this method by using hydriodic acid in toluene to separate the organic molecules from the harsh acidic conditions in the aqueous phase and allow milder reaction conditions. With this method benzylic and α-carbonyl alcohols are deoxygenated successfully. Even catalytic amounts of hydriodic acid are sufficient for the deoxygenation when excess of red phosphorous is used as terminal reducing agent.

In chapter 3 we describe the synthesis of the natural products ruscozepine A and B isolated from *Ruscus aculeatus* L. and analogous compounds. An existing synthetic pathway for the basic benzoxepine structure was improved for the synthesis of the ruscozepines. Especially a mild procedure for the intramolecular Friedel-Crafts acylation is applied, because typically used procedures were not favorable. Unfortunately the developed synthesis was not applicable for the synthesis of an analogous benzazepine. Pharmacological testing revealed a high antioxidant activity by an ORAC-fluoresceine assay, while no anti-inflammatory activity was observed in an ICAM-1 expression inhibition assay.

5 Zusammenfassung

Der erste Teil dieser Dissertation (Kapitel 1 und 2) befasst sich mit der Deoxygenierung von Alkoholen. Im ersten Kapitel sind katalytische Deoxygenierungsmethoden zusammengefasst, die derzeit Anwendung in der organischen Chemie finden. Anhand aktueller Beispiele werden die unterschiedlichen Strategien zur Deoxygenierung von Alkoholen aufgezeigt, die entweder auf einer zweistufigen oder direkten Methode beruhen. Bei den häufig genutzten zweistufigen Methoden werden die Alkohole erst in einen entsprechenden Ester oder Ether umgewandelt um dann reduktiv mit Hilfe eines Palladium, Nickel oder Rhodium Katalysators gespalten zu werden. Die direkten Deoxygenierungen sind die bevorzugten Methoden; da hierbei ein Katalysator die C-O Bindung aktiviert, ist keine Umwandlung in eine geeignete Abgangsgruppe notwendig. Für gewöhnlich werden Lewis Säuren für diese Aktivierung genutzt, wobei Silane als typische Reduktionsmittel eingesetzt werden.

Kapitel 2 berichtet über die Deoxygenierung von Benzylalkoholen mit Iodwasserstoffsäure in einem zweiphasigen Medium. Über die Verwendung von Iodwasserstoffsäure zur Deoxygenierung von Alkoholen berichtete erstmals Killiani vor 140 Jahren, um Gluconsäure in kochender Iodwasserstoffsäure mit rotem Phosphor zu den entsprechenden Kohlenwasserstoffen zu deoxygenieren. Wir griffen diese Methode wieder auf indem wir Iodwasserstoffsäure in Toluol nutzten um organische Moleküle von der starken Mineralsäure in der wässrigen Phase zu separieren um somit mildere Reaktionsbedingungen zu erhalten. Unter diesen Bedingungen können Benzyl- und α-Carbonylalkohole erfolgreich deoxygeniert werden. Wird roter Phosphor im Überschuss eingesetzt, sind sogar katalytische Mengen von Iodwasserstoffsäure hinreichend um Benzylalkohole zu deoxygenieren.

In Kapitel 3 wird die Synthese der Naturstoffe Ruscozepin A und B, isoliert aus dem stechenden Mäusedorn (*Ruscus aculeatus* L.), und analogen Substanzen beschrieben. Für die Synthese der Ruscozepine wurde ein bekannter Syntheseweg für die Benzoxepingrundstruktur verbessert und auf analoge Substanzen übertragen. Besonders die Anwendung einer milden Variante der Friedel-Crafts Acylierung war essentiell, da etablierte Methoden dieser Reaktion nicht zum gewünschten Ergebnis führten. Allerdings konnte die dabei etablierte Syntheseroute nicht auf die Synthese eines analogen

Benzazepins angewandt werden. Die Pharmakologische Testung dieser Substanzen offenbarte ein hohes antioxidatives Potential in einem ORAC-Fluorescein Assay, während keine entzündungshemmenden Eigenschaften in einem ICAM-1 Expression Inhibitions Assay beobachtet werden konnten.

6 Appendix

6.1 Abbreviations

[BMIM][BF_4]	1-Butyl-3-methyl-imidazolium-tetrafluorborate
[BSO_3BIM][NTf_2]	1-(4-Butylsulfonic acid)-3-(n-butyl)imidazolium-bis(trifluormethyl-sulfonyl)imide
[EMIM][NTf2]	1-Ethyl-3-methylimidazoliumbis(trifluormethylsulfonyl)imid
°C	Degree Celsius
µL	Micro liter
µM	Micro molar
µW	Micro watt
^{13}C NMR	Carbon NMR
^{1}H NMR	Proton NMR
1-OL	1-Octanol
Å	Angstrom (10^{-10} meters)
AAPH	2,2´-Azobis-(2-methylpropionamide)-dihydrochloride
ACN	Acetonitrile
APCI	Atmospheric-pressure chemical ionization
BzCl	Benzoyl chloride
C(sp^2)	Carbon in sp^2 hybridization
C(sp^3)	Carbon in sp^3 hybridization
Ca(NTf_2)$_2$	Calcium(II) bis(trifluoromethanesulfonimide)
calcd.	Calculated
Cbz	Carboxybenzyl
$CDCl_3$	Deuterated chloroform
CI	Chemical ionization
C–O	Carbon oxygen bond
cod	1,5-Cyclooctadiene
cot	1,3,5-Cyclooctatriene
CVI	Chronic venous insufficiency
DBPB	2,2-Di-*tert*butylperoxybutane
DBPO	Dibenzoyl peroxide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMAP	4-Dimethylamino-pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
DOE	1,1-Dioctylether
dppf	(1,3-Bis(diphenyl-phosphino)ferrocene)
dppp	(1,3-Bis(diphenyl-phosphino)propane)
e^-	Electron
ECGM	Endothelial cell growth medium
EDTA	Ethylenediamine-tetraacetic acid
EE	Ethoxyethyl
EI	Electron impact ionization
eq.	Equivalent

ES	Electrospray
ESI	Electrospray ionization
Et_2O	Diethyl ether
Et_3SiH	Triethylsilane
EtOAc	Ethyl acetate
EtOH	Ethanol
eV	Electron volts
F/mol	Farad per mol
FACS	Fluorescence-activated cell sorting
FITC	Fluorescein isothiocyanate
FCS	Fetal calf serum
FT-IR	Fourier transform infrared spectroscopy
h	Hour
H^+	Proton
HDO	Hydrodeoxygenation
HI	Hydriodic acid
HMEC-1	Human microvascular endothelial cells
HR-MS	High resolution mass spectrometry
ICAM-1	Intercellular adhesion molecule
LAH	Lithium aluminium hydride
$LiAlH_4$	Lithium aluminium hydride
$LiBHEt_3$	Lithium triethylborohydride
LPS	Lipopolysaccharide
M	Molar concentration
mA/cm^2	Milli ampere per square centimeter (electric current density)
mean±SD	Reference range (standard deviation)
$MeNO_2$	Nitromethane
MeOD	Deuterated methanol, MeOH-d_4
MeOH	Methanol
$MgSO_4$	Magnesium sulfate
MHz	Mega hertz
min	Minute
mL	Milli liter
mm	Milli meter
mmol	Milli mole
$Mo(CO)_6$	Molybdenum hexacarbonyl
mol%	Mole percent
MOM	Methoxymethyl
Mp	Melting point
MS	Mass spectrometry
Ms	Mesylate
MSA	Methanesulfonic acid
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide
N	Normal concentration
NBS	N-Bromosuccinimide
n-BuLi	n-Butyl lithium
Nf	Nafion
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
$Ni(cod)_2$	Bis(1,5-cyclooctadiene)nickel
Ni/C_g	Nickel on graphite
nm	Nano meter
NMR	Nuclear magnetic resonance
ORAC	Oxygen radical absorbance capacity
PCy_3	Tricyclohexylphosphine
Pd/C	Palladium on charcoal
PE	petroleum ether

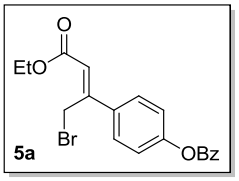
PPA	Polyphosphoric acid
PPh_3	Triphenylphosphine
ppm	Parts per million
P_{red}	Red phosphorous
*p*TSA	para-Toluenesulfonic acid
R_f	Retention factor
$RhCl(PPh_3)_3$	Wilkinson catalyst
ROS	Reactive oxygen species
Ru/C	Ruthenium on charcoal
sat.	Saturated
SCE	Saturated calomel electrode
SET	Single electron transfere
TBDMS	*tert*-Butyldimethylsilyl
TBST	Tri-*tert*-butoxysilanethiol
TEAC	Trolox equivalent antioxidant capacity
TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
Tf	Triflate
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
THFA	4-(2-Tetrahydrofuryl)-2-butanol
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride
TNF-α	Tumor necrosis factor alpha
Trolox	6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid
Ts	Tosyl
UV	Ultra violet
V	Volt
Vis	Visible light
wt.-%	Weight percent

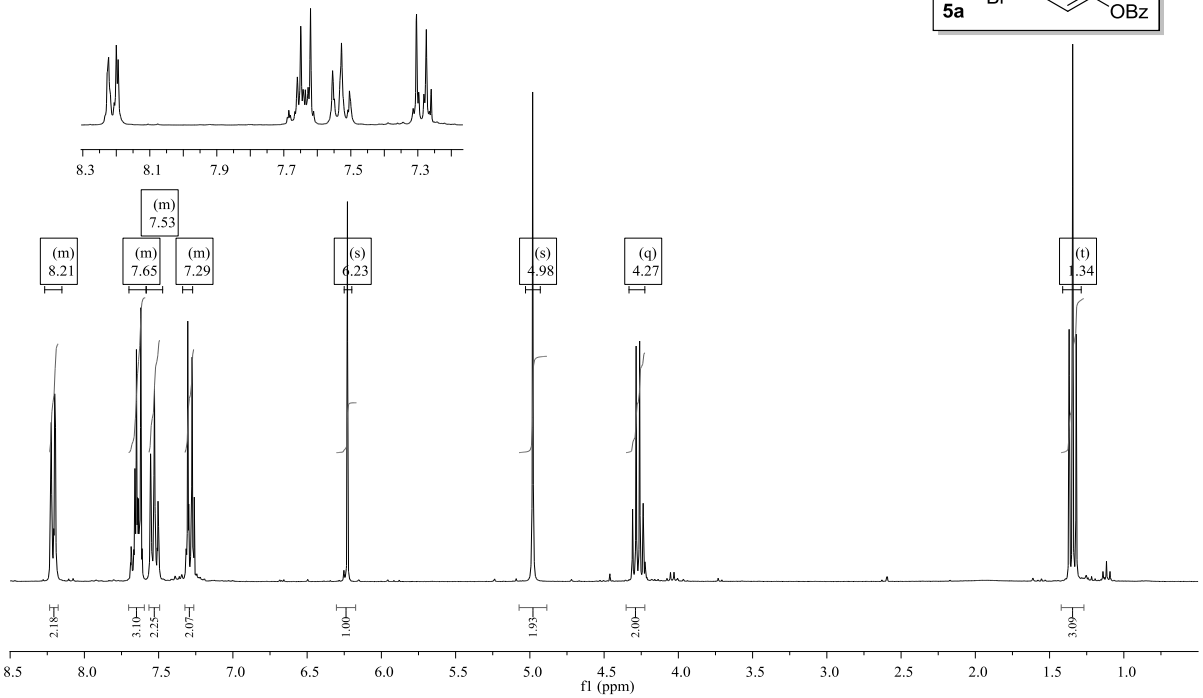
6.2 Copies of selected NMR – Spectra

*4-(1-Bromo-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate (**5a**)*

^{1}H-NMR (300 MHz, CDCl3)

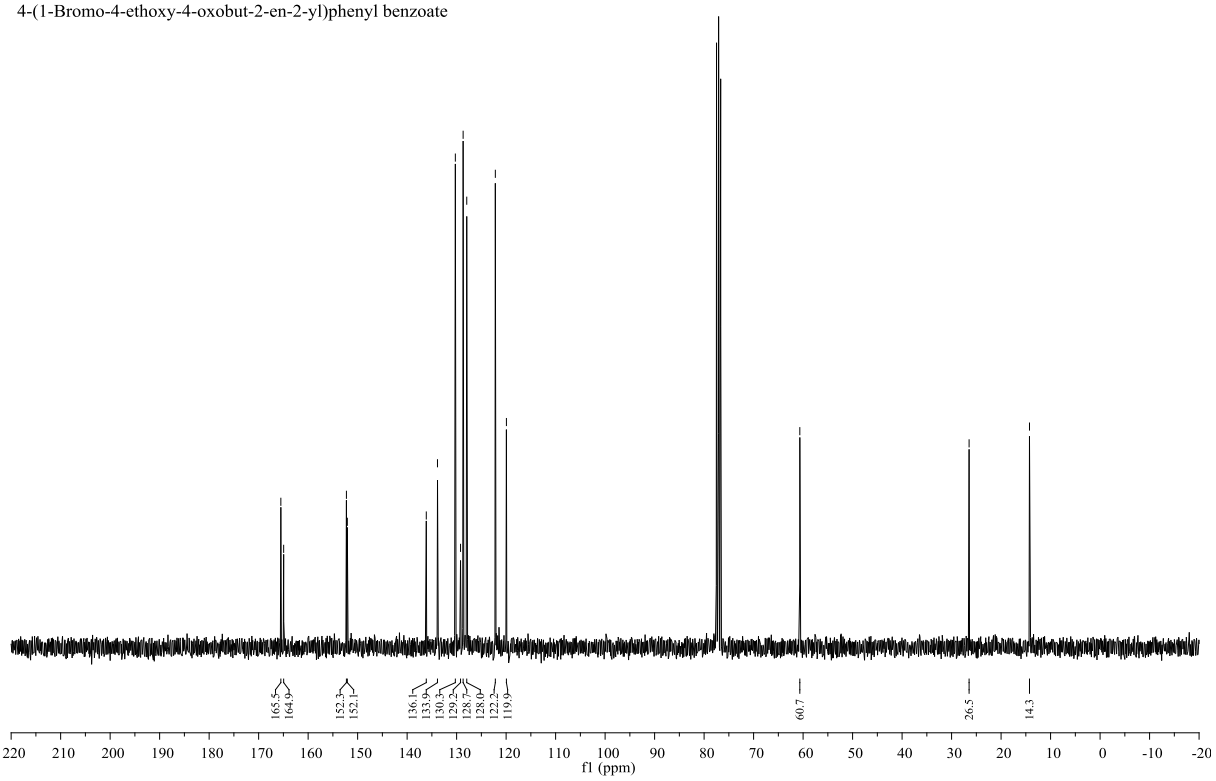
4-(1-Bromo-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate





^{13}C-NMR (75 MHz, CDCl3)

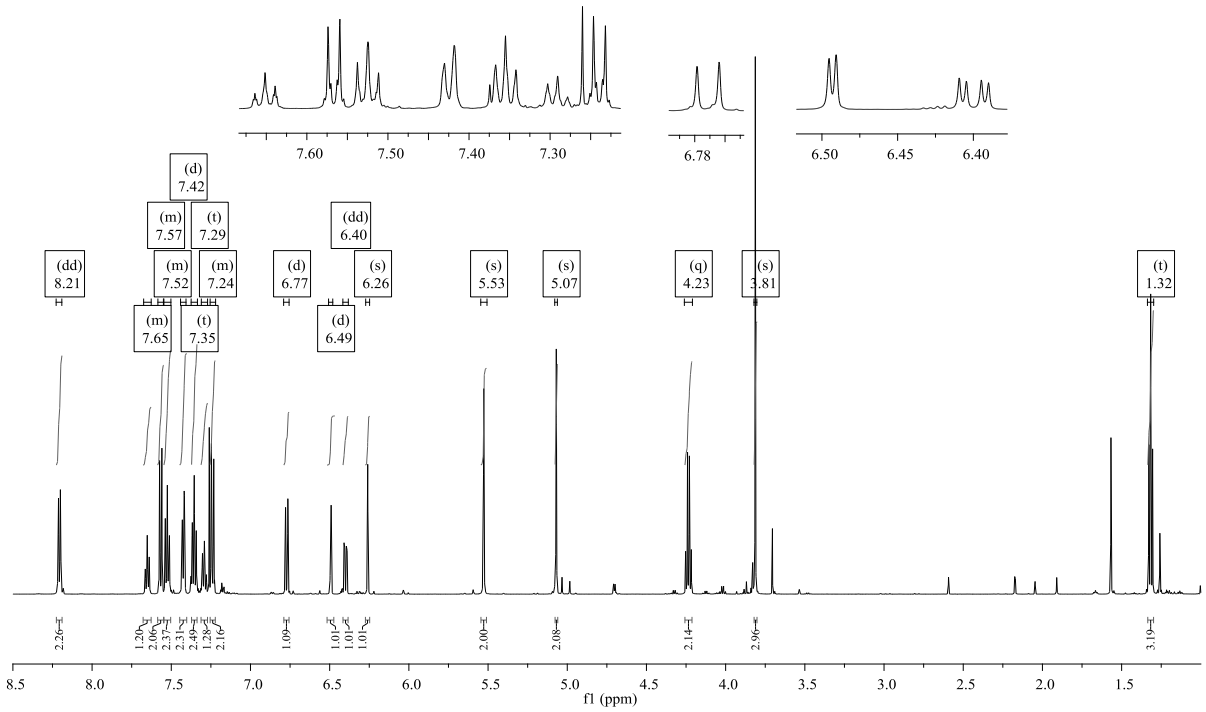
4-(1-Bromo-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate



*4-(1-(4-(Benzyloxy)-3-methoxyphenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate (**3b**)*

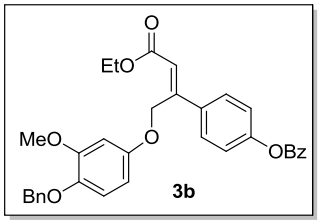
^{1}H-NMR (600 MHz, CDCl3)

4-(1-(4-(Benzyloxy)-3-methoxyphenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate



^{13}C-NMR (151 MHz, CDCl3)

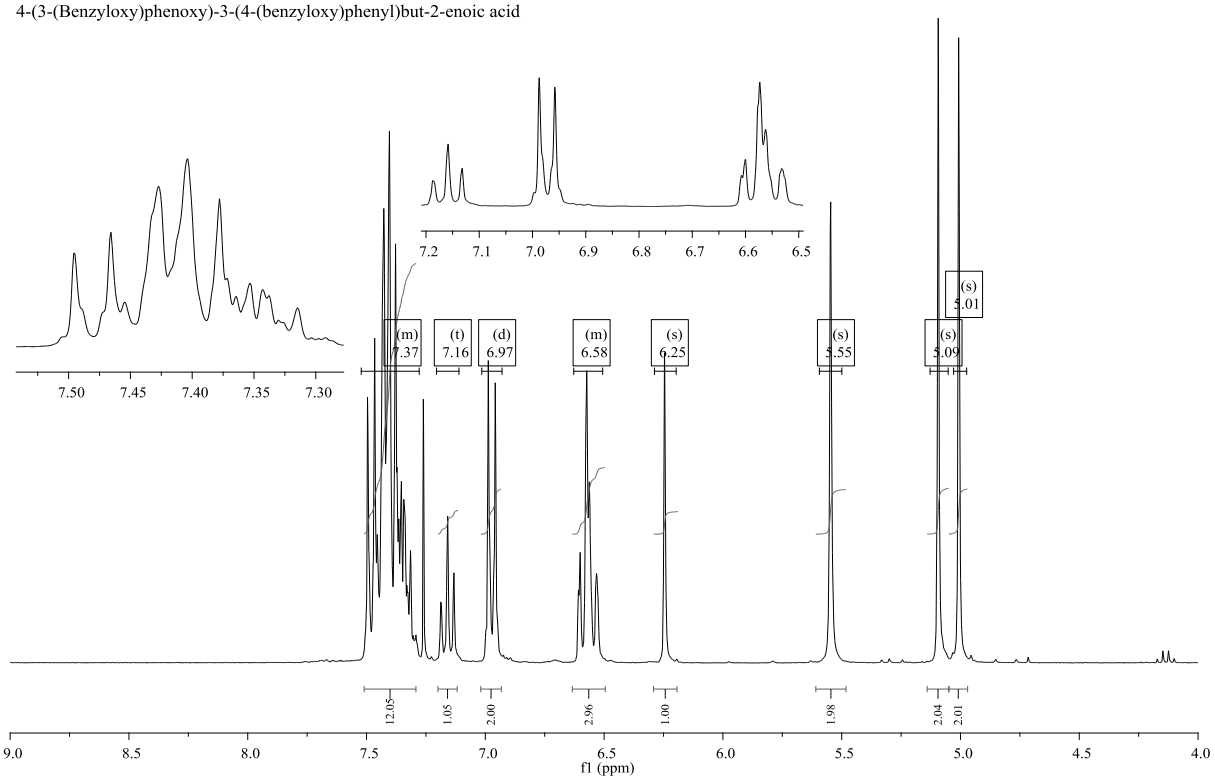
4-(1-(4-(Benzyloxy)-3-methoxyphenoxy)-4-ethoxy-4-oxobut-2-en-2-yl)phenyl benzoate



*4-(3-(Benzyloxy)phenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid (**10a**)*

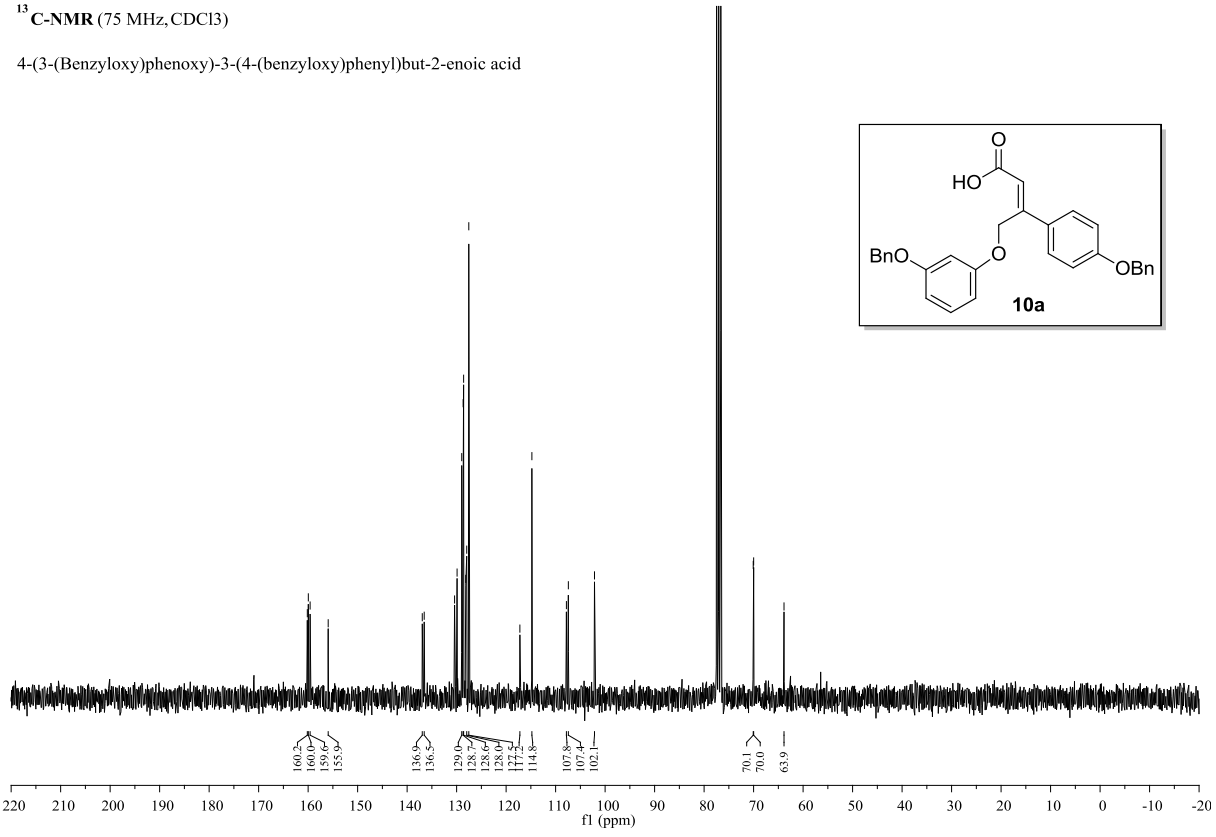
^{1}H-NMR (300 MHz, CDCl3)

4-(3-(Benzyloxy)phenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid



^{13}C-NMR (75 MHz, CDCl3)

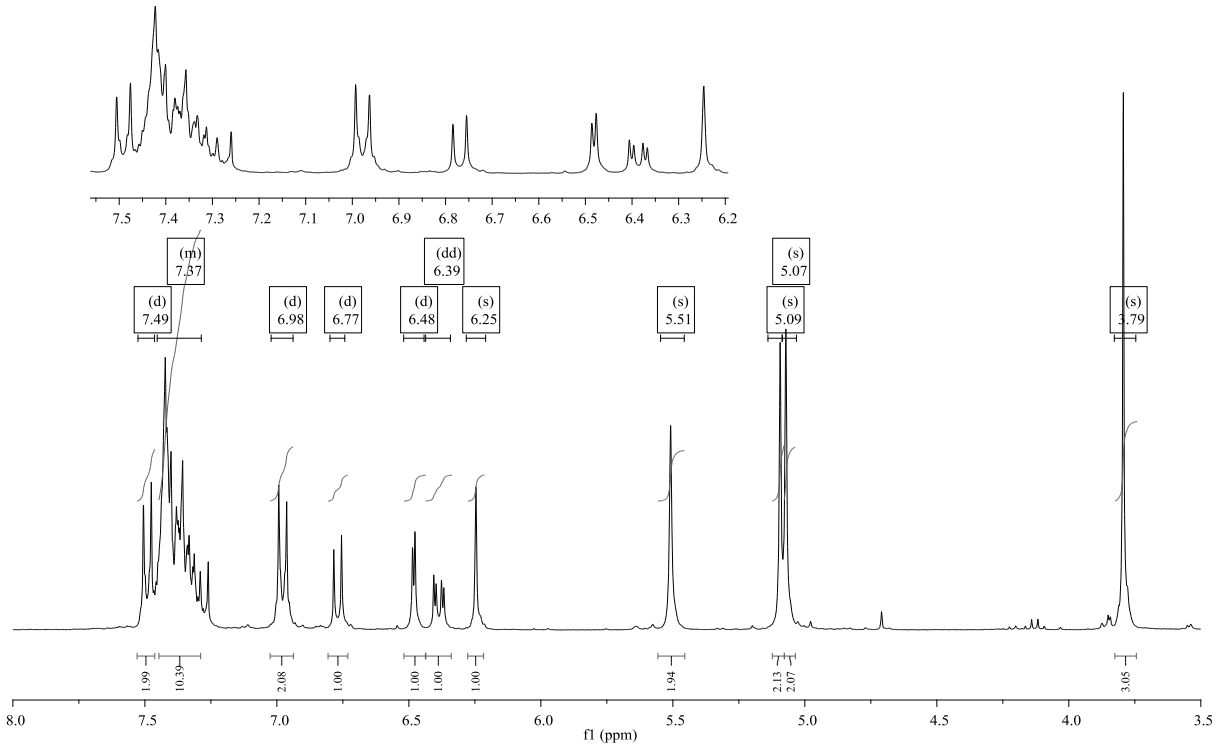
4-(3-(Benzyloxy)phenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid



*4-(4-(Benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid (**10b**)*

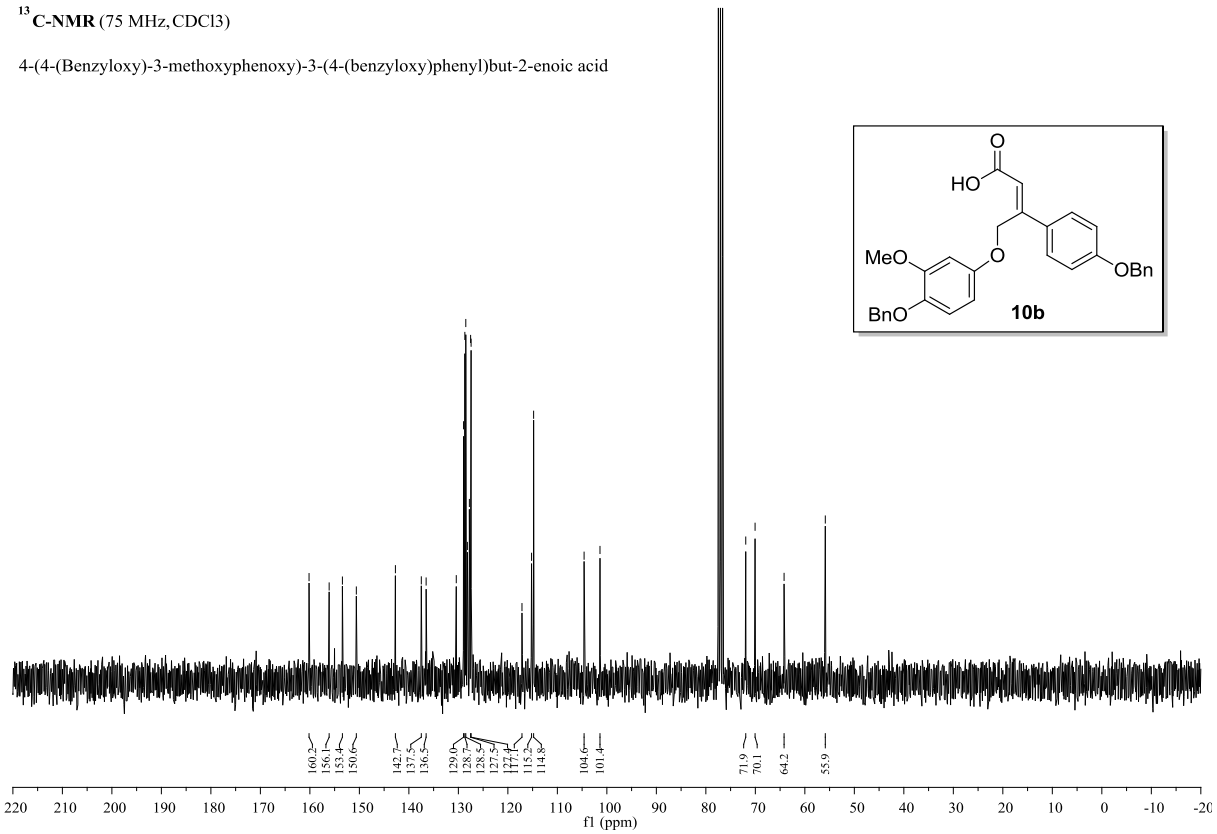
^{1}H-NMR (300 MHz, CDCl3)

4-(4-(Benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid



^{13}C-NMR (75 MHz, CDCl3)

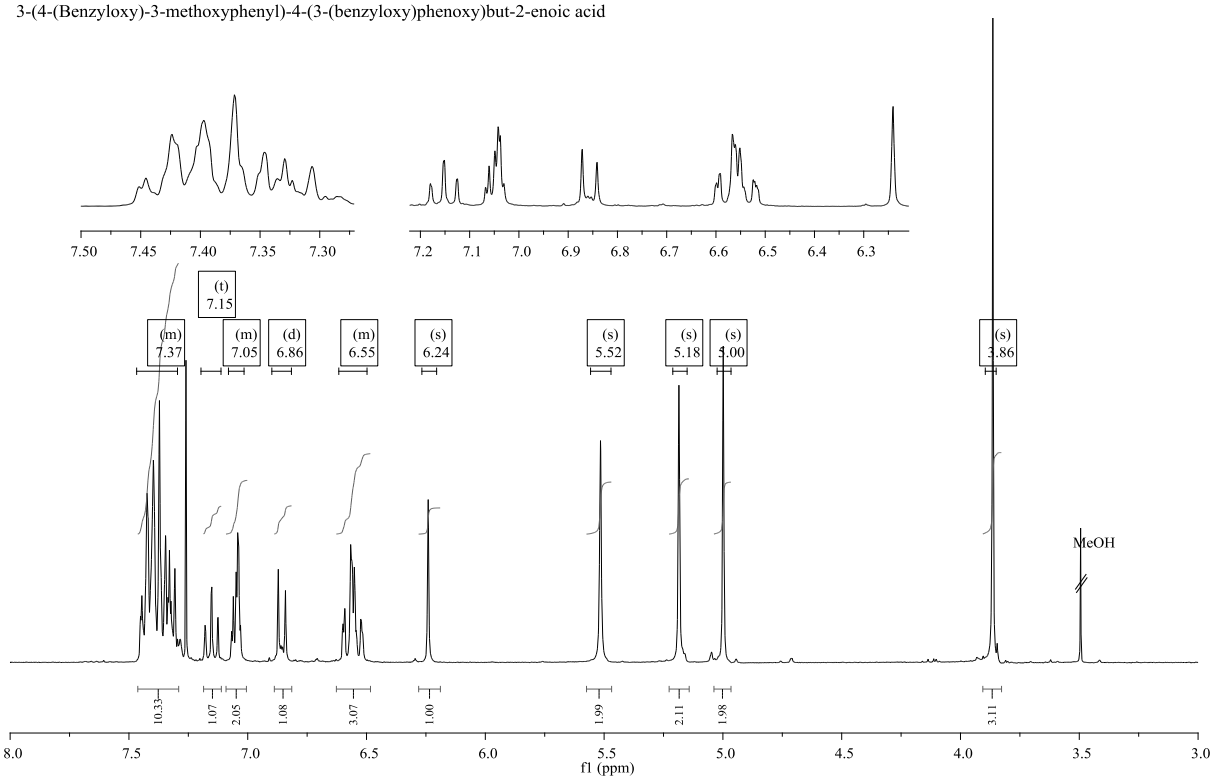
4-(4-(Benzyloxy)-3-methoxyphenoxy)-3-(4-(benzyloxy)phenyl)but-2-enoic acid



*3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)phenoxy)but-2-enoic acid (**10c**)*

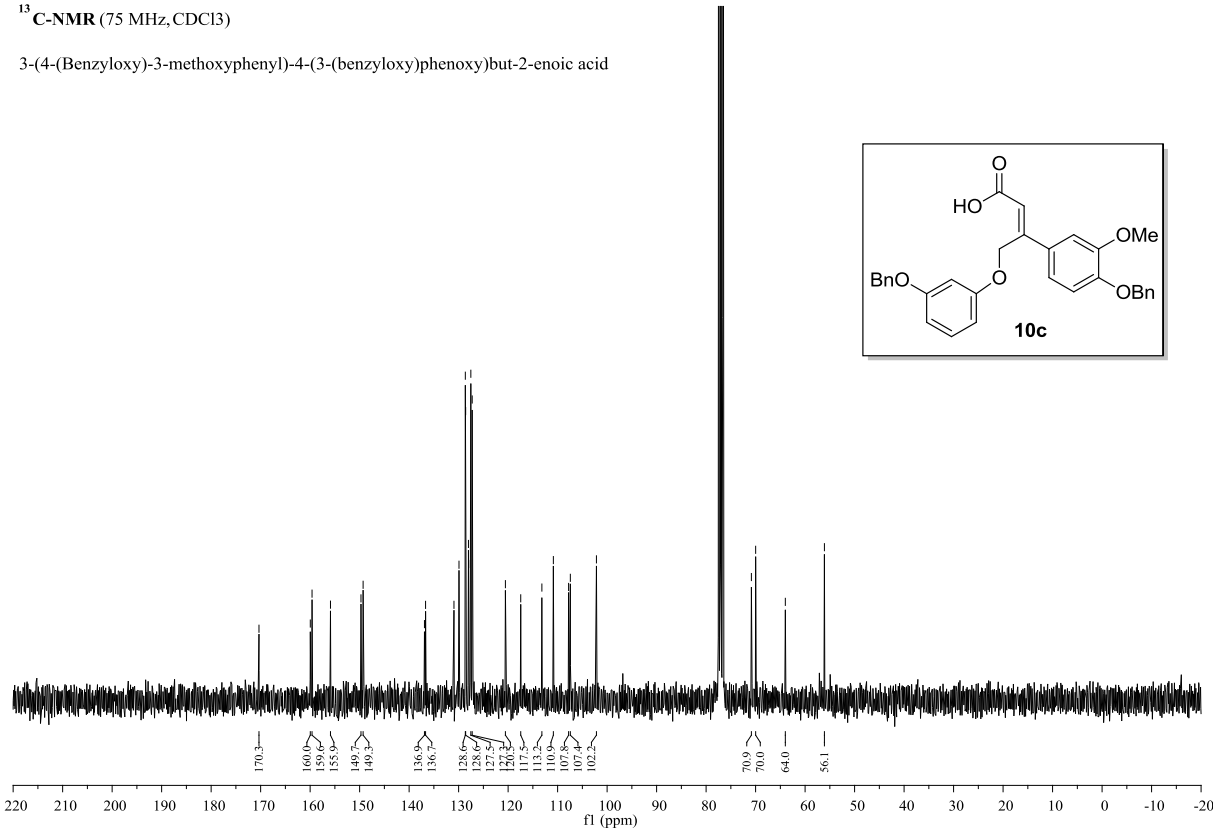
^{1}H-NMR (300 MHz, CDCl3)

3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)phenoxy)but-2-enoic acid



^{13}C-NMR (75 MHz, CDCl3)

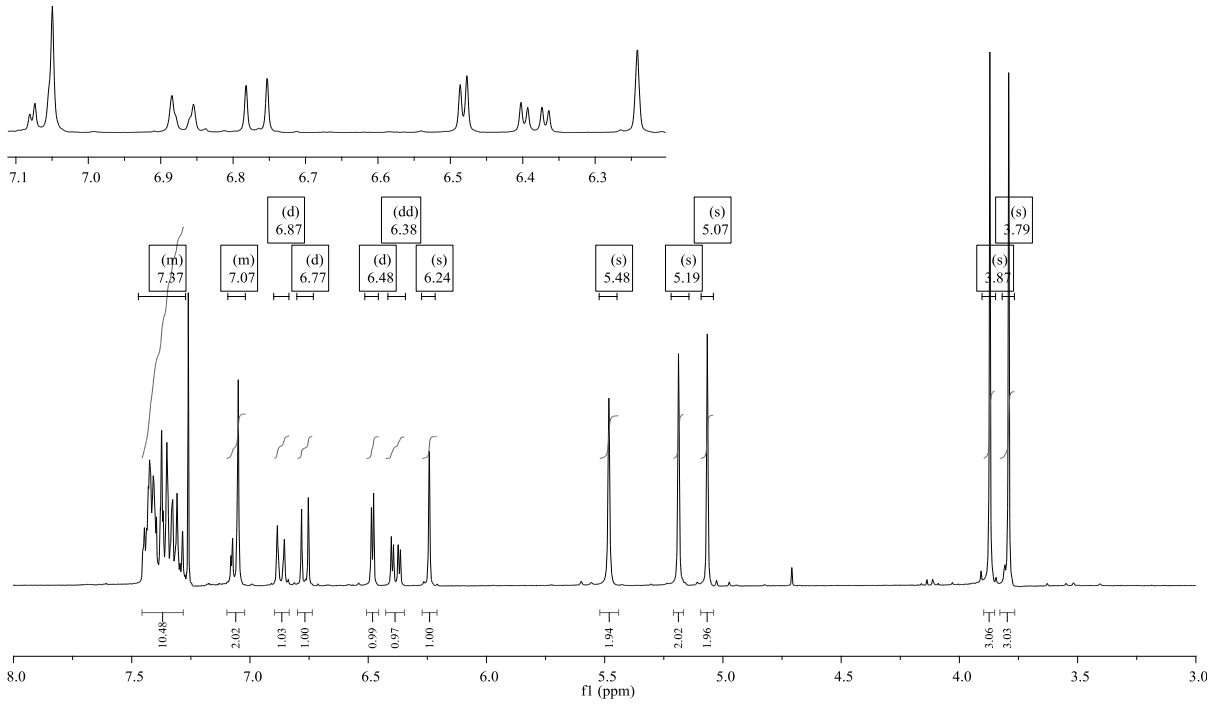
3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)phenoxy)but-2-enoic acid



*3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)-4-methoxyphenoxy)but-2-enoic acid (**10d**)*

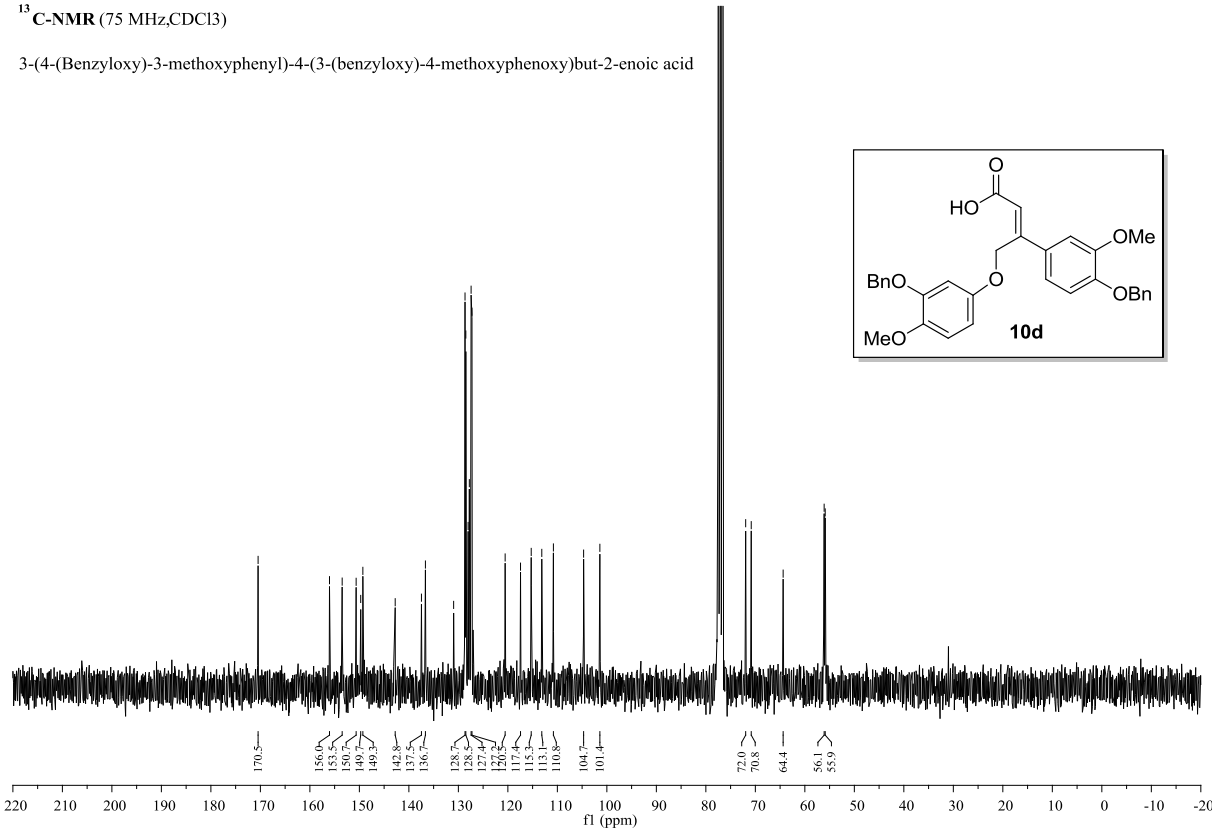
^{1}H-NMR (300 MHz,CDCl3)

3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)-4-methoxyphenoxy)but-2-enoic acid



^{13}C-NMR (75 MHz,CDCl3)

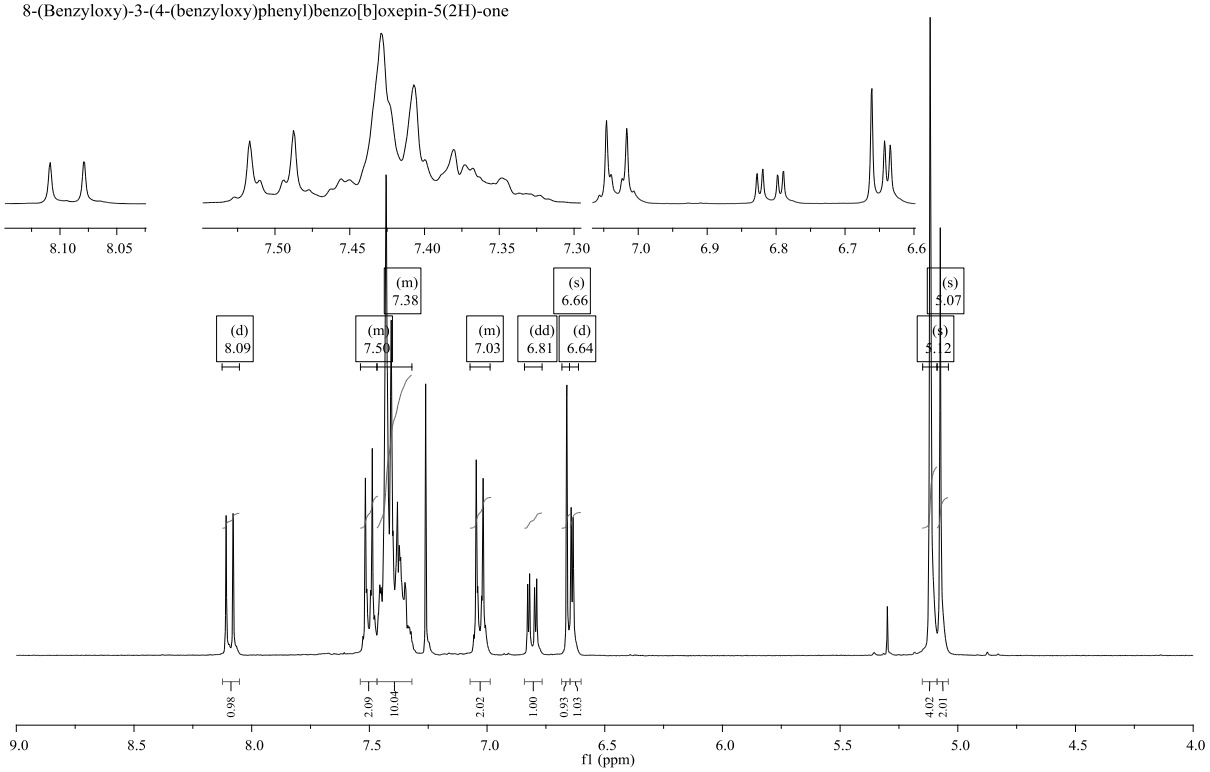
3-(4-(Benzyloxy)-3-methoxyphenyl)-4-(3-(benzyloxy)-4-methoxyphenoxy)but-2-enoic acid



*8-(Benzyloxy)-3-(4-(benzyloxy)phenyl)benzo[b]oxepin-5(2H)-one (**2a**)*

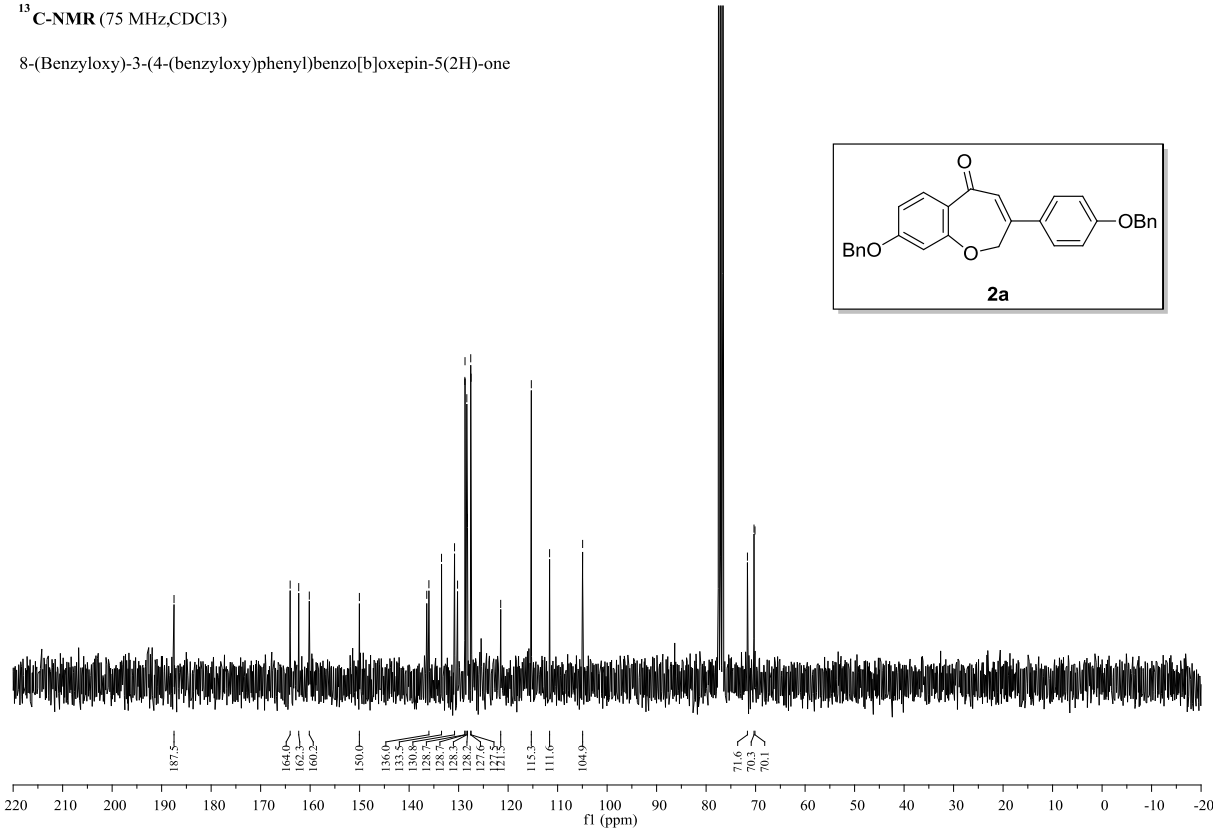
^{1}H-NMR (300 MHz,CDCl3)

8-(Benzyloxy)-3-(4-(benzyloxy)phenyl)benzo[b]oxepin-5(2H)-one



^{13}C-NMR (75 MHz,CDCl3)

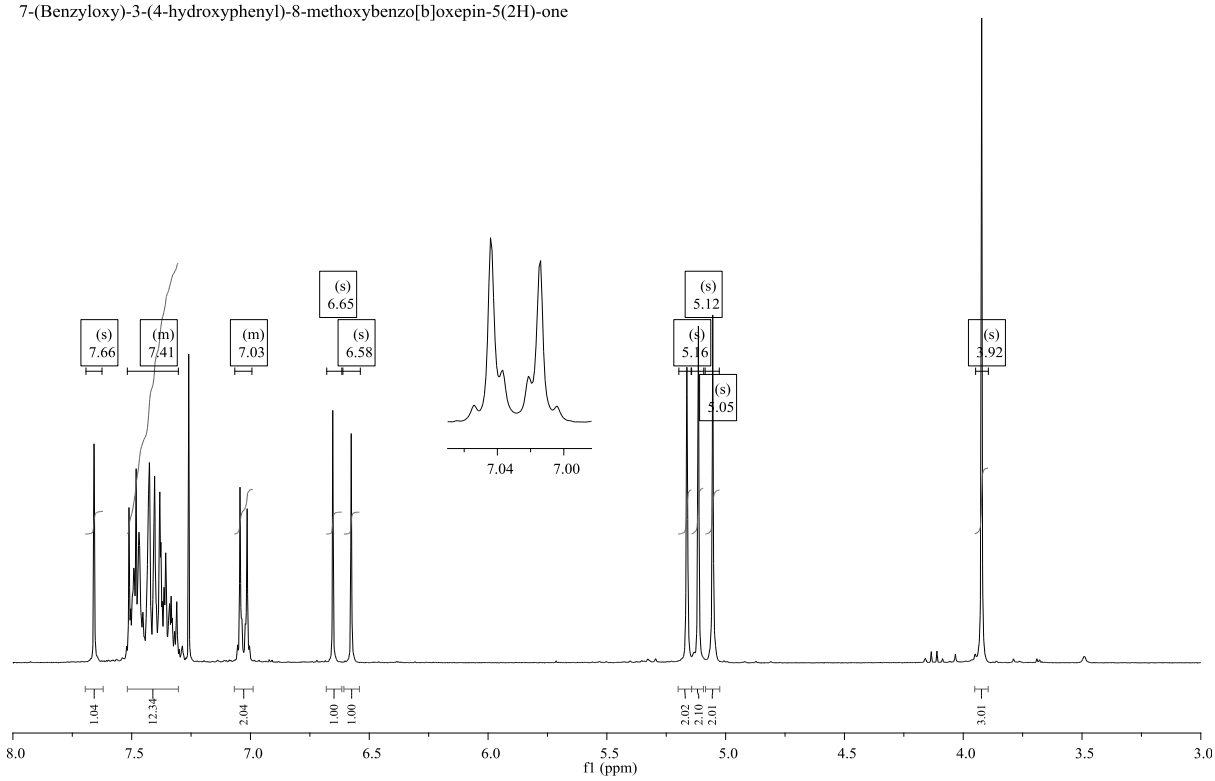
8-(Benzyloxy)-3-(4-(benzyloxy)phenyl)benzo[b]oxepin-5(2H)-one



*7-(Benzyloxy)-3-(4-hydroxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one (**2b**)*

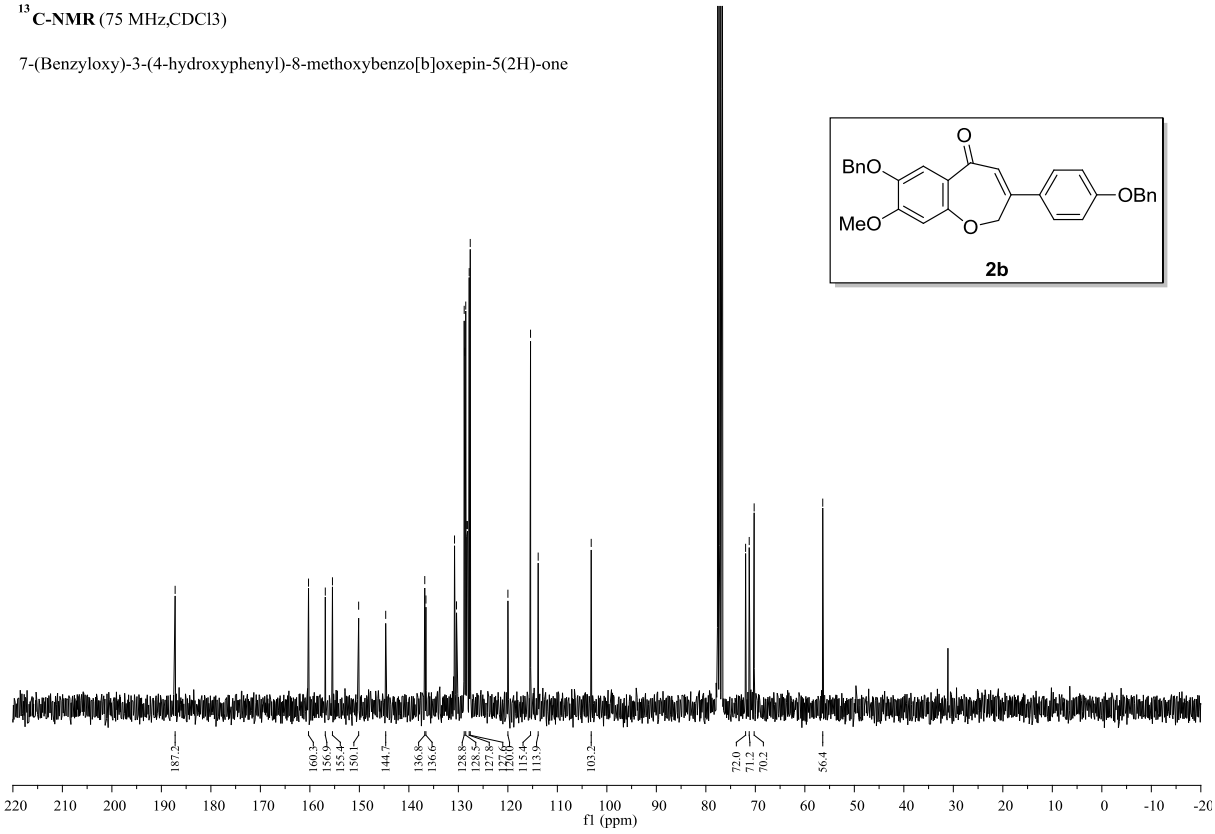
^{1}H-NMR (300 MHz,CDCl3)

7-(Benzyloxy)-3-(4-hydroxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one



^{13}C-NMR (75 MHz,CDCl3)

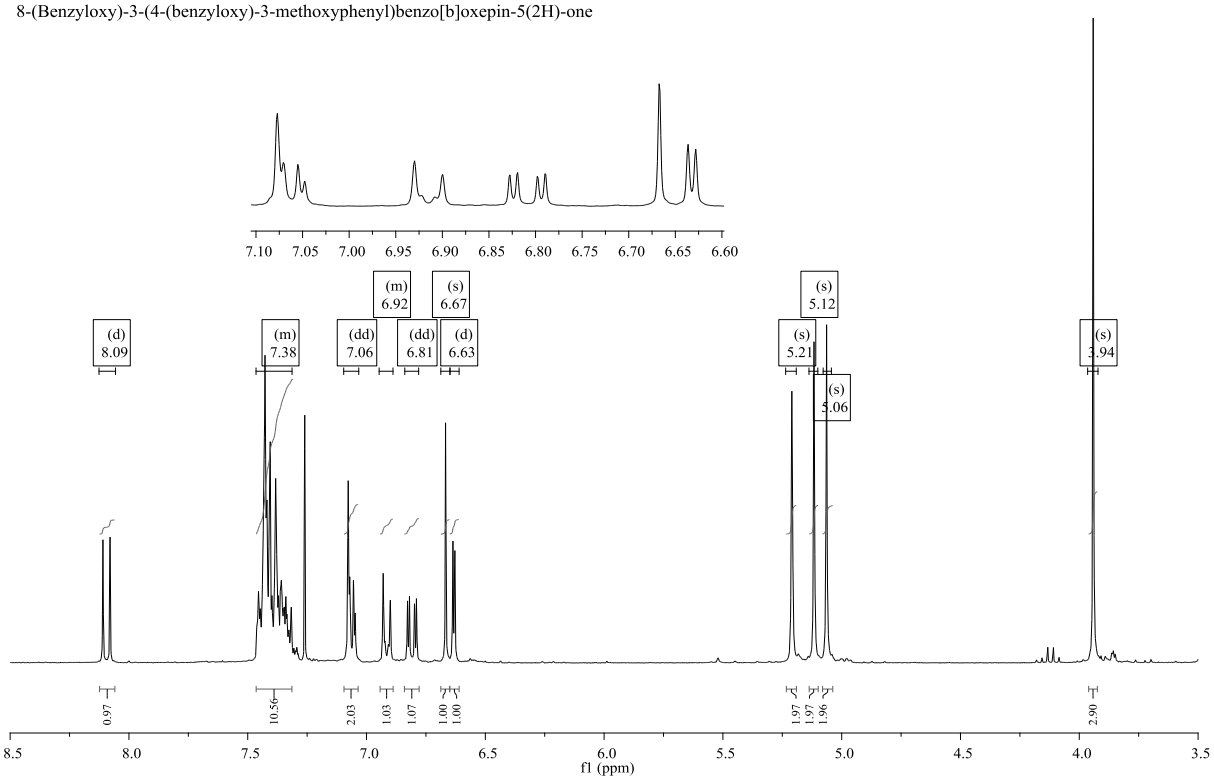
7-(Benzyloxy)-3-(4-hydroxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one



*8-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)benzo[b]oxepin-5(2H)-one (**2c**)*

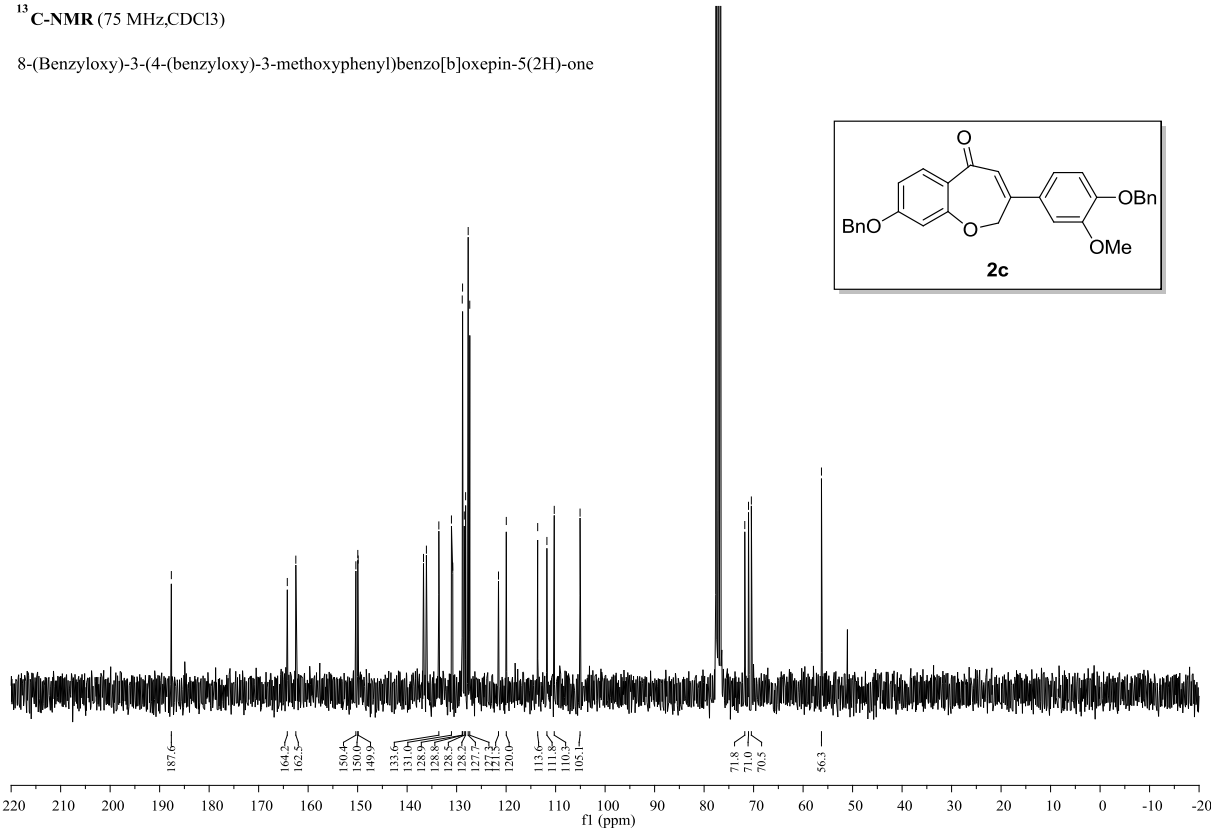
^{1}H-NMR (300 MHz,CDCl3)

8-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)benzo[b]oxepin-5(2H)-one



^{13}C-NMR (75 MHz,CDCl3)

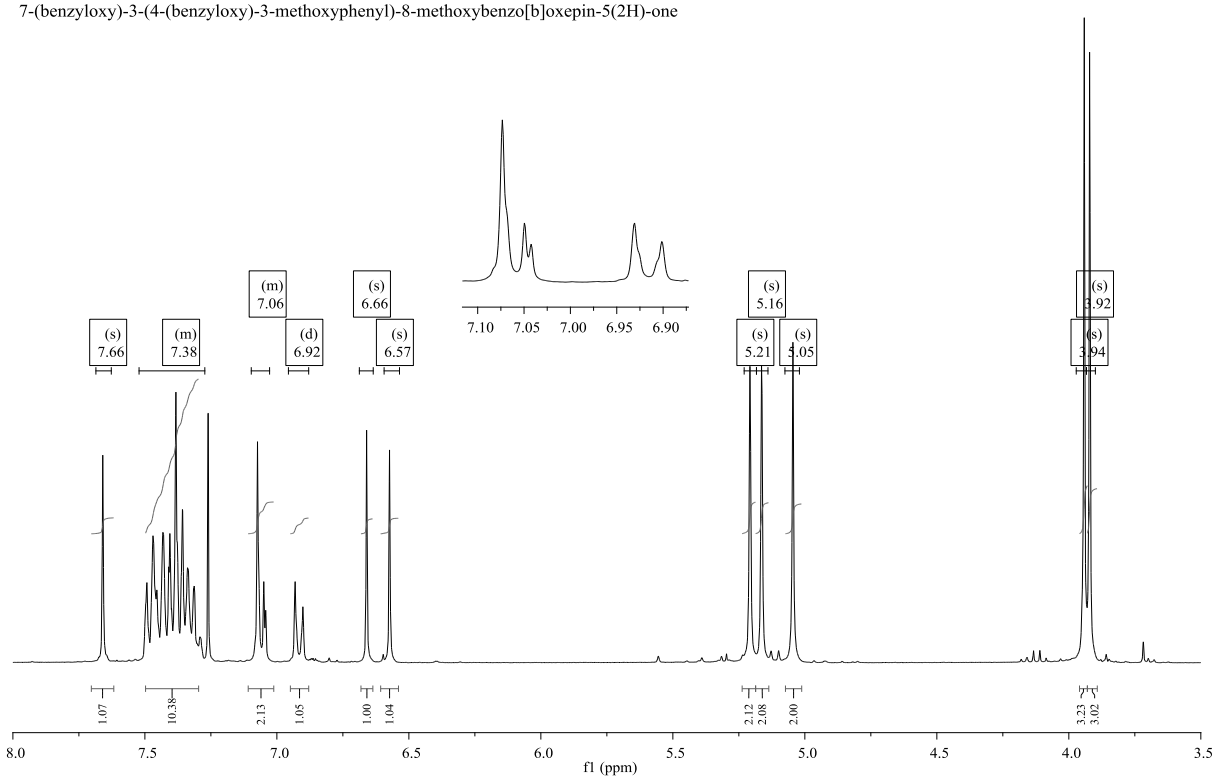
8-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)benzo[b]oxepin-5(2H)-one



*7-(Benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one (**2d**)*

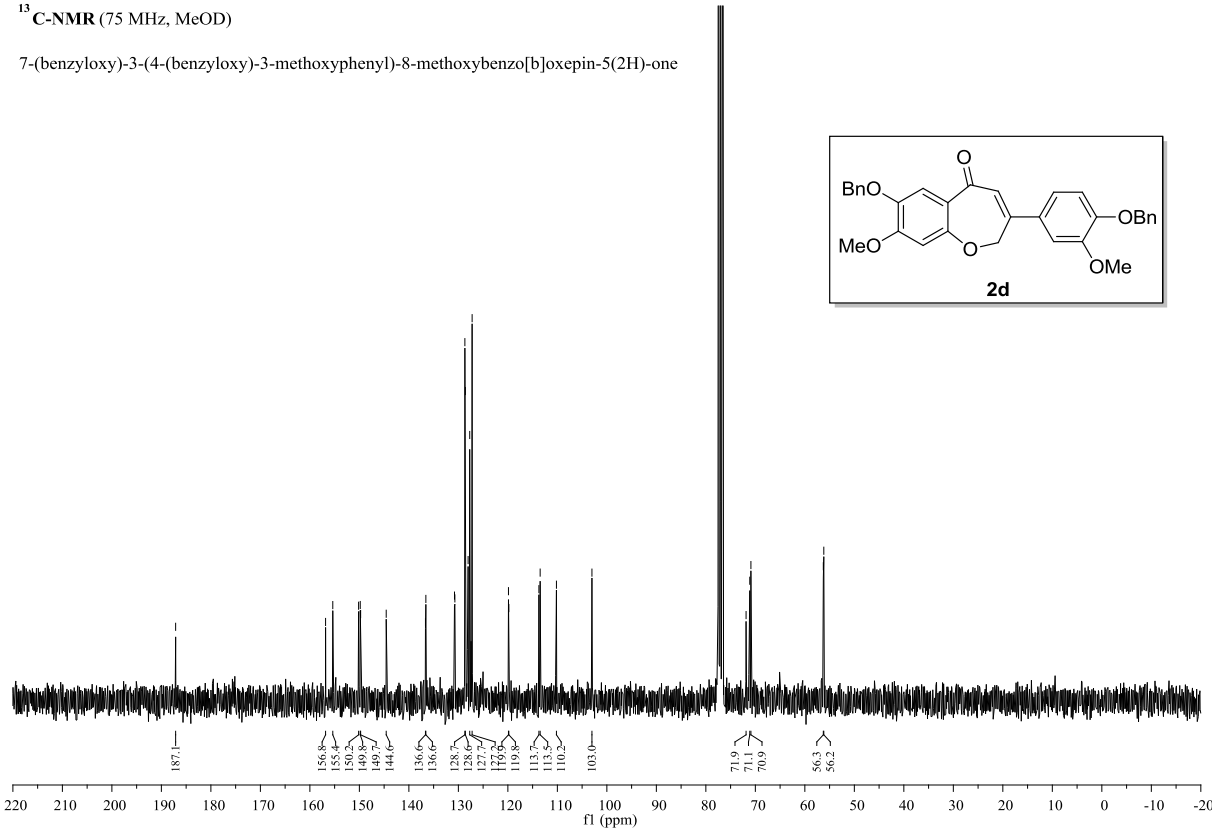
^{1}H-NMR (300 MHz, MeOD)

7-(benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one



^{13}C-NMR (75 MHz, MeOD)

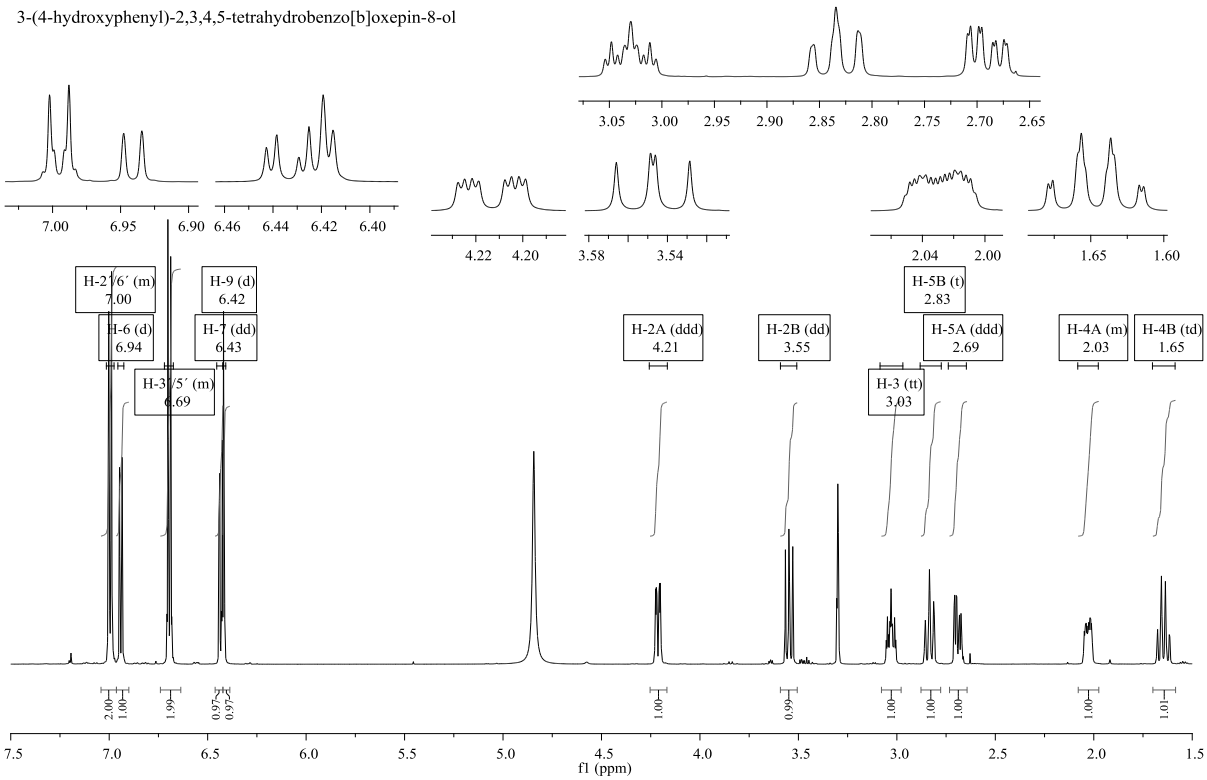
7-(benzyloxy)-3-(4-(benzyloxy)-3-methoxyphenyl)-8-methoxybenzo[b]oxepin-5(2H)-one



*3-(4-Hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-8-ol (**16a**)*

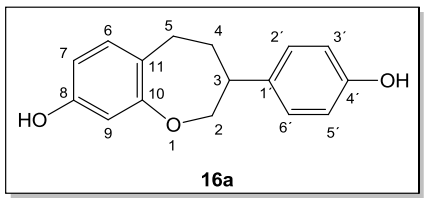
^{1}H-NMR (600 MHz,MeOD)

3-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-8-ol



^{13}C-NMR (151 MHz,MeOD)

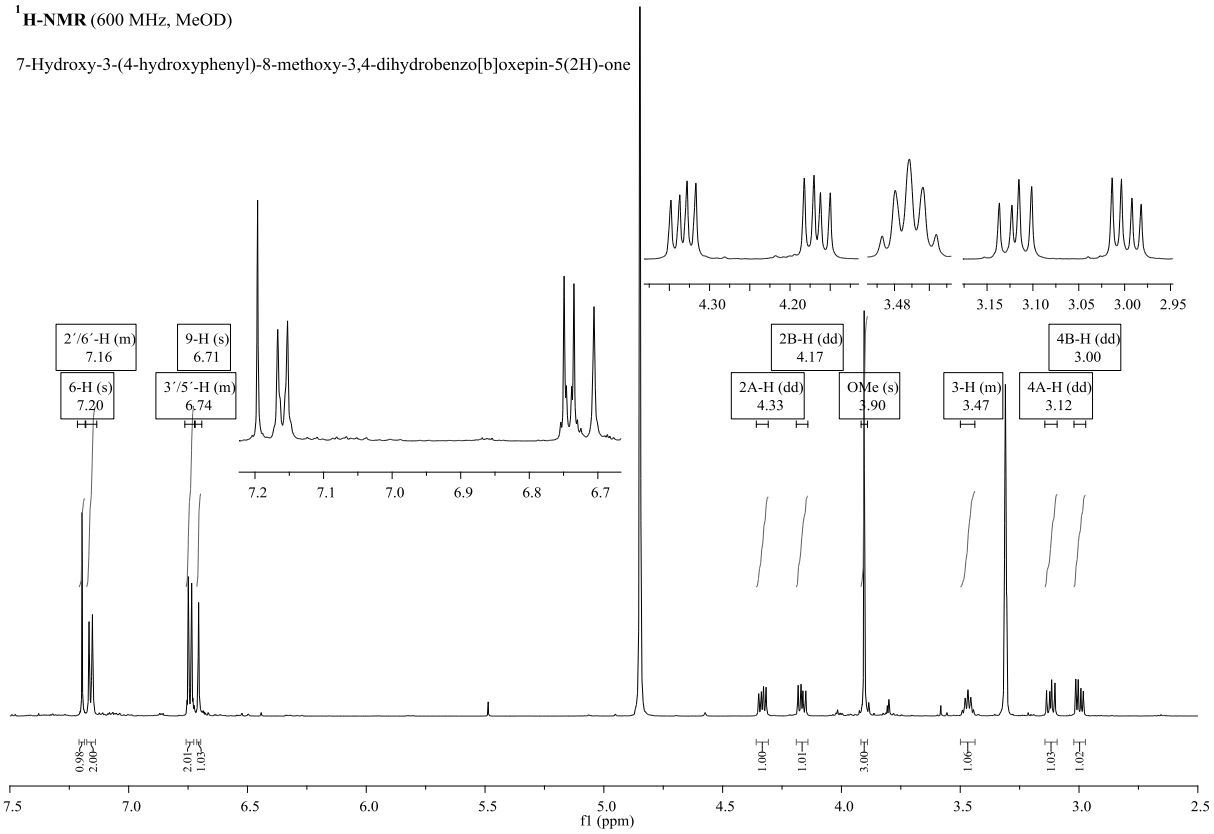
3-(4-hydroxyphenyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-8-ol



*7-Hydroxy-3-(4-hydroxyphenyl)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one (**11b**)*

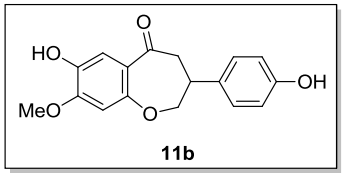
^{1}H-NMR (600 MHz, MeOD)

7-Hydroxy-3-(4-hydroxyphenyl)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one

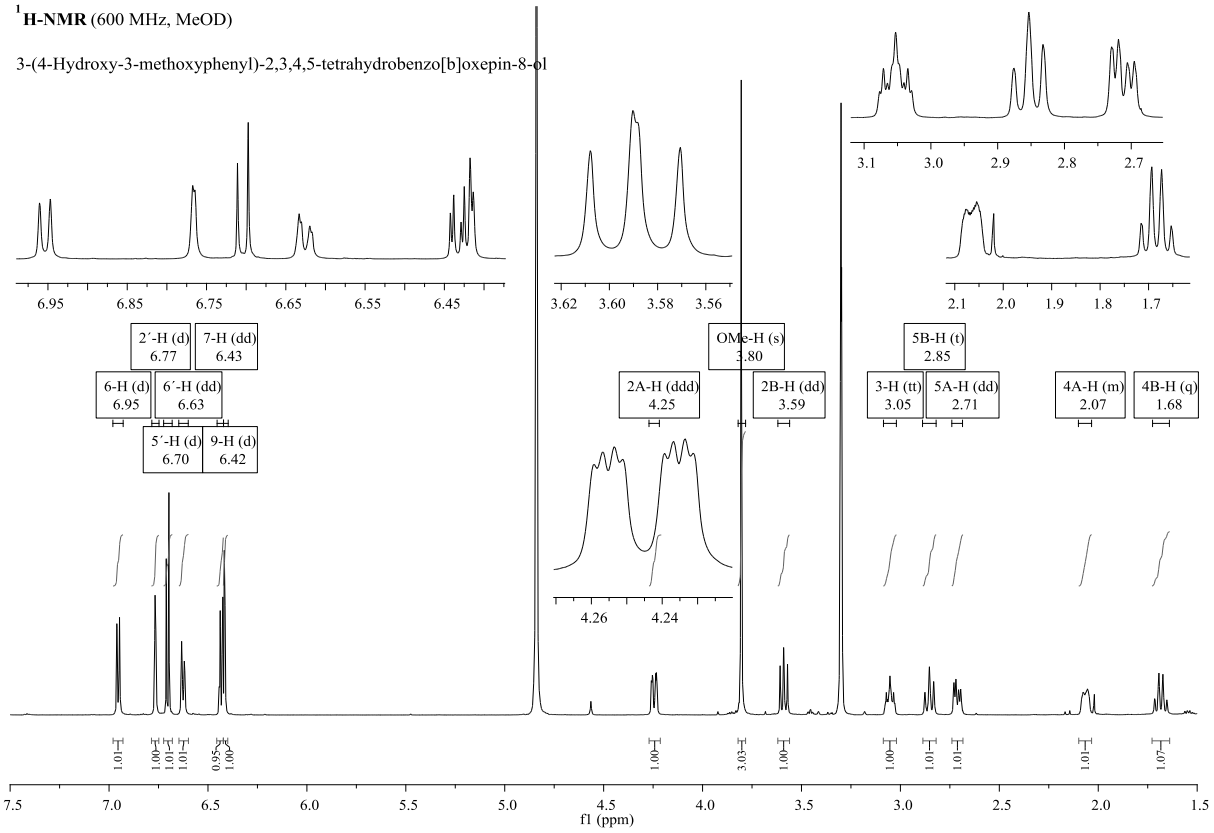


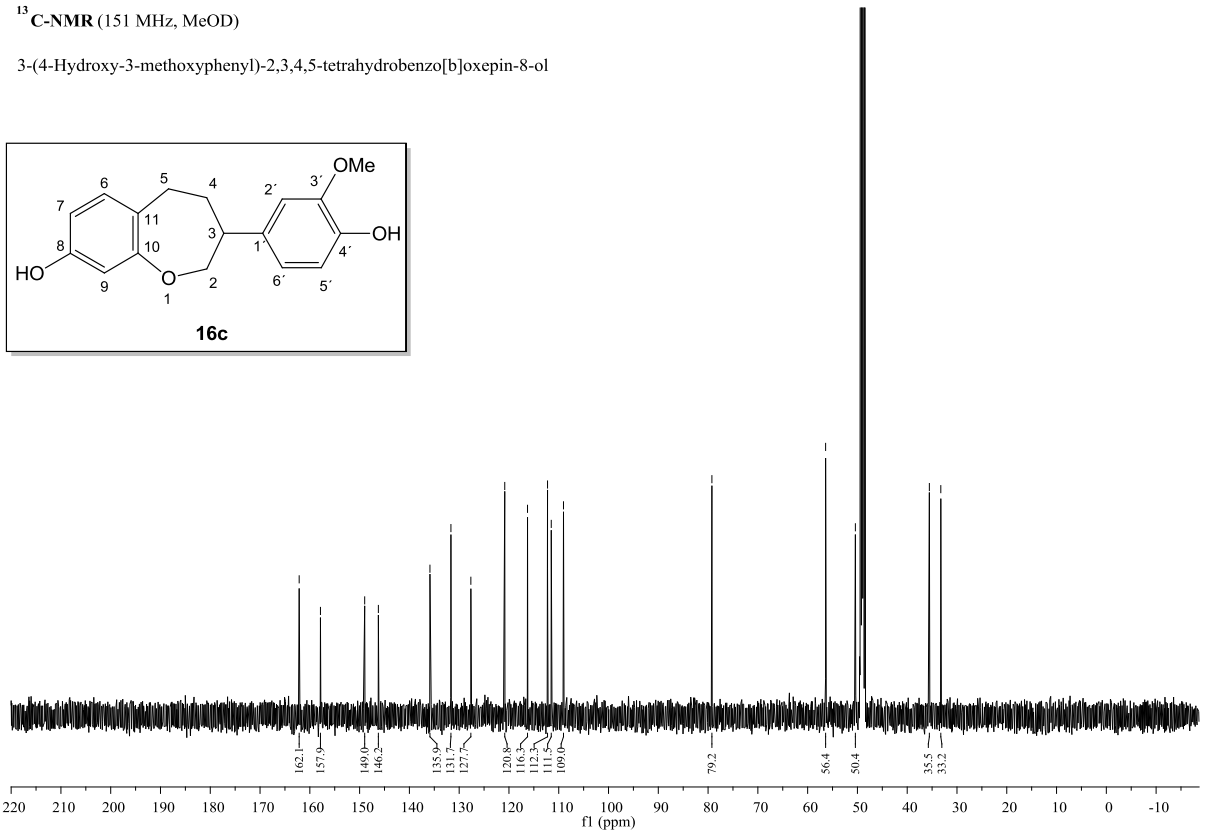
^{13}C-NMR (151 MHz, MeOD)

7-Hydroxy-3-(4-hydroxyphenyl)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one

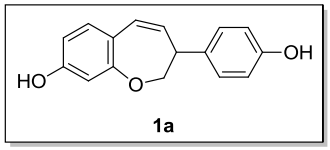


*3-(4-Hydroxy-3-methoxyphenyl)-2,3,4,5-tetrahydrobenzo[b]oxepin-8-ol (**16c**)*



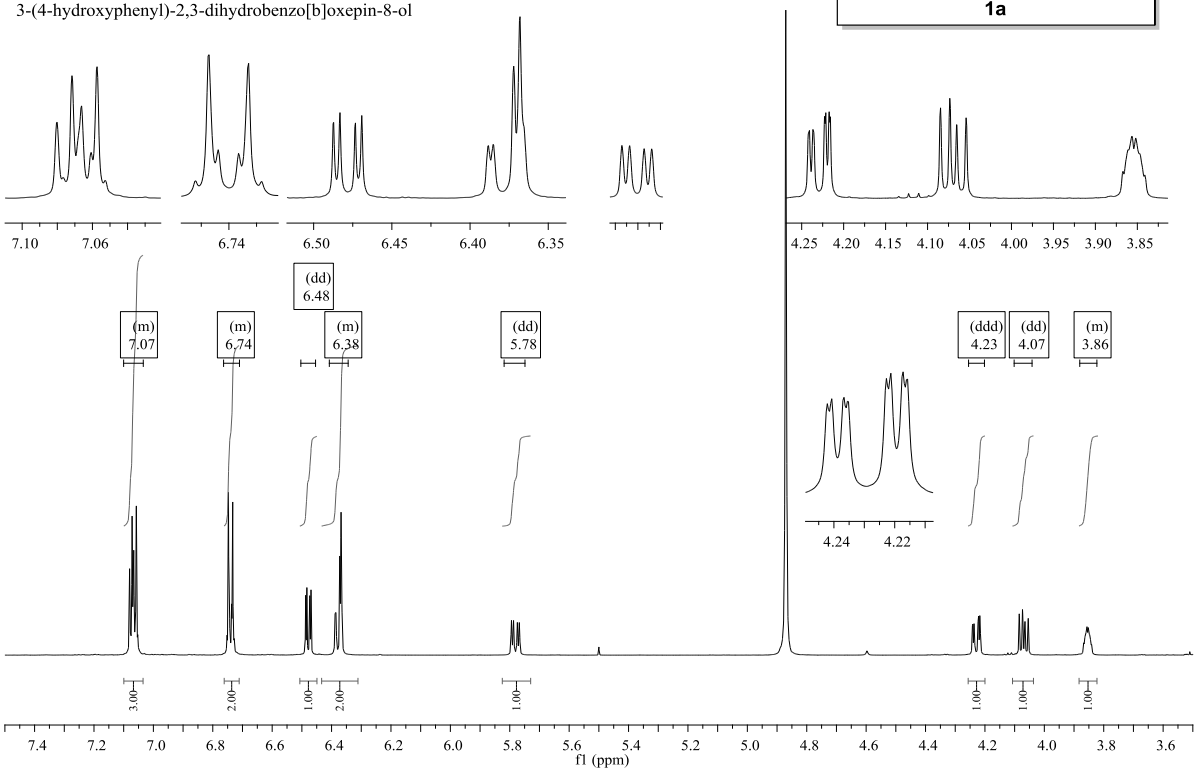


*3-(4-Hydroxyphenyl)-2,3-dihydrobenzo[b]oxepin-8-ol (**1a**)*



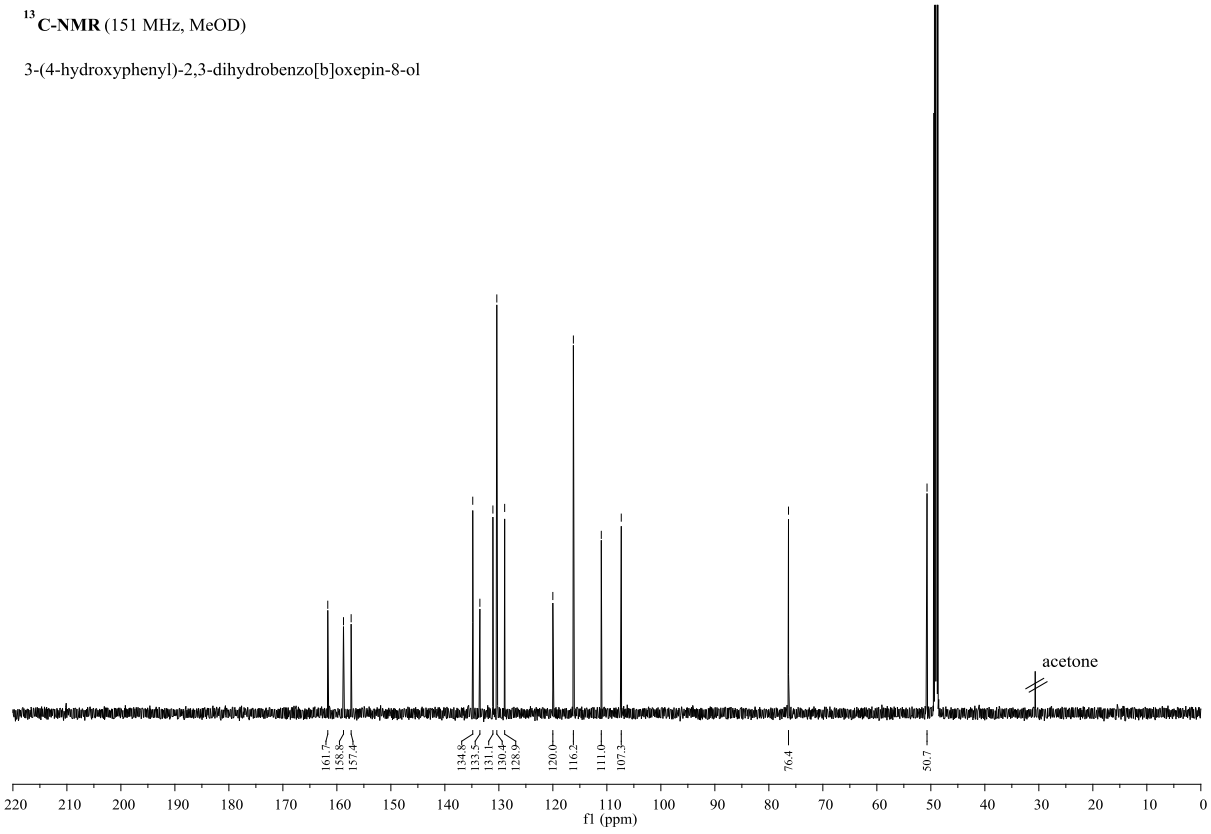
^{1}H-NMR (600 MHz, MeOD)

3-(4-hydroxyphenyl)-2,3-dihydrobenzo[b]oxepin-8-ol



^{13}C-NMR (151 MHz, MeOD)

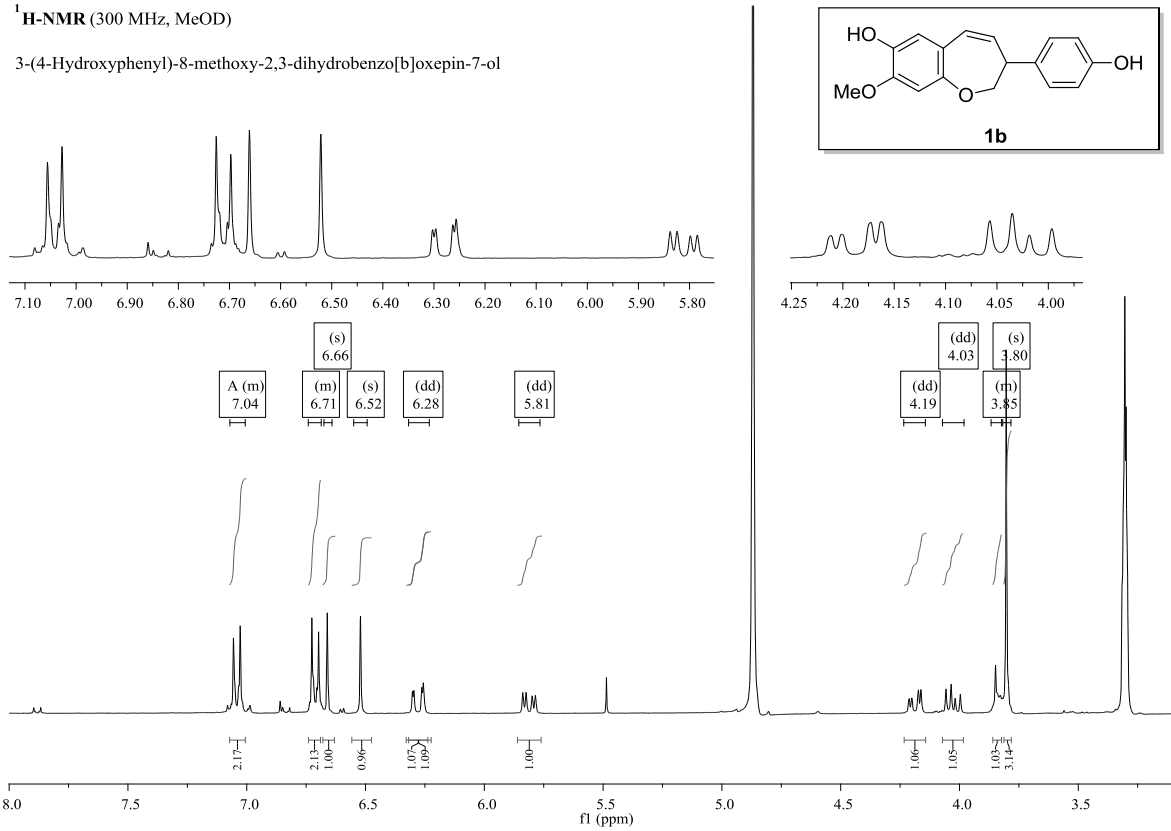
3-(4-hydroxyphenyl)-2,3-dihydrobenzo[b]oxepin-8-ol



*3-(4-Hydroxyphenyl)-8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol (**1b**)*

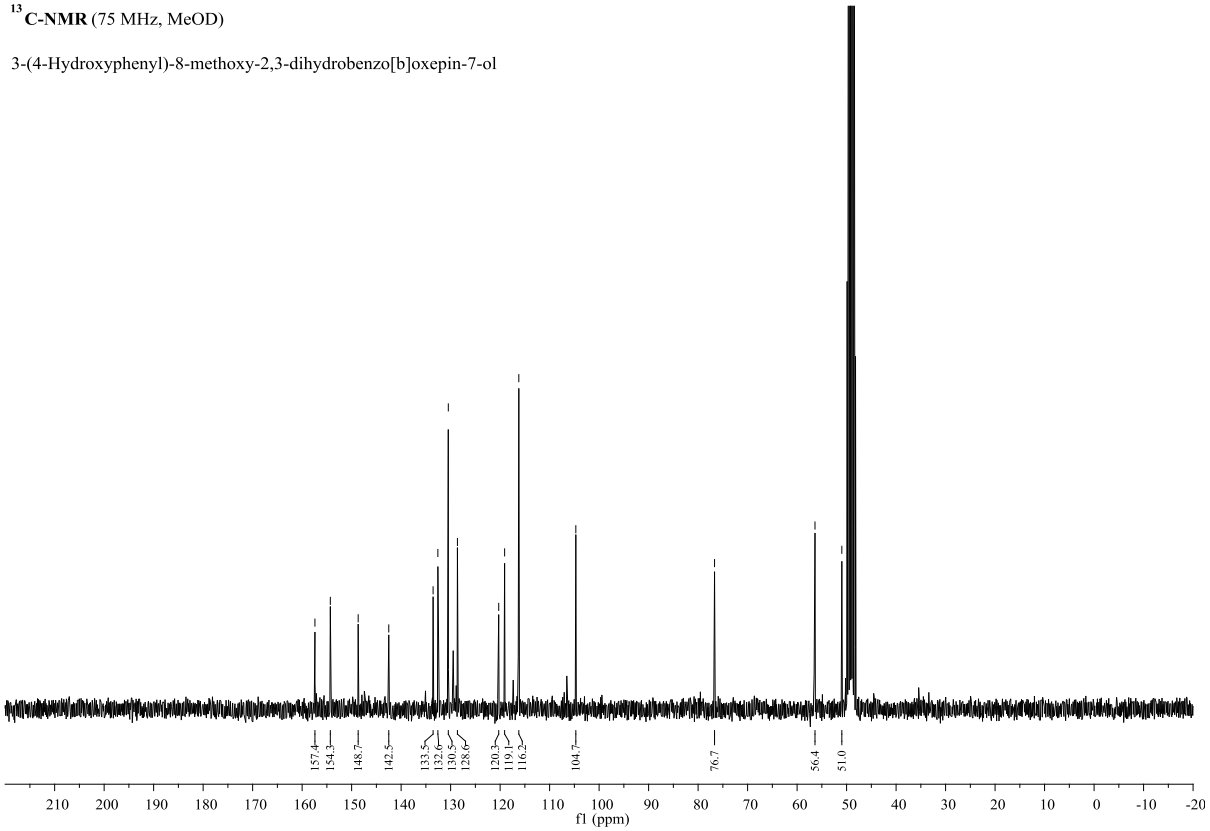
^{1}H-NMR (300 MHz, MeOD)

3-(4-Hydroxyphenyl)-8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol



^{13}C-NMR (75 MHz, MeOD)

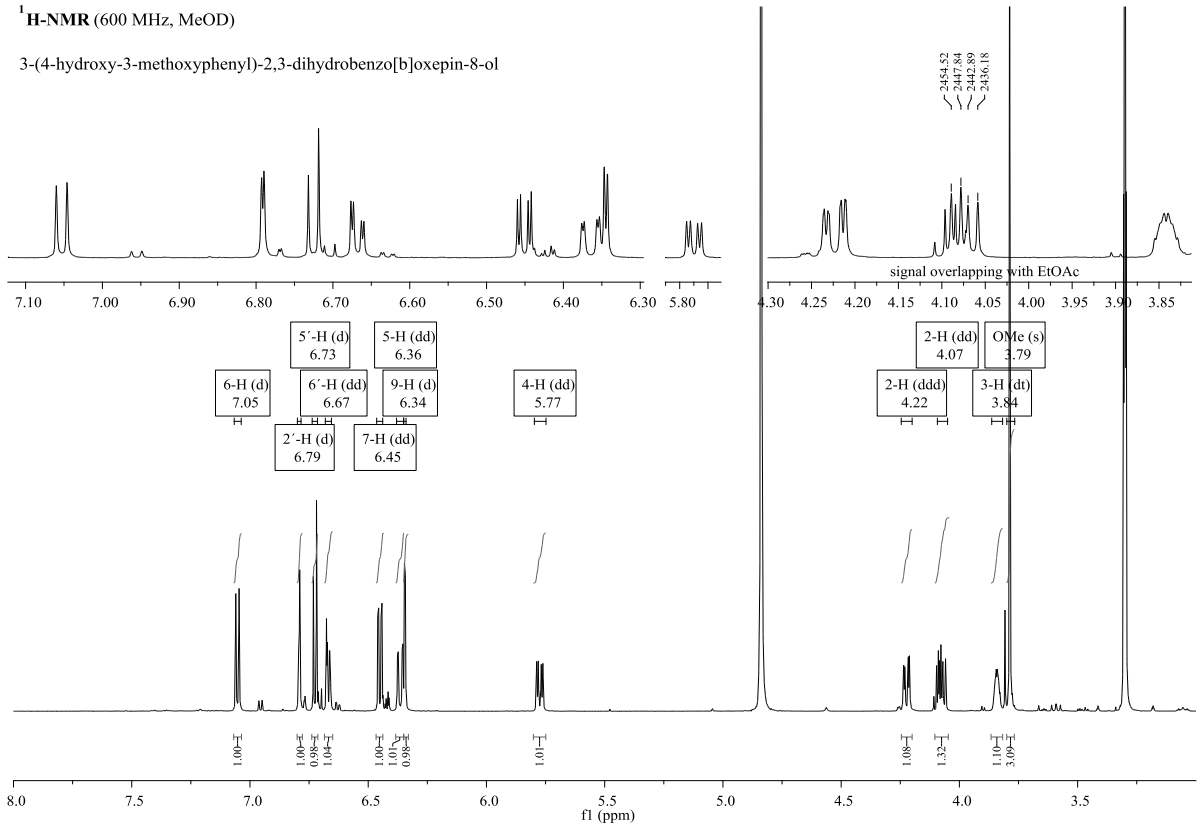
3-(4-Hydroxyphenyl)-8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol



*3-(4-Hydroxy-3-methoxyphenyl)-2,3-dihydrobenzo[b]oxepin-8-ol (**1c**)*

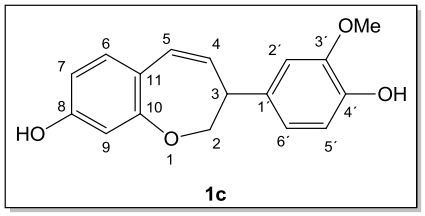
^{1}H-NMR (600 MHz, MeOD)

3-(4-hydroxy-3-methoxyphenyl)-2,3-dihydrobenzo[b]oxepin-8-ol

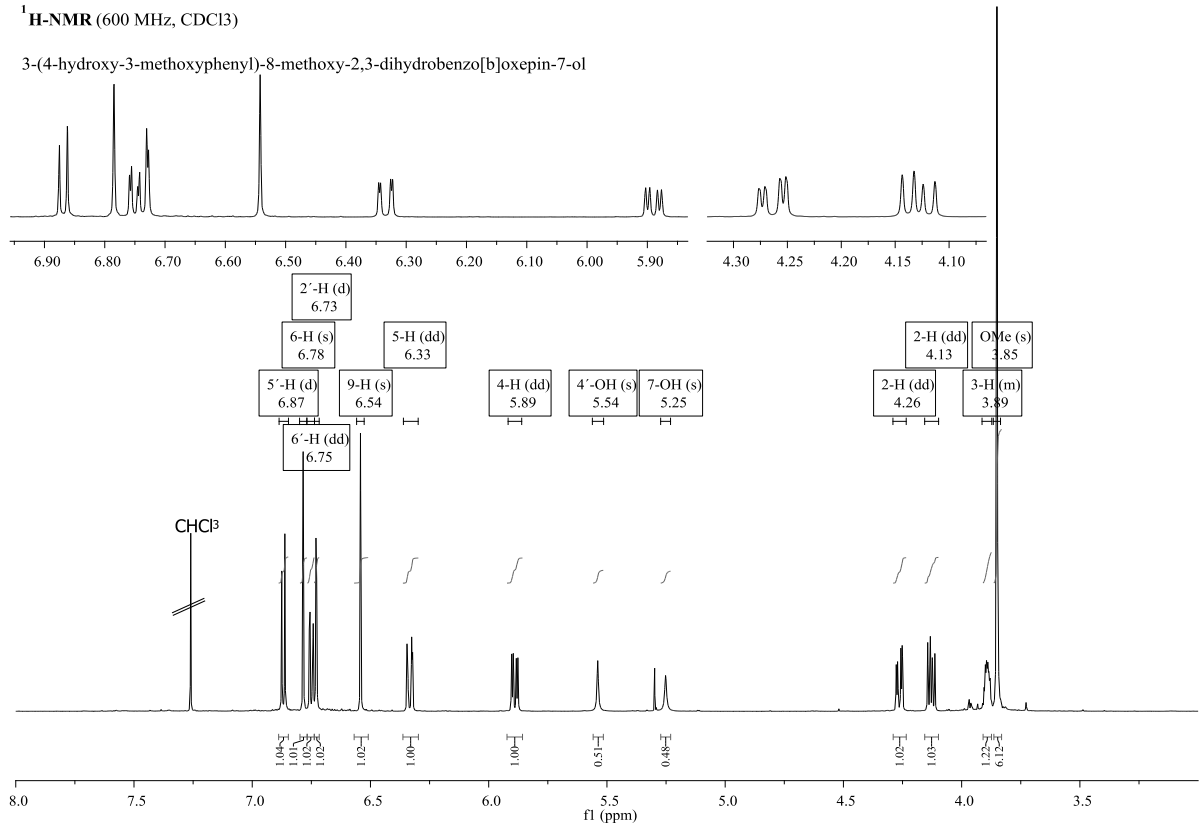


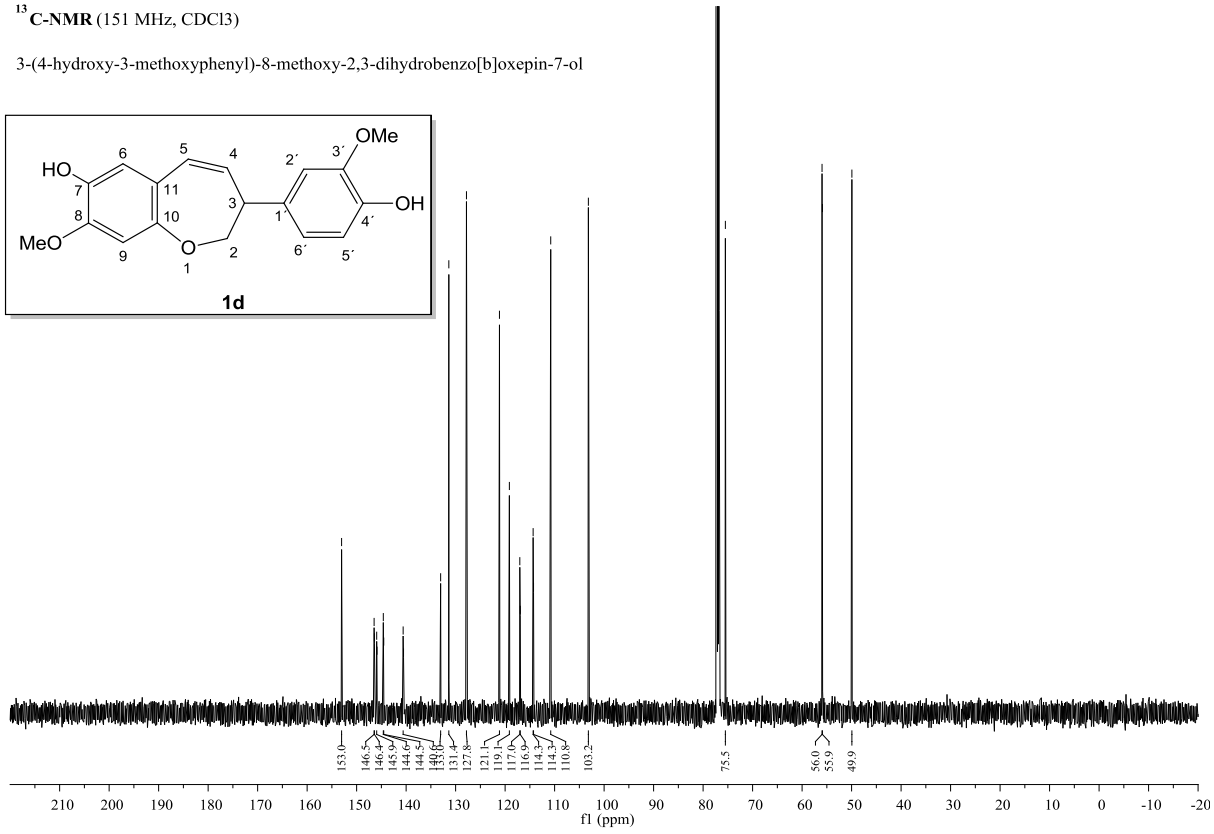
^{13}C-NMR (151 MHz, MeOD)

3-(4-hydroxy-3-methoxyphenyl)-2,3-dihydrobenzo[b]oxepin-8-ol

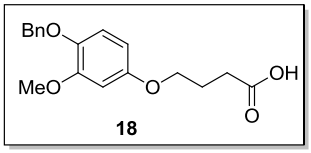


*3-(4-Hydroxy-3-methoxyphenyl)-8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol (**1d**)*



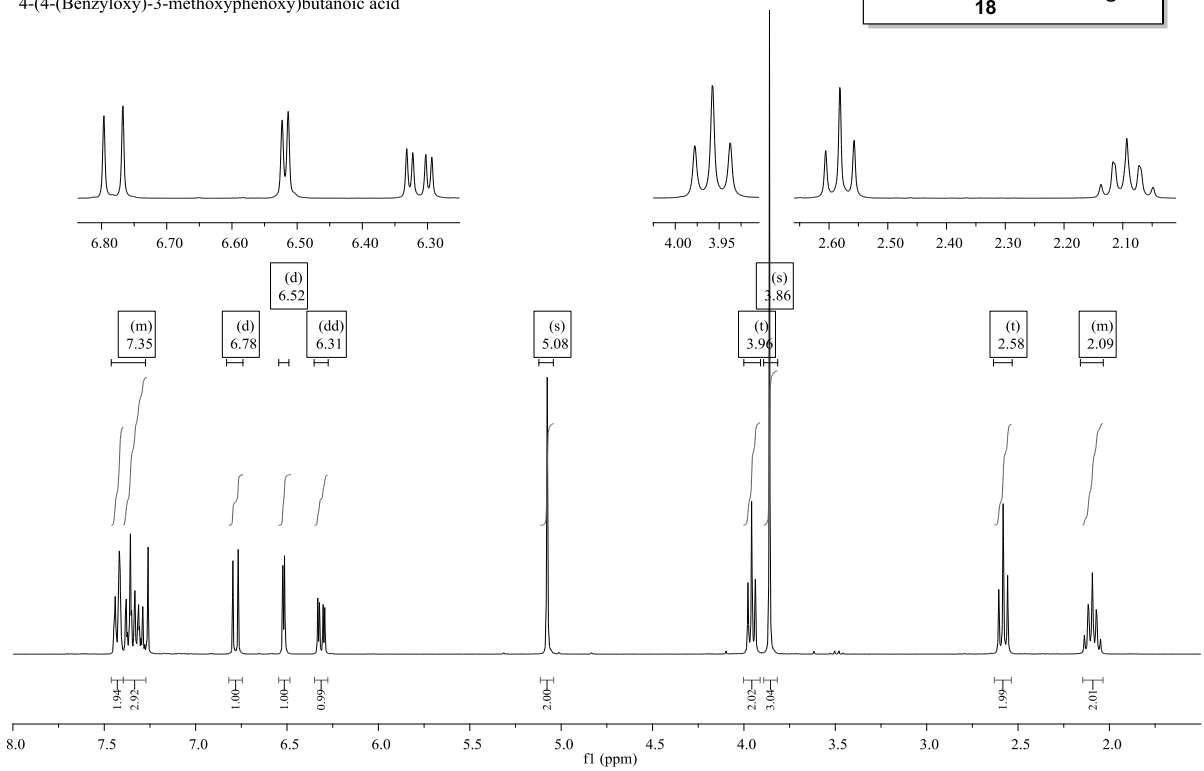


*4-(4-(Benzyloxy)-3-methoxyphenoxy)butanoic acid (**18**)*



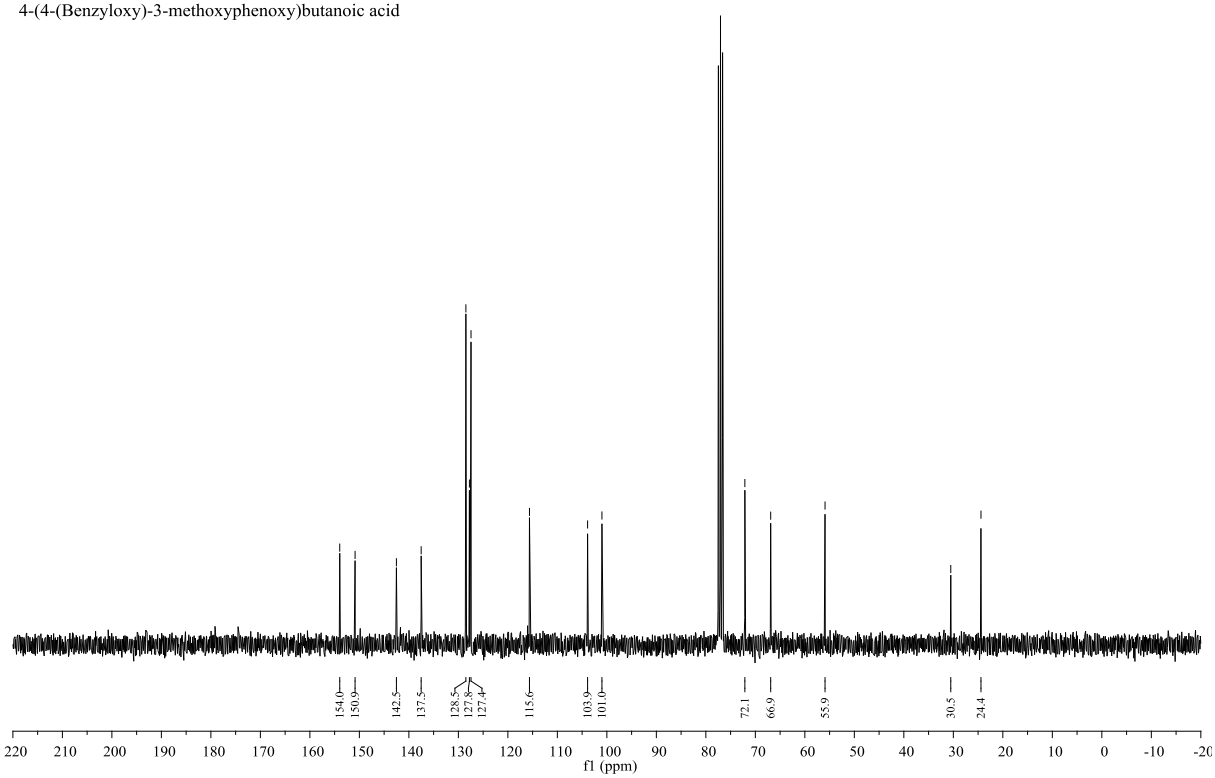
[1]H-NMR (300 MHz, CDCl3)

4-(4-(Benzyloxy)-3-methoxyphenoxy)butanoic acid

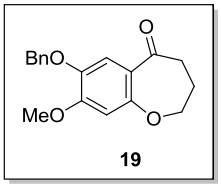


[13]C-NMR (75 MHz, CDCl3)

4-(4-(Benzyloxy)-3-methoxyphenoxy)butanoic acid

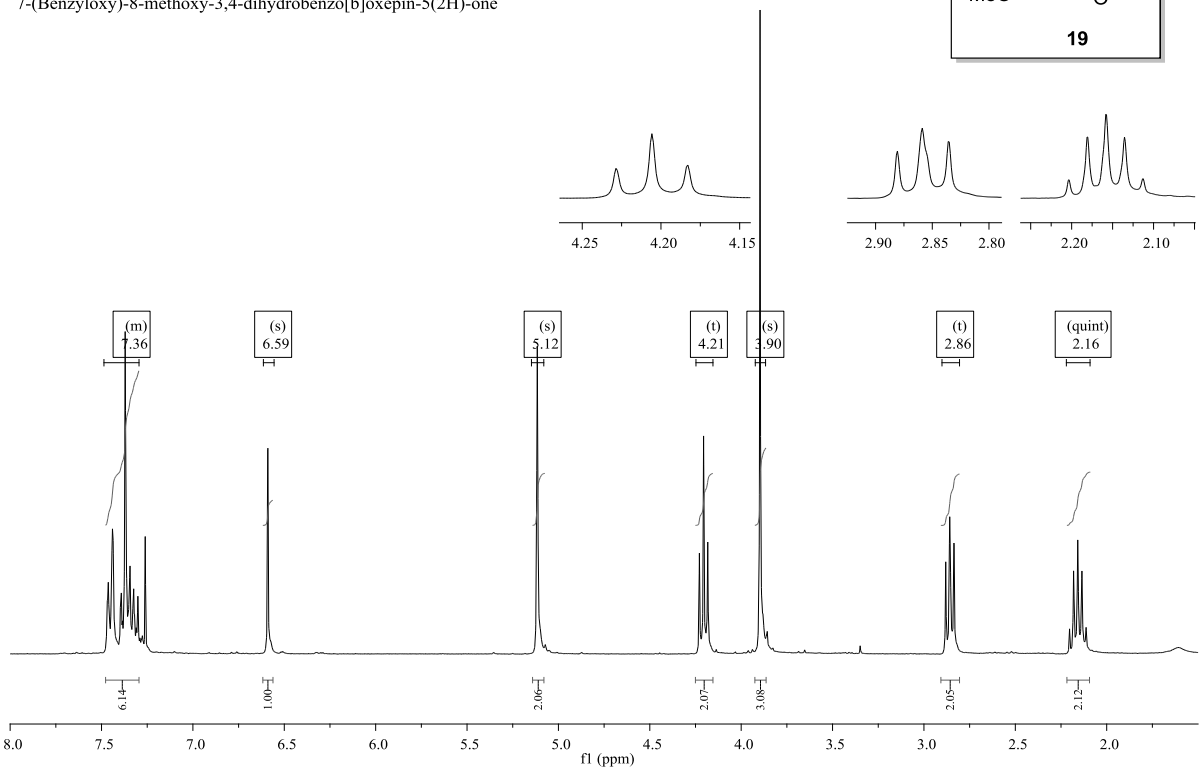


*7-(Benzyloxy)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one (**19**)*



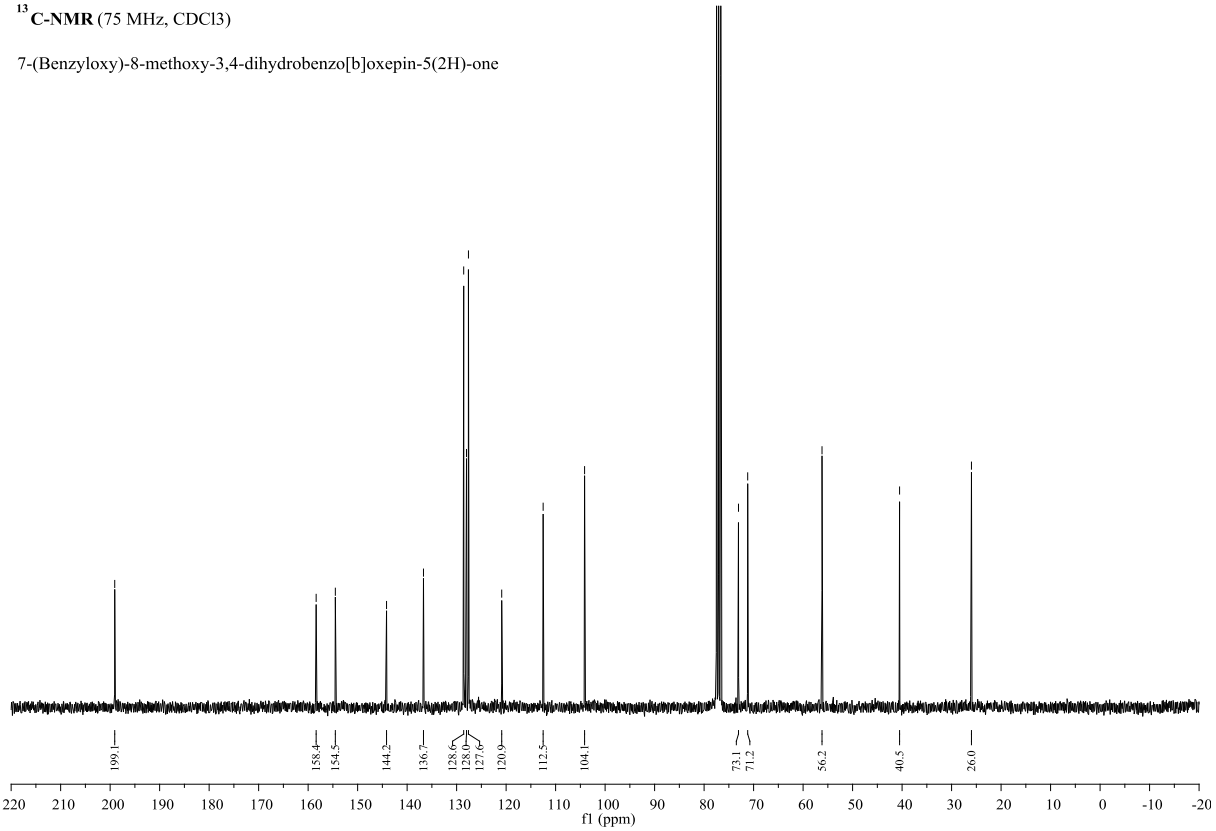
^{1}H-NMR (300 MHz, CDCl3)

7-(Benzyloxy)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one

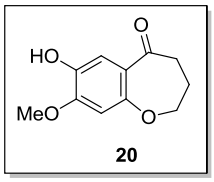


^{13}C-NMR (75 MHz, CDCl3)

7-(Benzyloxy)-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one

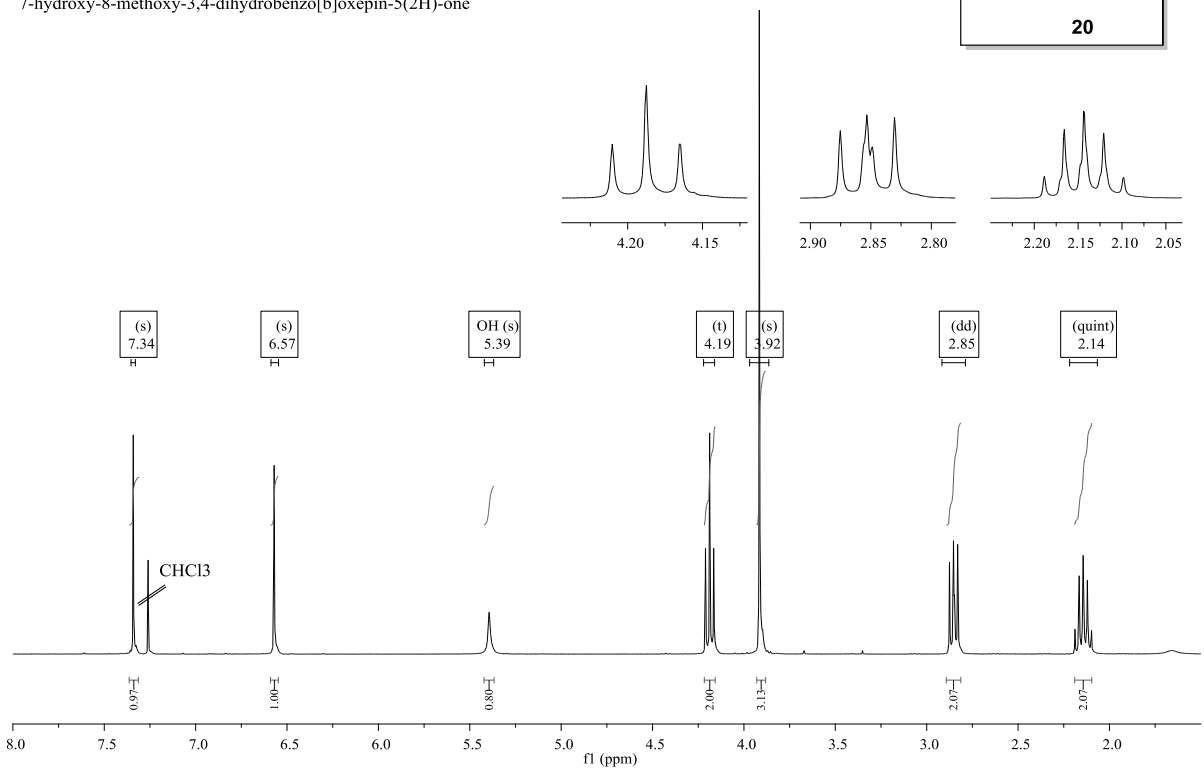


*7-Hydroxy-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one (**20**)*



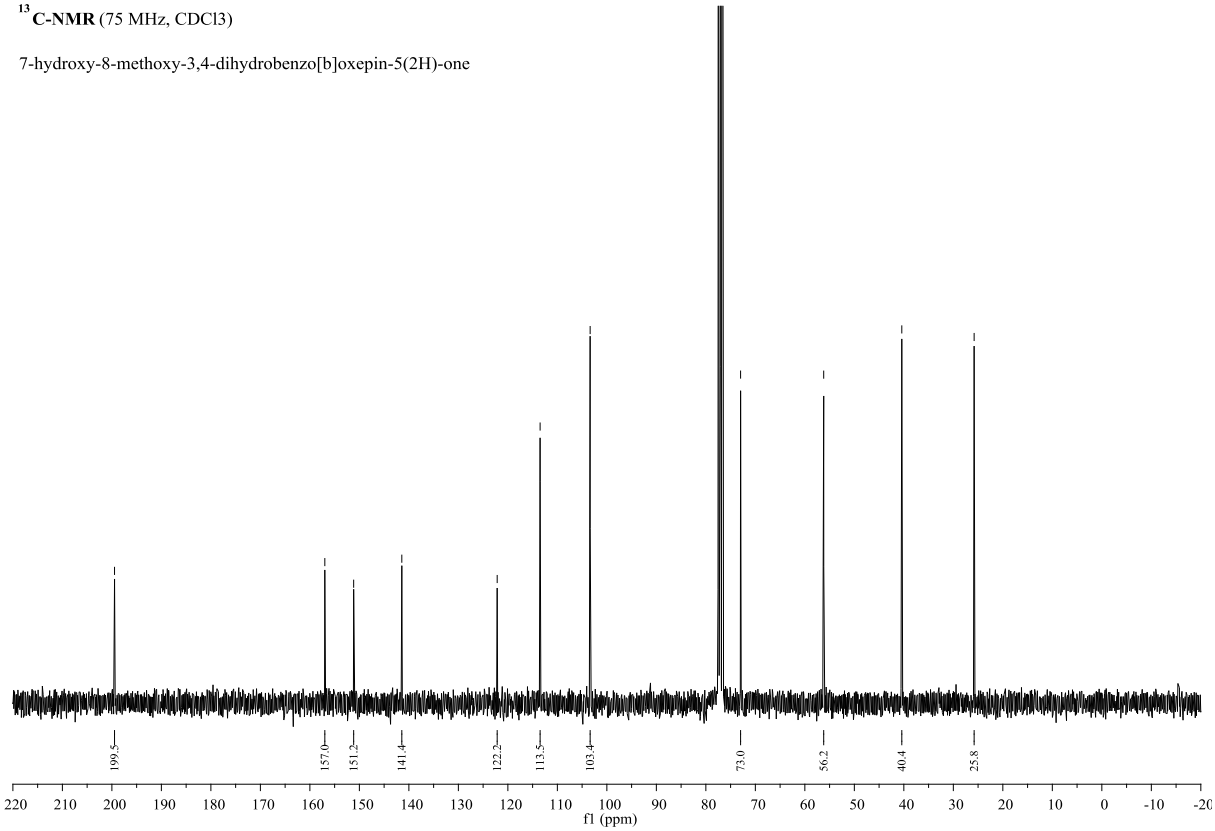
[1]H-NMR (300 MHz, CDCl3)

7-hydroxy-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one

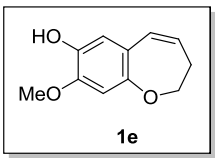


[13]C-NMR (75 MHz, CDCl3)

7-hydroxy-8-methoxy-3,4-dihydrobenzo[b]oxepin-5(2H)-one

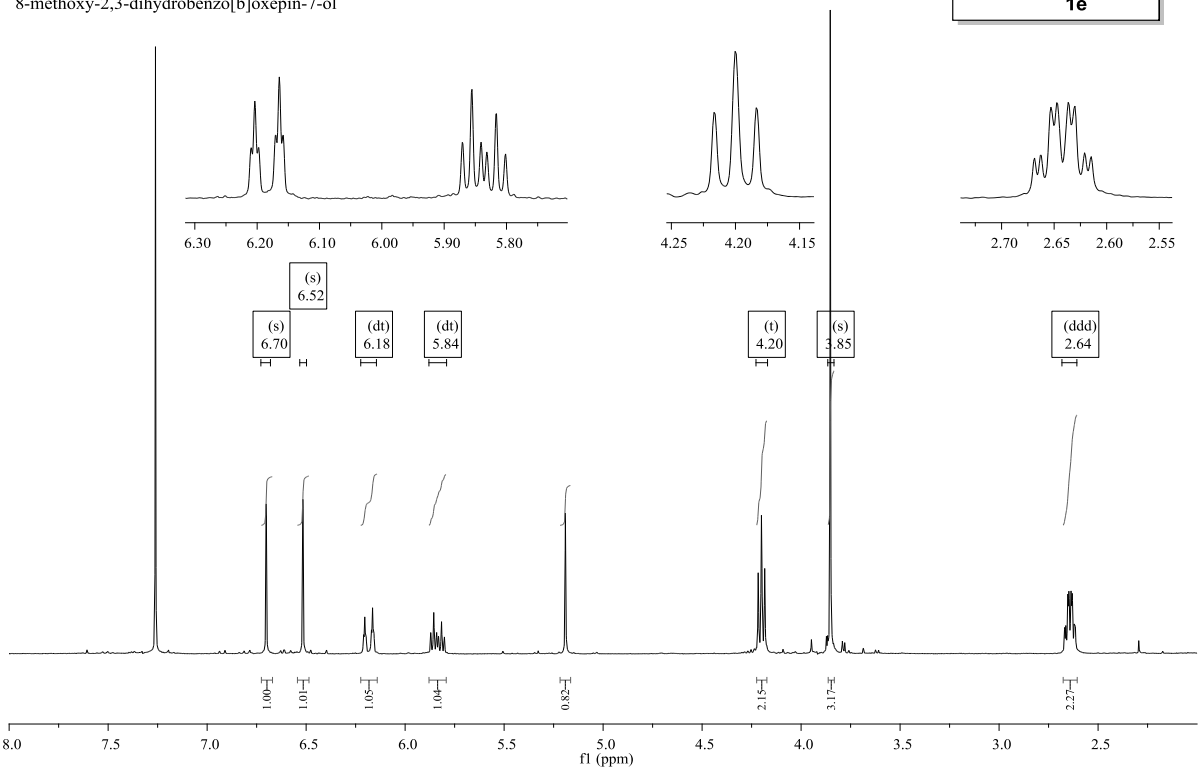


*8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol (**1e**)*



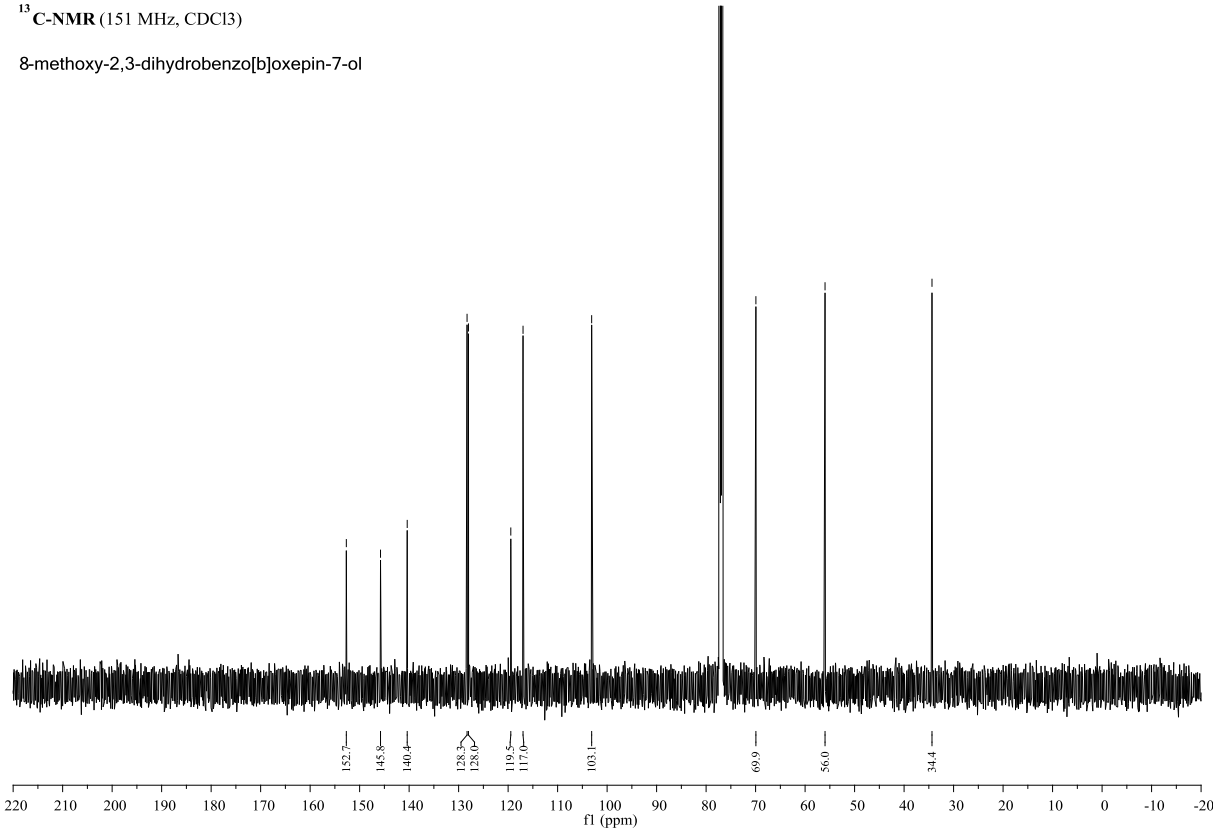
[1]H-NMR (300 MHz, CDCl3)

8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol



[13]C-NMR (151 MHz, CDCl3)

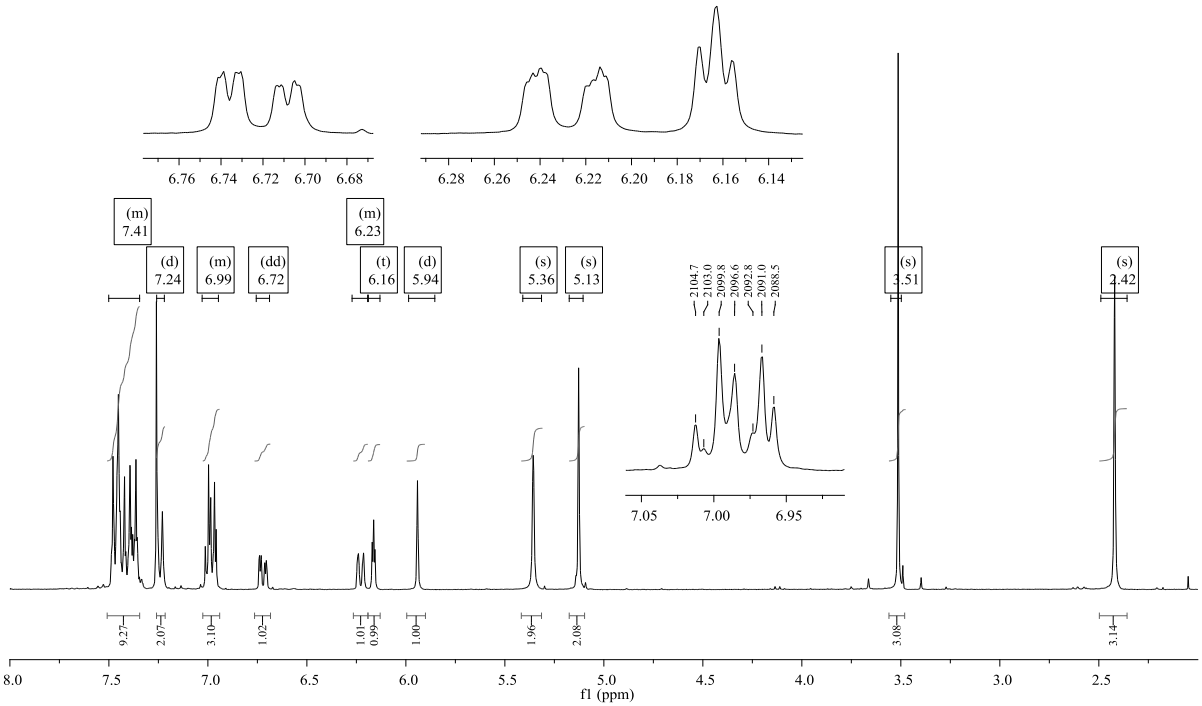
8-methoxy-2,3-dihydrobenzo[b]oxepin-7-ol



*3-(4-(Benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)but-2-enoic acid (**24**)*

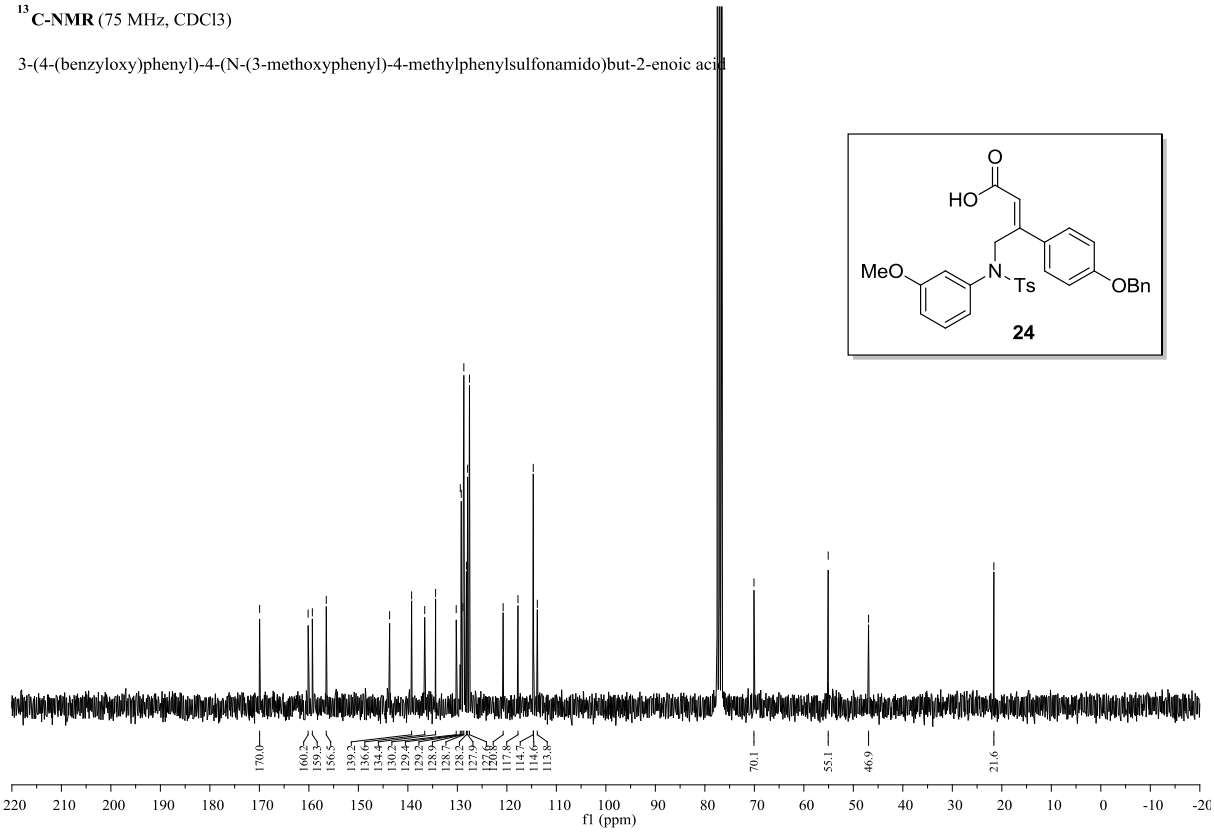
^{1}H-NMR (300 MHz, CDCl3)

3-(4-(benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)but-2-enoic acid



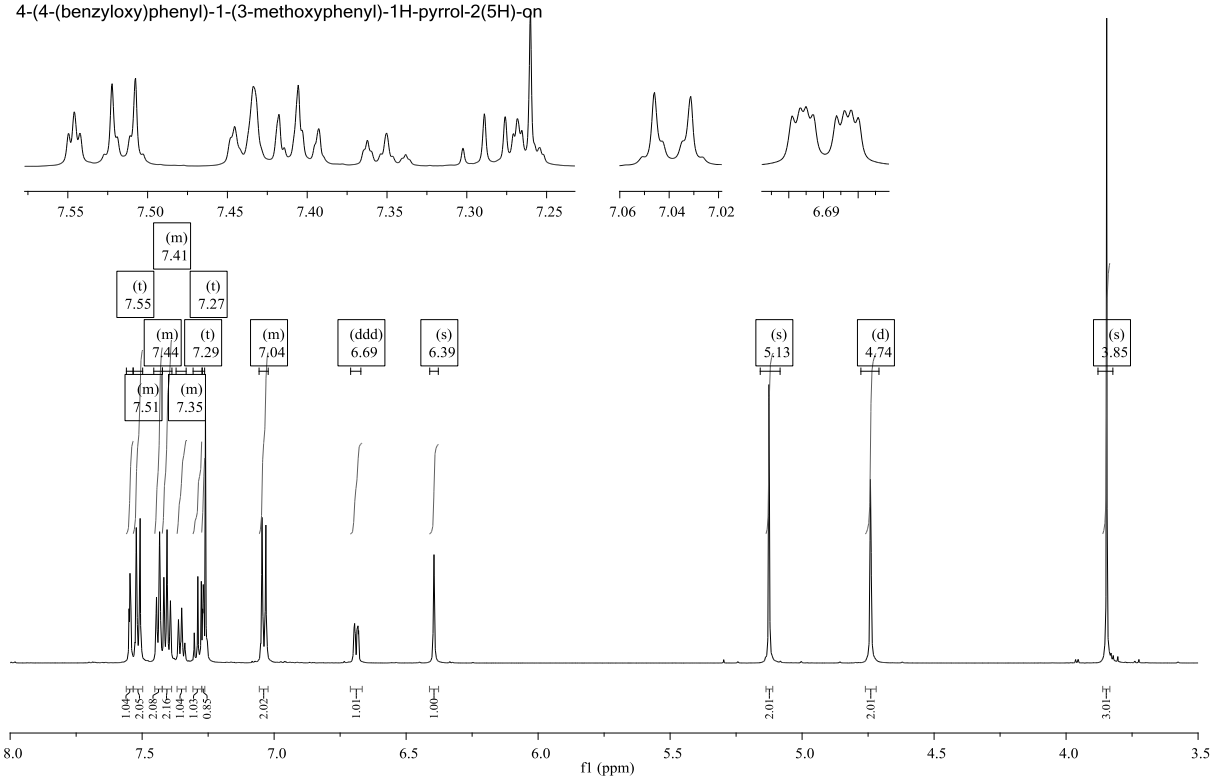
^{13}C-NMR (75 MHz, CDCl3)

3-(4-(benzyloxy)phenyl)-4-(N-(3-methoxyphenyl)-4-methylphenylsulfonamido)but-2-enoic acid

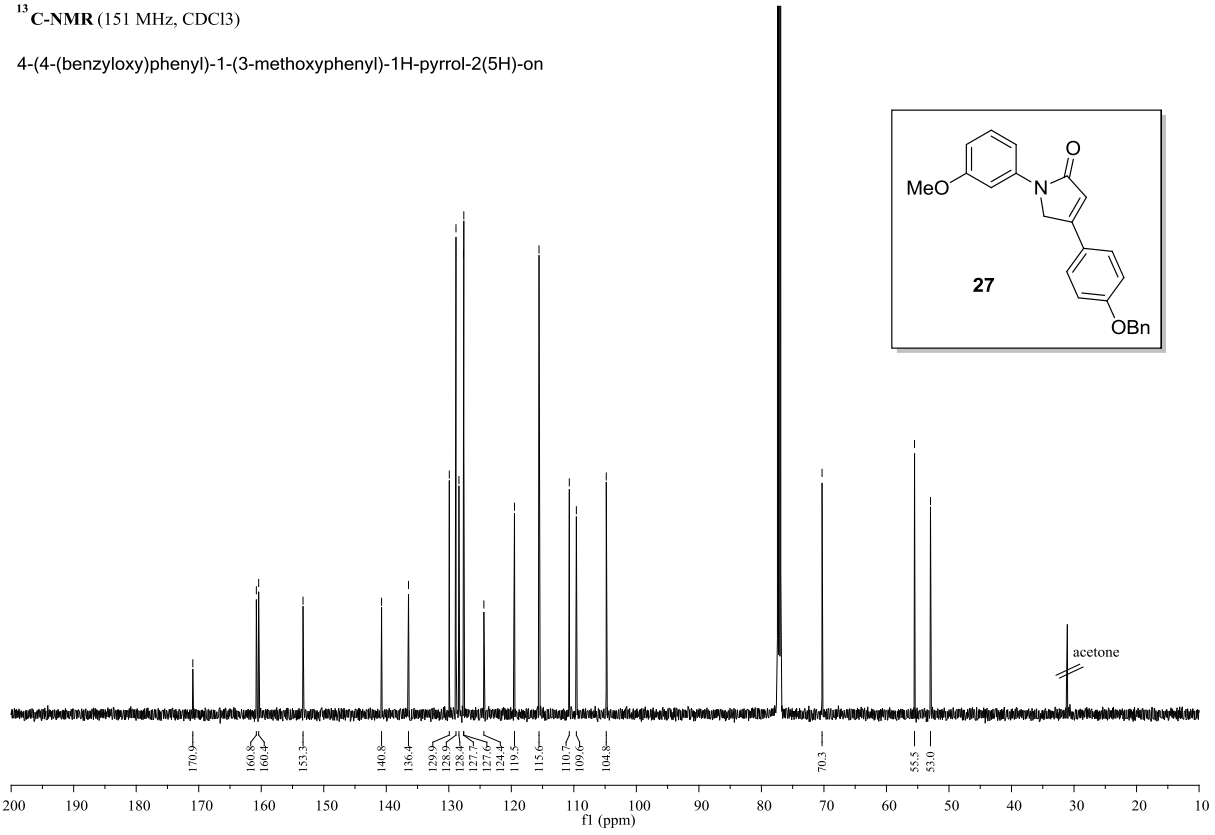


*4-(4-(Benzyloxy)phenyl)-1-(3-methoxyphenyl)-1H-pyrrol-2(5H)-one (**27**)*

^{1}H-NMR (600 MHz, CDCl3)



^{13}C-NMR (151 MHz, CDCl3)



6.3 List of Presentations and Publications

Presentations

24.09. – 26.09.2012 **ORCHEM 2012** in Weimar
Poster-presentation: "Synthesis of Ruscozepine A and B, novel natural products isolated from Butcher´s Broom"

26.08. – 30.08.2012 **4th EuCheMS Chemistry Congress** in Prague (Czech Republic)
Poster-presentation: "Synthesis of Ruscozepine A and B, novel natural products isolated from Butcher´s Broom"

29.08. – 02.09.2010 **3rd EuCheMS Chemistry Congress** in Nurnberg
Poster-presentation: "Application of chiral metal complexes for the investigation of a novel asymmetric Nitro-Aldol-(Henry)-Reaction"

14.03. – 17.03.2010 **Frontiers in Medicinal Chemistry** in Munster
Poster-presentation: "Application of metal complex catalyzed stereoselective reactions for total synthesis of bioactive natural products"

30.08. – 02.09.2009 **GDCh Wissenschaftsforum** in Frankfurt a. Main
Poster-presentation: "Towards the total synthesis of a new fungal metabolite"

Publications

„Reduction of benzylic alcohols and α-hydroxycarbonyl compounds by hydriodic acid in a biphasic reaction medium" Dobmeier, M.; Herrmann, J. M.; Lenoir, D.; König, B. *Beilstein Journal of Organic Chemistry* **2012**, *8*, 330.

„6-Methyl-2-nitro-1-phenyl-hept-4-en-3-ol" Herrmann, J. M.; König, B. *Molbank* **2011**, *2011*, M718.

6.4 Curriculum Vitae

Personal data

Josef Maximilian Herrmann
born on 07.12.1983 in Regensburg
married

Schuegrafstraße 11
93051 Regensburg

josef.m.herrmann@gmx.de

University education

12/2009 – 06/2013 **PhD** supervised by Prof. Dr. Burkhard König at the Institute of Organic Chemistry, University of Regensburg, in the research area of Medicinal Chemistry, sponsored by the *Bayrischen Eliteförderung* with a *PhD scholarship*.
Research areas:

- Syntheses of natural products for pharmacological testing
- Studies on the defunctionalisation of alcohols

10/2007 - 9/2009 Degree program **Medicinal Chemistry**
Diploma thesis supervised by Prof. Dr. Burkhard König
Title: „Synthesis of a new fungal metabolite“
Degree: Diplom Chemiker (1,3)

10/2004 - 9/2007 Undergraduate studies in **Chemistry** at the University of Regensburg
Degrees: Basisstudium Abschlussprüfung (1,5)
Diplomvorprüfung (1,5)

Civilian service

8/2003 - 6/2004	Nursing service in the BRK Senioren Wohn- und Pflegeheim Schloss Eggmühl

School education

9/1994 - 6/2003	Secondary school: Burkhart-Gymnasium in Mallersdorf-Pfaffenberg Degree: Abitur (2,5)
9/1990 - 7/1994	Elementary school: Placidus-Heinrich-Volksschule in Schierling

Additional qualifications

Languages	German (native speaker), English (business fluent), Latin (basic knowledge), Spanish (basics knowledge)
Chemical Analysis	detailed knowledge of spectroscopical analytics and chromatographic separation methods
EDP	good knowledge of chemistry software (ChemDraw, MestRec, TopSpin, Excel, Origin) and word processing (MS Office)
Other	umfassende Sachkunde nach § 5 i. V. m. § 2 der Chemikalien-Verbots-verordnung

Personal Interests

Sailing, Fishing, Scuba Diving, Hiking

6.5 Danksagungen

Mein größter Dank gilt meinem Doktorvater Prof. Dr. Burkhard König für die Hilfe bei allen Projekten an denen ich mitwirken durfte und für seine stets freundliche und aufmunternde Persönlichkeit. Ich möchte Ihm dafür danken, dass seine Tür bei Problemen stets offen stand, für all seine neuen Ideen und Inspirationen bei synthetischen Problemen und die Möglichkeit selbstständig arbeiten zu können.

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Für die gute Zusammenarbeit bei dem Projekt zur Defunktionalisierung von Alkoholen möchte ich mich bei Michael Dobmeier und Prof. Dr. Dieter Lenoir bedanken.

Prof. Dr. Jörg Heilmann und Dr. Guido Jürgenliemk danke ich besonders für die gute Zusammenarbeit und die hilfreichen Diskussionen während des Projekts zur Synthese der Ruscozepine, außerdem danke ich Monika Untergehrer und Gabriele Brunner für die Durchführung und Auswertung der pharmakologischen Testungen.

Der NMR-Abteilung und der Zentralen Analytik der Universität Regensburg möchte ich ganz herzlich für die schnelle und gewissenhafte Durchführung aller Messungen danken. Prof. Dr. Oliver Reiser danke ich für die Nutzung des IR Spektrometers seiner Arbeitsgruppe. Für die Durchführung von HPLC-Analysen und die Unterstützung bei der Messung von GC-Analysen danke ich Dr. Rudolf Vasold und Simone Strauß. Ganz herzlich möchte ich mich auch bei Regina Hoheisel für die Hilfe und Unterstützung bei CV-Messungen bedanken.

Susanna Schmidbauer und Andreas Hohenleutner danke ich vielmals für das Korrekturlesen dieser Arbeit.

Unseren Sekretärinnen Viola Rappenegger und Elisabeth Liebl möchte ich für die organisatorische Hilfe während der letzten Jahre danken. Für die Bestellung von

Chemikalien, Geräten und die Reperatur und Wartung des Laborequipments möchte ich Britta Badziura, Susanne Schulze und Ernst Lautenschlager danken.

Allen Praktikanten und Bachelor Studenten danke ich für die tatkräftige Unterstützung im Labor.

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