Development of New Methods for the Transition Metal-Catalyzed Synthesis of Annulated Pyrans

Dissertation for Obtaining the Doctoral Degree

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Preliminary remarks

The work presented in this thesis was carried out under the supervision of Prof. Dr. Uwe Beifuss at the Institute of Chemistry, University of Hohenheim, from September 2015 to September 2023. Part of the results have already been published in an international peer reviewed journal:

- Mehran Khoshbakhsh Foumani, Jürgen Conrad, Wolfgang Frey, and Uwe Beifuss "Flexible Approach for the Synthesis of Annulated 4*H*-Pyrans Based on a Cu(I)-Catalyzed C-Allylation/O-Vinylation Reaction of Cyclic 1-Bromoallyl Tosylates with Cyclic and Acyclic 1,3-Dicarbonyls", *J. Org. Chem.* **2022**, *87*, 8316−8341.

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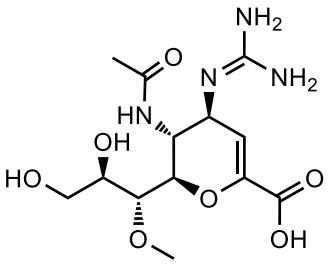
I Introduction

1 General introduction

Organic chemistry explores the fascinating world from the simplest hydrocarbons to the most complex biomolecules. In recent decades, organic synthesis has made significant progress and has become a versatile tool not only for organic chemistry but also for the life and materials sciences.[1] Through the further development of known synthetic methods and the invention of new ones, organic synthesis has now reached a very high level of performance. This has led to the fact that today almost any molecule, regardless of whether it is a natural substance or not, can be made synthetically accessible. This performance has had a lasting impact on the design and synthesis of organic compounds.[2] Nevertheless, there is of course still a great need for the development of novel synthetic methods that can be used to carry out transformations that are not yet possible today. In the advancement of organic synthesis, the sustainability of reactions has become a crucial factor that goes far beyond traditional parameters such as selectivity and yield. Atom-efficient reactions, catalytic approaches, energy-efficient transformations, the use of renewable raw materials, the use of safer solvents and reagents, and the avoidance of waste are all important aspects in the development of sustainable chemical reactions today.[3] Due to their efficiency and, in many cases, environmental friendliness, transition metal-catalyzed reactions are becoming increasingly popular.[4] The potential of transition metal-catalyzed reactions can be further exploited by using them in domino and multicomponent reactions. This often greatly simplifies the synthesis of both carbocyclic and heterocyclic ring systems.[5] Transition metal-catalyzed reactions have expanded the possibilities of chemical design and integrated sustainable practices into modern organic synthesis.

In organic chemistry, cyclic compounds are divided into carbocycles and heterocycles. Heterocycles are characterized by the presence of at least one heteroatom within their ring structure, most commonly nitrogen, oxygen, or sulfur. Heterocycles are common structural motifs in natural products that often have interesting pharmacological properties. Many non-natural heterocycles are also of great interest due to their often pronounced biological activities, e.g. for medicinal chemistry and agricultural chemistry.[6]

Oxygen-containing heterocycles, such as furans and pyrans, and their derivatives are commonly found as structural motifs in a large number of natural products, such as furan fatty acids, lignans, coumarins, flavonolignans, flavonoids, isoflavonoids, iridoids, vitamins and carbohydrates, as well as in many synthetic drugs.[7] An example of a synthetic drug is laninamivir (**1**), a compound with a 5,6-dihydro-4*H*-pyran skeleton used to treat influenza (Figure 1).[8]



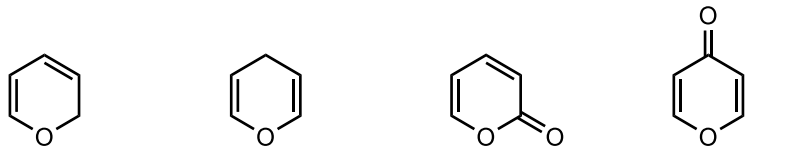
1
laninamivir
(4*S*,5*R*,6*R*)-5-acetamido-4-guanidino-6-((1*R*,2*R*)-2,3-dihydroxy-1-methoxypropyl)-5,6-dihydro-4*H*-pyran-2-carboxylic acid

Figure 1. Structure of laninamivir (**1**), a pyran-containing marketed drug.

Among the *O*-heterocycles, compounds with a pyran skeleton are widely distributed in nature. Pyrans are characterized by a remarkably rich and diverse chemistry.[9] The abundant occurrence of pyran rings in bioactive compounds makes them attractive synthetic targets and continues to stimulate the development of novel synthetic approaches. Although many traditional methods for the synthesis of pyrans are still of great value, the development of new synthetic methods is also opening access to new biologically active pyrans.

2 The structure and properties of pyrans and related ring systems

Pyrans, as *O*-heterocycles contain a six-membered ring with one oxygen and five carbon atoms. The different representatives of the family of unsaturated pyrans can all be traced back to four parent compounds:[9a] 2*H*-pyran (**2**), 4*H*-pyran (**3**), 2*H*-pyran-2-one (**4**) and 4*H*-pyran-4-one (**5**) (Figure 2).



2 2*H*-pyran | **3** 4*H*-pyran | **4** 2*H*-pyran-2-one | **5** 4*H*-pyran-4-one

Figure 2. Structures of the parent pyrans.

The bi-, tri-, and polycyclic pyrans, such as the chromenes **6**, **7**, chromone (**8**), coumarin (**9**), xanthene (**10**), xanthone (**11**), 6*H*-dibenzo[*b*,*d*]pyran (**12**), 6*H*-dibenzo[*b*,*d*]pyran-6-one (**13**), 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran (**14**), and 6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (**15**) (Figure 3) can be derived from the parent compounds **2–5** (Figure 2).

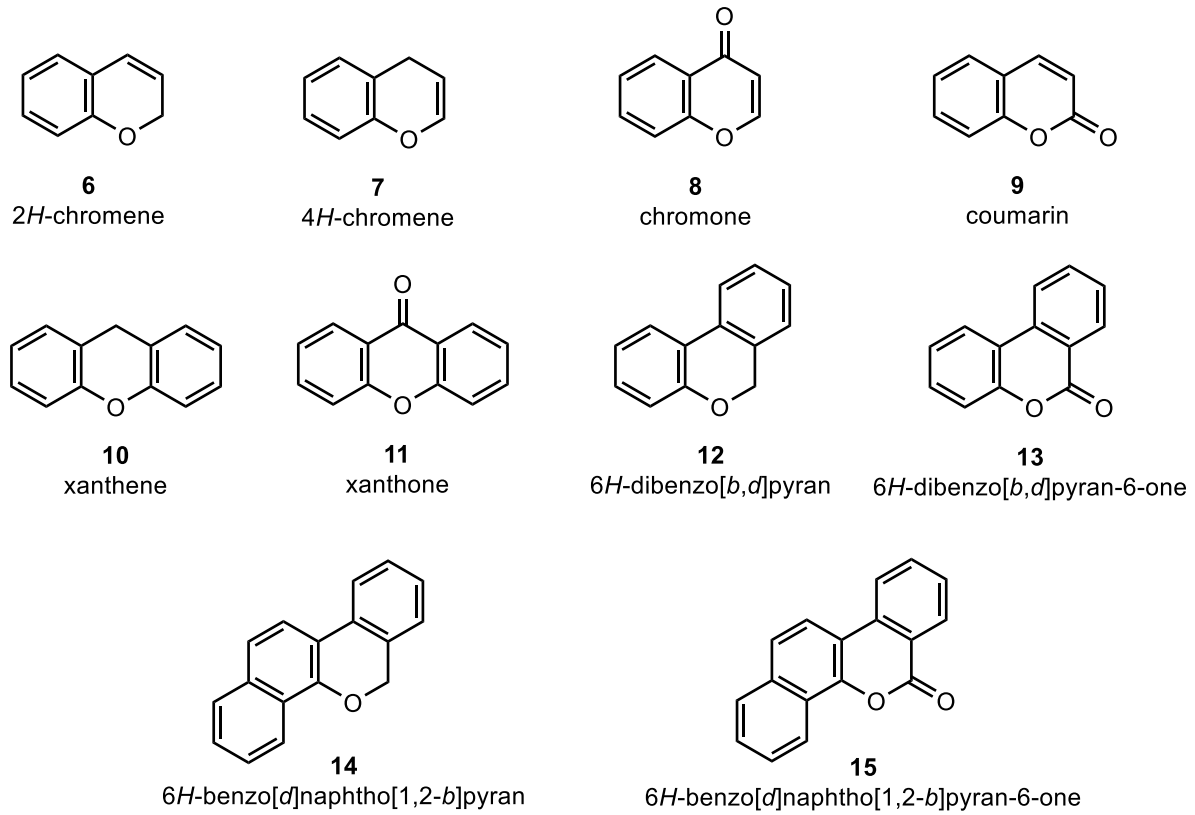


Figure 3. Structures of bi-, tri-, and tetracyclic pyrans **6–15**.

2.1 Biological properties

The presence of a pyran nucleus in numerous naturally occurring and synthetic compounds with biological activities has been well established. Figure 4 shows selected synthetic biologically active compounds with a pyran core, including **16** with antioxidant activity[10] and **17** with antitumor activity against numerous human tumor cell lines.[11] In addition, **18**, an *O*-linked coumarin-monoterpene conjugate shows antiviral activity and cytotoxicity against respiratory syncytial virus (RSV).[12] Compound **19** has been used as a potent inhibitor of steroid sulfatase (STS), an enzyme involved in the biosynthesis of estrogen in the mammary gland.[13] Irosustat (**20**) shows efficacy as a glucosinolate sulfatase (GSS) inhibitor, which could be a promising benign insecticide by exploiting the plant glucosinolate-myrosinase system.[14] Among the naturally occurring pyrans, cannabitriol (**21**), belongs to the $\Delta^{6a,10a}$-tetrahydrocannabinol (THC) category, and has been isolated from *Cannabis sativa* L.[15]

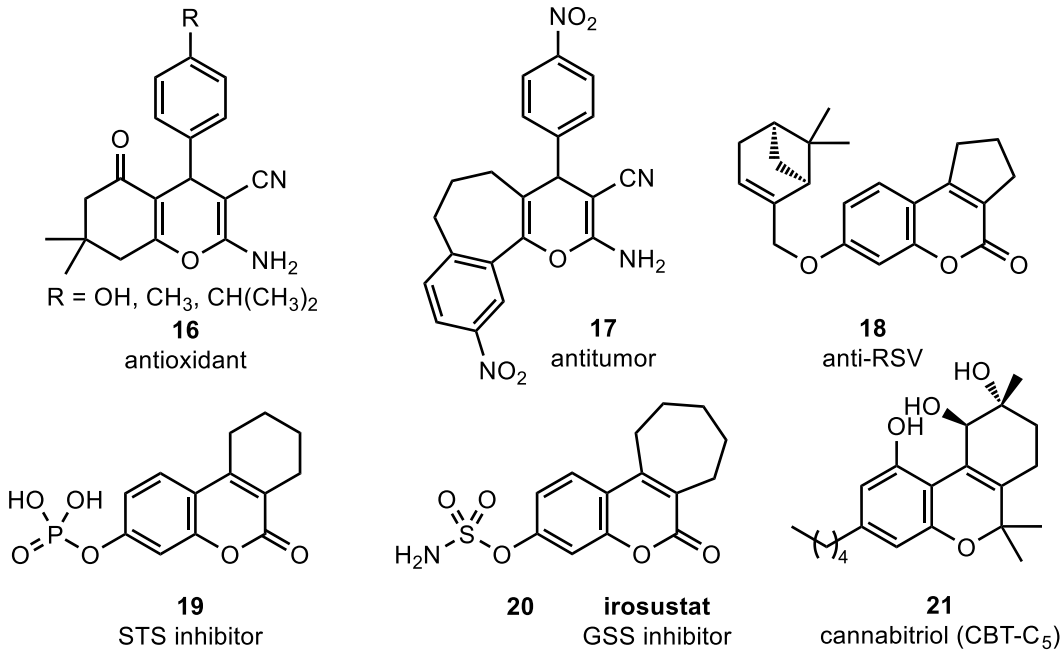


Figure 4. Selected examples of biologically active synthetic (**16–20**) and natural (**21**) pyrans.

2.2 Photophysical and photochemical properties

Fluorescence bioimaging is a powerful method for observing the production, trafficking, and biological functions of biomolecules in living systems. Pyran-containing fluorophores, such as rhodamine 6G chloride (**22**) and fluorescein (**23**), have been used as fluorescent markers and small-molecule detectors in living cells for biotechnology and medical research.[16] Their popularity in fluorescence imaging is due to their water solubility, their high stability, and their brightness. (Figure 5).

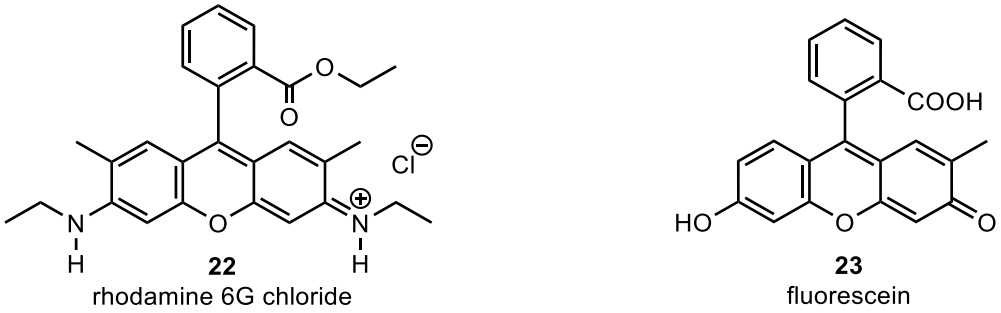
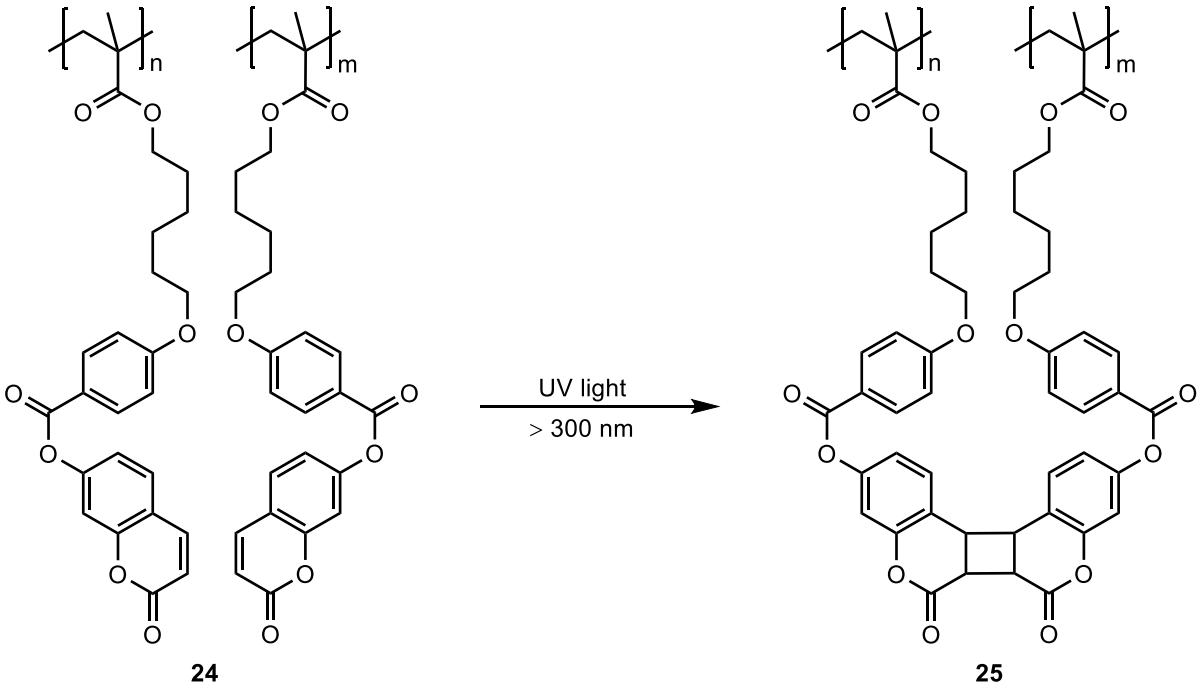


Figure 5. Structures of rhodamine 6G chloride (**22**) and fluorescein (**23**).

An example of the interesting photochemical properties of coumarins is the photochemical [2+2]-cycloaddition of two coumarins **24**, in which the corresponding cyclobutane **25** is formed under UV irradiation (Scheme 1). The product is in use to align liquid crystal molecules in liquid crystal displays to ensure optimal performance.[17]



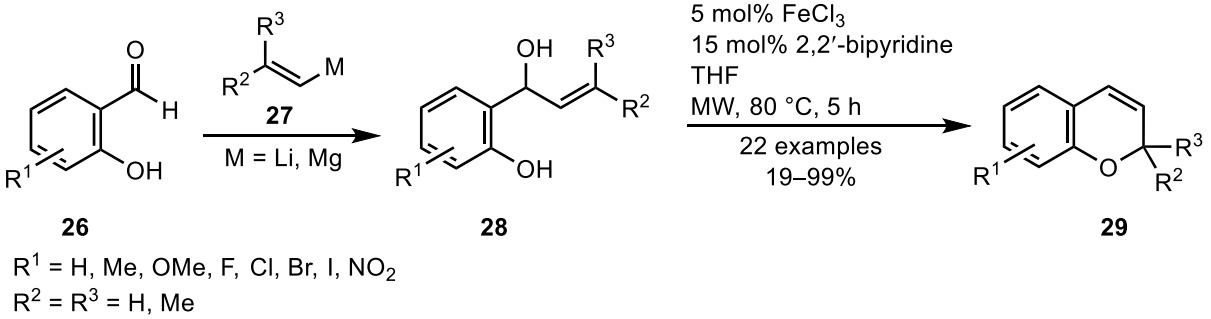
24 **25**

Scheme 1. Photochemical [2+2]-cycloaddition of two coumarins **24**.

3 Synthesis of annulated pyrans

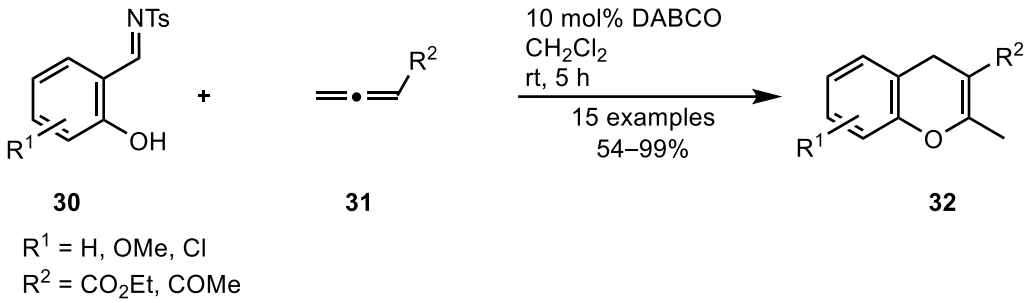
3.1 Some general methods for the synthesis of annulated pyrans

The biological and pharmacological activities of 2*H*- and 4*H*-pyran containing heterocycles, including HIV protease inhibiting,[18] antimicrobial,[19] and antitumor properties,[20] make this scaffold an important chemical entity. A number of methods have been published for the synthesis of 2*H*- and 4*H*-chromenes.[21, 9c] As an example, Cossy et al. have demonstrated that 2*H*-chromenes **29** can be synthesized by an acid-catalyzed intramolecular cyclization of 2-(1-hydroxyallyl)phenols **28**. The required precursors could be obtained from salicylaldehydes **26** and vinyl organometallics **27** (Scheme 2).[21c]



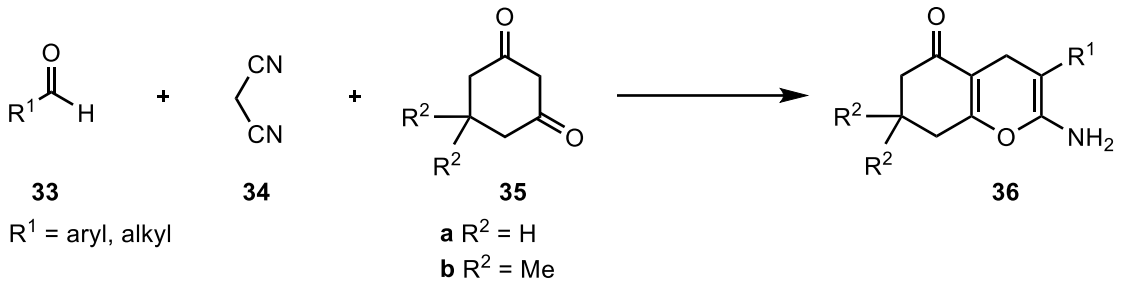
Scheme 2. Acid-catalyzed synthesis of 2*H*-chromenes **29** according to Cossy et al.

Shi and Shi have reported an interesting method for the synthesis of 4*H*-chromenes **32** based on a DABCO-catalyzed reaction of salicyl *N*-tosylimines **30** with allenic esters and ketones **31** (Scheme 3).[22]



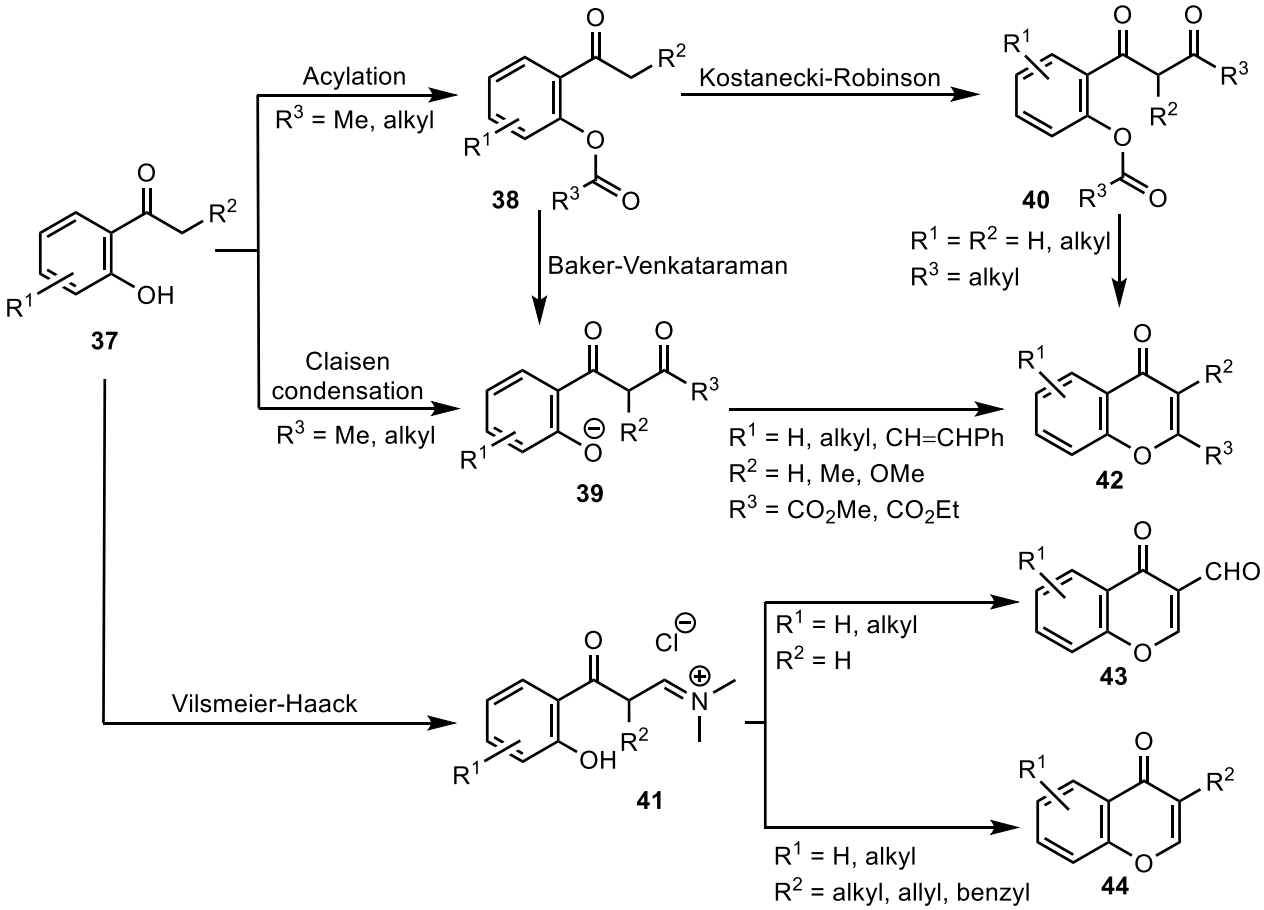
Scheme 3. DABCO-catalyzed synthesis of 4*H*-chromenes **32** according to Shi and Shi.

The three-component reaction between an aldehyde **33**, malononitrile (**34**) and a cyclic 1,3-dicarbonyl **35** has been reported for the synthesis of partially saturated 4*H*-chromenes **36**. It has been found that a wide range of catalysts can be employed to catalyze this transformation (Scheme 4).[23]



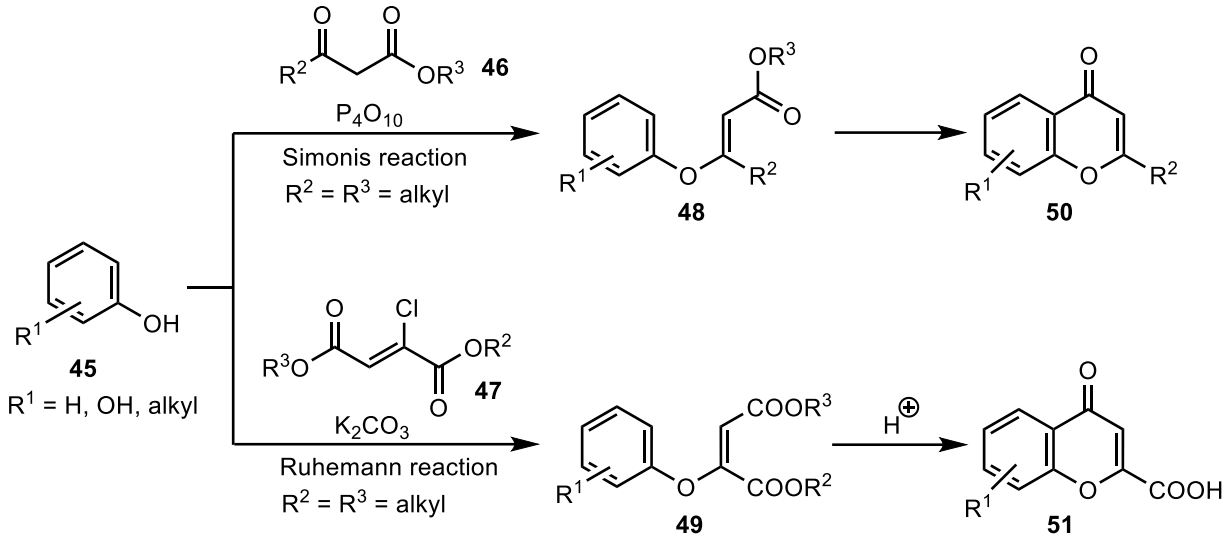
Scheme 4. Three-component reaction for the synthesis of partially saturated 4*H*-chromenes **36**.

For the synthesis of substituted chromones **42–44** numerous classical methods are available which make use of *o*-hydroxyarylalkylketones **37** and phenols **45** as substrates.[24] The methods starting from *o*-hydroxyarylalkylketones **37** include the Claisen condensation,[25] the Baker-Venkataraman rearrangement,[26] the Kostanecki-Robinson reaction[27] and the Vilsmeier-Haack reaction[28] (Scheme 5).



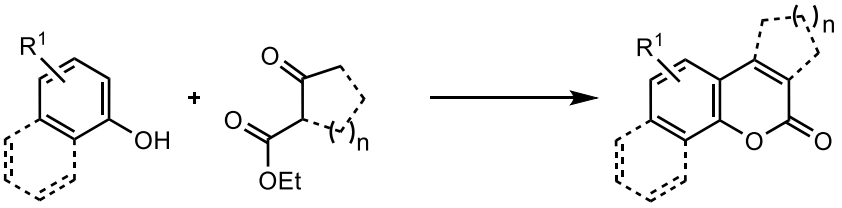
Scheme 5. Some classical methods for the synthesis of substituted chromones **42–44** starting from *o*-hydroxyarylalkylketones **37** according to Borges et al.[24b]

For the synthesis of substituted chromones **50**, **51** that make use of phenols **45** as starting materials, the Simonis reaction[24b, 29] and the Ruhemann reaction[24b, 30] have proven successful (Scheme 6).



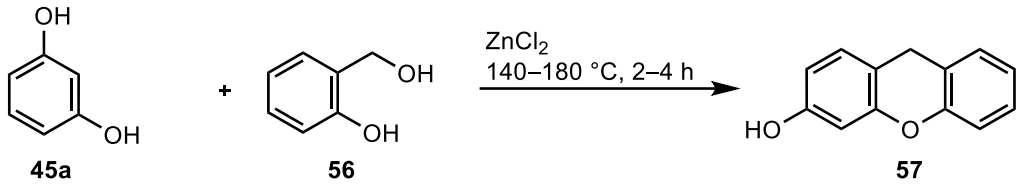
Scheme 6. Synthesis of substituted chromones **50**, **51** starting from phenols **45** according to Borges et al.[24b]

The Pechmann condensation[31] between phenols **45** or naphtols **52** and acyclic **46** as well as cyclic *β*-keto esters **53**, has been widely used for the successful synthesis of annulated coumarins **54**, **55** (Scheme 7).[32] However, the classical Pechmann procedure has a number of drawbacks, including harsh reaction conditions, long reaction times, large excess of acid, and the formation of salt waste due to acid neutralization.



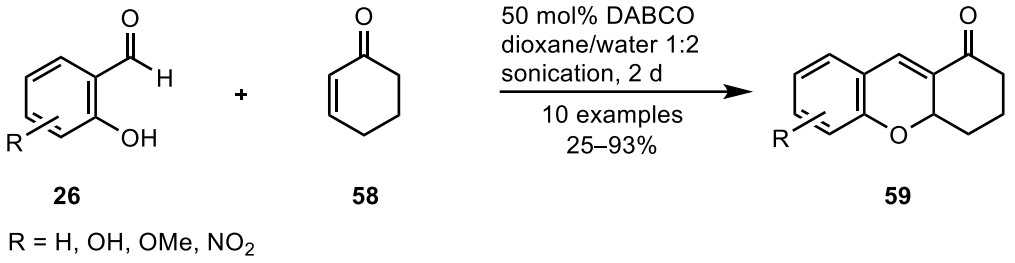
Scheme 7. The Pechmann condensation for the synthesis of annulated coumarins **54**, **55** according to Samant et al.[32c]

One of the first strategies for the synthesis of xanthenes[33] has been reported by Sen et al., who, for example, were able to obtain 3-hydroxyxanthene (**57**) through the condensation of resorcinol (**45a**) with saligenin (**56**) (Scheme 8).[33b]



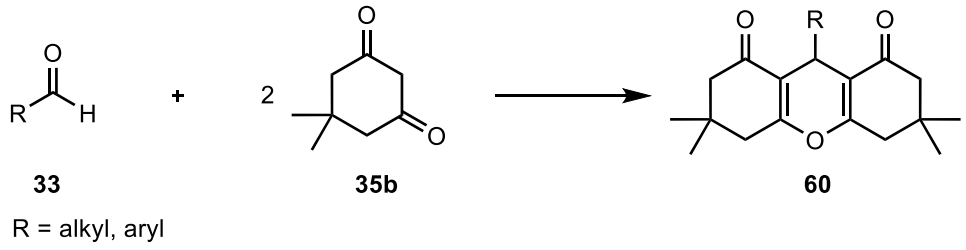
Scheme 8. Synthesis of 3-hydroxyxanthene (**57**) by Sen et al.

Only a limited number of methods have been reported for the synthesis of partially saturated xanthenes. Bräse et al. have disclosed an interesting method for the synthesis of tetrahydroxanthenones **59** that is based on a domino oxa-Michael addition/aldol condensation reaction between salicylaldehydes **26** and 2-cyclohexen-1-one (**58**) (Scheme 9).[34] Based on this domino process, a modular strategy for the synthesis of substituted tetrahydroxanthenones has been developed that is suitable for application to the total synthesis of secalonic acids, i.e. natural products with a tetrahydroxanthenone backbone.[35]



Scheme 9. Synthesis of tetrahydroxanthenones **59** based on a domino oxa-Michael addition/aldol condensation reaction.

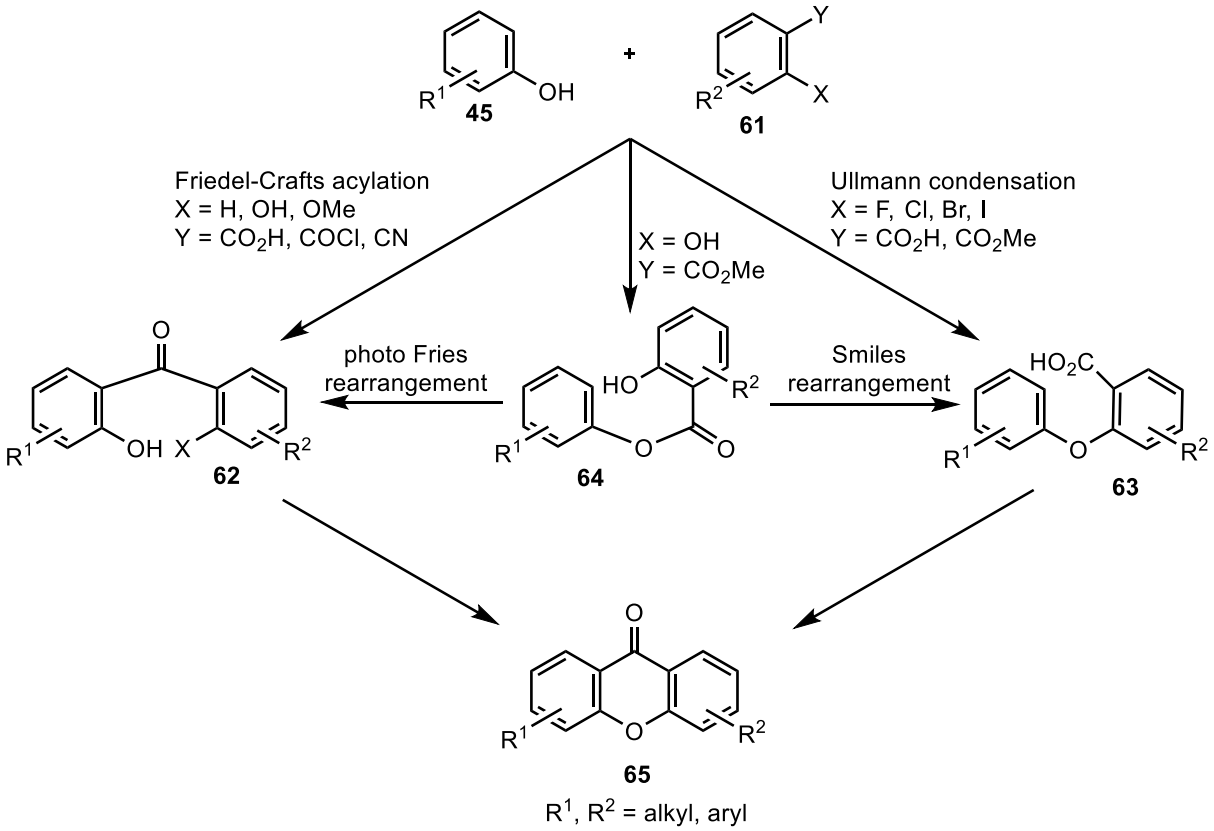
A one-pot three-component reaction using 1 equivalent of an aromatic or an aliphatic aldehyde **33** and 2 equivalents of 5,5-dimethyl-1,3-cyclohexanedione (**35b**) has shown success in the synthesis of partially saturated xanthenes **60** under different reaction conditions. (Scheme 10).[36]



Scheme 10. One-pot three-component synthesis of partially saturated xanthenes **60**.

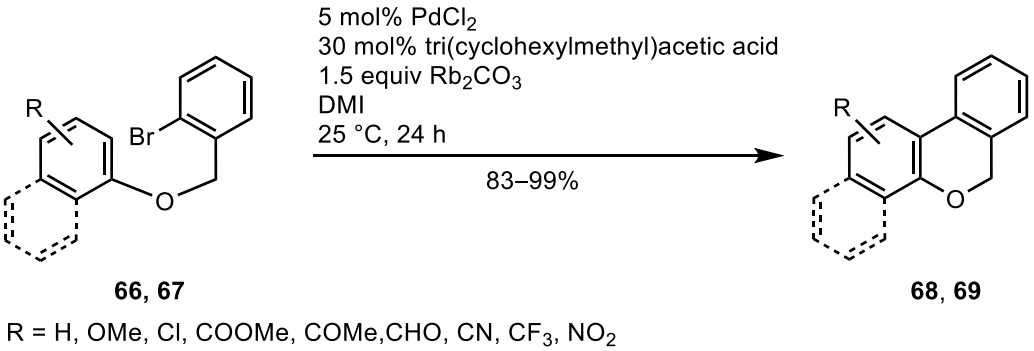
The synthesis of xanthones **65** is well established.[37] Typical routes for their preparation involve the synthesis of benzophenones **62** or diaryl ethers **63** as intermediates, which are suitable for subsequent cyclization. Benzophenones **62** are accessible by Friedel–Crafts acylation[38] and

diaryl ethers **63** can be obtained by Ullmann condensation. The xanthone skeleton can also be elaborated from aryl benzoates **64** followed by photo Fries rearrangement[39] to benzophenones **62** or by Smiles rearrangement[40] to diaryl ethers **63** (Scheme 11).



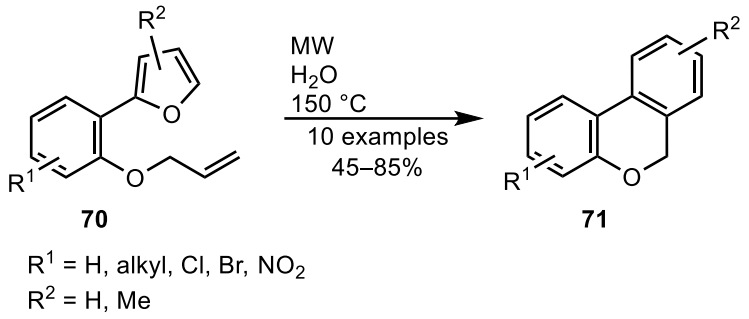
Scheme 11. Some classical methods for the synthesis of xanthones **65** according to Sousa and Pinto.[37c]

Tsuji et al., have published a study on the $PdCl_2$-catalyzed intramolecular *C*-arylation of 2-bromobenzyloxy benzenes **66** and 2-bromobenzyloxy naphthalenes **67** using a bulky carboxylic acid as ligand.[41] They have shown that their reaction conditions allowed the synthesis of both 6*H*-dibenzo[*b*,*d*]pyrans **68** and 6*H*-benzo[*d*]naphtho[1,2-*b*]pyrans **69** (Scheme 12).



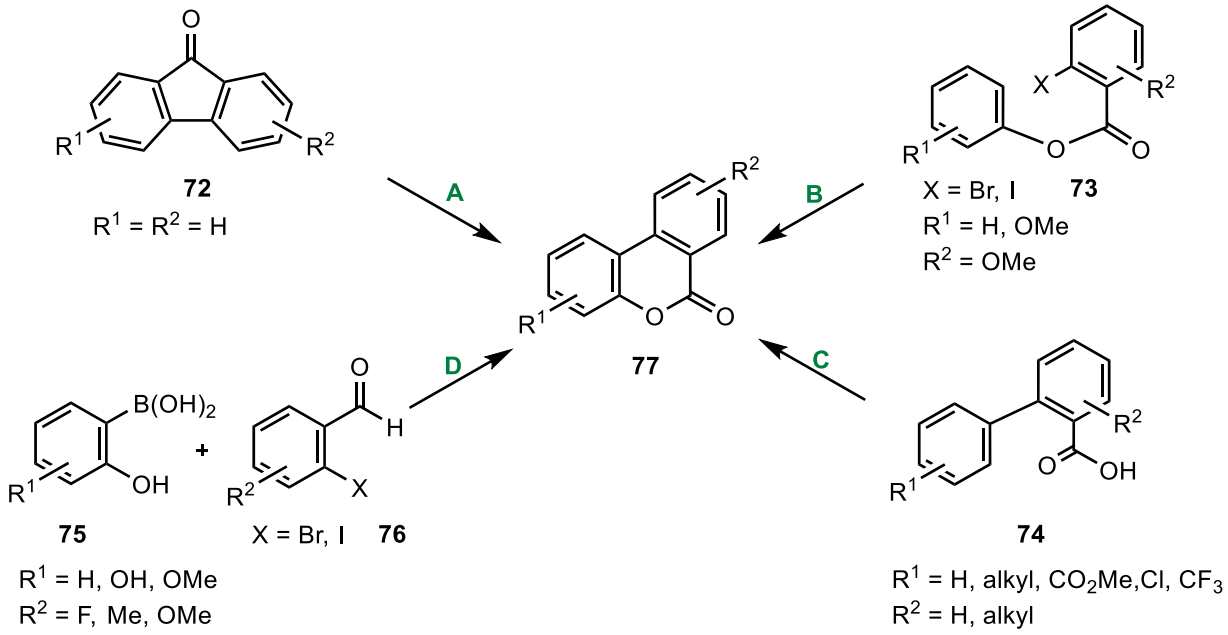
Scheme 12. Pd-catalyzed intramolecular *C*-arylation for the synthesis of 6*H*-dibenzo[*b*,*d*]pyrans **68** or 6*H*-benzo[*d*]naphtho[1,2-*b*]pyrans **69**.

A catalyst-free intramolecular Diels-Alder reaction under microwave irradiation in water also allows the formation of 6*H*-dibenzo[*b*,*d*]pyrans **71** (Scheme 13).[42]



Scheme 13. Intramolecular Diels-Alder reaction for synthesis of 6*H*-dibenzo[*b*,*d*]pyrans **71**.

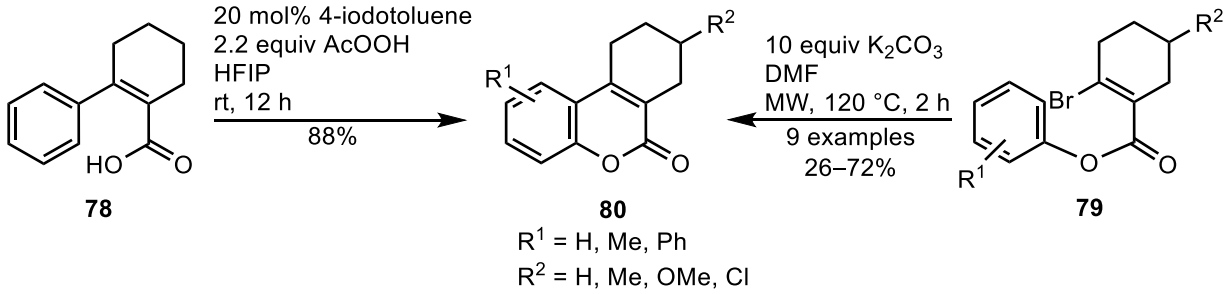
Several approaches, such as the Baeyer-Villiger oxidation of fluorenones **72** (Scheme 14**A**)[43] and the intramolecular C−C cross-coupling reaction of aryl *o*-benzoates **73** (Scheme 14**B**)[44] have been developed for the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones **77**. Alternative methods include the C−H activation/lactonization of 2-arylbenzoic acids **74** (Scheme 14**C**)[45] and the domino Suziki-Miyaura cross-coupling/lactonization between *o*-hydroxyarylboronic acids **75** and 2-halobenzaldehydes **76** (Scheme 14**D**).[46]



Scheme 14. Classical methods for the synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones **77**.

Despite the significant progress that has been made in the efficient synthesis of 6*H*-dibenzo[*b*,*d*]pyran-6-ones **77**, only a limited number of reactions are known for the synthesis of partially saturated annulated coumarins, in particular 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-ones **80**. A couple of years ago it has been reported that **80** ($R^1 = R^2 = H$)

can be synthesized by the iodine(III)-catalyzed lactonization of **78** that is based on a C(sp^2)−H functionalization/C−O bond formation (Scheme 15).[47] Scope and limitations have not been studied so far. It has also been found that 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-ones **80** could be synthesized when carboxylic esters **79** were reacted under microwave conditions in the presence of a large excess of K_2CO_3 (Scheme 15).[48]



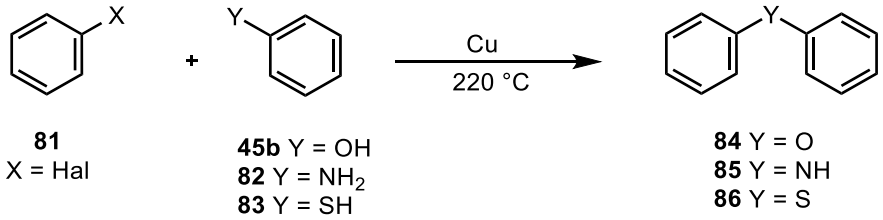
Scheme 15. Two methods for the synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromen-6-ones **80**.

3.2 Transition metal-catalyzed synthesis of annulated pyrans

Transition metal-catalyzed reactions have become one of the most powerful tools in organic synthesis in recent decades, playing an important role in the synthesis of carbocyclic and heterocyclic scaffolds via C−C as well as C−O, C−N and C−S bond formation.[4b, 49] A variety of transition metals have been used for the synthesis of complex organic molecules, including biologically active compounds and natural products. In the following sections, the use of copper and ruthenium catalysts for the synthesis of annulated pyrans will be discussed.

3.2.1 Copper-catalyzed synthesis of annulated pyrans

Copper has different oxidation states (Cu^0, Cu^I, Cu^{II}, Cu^{III}) and can be involved in one-electron as well as two-electron processes. Since the beginning of the 20th century, considerable progress has been made in Cu-catalysis. Some of the most iconic examples for copper-mediated reactions have been reported by Fritz Ullmann.[50] It has been found that the synthesis of diphenyl ether (**84**), diphenyl amine (**85**) and diphenyl thioether (**86**) can be achieved when an aryl halide **81** is reacted with one of the corresponding nucleophiles **45b**, **82**, **83** as a coupling partner in the presence of stoichiometric amounts of Cu (Scheme 16).[51]



Scheme 16. Ullmann condensations.

Over the years, copper-catalyzed inter- and intramolecular couplings of a wide range of *C*-,[52] *N*-,[53] *O*-[54] and *S*-nucleophiles[55] with aryl and vinyl halides as substrates, which are also known as Ullmann condensations, have been developed as powerful tools in organic synthesis.[56] The increase in the importance of copper-catalyzed reactions in organic synthesis has been driven by a number of factors:

- Copper and its salts are readily available, and much cheaper than other transition metals such as palladium, rhodium, iridium or gold.
- Usually, there is no requirement to use preformed Cu(I) complexes in Cu(I)-catalyzed reactions.
- Simple and inexpensive bases and ligands are commonly sufficient for Cu(I)-catalyzed reactions.

- Many Cu(I)-catalyzed reactions can be run under mild reaction conditions.
- Most Cu(I)-catalyzed reactions are robust and scalable.

Figure 6 displays four common structures that are appropriate substrates for the copper-catalyzed intramolecular C−O bond formation in the synthesis of pyrans and related compounds. Compared to aryl halides of types **A** and **B**, only a limited number of vinylic compounds of types **C** and **D** have been utilized as substrates for the synthesis of *O*-containing ring systems via copper-catalyzed intramolecular C−O couplings.

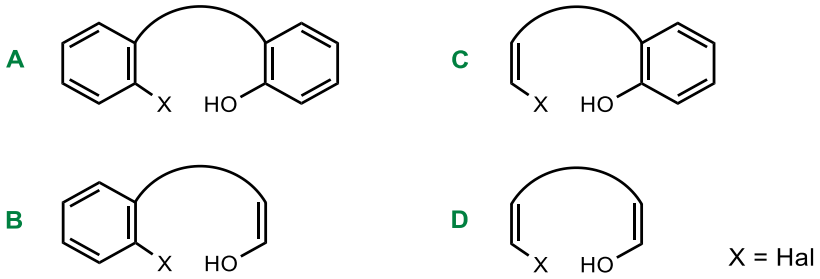
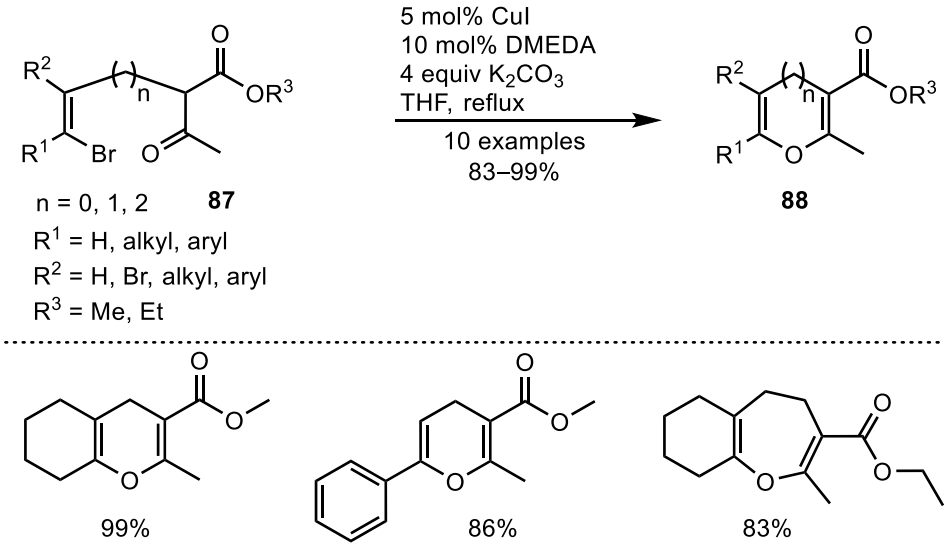


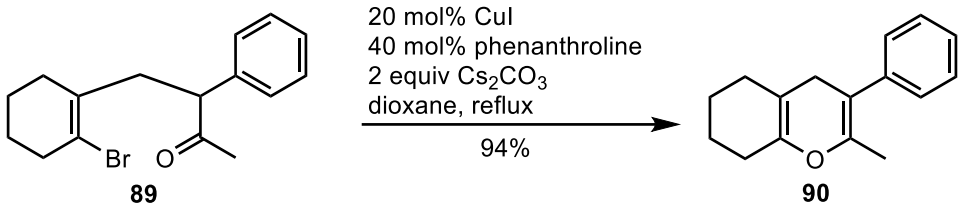
Figure 6. Suitable aryl halides (**A**, **B**) and vinyl halides (**C**, **D**) for copper-catalyzed intramolecular C−O bond formation.

As an example, for the use of structure **D** (Figure 6), Fang and Li have reported the use of *β*-ketoesters **87** as substrates in Cu(I)-catalyzed intramolecular *O*-vinylations. This method allows for the efficient access to both annulated pyrans **88** and 5 and 7-membered cyclic alkenyl ethers (Scheme 17).[57]



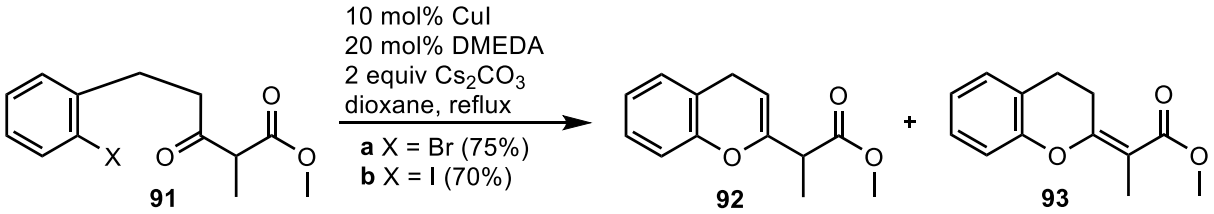
Scheme 17. CuI-catalyzed intramolecular *O*-vinylation of **87** according to Fang and Li.

The authors have also reported a single intramolecular *O*-vinylation reaction using a ketone instead of a *β*-ketoester to synthesize the annulated pyran **90** in 94% yield. The reaction was performed using 20 mol% CuI as catalyst, 40 mol% phenanthroline as ligand and Cs_2CO_3 as base in dioxane (Scheme 18).[58] Scope and limitations of this approach to annulated pyran **90** have not been studied.



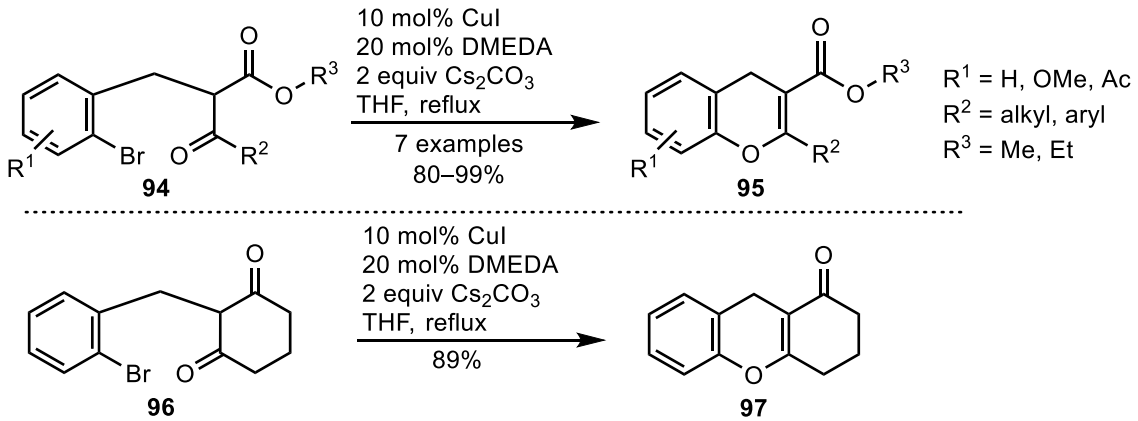
Scheme 18. CuI-catalyzed intramolecular *O*-vinylation of **89** according to Li et al.

The Li group has extended their research to copper(I)-catalyzed intramolecular *O*-arylations. In 2006, they have reported that annulated pyrans **92** and **93** could be synthesized with an overall 75% yield and a ratio of ~1:1 by reacting aryl bromide **91a** with 10 mol% CuI and 20 mol% DMEDA (Scheme 19).[59] Furthermore, the replacement of **91a** by aryl iodide **91b** under the same conditions led to the formation of only **93** in yield of 70 %.



Scheme 19. CuI-catalyzed intramolecular *O*-arylation of **91** according to Fang and Li.

In addition, they have expanded the scope of the intramolecular *O*-arylation using readily available *α*-(2-bromobenzyl)-*β*-keto esters **94** as substrates to yield several 4*H*-chromenes **95**. With **96** as substrate, 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**97**) was formed (Scheme 20).[59]



Scheme 20. Cu(I)-catalyzed intramolecular *O*-arylation for the synthesis of 4*H*-chromenes **95** and 2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**97**).

There is no doubt that the use of intramolecular copper-catalyzed arylations and vinylations of *O*-nucleophiles offers excellent opportunities for the synthesis of 6-membered *O*-heterocycles. However, this approach has limitations because it is restricted to the formation of only one new bond per reaction. It would be more efficient to form multiple bonds in a single synthetic step without isolating intermediates, just by altering reaction conditions or adding reagents. Domino reactions, which are also known as tandem or cascade reactions, involve a series of consecutive steps without isolating intermediates. Such reactions progress through multiple reaction steps.[60] Whether or not a domino reaction takes place depends largely on the presence of sufficiently reactive functionalities in the substrates or the intermediates that are passed through in the course of a domino reaction. The importance of Cu-catalyzed cross-couplings for the synthesis of cyclic compounds in one synthetic step can be significantly increased when they are embedded in domino processes. This can, for example, be achieved by using bisfunctionalized substrates, such as biselectrophiles, bisnucleophiles and mixed electrophiles/nucleophiles. Regarding the synthesis of annulated pyrans, in Figure 7 some typical 1,3-bisfunctionalized mixed electrophiles/nucleophiles (**A**, **B**) and 1,3-biselectrophiles (**C**, **D**) are shown.

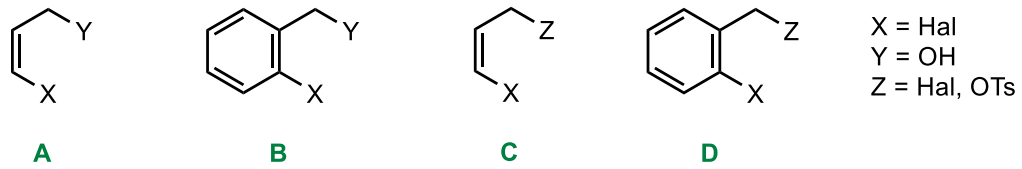
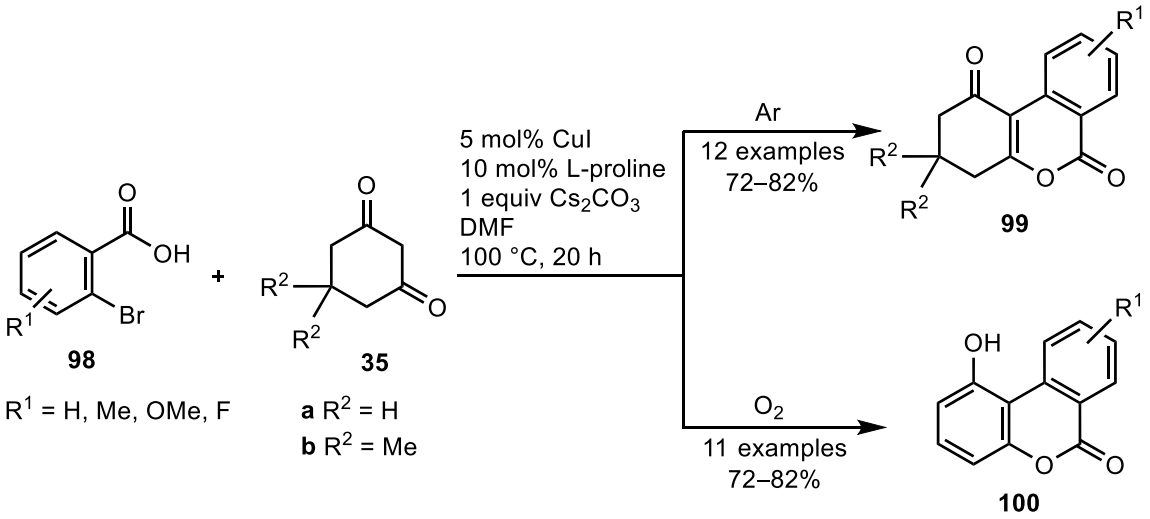


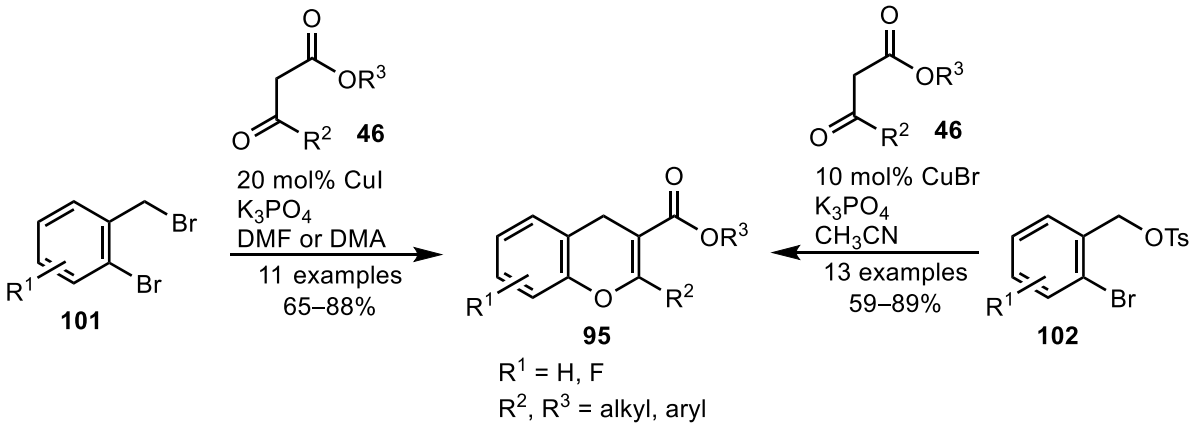
Figure 7. 1,3-Bisfunctionalized mixed electrophiles/nucleophiles (**A**, **B**) and 1,3-biselectrophiles (**C**, **D**) for the synthesis of 6-membered ring systems.

As an example for a CuI-catalyzed domino reaction, 2-bromobenzoic acids **98** as 1,3-bisfunctionalized substrates were reacted with cyclohexane-1,3-diones **35** in the presence of CuI, L-proline and Cs_2CO_3 in *N*,*N*-dimethylformamide (DMF). When the reactions were performed under argon, the corresponding 1*H*-benzo[*c*]chromene-1,6(2*H*)-diones **99** were formed. In the presence of O_2, a subsequent aromatization took place to deliver the 1-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-ones **100** (Scheme 21).[61]



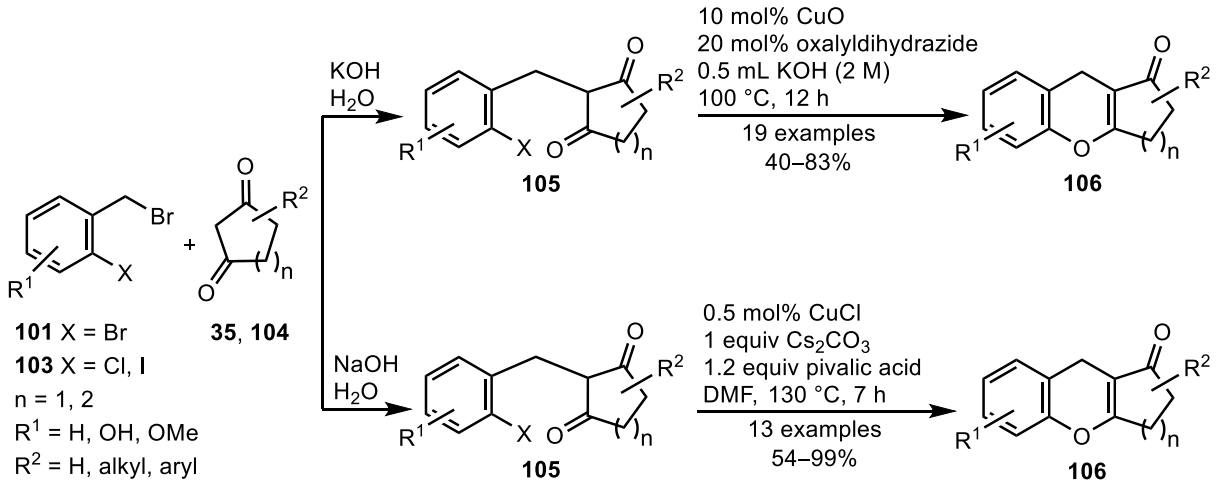
Scheme 21. Synthesis of 1*H*-benzo[*c*]chromene-1,6(2*H*)-diones **99** and 1-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-ones **100**.

The Cu(I)-catalyzed annulation of vinylic/allylic 1,3-biselectrophiles **C** (Figure 7) for the synthesis of pyrans has not yet been reported. For the first time, this dissertation will address the use of 1,3-bisfunctionalized substrates of type **C** in Cu(I)-catalyzed reactions with cyclic and acyclic 1,3-dicarbonyls as 1,3-bisnucleophiles for the synthesis of annulated and bisannulated 4*H*-pyrans. However, the reaction between aromatic/benzylic 1,3-biselectrophiles **D** (Figure 7) and 1,3-bisnucleophiles can be carried out successfully.[62] For example, Beifuss and coworkers have reported that the Cu(I)-catalyzed domino reaction between 2-bromobenzyl bromides **101** and acyclic *β*-ketoesters **46** delivers 4*H*-chromenes **95** in yields up to 88% (Scheme 22).[62h] The group also succeeded in synthesizing 4*H*-chromenes **95** using the corresponding 2-halobenzyl tosylates **102** as substrates (Scheme 22).[62d]



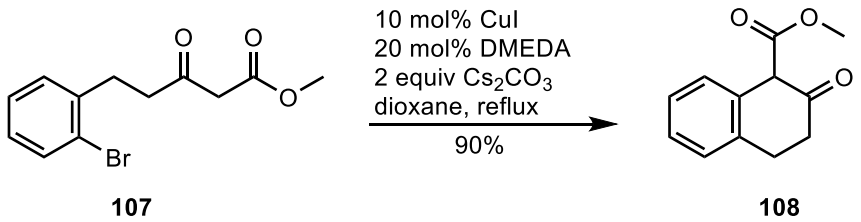
Scheme 22. Synthesis of 4*H*-chromenes **95** using 1,3-aromatic/benzylic biselectrophiles **101** and **102** as substrates.

Some examples are known where researchers have identified limitations using bisfunctionalized substrates in Cu(I)-catalyzed domino reactions for the synthesis of *O*-heterocycles, such as the competition between *C*- and *O*-nucleophiles in the cyclization step of the domino reaction. For example, both Beifuss et al. and the Mao group reported the competition between *C*- and *O*-benzylation in the copper-catalyzed reaction between 2-halobenzyl bromides **101**, **103** and cyclic 1,3-dicarbonyls **35**, **104**. Therefore, the corresponding annulated 4*H*-chromenes **106** have been synthesized using a two-step process (Scheme 23).[62b,g]



Scheme 23. Copper-catalyzed synthesis of annulated 4*H*-chromenes **106** in two steps.

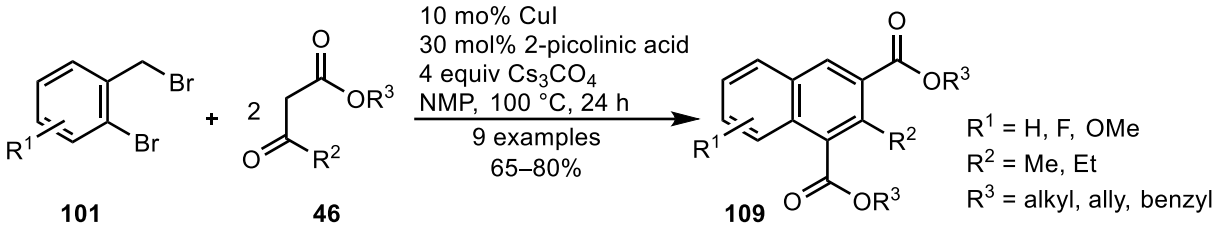
Fang and Li have reported that refluxing methyl 5-(2-bromophenyl)-3-oxopentanoate (**107**) in the presence of 10 mol% CuI, 20 mol% DMEDA and Cs_2CO_3 in dioxane leads to the unexpected formation of methyl 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (**108**) via intramolecular *C*-arylation rather than *O*-arylation. The scope of the reaction has been studied to some extent (Scheme 24).[59]



Scheme 24. CuI-catalyzed synthesis of 2-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (**108**).

Beifuss and coworkers[62h] have also reported that *C*-arylation took place in a Cu(I)-catalyzed domino reaction between 2-bromobenzyl bromides **101** and two molecules of a *β*-ketoester **46** to give the corresponding naphthalenes **109** (Scheme 25). However, by changing the ratio of

the substrates and the reaction conditions, they were able to switch the direction of the reaction from *C*- to *O*-arylation. Under these conditions, only 4*H*-chromenes **95** were obtained (Scheme 22).[62h]



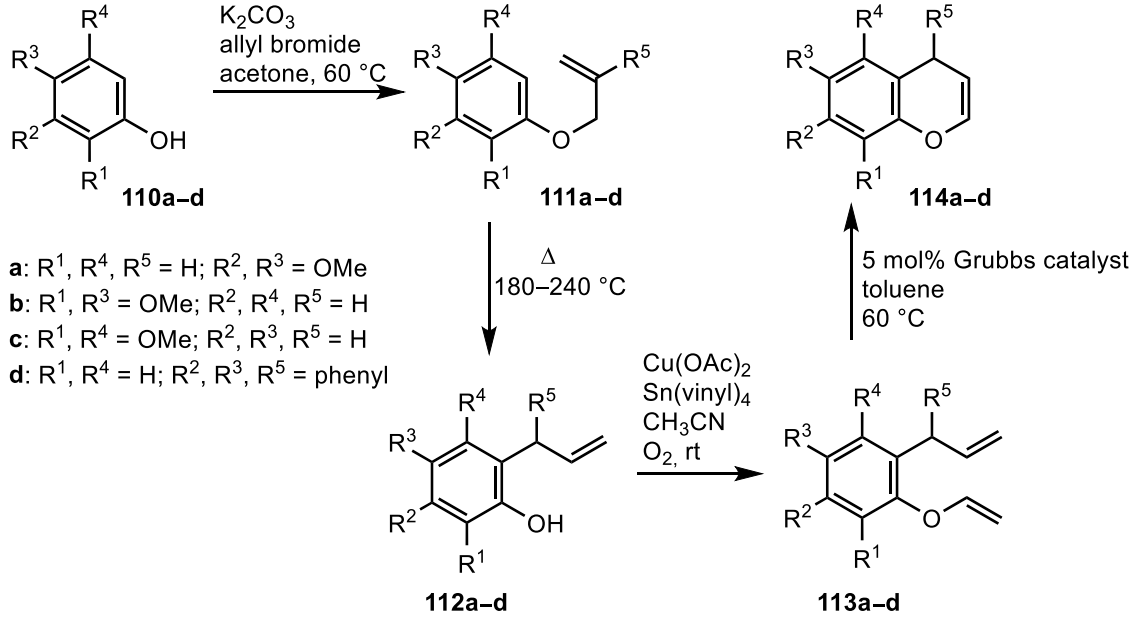
101 **46** **109**

Scheme 25. Cu(I)-catalyzed synthesis of naphthalenes **109**.

3.2.2 Ruthenium-catalyzed synthesis of annulated pyrans

Ruthenium complexes are widely studied as catalysts for important synthetic transformations,[63] including reductions,[64] oxidations[65] and metathesis reactions.[66] In organic synthesis, metathesis reactions have become a powerful and valuable tool for C−C bond formation.[67] A variety of catalysts have shown efficacy in catalyzing metathesis reactions, but the most commonly employed catalysts are ruthenium complexes, due to their pronounced stability and high functional group tolerance.[68]

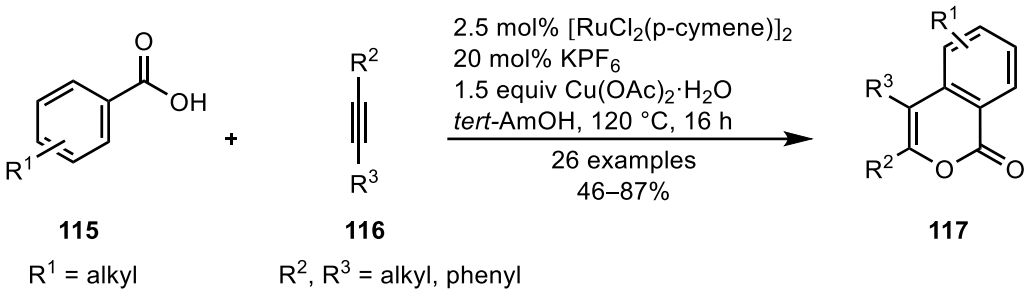
Otterlo and coworkers have reported a ring-closing metathesis (RCM) for the synthesis of 4*H*-chromenes **114**, with a focus on **114a**, which occurs naturally as a fragrance component of the plant *Wisteria sinensis*.[69] As shown in Scheme 26, phenols **110** were first converted to their corresponding aryl allyl ethers **111** using allyl bromide as reagent. The aryl allyl ethers **111** were then subjected to thermal Claisen rearrangement to give the phenols **112**. Under copper-catalyzed conditions, vinylation afforded the 1-allyl-2-vinyloxy benzenes **113**. Finally, the ruthenium-catalyzed RCM of **113** afforded the 4*H*-chromenes **114** in yields ranging between 63 and 98%.



Scheme 26. Ru-catalyzed RCM for the synthesis of 4*H*-chromenes **114**.

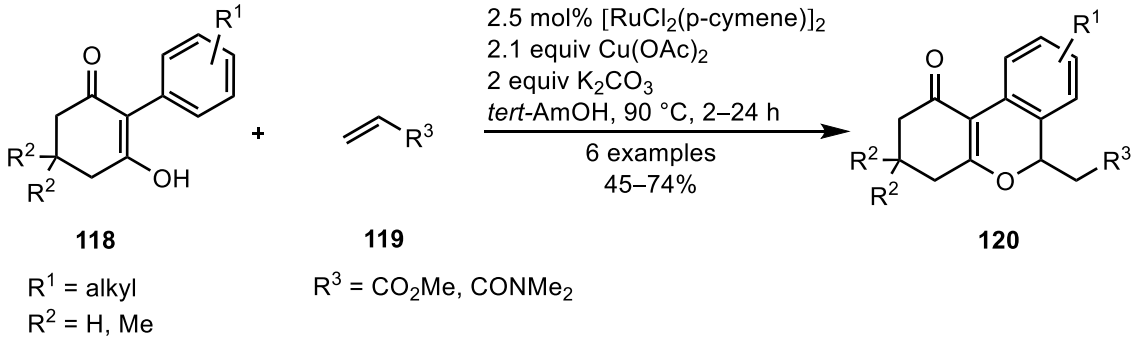
Direct C−H bond functionalization catalyzed by ruthenium complexes has been extensively studied.[70] However, only a few examples of ruthenium-catalyzed syntheses of annulated pyrans have been published. Among them, Ackermann´s group has reported an isocoumarin synthesis via the Ru-catalyzed annulation of substituted benzoic acids **115** with alkynes **116** (Scheme 27).[71] The reaction starts with an *ortho*-C−H bond cycloruthenation to form a five-

membered ruthenacycle intermediate, followed by regioselective alkyne insertion. Subsequent reductive elimination gives the desired isocoumarin **117** and regenerates the active ruthenium species for the next catalytic cycle using copper acetate. Later on, Wu et al. have performed the same transformation using 5 mol% $[RuCl_2(p\text{-cymene})]_2$ and 2 equivalents of pivalic acid in water at 80 °C under air.[72]



Scheme 27. Ru-catalyzed synthesis of isocoumarins **117**.

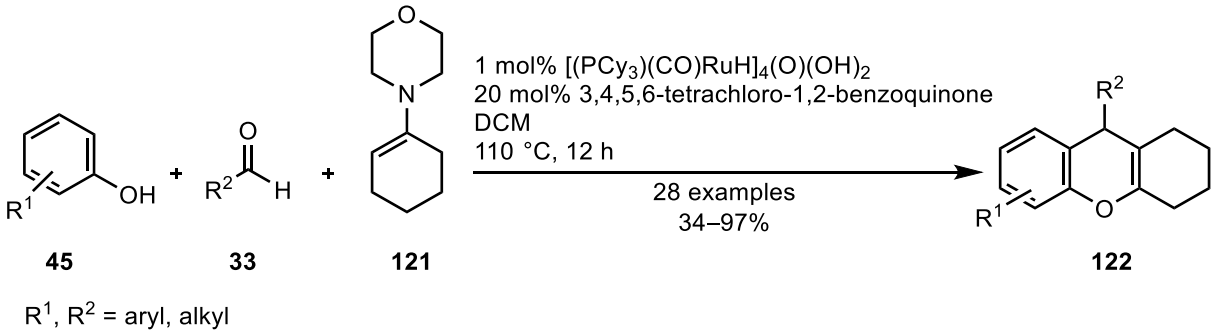
Lam and coworkers have reported the Ru-catalyzed annulation of 2-aryl-3-hydroxy-2-cyclohexenones **118** with alkenes **119** (Scheme 28).[73] The resulting *O*-heterocycles **120** were formed in a reaction between 1 equivalent **118** and 2 equivalents **119**, in the presence of 2.5 mol% $[RuCl_2(p\text{-cymene})]_2$, 2.1 equivalents $Cu(OAc)_2$ and 2.0 equivalents K_2CO_3.



Scheme 28. Ru-catalyzed synthesis of 2,3,4,6-tetrahydro-1*H*-benzo[*c*]chromen-1-ones **120**.

Multicomponent reactions (MCRs) can be defined as one-pot chemical reactions among more than two substrate molecules that produce a single organic molecule that retains all or most of the atoms of the reactants.[74] They avoid the isolation and purification of reaction intermediates and are therefore preferred over multistep synthesis. Their operational simplicity, high bond-forming efficiency, high atom economy, and low waste production minimize the cost, time and energy required to perform chemical syntheses. The use of the inert C−H bond as a coupling site in multicomponent reactions significantly expands the range of applications of both C−H bond functionalizations and multicomponent reactions. Several reports have been devoted to

the development of the implementation of C−H bond functionalization in multicomponent reactions.[75] Recently, a Ru-catalyzed multicomponent reaction between phenols **45**, aldehydes **33** and 4-(1-cyclohexene-1-yl)morpholine (**121**) has been developed for the synthesis of xanthenes **122** (Scheme 29).[76] The reaction takes place using the tetranuclear Ru complex $[(PCy_3)(CO)RuH]_4(O)(OH)_2$ as catalyst and 3,4,5,6-tetrachloro-1,2-benzoquinone as ligand.



45 **33** **121** **122**

R^1, R^2 = aryl, alkyl

Scheme 29. Ru-catalyzed MCR for the synthesis of xanthenes **122**.

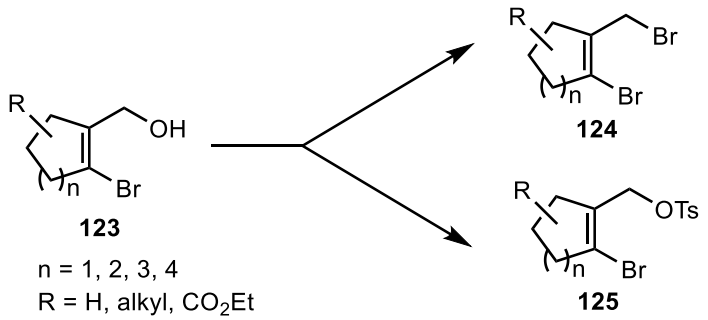
4 Aim of the work

Transition metal-catalyzed reactions have become essential tools in the preparation of heterocycles. Oxygen-containing heterocycles are of particular interest as they are ubiquitous in various naturally occurring and synthetic compounds such as natural products, pharmaceuticals, and agrochemicals. Among *O*-heterocycles, pyrans have attracted significant attention due to their numerous versatile biological properties and diverse applications in the synthesis of various classes of compounds, including chromenes, flavonoids, coumarins, xanthenes, and xanthones.

Although transition metal-catalyzed reactions have been successfully employed to synthesize numerous classes of heterocycles, there is still great potential to be explored in this field of research. In addition, only a limited number of methods are known for the synthesis of partially saturated pyrans and annulated pyrans. Therefore, there is a significant need for the development of new synthetic methods for the efficient preparation of annulated and bisannulated pyrans.

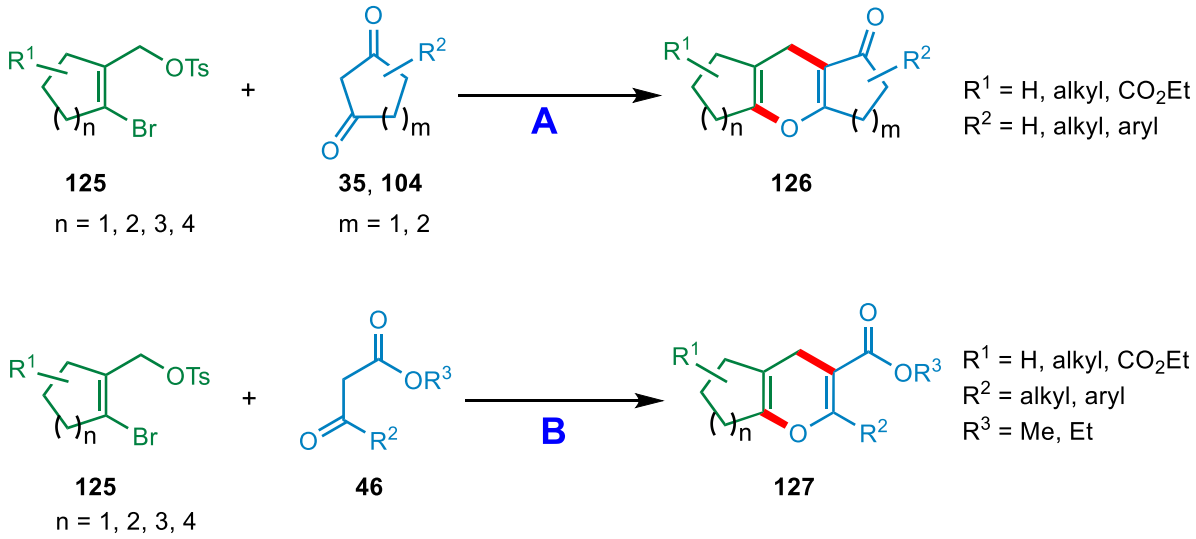
In organic synthesis, the efficiency of synthetic methods can be significantly increased by using domino reactions, in which multiple bonds are formed in one reaction step, instead of forming one bond after the other. This can be delivered for example by the use of bisfunctionalized substrates, which have not yet received sufficient attention.

The present work aims to develop novel transition metal-catalyzed synthetic methods for the preparation of annulated as well as bisannulated partially saturated pyrans. To achieve these transformations, the first goal is to synthesize new 1,3-biselectrophilic substrates. In the first approach, suitable 1-bromoallyl bromides **124** had to be synthesized. However, since 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) (n = 2, R = H) was found to be skin and eye irritating, it was decided to test whether the 1-bromoallyl bromides **124** could be replaced by the corresponding 1-bromoallyl tosylates **125**. Both the 1-bromoallyl bromides **124** and the 1-bromoallyl tosylates **125** should be synthesized from the corresponding 1-bromoallyl alcohols **123** (Scheme 30).



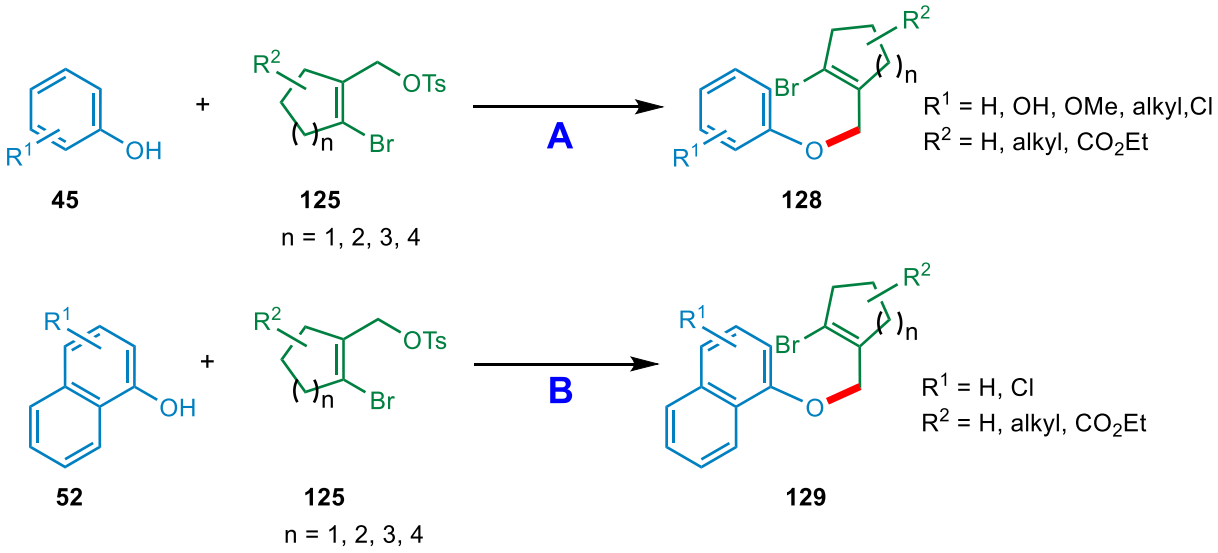
Scheme 30. Proposed synthesis of 1,3-biselectrophilic substrates **124** and **125**.

The first objective of this thesis was to study whether bisannulated and annulated pyrans **126**, **127** can be made available from 1-bromoallyl tosylates **125** as biselectrophiles and 1,3-dicarbonyls **35**, **46**, **104** as bisnucleophiles under Cu(I)-catalyzed reaction conditions by means of a Cu(I)-catalyzed transition-metal domino *C*-allylation/*O*-vinylation (Scheme 31). For this purpose, it was planned to optimize the reaction conditions of a model reaction, followed by studying scope and limitations of the method.



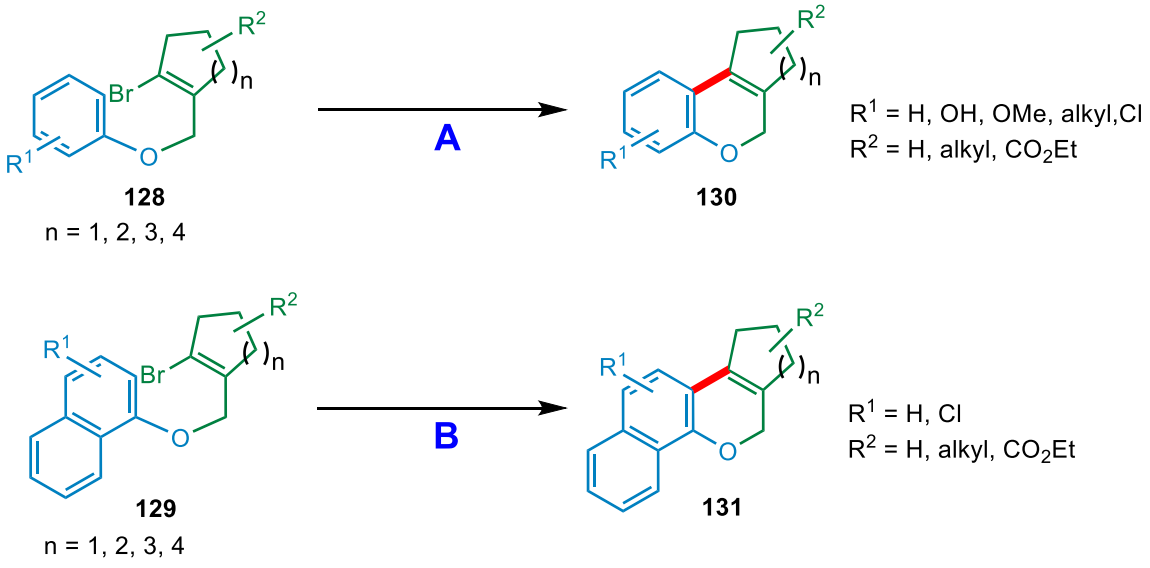
Scheme 31. Proposed synthesis of bisannulated and annulated 4*H*-pyrans **126**, **127** based on a domino *C*-allylation/*O*-vinylation between cyclic 1-bromoallyl tosylates **125**, 1,3-dicarbonyls **35**, **104** (reaction **A**) and **46** (reaction **B**).

In pursuit of the main objective of developing new synthetic methods for the formation of annulated and bisannulated pyrans, the second objective of this thesis was established. Initially, novel substrates, namely 2-bromo-1-(aryloxymethyl)cycloalk-1-enes **128** and 2-bromo-1-(naphthalenoxymethyl)cycloalk-1-enes **129** should be prepared by the reaction between phenols **45** or naphthols **52** and the previously synthesized 1-bromoallyl tosylates **125** (Scheme 32).



Scheme 32. Proposed synthesis of 2-bromo-1-(aryloxymethyl)cycloalk-1-enes **128** (reaction **A**) and 2-bromo-1-(naphthalenoxymethyl)cycloalk-1-enes **129** (reaction **B**).

Subsequently, the substrates **128** and **129** were to be efficiently and selectively converted to the corresponding 3,4-annulated 2*H*-chromenes **130** and 3,4-annulated 2*H*-naphtho[1,2-*b*]pyrans **131** by transition metal-catalyzed intramolecular aromatic C−H alkenylation, respectively. For this purpose, it was planned to optimize the reaction conditions of a model reaction employing a range of transition metal catalysts, such as $Pd(OAc)_2$, $Cu(acac)_2$ and $RuCl_2(PPh_3)_3$, followed by studying scope and limitations of the newly developed method (Scheme 33).

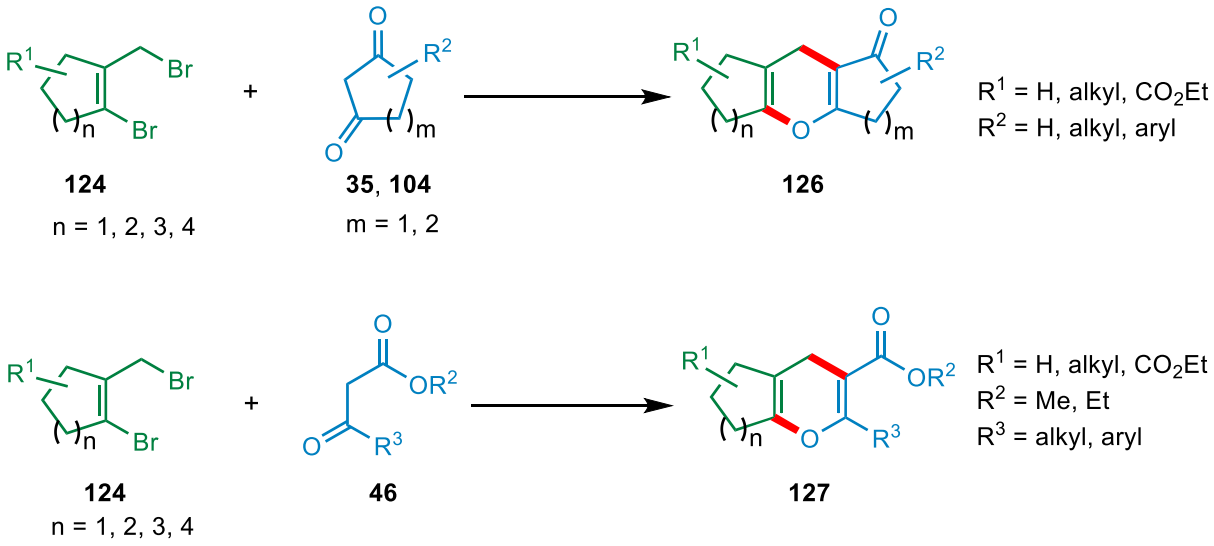


Scheme 33. Proposed synthesis of 3,4-annulated 2*H*-chromenes **130** and 3,4-annulated 2*H*-naphtho[1,2-*b*]pyrans **131** based on a transition metal-catalyzed intramolecular aromatic C−H alkenylation of 2-bromo-1-(aryloxymethyl)cycloalk-1-enes **128** (reaction **A**) and 2-bromo-1-(naphthalenoxymethyl)cycloalk-1-enes **129** (reaction **B**).

II Results and Discussion

1 Cu(I)-catalyzed synthesis of 4*H*-pyrans[77]

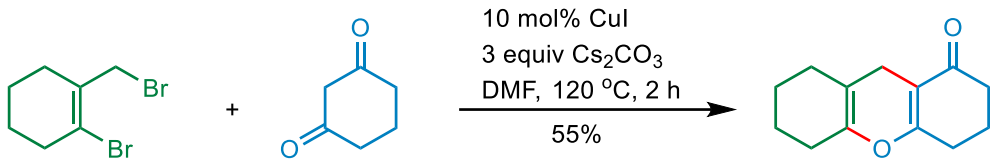
Previous studies performed in the research group of Beifuss on Cu(I)-catalyzed reactions for the synthesis of carbo- and heterocycles[54e, 62d,g,h] provided significant insights towards the development of a new straightforward synthetic approach to various annulated and bisannulated 4*H*-pyrans. Along these lines, a synthetic method was designed for the preparation of bisannulated and annulated 4*H*-pyrans **126**, **127** that is based on the reaction of 1-bromoallyl bromides **124** as biselectrophiles with cyclic and acyclic 1,3-dicarbonyls **35**, **46**, **104** as bisnucleophiles (Scheme 34). It is assumed that the annulations start with an intermolecular *C*-allylation which is followed by a Cu(I)-catalyzed intramolecular Ullmann type *O*-vinylation. A detailed account of the findings from this research is presented in this chapter.



Scheme 34. Synthesis of bisannulated and annulated 4*H*-pyrans **126**, **127** based on the Cu(I)-catalyzed *C*-allylation/*O*-vinylation reaction of cyclic 1-bromoallyl bromides **124** with cyclic and acyclic 1,3-dicarbonyls **35**, **46**, **104**.

1.1 Optimization of the model reaction between 1-bromo-2-(bromomethyl)cyclohex-1-ene (124a) and 1,3-cyclohexanedione (35a)

In order to assess the feasibility of the proposed *C*-allylation/*O*-vinylation sequence, the reaction between 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) and 1,3-cyclohexanedione (**35a**) to 2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126a**) was chosen as a model reaction.



124a **35a** **126a**

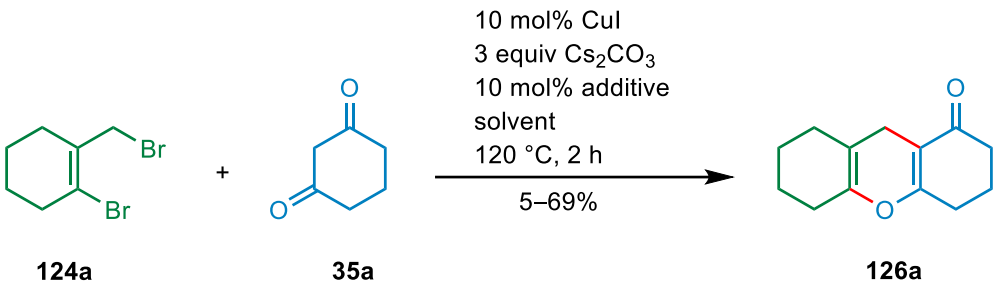
Scheme 35. Initial experiment for the Cu(I)-catalyzed synthesis of 2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126a**) from 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) and 1,3-cyclohexanedione (**35a**).

In the initial experiment, 1 equiv of 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) and 2 equiv of 1,3-cyclohexanedione (**35a**) were reacted in the presence of 10 mol% CuI as catalyst and 3 equiv Cs_2CO_3 as base (Scheme 35). The transformation was run in DMF at 120 °C for 2 h. Gratifyingly, the initial attempt furnished 2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126a**) as the product of the envisaged *C*-allylation/*O*-vinylation sequence in 55% yield. It should be mentioned that the reaction was performed in the absence of any additive.

1.1.1 Influence of additives and solvents

With this promising result in hand, the most important aims were to optimize the model reaction and to study scope and limits of this new method for the synthesis of bisannulated and annulated 4*H*-pyrans. To optimize the reaction conditions, the influence of additives, solvents, bases, reaction temperature, substrate concentrations on the yield of the model reaction was studied. To study scope and limitation of the new method, the reaction was performed with a number of different 1-bromoallyl tosylates **125** and a number of different 1,3-dicarbonyls **35**, **46**, **104**. The results concerning the optimization are disclosed in Tables 1−3 and the results concerning scope and limitation are shown in Tables 4−6.

Table 1. Influence of additives and solvents on the outcome of the model reaction.[a]



124a **35a** **126a**

entry	additive	solvent	yield **126a** (%)
1	acetic acid	H_2O	5[b]
2	isovaleric acid	DMF	37
3	tartaric acid	DMF	52
4	phenanthroline	DMF	53
5	8-hydroxyquinoline	DMF	54
6	L-proline	DMF	54
7	acetic acid	*i*-PrOH	55[c]
8	2-picolinic acid	DMSO	55
9	2-picolinic acid	CH_3CN	56[c]
10	acetic acid	NMP	56
11	pivalic acid	DMF	56
12	propionic acid	DMF	57
13	citric acid	DMF	59
14	bipyridine	DMF	60
15	acetic acid	DMF	64
16	2-picolinic acid	NMP	67
17	2-picolinic acid	DMF	69

[a]The reactions were performed using 1 mmol **124a** and 2 mmol **35a** in a round-bottomed flask under argon. [b]T = 90 °C. [c]T = 70 °C).

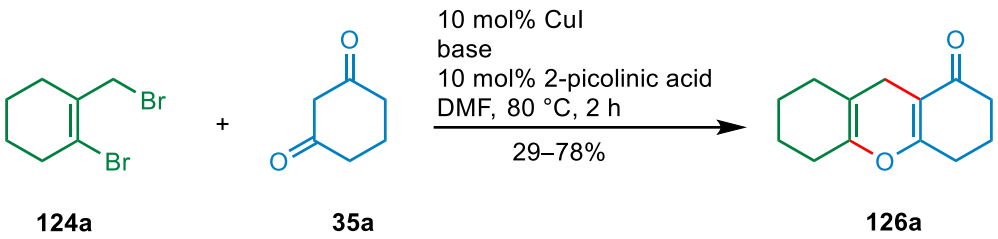
First, the impact of additives and solvents on the yield of the model reaction was explored (Table 1). The findings provided valuable insights for optimizing the reaction conditions and selecting the most suitable additives and solvents to achieve high yields of model compound **126a**. The experiments revealed that the reactions could be carried out in the presence of various additives in various solvents with yields ranging from only 5% with acetic acid in H_2O (Table

1, entry 1) to 69% using 2-picolinic acid as additive and DMF as solvent (Table 1, entry 17). Among all additives used, only two acidic additives exhibited yields surpassing 60%. Acetic acid led to the isolation of compound **126a** in 64% yield (Table 1, entry 15), while 2-picolinic acid resulted in the formation of **126a** in 67% yield in *N*-methyl-2-pyrrolidone (NMP) and 69% yield in DMF (Table 1, entries 16, 17). To further optimize the reaction conditions, subsequent experiments were conducted using different solvents with acetic acid and 2-picolinic acid as additives. Notably, these investigations demonstrated that the reaction could be successfully conducted in alternative solvents, including NMP, *i*-PrOH, dimethyl sulfoxide (DMSO) and CH_3CN (Table 1, entries 7−10, 16). However, it was observed that the highest yield for **126a**, utilizing 10 mol% of 2-picolinic acid as additive, was achieved when DMF was employed as the solvent (Table 1, entry 17). Hence, all subsequent reactions were carried using 2-picolinic acid as additive and DMF as the solvent.

1.1.2 Influence of bases, reaction temperature and substrate concentrations

Next, the impact of different bases, reaction temperatures and substrate concentrations on the outcome of the model reaction were addressed. These discoveries are valuable for understanding the factors affecting the efficacy of the model reaction. The obtained yields are displayed in Table 2, arranged in ascending order from lowest to highest yields.

Table 2. Influence of different bases, the reaction temperature and the amounts of **124a**, **35a** and Cs_2CO_3 on the outcome of the model reaction.[a]



124a **35a** **126a**

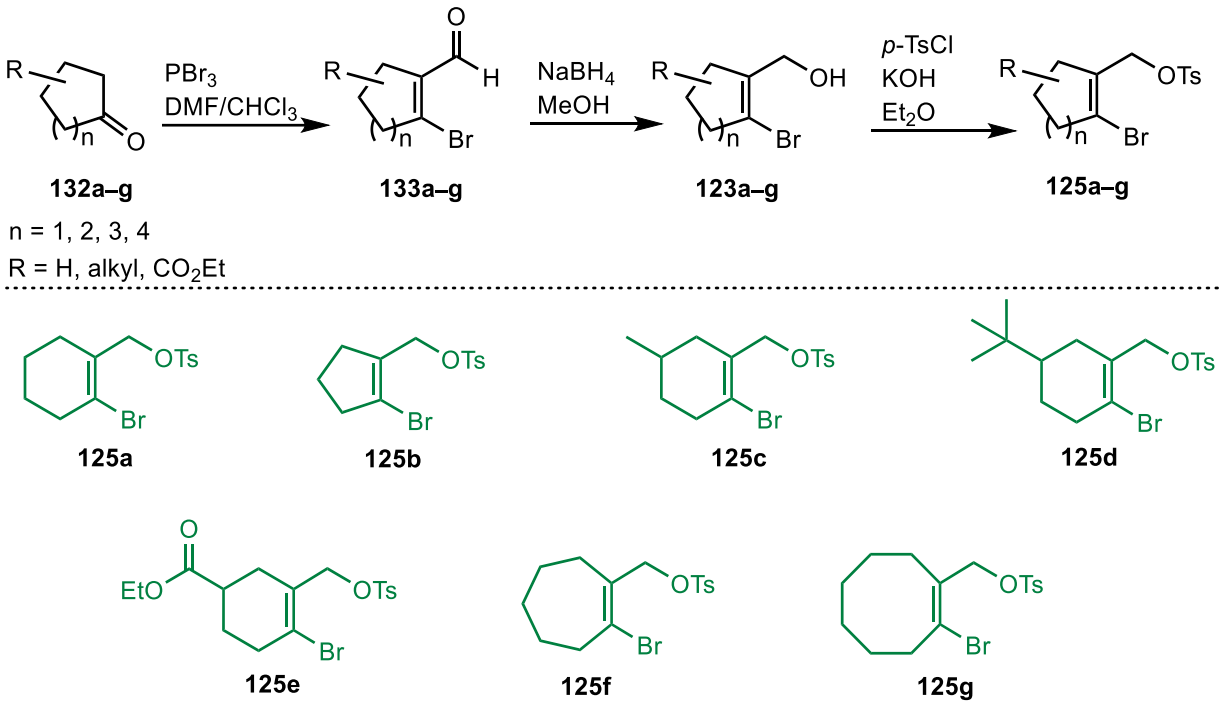
entry	molar ratio **124a** : **35a**	Base (equiv)	yield **126a** (%)
1	1:1	Cs_2CO_3 (2)	-[b]
2	1:2	$NaHCO_3$ (3)	29[c]
3	1:2	K_2CO_3 (3)	39[c]
4	1:2	Cs_2CO_3 (3)	41[d]
5	1:2	K_3PO_4 (3)	47[c]
6	1:2	Cs_2CO_3 (3)	61[e]
7	1:2	Cs_2CO_3 (3)	66
8	1:2	Cs_2CO_3 (3)	69[c]
9	1:1	Cs_2CO_3 (2)	70
10	1:1	Cs_2CO_3 (2)	74[f]
11	1:1.2	Cs_2CO_3 (2.4)	75[f]
12	1:1.2	Cs_2CO_3 (2.2)	77[f]
13	1:1.2	Cs_2CO_3 (2.2)	78[f,g]

[a]The reactions were performed in a round-bottom flask under argon. [b]The reaction was performed in the absence of a Cu source. [c]T = 120 °C. [d]T = 70 °C. [e]T = 90 °C. [f]The reaction was performed in the presence of 70 mg molecular sieves (4 Å). [g]The reaction was performed in a sealed vial under argon.

First of all, however, the importance of the presence of a Cu(I) salt for the successful course of the reaction was demonstrated. For this purpose, a control experiment was run. It was found that in the absence of any copper source, no product was formed (Table 2, entry 1). Next, the reaction was performed with a number of different bases. When Cs_2CO_3 was replaced with $NaHCO_3$ as the base, the yield of **126a** dropped to 29% (Table 2, entry 2). Similarly, the substitution of Cs_2CO_3 with K_2CO_3 resulted in a decrease of the yield to 39% (Table 2, entry 3). When Cs_2CO_3 was replaced with K_3PO_4 **126a** was isolated in a yield of 47% (Table 2, entry

5). These experiments showed that Cs_2CO_3 can be replaced by other bases; however, they also demonstrated that the yields were significantly lower with all other bases. Consequently, Cs_2CO_3 was chosen as the base for all subsequent reactions due to its relatively higher yield compared to the other bases. Next, the influence of the reaction temperature was addressed. When the reaction temperature was lowered from 120 ^oC to 70 ^oC, the yield of **126a** decreased from 69% to 41% (Table 2, entries 8, 4). However, the transformation could be successfully conducted at 80 ^oC without any significant loss of yield (Table 2, entry 7). Therefore, it was decided to carry out all further reactions at 80 ^oC. In all previous reactions 1 equiv of 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) was reacted with a twofold excess of 1,3-cyclohexanedione (**35a**) and three equiv of Cs_2CO_3 as a base. To address the potential influence of the water that is formed during the reaction on enolate formation and yield, the model reaction was run in the presence of molecular sieves (4 Å) (Table 2, entries 10−13). Due to the increase in yield observed when the reactions were run in the presence of molecular sieves, all subsequent reactions were carried out in the presence of 70 mg of molecular sieves (4 Å) per mmol of substrate **124**. Surprisingly, it was found that reducing the amount of **35a** to 1 equivalent and reducing the amount of Cs_2CO_3 to 2 equivalents resulted in a slight improvement in the yield of **126a** to 74% (Table 2, entry 10). To further optimize the reaction conditions, some additional adjustments in the molar ratio of **124a**/**35a** and the amount of base were made. These modifications led to a slight increase in yield to 75% and 77%, resp. (Table 2, entries 11, 12). Similar results were obtained when the model reaction was performed in a sealed vial instead of an open flask (Table 2, entry 13).

During the course of the optimization, 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) was found to be irritating to both skin and eyes. In order to avoid these undesirable effects, an alternative compound, namely 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**), was synthesized following the synthetic pathway outlined in Scheme 36 and used as the starting material for subsequent experiments. In addition to **125a** a number of 2-bromo-1-(4'-methylbenzenesulfonatemethyl)-1-enes **125** were synthesized.



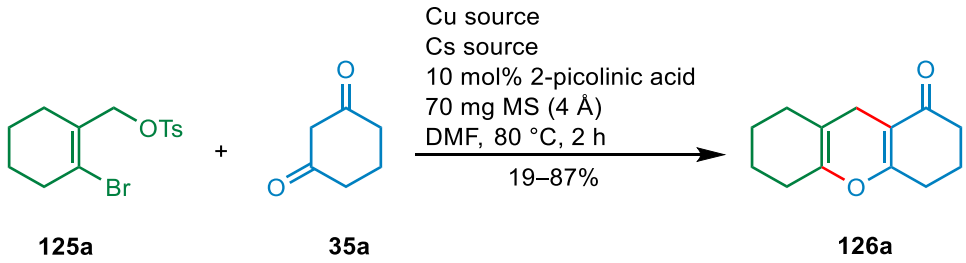
Scheme 36. Synthesis of the 2-bromo-1-(4'-methylbenzenesulfonatemethyl)-1-enes **125a–g**.

According to Arnold et al. the 1-bromoallyl tosylates **125a–g** were synthesized in three steps.[78] In the first step, the *α*-methylene ketones **132a–g** were subjected to Vilsmeier-Haack conditions. This reaction led to the formation of 2-bromo-1-enecarbaldehydes **133a–g**. The reduction of these aldehydes resulted in the formation of (2-bromo-1-en-1-yl)methanols **123a–g**. A final tosylation of **123a–g** furnished the required 2-bromo-1-(4'-methylbenzenesulfonatemethyl)-1-enes **125a–g** (Scheme 36).

1.2 Optimization of the model reaction between 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (125a) and 1,3-cyclohexanedione (35a)

With 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) in hand this compound was reacted with 1,3-cyclohexanedione (**35a**) under the reaction conditions previously optimized for the synthesis of **126a** using 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) as substrate (Table 2, entry 13). The experiment showed that the replacement of 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) with the corresponding tosylate **125a** increased the yield of **126a** from 78 to 87% (Table 3, entry 1). Subsequently, a number of additional optimization reactions using **125a** as the substrate were carried out (Table 3).

Table 3. Optimization reactions with 2-bromo-1-(4'-methylbenzenesulfonatemethyl) cyclohex-1-ene (**125a**) as substrate.[a]



125a **35a** **126a**

entry	Cu source (mol%)	base (equiv)	yield **126a** (%)
1	CuI (10)	Cs_2CO_3 (2.2)	87
2	CuI (10)	Cs_2CO_3 (1.1)	19
3	CuI (10)	Cs_2CO_3 (3.3)	84
4	CuCl (10)	Cs_2CO_3 (2.2)	77
5	CuBr (10)	Cs_2CO_3 (2.2)	73
6	CuI (5)	Cs_2CO_3 (2.2)	46
7	CuI (10)	Cs_2CO_3 (2.2)	41[b]
8	CuI (10)	CsF (2.2)	43
9	CuI (10)	CsOAc (2.2)	28

[a]The reactions were performed in a sealed vial with 0.5 mmol of **125a** and 0.6 mmol of **35a** under argon. [b]The reaction was performed using 5 mol% 2-picolinic acid.

First, the impact of the amount of Cs_2CO_3 was studied. As expected, when the amount of Cs_2CO_3 was decreased from 2.2 equivalents to 1.1 equiv, a notable decline in the yield of **126a** was observed. Under these conditions, **126a** was formed in only 19% (Table 3, entry 2). This reduction in yield emphasizes the importance of an adequate amount of Cs_2CO_3 in the reaction. On the other hand, increasing the amount of Cs_2CO_3 to 3.3 equiv, had only a negligible effect on the yield of compound **126a** (Table 3, entry 3). This indicates that beyond a particular threshold, additional amounts of Cs_2CO_3 do not significantly contribute to the overall yield. To explore alternative Cu(I) catalysts sources, the model reaction was performed using 10 mol% CuCl and 10 mol% CuBr (Table 3, entries 4, 5). It was found that the yields obtained with 10 mol% CuCl and 10 mol% CuBr, resp., were inferior to those achieved with 10 mol% CuI. This suggests that CuI is a more efficient catalyst for the synthesis of **126a**.

Furthermore, when the amount of CuI was reduced to 5 mol%, there was a significant decrease in the yield of **126a** from 87% to 46% (Table 3, entry 6). This decrease emphasizes the significance of maintaining an appropriate concentration of CuI for optimal yield. In addition, a reduction in the amount of 2-picolinic acid from 10 mol% to 5 mol% dropped the yield of **126a** to 41% (Table 3, entry 7). To study the impact of different anions of the cesium base, the model reaction was conducted with 2.2 equiv of CsF and CsOAc, respectively (Table 3, entries 8, 9). However, these experiments have confirmed that Cs_2CO_3 still remains the optimal base for this model reaction, as it yielded higher amounts of **126a** as compared to other cesium bases. In conclusion, the most favorable reaction conditions established for substrate **124a** were also found to be ideal for substrate **125a**. Therefore, all subsequent annulations were performed using 1-bromoallyl tosylates **125a–g** as substrates, following the conditions outlined in Table 3, entry 1.

With the optimized conditions at hand, the applicability of the new synthetic method for the preparation of 4*H*-pyran derivatives has been studied. For this purpose, a collection of different 1,3-dicarbonyls **35a–h**, **104**, **46a–e**, **134a–c** was chosen as substrates (Figure 8). Reactions between 1-bromoallyl tosylates **125a–g** as biselectrophiles and cyclic and acyclic 1,3-dicarbonyls **35a–h**, **104**, **46a–e** as bisnucleophiles confirmed the successful application of the optimized synthetic method for the synthesis of a broad range of annulated and bisannulated 4*H*-pyrans. The results obtained are displayed in Tables 4−6.

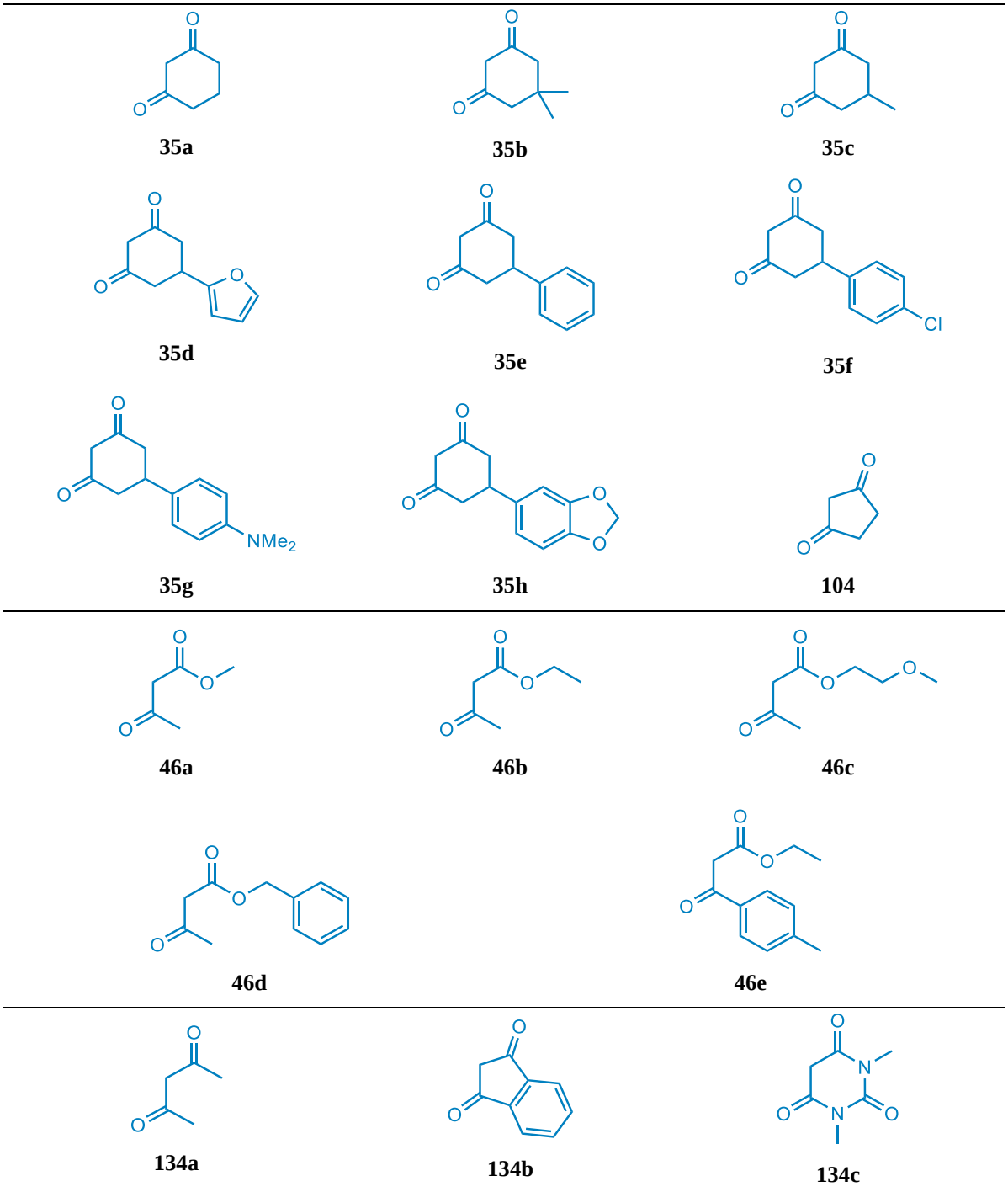
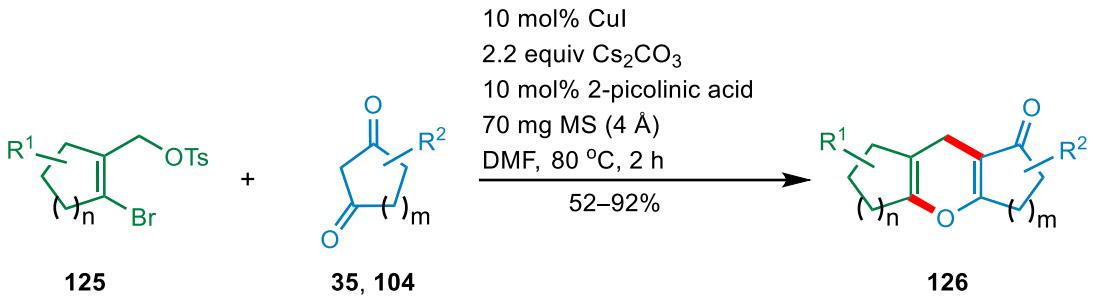


Figure 8. Selected 1,3-dicarbonyls used as substrates for the synthesis of 4*H*-pyrans.

1.3 Synthesis of xanthenes and related bisannulated 4*H*-pyrans 126a–p

The scope of the newly developed Cu(I)-catalyzed process was initially studied by performing reactions between 1-bromoallyl tosylates **125a–g** and cyclic 1,3-dicarbonyls **35a–h**, **104**. The results are summarized in Table 4.

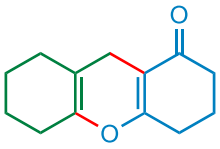
Table 4. Reaction of 1-bromoallyl tosylates **125a–g** with cyclic 1,3-diketones **35a–h**, **104**.[a]



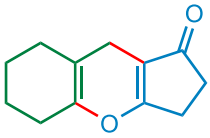
125 **35**, **104** **126**

n = 1, 2, 3, 4; R^1 = H, alkyl, CO_2Et

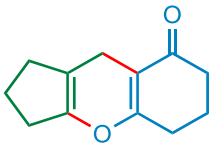
m = 1, 2; R^2 = H, alkyl, aryl



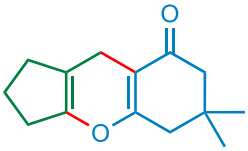
126a, 87%



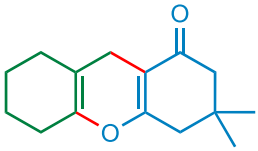
126b, 78%



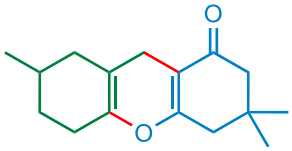
126c, 76%



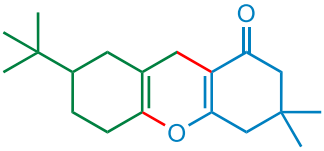
126d, 81%



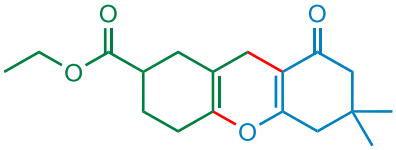
126e, 92%



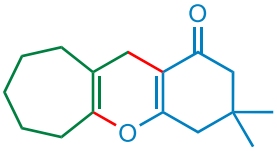
126f, 79%



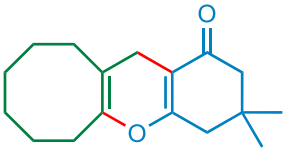
126g, 89%



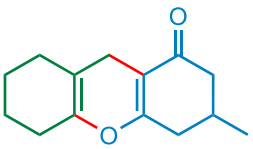
126h, 52%



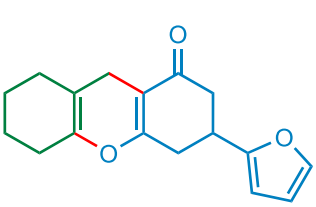
126i, 64%



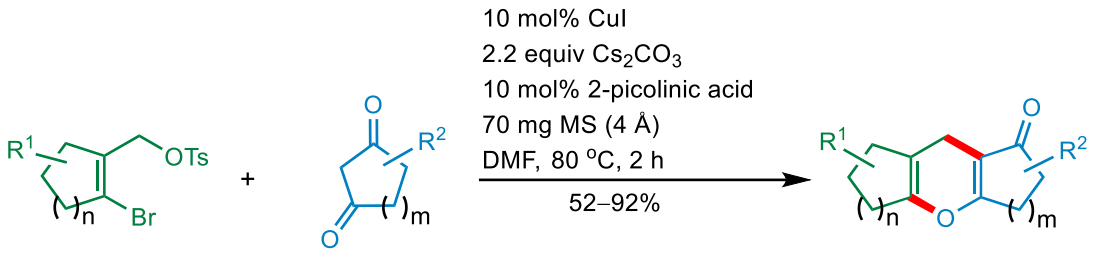
126j, 71%



126k, 83%



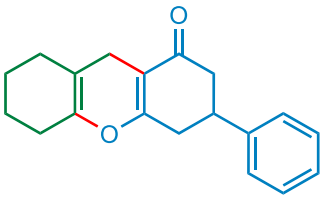
126l, 79%



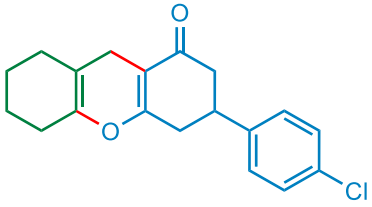
125 **35**, **104** **126**

n = 1, 2, 3, 4
R^1 = H, alkyl, CO_2Et

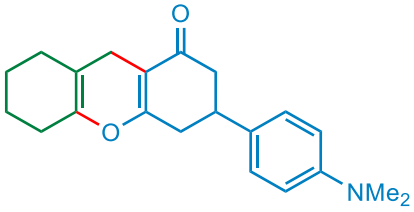
m = 1, 2
R^2 = H, alkyl, aryl



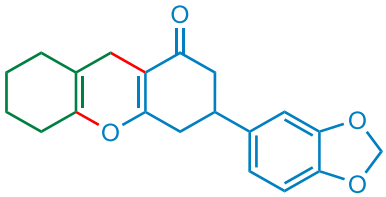
126m, 74%



126n, 72%



126o, 86%



126p, 54%

[a]All reactions were performed using 0.5 mmol of **125** and 0.6 mmol of **35**, **104** in a sealed vial under argon.

The successful reaction between 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) and cyclohexane-1,3-dione (**35a**), which resulted in the formation of a 6-6-6-system, prompted further investigation to determine whether the novel transformation allowed for the synthesis of other skeletal structures, such as 6-6-5-, 5-6-6-, 7-6-6- and 8-6-6-systems. For the synthesis of a 6-6-5-system, **125a** was reacted with cyclopentane-1,3-dione (**104**). The reaction was carried out under standard conditions and yielded exclusively 2,3,4,5,6,7-hexahydrocyclopenta[*b*]chromen-1(9*H*)-one (**126b**) in 78% yield. Subsequently, it was successfully demonstrated that the reactions of the five-membered 1-bromoallyl tosylate **125b** with cyclohexane-1,3-dione (**35a**) and dimedone (**35b**), respectively, delivered the corresponding bisannulated 5-6-6 skeletons, namely **126c** and **126d**, with yields of 76% and 81%, respectively. The successful reaction between **125b** and dimedone (**35b**) prompted us to study the transformation of 5,5-dimethyl-cyclohexane-1,3-dione (**35b**) with the six-membered

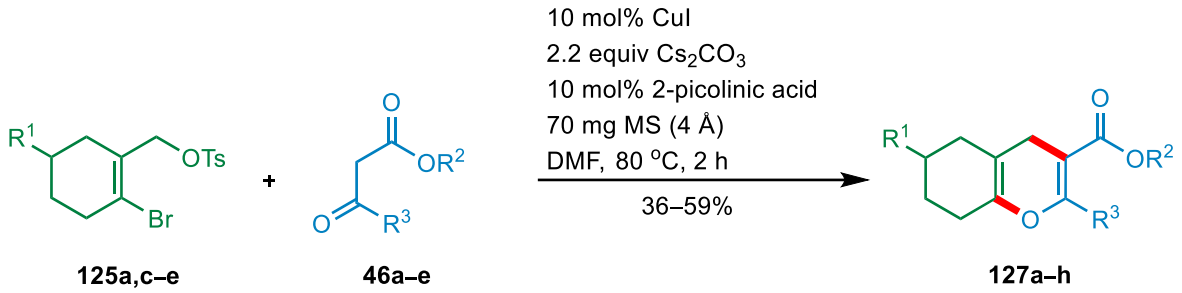
1-bromoallyl tosylate **125a**. It was found that the reaction proceeded readily to give the corresponding 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**) in 92% yield, surpassing the yield obtained for **126a**. The excellent yield for the reaction between the unsubstituted six-membered 1-bromoallyl tosylate **125a** and dimedone (**35b**) encouraged us to study the transformation of the 4-substituted 1-bromoallyl tosylates **125c**, **125d** and **125e** with dimedone (**35b**). Using 1-bromoallyl tosylates **125c** and **125d** carrying an electron-donating group at C-4, the annulation products **126f** and **126g** were isolated with yields of 79% and 89%, respectively. To study the effect of an electron-withdrawing group at C-4 of the bromoallyl tosylate on the course of the annulation process, ethyl 4-bromo-3-(4'-methylbenzenesulfonatemethyl)cyclohex-3-ene-1-carboxylate (**125e**) was reacted with dimedone (**35b**). The experiment clearly demonstrated that the expected annulation product, namely ethyl 3,3-dimethyl-1-oxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthene-7-carboxylate (**126h**) was formed. However, the isolated yield was only 52%. Further experiments between dimedone (**35b**) and the seven- and eight-membered 1-bromoallyl tosylates, **125f** and **125g**, were performed. The reaction of the seven-membered 1-bromoallyl tosylate **125f** yielded the 7-6-6-system **126i** in 64%, while the reaction with the eight-membered 1-bromoallyl tosylate **125g** provided the 8-6-6-system **126j** in 71% yield. Although the yields of **126i** and **126j** were lower than that of **126e**, these two experiments demonstrated the broad applicability of the new transformation. At last, 1-bromoallyl tosylate **125a** was reacted with various 5-monosubstituted cyclohexane-1,3-diones, namely 5-methyl-1,3-cyclohexanedione (**35c**), 5-(2-furyl)-1,3-cyclohexanedione (**35d**), 5-phenyl-1,3-cyclohexanedione (**35e**), 5-(chlorophenyl)-1,3-cyclohexanedione (**35f**), 5-[4-(dimethylamino)phenyl]-1,3-cyclohexanedione (**35g**), and 5-[3,4-(methylenedioxy)phenyl]-1,3-cyclohexanedione (**35h**) under the optimized reaction conditions. The annulation products **126k–p** were formed in yields ranging from 54 to 86%.

It has been demonstrated that the Cu(I)-catalyzed reaction of cyclic 1,3-dicarbonyls **35**, **104** and 1-bromoallyl tosylates **125** described here provides access to a number of bisannulated 4*H*-pyran derivatives, including 6-6-6-, 6-6-5-, 5-6-6-, 7-6-6- and 8-6-6-skeletons. The exclusive formation of the bisannulation products **126** that are derived from a domino intermolecular *C*-allylation/intramolecular *O*-vinylation, is remarkable. Important to note that the formation of byproducts resulting from an intermolecular *O*-allylation has not been observed. The results presented demonstrate that the first step of the domino process, the intermolecular *C*-allylation, is completely chemoselective.

1.4 Synthesis of chromenes 127a–h

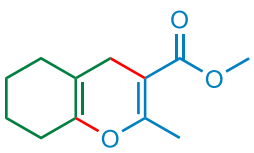
To further study the scope of the new Cu(I)-catalyzed domino intermolecular *C*-allylation/intramolecular *O*-vinylation domino process, reactions between 1-bromoallyl tosylates **125a,c–e** and acyclic *β*-ketoesters **46a–e** were performed. The results of this study are summarized in Table 5.

Table 5. Reaction of 1-bromoallyl tosylates **125a,c–e** with acyclic *β*-ketoesters **46a–e**.[a]

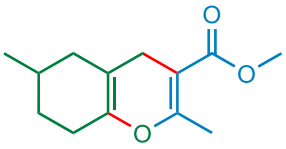


125a,c–e **46a–e** **127a–h**

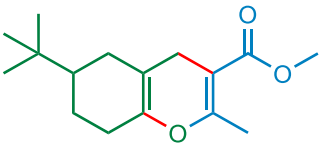
R^1 = H, alkyl, CO_2Et R^2 = Me, Et, CH_2CH_2OMe, CH_2Ph
R^3 = Me, aryl



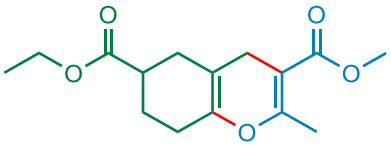
127a, 43%



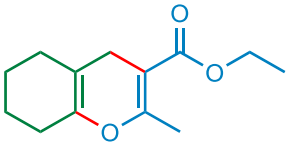
127b, 46%



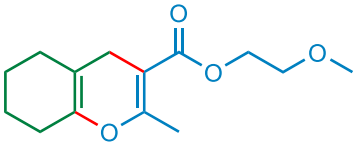
127c, 52%



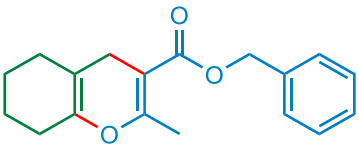
127d, 38%



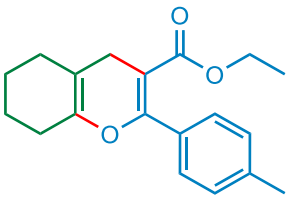
127e, 57%



127f, 36%



127g, 58%



127h, 59%

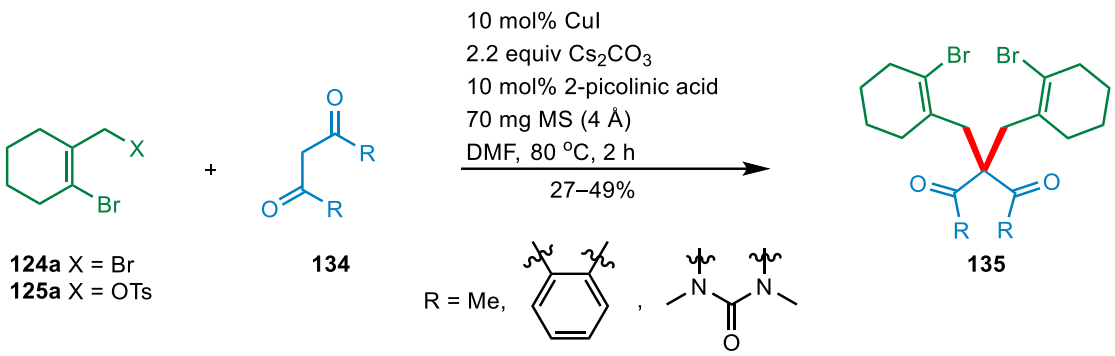
[a]All reactions were performed using 0.5 mmol of **125** and 0.6 mmol of **46** in a sealed vial under argon.

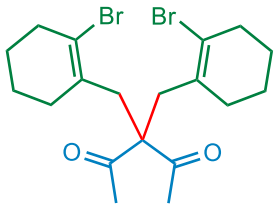
To start with, methyl acetoacetate (**46a**) was reacted with 1-bromoallyl tosylate **125a** under the standard reaction conditions outlined in Table 3, entry 1. This reaction furnished a single product, that was identified as methyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127a**), in 43 % yield. Methyl acetoacetate (**46a**) was also reacted with the 4-substituted 1-bromoallyl tosylates **125c–e** to deliver methyl 2,6-dimethyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127b**), methyl 6-(*tert*-butyl)-2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127c**) and 6-ethyl 3-methyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3,6-dicarboxylate (**127d**) with yields ranging from 38 to 52%. As already observed for the reactions between bromoallyl tosylates **125a,c–e** and dimedone (**35b**), the yields of the annulation products were dependent on the structural characteristics of the bromoallyl tosylates, i.e., the nature of the C-4 substituent. To study the influence of the structure of the *β*-ketoester **46** on the annulation additional experiments were performed using ethyl acetoacetate (**46b**), 2-methoxyethyl acetoacetate (**46c**), benzyl acetoacetate (**46d**) and ethyl (4-methylbenzoyl)acetate (**46e**) as substrates. The results obtained showed that the type of *β*-ketoester employed has a significant influence on both the yield and stability of the resulting 4*H*-chromene-3-carboxylates. The best result was obtained when 1-bromoallyl tosylate **125a** was reacted with **46e** to give ethyl 2-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127h**) in 59% yield. So far, only one example of a 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate is known in the literature. This compound, i.e. **127a**, has been synthesized by Fang and Li by means of a Cu(I)-catalyzed intramolecular *O*-vinylation.[57]

1.5 Synthesis of double alkylated compounds 135a–c

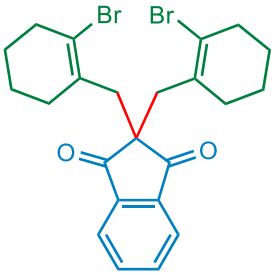
The Cu(I)-catalyzed intermolecular *C*-allylation/intramolecular *O*-vinylation was shown to allow the reaction of 1-bromoallyl tosylates **125a–g** with cyclic 1,3-diketones **35a–h**, **104** and acyclic *β*-ketoesters **46a–e**, leading to the formation of a wide range of annulated and bisannulated 4*H*-pyrans **126a–p** and **127a–h**. Nonetheless, it is essential to note that this methodology exhibits some limitations, which will be discussed in this chapter.

Table 6. Reaction of 1-bromoallyl bromide **124a**/1-bromoallyl tosylate **125a** with dicarbonyls **134a–c**.[a]

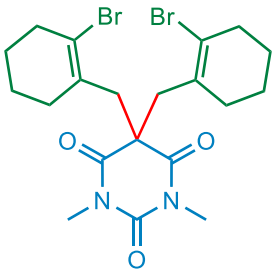




135a, 27%[b] / 38%[c]



135b, 37%[b] / 49%[c]



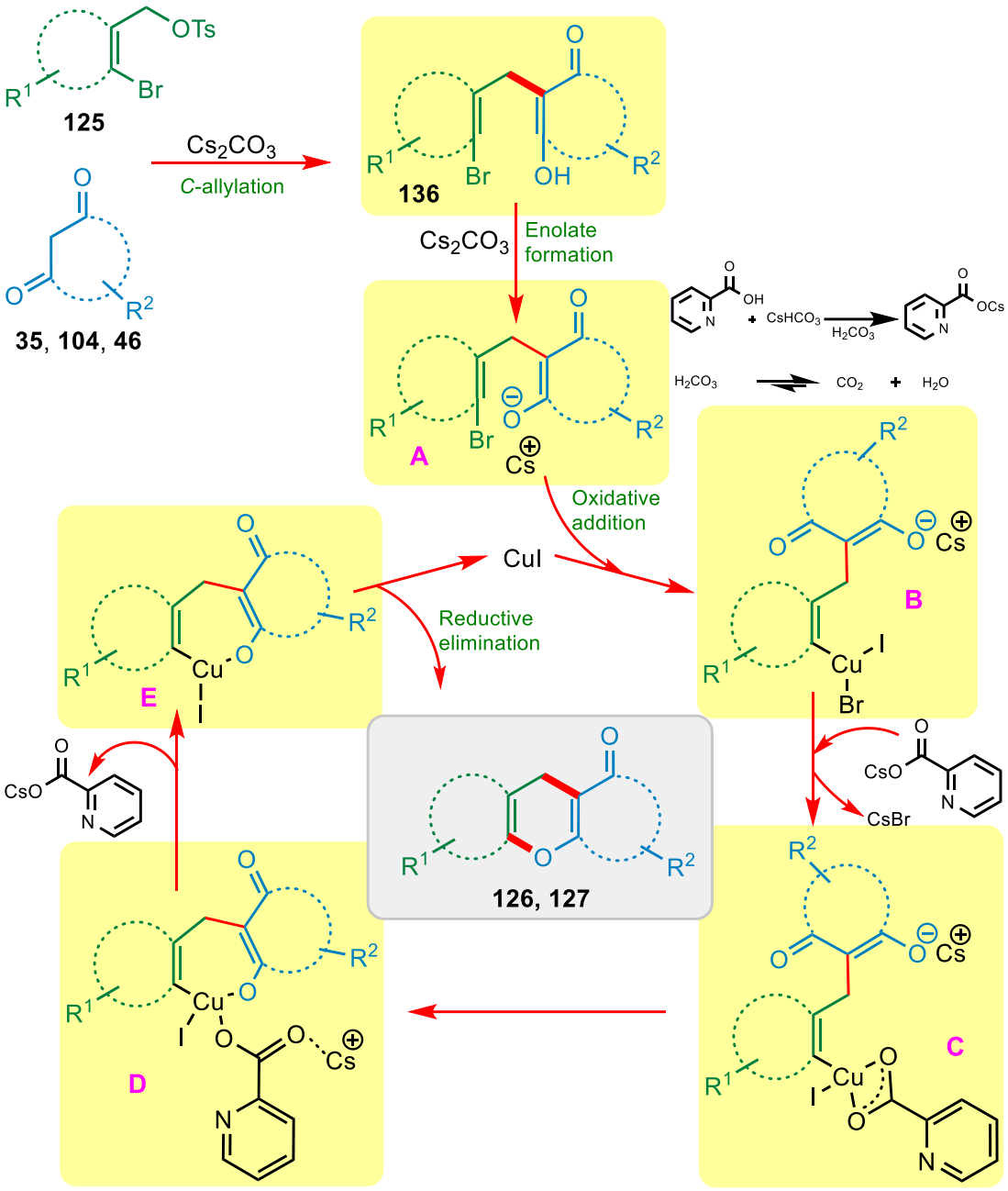
135c, 36%[b] / 47%[c]

[a]All reactions were performed using 0.5 mmol of **124a**/**125a** and 0.6 mmol of **134** in a sealed vial under argon. [b]Yield refers to reaction using **124a** as substrate. [c]Yield refers to reaction using **125a** as substrate.

The expected annulation products were not formed when 1-bromoallyl tosylate **125a** was reacted with acetylacetone (**134a**), 1,3-indanedione (**134b**) and 1,3-dimethylbarbituric acid (**134c**) under standard conditions. Surprisingly, the reaction yielded symmetrical compounds instead, namely 3,3-bis[(2-bromocyclohex-1-en-1-yl)methyl]pentane-2,4-dione (**135a**) in 38%, 2,2-bis[(2-bromocyclohex-1-en-1-yl)methyl]-2*H*-indene-1,3-dione (**135b**) in 49% and 5,5-bis[(2-bromocyclohex-1-en-1-yl)methyl]-1,3-dimethylbarbituric acid (**135c**) in 47% (Table 6). It is evident that these products arise from a double alkylation process. However, the reason for this unexpected reaction behavior remains unclear. To further investigate the possibility of achieving the desired annulation, an alternative substrate, namely 1-bromoallyl bromide **124a**, was tested. The reactions between **124a** and **134a–c** were carried out using the successful reaction conditions developed for the model reaction with **125a** as substrate (Table 3, entry 1). However, no annulation products were observed in any of the cases. Instead, the identical double alkylation products (**135a–c**) were consistently isolated. It should be noted that the

yields obtained using **124a** as the substrate were slightly lower compared to those obtained with **125a** (27−37%). As a result, it has been established that the reactions of both **124a** and **125a** with the dicarbonyls **134a–c** under standard conditions do not produce the expected annulation products.

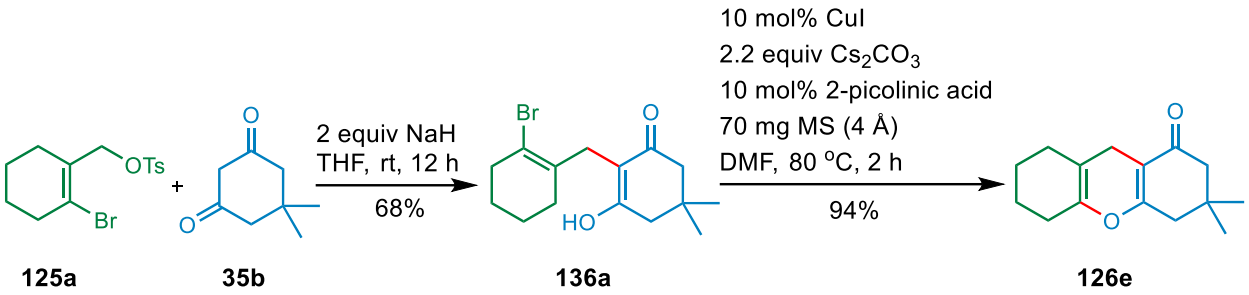
1.6 Mechanism



Scheme 37. Plausible reaction mechanism for the Cu(I)-catalyzed reaction of cyclic 1-bromoallyl tosylates **125** with the 1,3-diketones **35**, **104** and *β*-ketoesters **46**.

In accordance with previous research conducted in the Beifuss group,[62g] a plausible reaction mechanism for the annulations based on a Cu(I)-catalyzed domino intermolecular *C*-allylation/intramolecular *O*-vinylation process is illustrated in Scheme 37.

It is assumed that the reaction starts with an intermolecular *C*-allylation between a 1,3-dicarbonyl **35**, **104**, **46** and a 1-bromoallyl tosylate **125**. This reaction yields an intermediate of type **136**. Subsequently, in the second step an intramolecular *O*-vinylation takes place. It is initiated by the deprotonation of intermediate **136** with Cs_2CO_3 to form the corresponding cesium enolate **A** along with $CsHCO_3$. Upon reaction of $CsHCO_3$ with 2-picolinic acid, carbonic acid and cesium picolinate are generated. The decomposition of carbonic acid (H_2CO_3) results in the liberation of CO_2 and H_2O. The latter is removed from the reaction by adsorption using molecular sieves 4 Å. By means of an oxidative addition process, the Cu(III) species **B** is generated by the reaction between vinyl bromide **A** and the copper(I) salt. The exchange of bromide with picolinate induces the formation of copper complex **C**, which is facilitated by cesium picolinate. Subsequently, an intramolecular attack of cesium enolate on the chelated copper center furnishes intermediate **D**. This process results in the release of cesium picolinate, ultimately generating **E**. Finally, the generation of annulation products **126** or **127** occurs through the reductive elimination of **E**, which is accompanied by the formation of CuI.



Scheme 38. Synthesis of the proposed intermediate **136a** and its Cu(I)-catalyzed conversion into **126e**.

As depicted in Scheme 37, it is assumed that intermediate **136** is formed as the result of an intermolecular allylation. In order to provide evidence for the proposed mechanism, it was studied whether **136a** can act as a substrate for the Cu(I)-catalyzed intramolecular *O*-vinylation. To accomplish the synthesis of the proposed intermediate **136a**, 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) and dimedone (**35b**) were reacted under basic conditions (NaH). As expected, 2-[(2-bromocyclohex-1-en-1-yl)methyl]-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**136a**) was formed with a yield of 68% (Scheme 38).[62d] Subsequently, **136a** underwent a successful intramolecular *O*-vinylation reaction, when it was reacted with 10 mol% CuI as catalyst, 2.2 equiv Cs_2CO_3 as base and 10 mol% 2-picolinic acid as ligand in the presence of molecular sieves (4 Å) in DMF at 80 °C for 2 h (Scheme 38). The annulation product **126e** was obtained exclusively in 94% yield. This finding indicates that compounds of type **136** can effectively function as intermediates for the synthesis of annulated 4*H*-pyrans **126** and **127**. Furthermore, it provides substantial evidence in support of the proposed reaction mechanism depicted in Scheme 37.

1.7 Structure elucidation of 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126e)

A thorough investigation based on data obtained from 2D NMR spectroscopy, IR spectroscopy, and mass spectrometry has been conducted to elucidate the structures of the 1-bromoallyl tosylates **125**, the annulation products **126** and **127** as well as the double alkylated compounds **135** synthesized in this work. Nevertheless, to attain accurate structural elucidation of newly discovered compounds, 2D NMR analysis was further complemented by performing spectral simulations using NUMMRIT algorithm implemented in SpinWorks software.[79] To provide an illustrative example, in this chapter the structural elucidation process of 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**) is illustrated.

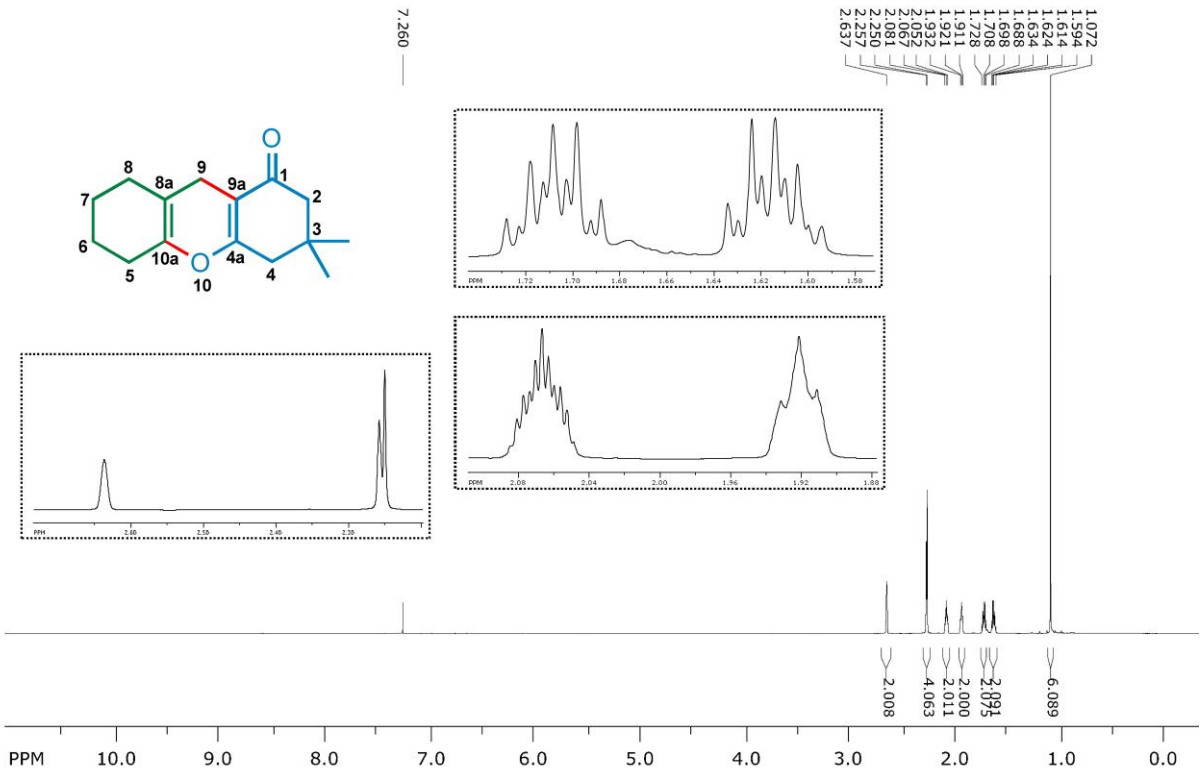


Figure 9. ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) of compound **126e**.

Figure 9 presents the ^{1}H NMR spectrum of **126e**, which was recorded on a 600 MHz spectrometer using deuterated chloroform as the solvent. In this spectrum, a total of seven hydrogen peaks were observed and subsequently integrated.

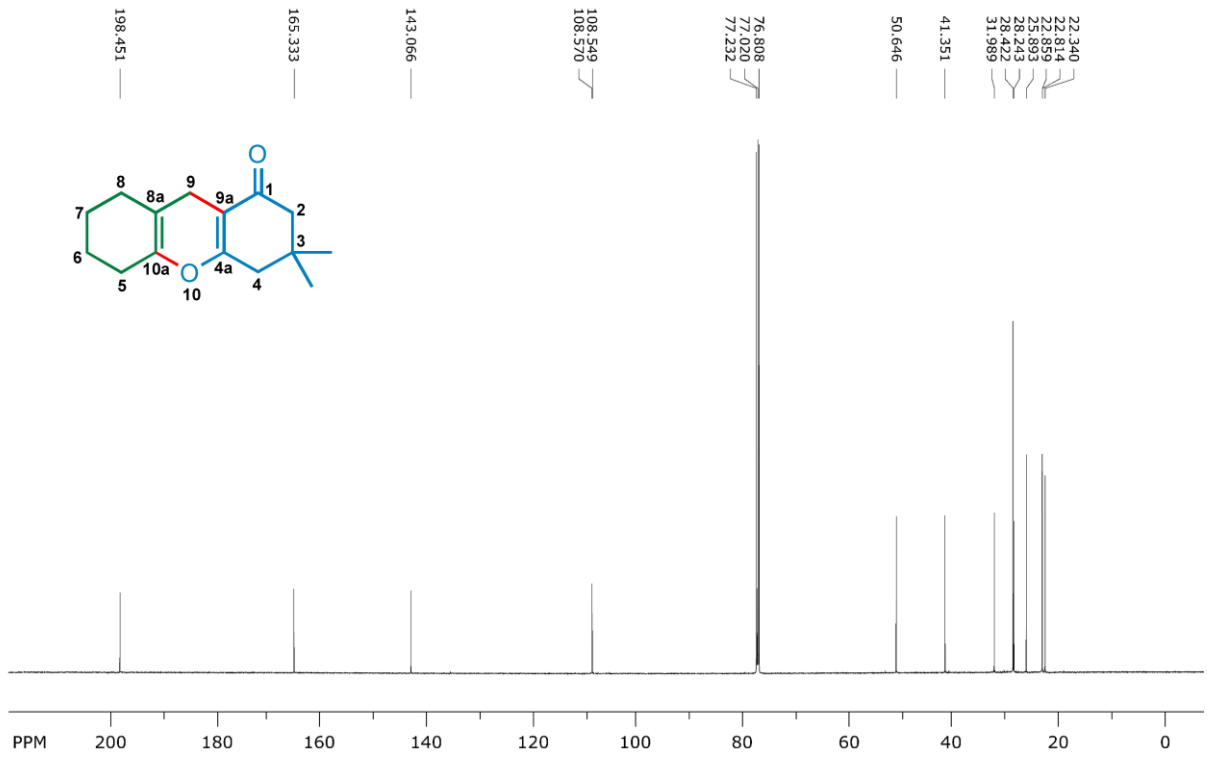


Figure 10. ^{13}C NMR spectrum ($CDCl_3$, 150 MHz) of compound **126e**.

In the ^{13}C NMR spectrum, a total of fourteen signals were detected (Figure 10). Among them, C-1 exhibited the highest chemical shift value at δ = 198.4 ppm, indicative for a carbonyl group. Four signals, namely δ = 165.3, 143.1, 108.6 and 108.5 ppm, represent olefinic carbons and nine carbons resonate in the region δ = 20−55 ppm. The ^{1}H and ^{13}C NMR data were completely assigned using COSY, HSQC and HMBC spectra.

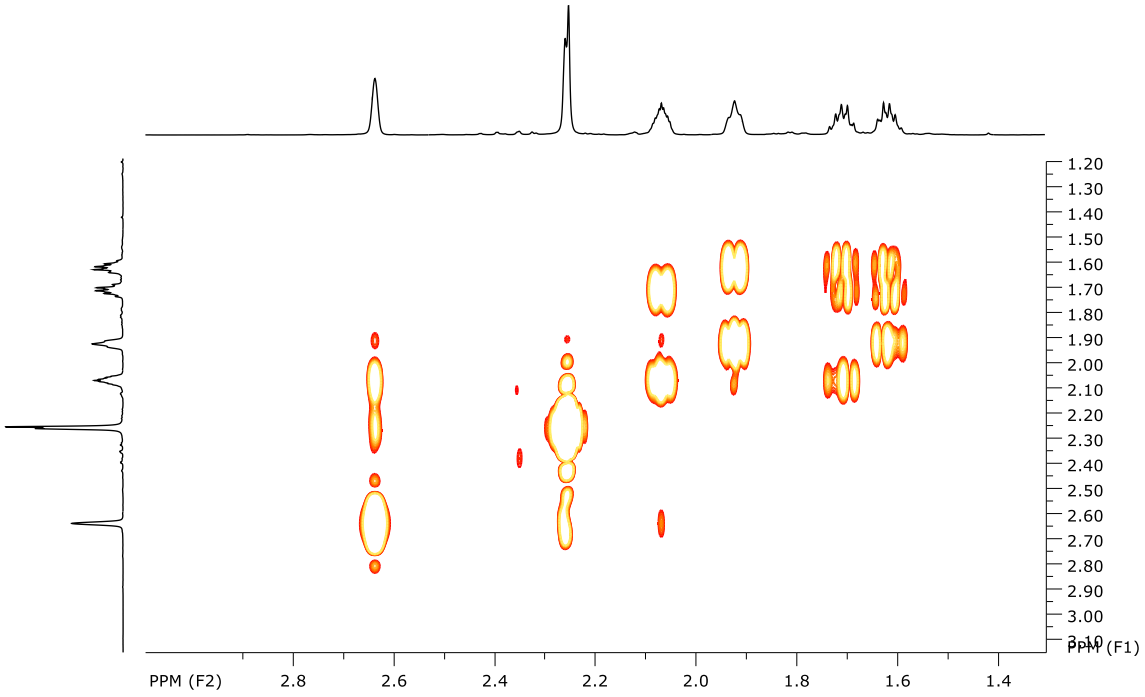


Figure 11. ^{1}H-^{1}H COSY spectrum ($CDCl_3$, 500 MHz) of compound **126e**.

In the COSY spectrum of **126e** (Figure 11), hydrogens 5-H_2 resonating at δ = 2.07 ppm show a cross correlation with protons 6-H_2 resonating at δ = 1.71 ppm (Figure 11). A further correlation of the latter with 7-H_2 at δ = 1.61 ppm, which itself shows an additional correlation with 8-H_2 at δ = 1.92 ppm, established the proton spin system 5-H_2 to 8-H_2.

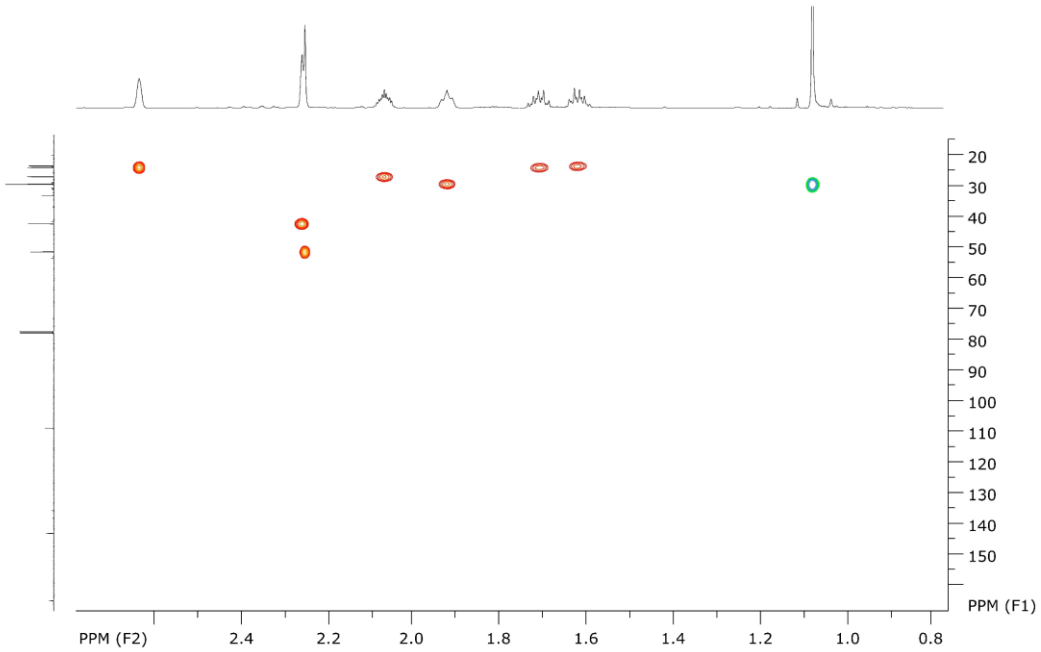


Figure 12. ^{1}H-^{13}C HSQC spectrum ($CDCl_3$, 500, 125 MHz) of compound **126e**.

The carbons of the above spin system 5-H_2 to 8-H_2 were identified by HSQC as C-5 at δ = 25.9, C-6 at δ = 22.9, C-7 at δ = 22.3 and C-8 at δ = 28.2 ppm (Figure 12).

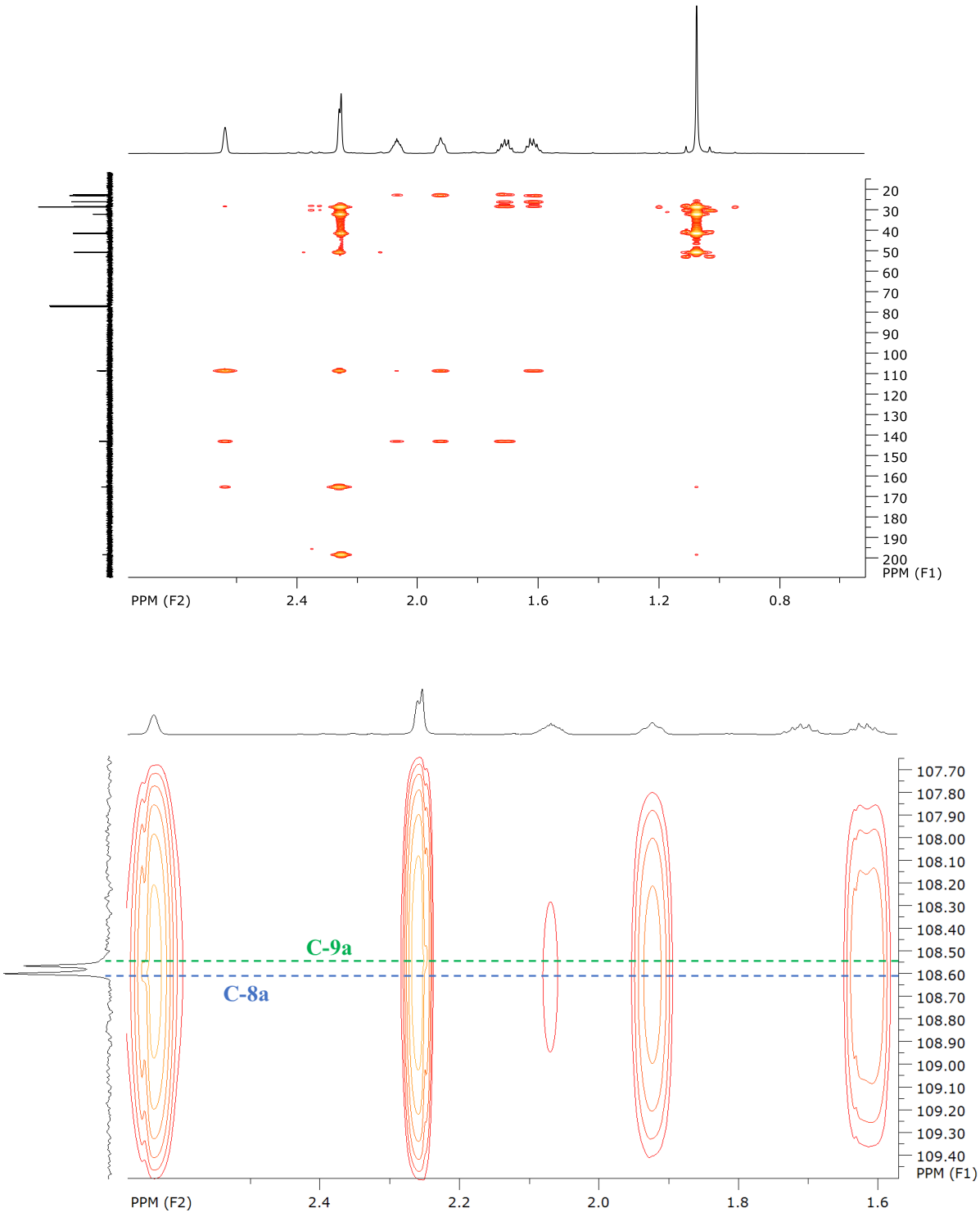


Figure 13. Full ^{1}H-^{13}C HMBC spectrum (up) and expansion (down) of compound **126e** ($CDCl_3$, 500, 125 MHz).

In the HMBC experiment (Figure 13) the quaternary carbon C-8a at δ = 108.6 ppm exhibited ^{1}H-^{13}C long-range correlations with 7-H_2, 8-H_2 and 9-H_2 at δ = 2.64 ppm (C-9 at δ = 22.8 ppm). The signal at δ = 143.1 ppm was attributed to C-10a because of its HMBC correlations with 9-H_2, 8-H_2, 6-H_2 and 5-H_2. A $^{3}J_{H,C}$ coupling of 9-H_2 along with a $^{2}J_{H,C}$ coupling of 4-H_2 ($\delta_{H/C}$ = 2.26/50.6 ppm) to oxygen-bearing quaternary carbon at δ = 165.3 ppm indicates the C-4a

position of the latter. A sharp proton singlet at δ = 1.07 ppm integrating for 6 hydrogens represents the most shielded methyl groups (2 × 3-*C*H_3 at δ = 28.4 ppm). The C-3 position of both methyl groups was established by the HMBC correlations between the methyl protons and C-4 at δ = 41.3 ppm, C-2 at δ = 50.6 ppm and quaternary carbon C-3 at δ = 31.9 ppm. Furthermore, a strong HMBC correlation between 2-H_2 at δ = 2.25 ppm and ^{13}C signal at δ = 198.4 ppm indicates the C-1 position of the carbonyl group. Finally, the quaternary carbon at δ = 108.5 ppm was assigned as C-9a by the observed two $^{3}J_{H,C}$ couplings to 2-H_2 and 4-H_2. In accordance with the observed mass of 232 amu an ether linkage between C-10a and C-4a in **126e** was established.

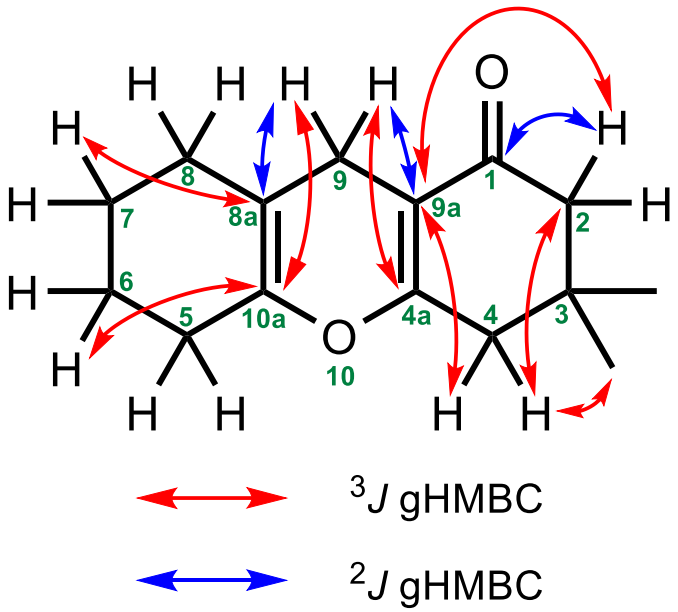
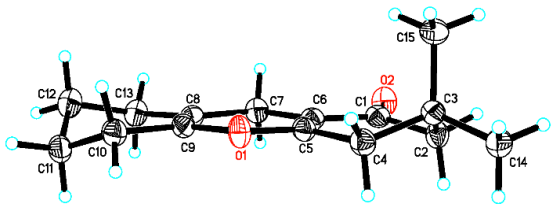


Figure 14. Important HMBC correlations (H↔C) for **126e**.

Important HMBC correlations for 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**) are presented in Figure 14.



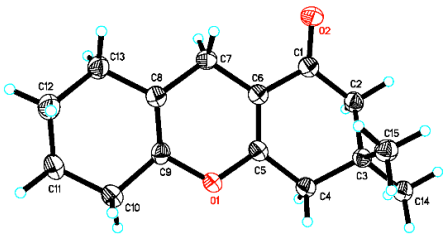


Figure 15. X-ray crystal structure of 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**). The probability of the ellipsoid contour on the plots is 50%.

As shown in Figure 15, X-ray crystallography provided conclusive confirmation of the structure of the annulation product **126e**.

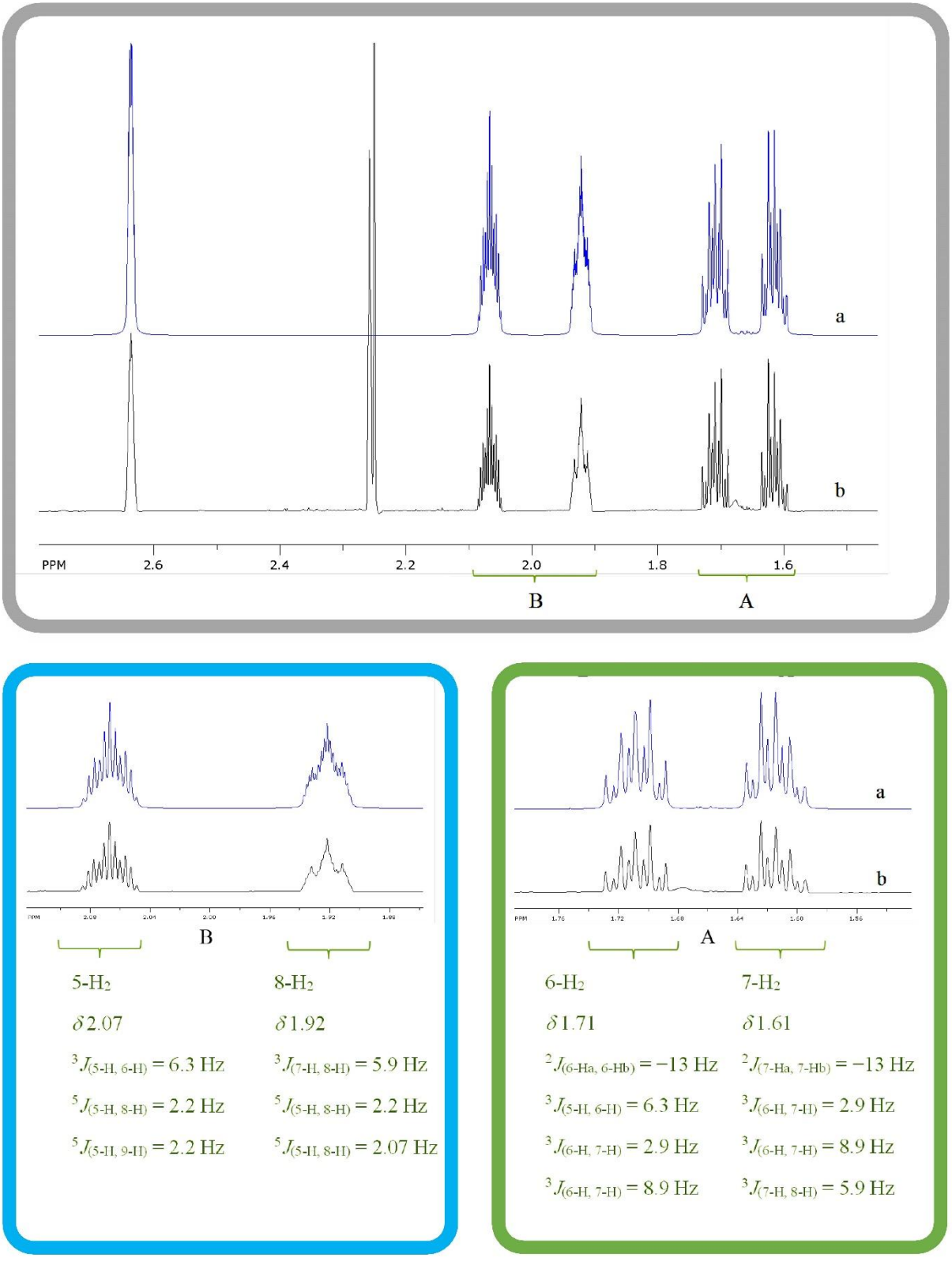


Figure 16. The simulated (a) and the experimental (b) ^{1}H NMR spectra (600 MHz) of the region between δ = 1.50 and δ = 2.70 ppm for **126e**. The expansions of the regions A and B show the protons attached to C-6 and C-7 (A) and C-5 and C-8 (B), respectively.

NMR spectroscopy was employed to unambiguously determine the structures of products **126**, **127**, and **135**. A comprehensive analysis of the COSY, HSQC, and HMBC spectra facilitated the full assignment of all ^{1}H and ^{13}C chemical shifts. It should be mentioned that the ^{1}H NMR spectra of compounds **126a–p** and **127a–h** exhibit very similar splitting patterns to **126e** for the protons resonating within the range of δ = 1.50−2.10 ppm. However, the direct determination of coupling constants ($J_{H,H}$) for 5-H_2, 6-H_2, 7-H_2, and 8-H_2 on **126e** was not possible due to the complexity of assigning second-order multiplet patterns. Consequently, a spectral simulation and analysis program was utilized. Figure 16 shows the ^{1}H NMR spectra of both simulated (a) and experimental (b) signals within the range of δ = 1.50−2.70 ppm for **126e**. The expanded regions provide a more detailed depiction of the protons attached to C-6 and C-7 (Figure 16A) and C-5 and C-8 (Figure 16A). Based on the computational study, proton-proton coupling constants ($J_{H,H}$) were measured for 5-H_2, 6-H_2, 7-H_2, and 8-H_2. The findings indicate that the geminal protons on C-6 as well as on C-7 exhibit a coupling constant ($^{2}J_{H,H}$) of |−13| Hz. Additionally, the vicinal coupling ($^{3}J_{H,H}$) between 5-H and 6-H is measured at 6.3 Hz, while $^{3}J_{H,H}$ between 7-H and 8-H is found to be 5.9 Hz. However, the calculation of vicinal coupling ($^{3}J_{H,H}$) between 6-H and 7-H resulted in two distinct coupling constants: 8.9 and 2.9 Hz. Furthermore, two long-range coupling constants ($^{5}J_{H,H}$) were obtained for the protons on C-5, one with 8-H and another with 9-H.

1.8 Conclusion

In summary, a novel and straightforward regioselective method has been developed for the synthesis of annulated and bisannulated 4*H*-pyrans. This method involves the reaction between cyclic 1-bromoallyl tosylates and 1,3-dicarbonyls using 10 mol% CuI as catalyst, 2.2 equiv Cs_2CO_3 as base and 10 mol% 2-picolinic acid as ligand in the presence of molecular sieves (4 Å) in DMF at 80 °C for 2 h in a sealed vial. By employing this method, bisannulated 4*H*-pyrans **126a–p** were successfully synthesized with excellent yields of up to 92%. The significance of this approach lies in its ability to provide access to five different heterocyclic frameworks. These include the 2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (6-6-6), the 2,3,4,5,6,7-hexahydrocyclopenta[*b*]chromen-1(9*H*)-one (6-6-5), the 2,3,4,6,7,8-hexahydrocyclopenta[*b*]chromen-1(9*H*)-one (5-6-6), the 3,4,6,7,8,9,10,11-octahydrocyclohepta[*b*]chromen-1(2*H*)-one (7-6-6) and the 2,3,4,6,7,8,9,10,11,12-decahydro-1*H*-cycloocta[*b*]chromen-1-one (8-6-6) ring systems. The high efficiency, the great flexibility and the easy feasibility make this new synthetic route a particularly valuable tool for the preparation of annulated and bisannulated pyrans. By proposing a reaction mechanism and conducting control experiments it was assumed that the annulations proceed via an intermolecular *C*-allylation, followed by a Cu(I)-catalyzed intramolecular Ullmann type *O*-vinylation. The reaction is not limited to cyclic 1,3-dicarbonyls as substrates. Six-membered 1-bromoallyl tosylates could also be reacted with acyclic *β*-ketoesters. These experiments yielded exclusively the corresponding 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates **127a–h** in yields up to 59%.

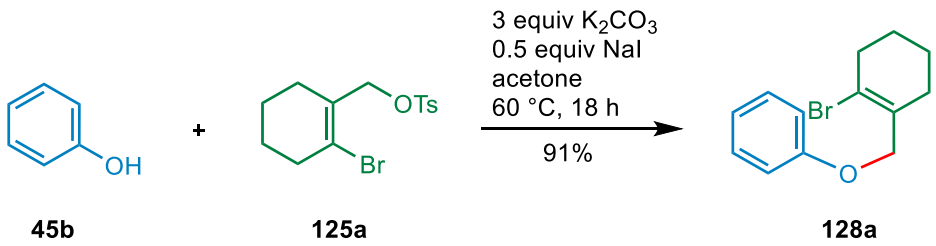
2 Ru-catalyzed synthesis of 2*H*-pyran-2-ones

Given the progress made in the synthesis of annulated and bisannulated 4*H*-pyrans via Cu-catalyzed domino intermolecular *C*-allylation/intramolecular *O*-vinylation, the aim of this project was to expand the scope of research by exploring the feasibility of transition metal-catalyzed intramolecular aromatic C−H alkenylation reactions of by a cyclization of 2-halo-1-(aryloxymethyl)cycloalk-1-enes **128** to 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromenes and related compounds **130**. Using a model reaction, it was demonstrated that this type of cyclization could be realized. However, the cyclization product **130a** could not be obtained in analytically pure form.

Therefore, the transition metal-catalyzed intramolecular aromatic C−H alkenylation was combined with an allylic oxidation to a new domino process for the synthesis of annulated 2*H*-pyran-2-ones. The results of both approaches are based on transition metal-catalyzed intramolecular aromatic C−H alkenylation reactions and have a significant potential to advance the field of C−H activation. A detailed account of the findings from this research is presented in this chapter.

2.1 Model reactions for the transition metal-catalyzed intramolecular aromatic C−H alkenylation

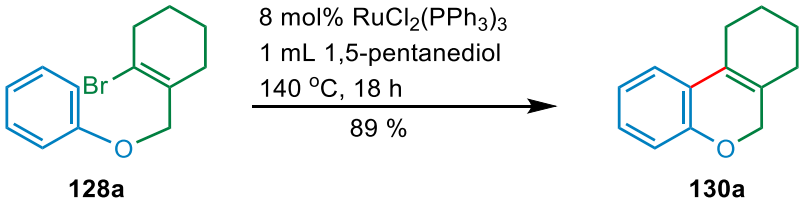
As already pointed out the project initially focused on finding an efficient method for the synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromenes and related compounds **130** by a cyclization of an 2-bromo-1-(aryloxymethyl)cycloalk-1-enes **128**. To study the feasibility of this approach, the cyclization of 1-[(2-bromocyclohex-1-en-1-yl)methoxy]benzene (**128a**) was chosen as a model reaction. Substrate **128a** could be synthesized by reaction between phenol (**45b**) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) in 91% yield (Scheme 39).



Scheme 39. Synthesis of the 1-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]benzene (**128a**).

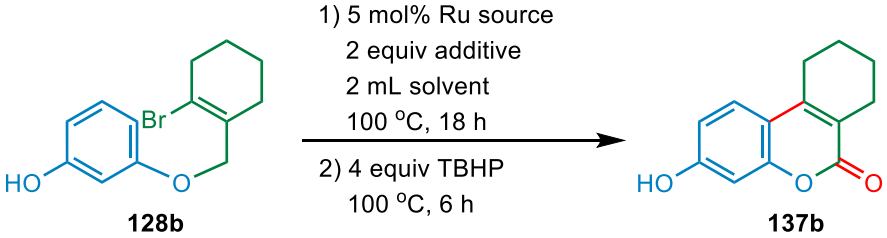
Since the transformation of **128a** into **130a** involves C−H activation it was assumed that the reaction could be achieved by using combinations of a transition metal catalyst and an oxidant.

To either promote the reactivity of the bromoalkene moiety or facilitate the metalation of the arene moiety of **128a**, a broad spectrum of transition metal complexes, oxidants, bases, solvents, reaction temperatures, and reaction times were screened. The findings of these experiments are presented in Tables 7−10.



Scheme 40. Synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**) via ruthenium-catalyzed intramolecular cyclization.

Finally, it was established that the cyclization of **128a** to **130a** can be performed under optimized conditions using 8 mol% $RuCl_2(PPh_3)_3$ as catalyst, 1 mL 1,5-pentanediol (9.54 mM) as both solvent and ligand at 140 °C for 18 h in a sealed vial under argon to give **130a** with a yield of 89% (Scheme 40). It was assumed that employing 1,5-pentanediol enhances the efficiency of $RuCl_2(PPh_3)_3$ as a catalyst for the reaction. However, the presence of impurities of unknown structure causing a broad band in thin layer- and column chromatography prevented the adequate purification of **130a**. Despite several attempts to improve the purification, **130a** could not be obtained in high purity. Therefore, it was decided to include an additional oxidation step, resulting in the transformation of the project into a domino cyclization/oxidation process. To study the feasibility of this approach the transformation of 3-[(2-bromocyclohex-1-en-1-yl)methoxy]phenol (**128b**) into 3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137b**) was chosen as a model reaction (Scheme 41). The optimization of this model reaction is summarized in Table 11.



Scheme 41. Model reaction for the synthesis of 3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137b**) from 3-[(2-bromocyclohex-1-en-1-yl)methoxy]phenol (**128b**).

2.1.1 Optimization of the cyclization of 1-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]benzene (128a) to 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (130a)

Initially, however, the focus was on the optimization of the intramolecular cyclization of **128a**. Firstly, the impact of various catalysts and oxidants on the yield of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**) was studied. The main objective was to identify the optimal combination of catalyst and oxidant for achieving high yields of **130a**.

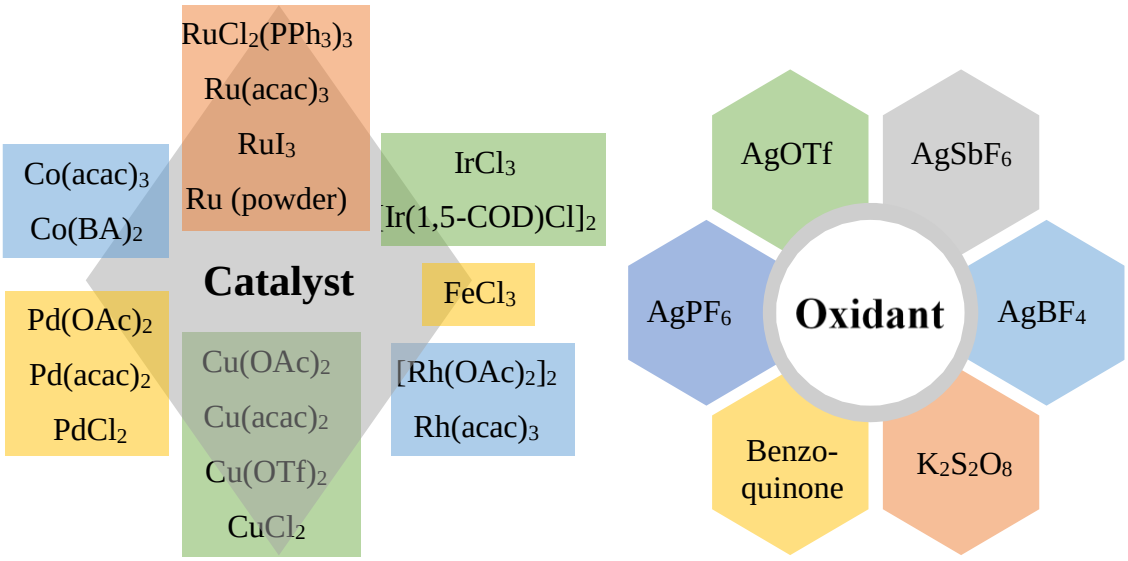
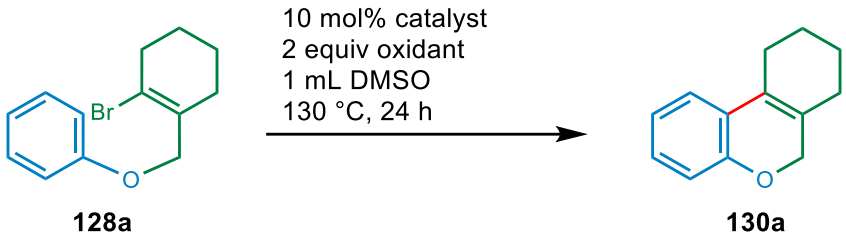


Figure 17. Selected catalysts and oxidants used for the optimization of the cyclization of **128a** to **130a**.

A range of transition metal complexes and oxidants was chosen, as shown in Figure 17. The catalysts selected included a variety of metal complexes, particularly ruthenium, iridium, rhodium, copper, palladium and cobalt compounds. The oxidants chosen include some Ag(I) species as well as $K_2S_2O_8$ and benzoquinone. To identify optimal conditions, each catalyst was subjected to individual reactions with each oxidant.

Table 7. Influence of catalysts and oxidants on the synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**).[a]



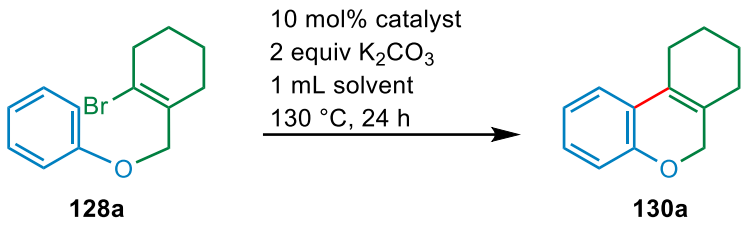
128a **130a**

entry	catalyst	oxidant	yield **130a** (%)
1	$Pd(OAc)_2$	AgOTf	36
2	$Pd(acac)_2$	AgOTf	23
3	$Pd(OAc)_2$	benzoquinone	41
4	$Pd(acac)_2$	benzoquinone	19
5	$RuCl_2(PPh_3)_3$	benzoquinone	16

[a]The reactions were performed in a sealed vial with 0.5 mmol **128a** under argon.

In all reactions, 0.5 mmol **128a** was added to a sealed vial containing 10 mol% of a catalyst and 2 equiv of an oxidant. The reactions were carried out in 1 mL DMSO at 130 °C for 24 h. Despite conducting a total of 108 reactions, only 5 produced desirable results, whilst the remaining experiments failed to yield the expected product (Table 7). It was found that the combination $Pd(OAc)_2$ / AgOTf produced a greater yield (36%) than the combination $Pd(acac)_2$ / AgOTf (23%) (Table 7, entries 1, 2). Similarly, comparing entries 3 and 4 of Table 7, $Pd(OAc)_2$ (41%) performed better than $Pd(acac)_2$ (19%) when benzoquinone was used as the oxidant. These results indicate that $Pd(OAc)_2$ is more effective than other selected metal complexes in facilitating the transformation of **128a** to **130a**. Interestingly, the combination of $RuCl_2(PPh_3)_3$ and benzoquinone also yielded **130a**, albeit at a lower yield (16%; Table 7, entry 5). These unsatisfactory results underline the challenges that have been encountered in the investigation of the optimum conditions for the catalyst /oxidant combinations. Further experimentation was required to uncover the underlying factors affecting the transformation. Therefore, the efficiency of various transition metal complexes as catalysts for the transformation of **128a** to **130a** under basic conditions was studied. In addition, the impact of various solvents on the reaction outcome of the model cyclization was explored (Table 8).

Table 8. Influence of catalysts and solvents on the synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**) under basic conditions.[a]



128a **130a**

entry	catalyst	solvent	yield **130a** (%)
1	$Pd(OAc)_2$	DMA	88
2	$Pd(OAc)_2$	NMP	87
3	$Co(acac)_2$	NMP	N.R.
4	$NiCl_2(PPh_3)_2$	NMP	N.R.
5	$CuBr_2$	DMA	N.R.
6	Cu_2O	DMA	N.R.
7	CuOAc	DMA	N.R.
8	$Cu(acac)_2$	DMA	9
9	$Cu(acac)_2$	DMF	18[b]
10	$RuCl_2(PPh_3)_3$	DMF	N.R.
11	$RuCl_2(PPh_3)_3$	toluene	N.R.[c]
12	$RuCl_2(PPh_3)_3$	CH_3CN	N.R.[d]
13	$RuCl_2(PPh_3)_3$	DCE	N.R.[d]
14	$RuCl_2(PPh_3)_3$	THF	N.R.[e]
15	$RuCl_2(PPh_3)_3$	NMP	32
16	$RuCl_2(PPh_3)_3$	DMSO	38
17	$RuCl_2(PPh_3)_3$	DMSO	40[f,g,h]

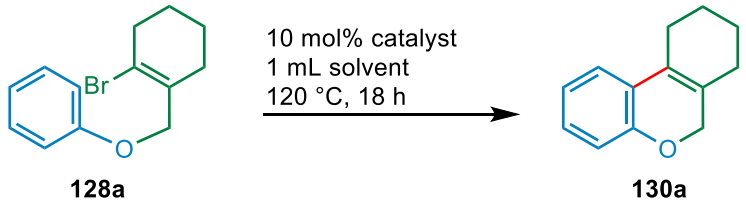
[a]The reactions were performed in a sealed vial with 0.5 mmol **128a** under argon. [b]The reaction was performed in the presence of 1 mol% $Pd(OAc)_2$. [c]T = 100 °C. [d]T = 70 °C. [e]T = 60 °C. [f]T =120 °C. [g]t = 18 h. [h]K_2CO_3 was replaced by ethylene glycol.

Table 8 summarizes the results that were obtained when the reaction was performed using different catalysts and solvents under basic conditions. The experiments were performed in sealed vials charged with 10 mol% catalyst, 2 equiv K_2CO_3 and 1 mL solvent at 130 °C for 24 h. It was found that the use of $Pd(OAc)_2$ as catalyst in *N*,*N*-dimethylacetamide (DMA) delivered the product in 88%, while the use of NMP resulted in 87% yield (Table 8, entries 1, 2).

Obviously, both solvents are viable options, although DMA appears to be slightly more favorable. In contrast, the use of $Co(acac)_2$ and $NiCl_2(PPh_3)_2$ as catalysts in NMP failed to yield any of the cyclization product (Table 8, entries 3, 4). Similar disappointing outcomes were observed when using $CuBr_2$, Cu_2O, and CuOAc as catalysts and DMA as solvent (Table 8, entries 5−7). Among the copper sources, only $Cu(acac)_2$ in DMA delivered the product, albeit in a low yield of 9% (Table 8, entry 8). A further experiment revealed that the yield could be improved to 18% by adding 1 mol% $Pd(OAc)_2$ to the reaction catalyzed by $Cu(acac)_2$ in DMF (Table 8, entry 9). Next, $RuCl_2(PPh_3)_3$ was employed as the catalyst in various solvents, such as DMF, toluene, acetonitrile, dichloroethane (DCE) and tetrahydrofuran (THF) (Table 8, entries 10−14). However, none of these combinations led to product formation. These findings suggest that the selected conditions were not suitable for $RuCl_2(PPh_3)_3$ to be an effective catalyst. However, when the reaction with $RuCl_2(PPh_3)_3$ as catalyst was performed in NMP and DMSO, respectively, the product was formed. The yield in NMP was moderate (32%; Table 8, entry 15), while DMSO as solvent showed a slightly better yield (38%; Table 8, entry 16). Interestingly, it was discovered that the use of ethylene glycol instead of K_2CO_3 in the reaction catalyzed by $RuCl_2(PPh_3)_3$ in DMSO further increased the yield of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**) to 40% (Table 8, entry 17).

In conclusion, despite the very promising results obtained with $Pd(OAc)_2$ and K_2CO_3 as catalysts, the methodology is well-established.[80] It is evident that the exploration of alternative catalysts could lead to exciting advances. In order to discover a novel synthetic method and replace palladium with a cheaper catalyst, recent results with $RuCl_2(PPh_3)_3$ have provided valuable inspiration. The ability to replace the base with ethylene glycol opened up new possibilities and encouraged us to further optimize the model reaction.

Table 9. Influence of solvents and Ru-sources on the synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**).[a]



128a **130a**

entry	catalyst	solvent	yield **130a** (%)
1	$RuCl_2(PPh_3)_3$	1,5-pentanediol	82
2	$RuCl_2(PPh_3)_3$	1,4-butanediol	68
3	$RuCl_2(PPh_3)_3$	ethylene glycol	63
4	$RuCl_2(PPh_3)_3$	glycerol	N.R.
5	$RuCl_2(PPh_3)_3$	PEG-400	trace
6	$RuCl_2(PPh_3)_3$	1,3-propanediol	trace
7	$RuCl_2(PPh_3)_4$	1,5-pentanediol	51
8	$RuH_2(PPh_3)_4$	1,5-pentanediol	N.R.
9	$RuCl_3(NH_3)_6$	1,5-pentanediol	N.R.
10	$Ru(acac)_3$	1,5-pentanediol	trace
11	RuI_3	1,5-pentanediol	N.R.
12	$RuCl_3 \cdot x\ H_2O$	1,5-pentanediol	N.R.
13	$RuO_2 \cdot x\ H_2O$	1,5-pentanediol	N.R.
14	Ru	1,5-pentanediol	N.R.

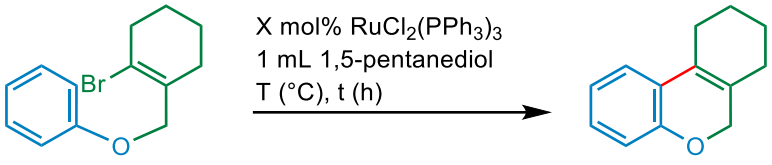
[a]The reactions were performed using 0.5 mmol **128a** in a sealed vial under argon.

Table 9 summarizes the results of a study on the influence of different solvents and different Ru-sources on the yield of **130a**. The role of diols as solvents is particularly important in the formation of the desired product. Among all solvents tested, 1,5-pentanediol demonstrated the most favorable outcome, resulting in 82% yield of **130a** when used in combination with $RuCl_2(PPh_3)_3$ as catalyst (Table 9, entry 1). The reaction with $RuCl_2(PPh_3)_3$ as catalyst could also be carried out in 1,4-butanediol and ethylene glycol with yields of 68% and 63%, respectively (Table 9, entries 2, 3).

In contrast, glycerol, PEG-400 and 1,3-propanediol were found to be unsuitable solvents for the $RuCl_2(PPh_3)_3$-catalyzed model reaction (Table 9, entries 4–6). As a result, all subsequent experiments were carried out using 1,5-pentanediol as the solvent. Further experiments on the effect of different Ru catalysts on the outcome of the formation of **130a** revealed that

$RuCl_2(PPh_3)_3$ exhibited higher yields compared to other Ru sources such as $RuCl_2(PPh_3)_4$, $RuH_2(PPh_3)_4$, $RuCl_3(NH_3)_6$, $Ru(acac)_3$, RuI_3, $RuCl_3 \cdot x\ H_2O$, $RuO_2 \cdot x\ H_2O$, and Ru-powder (Table 9, entries 7−14). While the use of $RuCl_2(PPh_3)_4$ in 1,5-pentanediol resulted in a 51% yield of **130a**, the other Ru compounds did not catalyze the transformation in question. In conclusion, the choice of both the solvent and the Ru catalyst significantly affected the yield of **130a**. These results contributed to a better understanding of the factors affecting the synthesis of **130a** and served as a basis for further studies.

Table 10. Influence of reaction temperature, reaction time and the amount of $RuCl_2(PPh_3)_3$ on the synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**).[a]



128a **130a**

entry	mol% $RuCl_2(PPh_3)_3$	T (°C)	t (h)	yield **130a** (%)
1	10	160	18	69
2	10	140	18	87
3	10	100	18	N.R.
4	10	80	18	N.R.
5	10	60	18	N.R.
6	10	rt	18	N.R.
7	10	140	24	85
8	10	140	12	38
9	10	140	6	29
10	8	140	18	89
11	6	140	18	71
12	4	140	18	23
13	2	140	18	trace
14	---	140	18	N.R.[c]
15	8	140	18	N.R.[d]

[a]The reactions were performed using 0.5 mmol **128a** in a sealed vial under argon. [c]The reaction was performed in the absence of any catalyst. [d]The reaction was performed in the absence of 1,5-pentanediol.

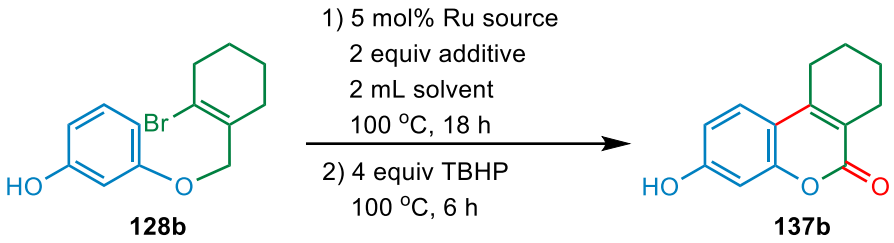
The results of the study concerning the influence of the reaction temperature, the reaction time and the amount of $RuCl_2(PPh_3)_3$ on the synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**) are presented in Table 10. In the first set of experiments, the impact of the reaction temperature was addressed. For this purpose, the precursor **128a** was reacted in the presence of 10 mol% $RuCl_2(PPh_3)_3$ for 18 h at different temperatures. At 160 °C and 140 °C, the yields were 69% and 87%, respectively (Table 10, entries 1, 2). However, at lower temperatures (100 °C, 80 °C, 60 °C and room temperature), the reaction did not proceed at all (Table 10, entries 3−6). These findings showed that a certain minimum temperature is required to facilitate the conversion. The influence of the reaction time on the product yield was then investigated while keeping the temperature at 140 °C and the catalyst loading at 10 mol% constant. When the reaction time was extended to 24 h, the yield remained relatively high (85%; Table 10, entry 7). However, significantly lower yields of 38% and 29% were obtained when the reaction time was reduced to 12 and 6 h, respectively (Table 10, entries 8, 9). This observation suggested that a reaction time of 18 h is favorable for obtaining high yields of **130a**.

Further experiments were performed to study the impact of varying the amount of $RuCl_2(PPh_3)_3$. For this purpose, experiments were carried out with catalyst loadings of at 8, 6, 4 and 2 mol%, respectively, at 140 °C for 18 h (Table 10, entries 10−13). The results showed that a slight decrease in catalyst loading from 10 mol% to 8 mol% resulted in a slight increase in yield of **130a** to 89% (Table 10, entry 10). However, as the catalyst loading was reduced to 6 and 4 mol%, the yields decreased to 71% and 23%, respectively (Table 10, entries 11, 12). When the catalyst loading was further reduced to 2 mol%, only traces of **130a** were observed (Table 10, entry 13). Finally, some control experiments were conducted to define the role of the catalyst and the 1,5-pentanediol. When the reaction was performed in the absence of any catalyst, no transformation occurred. This confirmed the important role of the catalyst in the reaction (Table 10, entry 14). Similarly, no reaction took place in the absence of 1,5-pentanediol, highlighting the importance of this diol as a key component in the reaction (Table 10, entry 15). In conclusion, the reaction conditions of the model reaction were optimized to react 0.5 mmol of **128a** in the presence of 8 mol% $RuCl_2(PPh_3)_3$ as catalyst in 1 mL 1,5-pentanediol as solvent. The reaction was performed in a sealed vial under argon at 140 °C for 18 h to yield 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**) in 89%.

2.1.2 Optimization of the domino cyclization/oxidation of 128b to 3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (137b)

During our attempts to obtain **130a** in analytically pure form, spot-tailing was observed during the chromatographic purification process. Tailing during chromatographic separations is often an indicator of impurities of the compounds to be separated and can lead to inadequate separations. Despite numerous attempts to purify compound **130a** by PTLC and column chromatography on silica gel and aluminum oxide, the compound could not be isolated in analytically pure form and the nature of the impurity remained unknown. Faced with this challenge, it was decided to slightly change the direction of the project by combining the ruthenium-catalyzed intramolecular aromatic C−H alkenylation with an allylic oxidation. Although this modification could not solve the purification problem of **130a**, it opened up the possibility for the synthesis of 3,4-annulated coumarins and annulated naphthopyranones via a ruthenium-catalyzed domino intramolecular aromatic C−H alkenylation/allylic oxidation. Consequently, to fully explore the potential of this new approach to 3,4-annulated coumarins and annulated naphthopyranones, it was decided to optimize the new domino reaction.

Table 11. Optimization reactions for the synthesis of 3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137b**) using 3-[(2-bromocyclohex-1-en-1-yl)methoxy]phenol (**128b**) as the substrate.[a]



128b **137b**

entry	Ru source	additive	solvent	yield **137b** (%)
1	$Ru(acac)_3$	—	DMSO	19
2	$RuCl_2(PPh_3)_4$	—	DMSO	16
3	$RuCl_2(PPh_3)_3$	—	DMSO	42
4	$RuH_2(PPh_3)_4$	—	DMSO	N.R.[b]
5	RuI_3	—	DMSO	N.R.
6	$RuCl_2(PPh_3)_3$	glycerol	DMSO	N.R.
7	$RuCl_2(PPh_3)_3$	polyethylene glycol 400	DMSO	N.R.
8	$RuCl_2(PPh_3)_3$	ethylene glycol	DMSO	41 / 39[c]
9	$RuCl_2(PPh_3)_3$	1,3-propanediol	DMSO	53
10	$RuCl_2(PPh_3)_3$	1,5-pentanediol	DMSO	72
11	$RuCl_2(PPh_3)_3$	1,5-pentanediol	DMA	76
12	$RuCl_2(PPh_3)_3$	1,5-pentanediol	NMP	69
13	$RuCl_2(PPh_3)_3$	1,5-pentanediol	DMF	62
14	$RuCl_2(PPh_3)_3$	1,5-pentanediol	THF	N.R.[d]
15	$RuCl_2(PPh_3)_3$	1,5-pentanediol	DMA	N.R.[e]
16	$RuCl_2(PPh_3)_3$	1,5-pentanediol	DMA	28[f]
17	$RuCl_2(PPh_3)_3$	1,5-pentanediol	DMA	76[g]

[a]The reactions were performed using 1 mmol **128b** in a sealed vial under argon. [b]N.R. = No Reaction. [c]The reaction was performed using 8 mol% $RuCl_2(PPh_3)_3$. [d]T = 60 °C. [e]The reaction was performed in the absence of an additional oxidant in an open vial. [f]TBHP was replaced by H_2O_2. [g]TBHP was replaced by DTBP.

As a model reaction for the proposed ruthenium-catalyzed domino reaction involving an intramolecular aromatic C−H alkenylation and an allylic oxidation the conversion of 3-[(2-

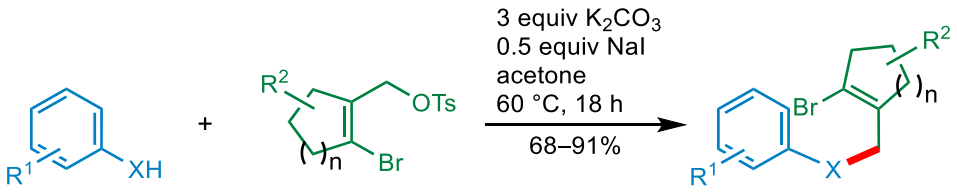
bromocyclohex-1-en-1-yl)methoxy]phenol (**128b**) into 3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137b**) was chosen (Table 11). It was assumed that the intramolecular aromatic C−H alkenylation occurs first to yield the cyclization product, which subsequently undergoes allylic oxidation to form **137b**. To find out the optimal reaction conditions, **128b** was stirred with of 5 mol% of a ruthenium compound as the catalyst in DMSO at 100 °C. After complete consumption of the substrate (18 h, TLC) an excess of *tert*-butyl hydroperoxide (TBHP) as an oxidant (4 equiv) was added by syringe within 10 min (Table 11, entries 1−5). It was found that the desired product could be isolated with $Ru(acac)_3$, $RuCl_2(PPh_3)_4$ and $RuCl_2(PPh_3)_3$ as catalysts with yields of 19, 16 and 42% respectively (Table 11, entries 1−3). However, no transformation was observed when $RuH_2(PPh_3)_4$ and RuI_3 were used as ruthenium source (Table 11, entries 4, 5). Based on these results, all further reactions were carried out with 5 mol% of $RuCl_2(PPh_3)_3$ as the catalyst. As a general trend, we have already observed that the yield of the product of the intramolecular aromatic C−H alkenylation increased with the use of 1,5-pentanediol, a hydroxyl group-containing additive, suggesting that more reactive catalysts were generated in situ. It was assumed that aliphatic diols as additives could act either a *O*-monodentate or as *O*,*O*-bidentate ligands to effectively coordinate with ruthenium. Therefore, a series of model reactions were carried out in the presence of various hydroxyl group-containing compounds as additives. Specifically, the effect of glycerol, polyethylene glycol 400, ethylene glycol, 1,3-propanediol and 1,5-pentanediol on the outcome of the $RuCl_2(PPh_3)_3$-catalyzed domino reaction was studied. It was established that the reaction did not take place when either glycerol or polyethylene glycol 400 were employed as additives (Table 11, entries 6, 7). Running the reaction in the presence of ethylene glycol had no effect on the outcome of the reaction, even when the amount of $RuCl_2(PPh_3)_3$ was increased to 8 mol%. Under these conditions, **137b** was isolated in 41 and 39% yield, respectively (Table 11, entry 8). However, the combinations of 5 mol% $RuCl_2(PPh_3)_3$ with 2 equivalents of 1,3-propanediol or 1,5-pentanediol were remarkably successful in increasing the yield of the desired product. Under these conditions, **137b** was formed in 53 and 72% yield, respectively (Table 11, entries 9, 10). All further reactions were performed using 1,5-pentanediol as additive. Subsequently, the influence of different solvents on the outcome of the model reaction was studied. These experiments revealed that the reaction could be carried out successfully in DMA, NMP, and DMF (Table 11, entries 11−13), but not in THF (Table 11, entry 14). Since the highest yield of **137b** was obtained with DMA as solvent, all further reactions were performed in DMA. In an attempt to replace TBHP with atmospheric oxygen as the oxidant, the model reaction was performed in an open vial. However, the desired product was not formed even in

traces (Table 11, entry 15). Furthermore, it was studied whether TBHP could be replaced with H_2O_2. It was found that the yield of **137b** was reduced to 28% when H_2O_2 was employed as the oxidant (Table 11, entry 16). In another experiment it was demonstrated that the allylic oxidation could also be performed using di-*tert*-butyl peroxide (DTBP) as the oxidant to deliver **137b** in 76% (Table 11, entry 17). Since the yields of **137b** obtained with TBHP and DTBP are identical, it was decided run all further reaction in DTBP which has a number of advantages over TBHP, including its higher stability at higher temperatures.

2.2 Synthesis of 3,4-annulated coumarins 137a–k

Having established optimal reaction conditions, scope and limitations of the new synthetic method were studied in order to expand the access to 3,4-annulated coumarins **137** and annulated naphthopyranones **138**. The findings are summarized in Tables 13 and 14. For this purpose, a number of 2-bromo-1-(aryloxymethyl)cycloalk-1-enes **128a–o** were synthesized by reaction between a phenol **45** and a 2-bromo-1-(4′-methylbenzenesulfonatemethyl)-1-ene **125** in the presence of 3 equiv K_2CO_3 and 0.5 equiv NaI in acetone. The required allyl aryl ethers **128** were isolated with yields between 68 and 91% (Table 12, entries 1−15). In a similar way, the allyl aryl thioether **128p** was synthesized (Table 12, entry 16).

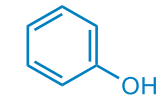
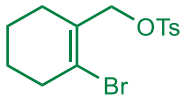
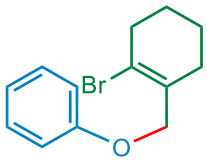
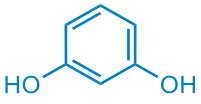
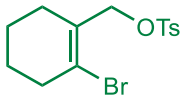
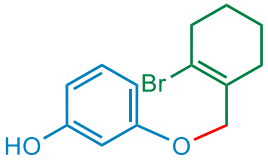
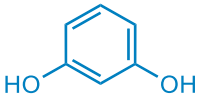
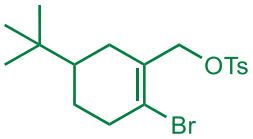
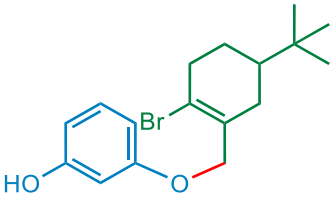
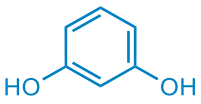
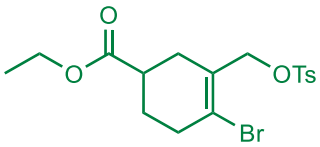
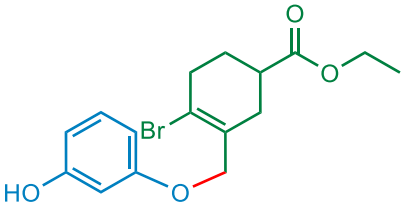
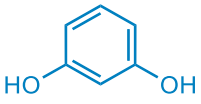
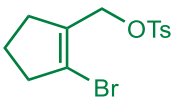
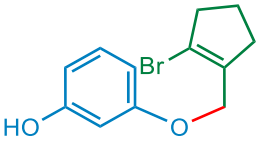
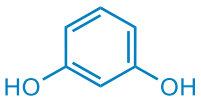
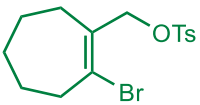
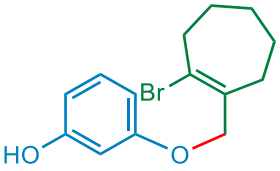
Table 12. Synthesis of the 2-bromo-1-(aryloxymethyl)cycloalk-1-enes **128a–o** and [(2'-bromocyclohex-1'-en-1'-yl)methyl]phenylsulfane (**128p**).

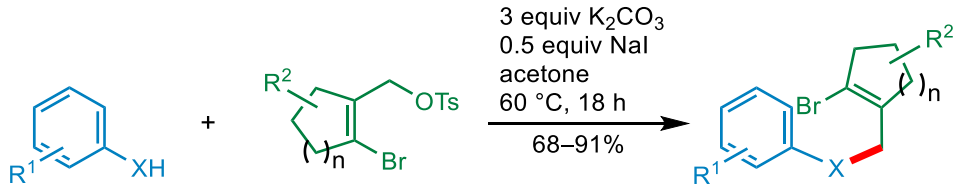


45, **83**
45 X = O
83 X = S

125
n = 1, 2, 3, 4

128
R^1 = H, OH, OMe, alkyl, Cl
R^2 = H, alkyl, CO_2Et

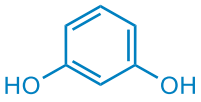
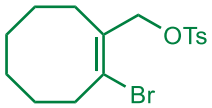
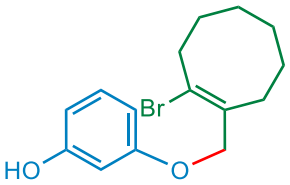
entry	**45**, **83**	**125**	**128**	yield (%)
1	 **45b**	 **125a**	 **128a**	91
2	 **45a**	 **125a**	 **128b**	87
3	 **45a**	 **125d**	 **128c**	89
4	 **45a**	 **125e**	 **128d**	73
5	 **45a**	 **125b**	 **128e**	78
6	 **45a**	 **125f**	 **128f**	79



45, **83**
45 X = O
83 X = S

125
n = 1, 2, 3, 4

128
R^1 = H, OH, OMe, alkyl, Cl
R^2 = H, alkyl, CO_2Et

entry	**45, 83**	**125**	**128**	yield (%)
7				68
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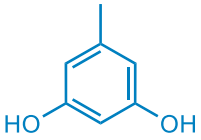
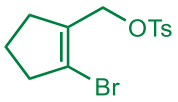
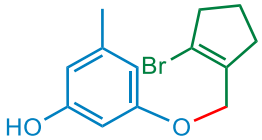
8				79
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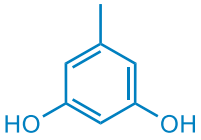
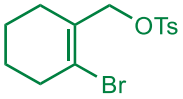
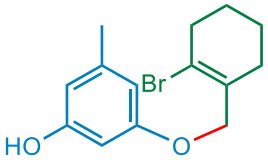
9				88
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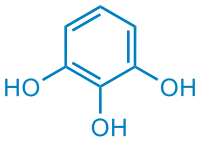
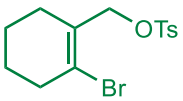
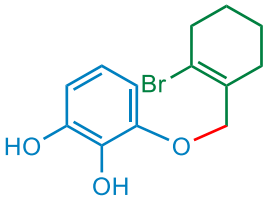
10				81
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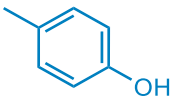
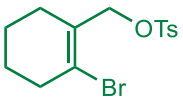
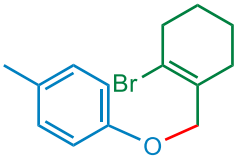
11				88
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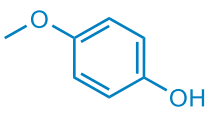
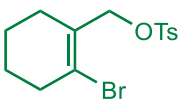
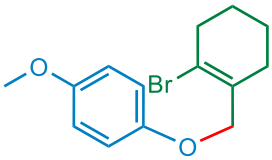
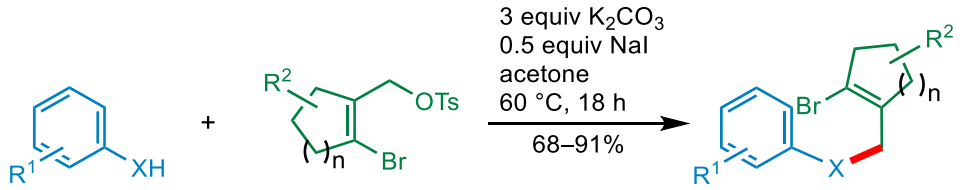
12				84
	45f	**125a**	**128l**	



45, **83**
45 X = O
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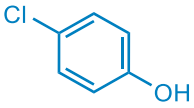
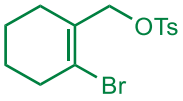
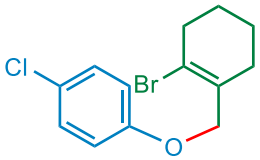
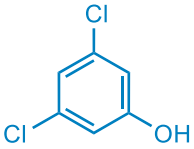
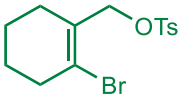
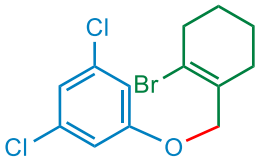
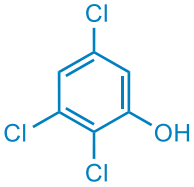
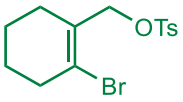
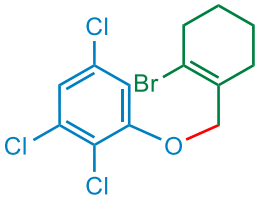
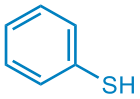
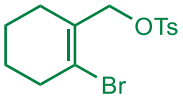
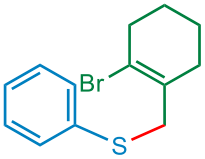
125
n = 1, 2, 3, 4

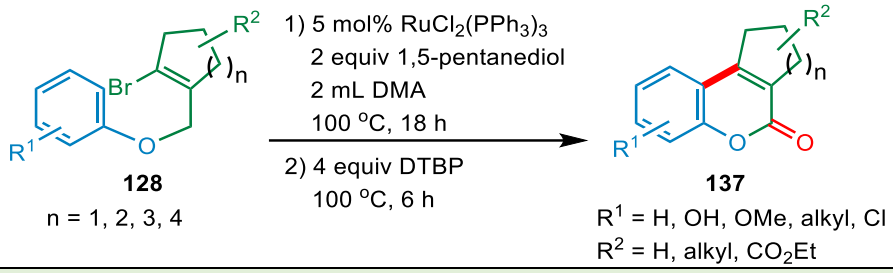
128
R^1 = H, OH, OMe, alkyl, Cl
R^2 = H, alkyl, CO_2Et

entry	**45**, **83**	**125**	**128**	yield (%)
13	 **45g**	 **125a**	 **128m**	78
14	 **45h**	 **125a**	 **128n**	72
15	 **45i**	 **125a**	 **128o**	69
16	 **83**	 **125a**	 **128p**	78

[a]All reactions were performed using 4 mmol of **45**, **83** and 2 mmol of **125** in a round-bottomed flask.

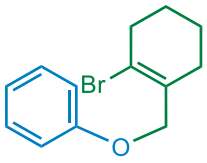
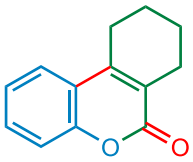
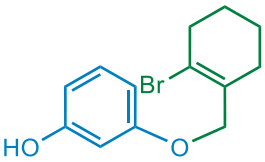
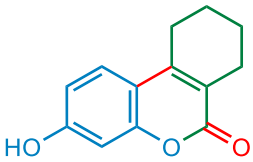
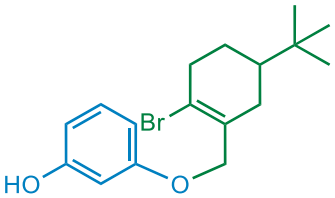
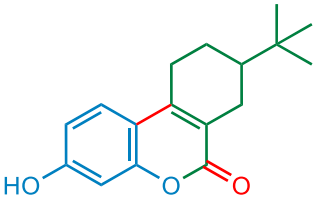
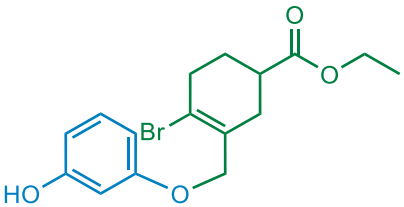
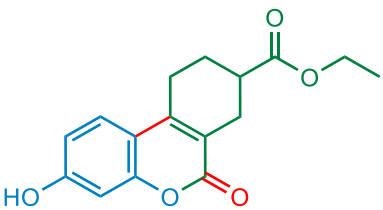
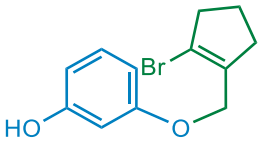
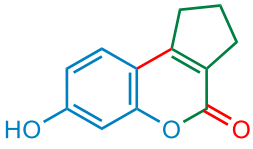
To broaden access to 3,4-annulated coumarins **137**, the 2-bromo-1-(aryloxymethyl)cycloalk-1-enes **128a–o** and the corresponding thioether **128p** were used to investigate the scope and limitations of the new synthesis method. The findings are summarized in Tables 13.

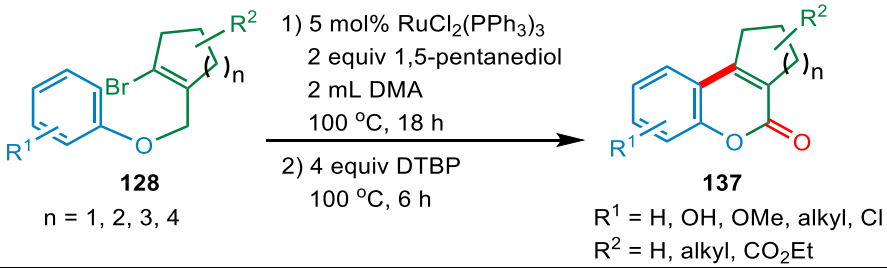
Table 13. Synthesis of 3,4-annulated coumarins **137a–k** under optimized reaction conditions.[a]

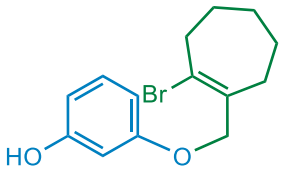
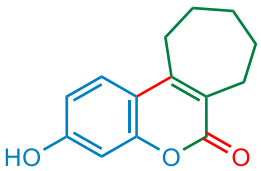
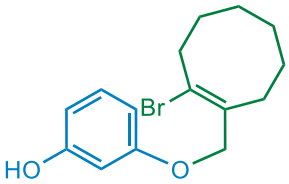
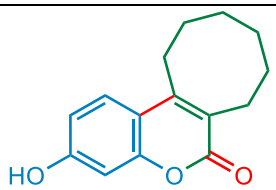
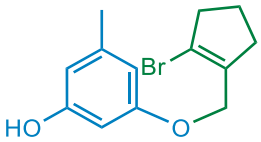
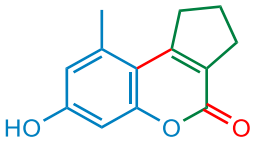
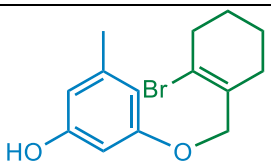
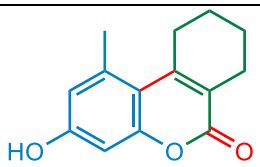
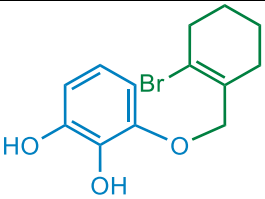
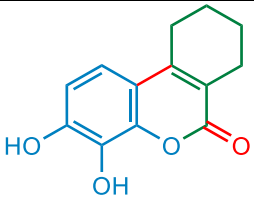
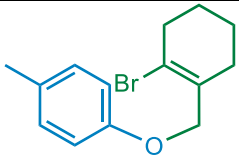
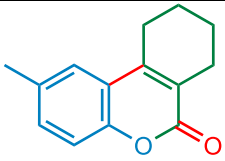


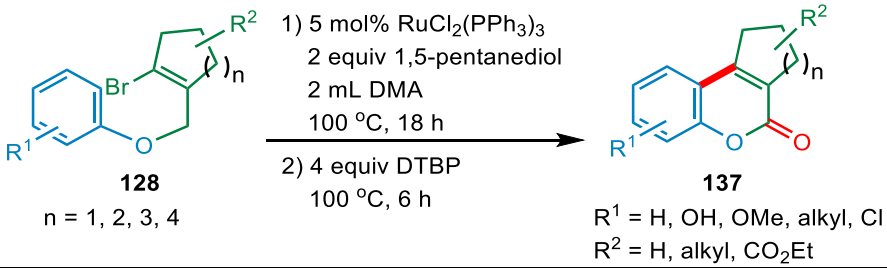
128
n = 1, 2, 3, 4

137
R^1 = H, OH, OMe, alkyl, Cl
R^2 = H, alkyl, CO_2Et

entry	**128**	**137**	yield (%)
1	 **128a**	 **137a**	61
2	 **128b**	 **137b**	76
3	 **128c**	 **137c**	83
4	 **128d**	 **137d**	68
5	 **128e**	 **137e**	71

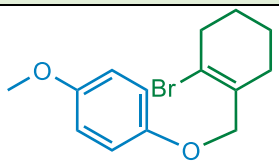
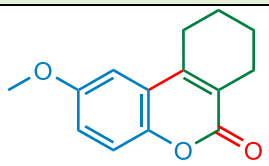
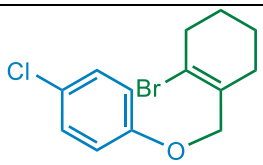
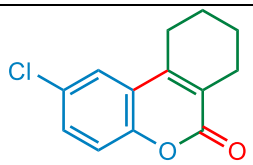
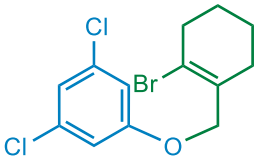
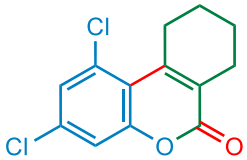
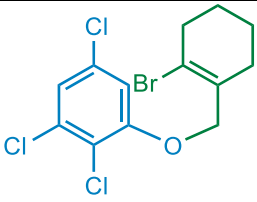
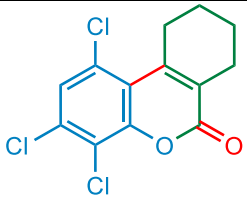
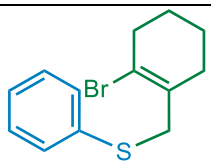
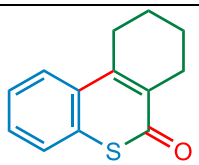


entry	**128**	**137**	yield (%)
6			69
	128f	**137f**	
7			72
	128g	**137g**	
8			72
	128h	**137h**	
9			78
	128i	**137i**	
10			67
	128j	**137j**	
11			62
	128k	**137k**	



128
n = 1, 2, 3, 4

137
R^1 = H, OH, OMe, alkyl, Cl
R^2 = H, alkyl, CO_2Et

entry	**128**	**137**	yield (%)
12	 **128l**	 **137l**	N.R.
13	 **128m**	 **137m**	N.R.
14	 **128n**	 **137n**	N.R.
15	 **128o**	 **137o**	N.R.
16	 **128p**	 **137p**	N.R.

[a]The reactions were performed using 1 mmol **128** in a sealed vial under argon.

With the allyl aryl (thio)ethers **128** in hand, the domino reactions were performed under standard conditions. Following the reaction of **128a**, which gave **137a** in 61% isolated yield (Table 13, entry 1) the reaction with the resorcinol-derived allyl aryl ether **128b** was investigated. Interestingly, because the OH group is in *meta*-position to the ether bridge, there

are two *ortho*-positions and one *para*-position where C−H activation and thus ring closure can occur. It is noteworthy that the ring closure occurs exclusively at the C-atom that is in *ortho*-position to the ether bridge and in *para*-position to the OH group, yielding product **137b** exclusively in 76% (Table 13, entry 2). To determine the effects of electron-donating (*tert*-butyl) and electron-withdrawing (ethoxycarbonyl) substituents on the cyclohexenyl moiety of the starting material on the outcome of the domino reaction, compounds **128c** and **128d** were reacted under standard conditions to deliver **137c** in 83% and **137d** in 68% yield, respectively (Table 13, entries 3, 4). It turned out that the electron-donating *tert*-butyl substituent led to an increase of the yield, while the electron-withdrawing ethoxycarbonyl substituent dropped the yield when compared with the yield of **137b**. The successful synthesis of **137e–g** with yields ranging between 69 and 72% clearly demonstrated that the domino reaction is not only useful for the preparation of 3,4-annulated six-membered coumarins but also valuable or the preparation of 3,4-annulated five-, seven-, and eight-membered coumarins (Table 13, entries 5−7). Compared to the conversions of resorcinol-based substrates **128e** and **128b**, the intramolecular domino annulation/allylic oxidation of the orcinol-based substrates **128h** and **128i** yielded the corresponding products **137h** and **137i** in slightly higher yields of 72 and 78 %, respectively (Table 13, entries 8, 9). The next experiment demonstrated that not only allylic ethers derived from phenol, resorcinol and orcinol can undergo the domino reaction, but also an ether derived from pyrogallol. When 3-[(2-bromocyclohex-1-en-1-yl)methoxy]benzene-1,2-diol (**128j**) was reacted under standard conditions, 3,4-dihydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137j**) was formed exclusively (Table 13, entry 10). However, the yield of **137j** did not exceed 67%. To study the impact of substituents on the aromatic ring of the reactants, **128k** with a methyl group, **128l** with a methoxy group and **128m** with a chlorine atom in *para*-position to the ether bridge were synthesized and subjected to the standard reaction conditions. It was found that the substrate with the methyl group in *para*-position delivered the expected product **137k** in 62% yield (Table 13, entry 11). However, the domino reaction could not be achieved with substrates **128l** and **128m** carrying one electron-withdrawing substituent in *para*-position to the ether bridge (Table 13, entries 12, 13). For substrates **128n** and **128o** with more than one chlorine atom on the aromatic ring the domino reaction could not be accomplished as well (Table 13, entries 14, 15). Finally, the thioether **128p** was reacted under standard condition. Again, the domino reaction could not be achieved (Table 13, entry 16).

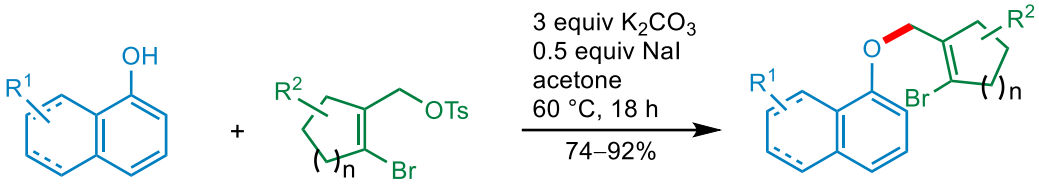
To summarize, the ruthenium-catalyzed domino reaction involving an intramolecular aromatic C−H alkenylation and an allylic oxidation allows the regioselective preparation of 3,4-

annulated coumarins **137** with yields up to 91%. It is clear that the outcome of the cyclizations based on C−H activation depends on the substituent pattern of the aromatic rings. In phenol-, resorcinol- and pyrogallol-derived substrates the cyclizations are highly selective. The ring closure occurs only at the C-atom that is in *ortho*-position to the ether bridge and in *para*-position to the OH group. It should be mentioned that the reaction can be performed at comparably low temperatures and neither introduction nor removal of directing groups is necessary to achieve high regioselective cyclizations.

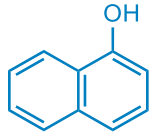
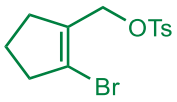
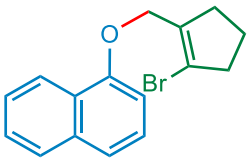
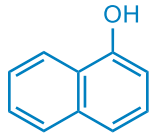
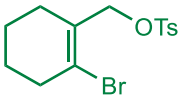
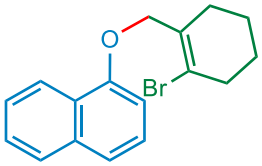
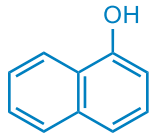
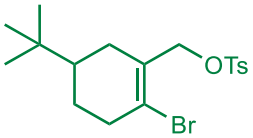
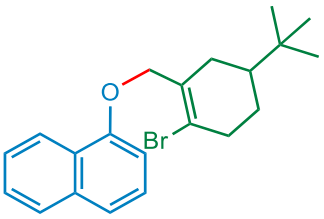
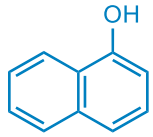
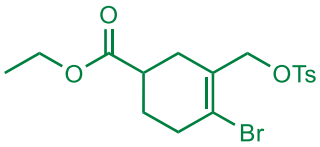
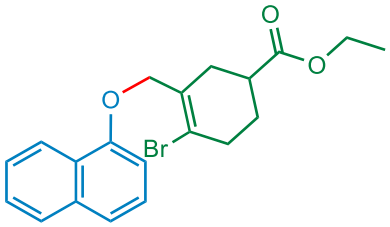
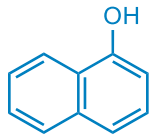
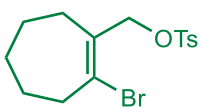
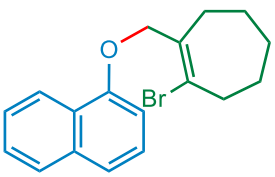
2.3 Synthesis of annulated naphthopyranones 138a–h

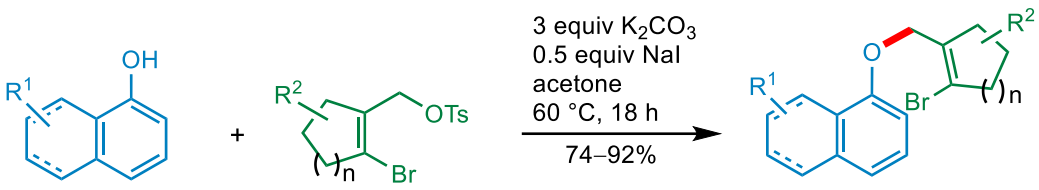
Further studies on the scope of the new method should determine whether it is also suitable for the synthesis of annulated naphthopyranones **138** and similar compounds. The findings are summarized in Table 15. For this purpose, a number of allyl α-naphthyl ethers **129a–g** were synthesized by reaction between an α-naphthol **52** and a 2-bromo-1-(4′-methylbenzenesulfonatemethyl)-1-ene **125** in the presence of 3 equiv K_2CO_3 and 0.5 equiv NaI in acetone. The required allyl α-naphthyl ethers **129a–g** were isolated with yields between 74 and 92% (Table 14, entries 1−7). In a similar way the tetrahydronaphthalene-derived ether **129h** was prepared (Table 14, entry 8).

Table 14. Synthesis of the 2-bromo-1-(naphthalenoxymethyl)cycloalk-1-enes **129a–g** and 5-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]-1,2,3,4-tetrahydronaphthalene (**129h**).



52 **125** n = 1, 2, 3, 4 **129** R^1 = H, Cl R^2 = H, alkyl, CO_2Et

entry	**52**	**125**	**129**	yield (%)
1	 **52a**	 **125b**	 **129a**	81
2	 **52a**	 **125a**	 **129b**	89
3	 **52a**	 **125d**	 **129c**	92
4	 **52a**	 **125e**	 **129d**	79
5	 **52a**	 **125f**	 **129e**	83

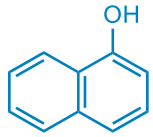
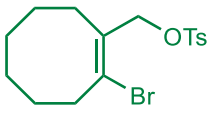
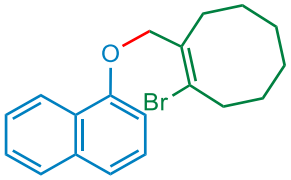
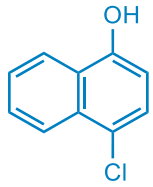
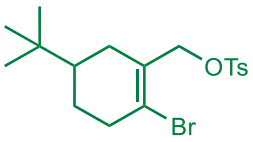
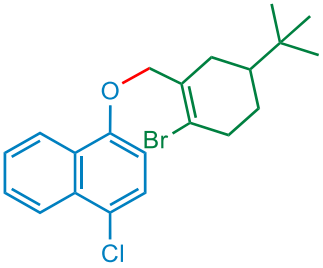
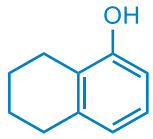
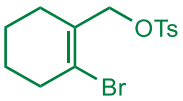
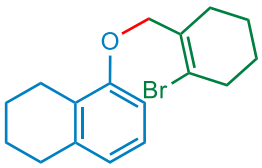


52 **125** **129**

n = 1, 2, 3, 4

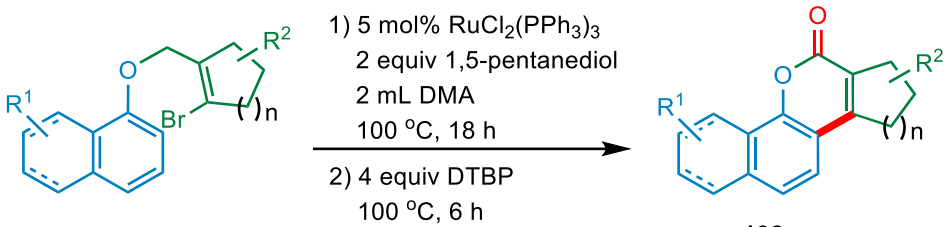
R^1 = H, Cl

R^2 = H, alkyl, CO_2Et

entry	**52**	**125**	**129**	yield (%)
6				74
	52a	**125g**	**129f**	
7				77
	52b	**125d**	**129g**	
8				79
	52c	**125a**	**129h**	

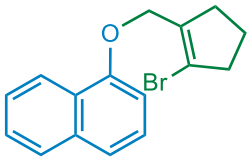
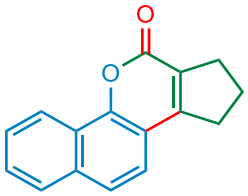
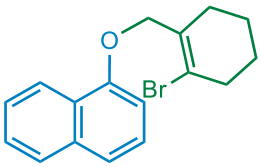
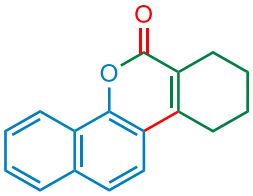
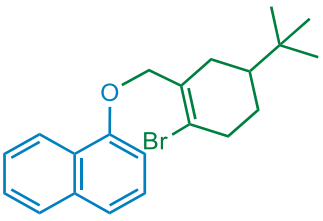
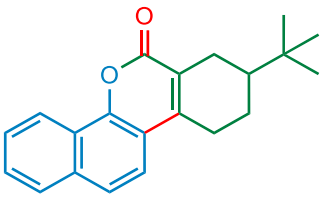
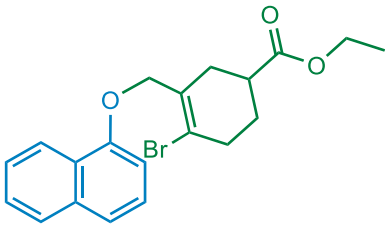
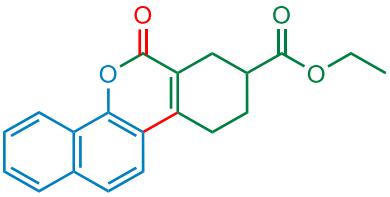
[a]All reactions were performed using 4 mmol of **52** and 2 mmol of **125** in a round-bottomed flask.

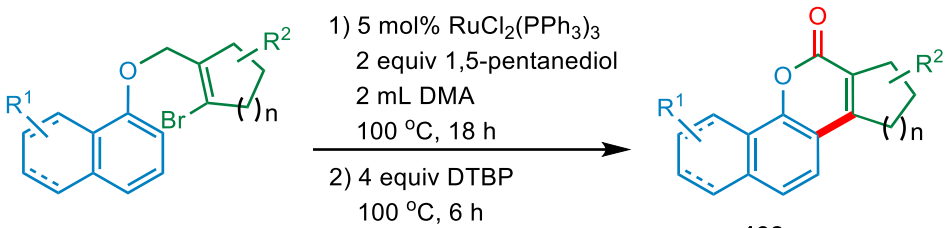
Table 15. Synthesized annulated naphthopyranones **138a–g** and 1,2,3,4,7,8,9,10-octahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (**138h**) under the optimized reaction conditions.[a]



129
n = 1, 2, 3, 4

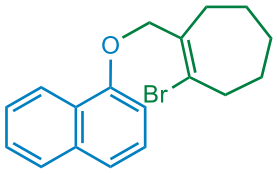
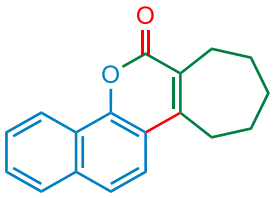
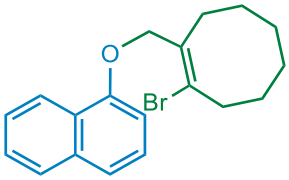
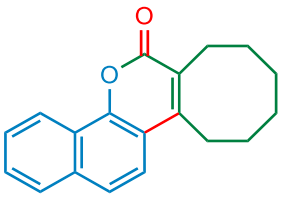
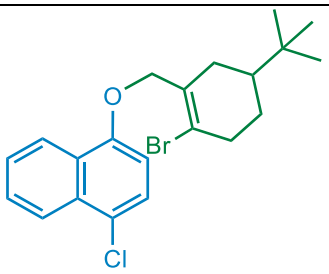
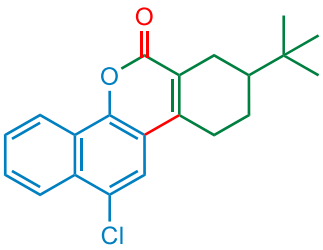
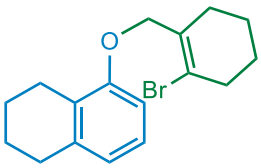
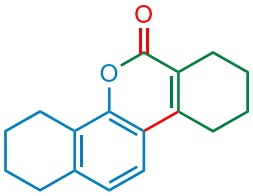
138
R^1 = H, Cl
R^2 = H, alkyl, CO_2Et

entry	**129**	**138**	yield (%)
1	 **129a**	 **138a**	79
2	 **129b**	 **138b**	88
3	 **129c**	 **138c**	90
4	 **129d**	 **138d**	78



129
n = 1, 2, 3, 4

138
R^1 = H, Cl
R^2 = H, alkyl, CO_2Et

entry	**129**	**138**	yield (%)
5			82
	129e	**138e**	
6			84
	129f	**138f**	
7			81
	129g	**138g**	
8			74
	129h	**138h**	

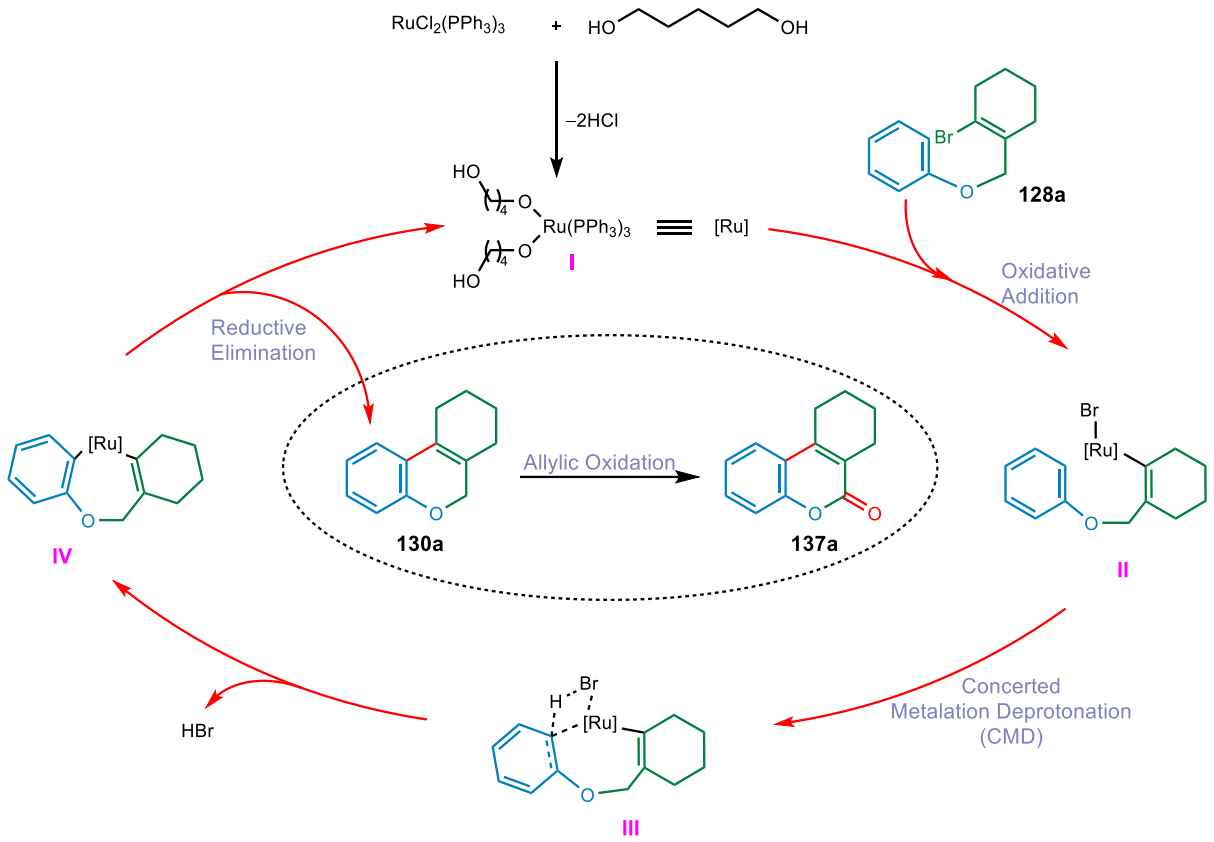
[a]The reactions were performed using 1 mmol **129** in a sealed vial under argon.

To start with, substrate **129a** was successfully synthesized by reaction between 1-naphthol (**52a**) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclopent-1-ene (**125b**) in 81% yield and characterized using standard techniques (Table 14, entry 1). The annulation reaction was conducted under standard conditions, yielding compound **138a** in a remarkable 79% yield

(Table 15, entry 1). It should be noted that **138a** can be regarded as a heterocyclic derivative of the steroid equilenin,[81] a naturally occurring steroidal estrogen found in the urine of pregnant mares. In this sense, **138a** can be considered as an 11-oxasteroid.[82] Heterosteroids, which include aza-, oxa-, and thiasteroids, are of great importance in medicinal chemistry due to their diverse biological activities, which are quite different from those of carbocyclic steroids. The successful transformation of **129a**, which resulted in the formation of the 6-6-6-5-system **138a**, prompted further investigation to determine whether the novel transformation allowed for the synthesis of other skeletal structures, such as 6-6-6-6-, 6-6-6-7- and 6-6-6-8-systems. For the synthesis of a 6-6-6-6-system, **129b** was reacted under standard conditions to give exclusively 7,8,9,10-tetrahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (**138b**) in 88% yield (Table 15, entry 2). Subsequently, it was successfully demonstrated that the reactions of **129c** and **129d** also delivered the corresponding 6-6-6-6-skeletons, namely **138c** and **138d**, with yields of 90% and 78%, respectively (Table 15, entries 3, 4). The reaction of **129e** yielded the 6-6-6-7-system **138e** in 82% yield, while the reaction of **129f** provided the 6-6-6-8-system **138f** in 84% yield (Table 15, entries 5, 6). Finally, two experiments were conducted utilizing **129g** and **129h** as starting materials to produce **138g** and **138h** with yields of 81% and 74%, respectively (Table 15, entries 7, 8). The results presented show that the ruthenium-catalyzed domino intramolecular aromatic C−H alkenylation/ allylic oxidation allows the regioselective synthesis of annulated naphthopyranones **138** with yields up to 90%.

2.4 Mechanism

Several studies have supported the significance of the concerted metalation-deprotonation (CMD) process for the direct arylation of Ar−H with Ar−X.[80a, 83] Against this background, a plausible reaction mechanism for the ruthenium-catalyzed intramolecular aromatic C−H alkenylation reaction has been developed which is outlined in Scheme 42, using the cyclization of **128a** into **130a** as an example. Subsequently, **130a** undergoes allylic oxidation[84] to **137b**.



Scheme 42. Plausible mechanism for the ruthenium-catalyzed domino intramolecular aromatic C−H alkenylation/allylic oxidation reaction of 1-[(2-bromocyclohex-1-en-1-yl)methoxy]benzene (**128a**) to 7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137a**).

It is assumed that the catalyst $RuCl_2(PPh_3)_3$ initially reacts with 1,5-pentanediol to produce the active ruthenium complex **I**. It must be pointed out that it remains unclear whether the diol acts as an *O*,*O*-bidentate or as an *O*-monodentate ligand as shown here. Upon oxidative addition of the alkenyl halide **128a** to complex **I**, an alkenylruthenium intermediate (**II**) is formed. Subsequently, ruthenium interacts with the *ortho*-carbon atom of the aromatic ring through a concerted metalation-deprotonation process. This activates the C−H bond by forming intermediate **III**. Cleavage of the *ortho* C−H bond and elimination of HBr yields intermediate **IV**. The final step of the catalytic cycle involves the reductive elimination reaction of the 7-membered ruthenacycle intermediate **IV**, resulting in the formation of compound **130a** and regeneration of catalyst **I**. Subsequently, oxidation of the allylic hydrogens of the pyran core in compound **130a** using DTBP as reagent yields the final product **137a**.

2.5 Structure elucidation of 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (137e)

The structures of all products **137** and **138** were unambiguously established by NMR spectroscopy, IR spectroscopy and mass spectrometry. As an illustrative example, this chapter describes the analysis of the ^{1}H NMR-, ^{13}C NMR-, COSY-, HSQC- and HMBC spectra to elucidate the structure of 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137e**).

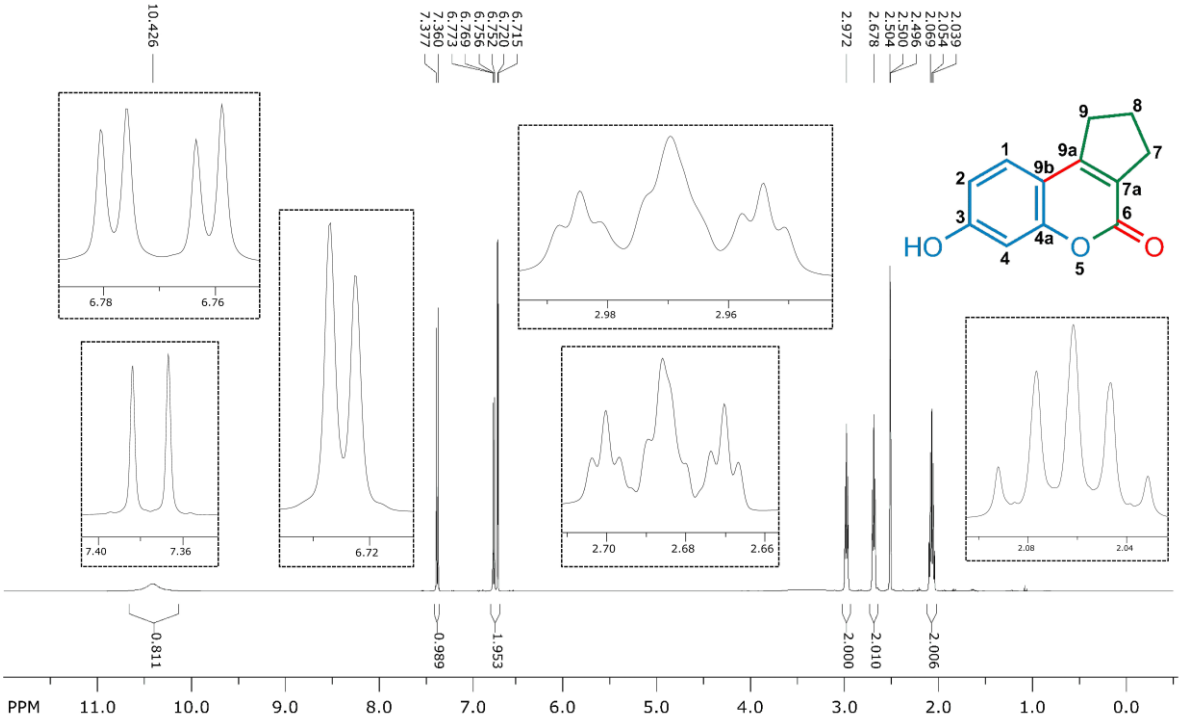


Figure 18. ^{1}H NMR spectrum (DMSO-d_6, 600 MHz) of 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137e**).

Figure 18 presents the ^{1}H NMR spectrum of **137e**, which was recorded on a 600 MHz spectrometer using deuterated DMSO as the solvent. In this spectrum, a total of seven hydrogen peaks were observed and subsequently integrated. In the range of δ = 6.50−7.50 ppm a typical pattern for a trisubstituted phenyl ring is observable.

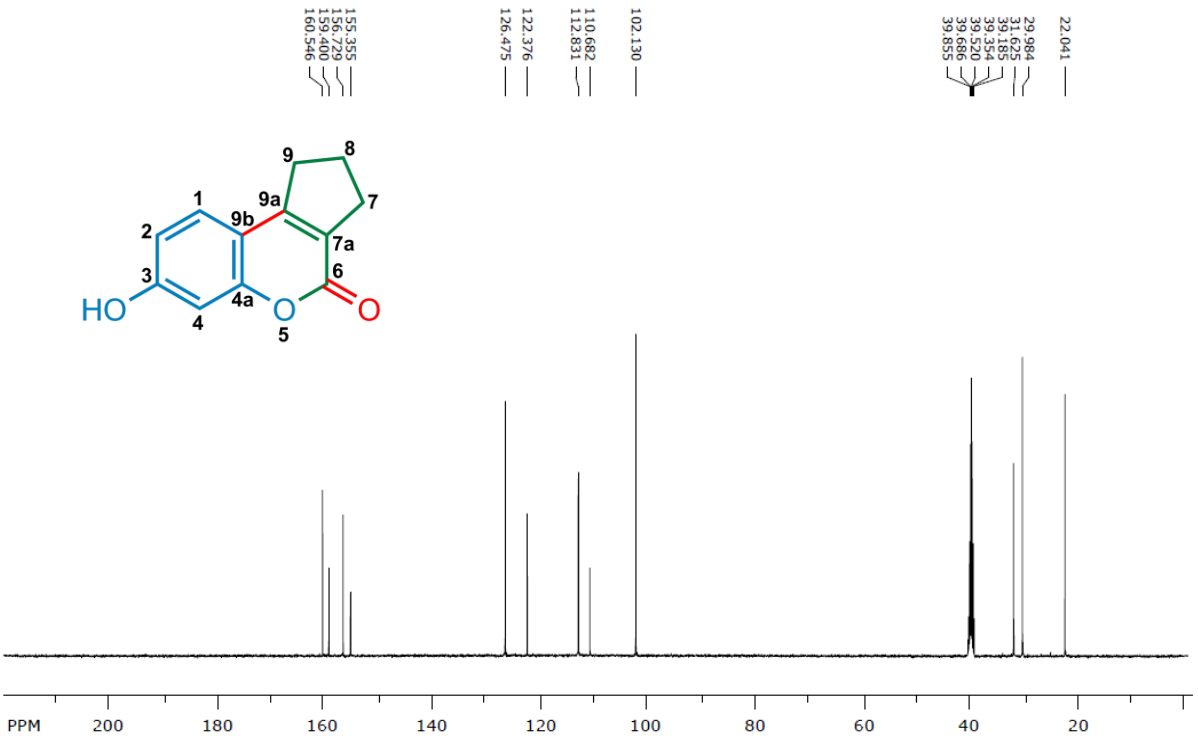


Figure 19. ^{13}C NMR spectrum (DMSO-d_6, 150 MHz) of 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137e**).

In the ^{13}C NMR spectrum, a total of 12 signals were detected (Figure 19). Nine signals in the region δ = 100−165 ppm stand for phenolic and olefinic carbons and three carbons in the region δ = 20−35 ppm represent the remaining alicyclic carbons. The ^{1}H and ^{13}C NMR data were completely assigned by COSY, HSQC and HMBC.

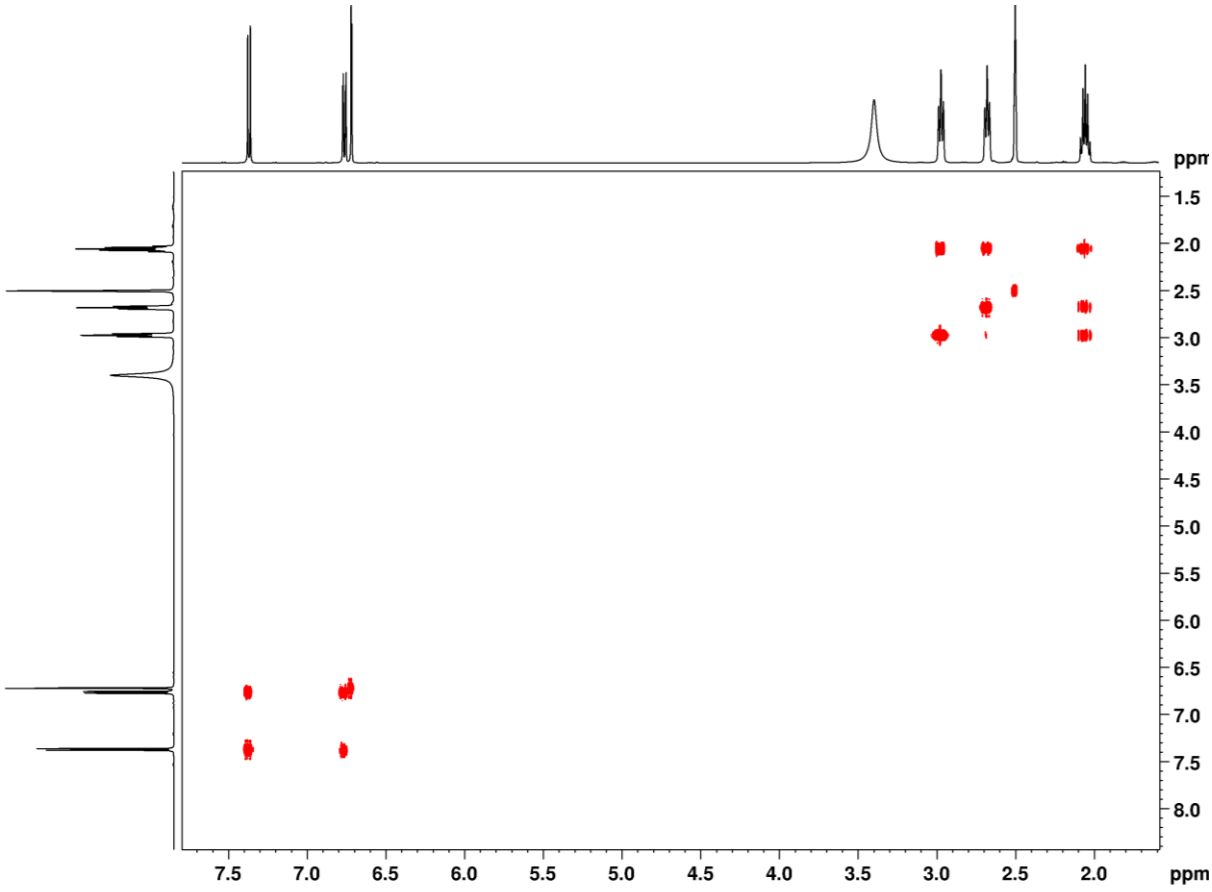


Figure 20. ^{1}H-^{1}H COSY spectrum (DMSO-d_6, 500 MHz) of 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137e**).

In the COSY spectrum of **137e** two cross correlations of hydrogens 8-H_2 at δ = 2.05 ppm with 7-H_2 at δ = 2.68 ppm and with 9-H_2 at δ = 2.97 ppm established the proton spin system 7-H_2 to 9-H_2 on the cyclopentene ring. The typical 1,2,4-aromatic proton coupling pattern was confirmed by the COSY spectrum shown in Figure 20.

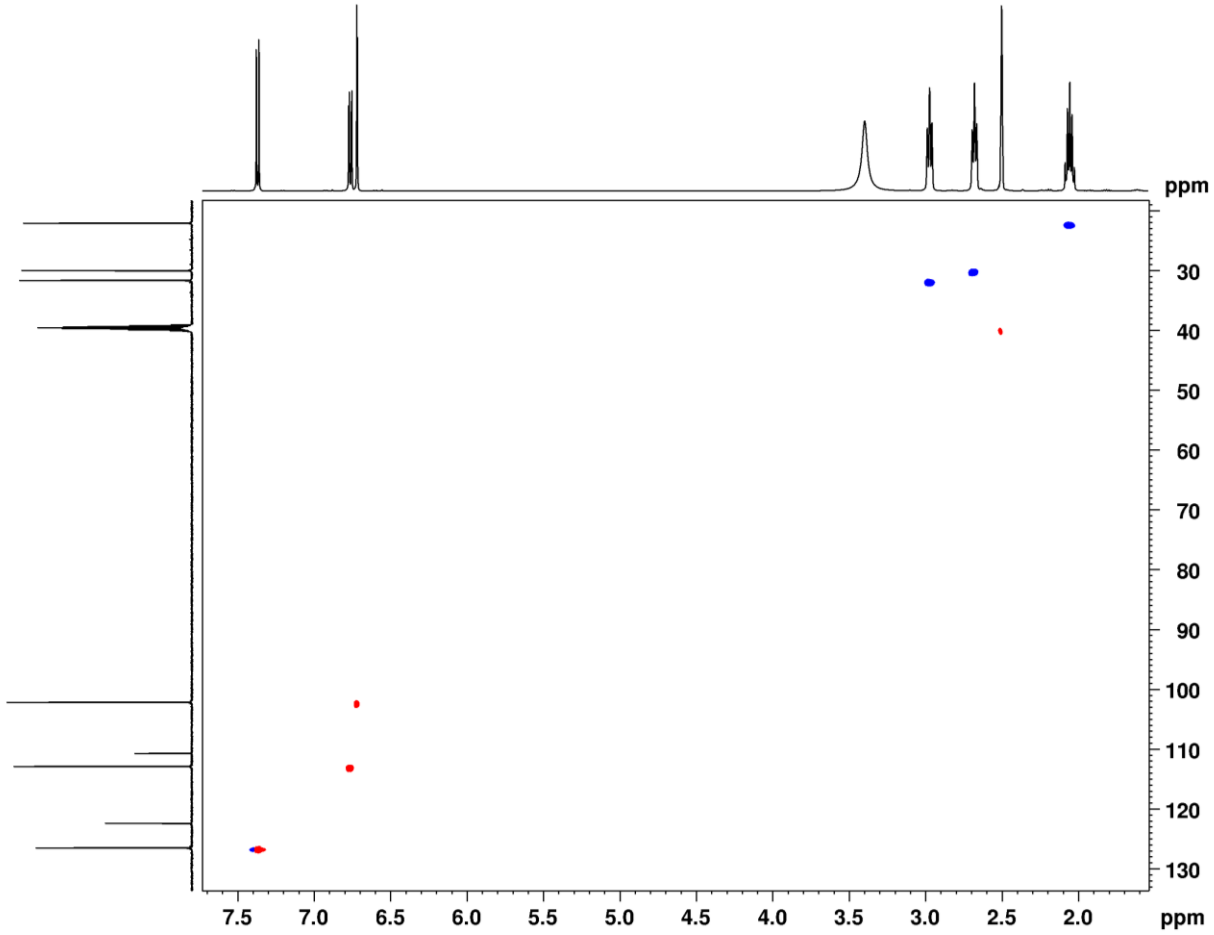


Figure 21. ^{1}H-^{13}C HSQC spectrum (DMSO-d_6, 500, 125 MHz) of 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137e**).

The proton bearing carbons of the cyclopentene and aromatic ring were distinguished as C-1 at δ = 126.5, C-2 at δ = 110.7, C-4 at δ = 102.1, C-7 at δ = 31.6, C-8 at δ = 29.9 and C-9 at δ = 22.0 ppm by HSQC (Figure 21).

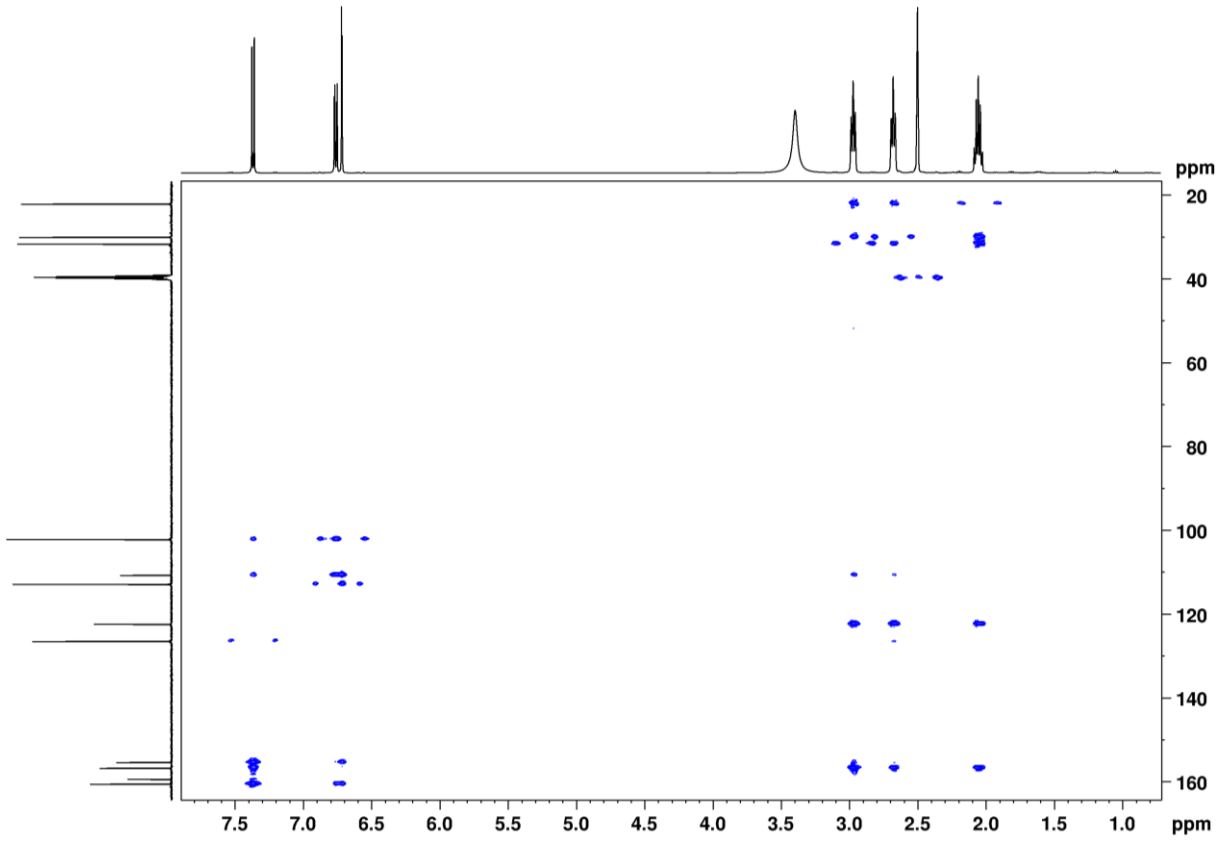


Figure 22. ^{1}H-^{13}C HMBC spectrum (DMSO-d_6, 500, 125 MHz) of 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137e**).

In the HMBC experiment (Figure 22) carbons C-7a (δ = 122.0 ppm) and C-9a (δ = 156.7 ppm) demonstrate HMBC correlations with 7-H_2, 8-H_2 and 9-H_2. Carbon 9a shows an extra correlation with 1-H. The carbon C-9b at δ = 110.7 ppm exhibits ^{1}H-^{13}C correlations with 1-H at δ = 7.37 ppm, 2-H at δ = 6.76 ppm, 4-H at δ = 6.71 ppm, 9-H_2 and 7-H_2. The hydroxyl group appears as a broad singlet at δ = 10.43 ppm. The phenolic carbon C-3 at δ = 160.5 ppm shows HMBC correlations with 1-H, 2-H and 4-H. Long range correlations between 1-H and 4-H with the carbon signal at δ = 155.3 ppm assigns C-4a. In agreement with a mass of 202 amu, the observed chemical shift of the remaining carbon at δ = 159.4 ppm was attributed to the carboxyl C-6 of an unsaturated lactone in **137e**.

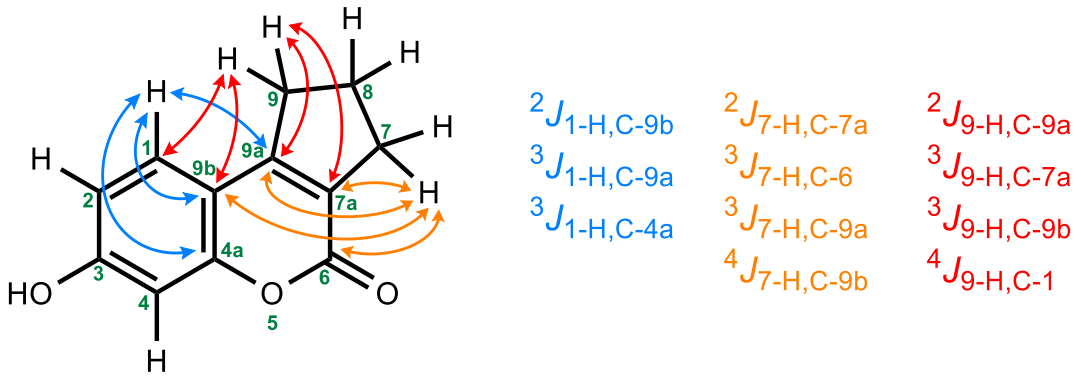


Figure 23. Important HMBC correlations (H↔C) for 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137e**).

Important HMBC correlations for 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137e**) are presented in Figure 23.

2.6 Conclusion

In conclusion, a novel and straightforward regioselective method for the efficient synthesis of annulated 2*H*-pyran-2-ones has been developed. The initial goal was to develop a new approach to 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromenes **130** based on a transition metal-catalyzed intramolecular aromatic C−H alkenylation of 2-halo-1-(aryloxymethyl)cycloalk-1-enes **128**. As a result of extensive optimization work using the transformation of **128a** as a model reaction, it was shown that the cyclization to 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**) could be achieved in 89% yield when **128a** was reacted with 8 mol% $RuCl_2(PPh_3)_3$ as catalyst in 1,5-pentanediol at 140 °C for 18 h. Not only is it remarkable that the reaction proceeds in the absence of any base, but also that the 1,5-pentanediol plays an important role in achieving a high yield. Although the desired cyclization could be realized, it was not possible to isolate the product **130a** in analytically pure form. Therefore, the transition metal-catalyzed intramolecular aromatic C−H alkenylation was combined with an allylic oxidation to a new domino process for the synthesis of annulated 2*H*-pyran-2-ones **137** and **138**.

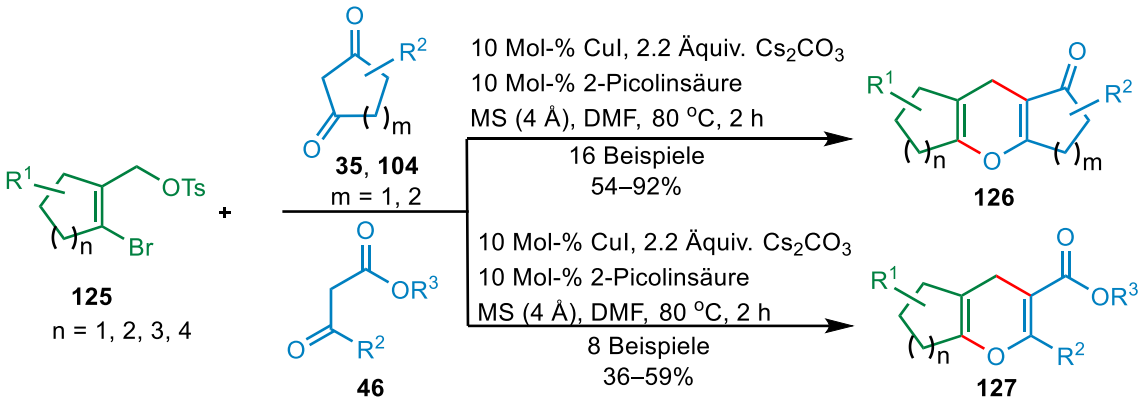
Optimization of the reaction conditions using the conversion of **128b** to **137b** as an example showed that the highest yield for **137b** was obtained when the first step was performed with 5 mol% $RuCl_2(PPh_3)_3$ as catalyst and 1,5-pentanediol as additive in DMA at 100 °C for 18 h and an excess of DTBP was used for the second step. After demonstrating that the Ru-catalyzed intramolecular aromatic C−H alkenylation can be combined with an allylic oxidation to form a new domino process, the scope and limitations were studied. Using the optimized reaction conditions, it was possible to synthesize a great variety of 3,4-annulated coumarins **137** with

yields up to 83% by reacting 2-bromo-1-(aryloxymethyl)cycloalk-1-enes **128a–k**. The high selectivity of the cyclization is worth to be mentioned. In phenol-, resorcinol- and pyrogallol-derived substrates the ring closure occurs only at the C-atom that is in *ortho*-position to the ether bridge and in *para*-position to the OH group of the substrate. It was also demonstrated that the Ru-catalyzed domino intramolecular aromatic C−H alkenylation / allylic oxidation allows the regioselective synthesis of a number of annulated naphthopyranones **138** with yields up to 90% using 2-bromo-1-(naphthalenoxymethyl)cycloalk-1-enes **129a–g** and 5-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]-1,2,3,4-tetrahydronaphthalene (**129h**).

3 Zusammenfassung and summary

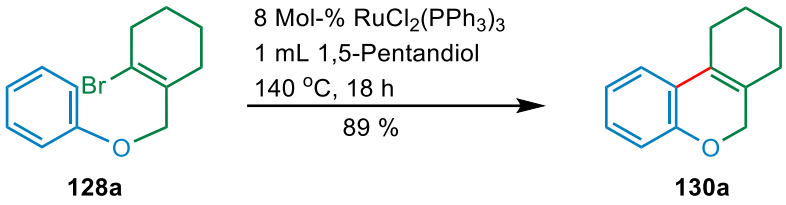
3.1 Zusammenfassung

Anellierte 4*H*-Pyrane sowie anellierte 2*H*-Pyran-2-one sind interessante Syntheseziele, jedoch sind die bislang für ihre Darstellung zur Verfügung stehenden Methoden beschränkt. Ziel der Arbeit war es, neue übergangsmetallkatalysierte Reaktionen zum effizienten und selektiven Aufbau von anellierten und bisanellierten partiell gesättigten Pyranen und Pyranonen zu entwickeln. Dabei sollten insbesondere 1,3-Biselektrophile als Substrate eingesetzt werden.



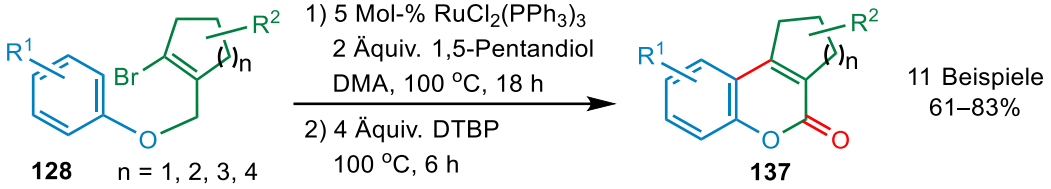
Schema 43. Synthese von bisanellierten und anellierten 4*H*-Pyranen **126** und **127**.

Der erste Teil der Arbeit ist der Entwicklung eines neuen Zugangs zu 4*H*-Pyranen **126** und **127** durch Umsetzung von cyclischen 1-Bromallyltosylaten **125** mit 1,3-Dicarbonylen gewidmet. Die Optimierung einer Modellreaktion ergab, dass man die höchsten Ausbeuten erhält, wenn man die beiden Substrate mit 10 Mol-% CuI, 2.2 Äquiv. Cs_2CO_3 und 10 Mol-% 2-Picolinsäure in Gegenwart von Molekularsieb (4 Å) in DMF bei 80 °C für 2 h umsetzt. Durch Umsatz von **125** mit cyclischen 1,3-Dicarbonylen **35**, **104** ließen sich so die bisanellierten 4*H*-Pyrane **126** in Ausbeuten von bis zu 92% synthetisieren (Schema 43). Die Bedeutung der Methode liegt darin, dass sie fünf verschiedene heterocyclische Gerüste zugänglich macht. Die neue Dominoreaktion ist nicht auf cyclische 1,3-Dicarbonyle **35**, **104** als Substrate beschränkt. Sechsgliedrige 1-Bromallyltosylate **125** ließen sich mit acyclischen *β*-Ketoestern **46** erfolgreich zu den 5,6,7,8-Tetrahydro-4*H*-chromen-3-carboxylaten **127** in Ausbeuten von bis zu 59% umsetzen (Schema 43). Die hohe Effizienz, gepaart mit großer Flexibilität und einfacher Durchführbarkeit machen diese neue Methode zu einem wertvollen Werkzeug für die Synthese. Es wird angenommen, dass die Anellierung als Dominoreaktion aufzufassen ist, die aus einer intermolekularen *C*-Allylierung und einer nachfolgenden Cu(I)-katalysierten intramolekularen *O*-Vinylierung vom Ullmann-Typ besteht.

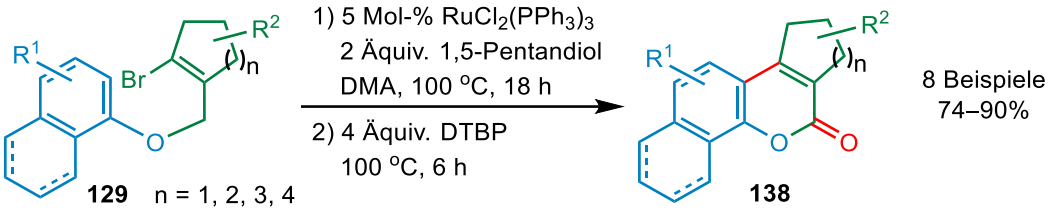


Schema 44. Synthese von 7,8,9,10-Tetrahydro-6*H*-benzo[*c*]chromen (**130a**).

Im zweiten Teil der Arbeit wurde eine neuartige regioselektive Methode für die effiziente Synthese von anellierten 2*H*-Pyran-2-onen entwickelt. Ursprüngliches Ziel war ein neuer Zugang zu 7,8,9,10-Tetrahydro-6*H*-benzo[*c*]chromenen **130**, der auf einer übergangsmetall-katalysierten intramolekularen aromatischen C−H-Alkenylierung von leicht aus 1-Bromallyltosylaten **125** zugänglichen 2-Halo-1-(aryloxymethyl)cycloalk-1-enen **128** basiert. Obwohl die gewünschte Cyclisierung von **128a** zu **130a** realisiert werden konnte, ließ sich das Produkt **130a** nicht in analytisch reiner Form gewinnen (Schema 44).



Schema 45. Synthese von 3,4-anellierten Cumarinen **137**.



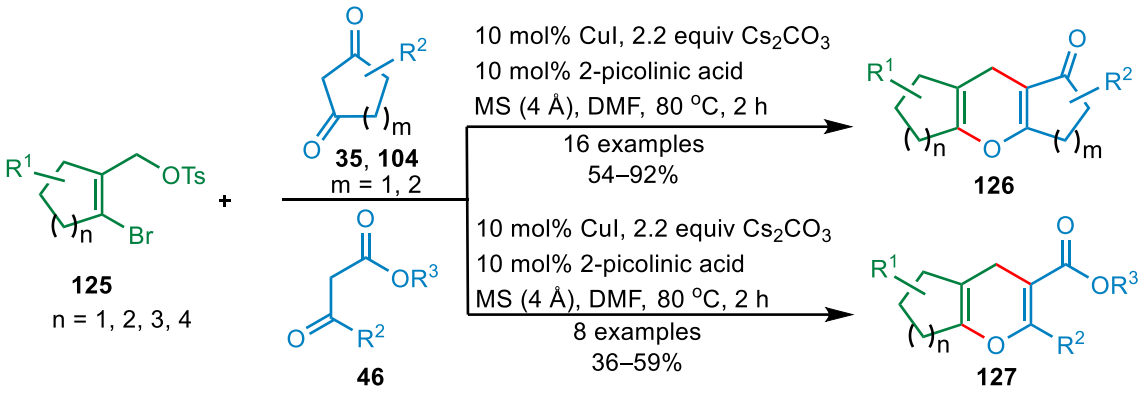
Schema 46. Synthese von anellierten Naphthopyranonen **138**.

Daher wurde die Ru-katalysierte intramolekulare aromatische C−H-Alkenylierung mit einer allylischen Oxidation zu einer neuen Dominoreaktion für die Synthese von anellierten 2*H*-Pyran-2-onen **137** und **138** kombiniert. Die Optimierung der Reaktionsbedingungen am Beispiel einer Modellreaktion ergab, dass die höchste Ausbeute erzielt wurde, wenn der erste Schritt mit $RuCl_2(PPh_3)_3$ als Katalysator und 1,5-Pentandiol als Additiv in DMA bei 100 °C für 18 h durchgeführt und für den zweiten Schritt ein Überschuss an DTBP verwendet wurde. Anschließend wurde die Anwendungsbreite der Methode untersucht. Unter den optimierten Reaktionsbedingungen war es möglich, durch Umsetzung von 2-Brom-1-(aryloxymethyl)cycloalk-1-enen **128** eine Vielzahl von 3,4-anellierten Cumarinen **137** mit Ausbeuten von bis zu 83% zu synthetisieren (Schema 45). Bemerkenswert ist die hohe Selektivität der Cyclisierung. In Substraten, die sich von Phenol, Resorcin und Pyrogallol ableiten, erfolgt der Ringschluss nur an dem C-Atom, das sich in *ortho*-Position zur

Etherbrücke und in *para*-Position zur OH-Gruppe des Substrats befindet. Es wurde auch gezeigt, dass die Ru-katalysierte intramolekulare aromatische C−H-Alkenylierung/Allyloxidation von Allyl-*α*-(tetrahydro)naphthylethern **129** die regioselektive Synthese von anellierten Naphthopyranonen **138** mit Ausbeuten von bis zu 90 % ermöglicht (Schema 46).

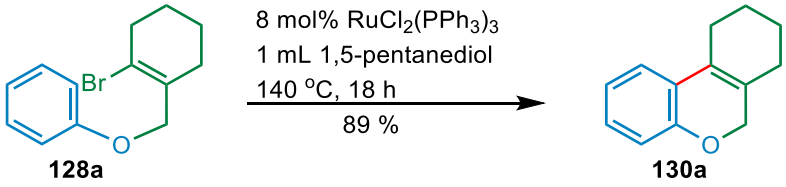
3.2 Summary

Annulated 4*H*-pyrans as well as fused 2*H*-pyran-2-ones are interesting synthetic targets, but the available methods for their preparation are limited. The aim of this work was to develop new transition metal-catalyzed reactions for the efficient and selective construction of annulated and bisannulated partially saturated pyrans and pyranones. In particular, 1,3-biselectrophiles should be used as substrates.



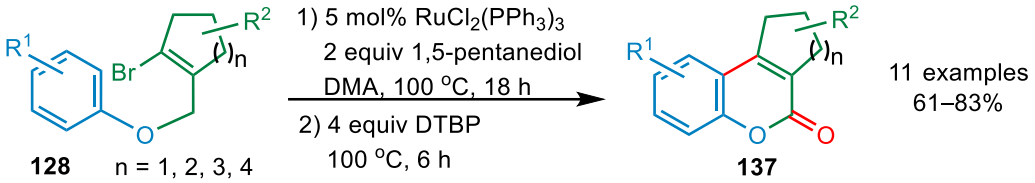
Scheme 47. Synthesis of bisannulated and annulated 4*H*-pyrans **126** und **127**.

The first part of the work is devoted to the development of a new access to 4*H*-pyrans **126** and **127** by reacting cyclic 1-bromoallyl tosylates **125** with 1,3-dicarbonyls. Optimization of a model reaction revealed that the highest yields were obtained when the two substrates were reacted with 10 mol% CuI, 2.2 equiv. Cs_2CO_3, and 10 mol% 2-picolinic acid in the presence of molecular sieve (4 Å) in DMF at 80 °C for 2 h. Reaction of **125** with cyclic 1,3-dicarbonyls **35**, **104** allowed the synthesis of bisannulated 4*H*-pyrans **126** in yields up to 92% (Scheme 47). The significance of this method is that it provides access to five different heterocyclic scaffolds. The new domino reaction is not limited to cyclic 1,3-dicarbonyls **35**, **104** as substrates. Six-membered 1-bromoallyl tosylates **125** could be successfully reacted with acyclic *β*-ketoesters **46** to give the 5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylates **127** in yields up to 59% (Scheme 47). The high efficiency coupled with great flexibility and easy feasibility make this new method a valuable tool for synthesis. The annulation is assumed to be a domino reaction consisting of an intermolecular *C*-allylation followed by a Cu(I)-catalyzed intramolecular Ullmann-type *O*-vinylation.

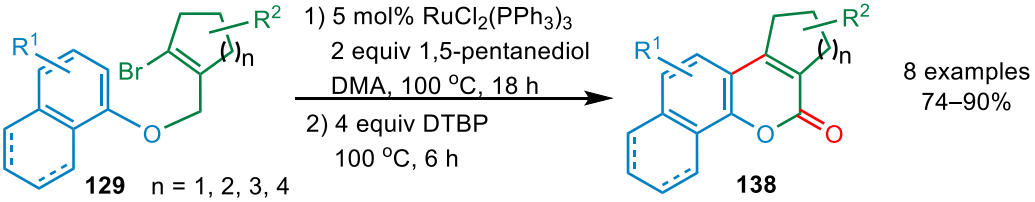


Scheme 48. Synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**).

In the second part of the work, a novel regioselective method for the efficient synthesis of annulated 2*H*-pyran-2-ones was developed. The initial goal was a new approach to 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromenes **130** based on a transition metal-catalyzed intramolecular aromatic C−H alkenylation of 2-halo-1-(aryloxymethyl)cycloalk-1-enes **128**, which are readily accessible from 1-bromoallyl tosylates **125**. Although the desired cyclization of **128a** to **130a** was achieved, the product **130a** could not be obtained in analytically pure form (Scheme 48).



Scheme 49. Synthesis of 3,4-annulated coumarins **137**.



Scheme 50. Synthesis of annulated naphthopyranones **138**.

Therefore, the Ru-catalyzed intramolecular aromatic C−H alkenylation was combined with an allylic oxidation to form a new domino reaction for the synthesis of annulated 2*H*-pyran-2-ones **137** and **138**. Optimization of the reaction conditions using a model reaction as an example showed that the highest yield was obtained when the first step was carried out with $RuCl_2(PPh_3)_3$ as catalyst and 1,5-pentanediol as additive in DMA at 100 °C for 18 h and an excess of DTBP was used for the second step. Then, scope and limitations of the method was investigated. Under the optimized reaction conditions, it was possible to synthesize a series of 3,4-annulated coumarins **137** with yields up to 83% by reacting 2-bromo-1-(aryloxymethyl)cycloalk-1-enes **128** (Scheme 49). The high selectivity of the cyclization is remarkable. In substrates derived from phenol, resorcinol, and pyrogallol, ring closure occurs only at the C atom that is in *ortho*-position to the ether bridge and in *para*-position to the OH group of the substrate. It has also been demonstrated that the Ru-catalyzed intramolecular aromatic C−H alkenylation/allylic oxidation of allyl-*α*-(tetrahydro)naphthyl ethers **129** allows the regioselective synthesis of annulated naphthopyranones **138** with yields up to 90% (Scheme 50).

III Experimental Part

1 General remarks

All commercially available reagents were purchased from Sigma Aldrich, ABCR, Alfa Aesar or Merck and were used without further purification. Glassware was dried overnight at 120 °C in an oven. Solvents used in reactions, extractions, and purifications were distilled prior to use. Reaction temperatures are reported as oil bath temperatures. For the synthesis in a vial, glass vials (10 mL) sealed by aluminum crimp tops with PTFE-coated silicone septa were used. Thin-layer chromatography (TLC) was performed on TLC silica gel 60 F_{254}. Compounds were visualized with UV light (λ = 254 nm) and by immersion in a 5% solution of vanillin in ethanolic sulfuric acid followed by heating. Products were purified by column chromatography on silica gel (0.04−0.063 mm). Melting points (M.p.) were determined on a Büchi melting point apparatus B-545 with open capillary tubes and are uncorrected. IR spectra were measured on a Bruker Alpha FT-IR spectrometer. NMR spectra were recorded on a VARIAN Inova 300, a VARIAN Inova 500 or a Bruker AVANCE III HD 600 MHz spectrometer using $CDCl_3$, CD_2Cl_2, and DMSO-d_6 as the solvents. The ^{1}H- and ^{13}C NMR chemical shifts were referenced to residual solvent signals ($CDCl_3$: ^{1}H NMR δ = 7.26 ppm, ^{13}C NMR δ = 77.02 ppm; CD_2Cl_2: ^{1}H NMR δ = 5.32 ppm, ^{13}C NMR δ = 53.84 ppm; DMSO-d_6: ^{1}H NMR δ = 2.50 ppm, ^{13}C NMR δ = 39.52 ppm). Structural assignments of all starting materials and all products are based on additional information from COSY-, HSQC- and HMBC experiments. Chemical shifts (δ) are given in parts per million (ppm), coupling constants (J) are reported in Hertz (Hz), and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), dd (doublet of doublet), dt (doublet of triplet), tt (triplet of triplet), qd (quartet of doublet), ddd (doublet of doublet of doublet), tdd (triplet of doublet of doublet), dddd (doublet of doublet of doublet of doublet) and br (broad). 1D- and 2D homonuclear NMR spectra were measured with standard pulse sequences. SpinWorks[79] was used for the evaluation of coupling constants of second-order spin multiplets. This software employs the Nummrit algorithm to enhance the accuracy of chemical shifts, coupling constants, amplitude, and linewidth. It accomplishes this by minimizing the square difference between the experimental and calculated spectra, utilizing initial assumptions of coupling constants and chemical shifts taken from the NMR spectra. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were obtained at 70 eV using a double-focusing sector field Finnigan MAT 95 or a Bruker Daltonics micrOTOF-Q mass spectrometer. Intensities are reported as percentages relative to the base peak (I = 100%). Single crystal X-ray data for compound **126e** were measured using a Bruker Kappa APEXII Duo X-ray single-crystal diffractometer.

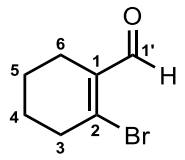
2 Cu(I)-catalyzed synthesis of xanthenes and related compounds 126, chromenes 127, and double alkylated compounds 135[77]

2.1 Synthesis of 2-bromo-1-enecarbaldehydes 133a–g

2.1.1 General procedure I[78, 85]

A solution of dry *N*,*N*-dimethylformamide (4.62 mL, 60 mmol, 3 equiv) and dry chloroform (40 mL) was prepared. Subsequently, phosphorus tribromide (PBr_3) (4.70 mL, 50 mmol, 2.5 equiv) was added dropwise to the stirred mixture. The resulting mixture was then stirred for 1 h at 0 °C. Afterwards, a solution of ketone **132** (20 mmol, 1 equiv) in dry chloroform (10 mL) was added dropwise to the formylation reagent with stirring. The solution turned dark brown and was stirred at room temperature overnight. Then, the reaction mixture was poured onto 100 g crushed ice and neutralized with a saturated solution of $NaHCO_3$. The solution was warmed up to room temperature and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The organic phases were combined and washed with a saturated solution of $NaHCO_3$ (2 × 100 mL), brine (2 × 100 mL) and water (2 × 100 mL). The resulting solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Due to their instability, the 2-bromo-1-enecarbaldehydes **133** were used for the reduction to the corresponding alcohols **123** without further purification.

2.1.2 2-Bromocyclohex-1-enecarbaldehyde (133a)



Following general procedure I, 2-bromocyclohex-1-enecarbaldehyde (**133a**) was synthesized by reaction of PBr_3 (4.70 mL, 50 mmol), DMF (4.62 mL, 60 mmol) and cyclohexanone (**132a**) (1.77 mL, 20 mmol). Analytically pure **133a** was obtained as a pale yellow oil (1.21 g, 6.39 mmol, 32%) after subjecting the crude product to column chromatography over silica gel (hexane/ethyl acetate = 40:1).

$\boldsymbol{R_f}$ = 0.76 (petroleum ether/ethyl acetate = 15:0.5).

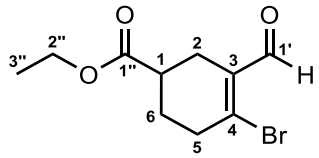
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924 (H─C═O), 2852, 1670 (C═O), 1602 (C═C), 1386, 749.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 10.01 (s, 1H, 1'-H), 2.77−2.71 (m, 2H, 3-H_2), 2.30−2.24 (m, 2H, 6-H_2), 1.79−1.63 (m, overlapped, 4H, 4-H_2 and 5-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 193.7 (C-1'), 143.6 (C-1), 135.3 (C-2), 38.8 (C-3), 24.9 (C-6), 24.2 (C-4), 21.1 (C-5).

LRMS (EI, 70 eV): *m/z* (%) = 188 (100) $[M]^+$, 173 (16), 159 (16), 109 (58) $[M - Br]^+$, 53 (24).
HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_7H_9BrO]^+$ 187.9837; found 187.9834.
Molecular weight: C_7H_9BrO (189.0520 g × mol^{-1}).

2.1.3 Ethyl 4-bromo-3-formylcyclohex-3-ene-1-carboxylate (133e)



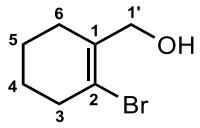
Following general procedure I, ethyl 4-bromo-3-formylcyclohex-3-ene-1-carboxylate (**133e**) was synthesized by reaction of PBr_3 (4.70 mL, 50 mmol), DMF (4.62 mL, 60 mmol) and 4-ethoxycarbonyl-cyclohexanon (**132e**) (3.4 g, 20 mmol). Analytically pure **133e** was obtained as a colorless oil (0.47 g, 1.79 mmol, 9%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).
$\boldsymbol{R_f}$ = 0.58 (cyclohexane/ethyl acetate = 3:2).
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 10.02 (s, 1H, 1'-H), 4.15 (q, *J* = 7.1 Hz, 2H, 2"-H_2), 2.85−2.81 (m, 2H, 5-H_2), 2.71−2.67 (m, 1H, 1-H), 2.63−2.61 (m, 1H, 2-Ha), 2.42−2.37 (m, 1H, 2-Hb), 2.11−2.06 (m, 1H, 6-Ha), 1.94−1.88 (m, 1H, 6-Hb), 1.25 (t, *J* = 7.1 Hz, 3H, 3"-H_3).
^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 192.9 (C-1'), 173.9 (C-1"), 142.2 (C-3), 133.5 (C-4), 60.8 (C-2"), 37.9 (C-1), 37.6 (C-5), 27.2 (C-2), 26.4 (C-6), 14.2 (C-3").
HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{10}H_{13}BrO_3Na]^+$ 282.9940; found 282.9939.
Molecular weight: $C_{10}H_{13}BrO_3$ (261.1150 g × mol^{-1}).

2.2 Synthesis of (2-bromo-cycloalk-1-en-1-yl)methanols 123a–g

2.2.1 General procedure II

A solution of the crude 2-bromo-1-enecarbaldehyde **133**, obtained from the reaction of 20 mmol of ketone **132** following general procedure I, was stirred in 40 mL of methanol at 0 °C. $NaBH_4$ (832 mg, 22 mmol, 1.1 equiv) was added portionwise and the resulting mixture was stirred at room temperature for 1 h. Next, water (60 mL) and dichloromethane (40 mL) were added and the reaction mixture was stirred for an additional 10 min. After phase separation, the aqueous phase was extracted with DCM (3 × 40 mL). The organic phases were combined and washed with brine (2 × 40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure product was obtained after subjecting the crude product to column chromatography over silica gel.

2.2.2 (2-Bromocyclohex-1-en-1-yl)methanol (123a)



Following general procedure II, (2-bromocyclohex-1-en-1-yl)methanol (**123a**) was synthesized by reduction of crude 2-bromocyclohex-1-enecarbaldehyde (**133a**) that has been obtained from reaction of 20 mmol of cyclohexanone (**132a**) according to general procedure I, using $NaBH_4$ (832 mg, 22 mmol). Analytically pure **123a** was obtained as a pale yellow oil (1.18 g, 6.20 mmol, 31% for two steps) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 10:1).

$\boldsymbol{R_f}$ = 0.34 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3301 (OH), 2930, 1657, 1434, 1331, 1006, 969, 795.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 4.22 (s, 2H, 1'-H_2), 2.53−2.47 (m, 2H, 3-H_2), 2.28−2.22 (m, 2H, 6-H_2), 1.69 (quint-like, J = 3.1 Hz, 4H, 4-H_2 and 5-H_2), 1.63 (br s, 1H, OH).

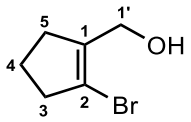
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 135.3 (C-1), 121.4 (C-2), 66.3 (C-1'), 36.6 (C-3), 29.1 (C-6), 24.6 (C-4), 22.3 (C-5).

LRMS (EI, 70 eV): *m/z* (%) = 190 (14) $[M]^+$, 111 (68) $[M - Br]^+$, 93 (56), 67 (100), 53 (24).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_6H_9BrO]^+$ 189.9993; found 189.9979.

Molecular weight: C_6H_9BrO (191.0680 g × mol^{-1}).

2.2.3 (2-Bromocyclopent-1-en-1-yl)methanol (123b)



Following general procedure II, (2-bromocyclopent-1-en-1-yl)methanol (**123b**) was synthesized by reduction of crude 2-bromocyclopent-1-enecarbaldehyde (**133b**) that has been obtained from reaction of 20 mmol of cyclopentanone (**132b**) according to general procedure I, using $NaBH_4$ (832 mg, 22 mmol). Analytically pure **123b** was obtained as a pale yellow oil (849 mg, 4.79 mmol, 24% for two steps) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 15:1).

$\boldsymbol{R_f}$ = 0.48 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3298 (OH), 2919, 1654, 1442, 1317, 1089, 1000, 956.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 4.24 (s, 2H, 1'-H_2), 2.65 (m, ^3J (3-H, 4-H) = 7.7 Hz, ^4J (3-H, 5-H) = 2.3 Hz, ^4J (3-H, 5-H) = 1.1 Hz, 2H, 3-H_2), 2.46 (m, ^3J (4-H, 5-H) = 7.4 Hz, ^4J (3-H, 5-H) = 2.4 Hz, ^4J (3-H, 5-H) = 1.1 Hz, 2H, 5-H_2), 1.96 (quint-like, J = 7.5 Hz, 2H, 4-H_2), 1.64 (s, 1H, OH).

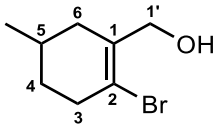
^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 139.7 (C-1), 117.9 (C-2), 60.4 (C-1'), 40.3 (C-3), 32.4 (C-5), 21.7 (C-4).

LRMS (EI, 70 eV): *m/z* (%) = 176 (14) $[M]^+$, 97 (100) $[M - Br]^+$, 67 (45).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_6H_9BrO]^+$ 175.9837; found 175.9812.

Molecular weight: C_6H_9BrO (177.0410 g × mol^{-1}).

2.2.4 (2-Bromo-5-methylcyclohex-1-en-1-yl)methanol (123c)



Following general procedure II, (2-bromo-5-methylcyclohex-1-en-1-yl)methanol (**123c**) was synthesized by reduction of crude 2-bromo-5-methylcyclohex-1-enecarbaldehyde (**133c**) that has been obtained from reaction of 20 mmol of 4-methylcyclohexanone (**132c**) according to general procedure I, using $NaBH_4$ (832 mg, 22 mmol). Analytically pure **123c** was obtained as a colorless oil (1.56 g, 7.60 mmol, 38% for two steps) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 12:1).

$\boldsymbol{R_f}$ = 0.36 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3212 (OH), 2923, 1656, 1433, 1331, 1057, 1026, 993, 928.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 4.25 (dd, ^2J (1'-Ha, 1'-Hb) = 12.2 Hz, ^3J (1'-Hb, OH) = 5.8 Hz, 1H, 1'-Hb), 4.19 (dd, ^2J (1'-Ha, 1'-Hb) = 12.2 Hz, ^3J (1'-Ha, OH) = 5.9 Hz, 1H, 1'-Ha), 2.60−2.49 (m, 2H, 3-H_2), 2.36 (dd, ^2J (6-Ha, 6-Hb) = 13.6 Hz, ^3J (6-Hb, 5-H) = 3.2 Hz, 1H, 6-Hb), 1.89−1.83 (m, 1H, 6-Ha), 1.80−1.74 (m, 1H, 5-H), 1.73−1.68 (m, 1H, 4-Hb), 1.49 (t, J = 6.2 Hz, 1H, OH), 1.48−1.34 (m, 1H, 4-Ha), 0.98 (d, J = 6.5 Hz, 3H, 5-CH_3).

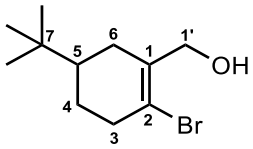
^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 134.7 (C-1), 121.1 (C-2), 66.3 (C-1'), 37.4 (C-6), 36.5 (C-3), 32.6 (C-4), 28.4 (C-5), 21.1 (5-CH_3).

LRMS (EI, 70 eV): *m/z* (%) = 204 (27) $[M]^+$, 125 (59) $[M - Br]^+$, 107 (100), 67 (26), 55 (35).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_8H_{13}BrO]^+$ 204.0150; found 204.0147.

Molecular weight: $C_8H_{13}BrO$ (205.0950 g × mol^{-1}).

2.2.5 (2-Bromo-5-(*tert*-butyl)cyclohex-1-en-1-yl)methanol (123d)



Following general procedure II, (2-bromo-5-(*tert*-butyl)cyclohex-1-en-1-yl)methanol (**123d**) was synthesized by reduction of crude 2-bromo-5-(*tert*-butyl)cyclohex-1-enecarbaldehyde (**133d**) that has been obtained from reaction of 20 mmol of 4-*tert*-butylcyclohexanone (**132d**) according to general procedure I, using $NaBH_4$ (832 mg, 22 mmol). Analytically pure **123d** was obtained as a white solid (2.126 g, 8.601 mmol, 43% for two steps) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 12:1).

M.p.: 43 − 44 °C.

R_f = 0.39 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3306 (OH), 2951, 2866, 1662, 1471, 1364, 1019, 972.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 4.26 (dd, ^2J (1'-Ha, 1'-Hb) = 12.0 Hz, ^3J (1'-Hb, OH) = 4.9 Hz, 1H, 1'-Ha), 4.20 (dd, ^2J (1'-Ha, 1'-Hb) = 12.1 Hz, ^3J (1'-Ha, OH) = 5.1 Hz, 1H, 1'-Hb), 2.57−2.51 (m, 2H, 3-H_2), 2.33 (dd, ^2J (6-Ha, 6-Hb) = 15.3 Hz, ^3J (6-Hb, 5-H) = 3.1 Hz, 1H, 6-Ha), 2.02−1.97 (m, 1H, 6-Hb), 1.82−1.78 (m, 1H, 4-Ha), 1.53 (t, J = 6.0, 1H, OH), 1.39−1.31 (m, overlapped, 2H, 4-Hb and 5-H), 0.89 (s, 9H, 3 × CH_3).

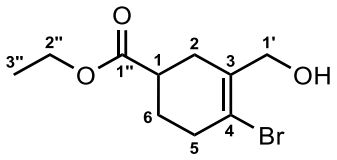
^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 135.3 (C-1), 121.2 (C-2), 66.5 (C-1'), 43.9 (C-5), 37.7 (C-3), 32.2 (C-7), 30.9 (C-6), 27.2 (3 × CH_3), 26.0 (C-4).

LRMS (EI, 70 eV): *m/z* (%) = 246 (7) $[M]^+$, 167 (31) $[M - Br]^+$, 149 (30), 93 (27), 57 (100).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{11}H_{19}BrO]^+$ 246.0619; found 246.0590.

Molecular weight: $C_{11}H_{19}BrO$ (247.1760 g × mol^{-1}).

2.2.6 Ethyl 4-bromo-3-(hydroxymethyl)cyclohex-3-ene-1-carboxylate (123e)



Following general procedure II, ethyl 4-bromo-3-(hydroxymethyl)cyclohex-3-ene-1-carboxylate (**123e**) was synthesized by reduction of crude ethyl 4-bromo-3-formylcyclohex-3-ene-1-carboxylate (**133e**) that has been obtained from the reaction of 100 mmol of ethyl 4-oxocyclohexanecarboxylate (**132e**) according to general procedure I, using $NaBH_4$ (4.16 g, 110 mmol). Analytically pure **123e** was obtained as a colorless viscous oil (3.52 g, 13.37 mmol, 13% for two steps) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 7:3).

$\boldsymbol{R_f}$ = 0.35 (cyclohexane /ethyl acetate = 3:2).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3413 (OH), 2934, 1726, 1436, 1174, 1023, 924.

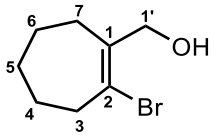
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 4.27 (d, J = 12.4 Hz, 1H, 1'-Ha), 4.22 (d, J = 12.3 Hz, 1H, 1'-Hb), 4.14 (q, J = 7.1 Hz, 2H, 2"-H_2), 2.65−2.61 (m, 1H, 1-H), 2.59−2.56 (m, 2H, 5-H_2), 2.55−2.53 (m, 1H, 2-Ha), 2.48−2.43 (m, 1H, 6-Ha), 2.03−1.99 (m, 1H, 2-Hb), 1.87−1.81 (m, 2H, 6-Hb and OH), 1.25 (t, J = 7.1 Hz, 3H, 3"-H_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 174.6 (C-1"), 133.7 (C-3), 120.0 (C-4), 65.9 (C-1'), 60.6 (C-2"), 38.9 (C-1), 35.5 (C-5), 30.9 (C-2), 26.8 (C-6), 14.2 (C-3").

HRMS (ESI): m/z $[M + Na]^+$ calcd. for $C_{10}H_{15}BrO_3Na$ 285.0097; found 285.0096.

Molecular weight: $C_{10}H_{15}BrO_3$ (263.1310 g × mol^{-1}).

2.2.7 (2-Bromocyclohept-1-en-1-yl)methanol (123f)



Following general procedure II, (2-bromocyclohept-1-en-1-yl)methanol (**123f**) was synthesized by reduction of crude 2-bromocyclohept-1-enecarbaldehyde (**133f**) that has been obtained from reaction of 20 mmol of cycloheptanone (**132f**) according to general procedure I, using $NaBH_4$ (832 mg, 22 mmol). Analytically pure **123f** was obtained as a pale yellow oil (1.52 g, 7.40 mmol, 37% for two steps) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 15:1).

$\boldsymbol{R_f}$ = 0.41 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3303 (OH), 2919, 1648, 1445, 1085, 1024, 993, 746.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 4.24 (s, 2H, 1'-H_2), 2.76 (ddd, ^2J (3-Ha, 3-Hb) = 11.1 Hz, ^3J (3-H, 4-H) = 5.4 Hz, 2H, 3-H_2), 2.37 (ddd, ^2J (7-Ha, 7-Hb) = 11.1 Hz, ^3J (6-H, 7-H) = 5.6 Hz, 2H, 7-H_2), 1.75 (quint, J = 6.1 Hz, 2H, 5-H_2), 1.64 (br s, 1H, OH), 1.60−1.52 (m, overlapped, 4H, 4-H_2 and 6-H_2).

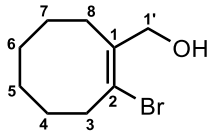
^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 140.6 (C-1), 124.6 (C-2), 68.4 (C-1'), 41.4 (C-3), 31.3 (C-7), 31.2 (C-5), 25.9 (C-6), 25.3 (C-4).

LRMS (EI, 70 eV): *m/z* (%) = 204 (13) $[M]^+$, 125 (54) $[M - Br]^+$, 107 (39), 91 (27), 81 (100), 67 (19), 57 (23), 55 (31).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_8H_{13}BrO]^+$ 204.0150; found 204.0148.

Molecular weight: $C_8H_{13}BrO$ (205.0950 g × mol^{-1}).

2.2.8 (2-Bromocyclooct-1-en-1-yl)methanol (123g)



Following general procedure II, (2-bromocyclooct-1-en-1-yl)methanol (**123g**) was synthesized by reduction of crude 2-bromocyclooct-1-enecarbaldehyde (**133g**) that has been obtained from reaction of 20 mmol of cyclooctanone (**132g**) according to general procedure I, using $NaBH_4$ (832 mg, 22 mmol). Analytically pure **123g** was obtained as a pale yellow oil (745 mg, 3.40 mmol, 17% for two steps) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 12:1).

R_f = 0.41 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3309 (OH), 2919, 1646, 1446, 1226, 1059, 1004, 952.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 4.27 (d, J = 6.2 Hz, 2H, 1'-H_2), 2.69 (ddd, ^2J (3-Ha, 3-Hb) = 12.4 Hz, ^3J (3-H, 4-H) = 5.2 Hz, 2H, 3-H_2), 2.40 (ddd, ^2J (8-Ha, 8-Hb) = 12.3 Hz, ^3J (7-H, 8-H) = 5.4 Hz, 2H, 8-H_2), 1.67−1.63 (m, 2H, 4-H_2), 1.62−1.58 (m, 2H, 7-H_2), 1.53 (t, J = 6.2, 1H, OH), 1.51−1.47 (m, overlapped, 4H, 5-H_2, 6-H_2).

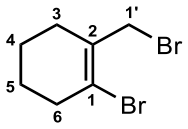
^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 137.9 (C-1), 123.6 (C-2), 66.4 (C-1'), 37.3 (C-3), 30.2 (C-8), 29.7 (C-7), 28.0 (C-4), 26.6 (C-5), 25.8 (C-6).

LRMS (EI, 70 eV): *m/z* (%) = 218 (26) $[M]^+$, 139 (67) $[M - Br]^+$, 121 (75), 95 (100), 67 (69), 55 (50).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_9H_{15}BrO]^+$ 218.0306; found 218.0295.

Molecular weight: $C_9H_{15}BrO$ (219.1220 g × mol^{-1}).

2.3 Synthesis of 1-bromo-2-(bromomethyl)cyclohex-1-ene (124a)



A solution of (2-bromocyclohex-1-en-1-yl)methanol (**123a**) (0.95 mg, 5 mmol, 1 equiv) in diethyl ether (25 mL) was stirred at 0 °C. Phosphorus tribromide (0.52 mL, 5.5 mmol, 1.1 equiv) was added dropwise, and the resulting mixture was stirred for 2 h. The reaction mixture was poured dropwise into ice water (50 mL) and the aqueous phase was extracted with diethyl ether (2 × 50 mL). The organic phases were combined and washed with a saturated solution of $NaHCO_3$ (2 × 50 mL). The resulting solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) was obtained as a pale yellow oil (1.09 g, 4.30 mmol, 86%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/diethyl ether = 4:1).

$\boldsymbol{R_f}$ = 0.58 (petroleum ether/ethyl acetate = 4:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2932, 1646, 1431, 1207, 973, 629.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 4.11 (s, 2H, 1'-H_2), 2.55−2.50 (m, 2H, 6-H_2), 2.31−2.27 (m, 2H, 3-H_2), 1.71 (quint-like, J = 3.1 Hz, 4H, 4-H_2 and 5-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 135.5 (C-1), 124.7 (C-2), 36.9 (C-1'), 36.6 (C-6), 29.3 (C-3), 24.5 (C-5), 22.3 (C-4).

LRMS (EI, 70 eV): *m/z* (%) = 254 (33) $[M]^+$, 173 (55) $[M - Br]^+$, 93 (100) $[M - Br_2]^+$, 74 (41), 65 (11), 53 (37).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_7H_{10}Br_2]^+$ 253.9129; found 253.9101.

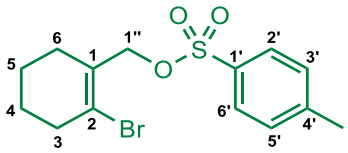
Molecular weight: $C_7H_{10}Br_2$ (253.9650 g × mol^{-1}).

2.4 Synthesis of 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cycloalk-1-enes 125a–g

2.4.1 General procedure III

A solution of (2-bromo-cycloalk-1-en-1-yl)methanol **123** (3.5 mmol, 1 equiv) in diethyl ether (15 mL) was prepared and stirred at 0 °C. To this solution, *p*-toluene sulfonyl chloride (*p*-TsCl) (787 mg, 4.13 mmol, 1.18 equiv) was added, followed by freshly powdered KOH (1.96 g, 35 mmol, 10 equiv). The mixture was stirred at room temperature for 4 h. Then, water (20 mL) was added and the reaction mixture was stirred for an additional 10 min. After phase separation, the aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic phases were combined and washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure product was obtained after subjecting the crude product to column chromatography over silica gel.

2.4.2 2-Bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (125a)



Following general procedure III, 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) was synthesized by reacting (2-bromocyclopent-1-en-1-yl)methanol (**123a**) (697 mg, 3.5 mmol), *para*-toluenesulfonyl chloride (*p*-TsCl) (787 mg, 4.13 mmol) and KOH (1.96 g, 35 mmol) in diethyl ether (15 mL). Analytically pure **125a** was obtained as a pale yellow oil (942 mg, 2.73 mmol, 78%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 10:1).

$\boldsymbol{R_f}$ = 0.44 (petroleum ether/ethyl acetate = 10:2).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2934, 1597, 1358 (S═O), 1172 (S═O), 928, 811, 659, 551.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.81 (d, J = 8.2 Hz, 2H, 2'-H and 6'-H), 7.34 (d, J = 8.1 Hz, 2H, 3'-H and 5'-H), 4.68 (s, 2H, 1''-H_2), 2.45−2.39 (m, overlapped, 5H, 3-H_2 and 4'-CH_3), 2.13−2.05 (m, 2H, 6-H_2), 1.66−1.54 (m, overlapped, 4H, 4-H_2 and 5-H_2).

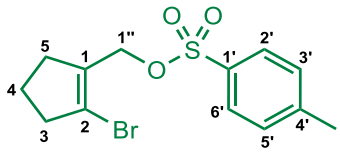
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 144.8 (C-4'), 133.1 (C-1), 129.7 (C-3' and C-5'), 129.2 (C-1'), 128.0 (C-2' and C-6'), 125.3 (C-2), 73.2 (C-1''), 36.7 (C-3), 28.5 (C-6), 24.2 (C-4), 21.7 (4'-CH_3), 21.6 (C-5).

LRMS (EI, 70 eV): *m/z* (%) = 344 (1) $[M]^+$, 172 (92) $[C_7H_{10}Br]^+$, 155 (12) $[C_7H_7O_2S]^+$, 93 (100) $[172 - Br]^+$, 91 (39) $[C_7H_7]^+$, 77 (18), 65 (8).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{14}H_{17}BrO_3S]^+$ 344.0082; found 344.0088.

Molecular weight: $C_{14}H_{17}BrO_3S$ (345.2510 g × mol^{-1}).

2.4.3 2-Bromo-1-(4'-methylbenzenesulfonatemethyl)cyclopent-1-ene (125b)



Following general procedure III, 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclopent-1-ene (**125b**) was synthesized by reacting (2-bromocyclopent-1-en-1-yl)methanol (**123b**) (620 mg, 3.5 mmol), *p*-TsCl (787 mg, 4.13 mmol) and KOH (1.96 g, 35 mmol) in diethyl ether (15 mL). Analytically pure **125b** was obtained as a pale yellow oil (792 mg, 2.39 mmol, 68%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 15:2).

$\boldsymbol{R_f}$ = 0.38 (petroleum ether/ethyl acetate = 10:2).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2953, 1597, 1358 (S═O), 1173 (S═O), 931, 811, 662, 552.

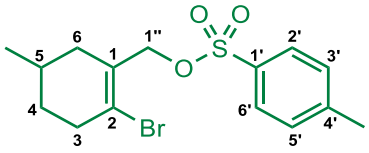
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.80 (d, J = 8.4 Hz, 2H, 2'-H and 6'-H), 7.34 (d, J = 8.1 Hz, 2H, 3'-H and 5'-H), 4.67 (s, 2H, 1"-H_2), 2.62−2.54 (m, 2H, 3-H_2), 2.45 (s, 3H, 4'-CH_3), 2.35−2.28 (m, 2H, 5-H_2), 1.86 (quint, J = 7.5 Hz, 2H, 4-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 144.8 (C-4'), 133.7 (C-1), 133.1 (C-1'), 129.7 (C-3' and C-5'), 127.9 (C-2' and C-6'), 123.1 (C-2), 67.5 (C-1"), 40.3 (C-3), 32.3 (C-5), 21.6 (4'-CH_3), 21.5 (C-4).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{15}BrO_3S]^+$ 329.9925; found 329.9926.

Molecular weight: $C_{13}H_{15}BrO_3S$ (331.2240 g × mol^{-1}).

2.4.4 2-Bromo-5-methyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (125c)



Following general procedure III, 2-bromo-5-methyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125c**) was synthesized by reacting (2-bromo-5-methylcyclohex-1-en-1-yl)methanol (**123c**) (718 mg, 3.5 mmol), *p*-TsCl (787 mg, 4.13 mmol) and KOH (1.96 g, 35 mmol) in diethyl ether (15 mL). Analytically pure **125c** was obtained as a pale yellow oil (842 mg, 2.34 mmol, 67%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 10:1).

$\boldsymbol{R_f}$ = 0.46 (petroleum ether/ethyl acetate = 10:2).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2951, 1597, 1358 (S═O), 1173 (S═O), 924, 811, 660, 551.

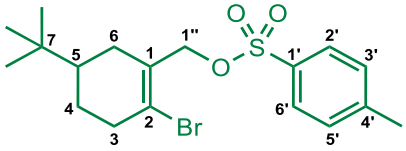
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.81 (d, J = 8.2 Hz, 2H, 2'-H and 6'-H), 7.34 (d, J = 8.0 Hz, 2H, 3'-H and 5'-H), 4.67 (s, 2H, 1"-H_2), 2.50−2.43 (m, overlapped, 5H, 3-H_2 and 4'-CH_3), 2.23−2.12 (m, 1H, 6-Hb), 1.76−1.59 (m, overlapped, 3H, 4-Hb, 5-H and 6-Ha), 1.33−1.19 (m, 1H, 4-Ha), 0.91 (d, J = 6.1 Hz, 3H, 5-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 144.8 (C-4'), 133.1 (C-1), 129.7 (C-3' and C-5'), 128.7 (C-1'), 128.0 (C-2' and C-6'), 124.9 (C-2), 73.1 (C-1"), 36.7 (C-3), 36.6 (C-6), 32.1 (C-4), 27.9 (C-5), 21.6 (4'-CH_3), 20.9 (5-CH_3).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{15}H_{19}BrO_3S]^+$ 358.0238; found 358.0233.

Molecular weight: $C_{15}H_{19}BrO_3S$ (359.2780 g × mol^{-1}).

2.4.5 2-Bromo-5-*tert*-butyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (125d)



Following general procedure III, 2-bromo-5-*tert*-butyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125d**) was synthesized by reacting (2-bromo-5-(*tert*-butyl)cyclohex-1-en-1-yl)methanol (**123d**) (865 mg, 3.5 mmol), *p*-TsCl (787 mg, 4.13 mmol) and KOH (1.96 g, 35 mmol) in diethyl ether (15 mL). Analytically pure **125d** was obtained as a pale yellow oil (1.18 g, 2.94 mmol, 84%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 12:1).

M.p.: 56 − 57 °C.

R_f = 0.46 (petroleum ether/ethyl acetate = 10:2).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2955, 1595, 1362 (S═O), 1176 (S═O), 916, 805, 654, 550.

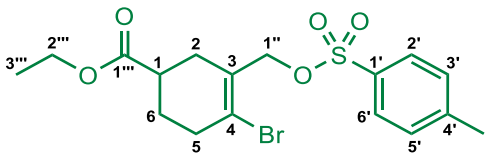
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.82 (d, J = 8.1 Hz, 2H, 2'-H and 6'-H), 7.34 (d, J = 8.0 Hz, 2H, 3'-H and 5'-H), 4.71 (dd, ^2J (1"-Ha, 1"-Hb) = 11.3 Hz, 2H, 1"-H_2), 2.51−2.41 (m, overlapped, 5H, 3-H_2 and 4'-CH_3), 2.06 (dd, ^2J (6-Ha, 6-Hb) = 14.8 Hz, ^3J (6-Hb, 5-H) = 3.4 Hz, 1H, 6-Hb), 1.81−1.67 (m, 2H, 4-Hb and 6-Ha), 1.28−1.09 (m, 2H, 4-Ha and 5-H), 0.81 (s, 9H, 3 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 144.8 (C-4'), 133.3 (C-1), 129.7 (C-3' and C-5'), 129.1 (C-1'), 128.1 (C-2' and C-6'), 125.2 (C-2), 73.5 (C-1"), 43.3 (C-5), 37.8 (C-3), 32.1 (C-7), 30.2 (C-6), 27.1 (3 × CH_3), 25.5 (C-4), 21.6 (4'-CH_3).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{18}H_{25}BrO_3S]^+$ 400.0708; found 400.0709.

Molecular weight: $C_{18}H_{25}BrO_3S$ (401.3590 g × mol^{-1}).

2.4.6 Ethyl 4-bromo-3-(4'-methylbenzenesulfonatemethyl)cyclohex-3-ene-1-carboxylate (125e)



Following general procedure III, ethyl 4-bromo-3-(4'-methylbenzenesulfonatemethyl)cyclohex-3-ene-1-carboxylate (**125e**) was synthesized by reacting ethyl 4-bromo-3-(hydroxymethyl)cyclohex-3-ene-1-carboxylate (**123e**) (1.33 g, 5 mmol), *p*-TsCl (1.12 g, 5.9 mmol) and KOH (2.80 g, 50 mmol) in diethyl ether (15 mL). Analytically pure **125e** was obtained as a colorless liquid (1.14 g, 2.73 mmol, 55%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 4:1).

R_f = 0.42 (cyclohexane/ethyl acetate = 3:2).

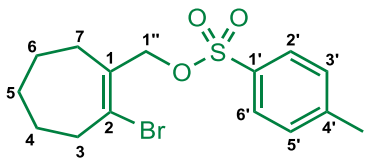
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.82 (d, J = 8.3 Hz, 2H, 2'-H and 6'-H), 7.35 (d, J = 8.2 Hz, 2H, 3'-H and 5'-H), 4.74 (d, J = 11.4 Hz, 1H, 1''-Ha), 4.65 (d, J = 11.5 Hz, 1H, 1''-Hb), 4.13 (q, J = 7.2 Hz, 2H, 2''-H_2), 2.55−2.48 (m, overlapped, 3H, 1-H and 5-H_2), 2.45 (s, 3H, 4'-CH_3), 2.39 (dd, J = 17.1, 5.6 Hz, 1H, 2-Ha), 2.32−2.27 (m, 1H, 6-Ha), 1.97−1.93 (m, 1H, 2-Hb), 1.76−1.70 (m, 1H, 6-Hb), 1.25 (t, J = 7.1 Hz, 3H, 3'''-H_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 174.0 (C-1'''), 144.9 (C-4'), 132.9 (C-3), 129.8 (C-3' and C-5'), 128.1 (C-2' and C-6'), 127.8 (C-1'), 124.4 (C-4), 72.6 (C-1''), 60.7 (C-2'''), 38.5 (C-1), 35.6 (C-5), 30.5 (C-2), 26.5 (C-6), 21.6 (4'-CH_3), 14.2 (C-3''').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{17}H_{21}BrO_5SNa]^+$ 439.0185; found 439.0188.

Molecular weight: $C_{17}H_{21}BrO_5S$ (417.3140 g × mol^{-1}).

2.4.7 2-Bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohept-1-ene (125f)



Following general procedure III, 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohept-1-ene (**125f**) was synthesized by reacting (2-bromocyclohept-1-en-1-yl)methanol (**123f**) (718 mg, 3.5 mmol), *p*-TsCl (787 mg, 4.13 mmol) and KOH (1.96 g, 35 mmol) in diethyl ether (15 mL). Analytically pure **125f** was obtained as a yellow oil (667 mg, 1.86 mmol, 53%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 15:1).

***R*f** = 0.41 (petroleum ether/ethyl acetate = 10:2).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2923, 1597, 1357 (S═O), 1173 (S═O), 923, 811, 667, 552.

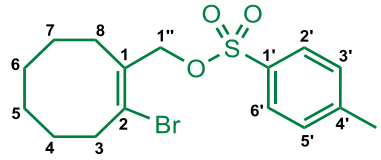
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.81 (d, J = 8.3 Hz, 2H, 2'-H and 6'-H), 7.34 (d, J = 8.1 Hz, 2H, 3'-H and 5'-H), 4.70 (br s, 2H, 1''-H_2), 2.78 (ddd, ^{2}J (3-Ha, 3-Hb) = 12.1 Hz, ^{3}J (3-H, 4-H) = 5.3 Hz, 2H, 3-H_2), 2.58 (s, 3H, 4'-CH_3), 2.36 (ddd, ^{2}J (7-Ha, 7-Hb) = 11.8 Hz, ^{3}J (6-H, 7-H) = 5.3 Hz, 2H, 7-H_2), 1.78−1.71 (m, 2H, 4-H_2), 1.62−1.52 (m, overlapped, 4H, 5-H_2 and 6-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 144.3 (C-4'), 132.6 (C-1), 131.3 (C-1'), 129.3 (C-3' and C-5'), 127.6 (C-2' and C-6'), 127.4 (C-2), 72.8 (C-1''), 36.9 (C-3), 29.4 (C-7), 28.9 (C-4), 27.4 (C-5), 25.9 (C-6), 21.2 (4'-CH_3).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{15}H_{19}BrO_3S]^+$ 358.0238; found 358.0234.

Molecular weight: $C_{15}H_{19}BrO_3S$ (359.2780 g × mol^{-1}).

2.4.8 2-Bromo-1-(4'-methylbenzenesulfonatemethyl)cyclooct-1-ene (125g)



Following general procedure III, 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclooct-1-ene (**125g**) was synthesized by reacting (2-bromocyclooct-1-en-1-yl)methanol (**123g**) (767 mg, 3.5 mmol), *p*-TsCl (787 mg, 4.13 mmol) and KOH (1.96 g, 35 mmol) in diethyl ether (15 mL). Analytically pure **125g** was obtained as a pale yellow oil (811 mg, 2.17 mmol, 62%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 15:1).

***R*f** = 0.51 (petroleum ether/ethyl acetate = 10:2).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 1597, 1359 (S═O), 1173 (S═O), 926, 812, 670, 552.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.81 (d, J = 8.3 Hz, 2H, 2'-H and 6'-H), 7.34 (d, J = 8.1 Hz, 2H, 3'-H and 5'-H), 4.70 (br s, 2H, 1''-H_2), 2.63 (ddd, ^{2}J (3-Ha, 3-Hb) = 12.2 Hz, ^{3}J (3-H, 4-H) = 5.2 Hz, 2H, 3-H_2), 2.45 (s, 3H, 4'-CH_3), 2.27 (ddd, ^{2}J (8-Ha, 8-Hb) = 11.9 Hz, ^{3}J (7-H, 8-H) = 5.3 Hz, 2H, 8-H_2), 1.64−1.58 (m, 2H, 4-H_2), 1.56−1.48 (m, 2H, 7-H_2), 1.46−1.39 (m, overlapped, 4H, 5-H_2 and 6-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 144.8 (C-4'), 133.0 (C-1), 131.8 (C-1'), 129.8 (C-3' and C-5'), 128.0 (C-2' and C-6'), 127.8 (C-2), 73.2 (C-1''), 37.4 (C-3), 29.8 (C-8), 29.4 (C-7), 27.8 (C-4), 26.4 (C-5), 25.5 (C-6), 21.6 (4'-CH_3).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{16}H_{21}BrO_3S]^+$ 372.0395; found 372.0394.

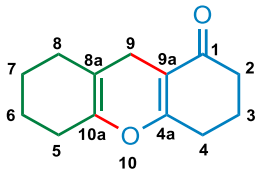
Molecular weight: $C_{16}H_{21}BrO_3S$ (373.3050 g × mol^{-1}).

2.5 Synthesis of xanthenes and related compounds 126a–p

2.5.1 General procedure IV

CuI (10 mg, 0.05 mmol, 0.1 equiv), Cs_2CO_3 (358 mg, 1.1 mmol, 2.2 equiv), a 1,3-dicarbonyl **35**, **46**, **104**, **134** (0.6 mmol, 1.2 equiv), 2-picolinic acid (6 mg, 0.05 mmol, 0.1 equiv), and 70 mg molecular sieves (4 Å) were added to an oven-dried 10 mL vial equipped with a magnetic stir bar. Subsequently, the vial was sealed, evacuated, and backfilled with argon three times. Next, 2-bromo-1-(4'-methylbenzenesulfonatemethyl)-1-ene **125** (0.5 mmol, 1 equiv) and dry DMF (2 mL) were added. The reaction mixture was stirred at 80 °C for 2 h in an oil bath. After cooling to room temperature, the vial was opened, and the reaction mixture was poured into water (20 mL). The mixture was extracted with diethyl ether (3 × 20 mL). The organic phases were combined and washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure product was obtained after subjecting the crude product to column chromatography over silica gel.

2.5.2 2,3,4,5,6,7,8,9-Octahydro-1*H*-xanthen-1-one (126a)



Following general procedure IV, 2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126a**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 1,3-cyclohexanedione (**35a**) (67 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126a** was obtained as a pale yellow oil (89 mg, 0.43 mmol, 87%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 20:1).

$\boldsymbol{R_f}$ = 0.44 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2937, 1622 (C═O), 1387, 1175, 1125, 1098, 997, 658.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 2.61 (br s, 2H, 9-H_2), 2.37 (t-like, J = 6.2 Hz, 4H, 2-H_2 and 4-H_2), 2.08−2.04 (m, ^3J (5-H, 6-H) = 6.2 Hz, ^5J (5-H, 8-H) = 2.2 Hz, ^5J (5-H, 9-H) = 2.2 Hz, 2H, 5-H_2), 1.96 (quint, ^3J = 6.4 Hz, 2H, 3-H_2), 1.94−1.89 (m, ^3J (7-H, 8-H) = 6.2 Hz, ^5J (5-H, 8-H) = 1.1 Hz, ^5J (5-H, 8-H) = 2.2 Hz, 2H, 8-H_2), 1.73−1.68 (m, ^2J (6-Ha, 6-Hb) = 12.3 Hz, ^3J (5-H, 6-H) = 6.2 Hz, ^3J (6-H, 7-H) = 2.5 Hz, ^3J (6-H, 7-H) = 8.7 Hz, 2H, 6-H_2), 1.63−1.58 (m, ^2J (7-Ha, 7-Hb) = 11.9 Hz, ^3J (6-H, 7-H) = 2.4 Hz, ^3J (6-H, 7-H) = 8.4 Hz, ^3J (7-H, 8-H) = 6.0 Hz, 2H, 7-H_2).

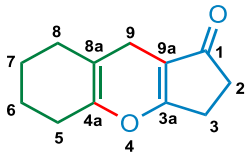
^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 198.6 (C-1), 167.1 (C-4a), 142.9 (C-10a), 109.8 (C-9a), 108.6 (C-8a), 36.7 (C-2), 28.2 (C-8), 27.5 (C-4), 25.8 (C-5), 22.9 (C-6), 22.8 (C-9), 22.3 (C-7), 20.7 (C-3).

LRMS (EI, 70 eV): *m/z* (%) = 204 (71) $[M]^+$, 203 (100) $[M - H]^+$, 176 (7) $[M - C_2H_4]^+$, 148 (10) $[176 - CO]^+$, 111 (13), 91 (11), 67 (16).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{16}O_2]^+$ 204.1150; found 204.1139.

Molecular weight: $C_{13}H_{16}O_2$ (204.2690 g × mol^{-1}).

2.5.3 2,3,4,5,6,7-Hexahydrocyclopenta[*b*]chromen-1(9*H*)-one (126b)



Following general procedure IV, 2,3,4,5,6,7-hexahydrocyclopenta[*b*]chromen-1(9*H*)-one (**126b**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 1,3-cyclopentanedione (**104**) (59 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126b** was obtained as a viscous pale yellow oil (74 mg, 0.39 mmol, 78%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 15:1).

R_f = 0.48 (petroleum ether/ethyl acetate = 6:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 1660 (C═O), 1384, 1255, 1088, 657.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.63 (br s, 2H, 9-H_2), 2.58−2.54 (m, 2H, 3-H_2), 2.45−2.41 (m, 2H, 2-H_2), 2.14 (m, ^3J (5-H, 6-H) = 6.2 Hz, ^5J (5-H, 8-H) = 2.2 Hz, ^5J (5-H, 9-H) = 2.2 Hz, 2H, 5-H_2), 1.94 (m, ^3J (7-H, 8-H) = 6.1 Hz, ^5J (5-H, 8-H) = 1.1 Hz, ^5J (5-H, 8-H) = 2.2 Hz, 2H, 8-H_2), 1.72 (m, ^2J (6-Ha, 6-Hb) = 11.3 Hz, ^3J (5-H, 6-H) = 5.7 Hz, ^3J (6-H, 7-H) = 3.2 Hz, ^3J (6-H, 7-H) = 8.9 Hz, 2H, 6-H_2), 1.63 (m, ^2J (7-Ha, 7-Hb) = 11.6 Hz, ^3J (6-H, 7-H) = 3.1 Hz, ^3J (6-H, 7-H) = 8.9 Hz, ^3J (7-H, 8-H) = 5.8 Hz, 2H, 7-H_2).

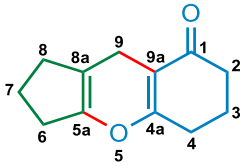
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 204.2 (C-1), 179.9 (C-4a), 144.5 (C-10a), 114.2 (C-9a), 108.1 (C-8a), 33.1 (C-2), 28.6 (C-8), 26.2 (C-5), 25.7 (C-3), 22.8 (C-8), 22.5 (C-6), 22.3 (C-7).

LRMS (EI, 70 eV): *m/z* (%) = 190 (75) $[M]^+$, 189 (100) $[M - H]^+$, 162 (12) $[M - C_2H_4]^+$, 161 (17) $[189 - C_2H_4]^+$, 111 (6), 91 (5), 79 (6).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{12}H_{14}O_2]^+$ 190.0994; found 190.0992.

Molecular weight: $C_{12}H_{14}O_2$ (190.2420 g × mol^{-1}).

2.5.4 2,3,4,6,7,8-Hexahydrocyclopenta[*b*]chromen-1(9*H*)-one (126c)



Following general procedure IV, 2,3,4,6,7,8-hexahydrocyclopenta[*b*]chromen-1(9*H*)-one (**126c**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 1,3-cyclohexanedione (**35a**) (67 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclopent-1-ene (**125b**) (166 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126c** was obtained as a pale yellow oil (72 mg, 0.38 mmol, 76%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 15:1).

***R*f** = 0.41 (petroleum ether/ethyl acetate = 6:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931, 1666 (C═O), 1602, 1385, 1238, 1090, 1043, 659.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.75 (br s, 2H, 9-H_2), 2.45−2.37 (m, overlapped, 6H, 2-H_2,4-H_2, and 6-H_2), 2.26 (t-like, ^3J (7-H, 8-H) = 6.3 Hz, 2H, 8-H_2), 1.98 (quint, ^3J = 6.4 Hz, 2H, 3-H_2), 1.90 (quint-like, ^3J = 7.1 Hz, 2H, 7-H_2).

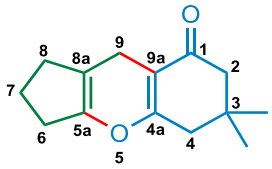
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 198.9 (C-1), 167.9 (C-4a), 146.3 (C-5a), 112.2 (C-9a), 110.2 (C-8a), 36.9 (C-2), 31.4 (C-8), 29.5 (C-4), 27.8 (C-6), 20.8 (C-9), 20.7 (C-3), 19.2 (C-7).

LRMS (EI, 70 eV): *m/z* (%) = 191 (100) $[M + H]^+$, 177 (6).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{12}H_{15}O_2]^+$ 191.1066; found 191.1066.

Molecular weight: $C_{12}H_{14}O_2$ (190.2420 g × mol^{-1}).

2.5.5 6,6-Dimethyl-2,3,4,6,7,8-hexahydrocyclopenta[*b*]chromen-1(9*H*)-one (126d)



Following general procedure IV, 6,6-dimethyl-2,3,4,6,7,8-hexahydrocyclopenta[*b*]chromen-1(9*H*)-one (**126d**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**35b**) (84 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclopent-1-ene (**125b**) (166 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126d** was obtained as a pale yellow oil (88 mg, 0.40 mmol, 81%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 15:1).

***R*f** = 0.43 (petroleum ether/ethyl acetate = 6:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931, 1666 (C═O), 1606, 1385, 1239, 1089, 1044, 658.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.76 (br s, 2H, 9-H_2), 2.45−2.36 (m, 2H, 6-H_2), 2.30 (s, 2H, 4-H_2), 2.27 (s, 2H, 2-H_2), 2.26−2.22 (m, 2H, 8-H_2), 1.91 (quint-like, ^{3}J = 7.1 Hz, 2H, 7-H_2), 1.08 (s, 6H, 2 × CH_3).

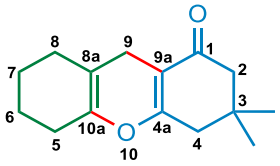
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 198.8 (C-1), 166.2 (C-4a), 146.4 (C-5a), 112.2 (C-9a), 108.9 (C-8a), 50.8 (C-2), 41.6 (C-4), 32.0 (C-3), 31.4 (C-8), 29.5 (C-6), 28.3 (2 × CH_3), 20.6 (C-9), 19.2 (C-7).

LRMS (EI, 70 eV): *m/z* (%) = 219 (100) $[M + H]^+$, 190 (5) $[M - C_2H_4]^+$, 161 (5) $[M - C_4H_9]^+$, 111 (12), 91 (8), 67 (16).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{14}H_{18}O_2]^+$ 218.1307; found 218.1286.

Molecular weight: $C_{14}H_{18}O_2$ (218.2960 g × mol^{-1}).

2.5.6 3,3-Dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126e)



Following general procedure IV, 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**35b**) (84 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126e** was obtained as a pale yellow oil (107 mg, 0.46 mmol, 92%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 20:1). Single crystals suitable for X-ray analysis were obtained from a solution in dichloromethane by slow evaporation at room temperature.

R_f = 0.46 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 1623 (C═O), 1378, 1191, 979.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 2.64 (br s, 2H, 9-H_2), 2.26 (s, 2H, 4-H_2), 2.25 (br s, 2H, 2-H_2), 2.07 (m, ^{3}J (5-H, 6-H) = 6.3 Hz, ^{5}J (5-H, 8-H) = 2.2 Hz, ^{5}J (5-H, 9-H) = 2.2 Hz, 2H, 5-H_2), 1.92 (m, ^{3}J (7-H, 8-H) = 5.9 Hz, ^{5}J (5-H, 8-H) = 2.2 Hz, ^{5}J (5-H, 8-H) = 2.07 Hz, 2H, 8-H_2), 1.71 (m, ^{2}J (6-Ha, 6-Hb) = 13 Hz, ^{3}J (5-H, 6-H) = 6.3 Hz, ^{3}J (6-H, 7-H) = 2.9 Hz, ^{3}J (6-H, 7-H) = 8.9 Hz, 2H, 6-H_2), 1.61 (m, ^{2}J (7-Ha, 7-Hb) = 13 Hz, ^{3}J (6-H, 7-H) = 2.9 Hz, ^{3}J (6-H, 7-H) = 8.9 Hz, ^{3}J (7-H, 8-H) = 5.9 Hz, 2H, 7-H_2), 1.07 (s, 6H, 2 × CH_3).

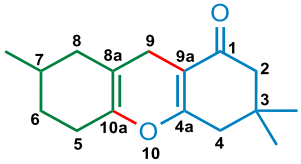
^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 198.4 (C-1), 165.3 (C-4a), 143.1 (C-10a), 108.6 (C-9a), 108.5 (C-8a), 50.6 (C-2), 41.3 (C-4), 31.9 (C-3), 28.4 (2 × CH_3), 28.2 (C-8), 25.9 (C-5), 22.9 (C-6), 22.8 (C-9), 22.3 (C-7).

LRMS (EI, 70 eV): *m/z* (%) = 232 (100) $[M]^+$, 217 (42) $[M - CH_3]^+$, 189 (14) $[217 - C_2H_4]^+$, 175 (17) $[189 - CH_2]^+$, 91 (12).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{15}H_{20}O_2]^+$ 232.1463; found 232.1473.

Molecular weight: $C_{15}H_{20}O_2$ (232.3230 g × mol^{-1}).

2.5.7 3,3,7-Trimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126f)



Following general procedure IV, 3,3,7-trimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126f**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**35b**) (84 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-5-methyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125c**) (180 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126f** was obtained as a pale yellow oil (97 mg, 0.40 mmol, 79%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 20:1).

$\boldsymbol{R_f}$ = 0.42 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2959, 1623 (C═O), 1390, 1193, 1137, 1089.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.62 (t-like, 2H, 9-H_2), 2.25 (s, 4H, 2-H_2 and 4-H_2), 2.20−2.01 (m, 2H, 5-H_2), 1.92 (d-like, ^2J (8-Ha, 8-Hb) = 16.4 Hz, 1H, 8-Ha), 1.79−1.57 (m, overlapped, 3H, 6-Ha, 7-H and 8-Hb), 1.41−1.25 (m, 1H, 6-Hb), 1.07 (s, 6H, 2 × CH_3), 0.97 (d, ^3J = 6.1 Hz, 3H, 7-CH_3).

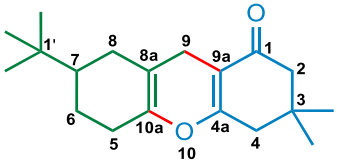
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 198.5 (C-1), 165.4 (C-4a), 142.8 (C-10a), 108.5 (C-9a), 107.9 (C-8a), 50.6 (C-2), 41.3 (C-4), 36.6 (C-8), 31.9 (C-3), 30.9 (C-6), 28.5 (C-7), 28.4 (2 × CH_3), 25.8 (C-5), 22.8 (C-9), 21.2 (7-CH_3).

LRMS (EI, 70 eV): *m/z* (%) = 246 (100) $[M]^+$, 231 (30) $[M - CH_3]^+$, 203 (10) $[231 - C_2H_4]^+$, 176 (14) $[203 - C_2H_3]^+$, 162 (7), 91 (4).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{16}H_{22}O_2]^+$ 246.1620; found 246.1628.

Molecular weight: $C_{16}H_{22}O_2$ (246.3500 g × mol^{-1}).

2.5.8 7-(*tert*-Butyl)-3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126g)



Following general procedure IV, 7-(*tert*-butyl)-3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126g**) was obtained by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**35b**) (84 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-5-*tert*-butyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125d**) (201 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126g** was obtained as a pale yellow oil (128 mg, 0.44 mmol, 89%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 30:1).

R_f = 0.41 (petroleum ether/ethyl acetate = 14:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954, 1659 (C═O), 1606, 1365, 1216, 1143, 985.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.69 (d, ^2J (9-Ha, 9-Hb) = 19.2 Hz, 1H, 9-Ha), 2.58 (d, ^2J (9-Ha, 9-Hb) = 19.1 Hz, 1H, 9-Hb), 2.25 (s, 4H, 2-H_2 and 4-H_2), 2.17−2.06 (m, 2H, 5-H_2), 1.90−1.85 (m, 1H, 6-Ha), 1.83−1.69 (m, 2H, 8-H_2), 1.41−1.21 (m, overlapped, 2H, 6-Hb and 7-H), 1.07 (s, 6H, 2 × 3-CH_3), 0.88 (s, 9H, 3 × CH_3).

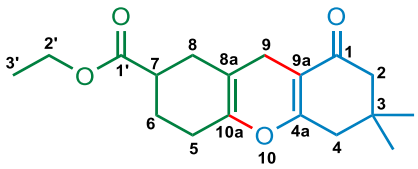
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 198.4 (C-1), 165.3 (C-4a), 143.0 (C-10a), 108.5 (C-9a), 108.3 (C-8a), 50.7 (C-2), 44.1 (C-7), 41.3 (C-4), 32.1 (C-1'), 31.9 (C-3), 29.7 (C-8), 28.4 (3-CH_3), 28.3 (3-CH_3), 27.2 (3 × CH_3), 27.0 (C-5), 24.1 (C-6), 23.0 (C-9).

LRMS (EI, 70 eV): *m/z* (%) = 288 (100) $[M]^+$, 273 (19) $[M - CH_3]^+$, 231 (6) $[M - C_4H_9]^+$, 91 (6), 57 (8).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{19}H_{28}O_2]^+$ 288.2084; found 288.2096.

Molecular weight: $C_{19}H_{28}O_2$ (288.4310 g × mol^{-1}).

2.5.9 Ethyl 3,3-dimethyl-1-oxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthene-7-carboxylate (126h)



Following general procedure IV, ethyl 3,3-dimethyl-1-oxo-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthene-7-carboxylate (**126h**) was synthesized by reacting CuI (19 mg, 0.1 mmol), Cs_2CO_3 (717 mg, 2.2 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**35b**) (168 mg, 1.2 mmol), 2-picolinic acid (12 mg, 0.1 mmol) and ethyl 4-bromo-3-(4'-methylbenzenesulfonatemethyl)cyclohex-3-ene-1-carboxylate (**125e**) (417 mg, 1 mmol) in DMF (4 mL). Analytically pure **126h** was obtained as a colorless liquid (157 mg, 0.52 mmol, 52%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 10:1).

R_f = 0.27 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2957, 1727, 1635, 1390, 1221, 1166, 1028.

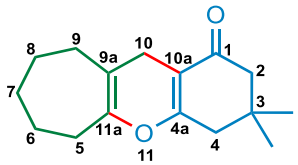
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 4.15 (q, J = 7.1 Hz, 2H, 2'-H_2), 2.70 (d, J = 18.6 Hz, 1H, 9-Ha), 2.63 (d, J = 18.9 Hz, 1H, 9-Hb), 2.62−2.57 (m, 1H, 7-H), 2.28−2.23 (m, overlapped, 5H, 5-H_2, 4-H_2 and 8-Ha), 2.19−2.01 (m, overlapped, 4H, 6-H_2 and 2-H_2), 1.86−1.80 (m, 1H, 8-Hb), 1.26 (t, J = 7.1 Hz, 3H, 3'-CH_3), 1.07 (s, 6H, 2 × 3-CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 198.3 (C-1), 174.8 (C-1'), 165.1 (C-4a), 142.4 (C-10a), 108.4 (C-9a), 107.0 (C-8a), 60.5 (C-2'), 50.6 (C-2), 41.2 (C-4), 39.1 (C-7), 32.0 (C-3), 30.3 (C-9), 28.5 (3-CH_3), 28.4 (3-CH_3), 25.2 (C-8), 25.0 (C-5), 22.6 (C-6), 14.2 (C-3').

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{18}H_{25}O_4]^+$ 305.1747; found 305.1739.

Molecular weight: $C_{18}H_{24}O_4$ (304.3860 g × mol^{-1}).

2.5.10 3,3-Dimethyl-3,4,6,7,8,9,10,11-octahydrocyclohepta[*b*]chromen-1(2*H*)-one (126i)



Following general procedure IV, 3,3-dimethyl-3,4,6,7,8,9,10,11-octahydrocyclohepta[*b*]chromen-1(2*H*)-one (**126i**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**35b**) (84 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohept-1-ene (**125f**) (180 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126i** was obtained as a pale yellow oil (79 mg, 0.32 mmol, 64%) after

subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 30:1).

***R*f** = 0.43 (petroleum ether/ethyl acetate = 15:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2982, 1736 (C═O), 1371, 1234, 1043.

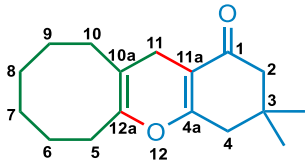
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.73 (s, 2H, 10-H_2), 2.26 (t-like, ^{3}J (5-H, 6-H) = 5.6 Hz, 2H, 5-H_2), 2.23−2.21 (m, overlapped, 4H, 2-H_2 and 4-H_2), 2.01 (t-like, ^{3}J (8-H, 9-H) = 5.5 Hz, 2H, 9-H_2), 1.70−1.62 (m, 2H, 7-H_2), 1.59−1.51 (m, overlapped, 4H, 6-H_2 and 8-H_2), 1.05 (s, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 198.3 (C-1), 165.5 (C-4a), 147.5 (C-11a), 112.5 (C-10a), 108.3 (C-9a), 50.6 (C-2), 41.2 (C-4), 31.9 (C-3), 31.7 (C-9), 31.6 (C-5), 30.9 (C-7), 28.4 (2 × CH_3), 25.9 (C-6), 25.2 (C-10), 24.9 (C-8).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{16}H_{23}O_2]^+$ 247.1693; found 247.1693.

Molecular weight: $C_{16}H_{22}O_2$ (246.3500 g × mol^{-1}).

2.5.11 3,3-Dimethyl-2,3,4,6,7,8,9,10,11,12-decahydro-1*H*-cycloocta[*b*]chromen-1-one (126j)



Following general procedure IV, 3,3-dimethyl-2,3,4,6,7,8,9,10,11,12-decahydro-1*H*-cycloocta[*b*]chromen-1-one (**126j**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (**35b**) (84 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclooct-1-ene (**125g**) (187 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126j** was obtained as a pale yellow oil (92 mg, 0.35 mmol, 71%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 30:1).

***R*f** = 0.46 (petroleum ether/ethyl acetate = 15:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 1632 (C═O), 1390, 1187, 1165, 1142, 1042, 659.

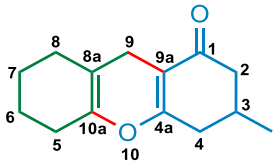
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.72 (s, 2H, 11-H_2), 2.28−2.24 (m, overlapped, 6H, 2-H_2, 4-H_2 and 5-H_2), 2.08 (t-like, ^{3}J (9-H, 10-H) = 5.6 Hz, 2H, 10-H_2), 1.64−1.55 (m, overlapped, 4H, 6-H_2 and 9-H_2), 1.54−1.45 (m, overlapped, 4H, 7-H_2 and 8-H_2), 1.07 (s, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 198.5 (C-1), 165.9 (C-4a), 145.0 (C-12a), 109.8 (C-11a), 108.4 (C-10a), 50.6 (C-2), 41.3 (C-4), 31.9 (C-3), 30.1 (C-10), 28.7 (C-5), 28.5 (C-9), 28.4 (2 × CH_3), 27.8 (C-6), 26.5 (C-7), 26.3 (C-8), 22.1 (C-11).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{17}H_{25}O_2]^+$ 261.1849; found 261.1848.

Molecular weight: $C_{17}H_{24}O_2$ (260.3770 g × mol^{-1}).

2.5.12 3-Methyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126k)



Following general procedure IV, 3-methyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126k**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5-methyl-1,3-cyclohexanedione (**35c**) (67 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126k** was obtained as a pale yellow oil (90 mg, 0.41 mmol, 83%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 20:1).

R_f = 0.46 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 1629 (C═O), 1390, 1189, 1098, 1012, 673.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 2.64 (d, ^2J (9-Ha, 9-Hb) = 19.9 Hz, 1H, 9-Ha), 2.60 (d, ^2J (9-Ha, 9-Hb) = 19.9 Hz, 1H, 9-Hb), 2.46 (dd, ^2J (2-Ha, 2-Hb) = 16.5 Hz, ^3J (2-Ha, 3-H) = 4.3 Hz, 1H, 2-Ha), 2.39 (dd, ^2J (4-Ha, 4-Hb) = 16.2 Hz, ^3J (3-H, 4-Ha) = 4.0 Hz, 1H, 4-Ha), 2.26−2.18 (m, 1H, 3-H), 2.17−2.11 (m, 1H, 4-Hb), 2.10−2.03 (m, overlapped, 3H, 2-Hb and 5-H_2), 1.91 (t-like, ^3J (7-H, 8-H) = 6.1 Hz, 2H, 8-H_2), 1.70 (m, ^2J (6-Ha, 6-Hb) = 12.3 Hz, ^3J (5-H, 6-H) = 6.2 Hz, ^3J (6-H, 7-H) = 2.4 Hz, ^3J (6-H, 7-H) = 8.7 Hz, 2H, 6-H_2), 1.60 (m, ^2J (7-Ha, 7-Hb) = 11.9 Hz, ^3J (6-H, 7-H) = 2.4 Hz, ^3J (6-H, 7-H) = 8.4 Hz, ^3J (7-H, 8-H) = 6.0 Hz, 2H, 7-H_2), 1.07 (d, ^3J (1'-H, 3-H) = 6.2 Hz, 3H, 3-CH_3).

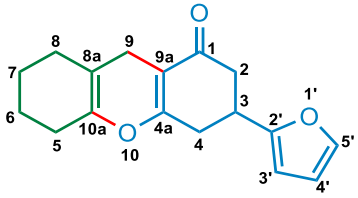
^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 198.6 (C-1), 166.5 (C-4a), 142.9 (C-10a), 109.4 (C-9a), 108.6 (C-8a), 45.0 (C-2), 35.6 (C-4), 28.3 (C-3), 28.2 (C-8), 25.9 (C-5), 22.9 (C-6), 22.8 (C-9), 22.3 (C-7), 21.0 (3-CH_3).

LRMS (EI, 70 eV): *m/z* (%) = 218 (100) $[M]^+$, 203 (18) $[M - CH_3]^+$, 176 (5) $[203 - C_2H_3]^+$, 148 (11) $[176 - CO]^+$, 91 (9).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{14}H_{18}O_2]^+$ 218.1307; found 218.1317.

Molecular weight: $C_{14}H_{18}O_2$ (218.2960 g × mol^{-1}).

2.5.13 3-(Furan-2'-yl)- 2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126l)



Following general procedure IV, 3-(furan-2'-yl)- 2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126l**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5-(2-furyl)-1,3-cyclohexanedione (**35d**) (107 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126l** was obtained as a pale yellow oil (107 mg, 0.40 mmol, 79%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 25:1).

***R*f** = 0.43 (petroleum ether/ethyl acetate = 10:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2943, 1626 (C═O), 1394, 1191, 1118, 1003, 730, 673.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.33 (dd, ^3J (4'-H, 5'-H) = 1.9 Hz, ^4J (3'-H, 5'-H) = 0.8 Hz, 1H, 5'-H), 6.30 (dd, ^3J (3'-H, 4'-H) = 3.2 Hz, ^3J (4'-H, 5'-H) = 1.8 Hz, 1H, 4'-H), 6.05 (dt, ^3J (3'-H, 4'-H) = 3.2 Hz, ^4J (3'-H, 5'-H) = 0.9 Hz, 1H, 3'-H), 3.48−3.42 (m, 1H, 3-H), 2.78 (ddd, ^2J (2-Ha, 2-Hb) = 16.3 Hz, ^3J (2-Ha, 3-H) = 4.3 Hz, ^4J (2-Ha, 4-H) = 1.2 Hz, 1H, 2-Ha), 2.73−2.62 (m, overlapped, 4H, 4-H_2 and 9-H_2), 2.58 (dd, ^2J (2-Ha, 2-Hb) = 16.4 Hz, ^3J (2-Hb, 3-H) = 11.3 Hz, 1H, 2-Hb), 2.07 (m, ^3J (5-H, 6-H) = 6.7 Hz, ^5J (5-H, 8-H) = 2.2 Hz, ^5J (5-H, 9-H) = 2.3 Hz, 2H, 5-H_2), 1.92 (m, ^3J (7-H, 8-H) = 6.2 Hz, ^5J (5-H, 8-H) = 1.2 Hz, ^5J (5-H, 8-H) = 2.4 Hz, 2H, 8-H_2), 1.72 (m, ^2J (6-Ha, 6-Hb) = 12.3 Hz, ^3J (5-H, 6-H) = 6.2 Hz, ^3J (6-H, 7-H) = 2.5 Hz, ^3J (6-H, 7-H) = 8.8 Hz, 2H, 6-H_2), 1.62 (m, ^2J (7-Ha, 7-Hb) = 11.8 Hz, ^3J (6-H, 7-H) = 2.4 Hz, ^3J (6-H, 7-H) = 8.4 Hz, ^3J (7-H, 8-H) = 6.0 Hz, 2H, 7-H_2).

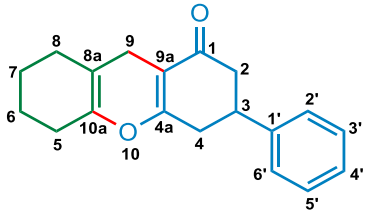
^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 196.8 (C-1), 165.4 (C-4a), 156.0 (C-2'), 143.1 (C-10a), 141.6 (C-5'), 110.1 (C-4'), 109.8 (C-9a), 108.7 (C-8a), 104.6 (C-3'), 40.9 (C-2), 32.3 (C-4), 32.2 (C-3), 28.2 (C-8), 25.8 (C-5), 22.9 (C-6), 22.8 (C-9), 22.3 (C-7).

LRMS (EI, 70 eV): *m/z* (%) = 270 (100) $[M]^+$, 189 (18) $[M - C_5H_5O]^+$, 175 (11), 162 (19), 148 (32), 91 (7).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{17}H_{18}O_3]^+$ 270.1256; found 270.1235.

Molecular weight: $C_{17}H_{18}O_3$ (270.3280 g × mol^{-1}).

2.5.14 3-Phenyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126m)



Synthesis using 0.5 mmol of 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) as substrate

Following general procedure IV, 3-phenyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126m**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5-phenyl-1,3-cyclohexanedione (**35e**) (113 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126m** was obtained as a pale yellow oil (104 mg, 0.37 mmol, 74%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 25:1).

Synthesis using 1 mmol of 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) as substrate

Following general procedure IV, 3-phenyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126m**) was synthesized by reacting CuI (19 mg, 0.1 mmol), Cs_2CO_3 (717 mg, 2.2 mmol), 5-phenyl-1,3-cyclohexanedione (**35e**) (207 mg, 1.2 mmol), 2-picolinic acid (12 mg, 0.1 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (344 mg, 1 mmol) in DMF (4 mL). Analytically pure **126m** was obtained as a pale yellow oil (206 mg, 0.73 mmol, 73%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 20:1).

$\boldsymbol{R_f}$ = 0.41 (petroleum ether/ethyl acetate = 12:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 1631 (C═O), 1391, 1184, 1120, 762, 698.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.36−7.33 (m, 2H, 3'-H, and 5'-H), 7.28−7.24 (m, overlapped, 3H, 2'-H, 4'-H, and 6'-H), 3.41−3.33 (m, 1H, 3-H), 2.72 (ddd, ^2J (2-Ha, 2-Hb) = 16.4 Hz, ^3J (2-Ha, 3-H) = 4.2 Hz, ^4J (2-Ha, 4-H) = 1.2 Hz, 1H, 2-Ha), 2.70−2.68 (m, 2H, 9-H_2), 2.66 (dd, ^3J (3-H, 4-H) = 12.2 Hz, ^4J (2-H, 4-H) = 1.6 Hz, 2H, 4-H_2), 2.61 (dd, ^2J (2-Ha, 2-Hb) = 16.2 Hz, ^3J (2-Hb, 3-H) = 12.6 Hz, 1H, 2-Hb), 2.09 (m, ^3J (5-H, 6-H) = 6.4 Hz, ^5J (5-H, 8-H) = 2.1 Hz, ^5J (5-H, 9-H) = 2.1 Hz, 2H, 5-H_2), 1.95 (dd-like, ^2J (8-Ha, 8-Hb) = 11.5 Hz, ^3J (7-H,

8-H) = 6.2 Hz, 2H, 8-H_2), 1.72 (m, ^2J (6-Ha, 6-Hb) = 12.4 Hz, ^3J (5-H, 6-H) = 6.3 Hz, ^3J (6-H, 7-H) = 2.5 Hz, ^3J (6-H, 7-H) = 8.8 Hz, 2H, 6-H_2), 1.63 (m, ^2J (7-Ha, 7-Hb) = 11.9 Hz, ^3J (6-H, 7-H) = 2.4 Hz, ^3J (6-H, 7-H) = 8.4 Hz, ^3J (7-H, 8-H) = 6.1 Hz, 2H, 7-H_2).

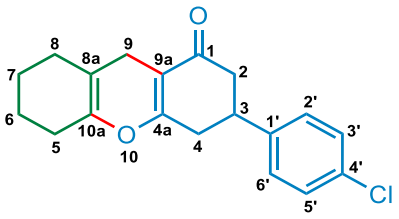
^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 197.7 (C-1), 166.2 (C-4a), 143.1 (C-10a), 142.8 (C-1'), 128.8 (C-3' and C-5'), 127.0 (C-4'), 126.7 (C-2' and C-6'), 109.7 (C-9a), 108.7 (C-8a), 43.8 (C-2), 38.8 (C-3), 35.1 (C-4), 28.2 (C-8), 25.9 (C-5), 23.0 (C-9), 22.9 (C-6), 22.3 (C-7).

LRMS (EI, 70 eV): *m/z* (%) = 280 (100) $[M]^+$, 189 (27) $[M - C_7H_7]^+$, 162 (43), 148 (23), 88 (35), 70 (71).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{19}H_{20}O_2]^+$ 280.1463; found 280.1445.

Molecular weight: $C_{19}H_{20}O_2$ (280.3670 g × mol^{-1}).

2.5.15 3-(4'-Chlorophenyl)-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126n)



Following general procedure IV, 3-(4'-chlorophenyl)-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126n**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5-(chlorophenyl)-1,3-cyclohexanedione (**35f**) (134 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126n** was obtained as a pale yellow oil (113 mg, 0.36 mmol, 72%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 25:1).

***R*$_f$** = 0.41 (petroleum ether/ethyl acetate = 12:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2930, 1627 (C═O), 1391, 1185, 1120, 1090, 1012, 821.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.31 (dd, ^3J (2'-H, 3'-H) = 8.4 Hz, ^4J (3'-H, 5'-H) = 2.0 Hz, 2H, 3'-H and 5'-H), 7.17 (dd, ^3J (2'-H, 3'-H) = 8.4 Hz, ^4J (2'-H, 6'-H) = 2.0 Hz, 2H, 2'-H and 6'-H), 3.41−3.30 (m, 1H, 3-H), 2.71 (ddd, ^2J (2-Ha, 2-Hb) = 16.2 Hz, ^3J (2-Ha, 3-H) = 4.3 Hz, ^4J (2-Ha, 4-H) = 0.9 Hz, 1H, 2-Ha), 2.69−2.67 (m, 2H, 9-H_2), 2.62 (dd-like, ^3J (3-H, 4-H) = 11.5 Hz, ^4J (2-H, 4-H) = 1.8 Hz, 2H, 4-H_2), 2.56 (dd, ^2J (2-Ha, 2-Hb) = 16.3 Hz, ^3J (2-Hb, 3-H) = 12.1 Hz, 1H, 2-Hb), 2.08 (m, ^3J (5-H, 6-H) = 6.1 Hz, ^5J (5-H, 8-H) = 2.0 Hz, ^5J (5-H, 9-H) = 2.2 Hz, 2H, 5-H_2), 1.95 (t-like, ^3J (7-H, 8-H) = 6.2 Hz, 2H, 8-H_2), 1.76−1.68 (m, 2H, 6-H_2), 1.67−1.58 (m, 2H, 7-H_2).

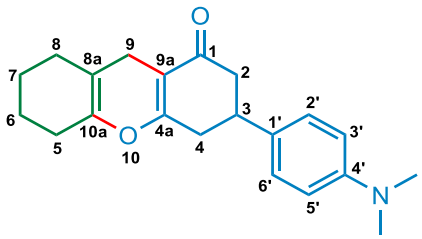
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 197.7 (C-1), 165.9 (C-4a), 143.1 (C-10a), 141.2 (C-1'), 132.7 (C-4'), 128.9 (C-3' and C-5'), 128.0 (C-2' and C-6'), 109.8 (C-9a), 108.7 (C-8a), 43.6 (C-2), 38.2 (C-3), 34.9 (C-4), 28.2 (C-8), 25.8 (C-5), 22.9 (C-9), 22.8 (C-6), 22.3 (C-7).

LRMS (EI, 70 eV): *m/z* (%) = 314 (100) $[M]^+$, 189 (25) $[M - C_7H_6Cl]^+$, 162 (24), 148 (19), 57 (14).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{19}H_{19}ClO_2]^+$ 314.1074; found 314.1054.

Molecular weight: $C_{19}H_{19}ClO_2$ (314.8090 g × mol^{-1}).

2.5.16 3-[4'-(Dimethylamino)phenyl]-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126o)



Following general procedure IV, 3-(4'-(dimethylamino)phenyl)-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126o**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5-[4-(dimethylamino)phenyl]-1,3-cyclohexanedione (**35g**) (139 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126o** was obtained as a pale yellow oil (139 mg, 0.43 mmol, 86%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 25:1).

R_f = 0.40 (petroleum ether/ethyl acetate = 12:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2937, 1632 (C═O), 1521, 1392, 1182, 1121, 812.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.12 (dd, ^3J (2'-H, 3'-H) = 8.6 Hz, ^4J (2'-H, 6'-H) = 2.1 Hz, 2H, 2'-H and 6'-H), 6.72 (dd, ^3J (2'-H, 3'-H) = 8.7 Hz, ^4J (3'-H, 5'-H) = 2.1 Hz, 2H, 3'-H and 5'-H), 3.34−3.23 (m, 1H, 3-H), 2.94 (s, 6H, 2 × CH_3), 2.71 (ddd, ^2J (2-Ha, 2-Hb) = 16.4 Hz, ^3J (2-Ha, 3-H) = 4.4 Hz, ^4J (2-Ha, 4-H) = 1.1 Hz, 1H, 2-Ha), 2.69−2.66 (m, 2H, 9-H_2), 2.62−2.59 (m, 2H, 4-H_2), 2.55 (dd, ^2J (2-Ha, 2-Hb) = 16.4 Hz, ^3J (2-Hb, 3-H) = 12.7 Hz, 1H, 2-Hb), 2.09 (m, ^3J (5-H, 6-H) = 6.2 Hz, ^5J (5-H, 8-H) = 2.2 Hz, ^5J (5-H, 9-H) = 2.1 Hz, 2H, 5-H_2), 1.95 (m, ^3J (7-H, 8-H) = 6.1 Hz, ^5J (5-H, 8-H) = 1.0 Hz, ^5J (5-H, 8-H) = 2.3 Hz, 2H, 8-H_2), 1.72 (m, ^2J (6-Ha, 6-Hb) = 12.3 Hz, ^3J (5-H, 6-H) = 6.2 Hz, ^3J (6-H, 7-H) = 2.4 Hz, ^3J (6-H, 7-H) = 8.7 Hz, 2H, 6-H_2), 1.63 (m, ^2J (7-Ha, 7-Hb) = 11.8 Hz, ^3J (6-H, 7-H) = 2.4 Hz, ^3J (6-H, 7-H) = 8.5 Hz, ^3J (7-H, 8-H) = 6.1 Hz, 2H, 7-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 198.2 (C-1), 166.5 (C-4a), 149.6 (C-4'), 143.1 (C-10a), 130.7 (C-1'), 127.2 (C-2' and C-6'), 112.8 (C-3' and C-5'), 109.5 (C-9a), 108.6 (C-8a),

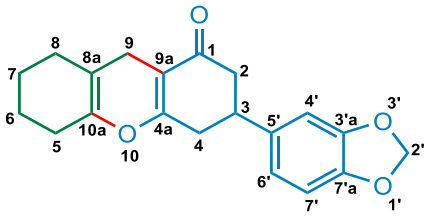
44.1 (C-2), 40.6 (2 × CH_3), 37.9 (C-3), 35.4 (C-4), 28.2 (C-8), 25.9 (C-5), 23.0 (C-9), 22.9 (C-6), 22.3 (C-7).

LRMS (EI, 70 eV): *m/z* (%) = 324 (77) $[M + H]^+$, 189 (21) $[M - C_9H_{12}N]^+$, 161 (85), 148 (91), 134 (100).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{21}H_{26}NO_2]^+$ 324.1958; found 324.1957.

Molecular weight: $C_{21}H_{25}NO_2$ (323.4360 g × mol^{-1}).

2.5.17 3-(Benzo-1,3-dioxol-5-yl)-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126p)



Following general procedure IV, 3-(benzo-1,3-dioxol-5-yl)-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126p**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 5-[3,4-(methylenedioxy)phenyl]-1,3-cyclohexanedione (**35h**) (139 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **126p** was obtained as a pale yellow oil (87 mg, 0.27 mmol, 54%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 25:1).

R_f = 0.41 (petroleum ether/ethyl acetate = 12:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2951, 1616 (C═O), 1488, 1393, 1245, 1188, 1038, 807, 634.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 6.77 (d, ^3J (6'-H, 7'-H) = 7.9 Hz, 1H, 7'-H), 6.73 (d, ^4J (4'-H, 6'-H) = 1.9 Hz, 1H, 4'-H), 6.68 (dd, ^3J (6'-H, 7'-H) = 7.9 Hz, ^4J (4'-H, 6'-H) = 1.8 Hz, 1H, 6'-H), 5.95 (s, 2H, 2'-H_2), 3.34−3.23 (m, 1H, 3-H), 2.70 (ddd, ^2J (2-Ha, 2-Hb) = 16.1 Hz, ^3J (2-Ha, 3-H) = 4.2 Hz, ^4J (2-Ha, 4-H) = 1.1 Hz, 1H, 2-Ha), 2.68−2.66 (m, 2H, 9-H_2), 2.61−2.57 (m, 2H, 4-H_2), 2.53 (dd, ^2J (2-Ha, 2-Hb) = 16.3 Hz, ^3J (2-Hb, 3-H) = 12.5 Hz, 1H, 2-Hb), 2.08 (m, ^3J (5-H, 6-H) = 6.2 Hz, ^5J (5-H, 8-H) = 2.3 Hz, ^5J (5-H, 9-H) = 2.2 Hz, 2H, 5-H_2), 1.94 (t-like, ^3J (7-H, 8-H) = 6.2 Hz, 2H, 8-H_2), 1.76−1.68 (m, 2H, 6-H_2), 1.66−1.59 (m, 2H, 7-H_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 197.6 (C-1), 166.1 (C-4a), 147.9 (C-3'a), 146.5 (C-7'a), 143.1 (C-10a), 136.8 (C-5'), 119.7 (C-6'), 109.7 (C-9a), 108.7 (C-8a), 108.4 (C-7'), 107.1 (C-4'), 101.1 (C-2'), 44.1 (C-2), 38.6 (C-3), 35.4 (C-4), 28.2 (C-8), 25.9 (C-5), 22.9 (C-9), 22.8 (C-6), 22.3 (C-7).

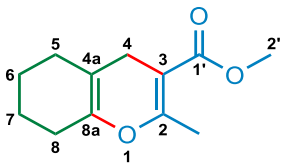
LRMS (EI, 70 eV): *m/z* (%) = 324 (100) $[M]^+$, 189 (38) $[M - C_8H_7O_2]^+$, 162 (17), 148 (32), 91 (12).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{20}H_{20}O_4]^+$ 324.1362; found 324.1356.

Molecular weight: $C_{20}H_{20}O_4$ (324.3760 g × mol^{-1}).

2.6 Synthesis of chromenes 127a–h

2.6.1 Methyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (127a)[57]



Following general procedure IV, methyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127a**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), methyl acetoacetate (**46a**) (70 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **127a** was obtained as a colorless oil (45 mg, 0.22 mmol, 43%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 50:1).

***R*f** = 0.59 (petroleum ether/ethyl acetate = 20:1).

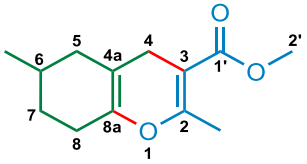
IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2932, 1711 (C═O), 1633, 1382, 1263, 1173, 1144, 1063, 766.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.71 (s, 3H, 2'-H_3), 2.73 (br s, 2H, 4-H_2), 2.23 (s, 3H, 2-CH_3), 2.01 (m, ^3J (7-H, 8-H) = 6.2 Hz, ^5J (5-H, 8-H) = 2.2 Hz, ^5J (4-H, 8-H) = 2.2 Hz, 2H, 8-H_2), 1.87 (m, ^3J (5-H, 6-H) = 6.3 Hz, ^5J (5-H, 8-H) = 1.1 Hz, ^5J (5-H, 8-H) = 2.1 Hz, 2H, 5-H_2), 1.69 (m, ^2J (7-Ha, 7-Hb) = 12.1 Hz, ^3J (7-H, 8-H) = 6.1 Hz, ^3J (6-H, 7-H) = 2.3 Hz, ^3J (6-H, 7-H) = 8.5 Hz, 2H, 7-H_2), 1.61 (m, ^2J (6-Ha, 6-Hb) = 11.7 Hz, ^3J (6-H, 7-H) = 2.2 Hz, ^3J (6-H, 7-H) = 8.2 Hz, ^3J (5-H, 6-H) = 5.9 Hz, 2H, 6-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 168.7 (C-1'), 160.9 (C-2), 142.9 (C-8a), 106.9 (C-4a), 100.1 (C-3), 51.1 (C-2'), 27.8 (C-8), 26.7 (C-5), 25.7 (C-4), 22.9 (C-7), 22.4 (C-6), 19.1 (2-CH_3).

Molecular weight: $C_{12}H_{16}O_3$ (208.2570 g × mol^{-1}).

2.6.2 Methyl 2,6-dimethyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (127b)



Following general procedure IV, methyl 2,6-dimethyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127b**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), methyl acetoacetate (**46a**) (70 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-5-methyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125c**) (180 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **127b** was obtained as a colorless oil (51 mg, 0.23 mmol, 46%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 50:1).

R_f = 0.58 (petroleum ether/ethyl acetate = 20:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954, 1717 (C═O), 1436, 1239, 1160, 1056, 771.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 3.70 (s, 3H, 2'-H_3), 2.72 (t-like, ^2J (4-Ha, 4-Hb) = 21.3 Hz, 2H, 4-H_2), 2.26 (s, 3H, 2-CH_3), 2.15−1.97 (m, 2H, 8-H_2), 1.88 (dd-like, ^2J (5-Ha, 5-Hb) = 15.6 Hz, ^3J (5-Ha, 6-H) = 3.9 Hz, 1H, 5-Ha), 1.78−1.66 (m, overlapped, 2H, 6-H and 7-Ha), 1.63−1.54 (m, 1H, 5-Hb), 1.38−1.25 (m, 1H, 7-Hb), 0.97 (d, ^3J = 6.3 Hz, 3H, 6-CH_3).

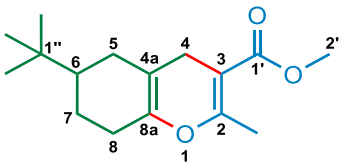
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 168.7 (C-1'), 160.9 (C-2), 142.6 (C-8a), 106.4 (C-4a), 100.1 (C-3), 51.2 (C-2'), 36.3 (C-5), 30.9 (C-7), 28.6 (C-6), 26.7 (C-4), 25.6 (C-8), 21.3 (6-CH_3), 19.1 (2-CH_3).

LRMS (EI, 70 eV): *m/z* (%) = 222 (17) $[M]^+$, 207 (100) $[M - CH_3]^+$, 191 (9) $[M - OCH_3]^+$, 163 (6) $[M - COOCH_3]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{18}O_3]^+$ 222.1256; found 222.1232.

Molecular weight: $C_{13}H_{18}O_3$ (222.2840 g × mol^{-1}).

2.6.3 Methyl 6-(*tert*-butyl)-2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (127c)



Following general procedure IV, methyl 6-(*tert*-butyl)-2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127c**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), methyl acetoacetate (**46a**) (70 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-5-*tert*-butyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125d**)

(201 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **127c** was obtained as a colorless oil (69 mg, 0.26 mmol, 52%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 50:1).

R_f = 0.56 (petroleum ether/ethyl acetate = 20:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2952, 1713 (C=O), 1435, 1177, 1073, 767.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.70 (s, 3H, 2'-H_3), 2.74 (dd, ^2J (4-Ha, 4-Hb) = 18.9 Hz, 2H, 4-H_2), 2.23 (s, 3H, 2-CH_3), 2.12−2.02 (m, 2H, 8-H_2), 1.90−1.84 (m, 1H, 7-Ha), 1.79−1.72 (m, 2H, 5-H_2), 1.35−1.21 (m, overlapped, 2H, 6-H and 7-Ha), 0.88 (s, 9H, 3 × CH_3).

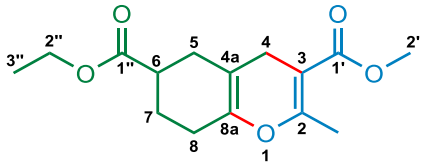
^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 168.7 (C-1'), 160.8 (C-2), 142.8 (C-8a), 106.7 (C-4a), 100.1 (C-3), 51.1 (C-2'), 44.1 (C-6), 32.1 (C-1''), 29.4 (C-5), 27.3 (3 × CH_3), 26.9 (C-8), 26.8 (C-4), 24.1 (C-7), 19.1 (2-CH_3).

LRMS (EI, 70 eV): *m/z* (%) = 264 (15) $[M]^+$, 249 (100) $[M - CH_3]^+$.

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{16}H_{24}O_3]^+$ 264.1720; found 264.1700.

Molecular weight: $C_{16}H_{24}O_3$ (264.3650 g × mol^{-1}).

2.6.4 6-Ethyl 3-methyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3,6-dicarboxylate (127d)



Following general procedure IV, 6-ethyl 3-methyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3,6-dicarboxylate (**127d**) was synthesized by reacting CuI (19 mg, 0.1 mmol), Cs_2CO_3 (717 mg, 2.2 mmol), methyl acetoacetate (**46a**) (140 mg, 1.2 mmol), 2-picolinic acid (12 mg, 0.1 mmol) and ethyl 4-bromo-3-(4'-methylbenzenesulfonatemethyl)cyclohex-3-ene-1-carboxylate (**125e**) (417 mg, 1 mmol) in DMF (4 mL). Analytically pure **127d** was obtained as a pale yellow liquid (106 mg, 0.38 mmol, 38%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 10:1).

R_f = 0.46 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2949, 1729, 1710, 1634, 1434, 1174, 1067, 766.

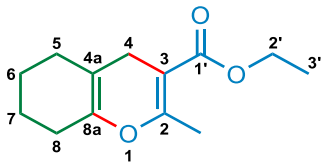
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 4.14 (q, J = 7.2 Hz, 2H, 2''-H_2), 3.70 (s, 3H, 2'-H_3), 2.78 (d, J = 17.6 Hz, 1H, 4-Ha), 2.70 (d, J = 18.2 Hz, 1H, 4-Hb), 2.60−2.55 (m, 1H, 6-H), 2.23−2.19 (m, overlapped, 4H, 5-Ha and 2-CH_3), 2.14−2.03 (m, overlapped, 4H, 8-H_2 and 7-H_2), 1.84−1.76 (m, 1H, 5-Hb), 1.25 (t, J = 7.2 Hz, 3H, 3''-CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 174.9 (C-1''), 168.4 (C-1'), 160.7 (C-2), 142.2 (C-8a), 105.4 (C-4a), 100.1 (C-3), 60.4 (C-2''), 51.2 (C-2'), 39.2 (C-6), 29.9 (C-4), 26.5 (C-5), 25.2 (C-8), 24.9 (C-7), 19.0 (2-CH_3), 14.2 (C-3'').

HRMS (EI): *m/z* $[M - H]^+$ calcd. for $[C_{15}H_{19}O_5]^+$ 279.1227; found 279.1224.

Molecular weight: $C_{15}H_{20}O_5$ (280.3200 g × mol^{-1}).

2.6.5 Ethyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (127e)



Following general procedure IV, ethyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127e**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), ethyl acetoacetate (**46b**) (78 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **127e** was obtained as a colorless oil (63 mg, 0.28 mmol, 57%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 50:1).

***R*$_f$** = 0.58 (petroleum ether/ethyl acetate = 20:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 1717 (C═O), 1449, 1322, 1168, 1128, 1067, 750.

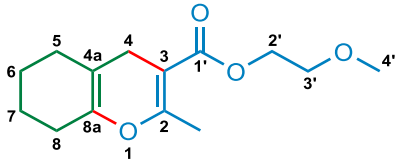
^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.27 (t, ^3J (2'-H, 3'-H) = 7.1 Hz, 3H, 3'-H_3), 1.56−1.63 (m, 2H, 6-H_2), 1.64−1.72 (m, 2H, 7-H_2), 1.87 (m, ^3J (5-H, 6-H) = 5.9 Hz, ^5J (5-H, 8-H) = 1.2 Hz, ^5J (5-H, 8-H) = 2.4 Hz, 2H, 5-H_2), 2.01 (m, ^3J (7-H, 8-H) = 6.3 Hz, ^5J (5-H, 8-H) = 2.2 Hz, ^5J (4-H, 8-H) = 2.2 Hz, 2H, 8-H_2), 2.22 (s, 3H, 2-CH_3), 2.72 (br s, 2H, 4-H_2), 4.16 (q, ^3J (2'-H, 3'-H) = 7.1 Hz, 2H, 2'-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 168.3 (C-1'), 160.6 (C-2), 142.8 (C-8a), 106.9 (C-4a), 100.3 (C-3), 59.8 (C-2'), 27.8 (C-8), 26.7 (C-5), 25.7 (C-4), 22.9 (C-7), 22.4 (C-6), 19.1 (2-CH_3), 14.4 (C-3').

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{18}O_3]^+$ 222.1250; found 222.1234.

Molecular weight: $C_{13}H_{18}O_3$ (222.2840 g × mol^{-1}).

2.6.6 (2'-Methoxyethyl) 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (127f)



Following general procedure IV, (2'-methoxyethyl) 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127f**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 2-methoxyethyl acetoacetate (**46c**) (96 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **127f** was obtained as a colorless oil (45 mg, 0.18 mmol, 36%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 45:1).

R_f = 0.55 (petroleum ether/ethyl acetate = 20:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2930, 1708 (C═O), 1632, 1383, 1262, 1174, 1145, 1061, 765.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 4.26 (t-like, ^3J (2'-H, 3'-H) = 4.8 Hz, 2H, 2'-H_2), 3.61 (t-like, ^3J (2'-H, 3'-H) = 4.8 Hz, 2H, 3'-H_2), 3.38 (br s, 3H, 4'-H_3), 2.75 (br s, 2H, 4-H_2), 2.23 (s, 3H, 2-CH_3), 2.01 (m, ^3J (7-H, 8-H) = 6.2 Hz, ^5J (5-H, 8-H) = 2.2 Hz, ^5J (4-H, 8-H) = 2.2 Hz, 2H, 8-H_2), 1.87 (m, ^3J (5-H, 6-H) = 6.0 Hz, ^5J (5-H, 8-H) = 1.2 Hz, ^5J (5-H, 8-H) = 2.3 Hz, 2H, 5-H_2), 1.69 (m, ^2J (7-Ha, 7-Hb) = 12.3 Hz, ^3J (7-H, 8-H) = 6.2 Hz, ^3J (6-H, 7-H) = 2.5 Hz, ^3J (6-H, 7-H) = 8.8 Hz, 2H, 7-H_2),1.60 (m, ^2J (6-Ha, 6-Hb) = 11.9 Hz, ^3J (6-H, 7-H) = 2.4 Hz, ^3J (6-H, 7-H) = 8.4 Hz, ^3J (5-H, 6-H) = 6.0 Hz, 2H, 6-H_2).

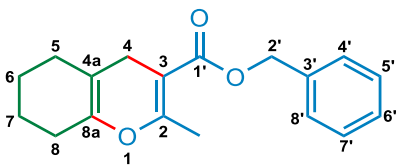
^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 168.2 (C-1'), 161.1 (C-2), 142.8 (C-8a), 107.0 (C-4a), 100.1 (C-3), 70.7 (C-3'), 62.9 (C-2'), 58.9 (C-4'), 27.8 (C-5), 26.6 (C-4), 25.7 (C-8), 22.8 (C-7), 22.4 (C-6), 19.2 (2-CH_3).

LRMS (EI, 70 eV): *m/z* (%) = 252 (8) $[M]^+$, 193 (100) $[M - CH_2CH_2OCH_3]^+$, 148 (21) $[M - COOCH_2CH_2OCH_3]^+$, 91 (5).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{14}H_{20}O_4]^+$ 252.1362; found 252.1367.

Molecular weight: $C_{14}H_{20}O_4$ (252.3100 g × mol^{-1}).

2.6.7 Benzyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (127g)



Following general procedure IV, benzyl 2-methyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127g**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1

mmol), benzyl acetoacetate (**46d**) (115 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **127g** was obtained as a pale yellow oil (82 mg, 0.29 mmol, 58%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 45:1).

R_f = 0.49 (petroleum ether/ethyl acetate = 20:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931, 1707 (C═O), 1630, 1383, 1260, 1171, 1144, 1049, 696.

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 7.39−7.34 (m, 4H, 4'-H, 5'-H, 7'-H and 8'-H), 7.33−7.28 (m, 1H, 6'-H), 5.18 (s, 2H, 2'-H_2), 2.78 (br s, 2H, 4-H_2), 2.25 (s, 3H, 2-CH_3), 2.02 (m, ^3J (7-H, 8-H) = 6.1 Hz, ^5J (5-H, 8-H) = 2.1 Hz, ^5J (4-H, 8-H) = 2.1 Hz, 2H, 8-H_2), 1.87 (m, ^3J (5-H, 6-H) = 5.9 Hz, ^5J (5-H, 8-H) = 1.1 Hz, ^5J (5-H, 8-H) = 2.3 Hz, 2H, 5-H_2), 1.64−1.56 (m, 2H, 6-H_2), 1.73−1.65 (m, 2H, 7-H_2).

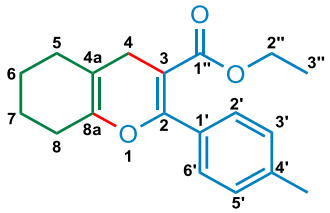
^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = 168.0 (C-1'), 161.3 (C-2), 142.9 (C-8a), 136.7 (C-3'), 128.5 (C-4' and C-8'), 127.9 (C-6'), 127.8 (C-5' and C-7'), 107.0 (C-4a), 100.0 (C-3), 65.6 (C-2'), 27.9 (C-5), 26.7 (C-4), 25.7 (C-8), 22.8 (C-7), 22.4 (C-6), 19.2 (2-CH_3).

LRMS (EI, 70 eV): *m/z* (%) = 284 (4) $[M]^+$, 193 (83) $[M - C_7H_7]^+$, 105 (100), 91 (60), 77 (28).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{18}H_{20}O_3]^+$ 284.1412; found 284.1401.

Molecular weight: $C_{18}H_{20}O_3$ (284.3550 g × mol^{-1}).

2.6.8 Ethyl 2-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (127h)



Following general procedure IV, ethyl 2-(*p*-tolyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (**127h**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), ethyl (4-methylbenzoyl)acetate (**46e**) (124 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **127h** was obtained as a colorless oil (88 mg, 0.29 mmol, 59%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 45:1).

R_f = 0.46 (petroleum ether/ethyl acetate = 20:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2929, 1722 (C═O), 1677, 1606, 1368, 1250, 1176, 1023, 814.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.27 (dd, ^{3}J (2"-H, 3"-H) = 8.1 Hz, ^{4}J (2"-H, 6"-H) = 1.9 Hz, 2H, 2"-H and 6"-H), 7.18 (dd, ^{3}J (2"-H, 3"-H) = 7.8 Hz, ^{4}J (3"-H, 5"-H) = 2.1 Hz, 2H, 3"-H and 5"-H), 3.99 (q, ^{3}J (2'-H, 3'-H) = 7.1 Hz, 2H, 2'-H_2), 2.93 (br s, 2H, 4-H_2), 2.38 (s, 3H, 4"-CH_3), 2.10 (m, ^{3}J (7-H, 8-H) = 6.3 Hz, ^{5}J (5-H, 8-H) = 2.2 Hz, ^{5}J (4-H, 8-H) = 2.2 Hz, 2H, 8-H_2), 1.96 (m, ^{3}J (5-H, 6-H) = 6.2 Hz, ^{5}J (5-H, 8-H) = 1.1 Hz, ^{5}J (5-H, 8-H) = 2.1 Hz, 2H, 5-H_2), 1.75 (m, ^{2}J (7-Ha, 7-Hb) = 12.3 Hz, ^{3}J (7-H, 8-H) = 6.2 Hz, ^{3}J (6-H, 7-H) = 2.3 Hz, ^{3}J (6-H, 7-H) = 8.7 Hz, 2H, 7-H_2), 1.67 (m, ^{2}J (6-Ha, 6-Hb) = 11.9 Hz, ^{3}J (6-H, 7-H) = 2.4 Hz, ^{3}J (6-H, 7-H) = 8.3 Hz, ^{3}J (5-H, 6-H) = 6.0 Hz, 2H, 6-H_2), 1.01 (t, ^{3}J (2'-H, 3'-H) = 7.1 Hz, 3H, 3'-H_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 168.2 (C-1'), 159.2 (C-2), 143.8 (C-8a), 138.9 (C-4"), 133.0 (C-1"), 128.4 (C-3" and C-5"), 128.3 (C-2" and C-6"), 106.6 (C-4a), 101.8 (C-3), 59.9 (C-2'), 27.9 (C-5), 27.5 (C-4), 25.9 (C-8), 22.9 (C-7), 22.4 (C-6), 21.4 (4"-CH_3), 13.8 (C-3').

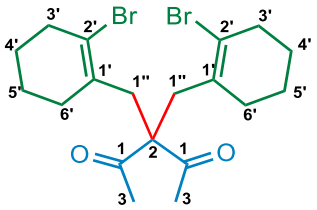
LRMS (EI, 70 eV): *m/z* (%) = 298 (12) $[M]^+$, 269 (100) $[M - C_2H_5]^+$, 225 (11) $[M - COOCH_2CH_3]^+$, 181 (73), 153 (38), 135 (22), 107 (17), 93 (33), 79 (12).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{19}H_{22}O_3]^+$ 298.1569; found 298.1569.

Molecular weight: $C_{19}H_{22}O_3$ (298.3820 g × mol^{-1}).

2.7 Synthesis of double alkylated compounds 135a–c

2.7.1 3,3-Bis[(2-bromocyclohex-1-en-1-yl)methyl]pentane-2,4-dione (135a)



Synthesis using 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) as substrate

Following general procedure IV, 3,3-bis[(2-bromocyclohex-1-en-1-yl)methyl]pentane-2,4-dione (**135a**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), acetylacetone (**134a**) (60 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol), 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) (127 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **135a** was obtained as a colorless oil (60 mg, 0.13 mmol, 27%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 20:1).

Synthesis using 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) as substrate

Following general procedure IV, 3,3-bis[(2-bromocyclohex-1-en-1-yl)methyl]pentane-2,4-dione (**135a**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), acetylacetone (**134a**) (60 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol), 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **135a** was obtained as a colorless oil (84 mg, 0.19 mmol, 38%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 20:1).

$\boldsymbol{R_f}$ = 0.46 (cyclohexane/ethyl acetate = 5:1).

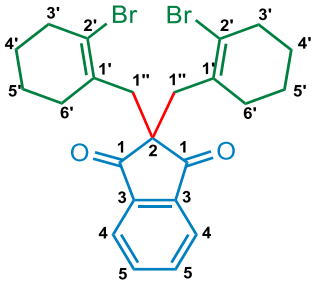
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 3.08 (s, 4H, 2 × 1''-H_2), 2.49 (t-like, J = 6.0 Hz, 4H, 2 × 3'-H_2), 2.24 (s, 6H, 2 × CH_3), 1.86 (t-like, J = 6.0 Hz, 4H, 2 × 6'-H_2), 1.60 (m, ^2J (5'-Ha, 5'-Hb) = 11.5 Hz, ^3J (4'-H, 5'-H) = 2.5 Hz, ^3J (4'-H, 5'-H) = 8.2 Hz, ^3J (5'-H, 6'-H) = 6.2 Hz, 8H, 2 × 4'-H_2 and 2 × 5'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 207.2 (2 × C-1), 131.6 (2 × C-1'), 124.0 (2 × C-2'), 69.7 (C-2), 39.9 (2 × C-1''), 37.4 (2 × C-3'), 30.9 (2 × C-6'), 27.8 (2 × CH_3), 24.4 (2 × C-4'), 22.5 (2 × C-5').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{19}H_{26}Br_2O_2Na]^+$ 469.0172; found 469.0182.

Molecular weight: $C_{19}H_{26}Br_2O_2$ (446.2230 g × mol^{-1}).

2.7.2 2,2-Bis[(2-bromocyclohex-1-en-1-yl)methyl]-2*H*-indene-1,3-dione (135b)



Synthesis using 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) as substrate

Following general procedure IV, 2,2-bis[(2-bromocyclohex-1-en-1-yl)methyl]-2*H*-indene-1,3-dione (**135b**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 1,3-indandione (**134b**) (88 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol), 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) (127 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **135b** was obtained as a white solid (91 mg, 0.18 mmol, 37%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 20:1).

Synthesis using 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) as substrate

Following general procedure IV, 2,2-bis[(2-bromocyclohex-1-en-1-yl)methyl]-2*H*-indene-1,3-dione (**135b**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 1,3-indandione (**134b**) (88 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol), 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **135b** was obtained as a white solid (120 mg, 0.24 mmol, 49%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 20:1).

M.p.: 153 − 155 °C.

$\boldsymbol{R_f}$ = 0.39 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2935, 1705 (C═O), 1588, 1431, 1350, 1233, 973, 803, 745.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.97 (dd, ^3J (4-H, 5-H) = 8.9 Hz, ^4J (4-H, 5-H) = 5.5 Hz, 2H, 2 × 4-H), 7.83 (dd, ^3J (4-H, 5-H) = 8.8 Hz, ^4J (4-H, 5-H) = 5.7 Hz, 2H, 2 × 5-H), 2.90 (s, 4H, 2 × 1''-H_2), 2.38 (t-like, J = 5.8 Hz, 4H, 2 × 3'-H_2), 1.75 (t-like, J = 5.9 Hz, 4H, 2 × 6'-

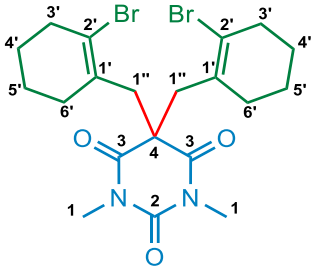
H_2), 1.39 (m, ^2J (5'-Ha, 5'-Hb) = 11.3 Hz, ^3J (4'-H, 5'-H) = 2.5 Hz, ^3J (4'-H, 5'-H) = 8.1 Hz, ^3J (5'-H, 6'-H) = 5.9 Hz, 8H, 2 × 4'-H_2 and 2 × 5'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 201.8 (2 × C-1), 141.9 (2 ×C-3), 135.5 (2 × C-1'), 131.1 (2 × C-5), 124.2 (2 × C-4), 123.1 (2 × C-2'), 57.8 (C-2), 42.7 (2 × C-1''), 36.9 (2 × C-3'), 32.2 (2 × C-6'), 24.5 (2 × C-4'), 22.4 (2 × C-5').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{23}H_{24}Br_2O_2Na]^+$ 515.0008; found 515.0016.

Molecular weight: $C_{23}H_{24}Br_2O_2$ (492.2510 g × mol^{-1}).

2.7.3 5,5-Bis[(2-bromocyclohex-1-en-1-yl)methyl]-1,3-dimethylbarbituric acid (135c)



Synthesis using 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) as substrate

Following general procedure IV, 5,5-bis[(2-bromocyclohex-1-en-1-yl)methyl]-1,3-dimethylbarbituric acid (**135c**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 1,3-dimethylbarbituric acid (**134c**) (94 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol), 1-bromo-2-(bromomethyl)cyclohex-1-ene (**124a**) (127 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **135c** was obtained as a white solid (90 mg, 0.18 mmol, 36%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 20:1).

Synthesis using 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) as substrate

Following general procedure IV, 5,5-bis[(2-bromocyclohex-1-en-1-yl)methyl]-1,3-dimethylbarbituric acid (**135c**) was synthesized by reacting CuI (10 mg, 0.05 mmol), Cs_2CO_3 (358 mg, 1.1 mmol), 1,3-dimethylbarbituric acid (**134c**) (94 mg, 0.6 mmol), 2-picolinic acid (6 mg, 0.05 mmol), 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (173 mg, 0.5 mmol) in DMF (2 mL). Analytically pure **135c** was obtained as a white solid (118 mg, 0.23 mmol, 47%) after subjecting the crude product to column chromatography over silica gel (petroleum ether/ethyl acetate = 20:1).

M.p.: 147 − 149 °C.

$\boldsymbol{R_f}$ = 0.38 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2943, 1680 (C═O), 1433, 1373, 1078, 968.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 3.30 (s, 6H, 2 × CH_3), 3.01 (s, 4H, 2 × 1''-H_2), 2.47 (t-like, J = 5.9 Hz, 4H, 2 × 3'-H_2), 1.81 (t-like, J = 5.8 Hz, 4H, 2 × 6'-H_2), 1.57 (m, ^{2}J (5'-Ha, 5'-Hb) = 11.6 Hz, ^{3}J (4'-H, 5'-H) = 2.5 Hz, ^{3}J (4'-H, 5'-H) = 8.1 Hz, ^{3}J (5'-H, 6'-H) = 6.2 Hz, 8H, 2 × 4'-H_2 and 2 × 5'-H_2).

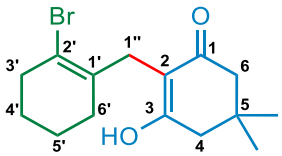
^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 170.1 (2 × C-3), 151.3 (C-2), 130.1 (2 × C-1'), 124.6 (2 × C-2'), 54.4 (C-4), 46.2 (2 × C-1''), 37.1 (2 × C-3'), 31.1 (2 × C-6'), 29.1 (2 × CH_3), 24.4 (2 × C-4'), 22.5 (2 × C-5').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{20}H_{26}Br_2N_2O_3Na]^+$ 525.0180; found 525.0183.

Molecular weight: $C_{20}H_{26}Br_2N_2O_3$ (502.2470 g × mol^{-1}).

2.8 Experiments towards the reaction mechanism

2.8.1 Synthesis of 2-[(2-bromocyclohex-1-en-1-yl)methyl]-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (136a)



An oven-dried 25 mL round-bottomed flask equipped with a magnetic stir bar was charged with a solution of 5,5-dimethyl-1,3-cyclohexanedione (**35b**) (0.56 g, 4 mmol, 2 equiv) in 5 mL freshly dried THF under argon. The mixture was cooled to 0 °C and NaH (60% dispersion in mineral oil) (155 mg, 4 mmol, 2 equiv) was added portionwise within 15 min. Afterwards, 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (0.69 g, 2 mmol, 1 equiv) was added at room temperature, and the resulting mixture was stirred for 12 h. The reaction mixture was poured into saturated NH_4Cl solution and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure 2-[(2-bromocyclohex-1-en-1-yl)methyl]-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**136a**) was obtained as a white solid (0.42 g, 1.36 mmol, 68%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 8:1).

M.p.: 176 − 177 °C.

$\boldsymbol{R_f}$ = 0.21 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2933 (OH), 1638 (C═O), 1560, 1352, 1255, 884, 622.

^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 10.49 (s, 1H, OH), 3.06 (s, 2H, 1''-H_2), 2.43−2.38 (m, 2H, 3'-H_2), 2.22 (br s, 4H, 4-H_2 and 6-H_2), 1.84−1.79 (m, 2H, 6'-H_2), 1.59−1.47 (m, overlapped, 4H, 4'-H_2 and 5'-H_2), 0.98 (s, 6H, 2 × CH_3).

^{13}C NMR (125 MHz, DMSO-d_6): δ [ppm] = 196.6 (C-1), 171.4 (C-3), 134.9 (C-1'), 117.7 (C-2'), 109.9 (C-2), 49.2 (C-6), 44.5 (C-4), 36.4 (C-3'), 31.5 (C-5), 29.1 (C-1''), 28.8 (C-6'), 28.1 (2 × CH_3), 24.4 (C-4'), 22.0 (C-5').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{15}H_{21}BrO_2Na]^+$ 335.0617; found 335.0619.

Molecular weight: $C_{15}H_{21}BrO_2$ (313.2350 g × mol^{-1}).

2.8.2 Synthesis of 126e from 136a

An oven-dried 10 mL vial equipped with a magnetic stir bar was charged with CuI (19 mg, 0.1 mmol, 0.1 equiv), Cs_2CO_3 (717 mg, 2.2 mmol, 2.2 equiv), 2-[(2-bromocyclohex-1-en-1-yl)methyl]-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**136a**) (313 mg, 1 mmol, 1 equiv), 2-picolinic acid (12 mg, 0.1 mmol, 0.1 equiv) and 140 mg molecular sieves (4 Å). Subsequently, the vial was sealed, evacuated, and backfilled with argon three times. Dry DMF (4 mL) was added and the reaction mixture was stirred at 80 °C for 2 h in an oil bath. After cooling to room temperature, the vial was opened, and the reaction mixture was poured into water (30 mL). The mixture was extracted with diethyl ether (3 × 30 mL). The organic phases were washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**) was obtained as a pale yellow oil (218 mg, 0.94 mmol, 94%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 10:1).

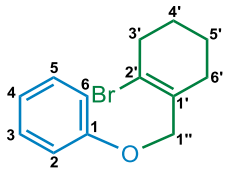
3 Ru-catalyzed synthesis of 3,4-annulated coumarins 137 and annulated naphthopyranones 138

3.1 Synthesis of 2-bromo-1-(aryloxymethyl)cycloalk-1-enes 128a–o and [(2'-bromocyclohex-1'-en-1'-yl)methyl]phenylsulfane (128p)

3.1.1 General procedure V

An oven-dried 100 mL round-bottomed flask equipped with a magnetic stir bar was charged with K_2CO_3 (3 equiv, 6 mmol), NaI (0.5 equiv, 1 mmol) and an appropriate phenol **45** or naphthol **52** (2 equiv, 4 mmol) in acetone (30 mL). 2-bromo-1-(4′-methylbenzenesulfonatemethyl)-1-ene **125** (1 equiv, 2 mmol) was added and the resulting mixture was stirred in a preheated oil bath at 60 °C for 18 h. The reaction mixture was cooled to room temperature, poured into water (30 mL) and stirred for an additional 10 min. After extraction with dichloromethane (3 × 20 mL) the combined organic phases were washed with brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure **128** or **129** was obtained after subjecting the crude product to column chromatography over silica gel.

3.1.2 1-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]benzene (128a)



Following general procedure V, 1-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]benzene (**128a**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), phenol (**45b**) (376 mg, 4 mmol), and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128a** was obtained as a colorless liquid (486 mg, 1.82 mmol, 91%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

***R*f** = 0.27 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2932, 1493, 1215, 1030, 750.

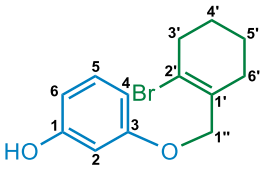
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.28 (ddd, J = 8.3, 7.8, 1.3 Hz, 2H, 3-H and 5-H), 6.96 (dt, J = 7.3, 1.1 Hz, 1H, 4-H), 6.93 (dd, J = 8.8, 0.9 Hz, 2H, 2-H and 6-H), 4.69 (s, 2H, 1"-H_2), 2.57−2.54 (m, 2H, 3'-H_2), 2.26−2.23 (m, 2H, 6'-H_2), 1.74−1.66 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 158.6 (C-1), 132.4 (C-2'), 129.5 (C-3 and C-5), 121.9 (C-1'), 120.8 (C-4), 114.7 (C-2 and C-6), 70.9 (C-1''), 36.7 (C-3'), 28.3 (C-6'), 24.6 (C-5'), 22.0 (C-4').

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{15}BrO]^+$ 266.0306; found 266.0309.

Molecular weight: $C_{13}H_{15}BrO$ (267.1660 g × mol^{-1}).

3.1.3 3-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]phenol (128b)[86]



Following general procedure V, 3-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]phenol (**128b**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), resorcinol (**45a**) (440 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128b** was obtained as a colorless liquid (493 mg, 1.74 mmol, 87%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

***R*$_f$** = 0.35 (cyclohexane/ethyl acetate = 5:1).

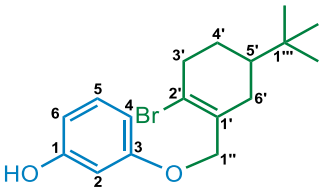
^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 7.12 (t, *J* = 8.1 Hz, 1H, 5-H), 6.44 (dd, *J* = 8.3, 2.2 Hz, 1H, 6-H), 6.34 (dd, *J* = 8.3, 2.3 Hz, 1H, 4-H), 6.32 (t-like, *J* = 2.2 Hz, 1H, 2-H), 4.64 (s, 2H, 1''-H_2), 2.59−2.55 (m, 2H, 3'-H_2), 2.27−2.23 (m, 2H, 6'-H_2), 1.74−1.65 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (150 MHz, DMSO-d_6): δ [ppm] = δ 159.5 (C-3), 158.6 (C-1), 132.5 (C-2'), 129.9 (C-5), 121.7 (C-1'), 108.2 (C-6), 105.1 (C-4), 101.8 (C-2), 70.4 (C-1''), 36.3 (C-3'), 28.2 (C-6'), 24.2 (C-5'), 21.6 (C-4').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{13}H_{15}BrO_2Na]^+$ 305.0148; found 305.0144.

Molecular weight: $C_{13}H_{15}BrO_2$ (283.1650 g × mol^{-1}).

3.1.4 3-[(2'-Bromo-5'-(*tert*-butyl)cyclohex-1'-en-1'-yl)methoxy]phenol (128c)



Following general procedure V, 3-[(2'-bromo-5'-(*tert*-butyl)cyclohex-1'-en-1'-yl)methoxy]phenol (**128c**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg,

1 mmol), resorcinol (**45a**) (440 mg, 4 mmol) and 2-bromo-5-*tert*-butyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125d**) (803 mg, 2 mmol) in acetone (30 mL). Analytically pure **128c** was obtained as a colorless liquid (604 mg, 1.78 mmol, 89%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

R_f = 0.29 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3384 (OH), 2986, 1594, 1282, 1142, 761.

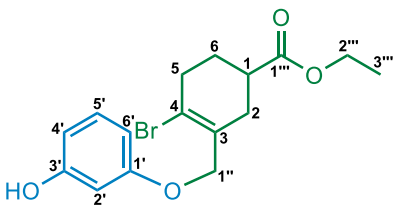
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.12 (t, J = 7.9 Hz, 1H, 5-H), 6.54 (ddd, J = 8.4, 2.2, 1.8 Hz, 1H, 6-H), 6.46 (t-like, J = 2.5 Hz, 1H, 2-H), 6.44 (dd, J = 8.4, 2.3 Hz, 1H, 4-H), 4.66 (d, J = 11.5 Hz, 1H, 1''-Ha), 4.62 (d, J = 11.6 Hz, 1H, 1''-Hb), 2.25 (t-like, J = 4.4 Hz, 2H, 3'-H_2), 2.32 (dd, J = 16.3, 4.4 Hz, 1H, 6'-Ha), 1.99−1.92 (m, 1H, 6'-Hb), 1.83−1.78 (m, 1H, 5'-H), 1.41−1.33 (m, 2H, 4'-H_2), 0.87 (s, 9H, 3 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 159.9 (C-3), 156.6 (C-1), 132.0 (C-2'), 130.1 (C-5), 122.1 (C-1'), 108.0 (C-6), 107.2 (C-4), 102.3 (C-2), 71.4 (C-1''), 43.5 (C-5'), 37.8 (C-3'), 32.2 (C-6'), 30.2 (C-1'''), 27.1 (3 × CH_3), 25.9 (C-4').

HRMS (ESI): *m/z* [M + Na]$^+$ calcd. for [$C_{17}H_{23}BrO_2Na$]$^+$ 361.0774; found 361.0774.

Molecular weight: $C_{17}H_{23}BrO_2$ (339.2730 g × mol^{-1}).

3.1.5 Ethyl 4-bromo-3-[(3'-hydroxyphenoxy)methyl]cyclohex-3-ene-1-carboxylate (128d)



Following general procedure V, ethyl 4-bromo-3-[(3'-hydroxyphenoxy)methyl]cyclohex-3-ene-1-carboxylate (**128d**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), resorcinol (**45a**) (440 mg, 4 mmol) and ethyl 4-bromo-3-(4'-methylbenzenesulfonatemethyl)cyclohex-3-ene-1-carboxylate (**125e**) (835 mg, 2 mmol) in acetone (30 mL). Analytically pure **128d** was obtained as a colorless liquid (518 mg, 1.46 mmol, 73%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

R_f = 0.38 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3384 (OH), 2976, 1703 (C=O), 1594, 1284, 1145, 763.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.11 (t, J = 8.1 Hz, 1H, 5'-H), 6.48 (dd, J = 8.4, 2.1 Hz, 1H, 4'-H), 6.45 (dd, J = 7.9, 2.3 Hz, 1H, 6'-H), 6.43 (t-like, J = 2.3 Hz, 1H, 2'-H), 6.17 (br

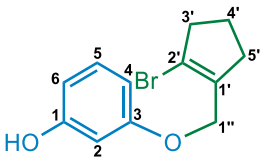
s, 1H, OH), 4.67 (d, *J* = 11.9 Hz, 1H, 1''-Ha), 4.62 (d, *J* = 12.3 Hz, 1H, 1''-Hb), 4.15 (q, *J* = 7.2 Hz, 2'''-H_2), 2.67−2.59 (m, overlapped, 3H, 5-H_2 and 1-H), 2.56 (dd, *J* = 17.1, 5.1 Hz, 1H, 2-Ha), 2.46−2.40 (m, 1H, 2-Hb), 2.01−1.99 (m, 1H, 6-Ha), 1.89−1.82 (m, 1H, 6-Hb), 1.25 (t, *J* = 7.1 Hz, 3H, 3'''-H_3).

^{13}C NMR (150 MHz, $CDCl_3$): *δ* [ppm] = 159.7 (C-1'), 157.0 (C-1'''), 156.9 (C-3'), 130.6 (C-4), 130.0 (C-5'), 120.9 (C-3), 108.2 (C-4'), 106.8 (C-6'), 102.3 (C-2'), 70.7 (C-1''), 60.9 (C-2'''), 38.7 (C-1), 35.5 (C-5), 30.3 (C-2), 26.7 (C-6), 14.1 (C-3''').

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{16}H_{20}BrO_4]^+$ 355.0539; found 355.0535.

Molecular weight: $C_{16}H_{19}BrO_4$ (355.2280 g × mol^{-1}).

3.1.6 3-[(2'-Bromocyclopent-1'-en-1'-yl)methoxy]phenol (128e)



Following general procedure V, 3-[(2'-bromocyclopent-1'-en-1'-yl)methoxy]phenol (**128e**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), resorcinol (**45a**) (440 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclopent-1-ene (**125b**) (662 mg, 2 mmol) in acetone (30 mL). Analytically pure **128e** was obtained as a colorless liquid (419 mg, 1.56 mmol, 78%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

***R*$_f$** = 0.34 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3369 (OH), 2945, 1593, 1281, 1142, 761.

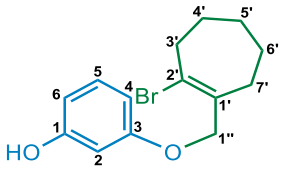
^{1}H NMR (600 MHz, $CDCl_3$): *δ* [ppm] = 7.13 (t-like, *J* = 8.2 Hz, 1H, 5-H), 6.52 (ddd, *J* = 8.3, 2.3, 0.9 Hz, 1H, 6-H), 6.45 (dd, *J* = 6.4, 2.4 Hz, 1H, 4-H), 6.43 (t-like, *J* = 2.3 Hz, 1H, 2-H), 5.02 (br s, 1H, OH), 4.63 (s, 2H, 1''-H_2), 2.69 (tt-like, *J* = 7.4, 1.5 Hz, 2H, 3'-H_2), 2.46 (tt-like, *J* = 7.3, 1.1 Hz, 2H, 5'-H_2), 1.97 (quint, *J* = 7.2 Hz, 2H, 4'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): *δ* [ppm] = *δ* 159.8 (C-3), 156.6 (C-1), 136.8 (C-2'), 130.2 (C-5), 119.6 (C-1'), 108.1 (C-6), 107.1 (C-4), 102.2 (C-2), 65.6 (C-1''), 40.3 (C-3'), 32.5 (C-5'), 21.6 (C-4').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{12}H_{13}BrO_2Na]^+$ 290.9991; found 290.9983.

Molecular weight: $C_{12}H_{13}BrO_2$ (269.1380 g × mol^{-1}).

3.1.7 3-[(2'-Bromocyclohept-1'-en-1'-yl)methoxy]phenol (128f)



Following general procedure V, 3-[(2'-bromocyclohept-1'-en-1'-yl)methoxy]phenol (**128f**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), resorcinol (**45a**) (440 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohept-1-ene (**125f**) (718 mg, 2 mmol) in acetone (30 mL). Analytically pure **128f** was obtained as a colorless liquid (469 mg, 1.58 mmol, 79%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

***R*f** = 0.31 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3345 (OH), 2922, 1594, 1284, 1144, 761.

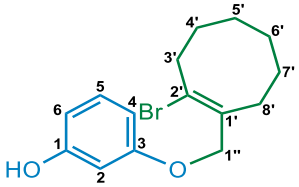
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.13 (t-like, J = 8.5 Hz, 1H, 5-H), 6.52 (ddd, J = 8.2, 2.3, 0.8 Hz, 1H, 6-H), 6.46−6.43 (m, 2H, 2-H and 4-H), 5.48 (s, 1H, OH), 4.64 (s, 2H, 1''-H_2), 2.79 (dd-like, J = 9.6, 5.5 Hz, 2H, 3'-H_2), 2.35 (dd-like, J = 10.7, 5.6 Hz, 2H, 7'-H_2), 1.73 (quint-like, J = 5.9 Hz, 2H, 4'-H_2), 1.58 (quint-like, J = 5.9 Hz, 2H, 5'-H_2), 1.46 (quint-like, J = 6.2 Hz, 2H, 6'-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 159.8 (C-3), 156.5 (C-1), 137.5 (C-2'), 130.1 (C-5), 125.6 (C-1'), 108.0 (C-6), 107.3 (C-4), 102.4 (C-2), 72.4 (C-1''), 41.5 (C-3'), 31.4 (C-7'), 30.0 (C-4'), 25.3 (C-5'), 25.2 (C-6').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{14}H_{17}BrO_2Na]^+$ 319.0304; found 319.0304.

Molecular weight: $C_{14}H_{17}BrO_2$ (297.1920 g × mol^{-1}).

3.1.8 3-[(2'-Bromocyclooct-1'-en-1'-yl)methoxy]phenol (128g)



Following general procedure V, 3-[(2'-bromocyclooct-1'-en-1'-yl)methoxy]phenol (**128g**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), resorcinol (**45a**) (440 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclooct-1-ene (**125g**) (747 mg, 2 mmol) in acetone (30 mL). Analytically pure **128g** was obtained as a colorless liquid (423 mg, 1.36 mmol, 68%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

***R*f** = 0.31 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3372 (OH), 2921, 1594, 1284, 1142, 761.

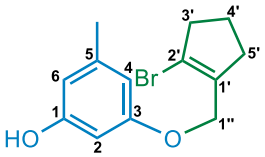
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.12 (t, *J* = 8.0 Hz, 1H, 5-H), 6.51 (ddd, *J* = 8.3, 2.8, 08 Hz, 1H, 6-H), 6.44 (t-like, *J* = 2.2 Hz, 1H, 2-H), 6.42 (dd, *J* = 7.4, 2.3 Hz, 1H, 4-H), 4.67 (s, 2H, 1''-H_2), 2.73 (dd-like, *J* = 12.1, 5.9 Hz, 2H, 3'-H_2), 2.39 (dd-like, *J* = 12.2, 6.0 Hz, 2H, 8'-H_2), 1.67 (quint-like, *J* = 6.1 Hz, 2H, 4'-H_2), 1.57 (quint-like, *J* = 5.9 Hz, 2H, 7'-H_2), 1.52−1.46 (m, overlapped, 4H, 5'-H_2 and 6'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = δ 159.9 (C-3), 156.7 (C-1), 134.8 (C-2'), 130.1 (C-5), 124.3 (C-1'), 107.9 (C-6), 107.2 (C-4), 102.3 (C-2), 70.6 (C-1''), 37.4 (C-3'), 29.5 (C-8'), 29.2 (C-7'), 28.1 (C-4'), 26.5 (C-5'), 25.8 (C-6').

HRMS (ESI): *m/z* [M + Na]$^+$ calcd. for [$C_{15}H_{19}BrO_2Na$]$^+$ 333.0461; found 333.0454.

Molecular weight: $C_{15}H_{19}BrO_2$ (311.2190 g × mol^{-1}).

3.1.9 3-[(2'-Bromocyclopent-1'-en-1'-yl)methoxy]-5-methylphenol (128h)



Following general procedure V, 3-[(2'-bromocyclopent-1'-en-1'-yl)methoxy]-5-methylphenol (**128h**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), orcinol (**45c**) (248 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclopent-1-ene (**125b**) (662 mg, 2 mmol) in acetone (30 mL). Analytically pure **128h** was obtained as a colorless liquid (443 mg, 1.57 mmol, 79%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

***R*f** = 0.33 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3363 (OH), 2918, 1591, 1141, 828.

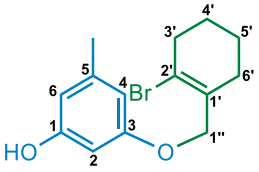
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 6.35 (dd-like, *J* = 2.3, 2.1 Hz, 1H, 6-H), 6.28 (dd-like, *J* = 2.3, 2.2 Hz, 1H, 4-H), 6.24 (t, *J* = 2.2 Hz, 1H, 2-H), 4.60 (s, 2H, 1''-H_2), 2.71−2.67 (m, 2H, 3'-H_2), 2.47−2.44 (m, 2H, 5'-H_2), 2.27 (s, 3H, 5-CH_3), 1.97 (quint-like, *J* = 7.5 Hz, 2H, 4'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = δ 159.6 (C-3), 156.4 (C-1), 140.6 (C-2'), 136.8 (C-5), 119.5 (C-1'), 108.8 (C-6), 108.1 (C-4), 99.2 (C-2), 65.6 (C-1''), 40.3 (C-3'), 32.5 (C-5'), 21.6 (C-4'), 21.5 (5-CH_3).

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for [$C_{13}H_{16}BrO_2$]$^+$ 283.0328; found 283.0327.

Molecular weight: $C_{13}H_{15}BrO_2$ (283.1650 g × mol^{-1}).

3.1.10 3-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]-5-methylphenol (128i)



Following general procedure V, 3-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]-5-methylphenol (**128i**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), orcinol (**45c**) (248 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128i** was obtained as a colorless liquid (523 mg, 1.76 mmol, 88%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

$\boldsymbol{R_f}$ = 0.33 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3375 (OH), 2931, 1591, 1142, 828.

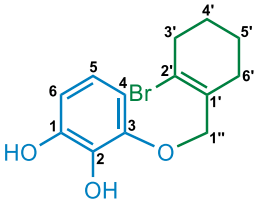
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 6.35 (br s, 1H, 6-H), 6.26 (br s, 1H, 4-H), 6.24 (t-like, J = 2.3 Hz, 1H, 2-H), 4.63 (s, 2H, 1"-H_2), 2.56−2.53 (m, 2H, 3'-H_2), 2.27 (s, 3H, 5-CH_3), 2.24−2.21 (m, 2H, 6'-H_2), 1.73−1.65 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 159.8 (C-3), 156.4 (C-1), 140.6 (C-2'), 132.3 (C-5), 121.9 (C-1'), 108.7 (C-6), 108.2 (C-4), 99.2 (C-2), 71.0 (C-1"), 36.7 (C-3'), 28.3 (C-6'), 24.6 (C-5'), 21.9 (C-4'), 21.6 (5-CH_3).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd. for [$C_{14}H_{17}BrO_2Na$]$^+$ 319.0304; found 319.0303.

Molecular weight: $C_{14}H_{17}BrO_2$ (297.1920 g × mol^{-1}).

3.1.11 3-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]benzene-1,2-diol (128j)



Following general procedure V, 3-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]benzene-1,2-diol (**128j**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), pyrogallol (**45d**) (504 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128j** was obtained as a colorless liquid (485 mg, 1.62 mmol, 81%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

$\boldsymbol{R_f}$ = 0.42 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3405 (OH), 2933, 1605, 1315, 1172, 776.

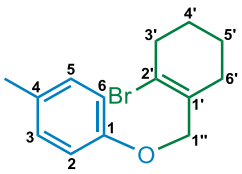
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.88 (t, J = 8.4 Hz, 1H, 5-H), 6.50 (d, J = 8.2 Hz, 2H, 4-H and 6-H), 5.53 (br s, 2H, 2 × OH), 4.55 (s, 2H, 1''-H_2), 2.60−2.56 (m, 2H, 3'-H_2), 2.35−2.31 (m, 2H, 6'-H_2), 1.73 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 149.4 (C-1 and C-3), 133.1 (C-2), 131.9 (C-5), 126.0 (C-2'), 125.0 (C-1'), 108.1 (C-4 and C-6), 76.2 (C-1''), 36.7 (C-3'), 30.4 (C-6'), 24.3 (C-5'), 22.2 (C-4').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{13}H_{15}BrO_3Na]^+$ 321.0097; found 321.0097.

Molecular weight: $C_{13}H_{15}BrO_3$ (299.1640 g × mol^{-1}).

3.1.12 1-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]-4-methylbenzene (128k)[87]



Following general procedure V, 1-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]-4-methylbenzene (**128k**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 4-methylphenol (**45e**) (432 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128k** was obtained as a colorless liquid (496 mg, 1.76 mmol, 88%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

R_f = 0.28 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2930, 1508, 1215, 1014, 806.

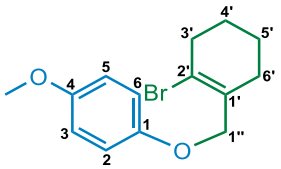
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.08 (d, J = 8.4 Hz, 2H, 3-H and 5-H), 6.83 (dd, J = 8.5, 2.2 Hz, 2H, 2-H and 6-H), 4.66 (s, 2H, 1''-H_2), 2.56−2.53 (m, 2H, 3'-H_2), 2.29 (s, 3H, 4-CH_3), 2.26−2.23 (m, 2H, 6'-H_2), 1.73−1.66 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 156.5 (C-1), 132.6 (C-2'), 130.1 (C-4), 129.9 (C-3 and C-5), 121.8 (C-1'), 114.5 (C-2 and C-6), 71.1 (C-1''), 36.7 (C-3'), 28.3 (C-6'), 24.6 (C-5'), 22.0 (C-4'), 20.5 (4-CH_3).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{14}H_{17}BrO]^+$ 280.0457; found 280.0440.

Molecular weight: $C_{14}H_{17}BrO$ (281.1930 g × mol^{-1}).

3.1.13 1-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]-4-methoxybenzene (128l)[87]



Following general procedure V, 1-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]-4-methoxybenzene (**128l**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 4-methoxyphenol (**45f**) (497 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128l** was obtained as a colorless liquid (499 mg, 1.68 mmol, 84%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

$\boldsymbol{R_f}$ = 0.28 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2932, 1504, 1224, 1037, 821.

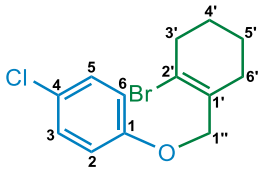
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.86 (dd, J = 9.2, 2.6 Hz, 2H, 3-H and 5-H), 6.83 (dd, J = 9.3, 2.7 Hz, 2H, 2-H and 6-H), 4.64 (s, 2H, 1''-H_2), 3.77 (s, 3H, CH_3), 2.56−2.52 (m, 2H, 3'-H_2), 2.26−2.22 (m, 2H, 6'-H_2), 1.73−1.66 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 153.9 (C-4), 152.9 (C-1), 132.6 (C-2'), 121.9 (C-1'), 115.6 (C-3 and C-5), 114.6 (C-2 and C-6), 71.7 (C-1''), 55.7 (CH_3), 36.7 (C-3'), 28.4 (C-6'), 24.6 (C-5'), 22.0 (C-4').

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{14}H_{17}BrO_2]^+$ 296.0406; found 296.0423.

Molecular weight: $C_{14}H_{17}BrO_2$ (297.1920 g × mol^{-1}).

3.1.14 1-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]-4-chlorobenzene (128m)[87]



Following general procedure V, 1-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]-4-chlorobenzene (**128m**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 4-chlorophenol (**45g**) (514 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128m** was obtained as a colorless liquid (470 mg, 1.56 mmol, 78%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2933, 1488, 1235, 1002, 821.

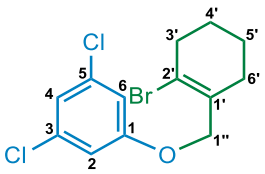
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.23 (dd, J = 6.8, 2.3 Hz, 2H, 3-H and 5-H), 6.85 (dd, J = 6.7, 2.2 Hz, 2H, 2-H and 6-H), 4.66 (s, 2H, 1''-H_2), 2.56−2.53 (m, 2H, 3'-H_2), 2.22−2.19 (m, 2H, 6'-H_2), 1.72−1.65 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 157.2 (C-1), 132.0 (C-2'), 129.3 (C-3 and C-5), 125.7 (C-4), 122.4 (C-1'), 116.1 (C-2 and C-6), 71.3 (C-1''), 36.7 (C-3'), 28.3 (C-6'), 24.6 (C-5'), 21.9 (C-4').

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{14}BrClO]^+$ 301.9889; found 301.9859.

Molecular weight: $C_{13}H_{14}BrClO$ (301.6080 g × mol^{-1}).

3.1.15 1-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]-3,5-dichlorobenzene (128n)



Following general procedure V, 1-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]-3,5-dichlorobenzene (**128n**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 3,5-dichlorophenol (**45h**) (652 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128n** was obtained as a yellow liquid (484 mg, 1.44 mmol, 72%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

R_f = 0.36 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2921, 1569, 1334, 1022, 796.

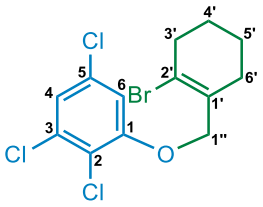
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.96 (t, J = 1.8 Hz, 1H, 4-H), 6.83 (d, J = 1.8 Hz, 2H, 2-H and 6-H), 4.64 (s, 2H, 1''-H_2), 2.57−2.54 (m, 2H, 3'-H_2), 2.21−2.18 (m, 2H, 6'-H_2), 1.74−1.67 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 159.6 (C-1), 135.4 (C-4), 131.3 (C-2'), 123.1 (C-1'), 121.2 (C-3 and C-5), 113.9 (C-2 and C-6), 71.6 (C-1''), 36.7 (C-3'), 28.4 (C-6'), 24.5 (C-5'), 21.9 (C-4').

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{13}BrCl_2O]^+$ 335.9498; found 335.9468.

Molecular weight: $C_{13}H_{13}BrCl_2O$ (336.0500 g × mol^{-1}).

3.1.16 1-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]-2,3,5-trichlorobenzene (128o)



Following general procedure V, 1-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]-2,3,5-trichlorobenzene (**128o**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 2,3,5-trichlorophenol (**45i**) (790 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128o** was obtained as a yellow liquid (511 mg, 1.38 mmol, 69%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

R_f = 0.35 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2930, 1563, 1257, 1011, 822.

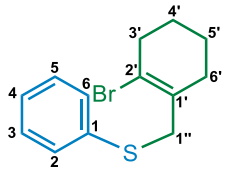
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.10 (d, J = 2.2 Hz, 1H, 4-H), 6.89 (d, J = 2.2 Hz, 1H, 6-H), 4.75 (s, 2H, 1''-H_2), 2.58−2.54 (m, 2H, 3'-H_2), 2.27−2.24 (m, 2H, 6'-H_2), 1.75−1.68 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 155.4 (C-1), 134.2 (C-4), 132.8 (C-2'), 131.0 (C-5), 123.0 (C-3), 122.2 (C-2), 120.8 (C-1'), 112.5 (C-6), 72.6 (C-1''), 36.7 (C-3'), 28.1 (C-6'), 24.5 (C-5'), 21.9 (C-4').

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{12}BrCl_3O]^+$ 369.9107; found 369.9085.

Molecular weight: $C_{13}H_{12}BrCl_3O$ (370.4920 g × mol^{-1}).

3.1.17 [(2'-Bromocyclohex-1'-en-1'-yl)methyl]phenylsulfane (128p)



Following general procedure V, [(2'-bromocyclohex-1'-en-1'-yl)methyl]phenylsulfane (**128p**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), thiophenol (**83**) (441 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **128p** was obtained as a pale yellow liquid (442 mg, 1.49 mmol, 78%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 5:1).

R_f = 0.26 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2929, 1583, 1435, 972, 736.

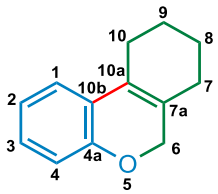
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.39 (ddd, *J* = 8.2, 7.8, 1.3 Hz, 2H, 3-H and 5-H), 7.28 (tdd, *J* = 7.7, 2.4, 0.8 Hz, 2H, 2-H and 6-H), 7.21 (tt, *J* = 8.1, 1.7 Hz, 1H, 4-H), 3.74 (s, 2H, 1''-H_2), 2.49−2.46 (m, 2H, 3'-H_2), 2.26−2.23 (m, 2H, 6'-H_2), 1.74−1.66 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 136.0 (C-1), 131.8 (C-2'), 130.6 (C-3 and C-5), 128.7 (C-2 and C-6), 126.5 (C-1), 122.6 (C-1'), 41.0 (C-1''), 36.8 (C-3'), 30.2 (C-6'), 24.7 (C-5'), 22.5 (C-4').

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{15}BrS]^+$ 282.0078; found 282.0075.

Molecular weight: $C_{13}H_{15}BrS$ (283.2270 g × mol^{-1}).

3.2 Synthesis of 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (130a)



An oven-dried 10 mL vial equipped with a magnetic stir bar was charged with $RuCl_2(PPh_3)_3$ (77 mg, 0.08 mmol). The vial was sealed, evacuated, and backfilled with argon three times. Next, 1-[(2-bromocyclohex-1-en-1-yl)methoxy]benzene (**128a**) (1 equiv) and 1,5-pentanediol (1 mL) were added. The reaction mixture was stirred in a preheated oil bath at 140 °C for 18 h. After cooling to room temperature, the vial was opened and the reaction mixture was poured into water (10 mL). The mixture was extracted with ethyl acetate (2 × 10 mL) and the combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure 7,8,9,10-tetrahydro-6*H*-benzo[*c*]chromene (**130a**) was obtained as a colorless liquid (83 mg, 0.45 mmol, 89%) after subjecting the crude product to column chromatography over silica gel impregnated with 4% oxalic acid (cyclohexane/methanol = 10:1).

R_f = 0.17 (cyclohexane/ethyl acetate = 6:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2928, 1489, 1227, 1024, 747.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.08 (ddd, *J* = 7.6, 7.5, 1.6 Hz, 2H, 2-H and 4-H), 6.88 (td, *J* = 7.5, 1.1 Hz, 1H, 3-H), 6.78 (dd, *J* = 7.9, 0.9 Hz, 1H, 1-H), 4.59 (s, 2H, 6-H_2), 2.34−2.31 (m, 2H, 10-H_2), 2.01−1.98 (m, 2H, 7-H_2), 1.81−1.76 (m, 2H, 9-H_2), 1.73−1.68 (m, 2H, 8-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 153.2 (C-4a), 127.7 (C-10a), 127.6 (C-3), 124.5 (C-2), 124.4 (C-1), 121.9 (C-7a), 121.0 (C-10b), 115.4 (C-4), 68.7 (C-6), 26.2 (C-7), 23.6 (C-10), 22.6 (C-8), 22.0 (C-9).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{14}O]^+$ 186.1045; found 186.1048.

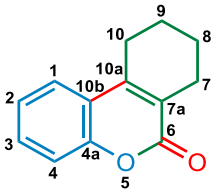
Molecular weight: $C_{13}H_{14}O$ (156.2540 g × mol^{-1}).

3.3 Synthesis of 3,4-annulated coumarins 137a–k

3.3.1 General procedure VI

An oven-dried 10 mL vial equipped with a magnetic stir bar was charged with $RuCl_2(PPh_3)_3$ (5 mol%) and 1,5-pentanediol (2 equiv) under argon. The vial was sealed, evacuated, and backfilled with argon three times. Dry DMA (2 mL) and starting material **128** or **129** (1 mmol) were added with stirring. The reaction mixture was stirred in a preheated oil bath at 100 °C for 18 h. Subsequently, DTBP (4 equiv) was added within 10 min using a syringe and the reaction mixture was stirred at 100 °C for an additional 18 h. After cooling to room temperature, the vial was opened and the reaction mixture was poured into water (20 mL). The mixture was extracted with ethyl acetate (2 × 20 mL) and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Analytically pure **137** or **138** was obtained after subjecting the crude product to column chromatography over silica gel.

3.3.2 7,8,9,10-Tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (137a)



Following general procedure VI, 7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137a**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 1-[(2-bromocyclohex-1-en-1-yl)methoxy]benzene (**128a**) (267 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137a** was obtained as a white solid (122 mg, 0.61 mmol, 61%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 118 − 120 °C.

$\boldsymbol{R_f}$ = 0.17 (cyclohexane/ethyl acetate = 5:1).

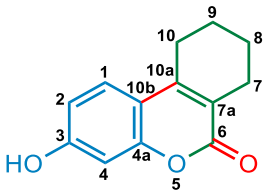
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.54 (dd, *J* = 7.9, 1.4 Hz, 1H, 1-H), 7.44 (ddd, *J* = 7.7, 1.5, 0.8 Hz, 1H, 4-H), 7.28 (dd, *J* = 8.3, 1.2 Hz, 1H, 3-H), 7.25 (ddd, *J* = 7.8, 7.3, 1.2 Hz, 1H, 2-H), 2.77 (tt-like, *J* = 6.2, 2.1 Hz, 2H, 10-H_2), 2.57 (tt-like, *J* = 6.2, 2.2 Hz, 2H, 7-H_2), 1.87−1.84 (m, 2H, 9-H_2), 1.82−1.78 (m, 2H, 8-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 161.7 (C-6), 151.9(C-4a), 146.9 (C-10a), 130.2 (C-3), 123.9 (C-2), 123.7 (C-1), 123.1 (C-7a), 120.1 (C-10b), 116.6 (C-4), 25.1 (C-7), 24.0 (C-10), 21.5 (C-8), 21.3 (C-9).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{13}H_{13}O_2]^+$ 201.0910; found 201.0910.

Molecular weight: $C_{13}H_{12}O_2$ (200.2370 g × mol^{-1}).

3.3.3 3-Hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (137b)[88]



Following general procedure VI, 3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137b**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 3-[(2-bromocyclohex-1-en-1-yl)methoxy]phenol (**128b**) (283 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137b** was obtained as a pale yellow solid (164 mg, 0.76 mmol, 76%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 222 − 224 °C.

***R*$_f$** = 0.15 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3207 (OH), 2941, 1679 (C═O), 1614, 1563, 1148, 709.

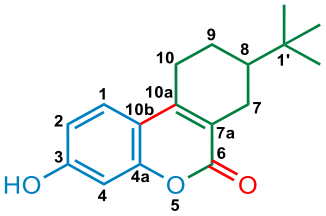
^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 7.48 (d, *J* = 8.8 Hz, 1H, 1-H), 6.76 (dd, *J* = 8.7, 2.4 Hz, 1H, 2-H), 6.66 (d, *J* = 2.4 Hz, 1H, 4-H), 4.98 (br s, 1H, OH), 2.69 (t-like, *J* = 6.1 Hz, 2H, 10-H_2), 2.35 (t-like, *J* = 5.8 Hz, 2H, 7-H_2), 1.75−1.66 (m, overlapped, 4H, 8-H_2 and 9-H_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ [ppm] = 161.1 (C-6), 159.9 (C-3), 153.1 (C-4a), 147.7 (C-10a), 125.1 (C-1), 118.4 (C-7a), 112.7 (C-10b), 111.9 (C-2), 101.9 (C-4), 24.6 (C-7), 23.5 (C-10), 21.3 (C-8), 20.9 (C-9).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{13}H_{12}O_3]^+$ 216.0786; found 216.0788.

Molecular weight: $C_{13}H_{12}O_3$ (216.2360 g × mol^{-1}).

3.3.4 8-(*tert*-Butyl)-3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (137c)



Following general procedure VI, 8-(*tert*-butyl)-3-hydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137c**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 3-[(2-bromo-5-(*tert*-butyl)cyclohex-1-en-1-yl)methoxy]phenol (**128c**) (339 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137c** was obtained as a white solid (226 mg, 0.83 mmol, 83%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 228 − 230 °C.

$\boldsymbol{R_f}$ = 0.15 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3396 (OH), 2951, 1677 (C═O), 1615, 1576, 1147, 642.

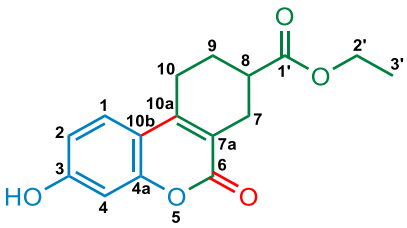
^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 10.32 (s, 1H, OH), 7.48 (d, J = 8.7 Hz, 1H, 1-H), 6.76 (dd, J = 8.7, 2.4 Hz, 1H, 2-H), 6.66 (d, J = 2.4 Hz, 1H, 4-H), 2.94 (dd, J = 18.3, 4.9 Hz, 1H, 7-Ha), 2.58−2.52 (m, 2H, 10-H_2), 2.01−1.95 (m, overlapped, 2H, 7-Hb and 9-Ha), 1.31 (tdd, J = 12.8, 4.8, 2.1 Hz, 1H, 8-H), 1.19 (qd, J = 12.5, 5.2 Hz, 1H, 9-Hb), 0.91 (s, 9H, 3 × CH_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ [ppm] = 161.2 (C-6), 159.9 (C-3), 153.0 (C-4a), 147.6 (C-10a), 125.1 (C-1), 118.6 (C-7a), 112.7 (C-10b), 111.8 (C-2), 101.9 (C-4), 42.9 (C-8), 32.0 (C-1'), 27.1 (3 × CH_3), 26.1 (C-10), 25.2 (C-7), 22.3 (C-9).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{17}H_{21}O_3]^+$ 273.1485; found 273.1489.

Molecular weight: $C_{17}H_{20}O_3$ (272.3440 g × mol^{-1}).

3.3.5 Ethyl 3-hydroxy-6-oxo-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-8-carboxylate (137d)



Following general procedure VI, ethyl 3-hydroxy-6-oxo-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-8-carboxylate (**137d**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and ethyl 4-bromo-3-[(3-hydroxyphenoxy)methyl]cyclohex-3-ene-1-carboxylate (**128d**) (355 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137d** was obtained as a pale yellow solid (196 mg, 0.68 mmol, 68%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 225 − 227 °C.

$\boldsymbol{R_f}$ = 0.17 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3366 (OH), 2965, 1702 (C═O), 1618, 1576, 1283, 1150, 646.

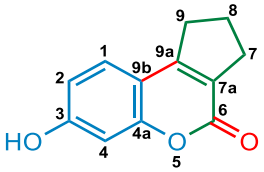
^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 10.4 (s, 1H, OH), 7.51 (d, J = 8.7 Hz, 1H, 1-H), 6.77 (dd, J = 8.6, 2.3 Hz, 1H, 2-H), 6.68 (d, J = 2.3 Hz, 1H, 4-H), 4.11 (q, J = 7.1 Hz, 2H, 2'-H_2), 2.88 (dt, J = 18.7, 4.9 Hz, 1H, 8-H), 2.78−2.71 (m, 2H, 10-H_2), 2.69 (dd-like, J = 17.5, 5.2 Hz, 1H, 7-Ha), 2.47 (dddd, J = 17.5, 8.2, 2.6, 0.9 Hz, 1H, 9-Ha), 2.15−2.10 (m, 1H, 7-Hb), 1.78−1.72 (m, 1H, 9-Hb), 1.21 (t, J = 7.2 Hz, 3H, 3'-H_3).

^{13}C NMR (150 MHz, DMSO-d_6): δ [ppm] = 174.0 (C-1'), 160.7 (C-6), 160.1 (C-3), 153.1 (C-4a), 147.1 (C-10a), 125.2 (C-1), 116.7 (C-7a), 112.8 (C-10b), 111.5 (C-2), 101.9 (C-4), 60.1 (C-2'), 37.6 (C-8), 25.7 (C-10), 23.9 (C-7), 23.4 (C-9), 14.1 (C-3').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{16}H_{16}O_5Na]^+$ 311.0890; found 311.0894.

Molecular weight: $C_{16}H_{16}O_5$ (288.2990 g × mol^{-1}).

3.3.6 3-Hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (137e)[89]



Following general procedure VI, 3-hydroxy-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137e**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 3-[(2-bromocyclopent-1-en-1-yl)methoxy]phenol (**128e**) (269 mg, 1 mmol)

in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137e** was obtained as a white solid (143 mg, 0.71 mmol, 71%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 234 − 236 °C.

R_f = 0.14 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3163 (OH), 2922, 1689 (C═O), 1618, 1556, 1131, 710.

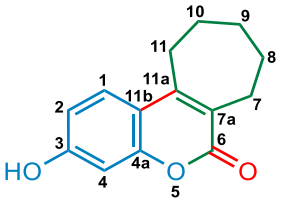
^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 10.43 (s, 1H, OH), 7.37 (d, J = 8.4 Hz, 1H, 1-H), 6.76 (dd, J = 8.3, 2.3 Hz, 1H, 2-H), 6.71 (d, J = 2.3 Hz, 1H, 4-H), 2.97 (tt-like, J = 7.1, 1.6 Hz, 2H, 9-H$_2$), 2.68 (tt-like, J = 7.2, 1.3 Hz, 2H, 7-H$_2$), 2.05 (quint, J = 7.5 Hz, 2H, 8-H$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ [ppm] = 160.5 (C-6), 159.4 (C-3), 156.7 (C-4a), 155.3 (C-9a), 126.5 (C-1), 122.4 (C-7a), 112.8 (C-9b), 110.7 (C-2), 102.1 (C-4), 31.6 (C-7), 29.9 (C-8), 22.0 (C-9).

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for [$C_{12}H_{11}O_3$]$^+$ 273.0703; found 273.0705.

Molecular weight: $C_{12}H_{10}O_3$ (202.2090 g × mol^{-1}).

3.3.7 3-Hydroxy-7,8,9,10,11-pentahydro-6*H*-benzo[*b*]cyclohepta[*d*]pyran-6-one (137f)[89]



Following general procedure VI, 3-hydroxy-7,8,9,10,11-pentahydro-6*H*-benzo[*b*]cyclohepta[*d*]pyran-6-one (**137f**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 3-[(2-bromocyclohept-1-en-1-yl)methoxy]phenol (**128f**) (297 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137f** was obtained as a white solid (158 mg, 0.69 mmol, 69%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 219 − 221 °C.

R_f = 0.15 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3199 (OH), 2921, 1672 (C═O), 1611, 1365, 832.

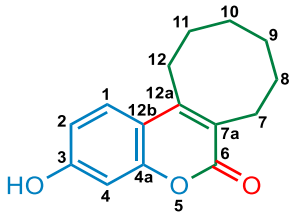
^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 7.62 (d, J = 8.9 Hz, 1H, 1-H), 6.70 (dd, J = 8.7, 2.3 Hz, 1H, 2-H), 6.58 (d, J = 2.4 Hz, 1H, 4-H), 4.02 (br s, 1H, OH), 2.89 (dd-like, J = 11.2, 5.6 Hz, 2H, 11-H$_2$), 2.73 (dd-like, J = 11.8, 5.9 Hz, 2H, 7-H$_2$), 1.80 (quint-like, J = 6.1 Hz, 2H, 10-H$_2$), 1.56 (quint-like, J = 5.9 Hz, 2H, 9-H$_2$), 1.46 (quint-like, J = 6.2 Hz, 2H, 8-H$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ [ppm] = 163.1 (C-6), 161.6 (C-3), 154.7 (C-4a), 154.2 (C-11a), 125.8 (C-1), 121.9 (C-7a), 113.8 (C-11b), 110.4 (C-2), 102.4 (C-4), 31.6 (C-11), 27.4 (C-7), 25.9 (C-10), 25.8 (C-8), 25.0 (C-9).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{14}H_{15}O_3]^+$ 231.1016; found 231.1016.

Molecular weight: $C_{14}H_{14}O_3$ (230.2630 g × mol^{-1}).

3.3.8 3-Hydroxy-7,8,9,10,11,12-hexahydro-6*H*-benzo[*b*]cycloocta[*d*]pyran-6-one (137g)[89]



Following general procedure VI, 3-hydroxy-7,8,9,10,11,12-hexahydro-6*H*-benzo[*b*]cycloocta[*d*]pyran-6-one (**137g**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 3-[(2-bromocyclooct-1-en-1-yl)methoxy]phenol (**128g**) (311 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137g** was obtained as a white solid (176 mg, 0.72 mmol, 72%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 211 − 213 °C.

R_f = 0.16 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3199 (OH), 2926, 1673 (C═O), 1610, 1320, 775.

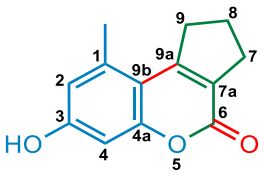
^{1}H NMR (600 MHz, DMSO-d_6): δ [ppm] = 10.37 (s, 1H, OH), 7.61 (d, J = 8.8 Hz, 1H, 1-H), 6.77 (dd, J = 8.6, 2.4 Hz, 1H, 2-H), 6.68 (d, J = 2.4 Hz, 1H, 4-H), 2.93 (dd-like, J = 11.2, 5.4 Hz, 2H, 12-H_2), 2.65 (dd-like, J = 11.9, 5.9 Hz, 2H, 7-H_2), 1.69 (quint-like, J = 6.4 Hz, 2H, 11-H_2), 1.56 (quint-like, J = 5.9 Hz, 2H, 8-H_2), 1.43 (quint-like, J = 5.5 Hz, 2H, 9-H_2), 1.32 (quint-like, J = 5.6 Hz, 2H, 10-H_2).

^{13}C NMR (150 MHz, DMSO-d_6): δ [ppm] = 160.8 (C-6), 160.1 (C-3), 153.9 (C-4a), 150.9 (C-12a), 126.1 (C-1), 121.6 (C-7a), 112.9 (C-12b), 111.2 (C-2), 102.2 (C-4), 29.5 (C-12), 29.0 (C-7), 26.5 (C-8), 25.8 (C-11), 25.4 (C-10), 25.3 (C-9).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{15}H_{17}O_3]^+$ 245.1172; found 245.1172.

Molecular weight: $C_{15}H_{16}O_3$ (244.2900 g × mol^{-1}).

3.3.9 3-Hydroxy-1-methyl-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (137h)



Following general procedure VI, 3-hydroxy-1-methyl-7,8,9-trihydro-6*H*-benzo[*b*]cyclopenta[*d*]pyran-6-one (**137h**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 3-[(2-bromocyclopent-1-en-1-yl)methoxy]-5-methylphenol (**128h**) (283 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137h** was obtained as a white solid (155 mg, 0.72 mmol, 72%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 227 − 229 °C.

R_f = 0.12 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3275 (OH), 2922, 1681 (C═O), 1606, 1280, 876, 657.

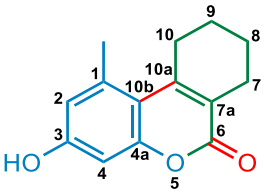
^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 10.39 (s, 1H, OH), 6.64 (s, 1H, 2-H), 6.54 (s, 1H, 4-H), 3.26 (tt-like, J = 7.4, 2.1 Hz, 2H, 9-H_2), 2.64 (tt-like, J = 7.6, 2.1 Hz, 2H, 7-H_2), 2.28 (s, 3H, 1-CH_3), 2.02 (quint, J = 7.7 Hz, 2H, 8-H_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ [ppm] = 159.2 (C-6), 155.8 (C-3), 155.1 (C-4a), 155.0 (C-9a), 141.9 (C-1), 123.5 (C-7a), 111.1 (C-9b), 107.4 (C-2), 105.8 (C-4), 35.7 (C-9), 29.2 (C-7), 22.2 (C-8), 21.4 (1-CH_3).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{13}H_{13}O_3]^+$ 217.0859; found 217.0857.

Molecular weight: $C_{13}H_{12}O_3$ (216.2360 g × mol^{-1}).

3.3.10 3-Hydroxy-1-methyl-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (137i)



Following general procedure VI, 3-hydroxy-1-methyl-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137i**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 3-[(2-bromocyclohex-1-en-1-yl)methoxy]-5-methylphenol (**128i**) (297 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137i** was obtained as a white solid (179 mg, 0.78 mmol, 78%)

after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 223 − 225 °C.

***R*f** = 0.12 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3217 (OH), 2929, 1654 (C═O), 1600, 1258, 1094, 735.

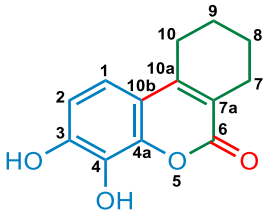
^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 10.37 (s, 1H, OH), 6.58 (d, J = 1.3 Hz, 1H, 2-H), 6.55 (d, J = 1.6 Hz, 1H, 4-H), 3.07 (tt-like, J = 5.7, 1.9 Hz, 2H, 10-H$_2$), 2.37 (tt-like, J = 5.6, 2.2 Hz, 2H, 7-H$_2$), 2.25 (s, 3H, 1-CH$_3$), 1.68−1.63 (m, overlapped, 4H, 8-H$_2$ and 9-H$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ [ppm] = 160.6 (C-6), 155.9 (C-3), 153.1 (C-4a), 149.6 (C-10a), 140.9 (C-1), 119.2 (C-7a), 112.1 (C-10b), 107.5 (C-2), 106.6 (C-4), 29.3 (C-7), 24.2 (C-10), 21.7 (C-8), 20.9 (C-9), 20.7 (1-CH$_3$).

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for [C$_{14}$H$_{15}$O$_3$]$^+$ 231.1016; found 231.1019.

Molecular weight: C$_{14}$H$_{14}$O$_3$ (230.2630 g × mol^{-1}).

3.3.11 3,4-Dihydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (137j)[90]



Following general procedure VI, 3,4-dihydroxy-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137j**) was synthesized by reacting RuCl$_2$(PPh$_3$)$_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 3-[(2-bromocyclohex-1-en-1-yl)methoxy]benzene-1,2-diol (**128j**) (299 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137j** was obtained as a yellow solid (155 mg, 0.67 mmol, 67%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 244 − 246 °C.

***R*f** = 0.22 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3462 (OH), 2926, 1672 (C═O), 1579, 1311, 1094, 758.

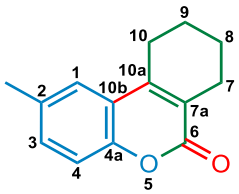
^{1}H NMR (500 MHz, DMSO-d_6): δ [ppm] = 9.55 (br s, 2H, 2 × OH), 7.01 (d, J = 8.7 Hz, 1H, 1-H), 6.78 (d, J = 8.5 Hz, 1H, 2-H), 2.71 (t-like, J = 6.2 Hz, 2H, 10-H$_2$), 2.39 (t-like, J = 5.4 Hz, 2H, 7-H$_2$), 1.76−1.67 (m, overlapped, 4H, 8-H$_2$ and 9-H$_2$).

^{13}C NMR (125 MHz, DMSO-d_6): δ [ppm] = 160.9 (C-6), 148.1 (C-3 and C-4a), 141.8 (C-10a), 131.9 (C-4), 123.8 (C-1), 118.3 (C-7a), 112.7 (C-10b), 112.0 (C-2), 24.7 (C-7), 23.6 (C-10), 21.3 (C-8), 20.9 (C-9).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{13}H_{13}O_4]^+$ 233.0808; found 233.0806.

Molecular weight: $C_{13}H_{12}O_4$ (232.2350 g × mol^{-1}).

3.3.12 2-Methyl-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (137k)[48]



Following general procedure VI, 2-methyl-7,8,9,10-tetrahydro-6*H*-benzo[*b*]cyclohexa[*d*]pyran-6-one (**137k**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 1-[(2-bromocyclohex-1-en-1-yl)methoxy]-4-mathylbenzene (**128k**) (282 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **137k** was obtained as a white solid (133 mg, 0.62 mmol, 62%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 20:1).

M.p.: 104 − 106 °C.

***R*$_f$** = 0.18 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 1705 (C═O), 1576, 1214, 1031, 813.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.34 (br s, 1H, 1-H), 7.25 (dd, *J* = 8.3, 1.9 Hz, 1H, 3-H), 7.20 (d, *J* = 8.3 Hz, 1H, 4-H), 2.78 (tt-like, *J* = 6.2, 2.3 Hz, 2H, 10-H_2), 2.59 (tt-like, *J* = 6.1, 2.2 Hz, 2H, 7-H_2), 2.41 (s, 3H, 2-CH_3), 1.88−1.78 (m, overlapped, 4H, 8-H_2 and 9-H_2).

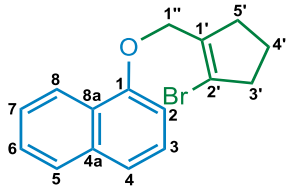
^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 161.9 (C-6), 150.1 (C-4a), 146.9 (C-10a), 133.5 (C-2), 131.2 (C-3), 123.6 (C-1), 123.1 (C-4), 119.9 (C-7a), 116.5 (C-10b), 25.2 (C-7), 24.1 (C-10), 21.6 (C-8), 21.4 (C-9), 21.1 (2-CH_3).

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{14}H_{14}O_2]^+$ 214.0994; found 214.0993.

Molecular weight: $C_{14}H_{14}O_2$ (214.2640 g × mol^{-1}).

3.4 Synthesis of 2-bromo-1-(naphthalenoxymethyl)cycloalk-1-enes 129a–h

3.4.1 1-[(2'-Bromocyclopent-1'-en-1'-yl)methoxy]naphthalene (129a)



Following general procedure V, 1-[(2'-bromocyclopent-1'-en-1'-yl)methoxy]naphthalene (**129a**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 1-naphthol (**52a**) (577 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclopent-1-ene (**125b**) (662 mg, 2 mmol) in acetone (30 mL). Analytically pure **129a** was obtained as a colorless liquid (491 mg, 1.62 mmol, 81%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 12:1).

***R*f** = 0.61 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2915, 1578, 1399, 1266, 1095, 768.

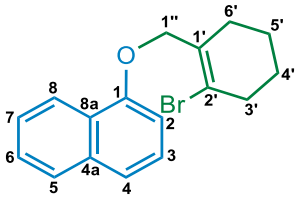
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.27 (dd, J = 7.4, 1.9 Hz, 1H, 5-H), 7.80 (dd, J = 7.9, 1.6 Hz, 1H, 4-H), 7.49 (ddd, J = 9.7, 6.8, 1.4 Hz, 2H, 6-H and 7-H), 7.44 (d, J = 8.2 Hz, 1H, 8-H), 7.38 (t, J = 7.7 Hz, 1H, 3-H), 6.87 (d, J = 7.5 Hz, 1H, 2-H), 4.86 (s, 2H, 1''-H_2), 2.76–2.73 (m, 2H, 5'-H_2), 2.58 (tt-like, J = 7.4, 2.5 Hz, 2H, 3'-H_2), 2.01 (quint, J = 7.4 Hz, 2H, 4'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 154.1 (C-1), 137.0 (C-4a), 134.5 (C-2'), 127.5 (C-4), 126.4 (C-5), 125.9 (C-1'), 125.7 (C-6), 125.2 (C-7), 122.0 (C-3), 120.4 (C-8a), 119.1 (C-8), 104.9 (C-2), 65.9 (C-1''), 40.3 (C-3'), 32.6 (C-5'), 21.6 (C-4').

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{16}H_{16}BrO]^+$ 303.0379; found 303.0378.

Molecular weight: $C_{16}H_{15}BrO$ (303.1990 g × mol^{-1}).

3.4.2 1-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]naphthalene (129b)



Following general procedure V, 1-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]naphthalene (**129b**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 1-naphthol (**52a**) (577 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **129b** was obtained as a

colorless liquid (565 mg, 1.78 mmol, 89%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 12:1).

***R*f** = 0.68 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931, 1578, 1400, 1265, 1238, 1092, 767.

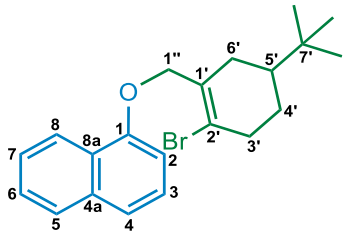
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 8.28 (dd, *J* = 7.1, 2.1 Hz, 1H, 5-H), 7.81 (dd, *J* = 6.9, 1.9 Hz, 1H, 4-H), 7.49 (ddd, *J* = 8.9, 6.1, 1.7 Hz, 2H, 6-H and 7-H), 7.44 (d, *J* = 8.1 Hz, 1H, 8-H), 7.39 (t, *J* = 7.6 Hz, 1H, 3-H), 6.86 (d, *J* = 7.2 Hz, 1H, 2-H), 4.89 (s, 2H, 1''-H_2), 2.61−2.58 (m, 2H, 6'-H_2), 2.38−2.34 (m, 2H, 3'-H_2), 1.77−1.69 (m, overlapped, 4H, 4'-H_2 and 5'-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 154.1 (C-1), 134.5 (C-4a), 132.4 (C-2'), 127.5 (C-4), 126.3 (C-5), 125.9 (C-1'), 125.6 (C-6), 125.1 (C-7), 122.0 (C-3), 121.6 (C-8a), 120.3 (C-8), 105.0 (C-2), 71.1 (C-1''), 36.7 (C-3'), 28.3 (C-6'), 24.6 (C-4'), 22.0 (C-5').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{17}H_{17}BrONa]^+$ 339.0355; found 339.0356.

Molecular weight: $C_{17}H_{17}BrO$ (317.2260 g × mol^{-1}).

3.4.3 1-[(2'-Bromo-5'-(*tert*-butyl)cyclohex-1'-en-1'-yl)methoxy]naphthalene (129c)



Following general procedure V, 1-[(2'-bromo-5'-(*tert*-butyl)cyclohex-1'-en-1'-yl)methoxy]naphthalene (**129c**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 1-naphthol (**52a**) (577 mg, 4 mmol) and 2-bromo-5-*tert*-butyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125d**) (803 mg, 2 mmol) in acetone (30 mL). Analytically pure **129c** was obtained as a colorless liquid (687 mg, 1.84 mmol, 92%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 12:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2959, 1578, 1401, 1266, 1238, 905, 769.

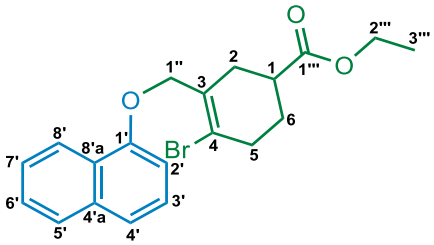
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 8.31 (dd, *J* = 6.9, 2.1 Hz, 1H, 5-H), 7.83 (dd, *J* = 6.9, 2.8 Hz, 1H, 4-H), 7.49 (ddd, *J* = 8.3, 6.1, 1.9 Hz, 2H, 6-H and 7-H), 7.47 (d, *J* = 8.1 Hz, 1H, 8-H), 7.42 (t, *J* = 7.6 Hz, 1H, 3-H), 6.91 (d, *J* = 7.5 Hz, 1H, 2-H), 4.92 (d, *J* = 11.6 Hz, 1H, 1''-Ha), 4.87 (d, *J* = 11.7 Hz, 1H, 1''-Hb), 2.67−2.63 (m, 2H, 3'-H_2), 2.51 (dd, *J* = 15.9, 4.2 Hz, 1H, 6'-Ha), 2.14−2.07 (m, 1H, 6'-Hb), 1.88−1.84 (m, 1H, 5'-H), 1.46−1.41 (m, 2H, 4'-H_2), 0.91 (s, 9H, 3 × CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 154.3 (C-1), 134.5 (C-4a), 132.3 (C-2'), 127.5 (C-4), 126.3 (C-5), 125.9 (C-1'), 125.7 (C-6), 125.2 (C-7), 121.9 (C-3), 121.6 (C-8a), 120.4 (C-8), 105.2 (C-2), 71.5 (C-1''), 43.6 (C-5'), 37.8 (C-3'), 32.2 (C-7'), 30.1 (C-6'), 27.2 (3 × CH_3), 25.9 (C-4').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{21}H_{25}BrONa]^+$ 395.0981; found 395.0982.

Molecular weight: $C_{21}H_{25}BrO$ (373.3340 g × mol^{-1}).

3.4.4 Ethyl 4-bromocyclohex-3-[(naphthalen-1'-yloxy)methyl]-3-ene-1-carboxylate (129d)



Following general procedure V, ethyl 4-bromocyclohex-3-[(naphthalen-1'-yloxy)methyl]-3-ene-1-carboxylate (**129d**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 1-naphthol (**52a**) (577 mg, 4 mmol) and ethyl 4-bromo-3-(4'-methylbenzenesulfonatemethyl)cyclohex-3-ene-1-carboxylate (**125e**) (835 mg, 2 mmol) in acetone (30 mL). Analytically pure **129d** was obtained as a colorless liquid (615 mg, 1.58 mmol, 79%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 12:1).

R_f = 0.68 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2933, 1727, 1578, 1399, 1174, 1094, 769.

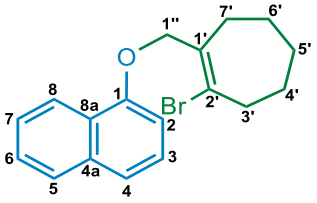
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.27 (dd, *J* = 7.3, 1.9 Hz, 1H, 5'-H), 7.81 (dd, *J* = 6.8, 1.9 Hz, 1H, 4'-H), 7.49 (ddd, *J* = 9.4, 6.9, 1.6 Hz, 2H, 6'-H and 7'-H), 7.44 (d, *J* = 8.2 Hz, 1H, 8'-H), 7.38 (t, *J* = 7.6 Hz, 1H, 3'-H), 6.85 (d, *J* = 7.5 Hz, 1H, 2'-H), 4.90 (s, 2H, 1''-H_2), 4.13 (q, *J* = 7.1 Hz, 2H, 2'''-H_2), 2.71−2.66 (m, 4H, 2-H_2 and 5-H_2), 2.61−2.56 (m, 1H, 1-H), 2.08−2.03 (m, 1H, 6-Ha), 1.95−1.89 (m, 1H, 6-Hb), 1.23 (t, *J* = 7.1 Hz, 3H, 3'''-H_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 174.5 (C-1'''), 154.1 (C-1'), 134.5 (C-4'a), 130.9 (C-4), 127.5 (C-4'), 126.4 (C-5'), 125.9 (C-3), 125.6 (C-6'), 125.3 (C-7'), 122.0 (C-3'), 120.7 (C-8'a), 120.5 (C-8'), 105.0 (C-2'), 70.9 (C-1''), 60.6 (C-2'''), 38.8 (C-1), 35.6 (C-5), 30.4 (C-2), 26.8 (C-6), 14.2 (C-3''').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{20}H_{21}BrO_3Na]^+$ 411.0566; found 411.0564.

Molecular weight: $C_{20}H_{21}BrO_3$ (389.2890 g × mol^{-1}).

3.4.5 1-[(2'-Bromocyclohept-1'-en-1'-yl)methoxy]naphthalene (129e)



Following general procedure V, 1-[(2'-bromocyclohept-1'-en-1'-yl)methoxy]naphthalene (**129e**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 1-naphthol (**52a**) (577 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohept-1-ene (**125f**) (718 mg, 2 mmol) in acetone (30 mL). Analytically pure **129e** was obtained as a colorless liquid (549 mg, 1.66 mmol, 83%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 12:1).

R_f = 0.65 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2920, 1579, 1400, 1267, 1094, 767.

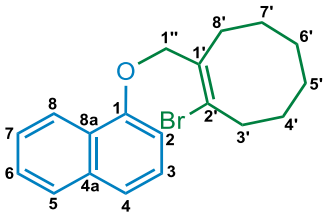
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.27 (dd, J = 7.5, 1.6 Hz, 1H, 5-H), 7.80 (dd, J = 7.3, 1.6 Hz, 1H, 4-H), 7.48 (ddd, J = 9.1, 6.8, 1.5 Hz, 2H, 6-H and 7-H), 7.44 (d, J = 8.2 Hz, 1H, 8-H), 7.38 (t, J = 7.7 Hz, 1H, 3-H), 6.85 (d, J = 7.4 Hz, 1H, 2-H), 4.87 (s, 2H, 1''-H_2), 2.85 (dd-like, J = 10.9, 5.3 Hz, 2H, 3'-H_2), 2.46 (dd-like, J = 10.8, 5.4 Hz, 2H, 7'-H_2), 1.77 (quint-like, J = 6.1 Hz, 2H, 4'-H_2), 1.63 (quint-like, J = 5.4 Hz, 2H, 5'-H_2), 1.53 (quint-like, J = 5.4 Hz, 2H, 6'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 154.2 (C-1), 137.8 (C-4a), 134.5 (C-2'), 127.5 (C-4), 126.3 (C-5), 125.9 (C-1'), 125.7 (C-6), 125.4 (C-7), 125.1 (C-3), 122.0 (C-8a), 120.3 (C-8), 105.2 (C-2), 72.5 (C-1''), 41.6 (C-3'), 31.5 (C-7'), 30.2 (C-4'), 25.6 (C-5'), 25.3 (C-6').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{18}H_{19}BrONa]^+$ 353.0511; found 353.0512.

Molecular weight: $C_{18}H_{19}BrO$ (331.2530 g × mol^{-1}).

3.4.6 1-[(2'-Bromocyclooct-1'-en-1'-yl)methoxy]naphthalene (129f)



Following general procedure V, 1-[(2'-bromocyclooct-1'-en-1'-yl)methoxy]naphthalene (**129f**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 1-naphthol (**52a**) (577 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclooct-1-ene (**125g**)

(747 mg, 2 mmol) in acetone (30 mL). Analytically pure **129f** was obtained as a colorless liquid (511 mg, 1.48 mmol, 74%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 12:1).

R_f = 0.65 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2921, 1579, 1400, 1268, 1093, 767.

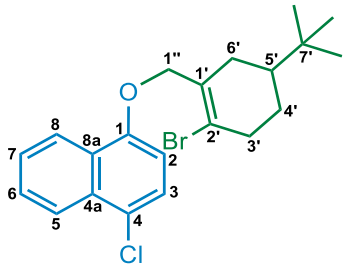
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.27 (dd, J = 7.6, 1.4 Hz, 1H, 5-H), 7.80 (dd, J = 7.2, 1.6 Hz, 1H, 4-H), 7.48 (ddd, J = 9.2, 6.8, 1.6 Hz, 2H, 6-H and 7-H), 7.43 (d, J = 8.2 Hz, 1H, 8-H), 7.38 (t, J = 7.7 Hz, 1H, 3-H), 6.87 (d, J = 7.5 Hz, 1H, 2-H), 4.89 (s, 2H, 1''-H_2), 2.78 (dd-like, J = 12.9, 5.7 Hz, 2H, 3'-H_2), 2.51 (dd-like, J = 12.3, 6.5 Hz, 2H, 8'-H_2), 1.73−1.64 (m, overlapped, 4H, 4'-H_2 and 7'-H_2), 1.46−1.53 (m, overlapped, 4H, 5'-H_2 and 6'-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 154.3 (C-1), 134.9 (C-4a), 134.5 (C-2'), 127.5 (C-4), 126.3 (C-5), 125.9 (C-1'), 125.7 (C-6), 125.2 (C-7), 124.3 (C-3), 122.1 (C-8a), 120.3 (C-8), 105.1 (C-2), 71.0 (C-1''), 37.5 (C-3'), 29.7 (C-8'), 29.5 (C-7'), 28.1 (C-4'), 26.6 (C-5'), 25.8 (C-6').

HRMS (ESI): *m/z* $[M - H]^+$ calcd. for $[C_{19}H_{20}BrO]^+$ 343.0703; found 343.0722.

Molecular weight: $C_{19}H_{21}BrO$ (345.2800 g × mol^{-1}).

3.4.7 1-[(2'-Bromo-5'-(*tert*-butyl)cyclohex-1'-en-1'-yl)methoxy]-4-chloronaphthalene (129g)



Following general procedure V, 1-[(2'-bromo-5'-(*tert*-butyl)cyclohex-1'-en-1'-yl)methoxy]-4-chloronaphthalene (**129g**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 4-chloro-1-naphthol (**52b**) (714 mg, 4 mmol) and 2-bromo-5-*tert*-butyl-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125d**) (803 mg, 2 mmol) in acetone (30 mL). Analytically pure **129g** was obtained as a pale yellow liquid (628 mg, 1.54 mmol, 77%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 12:1).

R_f = 0.67 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2957, 1589, 1365, 1261, 1075, 759.

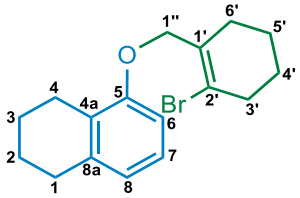
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.29 (d, J = 8.4 Hz, 1H, 5-H), 8.21 (d, J = 8.3 Hz, 1H, 8-H), 7.62 (t, J = 7.9 Hz, 1H, 7-H), 7.54 (t, J = 7.1 Hz, 1H, 6-H), 7.46 (d, J = 8.2 Hz, 1H, 3-H), 6.79 (d, J = 8.2 Hz, 1H, 2-H), 4.87 (d, J = 11.6 Hz, 1H, 1''-Ha), 4.83 (d, J = 11.7 Hz, 1H, 1''-Hb), 2.64−2.61 (m, 2H, 3'-H_2), 2.44 (dd, J = 15.6, 4.2 Hz, 1H, 6'-Ha), 2.06−2.01 (m, 1H, 6'-Hb), 1.86−1.82 (m, 1H, 5'-H), 1.42−1.39 (m, 2H, 4'-H_2), 0.87 (s, 9H, 3 × CH_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 153.4 (C-1), 131.9 (C-4a), 131.4 (C-2'), 127.4 (C-4), 126.8 (C-5), 125.9 (C-1'), 125.8 (C-6), 124.3 (C-7), 123.4 (C-3), 122.4 (C-8a), 122.0 (C-8), 105.4 (C-2), 71.7 (C-1''), 43.6 (C-5'), 37.8 (C-3'), 32.2 (C-7'), 30.1 (C-6'), 27.2 (3 × CH_3), 25.9 (C-4').

HRMS (EI): *m/z* $[M]^+$ calcd. for $[C_{21}H_{24}BrClO]^+$ 408.0673; found 408.0673.

Molecular weight: $C_{21}H_{24}BrClO$ (407.7760 g × mol^{-1}).

3.4.8 5-[(2'-Bromocyclohex-1'-en-1'-yl)methoxy]-1,2,3,4-tetrahydronaphthalene (129h)



Following general procedure V, 5-[(2'-bromocyclohex-1'-en-1'-yl)methoxy]-1,2,3,4-tetrahydronaphthalene (**129h**) was synthesized by reacting K_2CO_3 (829 mg, 6 mmol), NaI (150 mg, 1 mmol), 5,6,7,8-tetrahydro-1-naphthol (**52c**) (593 mg, 4 mmol) and 2-bromo-1-(4'-methylbenzenesulfonatemethyl)cyclohex-1-ene (**125a**) (690 mg, 2 mmol) in acetone (30 mL). Analytically pure **129h** was obtained as a colorless liquid (507 mg, 1.58 mmol, 79%) after subjecting the crude product to column chromatography over silica gel (cyclohexane/ethyl acetate = 12:1).

R_f = 0.66 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 1582, 1456, 1247, 1080, 762.

^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 7.06 (t, J = 7.7 Hz, 1H, 7-H), 6.71 (d, J = 7.6 Hz, 1H, 8-H), 6.66 (d, J = 8.1 Hz, 1H, 6-H), 4.68 (s, 2H, 1''-H_2), 2.76 (t, J = 6.1 Hz, 2H, 1-H_2), 2.67 (t, J = 5.9 Hz, 2H, 4-H_2), 2.57−2.53 (m, 2H, 3'-H_2), 2.26 (tt-like, J = 6.1, 2.1 Hz, 2H, 6'-H_2), 1.81−1.75 (m, overlapped, 4H, 3-H_2 and 4'-H_2), 1.74−1.67 (m, overlapped, 4H, 2-H_2 and 5'-H_2).

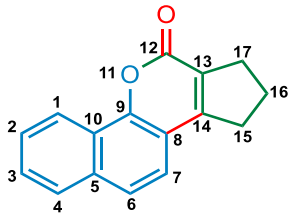
^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 156.2 (C-5), 138.5 (C-8a), 132.8 (C-2'), 126.1 (C-7), 125.7 (C-1'), 121.5 (C-8), 120.9 (C-4a), 107.9 (C-6), 70.8 (C-1''), 36.7 (C-3'), 29.6 (C-6'), 28.2 (C-1), 24.6 (C-4'), 23.2 (C-4), 22.8 (C-2 and C-3), 22.0 (C-5').

HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $[C_{17}H_{21}BrONa]^+$ 343.0668; found 343.0652.

Molecular weight: $C_{17}H_{21}BrO$ (321.2580 g × mol^{-1}).

3.5 Synthesis of annulated naphthopyranones 138a–h

3.5.1 7,8,9-Trihydro-6*H*-cyclopenta[*d*]naphtho[1,2-*b*]pyran-6-one (138a)[32c]



Following general procedure VI, 7,8,9-trihydro-6*H*-cyclopenta[*d*]naphtho[1,2-*b*]pyran-6-one (**138a**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 1-[(2-bromocyclopent-1-en-1-yl)methoxy]naphthalene (**129a**) (303 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **138a** was obtained as a yellow solid (187 mg, 0.79 mmol, 79%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 28:1).

M.p.: 218 − 220 °C.

$\boldsymbol{R_f}$ = 0.41 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2909, 1713, 1367, 1072, 807, 764.

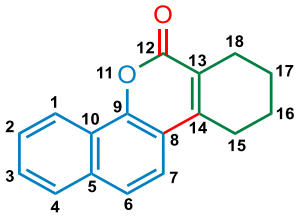
^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 8.54 (ddd, J = 7.2, 2.2, 0.8 Hz, 1H, 1-H), 7.83 (ddd, J = 7.1, 2.9, 0.9 Hz, 1H, 4-H), 7.64 (d, J = 8.5 Hz, 1H, 7-H), 7.60 (ddd, J = 7.6, 5.1, 2.6 Hz, 2H, 2-H and 3-H), 7.39 (d, J = 8.5 Hz, 1H, 6-H), 3.11 (tt, J = 7.1, 1.9 Hz, 2H, 15-H_2), 2.95 (tt, J = 7.5, 1.8 Hz, 2H, 17-H_2), 2.22 (quint, J = 7.5 Hz, 2H, 16-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 160.1 (C-12), 157.0 (C-9), 150.8 (C-14), 134.3 (C-5), 128.0 (C-7), 127.7 (C-4), 127.2 (C-6), 126.9 (C-10), 124.1 (C-3), 123.1 (C-2), 122.5 (C-1), 120.9 (C-13), 113.9 (C-8), 32.3 (C-17), 30.5 (C-15), 22.5 (C-16).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{16}H_{13}O_2]^+$ 237.0910; found 237.0911.

Molecular weight: $C_{16}H_{12}O_2$ (236.2700 g × mol^{-1}).

3.5.2 7,8,9,10-Tetrahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (138b)[32c]



Following general procedure VI, 7,8,9,10-tetrahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (**138b**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 1-[(2-bromocyclohex-1-en-1-yl)methoxy]naphthalene (**129b**) (317 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **138b** was obtained as a white solid (220 mg, 0.88 mmol, 88%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 28:1).

M.p.: 189 − 191 °C.

R_f = 0.49 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2935, 1697, 1367, 1042, 799, 756.

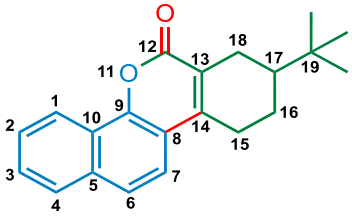
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.53 (dd, J = 7.2, 2.1 Hz, 1H, 1-H), 7.82 (dd, J = 6.8, 2.2 Hz, 1H, 4-H), 7.63 (d, J = 8.7 Hz, 1H, 7-H), 7.59 (ddd, J = 7.6, 6.2, 2.7 Hz, 2H, 2-H and 3-H), 7.53 (d, J = 8.8 Hz, 1H, 6-H), 2.84 (tt, J = 6.2, 1.8 Hz, 2H, 15-H_2), 2.63 (tt, J = 6.2, 1.9 Hz, 2H, 18-H_2), 1.91−1.87 (m, 2H, 16-H_2), 1.85−1.81 (m, 2H, 17-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 161.7 (C-12), 148.4 (C-9), 147.9 (C-14), 133.9 (C-5), 127.9 (C-7), 127.5 (C-4), 126.8 (C-6), 123.8 (C-10), 123.2 (C-3), 123.1 (C-2), 122.3 (C-1), 119.5 (C-13), 115.3 (C-8), 25.7 (C-18), 24.1 (C-15), 21.5 (C-17), 21.4 (C-16).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{17}H_{15}O_2]^+$ 251.1067; found 251.1067.

Molecular weight: $C_{17}H_{14}O_2$ (250.2970 g × mol^{-1}).

3.5.3 8-(*tert*-Butyl)-7,8,9,10-tetrahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (138c)



Following general procedure VI, 8-(*tert*-butyl)-7,8,9,10-tetrahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (**138c**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 1-[(2-bromo-5-(*tert*-butyl)cyclohex-1-en-1-yl)methoxy]naphthalene (**129c**) (373 mg, 1 mmol) in DMA (2 mL), followed by addition

of DTBP (0.7 mL, 4 mmol). Analytically pure **138c** was obtained as a white solid (274 mg, 0.9 mmol, 90%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 28:1).

M.p.: 243 − 245 °C.

R_f = 0.43 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2950, 1703, 1365, 1077, 802, 760.

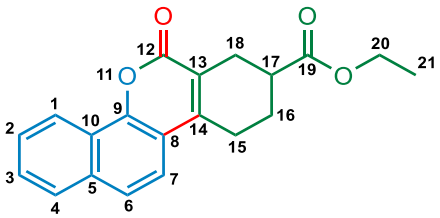
^{1}H NMR (600 MHz, CD_2Cl_2): δ [ppm] = 8.48 (dd, J = 7.3, 1.9 Hz, 1H, 1-H), 7.86 (dd, J = 6.4, 1.9 Hz, 1H, 4-H), 7.68 (d, J = 8.7 Hz, 1H, 7-H), 7.61 (ddd, J = 10.2, 6.9, 1.8 Hz, 2H, 2-H and 3-H), 7.57 (d, J = 8.7 Hz, 1H, 6-H), 3.08 (dd-like, J = 18.3, 4.9 Hz, 1H, 18-Ha), 2.79−2.75 (m, 1H, 18-Hb), 2.74−2.68 (m, 1H, 16-Ha), 2.23−2.13 (m, 2H, 15-H_2), 1.42 (tdd, J = 12.1, 4.8, 2.1 Hz, 1H, 17-H), 1.33 (qd, J = 12.5, 4.9 Hz, 1H, 16-Hb), 1.01 (s, 9H, 3 × CH_3).

^{13}C NMR (150 MHz, CD_2Cl_2): δ [ppm] = 161.6 (C-12), 148.4 (C-9), 147.8 (C-14), 134.0 (C-5), 127.9 (C-7), 127.7 (C-4), 126.9 (C-6), 123.7 (C-10), 123.6 (C-3), 123.1 (C-2), 122.0 (C-1), 120.0 (C-13), 115.3 (C-8), 43.5 (C-17), 32.3 (C-18), 27.2 (C-19), 27.0 (3 × CH_3), 25.9 (C-15), 22.9 (C-16).

HRMS (ESI): *m/z* [M + H]$^+$ calcd. for [$C_{21}H_{23}O_2$]$^+$ 307.1693; found 307.1695.

Molecular weight: $C_{21}H_{22}O_2$ (306.4050 g × mol^{-1}).

3.5.4 Ethyl 6-oxo-7,8,9,10-tetrahydro-6*H*-cyclohexa-[*d*]naphtho[1,2-*b*]pyran-8-carboxylate (138d)



Following general procedure VI, ethyl 6-oxo-7,8,9,10-tetrahydro-6*H*-cyclohexa-[*d*]naphtho[1,2-*b*]pyran-8-carboxylate (**138d**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and ethyl 4-bromo-3-[(naphthalen-1-yloxy)methyl]cyclohex-3-ene-1-carboxylate (**129d**) (389 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **138d** was obtained as a pale yellow solid (251 mg, 0.78 mmol, 78%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 28:1).

M.p.: 227 − 229 °C.

R_f = 0.48 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2919, 1730, 1698, 1223, 1077, 800, 757.

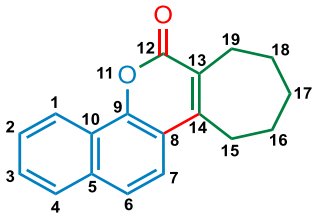
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.54 (dd, J = 7.2, 2.5 Hz, 1H, 1-H), 7.84 (dd, J = 6.8, 2.7 Hz, 1H, 4-H), 7.67 (d, J = 8.7 Hz, 1H, 7-H), 7.61 (ddd, J = 7.1, 6.9, 2.3 Hz, 2H, 2-H and 3-H), 7.54 (d, J = 8.6 Hz, 1H, 6-H), 4.19 (q, J = 7.1 Hz, 2H, 20-H_2), 3.05 (dt, J = 18.1, 4.9 Hz, 1H, 18-Ha), 3.03 (dd, J = 18.0, 3.8 Hz, 1H, 18-Hb), 2.88−2.82 (m, 1H, 17-H), 2.81−2.72 (m, 2H, 15-H_2), 2.32−2.28 (m, 1H, 16-Ha), 1.96−1.93 (m, 1H, 16-Hb), 1.29 (t, J = 7.1 Hz, 3H, 21-H_3).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 174.4 (C-19), 161.2 (C-12), 148.6 (C-9), 147.2 (C-14), 134.1 (C-5), 128.1 (C-7), 127.6 (C-4), 127.0 (C-6), 124.1 (C-10), 123.1 (C-3), 122.3 (C-2), 121.4 (C-1), 119.5 (C-13), 114.8 (C-8), 60.8 (C-20), 38.4 (C-17), 26.4 (C-18), 24.9 (C-19), 23.8 (C-15), 14.2 (C-21).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{20}H_{19}O_4]^+$ 323.1278; found 323.1279.

Molecular weight: $C_{20}H_{18}O_4$ (322.3600 g × mol^{-1}).

3.5.5 7,8,9,10,11-Pentahydro-6*H*-cyclohepta[*d*]naphtho[1,2-*b*]pyran-6-one (138e)



Following general procedure VI, 7,8,9,10,11-pentahydro-6*H*-cyclohepta[*d*]naphtho[1,2-*b*]pyran-6-one (**138e**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 1-[(2-bromocyclohept-1-en-1-yl)methoxy]naphthalene (**129e**) (331 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **138e** was obtained as a white solid (216 mg, 0.82 mmol, 82%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 28:1).

M.p.: 209 − 211 °C.

R_f = 0.44 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2919, 1697, 1355, 1097, 770.

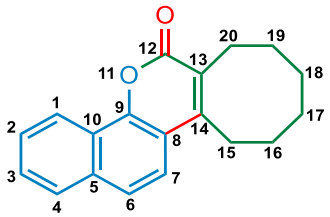
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.56 (ddd, J = 8.6, 4.6, 1.1 Hz, 1H, 1-H), 7.83 (ddd, J = 8.4, 4.8 1.1 Hz, 1H, 4-H), 7.68−7.64 (m, 2H, 6-H and 7-H), 7.59 (ddd, J = 7.3, 4.8, 0.9 Hz, 2H, 2-H and 3-H), 3.04 (dd-like, J = 10.6, 5.2 Hz, 2H, 15-H_2), 2.97 (dd-like, J = 10.8, 5.4 Hz, 2H, 19-H_2), 1.93 (quint-like, J = 5.7 Hz, 2H, 16-H_2), 1.72 (quint-like, J = 5.3 Hz, 2H, 17-H_2), 1.65 (quint-like, J = 5.4 Hz, 2H, 18-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 162.1 (C-12), 154.6 (C-9), 149.2 (C-14), 134.1 (C-5), 128.2 (C-7), 128.1 (C-4), 127.4 (C-6), 126.9 (C-10), 123.8 (C-3), 123.3 (C-2), 122.4 (C-1), 120.2 (C-13), 115.0 (C-8), 32.0 (C-19), 28.3 (C-15), 26.8 (C-16), 25.7 (C-18), 25.0 (C-17).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{18}H_{17}O_2]^+$ 265.1223; found 265.1226.

Molecular weight: $C_{18}H_{16}O_2$ (264.3240 g × mol^{-1}).

3.5.6 7,8,9,10,11,12-Hexahydro-6*H*-cycloocta[*d*]naphtho[1,2-*b*]pyran-6-one (138f)



Following general procedure VI, 7,8,9,10,11,12-hexahydro-6*H*-cycloocta[*d*]naphtho[1,2-*b*]pyran-6-one (**138f**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 1-[(2-bromocyclooct-1-en-1-yl)methoxy]naphthalene (**129f**) (345 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **138f** was obtained as a white solid (233 mg, 0.84 mmol, 84%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 28:1).

M.p.: 215 − 217 °C.

R_f = 0.44 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 1707, 1639, 1226, 1096.

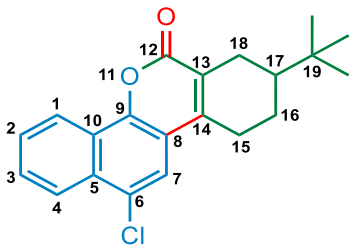
^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 8.58 (ddd, *J* = 6.8, 3.9, 0.8 Hz, 1H, 1-H), 7.85 (ddd, *J* = 6.9, 3.9 1.1 Hz, 1H, 4-H), 7.68 (d, *J* = 8.7 Hz, 1H, 7-H), 7.64 (d, *J* = 8.9 Hz, 1H, 6-H), 7.62−7.60 (m, 2H, 2-H and 3-H), 3.09 (dd-like, *J* = 12.9, 6.4 Hz, 2H, 15-H_2), 2.89 (dd-like, *J* = 12.1, 5.9 Hz, 2H, 20-H_2), 1.87 (quint-like, *J* = 6.2 Hz, 2H, 19-H_2), 1.78 (quint-like, *J* = 5.9 Hz, 2H, 16-H_2), 1.56 (quint-like, *J* = 5.6 Hz, 2H, 17-H_2), 1.44 (quint-like, *J* = 5.8 Hz, 2H, 18-H_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ [ppm] = 161.6 (C-12), 151.2 (C-9), 149.5 (C-14), 134.1 (C-5), 128.1 (C-7), 127.5 (C-4), 126.9 (C-6), 126.4 (C-10), 123.9 (C-3), 123.4 (C-2), 122.4 (C-1), 120.6 (C-13), 114.6 (C-8), 29.7 (C-20), 29.2 (C-15), 27.0 (C-19), 26.7 (C-16), 26.4 (C-17), 25.8 (C-18).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{19}H_{19}O_2]^+$ 279.1380; found 279.1382.

Molecular weight: $C_{19}H_{18}O_2$ (278.3510 g × mol^{-1}).

3.5.7 8-(*tert*-Butyl)-12-chloro-7,8,9,10-tetrahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (138g)



Following general procedure VI, 8-(*tert*-butyl)-12-chloro-7,8,9,10-tetrahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (**138g**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 1-[(2-bromo-5-(*tert*-butyl)cyclohex-1-en-1-yl)methoxy]-4-chloronaphthalene (**129g**) (408 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **138g** was obtained as a pale yellow solid (276 mg, 0.81 mmol, 81%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 28:1).

M.p.: 247 − 249 °C.

R_f = 0.49 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2949, 1709, 1363, 1114, 758.

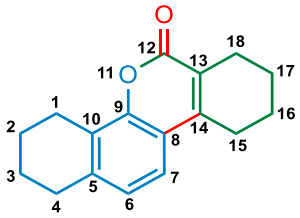
^{1}H NMR (500 MHz, CD_2Cl_2): δ [ppm] = 8.47 (ddd, *J* = 8.1, 1.7, 0.5 Hz, 1H, 1-H), 8.21 (ddd, *J* = 8.1, 1.6, 0.5 Hz, 1H, 4-H), 7.73−7.66 (m, 2H, 2-H and 3-H), 7.62 (br s, 1H, 7-H), 2.99 (dd-like, *J* = 18.3, 4.9 Hz, 1H, 18-Ha), 2.78−2.74 (m, 1H, 18-Ha), 2.71−2.62 (m, 1H, 16-Ha), 2.23−2.13 (m, 2H, 15-H_2), 1.42 (tdd, *J* = 12.2, 4.8, 2.1 Hz, 1H, 17-H), 1.33 (qd, *J* = 12.1, 4.9 Hz, 1H, 16-Hb), 1.01 (s, 9H, 3 × CH_3).

^{13}C NMR (125 MHz, CD_2Cl_2): δ [ppm] = 160.9 (C-12), 147.2 (C-9), 146.8 (C-14), 130.8 (C-5), 128.8 (C-6), 127.7 (C-4), 127.1 (C-7), 124.5 (C-10), 124.4 (C-3), 124.0 (C-2), 122.4 (C-1), 120.0 (C-13), 115.5 (C-8), 43.4 (C-17), 32.3 (C-18), 27.1 (C-19), 26.9 (3 × CH_3), 25.9 (C-15), 22.8 (C-16).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{21}H_{22}ClO_2]^+$ 341.1303; found 341.1304.

Molecular weight: $C_{21}H_{21}ClO_2$ (340.8470 g × mol^{-1}).

3.5.8 1,2,3,4,7,8,9,10-Octahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (138h)



Following general procedure VI, 1,2,3,4,7,8,9,10-octahydro-6*H*-cyclohexa[*d*]naphtho[1,2-*b*]pyran-6-one (**138h**) was synthesized by reacting $RuCl_2(PPh_3)_3$ (48 mg, 0.05 mmol), 1,5-pentanediol (208 mg, 2 mmol) and 5-[(2-bromocyclohex-1-en-1-yl)methoxy]-1,2,3,4-tetrahydronaphthalene (**129h**) (321 mg, 1 mmol) in DMA (2 mL), followed by addition of DTBP (0.7 mL, 4 mmol). Analytically pure **138h** was obtained as a white solid (188 mg, 0.74 mmol, 74%) after subjecting the crude product to column chromatography over silica gel (dichloromethane/methanol = 28:1).

M.p.: 177 − 179 °C.

$\boldsymbol{R_f}$ = 0.44 (cyclohexane/ethyl acetate = 5:1).

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2922, 1702, 1604, 1416, 1093, 827, 750.

^{1}H NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.29 (d, J = 8.2 Hz, 1H, 6-H), 6.98 (d, J = 8.1 Hz, 1H, 7-H), 2.91 (t, J = 5.9 Hz, 2H, 1-H_2), 2.82 (t, J = 6.1 Hz, 2H, 4-H_2), 2.76 (tt, J = 6.2, 1.9 Hz, 2H, 15-H_2), 2.57 (t, J = 6.4 Hz, 2H, 18-H_2), 1.87−1.76 (m, overlapped, 8H, 2-H_2 and 3-H_2 and 16-H_2 and 17-H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ [ppm] = 162.1 (C-12), 149.9 (C-9), 147.5 (C-14), 140.4 (C-5), 125.1 (C-7), 124.7 (C-6), 120.0 (C-10), 119.6 (C-13), 117.3 (C-8), 29.7 (C-18), 25.2 (C-15), 23.9 (C-4), 22.7 (C-1), 22.5 (C-3), 22.2 (C-2), 21.6 (C-17), 21.4 (C-16).

HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $[C_{17}H_{19}O_2]^+$ 255.1380; found 255.1380.

Molecular weight: $C_{17}H_{18}O_2$ (254.3290 g × mol^{-1}).

IV Appendix

1 References

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2 X-ray crystallographic data for 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (126e)

Table 16. Crystal data and structure refinement for 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**).

Identification code	bei11a
Empirical formula	C15 H20 O2
Formula weight	232.31
Temperature	130(2) K
Wavelength	1.54178 A
Crystal system, space group	Monoclinic, P 21/c
Unit cell dimensions	a = 11.7590(11) A alpha = 90° b = 5.6205(5) A beta = 90.041(6)° c = 18.7423(16) A gamma = 90°
Volume	1238.71(19) A^3
Z, Calculated density	4, 1.246 Mg/m^3
Absorption coefficient	0.636 mm^-1
F(000)	504
Crystal size	0.17 x 0.06 x 0.04 mm
Theta range for data collection	3.76 to 65.56 deg.
Limiting indices	-13<=h<=13, -6<=k<=6, -17<=l<=21
Reflections collected / unique	13683 / 2093 [R(int) = 0.0550]
Completeness to theta = 65.56	97.8 %
Absorption correction	Semi-empirical fromequivalents
Max. and min. transmission	0.7528 and 0.6925

Refinement method	Full-matrix least-squares onF^2
Data / restraints / parameters	2093 / 0 / 157
Goodness-of-fit on F^2	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0389, wR2 =0.1014
R indices (all data)	R1 = 0.0536, wR2 =0.1078
Extinction coefficient	0.0016(5)
Largest diff. peak and hole	0.221 and -0.143 e.A^-3

Table 17. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**).

	x	y	z	U(eq)
O(1)	814(1)	2007(2)	4179(1)	27(1)
C(1)	2806(1)	4763(3)	2892(1)	24(1)
O(2)	2890(1)	6502(2)	2500(1)	31(1)
C(2)	3771(1)	3005(3)	2976(1)	26(1)
C(3)	3868(1)	1943(3)	3729(1)	22(1)
C(4)	2709(1)	906(3)	3933(1)	25(1)
C(5)	1741(1)	2549(3)	3773(1)	23(1)
C(6)	1755(1)	4310(3)	3286(1)	23(1)
C(7)	725(1)	5827(3)	3139(1)	25(1)
C(8)	-275(1)	5042(3)	3579(1)	23(1)
C(9)	-196(1)	3288(3)	4052(1)	23(1)
C(10)	-1129(1)	2389(3)	4523(1)	27(1)
C(11)	-2285(1)	3172(3)	4238(1)	29(1)
C(12)	-2261(2)	5807(3)	4047(1)	33(1)
C(13)	-1387(1)	6296(3)	3462(1)	29(1)
C(14)	4771(1)	-8(3)	3735(1)	27(1)
C(15)	4214(1)	3874(3)	4263(1)	27(1)

Table 18. Bond length [A] and angles [deg] for 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**).

O(1)-C(5)	1.3647(18)
O(1)-C(9)	1.4088(19)
C(1)-O(2)	1.2269(19)
C(1)-C(6)	1.463(2)
C(1)-C(2)	1.513(2)
C(2)-C(3)	1.537(2)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(14)	1.526(2)
C(3)-C(15)	1.531(2)
C(3)-C(4)	1.531(2)
C(4)-C(5)	1.496(2)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.346(2)
C(6)-C(7)	1.506(2)
C(7)-C(8)	1.504(2)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(9)	1.329(2)
C(8)-C(13)	1.501(2)
C(9)-C(10)	1.495(2)
C(10)-C(11)	1.526(2)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900

C(11)-C(12)	1.524(2)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.530(2)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
C(5)-O(1)-C(9)	117.76(12)
O(2)-C(1)-C(6)	120.61(15)
O(2)-C(1)-C(2)	121.47(14)
C(6)-C(1)-C(2)	117.91(13)
C(1)-C(2)-C(3)	113.86(12)
C(1)-C(2)-H(2A)	108.8
C(3)-C(2)-H(2A)	108.8
C(1)-C(2)-H(2B)	108.8
C(3)-C(2)-H(2B)	108.8
H(2A)-C(2)-H(2B)	107.7
C(14)-C(3)-C(15)	108.69(13)
C(14)-C(3)-C(4)	110.13(13)
C(15)-C(3)-C(4)	110.08(12)

C(14)-C(3)-C(2)	109.70(12)
C(15)-C(3)-C(2)	110.12(13)
C(4)-C(3)-C(2)	108.12(12)
C(5)-C(4)-C(3)	113.11(13)
C(5)-C(4)-H(4A)	109.0
C(3)-C(4)-H(4A)	109.0
C(5)-C(4)-H(4B)	109.0
C(3)-C(4)-H(4B)	109.0
H(4A)-C(4)-H(4B)	107.8
C(6)-C(5)-O(1)	123.50(14)
C(6)-C(5)-C(4)	125.49(14)
O(1)-C(5)-C(4)	111.00(13)
C(5)-C(6)-C(1)	118.72(15)
C(5)-C(6)-C(7)	122.06(14)
C(1)-C(6)-C(7)	119.22(13)
C(8)-C(7)-C(6)	111.22(13)
C(8)-C(7)-H(7A)	109.4
C(6)-C(7)-H(7A)	109.4
C(8)-C(7)-H(7B)	109.4
C(6)-C(7)-H(7B)	109.4
H(7A)-C(7)-H(7B)	108.0
C(9)-C(8)-C(13)	120.47(14)
C(9)-C(8)-C(7)	121.97(15)
C(13)-C(8)-C(7)	117.55(13)
C(8)-C(9)-O(1)	123.37(14)
C(8)-C(9)-C(10)	126.35(15)
O(1)-C(9)-C(10)	110.28(13)

C(9)-C(10)-C(11)	110.50(13)
C(9)-C(10)-H(10A)	109.5
C(11)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5
C(11)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	108.1
C(12)-C(11)-C(10)	110.20(14)
C(12)-C(11)-H(11A)	109.6
C(10)-C(11)-H(11A)	109.6
C(12)-C(11)-H(11B)	109.6
C(10)-C(11)-H(11B)	109.6
H(11A)-C(11)-H(11B)	108.1
C(11)-C(12)-C(13)	110.80(14)
C(11)-C(12)-H(12A)	109.5
C(13)-C(12)-H(12A)	109.5
C(11)-C(12)-H(12B)	109.5
C(13)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	108.1
C(8)-C(13)-C(12)	113.31(14)
C(8)-C(13)-H(13A)	108.9
C(12)-C(13)-H(13A)	108.9
C(8)-C(13)-H(13B)	108.9
C(12)-C(13)-H(13B)	108.9
H(13A)-C(13)-H(13B)	107.7
C(3)-C(14)-H(14A)	109.5
C(3)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5

C(3)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(3)-C(15)-H(15A)	109.5
C(3)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(3)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5

Symmetry transformations used to generate equivalent atoms.

Table 19. Anisotropic displacement parameters (A^2 x 10^3) for 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**).

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	21(1)	31(1)	30(1)	9(1)	5(1)	1(1)
C(1)	26(1)	30(1)	16(1)	-1(1)	-1(1)	-3(1)
O(2)	31(1)	36(1)	26(1)	10(1)	4(1)	0(1)
C(2)	23(1)	32(1)	21(1)	1(1)	3(1)	0(1)
C(3)	22(1)	23(1)	21(1)	1(1)	0(1)	-1(1)
C(4)	24(1)	23(1)	28(1)	2(1)	1(1)	-1(1)
C(5)	22(1)	25(1)	21(1)	-1(1)	2(1)	-3(1)
C(6)	24(1)	25(1)	20(1)	-1(1)	0(1)	-2(1)
C(7)	25(1)	28(1)	21(1)	4(1)	0(1)	0(1)
C(8)	24(1)	26(1)	19(1)	-2(1)	0(1)	-1(1)
C(9)	20(1)	27(1)	22(1)	-2(1)	-1(1)	0(1)
C(10)	26(1)	29(1)	25(1)	0(1)	3(1)	-3(1)
C(11)	24(1)	38(1)	26(1)	-2(1)	3(1)	-4(1)
C(12)	28(1)	39(1)	32(1)	1(1)	3(1)	4(1)
C(13)	26(1)	34(1)	26(1)	2(1)	1(1)	3(1)
C(14)	25(1)	27(1)	29(1)	1(1)	0(1)	1(1)
C(15)	31(1)	27(1)	24(1)	0(1)	-2(1)	-1(1)

Table 20. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**).

	x	y	z	U(eq)
H(2A)	4495	3813	2857	31
H(2B)	3663	1694	2630	31
H(4A)	2593	-604	3671	30
H(4B)	2708	536	4449	30
H(7A)	903	7509	3248	30
H(7B)	527	5719	2626	30
H(10A)	-1022	3011	5012	32
H(10B)	-1098	630	4544	32
H(11A)	-2481	2227	3809	35
H(11B)	-2876	2881	4603	35
H(12A)	-2067	6749	4477	39
H(12B)	-3024	6310	3882	39
H(13A)	-1706	5788	2997	35
H(13B)	-1246	8030	3436	35
H(14A)	4839	-665	4218	40
H(14B)	5504	662	3588	40
H(14C)	4550	-1274	3403	40
H(15A)	3649	5156	4256	41
H(15B)	4960	4515	4131	41
H(15C)	4254	3188	4743	41

Table 21. Torsion angles [deg] for 3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-xanthen-1-one (**126e**).

O(2)-C(1)-C(2)-C(3)	145.44(15)
C(6)-C(1)-C(2)-C(3)	-35.5(2)
C(1)-C(2)-C(3)-C(14)	173.42(13)
C(1)-C(2)-C(3)-C(15)	-67.00(17)
C(1)-C(2)-C(3)-C(4)	53.30(18)
C(14)-C(3)-C(4)-C(5)	-166.29(12)
C(15)-C(3)-C(4)-C(5)	73.88(16)
C(2)-C(3)-C(4)-C(5)	-46.45(17)
C(9)-O(1)-C(5)-C(6)	3.4(2)
C(9)-O(1)-C(5)-C(4)	-175.46(12)
C(3)-C(4)-C(5)-C(6)	23.4(2)
C(3)-C(4)-C(5)-O(1)	-157.82(12)
O(1)-C(5)-C(6)-C(1)	178.70(13)
C(4)-C(5)-C(6)-C(1)	-2.6(2)
O(1)-C(5)-C(6)-C(7)	-1.1(2)
C(4)-C(5)-C(6)-C(7)	177.62(14)
O(2)-C(1)-C(6)-C(5)	-172.31(15)
C(2)-C(1)-C(6)-C(5)	8.6(2)
O(2)-C(1)-C(6)-C(7)	7.5(2)
C(2)-C(1)-C(6)-C(7)	-171.66(13)
C(5)-C(6)-C(7)-C(8)	-1.9(2)
C(1)-C(6)-C(7)-C(8)	178.34(13)
C(6)-C(7)-C(8)-C(9)	2.6(2)
C(6)-C(7)-C(8)-C(13)	-176.61(13)

C(13)-C(8)-C(9)-O(1)	178.71(13)
C(7)-C(8)-C(9)-O(1)	-0.5(2)
C(13)-C(8)-C(9)-C(10)	-1.5(2)
C(7)-C(8)-C(9)-C(10)	179.23(15)
C(5)-O(1)-C(9)-C(8)	-2.6(2)
C(5)-O(1)-C(9)-C(10)	177.61(12)
C(8)-C(9)-C(10)-C(11)	18.1(2)
O(1)-C(9)-C(10)-C(11)	-162.12(13)
C(9)-C(10)-C(11)-C(12)	-46.84(18)
C(10)-C(11)-C(12)-C(13)	61.45(18)
C(9)-C(8)-C(13)-C(12)	14.7(2)
C(7)-C(8)-C(13)-C(12)	-166.08(14)
C(11)-C(12)-C(13)-C(8)	-44.2(2)

Symmetry transformations used to generate equivalent atoms.

3 Abbreviations

A	Ångström
acac	acetylacetonate
br	broad
CBT	cannabitriol
$Co(BA)_2$	cobalt(II) benzoylacetonate
COSY	correlation spectroscopy
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublet
ddd	doublet of doublet of doublet
dddd	doublet of doublet of doublet of doublet
deg	degree
DMA	*N*,*N*-dimethylacetamide
DMEDA	1,2-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMSO	dimethyl sulfoxide
dt	doublet of triplet
DTBP	di-*tert*-butyl peroxide
EI	electron ionization
equiv	equivalent
ESI	electron spray ionization
et al.	et alia
Et_2O	diethyl ether
EtOH	ethanol
eV	electronvolt
GSS	glucosinolate sulfatase

h	hour
Hal	halogen
HFIP	hexafluoro-2-propanol
HMBC	heteronuclear multiple bond correlation
HRMS	high-resolution mass spectrum
HSQC	heteronuclear single quantum coherence
Hz	Hertz
IR	infrared spectroscopy
J	coupling constant
K	Kelvin
L	liter
m	multiplet
M^+	molecular ion
M.p.	melting point
m/*z*	mass to charge ratio
MCR	multicomponent reaction
MeOH	methanol
min	minute
mL	milliliter
mL	multiplet
LRMS	low-resolution mass spectrum
MS	molecular sieve
MW	microwave
N.R.	no reaction
nm	nanometer
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
OAc	acetate
OMe	methoxy
OTf	triflate
OTs	tosylate

p-TsCl	*para*-toluenesulfonyl chloride
PEG-400	polyethylene glycol 400
ppm	parts per million
PTFE	polytetrafluoroethylene
PTLC	preparative thin layer chromatography
q	quartet
qd	quartet of doublet
quint	quintet
RCM	ring-closing metathesis
R_f	retention factor
RSV	respiratory syncytial virus
rt	room temperature
s	singlet
STS	steroid sulfatase
t	triplet
TBHP	*tert*-butyl hydroperoxide
tdd	triplet of doublet of doublet
THC	tetrahydrocannabinol
THF	tetrahydrofuran
TLC	thin layer chromatography
tt	triplet of triplet
UV	ultraviolet
XRD	X-ray diffraction
°C	degree Celsius
δ	chemical shift
λ	wave length

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