Studies towards the Total Synthesis of Lingzhiol

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Comment on previously published parts of this doctoral thesis

As part of this doctoral project a number of BSc students have been supervised, which included but was not limited to the planning and direct supervision of their laboratory work and providing guidance in interpretation of results and compilation of their theses. As a result, some parts of this project have been already published in the following theses:

Chapter 2.2 in:

Bianca Marcia, *Studies Towards the Total Synthesis of Lingzhiol* (BSc Thesis), Tübingen, **2020**

Parts of Chapter 2.3 in:

Michelle Kammer, *Erforschung neuer Syntheserouten für die Totalsynthese von Lingzhiol* (BSc Thesis), Tübingen, **2021**

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Abbreviations

acac	acetylacetonate
AIBN	*α,α'*-Azoisobutyronitrile
APCI	Atmospheric pressure chemical ionization
Bn	Benzyl
BPO	Benzoyl peroxide
BTEAC	Benzyltriethylammonium chloride
Bz	Benzoyl
CBS	Corey–Bakshi–Shibata
CIP	Cahn-Ingold-Prelog
DB	Diabetic nephrophaty
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DIPA	*N,N*-Diisopropylamin
DIPEA	*N,N*-Diisopropyethylamin
DMA	*N,N*-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N,N'*-Dimethylpropylene urea
DMSO	Dimethyl sulfoxide
EDG	Electron-donating group(s)
ESI	Electrospray ionization
EWG	Electron-withdrawing group(s)
G.	Ganoderma
GC	Gas chromatography
GPP	Geranyl pyrophosphate
IUPAC	International Union of Pure and Applied Chemistry

KHMDS	Potassium hexamethyldisilazide
LiHMDS	Lithium hexamethyldisilazide
m-CPBA	*meta*-Chloroperbenzoic acid
MOM	Methoxymethyl
Mp	Melting point
MS	Mass spectrometry
MVA	Mevalonic acid/mevalonate
NBS	*N*-Bromosuccinimide
NHPI	*N*-Hydroxyphtalimide
NMO	*N*-Methylmorpholin *N*-oxide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PTSA	*para*-Toluenesulfonic acid
RB	Rose Bengal
R_f	Retention factor
ROS	Reactive oxygen species
RT	Room temperature
$TBABr_3$	Tetrabuthylammonium tribromide
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butyl hydroperoxide
TEA	Triethylamine
Tf	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMG	*N,N,N',N'*-Tetramethylguanidine
TMS	Trimethylsilyl
TPP	Tetraphenylporphyrin
XRD	X-ray diffraction

1. Introduction

1.1. A note on the graphical representation of stereochemistry

Before we could start presenting the following thesis, we must make a small excursion into some terms of stereochemistry and its representation in drawings. Although the experimental work presented later is racemic in nature (*i.e.*: no effort was taken to control the *absolute configuration* of the molecules), we will discuss enantioselective reactions in the literature summary. Furthermore, while the *absolute configuration* of our compounds later to be presented is inconsequential, we will meet instances in which the applicability of our proposed route will hinge on the correct *relative stereochemistry* of our molecules. Therefore, we find it worthwhile to clarify how we will depict the *absolute configuration* and the *relative stereochemistry* of molecules in our schemes. First, we will define these two terms: thus, under *absolute configuration* we mean the description of the three dimensional arrangement of substituents around a chiral element, whilst we use the term *relative stereochemistry* to describe the position of substituents on different atoms in a molecule relative to one another.[1] We shall refrain from using the term *relative configuration* due to its ambiguity.[2]

It is apparent from the definition, that *relative stereochemistry* describes a relation of substituents in a molecule, and as long as the relation itself remains unchanged, the *absolute configuration* of the individual stereocenters is irrelevant. This in turn raises the question how to depict these different layers of stereochemical information. While the drawing of *absolute configurations* is well established, such unanimous treatment of the depiction of *relative stereochemistry* is lacking. It is nevertheless imperative to use a system capable making this distinction, we will thus now lay down the basis to be used henceforth with regards to the depiction of stereochemistry.

Since the official recommendation of the International Union of Pure and Applied Chemistry (IUPAC) for depicting *relative stereochemistry* is vastly impractical (it would require us to draw both enantiomers of a given compound, or to add the phrase "+ enantiomer" to each structure),[3] we adapted a slightly modified system suggested by MAEHR.[4,5] The essence of the system is to use different types of bond drawings for *relative stereochemistry* and for *absolute configuration*, therefore we shall use bold or hashed *block* bonds (*Figure 1*, *red box*) to describe *relative stereochemistry*, while the bold or hashed *wedge* bonds (*Figure 1*, *green box*) are reserved for the depiction of *absolute configuration*.

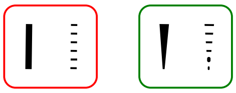


Figure 1 *Bond types used in the description of stereochemistry. Red box: relative stereochemistry; Green box: absolute configuration*

The practical application of this system is illustrated in *Figure 2* through the example of 4-hydroxyproline. In the *blue box* we can see the structure of 4-hydroxyproline which does not reveal any information about its stereochemistry. It can, however, become necessary to differentiate between its two diastereomeric forms, namely the *trans* and *cis* diastereomers (*red box*), in which the hydroxyl and carboxylic groups are on the opposite or the same side of the ring respectively. It is also apparent, that each *relative stereoisomer* is a mixture of its respective enantiomers (*green box*), to which *absolute configuration* and optical rotation can be assigned.

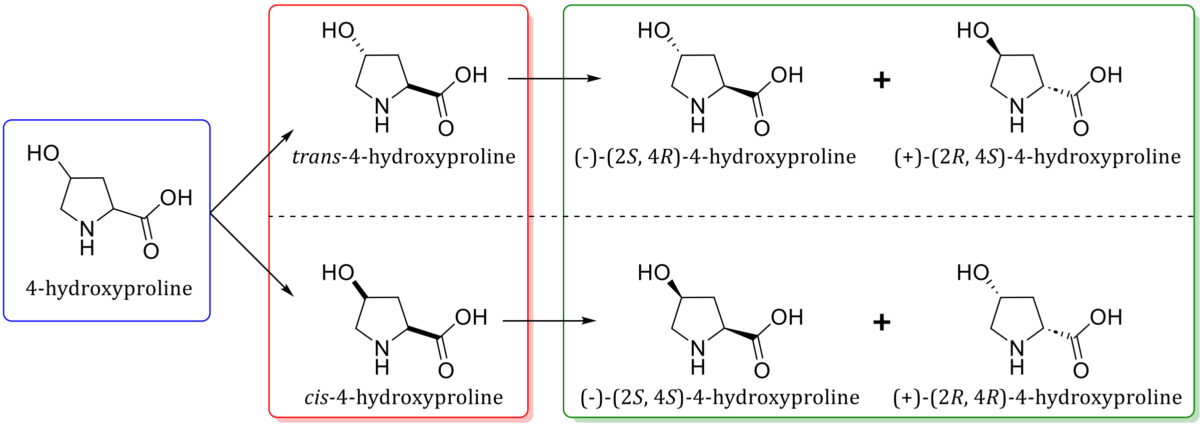


Figure 2 *Stereoisomerism of 4-hydroxyproline. Red box: Structure of 4-hydroxyproline; Green box: relative stereochemistry of 4-hydroxyproline; Blue box: absolute configuration of 4-hydroxyproline*

A consequence of the above introduced system can be seen in *Figure 3*. Since bold or hashed block bonds only describe a relative relationship, it follows that if we change every bond to its counterpart (that is, if we replace each *hashed* block bond with a *bold* block bond and vice versa) we, in fact, have the very same representation of stereochemistry. In other words, *cis*-4-hydroxyproline, for example, can be drawn with two different structures (one with two hashed and one with two bold block bonds) without any change of meaning. These drawings can be interchanged at will, and apart from a subjective notion of preference, they are identical. This is obviously not true for the wedge bonds. If we replace each *hashed* wedge bond with a *bold* one and vice versa, we acquire the enantiomer of the original structure, which are not identical.

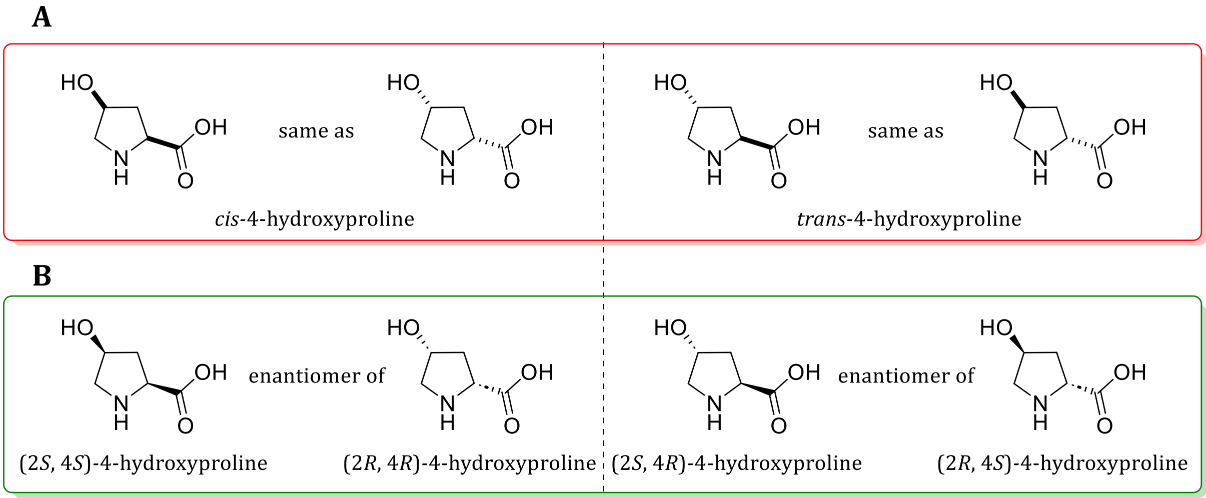


Figure 3 *Stereochemical depiction of 4-hydroxyproline.* ***A****: relative stereochemistry.* ***B****: absolute configuration*

Naturally, this system can be extended to an arbitrary number of stereocenters. It is also obvious, that in case of molecules with only a single stereocenter, the block bonds are meaningless, and their use is therefore incorrect.

Lastly, we wish to address the nomenclature of the *relative stereochemistry*. Unlike depiction and naming of *absolute configuration*, the description of relative relationship of substituents lacks a commonly accepted nomenclature. Several systems were developed which co-exist to give a large number of possible descriptors to the point of confusion (*l*/*u*, *threo*/*erythro*, *syn*/*anti*, *parf*/*pref* etc.).[6,7] Since our compounds with stereochemical issues are mostly cyclic molecules, we shall use the descriptors *cis*/*trans* to describe the relative relationship of substituents in accordance with already existing practice for cyclic compounds.[1] We will not use nuanced descriptors like *cisoid* or *transoid*[1] which will cause no loss of understandability.

In case we need to generate a full name (which we will see only in the Experimental section), we shall do so by observing the rules put forth by IUPAC. The relative stereochemistry will be denoted by applying the Cahn-Ingold-Prelog (CIP) sequence rules to the stereocenters, with an asterisk in the superscript indicating that the molecule containing stereocenters with the opposite configuration is also present (R^*, S^*). The rules shall be applied to the enantiomer, in which the centre of chirality with the lowest locant has the configuration "*R*" (*Figure 4*).[1,8] In these instances we will prefer to draw structures that correspond to the name, that is, if we were to change the *block* bonds to *wedge* bonds, we would acquire the enantiomer to which the CIP-descriptors correspond. Generally speaking, we will use trivial names along with the *cis*/*trans* descriptors rather than full IUPAC nomenclature (as can be seen through this example of 4-hydroxyproline).

(2*R**,4*R**)-4-hydroxypyrrolidine-2-carboxylic acid

(2*R**,4*S**)-4-hydroxypyrrolidine-2-carboxylic acid

Figure 4 *IUPAC nomenclature of **A**: cis-4-hydroxyproline and **B**: trans-4-hydroxyproline*

1.2. A short history of total synthesis

Since the advent of humanity, herbs have been used as remedies for various illnesses. The first written records, dating from around 2600 BC in Mesopotamia, listed about one thousand plant products, many of which are still being used today,[9] quite often in the same indication in which we use them with our current knowledge of medicine (the relaxing and painkilling effect of opium, for example, was known and used by the Egyptians as early as 1500 BC[10]). Every major ancient culture (Mesopotamian, Egyptian, Greek, Roman, Indian, Chinese etc.) had their own records about medicinally relevant herbal and animal products.[9,11] This vast knowledge was then inherited and extended by Arabian physicians through which it was (re)introduced into Western Europe and was codified in the early modern period producing the first pharmacopoeias standardizing herbal products used in healing.[9] The developing sciences however made it possible to actually determine the active ingredients of these plants and this search has culminated into the first *isolation* of pure natural products (strychnine, morphine, colchicine etc.) in the beginning of the 19th century.[9]

The first half of the 19th century was in any case a crucial period in the birth of organic chemistry. Up until this point it had been thought that organic molecules can be produced solely by living organisms, since a mysterious "living force" is required to convert inorganic elements into organic materials. This was proven wrong by WÖHLER in 1828, whose famous experiment, converting ammonium cyanate into urea upon heating, marked the beginning of what we now know as organic synthesis.[12,13] In the following decades many more organic molecules were synthesized, albeit these compounds tended to be "simple" aromatics, nevertheless synthetic chemistry in the 19th century could already achieve remarkable feats (eg.: EMIL FISCHER's synthesis of glucose in 1890).[12,13] The development of synthetic methods also made structure elucidation possible. Devoid of any practical physical method of mapping atomic connectivity of molecules, the only viable way of structure determination was to carefully degrade molecules into already known compounds and with that information, accumulated through years of hard labour, one could propose a structure to a given compound.[14,15]

The beginning of the 20th century saw a steep increase of molecular complexity conquered by synthetic chemists. The achievements of PERKIN (α-terpineol, 1904), ROBINSON (tropinone, 1917) or HANS FISCHER (haemin, 1929) among others foreshadowed the rapid development of the field.[12] Arguably the next milestone was reached with the appearance of ROBERT B. WOODWARD. His formal synthesis of quinine, with its mechanistically planned steps and control over stereochemistry, marked the beginning of the golden age of total synthesis. Indeed, from this point every aspect (chemoselectivity, stereochemistry etc.) could be and was expected to be controlled and with his leadership previously hopelessly complex targets (strychnine, B12 etc.) were conquered in mere decades. These achievements were also followed by the quick development of related fields (methodology, theory etc.).[12,13] The second half of the 20th century saw the peak of total synthesis. With the development of novel structure determination techniques as well as isolation and synthetic methods, a myriad of natural products with previously not seen core structure were isolated and synthesized. This period also gave rise to the rigorous, logical planning of synthetic routes (E. J. COREY).[12,15]

In the 90s however the symptoms of decline began to manifest. The trends in organic chemistry gradually shifted to methodology development, in which the synthesis of natural products was still present, however the goal of which was to showcase the applicability of a given method.[16] The existence of "pure" total synthesis had started to come into question. Structure determination was hardly a justification at this point (although sporadic errors in instrumental structure determination were indeed discovered through synthesis[14]) and the most problematic aspect of total synthesis was highlighted more and more often: its length and directly related to it: its overall yield.[17,18] Few of the then-existing total syntheses carried even the slightest possibility of industrial applicability due to their unacceptable length and/or their insignificant overall yields (see for example the total synthesis of Taxol®, a quite sought after antitumor drug, the chemical synthesis of which usually required 30-40 steps.[19]) Moreover, the emergence of "metabolic engineering" enabled the synthesis of complex secondary metabolites through genetic modification of cells in order to use them as "bioreactors" requiring cheap and basic starting materials, capable of achieving complex chemical synthesis in a single step.[18,20] Nevertheless, total synthesis has managed to survive. Natural products themself quite often are not the most optimal binding partners for therapeutic targets.[15] This necessitates the modification of the peripheral substitution pattern, which is often rather difficult on the natural product or on one of its advanced intermediate. Total synthesis however enables the production of a family of compounds from a common intermediate.[15] Also, modular total synthesis emerged as a tool for drug discovery, in which a natural product is divided into modules that can be modified during their synthesis, so upon their assembly they directly provide the natural product as well as its analogues and derivatives.[21]

Understandably, natural product chemistry has changed over the decades of its history. However, it is also clear that it will remain to be used extensively. The new challenges in medicinal chemistry demand that the horizon of potentially drug-like candidates be widened. In the 2000s it has become undeniable, that flat, heterocyclic compounds cannot live-up anymore to the demands of medicinal chemistry. It has also been shown, that the more complex (i.e.: more sp^3 carbons, more chiral centres etc.) molecules become, the higher their selectivity will be.[22–24] This fact will ensure, that the (bio)chemistry of natural products (or natural product-like molecules) will still be worthwhile to be pursued in the coming decades.[25–27]

1.3. Isolation, Structure and Biochemistry of Lingzhiol

Around 100 B.C. experiences accumulated by Chinese medical practitioners were compiled into a treatise called SHEN NONG BEN CAO JING.[28] The book collected the description of 365 materials, of which one of the most prized was called *Lingzhi*, a group of mushrooms, which in turn was sub-divided into six categories according to their colour. Later authors used different groupings, and also left accurate drawings of *Lingzhi*.[28] Of these six mushrooms two species (*Ganoderma lucidum* and *Ganoderma sinensis*) are accepted in contemporary legal traditional Chinese medicine. Their indication includes diabetes, cancer and cardiovascular diseases among others.[28–32]

The mushroom in our focus, *Ganoderma lucidum* is a white rot fungus found growing on woody plants and on logs mainly in Asia.[31,33] Due to the high regard of the members from the *Ganoderma* genus in Asian medical tracts, a great effort was taken to characterize their chemical constituents. *G. lucidum* was thus extensively researched revealing a plethora of natural products of different structures. By far the largest group of constituents are triterpenes (at least 140 different compounds), which tend to be highly oxygenated. The second most populous family belongs to the polysaccharides (about 100 members). These two compound families are to be held accountable for the majority of the fungus´ therapeutic effect.[31,33–37] Due to its potential health benefits, *G. lucidum* is widely consumed as functional food or in the form of supplements,[38–40] and even brewing beer fortified with the mushroom was investigated in order to harvest its beneficial properties.[41] Beyond its consumption in various forms, *G. lucidum* was also suggested as a potential candidate for bioengineering for the biomanufacturing of proteins and nutraceuticals due to its metabolic versatility and rich genome content,[42] and the mushroom’s mycelium was investigated to be used as a biodegradable scaffold for circuit boards and other applications in electronics.[43]

In 2013 a novel compound in racemic form was isolated from the ethanolic extract of *G. lucidum*. Structure determination revealed a hitherto not observed core structure consisting of a 6/6/5/5 ring system. The compound was named Lingzhiol (**1-1**) the structure of which can be seen in *Figure 5*.[44] The compound consists out of an aromatic hydroquinone ring (A) condensed with saturated ring B to form a tetralone like ring system, which is in turn condensed with five membered ring C, bridged by lactone ring D.

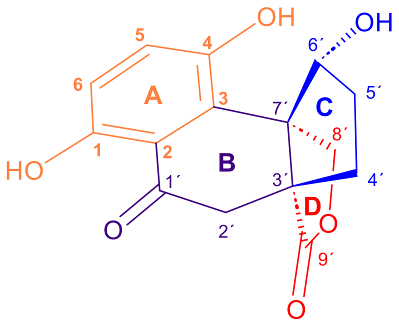
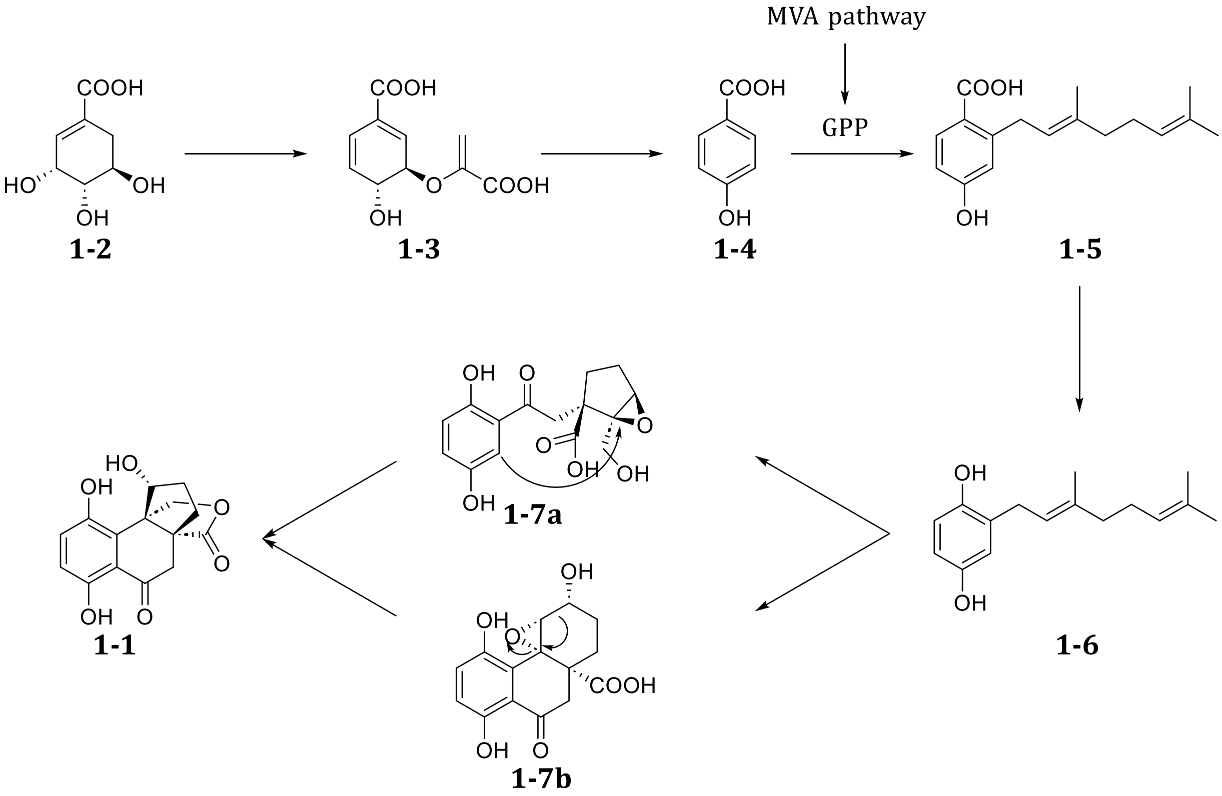


Figure 5 Structure of (-)-Lingzhiol[44]

Based on the mushroom´s therapeutic indications the compound was investigated whether it proved valuable treating diabetic nephropathy (DB).[44] DB is a chronic kidney disease occurring in patients suffering from either type of diabetes. One of the major factors in the occurrence of DB (and really in other complications of diabetes) is the high glucose induced overproduction of reactive oxygen species (ROS). ROS can, due to their nature, directly damage cells where they are produced, they are also capable of inducing some stress-sensitive pathways that result in cellular damage and also inducing the activation of transduction cascades and transcription factors that result in the excessive deposition of extracellular matrix leading to the scarring of the kidney (fibrosis). Antioxidants are thus suggested for the treatment of such conditions.[45,46] It was shown, that Lingzhiol can effectively reduce the overproduction of ROS in the kidney,[44] and similar results were acquired when this protective effect was investigated in liver cells.[47] The general antioxidant effect of structurally related compounds was also investigated and proven.[48]

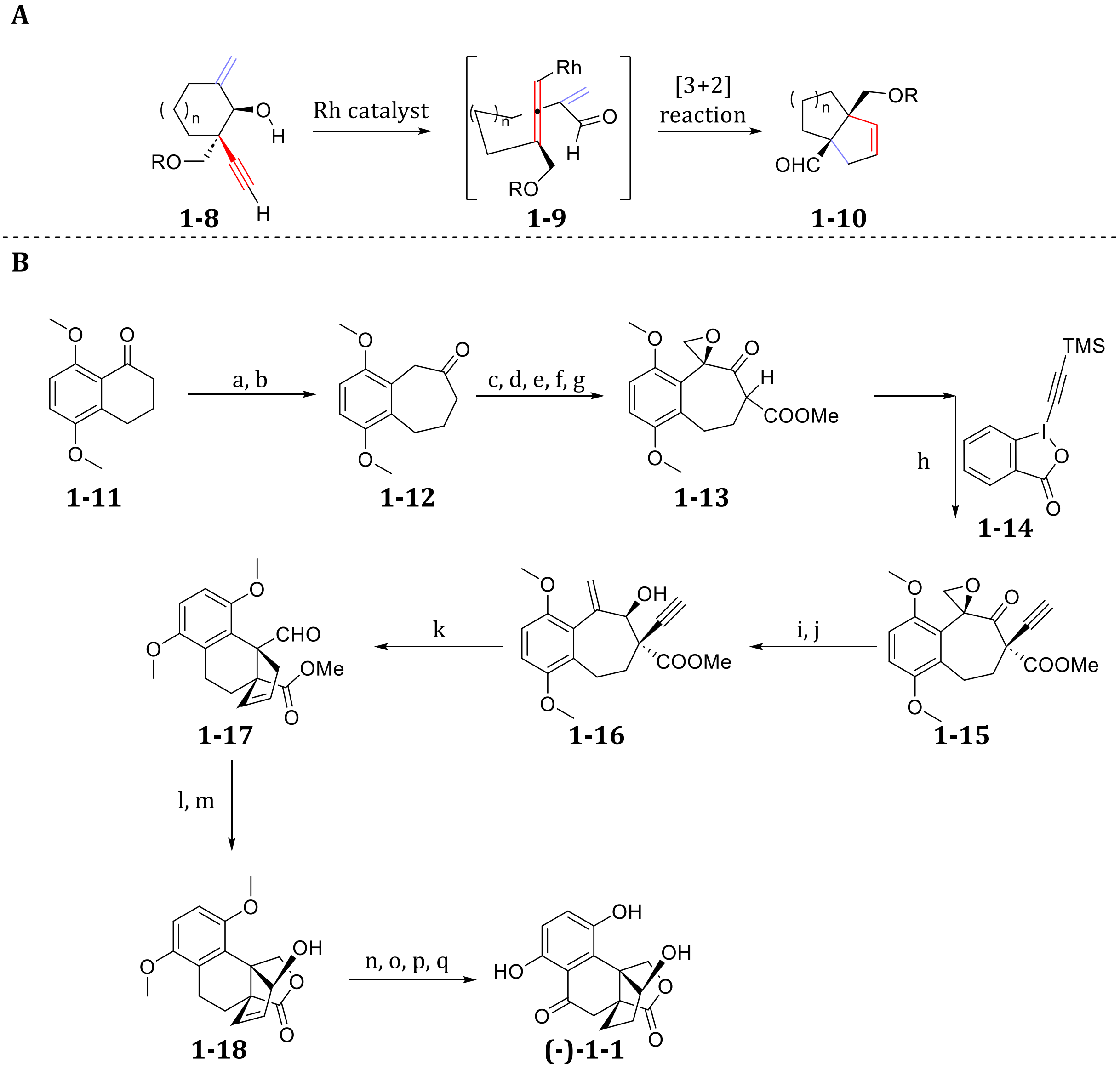
The biosynthesis of Lingzhiol remains unclear. The compound belongs to the *Ganoderma* meroterpenoid subclass of the shikimate-meroterpenoids, the biosynthesis of which has not been systematically researched due to its complex nature and the relative lack of interest in these natural products.[49] Nevertheless, one can propose an approximate route piecing together information found in literature. The origin of the terpenoid part of the molecule is easy to explain. Genetic study of *G. lucidum* showed the presence of all the required enzymes to the mevalonate (MVA) pathway (but none belonging to the methylerythritol 4-phosphate pathway, which is consistent with previous research stating that fungi can synthesize terpenes only through the MVA pathway).[50] The source of the aromatic part is a bit more obscure, however it is generally accepted, that it is formed through the shikimate pathway. The proposed biosynthesis of Lingzhiol can be seen in *Scheme 1*. Shikimic acid (**1-2**) is converted to 4-hydroxybenzoic acid (**1-4**) through chorismic acid (**1-3**)[51] followed by the geranylation of **1-4** to afford compound **1-5** which is then converted to the geranylated hydroquinone **1-6**.[52,53] The following steps remain to be obscure. The geranyl side chain is heavily modified through oxygenation and ring formation. Different advanced intermediates were proposed (e.g.: **1-7a** and **1-7b**) which can serve as precursors to Lingzhiol.[54]



Scheme 1 Proposed biosynthesis of Lingzhiol[51–54]

1.4. Total syntheses of Lingzhiol

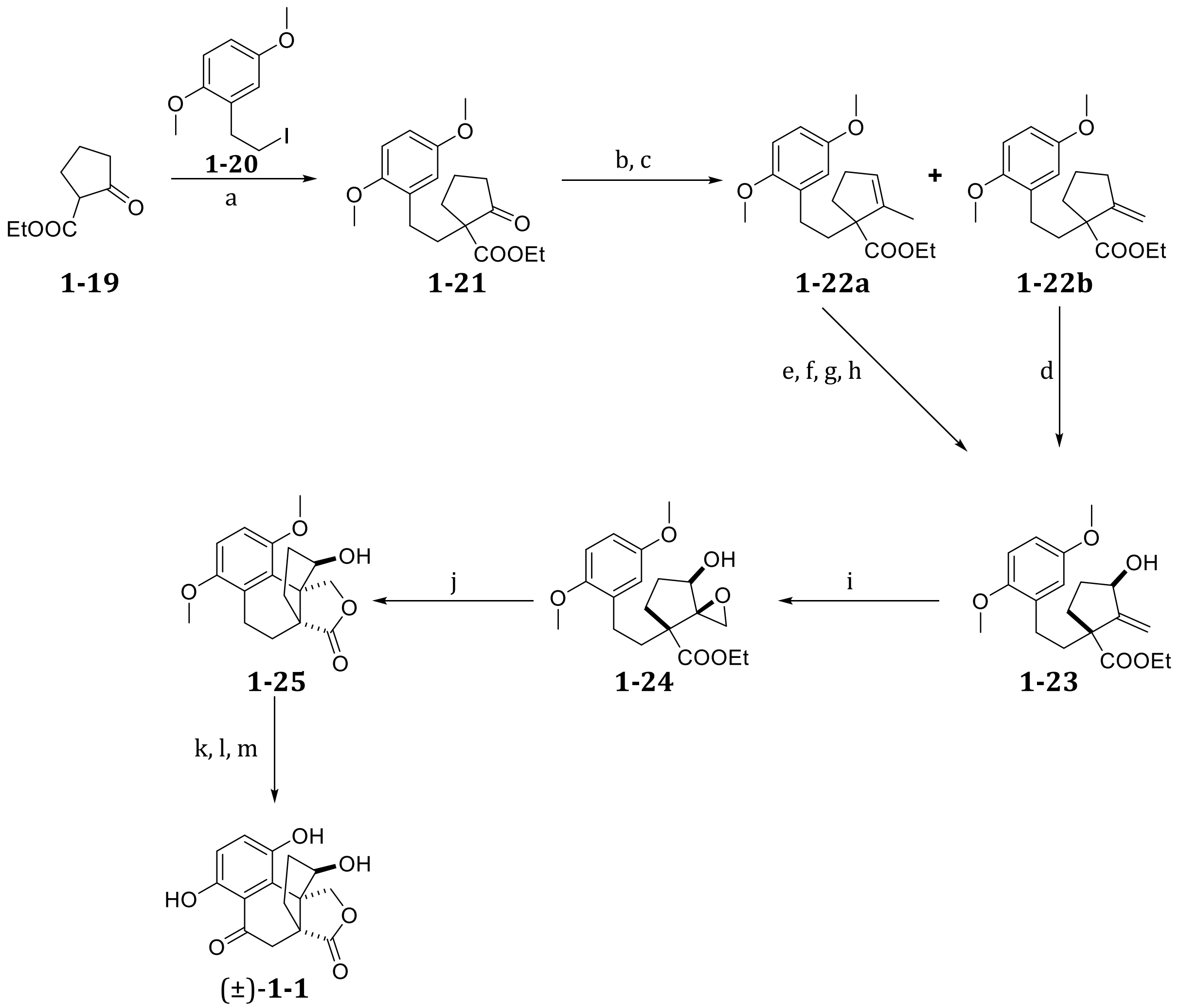
The first total synthesis of **1-1** was published in 2014 by R. LONG, J. HUANG *et al.*[55] It utilises a Rh catalysed [3+2] cycloaddition reaction to construct bicyclic systems (*Scheme 2A*). The total synthesis (*Scheme 2B*) starts with tetralone **1-11** which is converted to the ring enlarged analogue **1-12**, from which enantiomerically pure epoxide **1-13** (that existed as keto-enol tautomers) was synthesised.



***Scheme 2** First total synthesis of (-)-Lingzhiol. (**A**) Rh catalysed reaction to access bicyclic systems. (**B**) Total synthesis of (-)-Lingzhiol.*[55] *Reagents: **a.)** PPh_3CH_3Br, KO^{t}Bu, THF, 98% **b.)** PhI(OH)OTs, MeOH, 95%; **c.)** TEA.HCl, Et_2NH, $(CH_2O)_n$, 1,4-dioxane, 98%; **d.)** (R)-CBS, BH_3, THF, 91%, 92% ee; **e.)** m-CPBA, Na_2HPO_4, benzene; **f.)** DMP, $NaHCO_3$, DCM, 81% (two steps); **g.)** LiHMDS, ethyl cyanoformate, THF; **h.)** ^{n}Bu$_4$NF, THF, 62% (two steps); **i.)** NaI, MeCN, TFA, 92%; **j.)** $NaBH_4$, $CeCl_3.7H_2O$, EtOH, 63%; **k.)** $[Rh(CO)_2Cl]_2$, CO, DCE, 86%; **l.)** $NaBH_4$, MeOH, 89%; **m.)** SeO_2, 1,4-dioxane, 65%, **n.)** Pd/C, H_2, MeOH, 95%, **o.)** NBS, BPO, $NaHCO_3$, H_2O, CCl_4; **p.)** MnO_2, DCM, 71% (two steps); **q.)** ^{t}BuSH, $AlCl_3$, DCM, 71%*

The acetylenic side chain was introduced through reaction with WASER´S reagent (ethynyl-1,2-benziodoxol-3(1*H*)-one (**1-14**)) to afford **1-15** which was converted in two steps to the precursor of the Rh catalysed key reaction **1-16**. The ring closing took place with 86% yield affording **1-17**, that was transformed into compound **1-17** through reduction/spontaneous lactonization and RILEY oxidation at position 6´. **1-18** already possesses the core structure of Lingzhiol. A four-step sequence (reduction of the double bond, consecutive oxidation of benzylic position first to alcohol then to ketone, and deprotection of phenolic groups) finished the asymmetric synthesis of (-)-Lingzhiol (**1-1**).

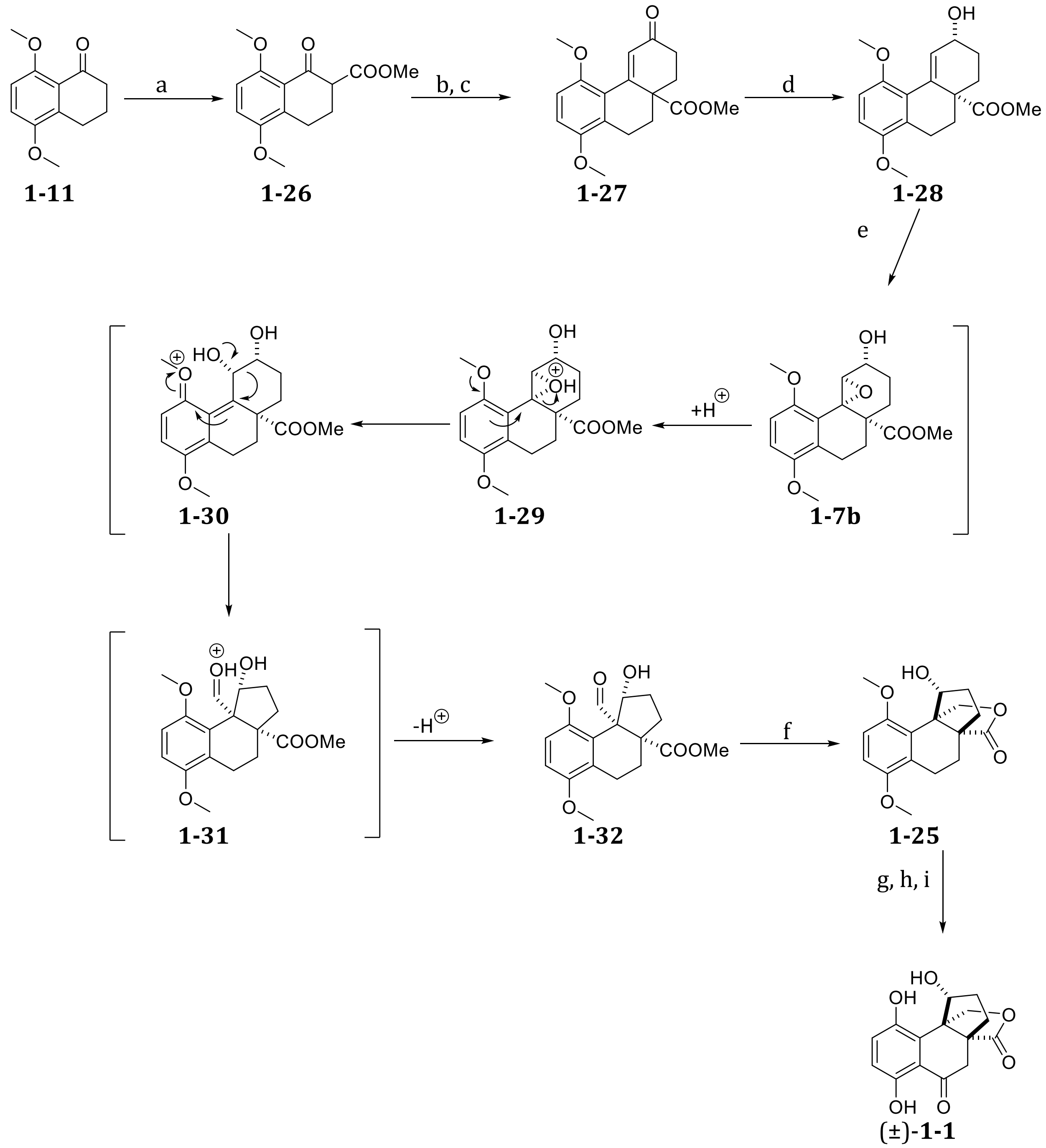
The second (racemic) total synthesis was achieved by H. B. QIN *et al.* in 2015,[56] that used an epoxy-arene cyclization to construct the core structure of Lingzhiol. The synthesis (*Scheme 3*) begins with ketoester **1-19**, which is alkylated with iodide **1-20** to afford **1-21** that was converted through two steps (GRIGNARD addition and elimination) to the isomeric mixture of *endo* and *exo* alkenes **1-22a** and **1-22b** respectively, with an *endo*/*exo* ratio of 2.2/1. The conversion of the minor *exo* alkene to Lingzhiol is straightforward: **1-22b** is oxygenated at the allylic position through well-known protocol to acquire **1-23** which is then epoxidized to afford the precursor to the key reaction. Treating **1-24** with boron trifluoride induces the epoxide opening/FRIEDEL-CRAFTS like ring closing sequence directly affording lactone **1-25**, which is then converted through familiar reactions (benzylic oxidation in two steps, deprotection) to racemic Lingzhiol. However, since not incorporating the major *endo* isomer **1-22a** in the synthesis would have been a major blow to the synthesis altogether, steps were taken to facilitate the conversion of **1-22a** to **1-23**. Ultimately a four-step procedure was devised (dihydroxylation, acylation of secondary alcohol, elimination of the tertiary alcohol, saponification) to allow the utilization of the major *exo* isomer **1-22a**.



Scheme 3 *Total synthesis of (±)-Lingzhiol according to H. B. Qin.*[56] *Reagents:* ***a.)*** ***1-20****,* K_2CO_3*, DMF, 78%;* ***b.)*** *MeMgI,* Et_2O*, 95%,* ***c.)*** *TEA,* $SOCl_2$*, DCM, 80% overall,* ***1-22a/1-22b****: 2.2/1;* ***d.)*** SeO_2*, TBHP, DCM, 40%;* ***e.)*** OsO_4*, NMO, acetone,* H_2O*;* ***f.)*** Ac_2O*, pyridine, DCM, 68% (two steps);* ***g.)*** *TEA,* $SOCl_2$*, DCM;* ***h.)*** K_2CO_3*, MeOH,* H_2O*, 85% (two steps);* ***i.)*** $VO(acac)_2$*, TBHP, DCM, 90%;* ***j.)*** $BF_3.Et_2O$*, DCM, 75%;* ***k.)*** *NBS, BPO,* H_2O*,* CCl_4*;* ***l.)*** MnO_2*, DCM, 50% (two steps);* ***m.)*** BBr_3*, DCM, 60%*

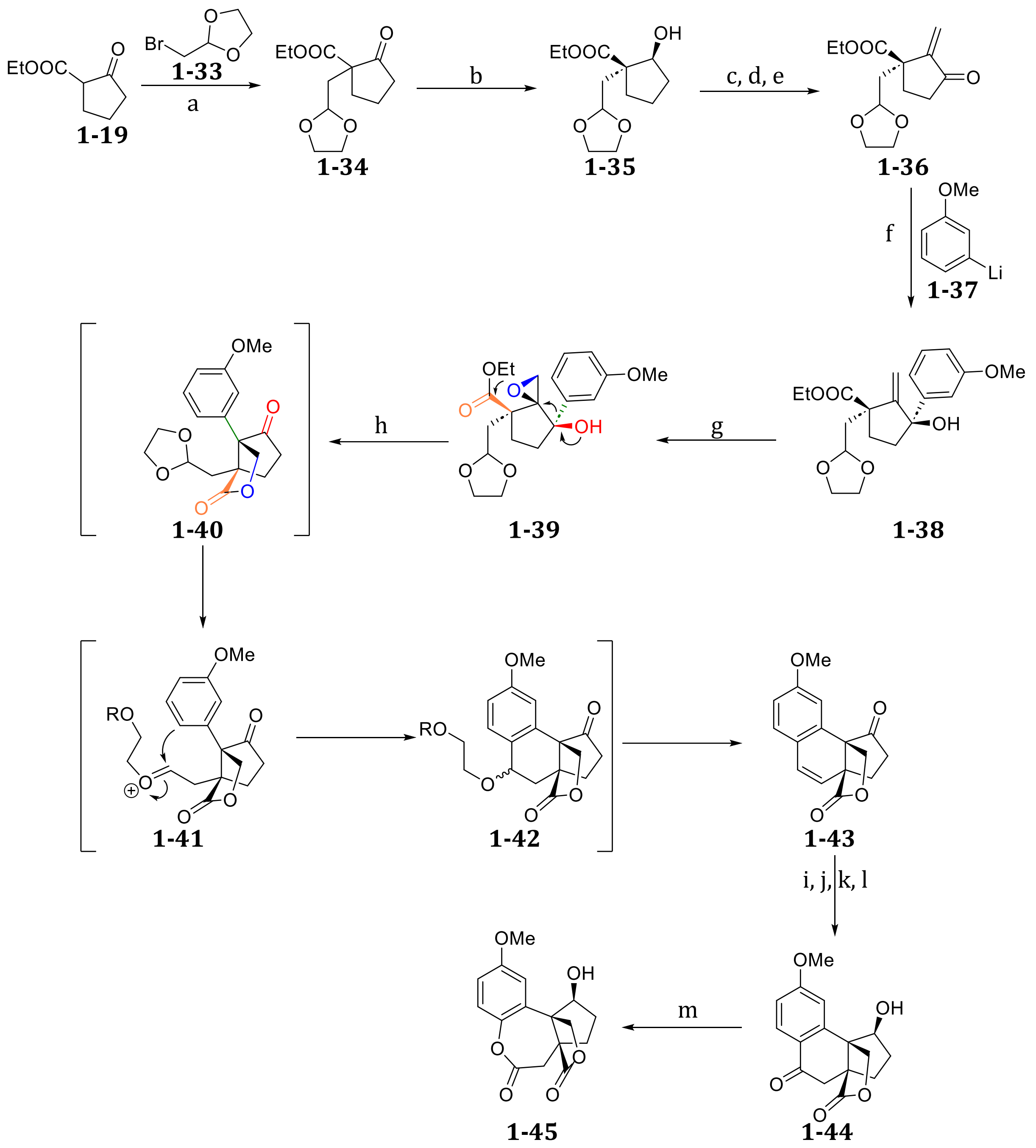
The next two total syntheses were published in the spring of 2016 by K. Gautam and V. Birman[57] and three weeks later independently by P. Xie *et al.*[58] Both approaches are almost identical (practically apart from the last three steps), using a Pinacol-type rearrangement to construct the core structure of Lingzhiol. They (*Scheme 4*) start with tetralone **1-11** which is converted to the ketoester **1-26** with its subsequent Robinson annulation with methyl vinyl ketone providing the α,β-unsaturated ketone **1-27**, that was subjected to Luche reduction to afford allylic alcohol **1-28**.Treating **1-28** with *meta*-chloroperbenzoic acid initially gave epoxide **1-7b** which upon protonation quickly underwent an epoxide ring opening, with the emerging cation being stabilised by the aromatic ring (**1-30**) followed by a Pinacol rearrangement on **1-30** affording aldehyde **1-32** after loss of proton. Reduction of aldehyde **1-32** with sodium borohydride gave precursor **1-25** already mentioned before. Standard oxidation and protecting group manipulations afforded racemic Lingzhiol. GAUTAM and BIRMAN also mentioned that their synthesis can be executed in an enantioselective fashion simply by employing an asymmetric catalytic version of the MICHAEL reaction on **1-26** which after ring closing affords enantiomerically pure **1-27** from which the total synthesis of (+)-Lingzhiol is warranted.[57]

In 2020 a third paper was published by C. S. SCHINDLER *et al.*[59] who also utilised the very same principle in order to achieve the enantioselective synthesis of both Lingzhiol enantiomers. By choosing an appropriate rare earth metal catalyst with chiral ligands they could synthesize both enantiomers of **1-27** in an enantioselective fashion.

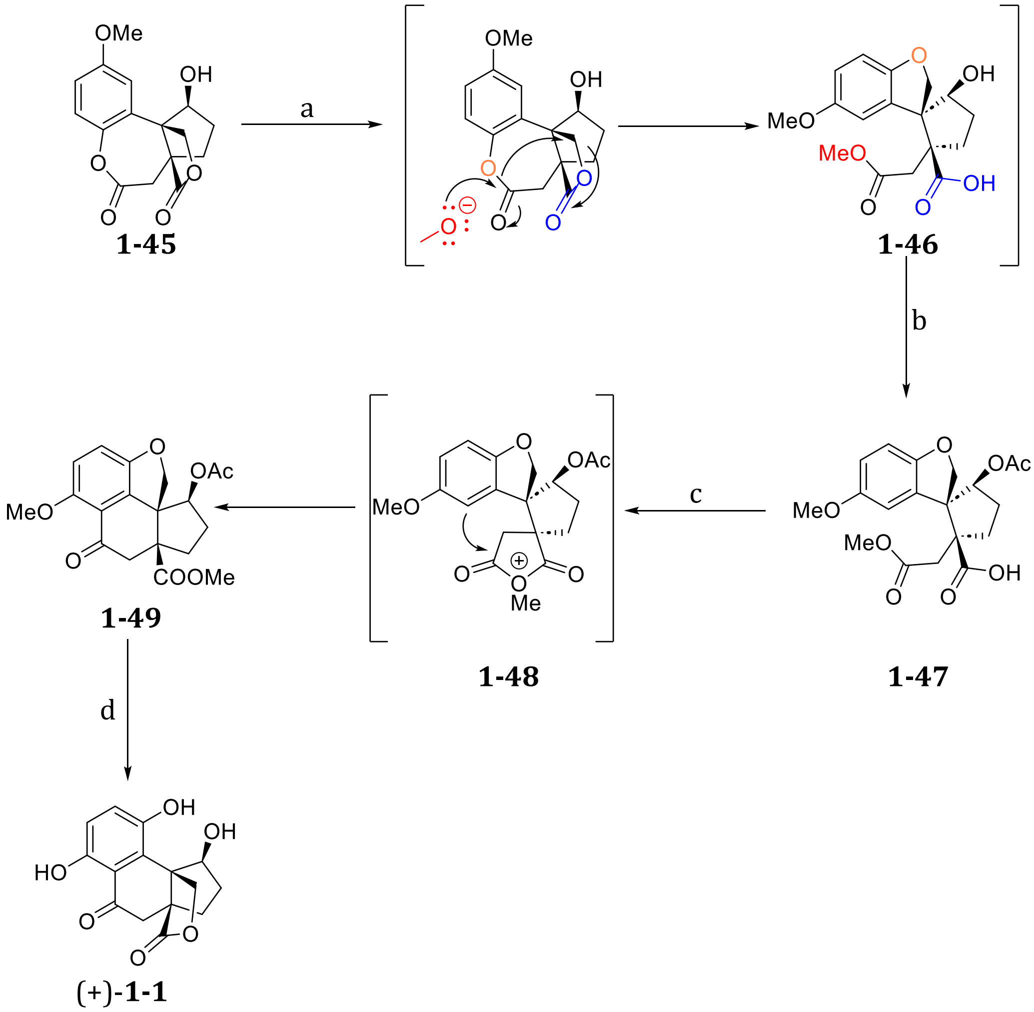


Scheme 4 *Total synthesis of Lingzhiol according to K. Gautam and V. Birman*[57] *and independently by P. Xie et al.*[58] *Reagents (according to Birman´s synthesis)*[57]*:* ***a.)*** *NaH, diethyl carbonate, THF, quant.;* ***b.)*** *MVK, TMG, DCM, 79%;* ***c.)*** *NaOMe, MeOH, 79%;* ***d.)*** *$NaBH_4$, $CeCl_3.7H_2O$, MeOH, 73%;* ***e.)*** *m-CPBA, then cat. TFA, MeOH;* ***f.)*** *$NaBH_4$, MeOH, 56% (two steps);* ***g.)*** *Ac_2O, pyridine, DMAP, DCM;* ***h.)*** *O_2, NHPI, AIBN, MeCN, 95%;* ***i.)*** *HCl, MeOH, H_2O, 90%. Last steps of Xie´s synthesis*[58]*:* ***g.)*** *MOMCl, DIPEA, DCM;* ***h.)*** *CrO_3, 3,5-dimethylpyrazole, DCM, 45% (two steps),* ***i.)*** *^{t}BuSH, $AlCl_3$, DCM, 70%.*

The fifth total synthesis (*Scheme 5*) again by H. B. QIN *et al*[60] starts with the alkylation of ketoester **1-19** with protected bromoacetaldehyde **1-33** to afford substituted ketoester **1-34** whose reduction with baker´s yeast provided **1-35** in an enantioselective fashion. **1-35** was then in turn converted to α,β-unsaturated ketone **1-36** the reaction of which with aryl lithium **1-37** afforded allylic alcohol **1-38** which was converted stereoselectively to the epoxide **1-39.** Treating this epoxide with trimethylsilyl trifluoromethanesulfonate induced its Pinacol rearrangement to compound **1-40** which then underwent a FRIEDEL-CRAFTS alkylation followed by elimination through **1-41** and **1-42** to provide lactone **1-43**, that was converted into **1-44** in a four-step sequence and was subjected to BAEYER-VILLIGER oxidation affording dilactone **1-45**. Treating dilactone **1-45** (*Scheme 6*) with potassium carbonate in methanol induced a skeletal rearrangement the product thereof was acylated and subsequently treated with trifluoroacetic anhydride that afforded advanced precursor **1-49**. Reaction with boron tribromide finished the total synthesis.

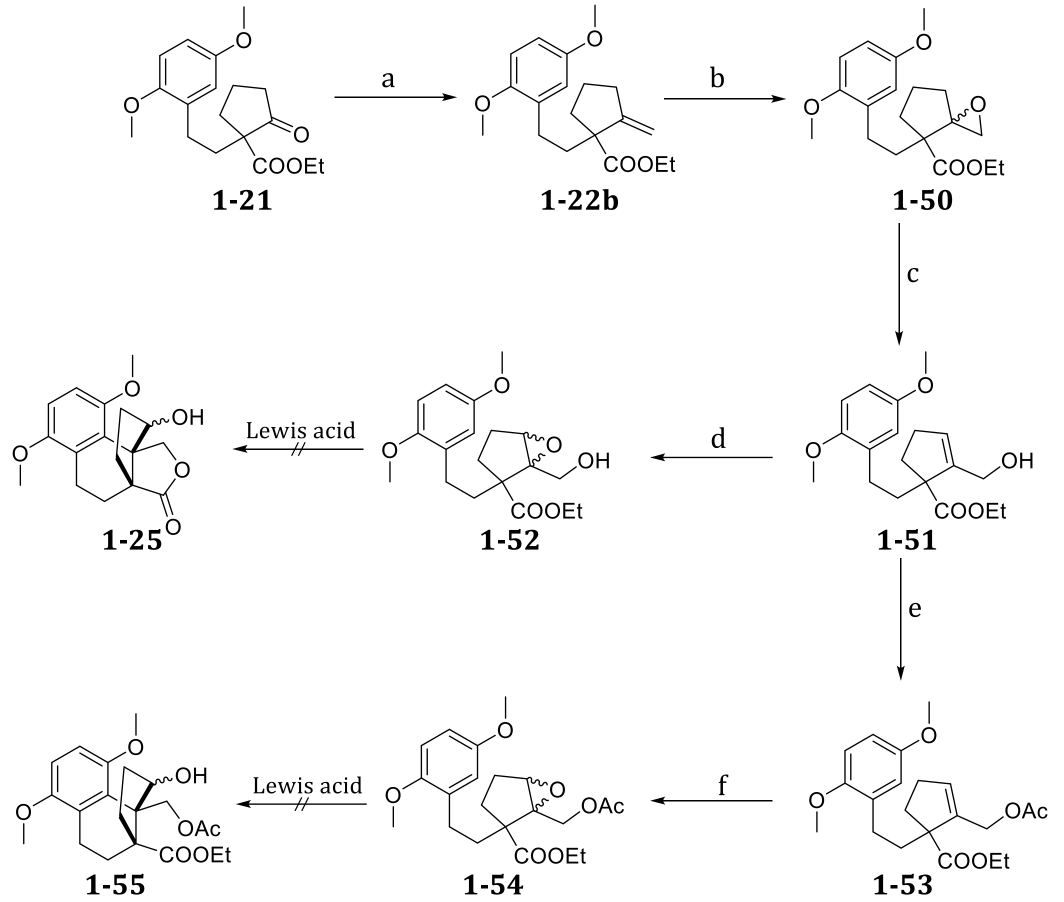


***Scheme 5** Total synthesis of (+)-Lingzhiol by H.B. Qin[60]: Synthesis of dilactone **1-45** Reagents: **a.)** **1-33**, K_2CO_3, KI, DMSO, 65%; **b.)** baker´s yeast, $HCOONH_4$, CuO, 20% aqueous sucrose, 40%; **c.)** DMP, DCM, 95%; **d.)** Ph_3PCH_3Br, ^tBuOK, toluene, 80%; **e.)** SeO_2, TBHP, DCM, 87%; **f.)** **1-37**, THF, 81%; **g.)** VO(acac)$_2$, TBHP, DCM, 95%; **h.)** TMSOTf, Lutidine, DCE, 75%; **i.)** NBS, THF, H_2O; **j.)** PCC, NaOAc, DCM, 85% (two steps); **k.)** Zn powder, AcOH, 95%; **l.)** $NaBH_4$, MeOH; **m.)** m-CPBA, $KHCO_3$, DCM, 80%.*



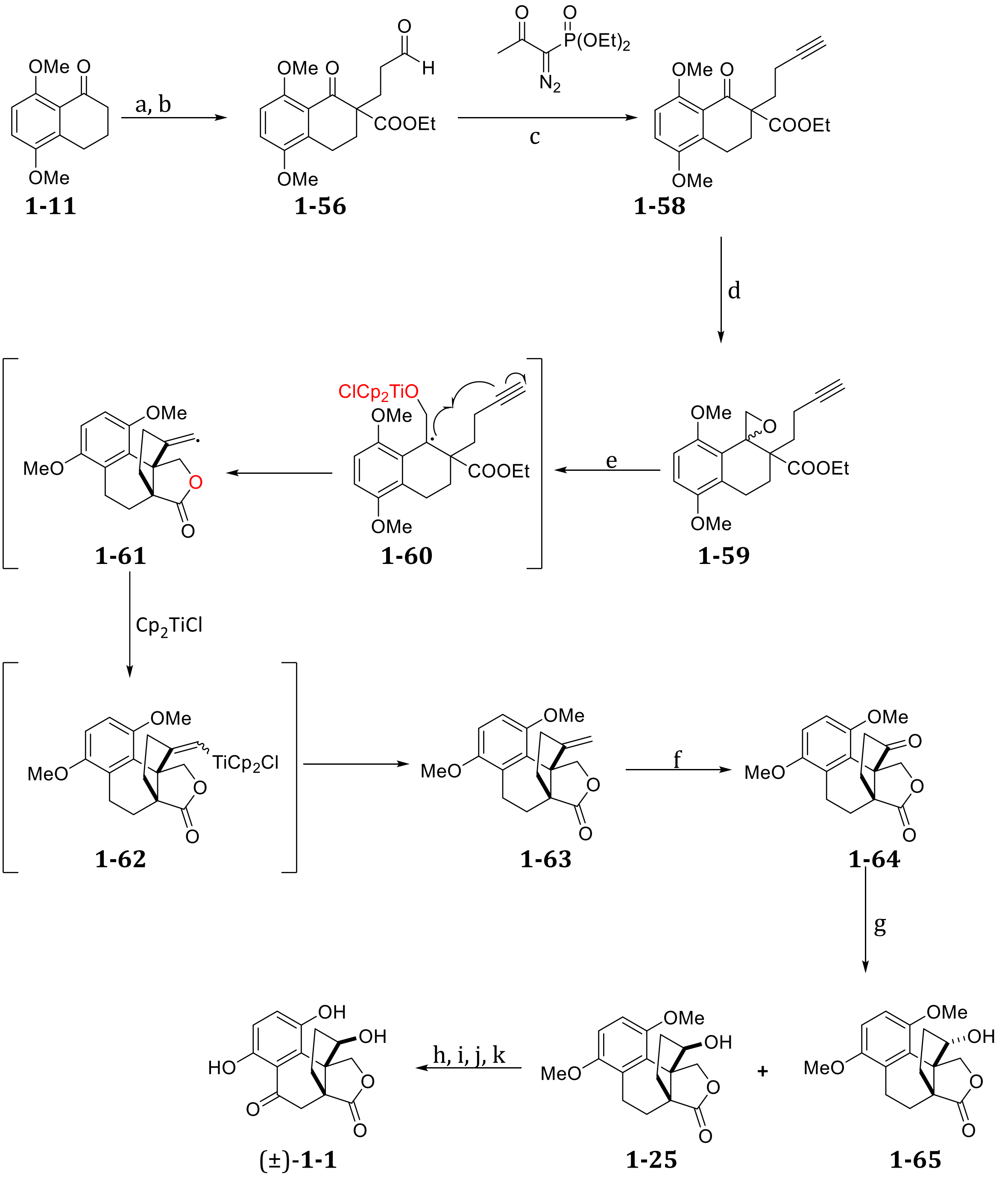
Scheme 6 *Total synthesis of (+)-Lingzhiol by H.B. QIN[60]: Completion of synthesis. Reagents:* ***a.)*** *K_2CO_3, MeOH, then acidic work-up;* ***b.)*** *Ac_2O, DMAP, DCM;* ***c.)*** *TFAA, TFA, 80% (three steps);* ***d.)*** *BBr_3, DCM, 90%.*

In 2017 RENGARASU and MAIER[61] published a study towards the total synthesis of Lingzhiol that was the first in our group (*Scheme 7*). Conceptually it is identical with that of H. B. QIN´s first route (see *Scheme 3*) and aimed to utilize a cationic ring closure to construct the core structure. Compound **1-21** was synthesized analogously and was converted to the *exo*-alkene **1-22b**. This was then epoxidized and the oxirane ring was subsequently opened to allylic alcohol **1-51** which was subjected to a second PRILEZHAEV reaction to afford the hoped precursor **1-52**. Treating this precursor with LEWIS acids however showed no promise of product formation irrespective of whether the primary alcohol was protected or not. This research did nevertheless make QIN´s route more efficient since the loss of material due to the unwanted *endo*-alkene **1-22a** (see *Scheme 3* and its discussion) was bypassed.



Scheme 7 *Synthetic plan by Rengarasu and Maier[61] towards Lingzhiol. Reagents:* ***a.)*** *Ph_3PCH_3Br, ^tBuOK, THF, 79%;* ***b.)*** *m-CPBA, $NaHCO_3$, DCM, 61%;* ***c.)*** *H_2SO_4, DCM, 33%;* ***d.)*** *m-CPBA, $NaHCO_3$, DCM, 59%;* ***e.)*** *Ac_2O, pyridine, 77%;* ***f.)*** *m-CPBA, $NaHCO_3$, DCM, 32%.*

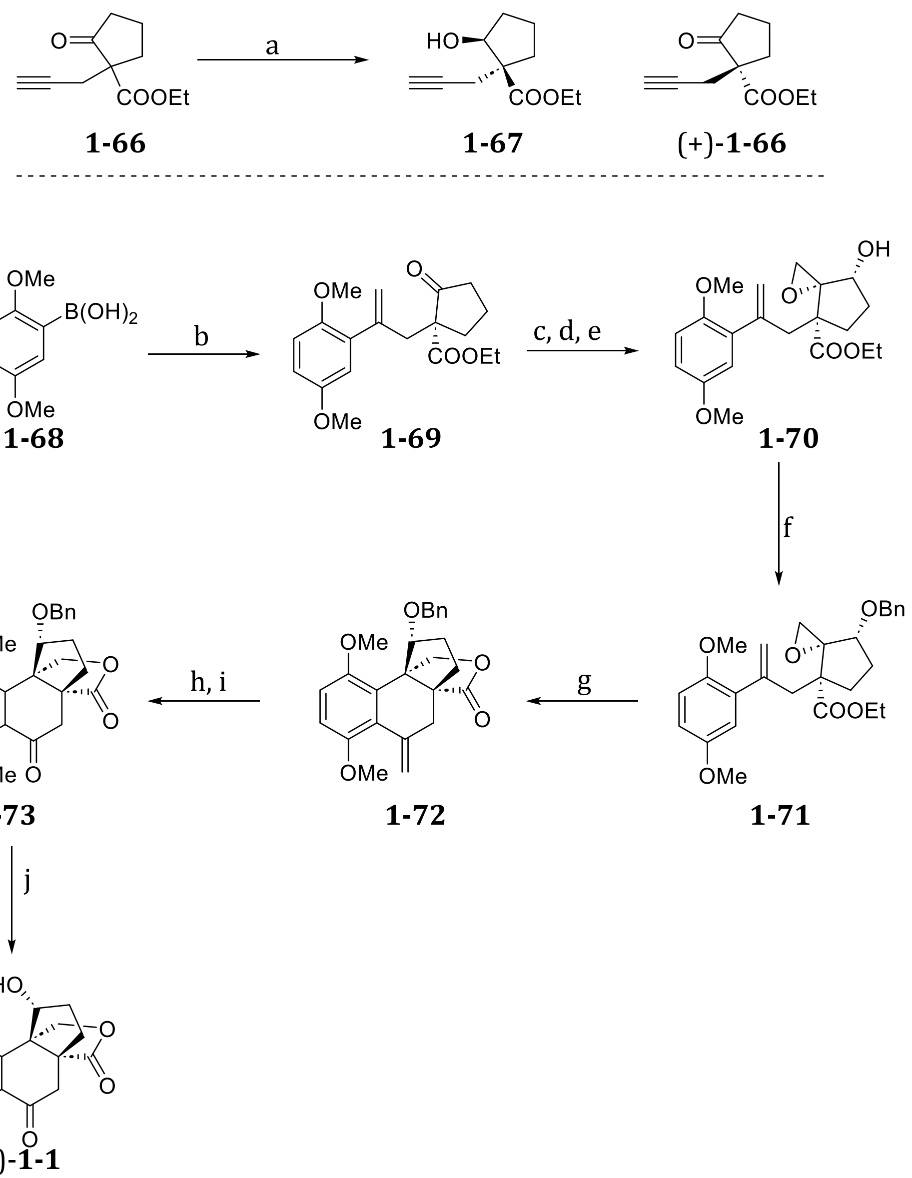
Mehl and Maier published the second total synthesis from our group in 2017[54]. It employs a titanium(III) induced radical ring opening of an epoxide followed by a radical ring closing (*Scheme 8*). The sequence starts with tetralone **1-11** which is converted to Michael adduct **1-56**, the treatment of which with the Ohira-Bestmann reagent (**1-57**) afforded the alkyne **1-58**.



__Scheme 8__ Total synthesis of Lingzhiol according to M*EHL and* M*AIER*[54] *Reagents:* ***a.)*** *NaH, diethyl carbonate, THF, 90%;* ***b.)*** *acrylaldehyde, TEA, DMF, 81%;* ***c.)*** ***1-57****, K_2CO_3, MeOH, 58%;* ***d.)*** *CH_2Br_2, ^nBuLi, THF, 43%;* ***e.)*** *Zn, Cp_2TiCl_2, THF, 69%;* ***f.)*** *$K_2OsO_4.2H_2O$, $NaIO_4$, THF, H_2O, 63%;* ***g.)*** *$NaBH_4$, $CeCl_3.7H_2O$, 86% (overall,* ***1-25/1-65****: 1/1);* ***h.)*** *Ac_2O, DMAP, pyridine, DCM, 98%;* ***i.)*** *O_2, NHPI, AIBN, MeCN, 42%;* ***j.)*** *HCl, MeOH, 66%;* ***k.)*** *$AlCl_3$, ^tBuSH, DCM, 50%.*

The introduction of epoxy function proved to be difficult. Conversion of the ketone group to exocyclic alkene was met with failure. COREY-CHAYKOWSKI conditions also failed. However, it was possible the form the required epoxide **1-59** through the reaction of ketone **1-57** with bromomethyl lithium. The epoxide was then treated with $Cp_2Ti^{III}Cl$ (formed in situ in the reaction of titanocene dichloride with zinc) which initiated a radical opening of the oxirane ring,[62] creating benzylic radical **1-60**, which then subsequently added onto the triple bond accompanied by lactone formation, with the formed vinyl radical **1-61** being reduced by means of a Ti^{III} species and eventually affording exocyclic alkene **1-63**. Cleavage of the double bond through LEMIEUX-JOHNSON reaction afforded ketone **1-64** the reduction of which under LUCHE conditions (which delivered the best diastereomeric ratio) gave alcohols **1-25** and **1-65** as a 1:1 mixture of diastereomers. Conversion of the required **1-25** to Lingzhiol was done analogously as discussed before. The “wrong” diastereomer **1-65** could be recycled through oxidation with DESS-MARTIN periodinane to **1-64**. MITSUNOBU-type inversion of the secondary alcohol was not successful.[54]

As of now, the latest total synthesis originates again from the working group of H. B. QIN.[63] Their synthesis (*Scheme 9*) starts with ketoester **1-66** the kinetic resolution thereof with baker´s yeast afforded alcohol **1-67** and ketoester (*R*)-**1-66**. The palladium catalysed addition of boronic acid **1-68** to (*R*)-**1-66** furnished alkene **1-69** that was elaborated into epoxide **1-70**, in which the alcohol function was protected as a benzyl ether and was treated with trimethylsilyl trifluoromethanesulfonate to induce a cationic cyclization affording the core structure of Lingzhiol **1-72** with an exocyclic alkene moity. **1-72** was subjected to LEMIEUX-JOHNSON reaction furnishing **1-73** that was converted to (-)-Lingzhiol upon treating it with boron tribromide.



Scheme 9** Total synthesis of Lingzhiol according to* Qin[63] *Reagents:* ***a.) *baker´s yeast,* $HCOONH_4$*,* CuO*, 20% aqueous sucrose, 43%;* ***b.)*** *(+)-**1-66**,* $Pd(PPh_3)_4$*,* $HCOOH$*, 1,4-dioxane, 80%;* ***c.)*** Ph_3PCH_3Br*,* ^tBuOK*, THF, 81%;* ***d.)*** SeO_2*, TBHP, DCM, 69%;* ***e.)*** $VO(acac)_2$*, TBHP, DCM, 82%;* ***f.)*** *NaH, BnBr, DMF, 75%;* ***g.)*** *TMSOTf, DCM, 51%;* ***h.)*** OsO_4*, NMO,* ^tBuOH*, THF;* ***i.)*** $NaIO_4$*, THF,* H_2O*, 74% (two steps);* ***j.)*** BBr_3*, DCM, 52%.*

1.5. Motivation

The aim of the present work is to present the results of our investigation of new synthetic strategies towards the total synthesis of Lingzhiol. During this project we have researched numerous, conceptually different synthetic routes which often chosen so that the possibility of a later enantioselective synthesis would be warranted. *Figure 6* summarises the different disconnection points, which we considered for the total synthesis of Lingzhiol.

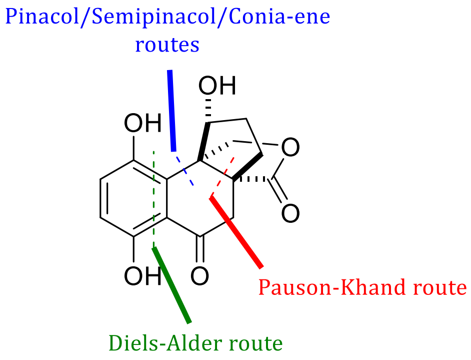
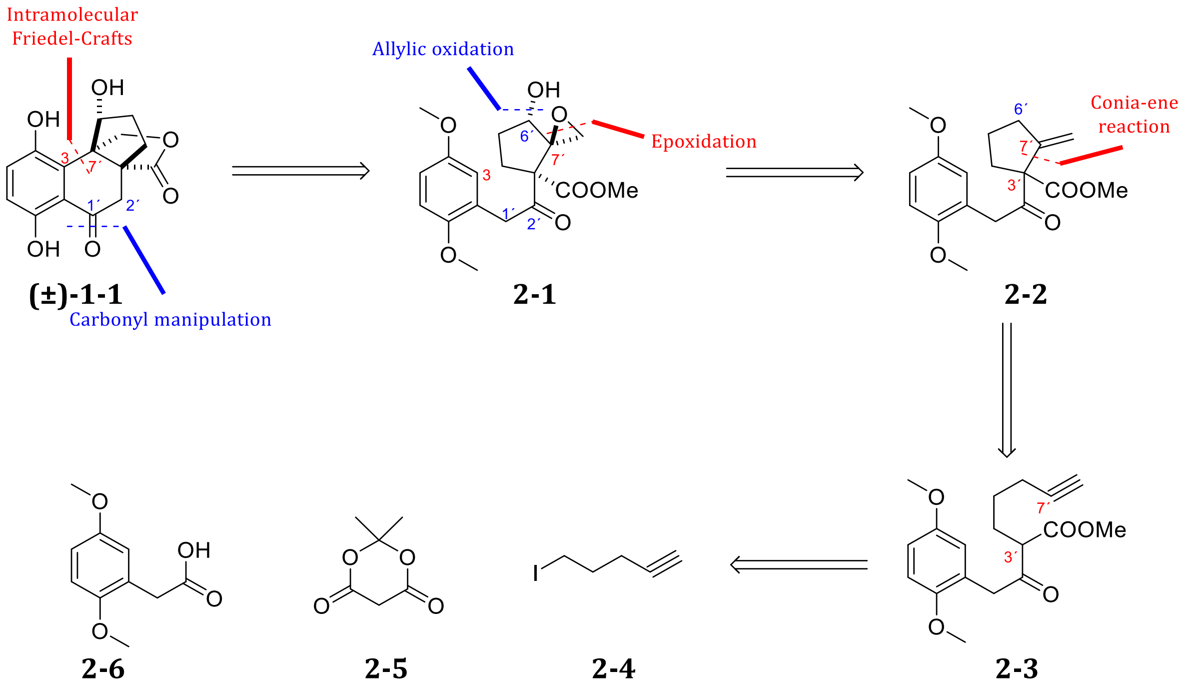


Figure 6 *Investigated disconnection points for the total synthesis of Lingzhiol*

2. Results and Discussion

2.1. Conia-ene reaction as key step

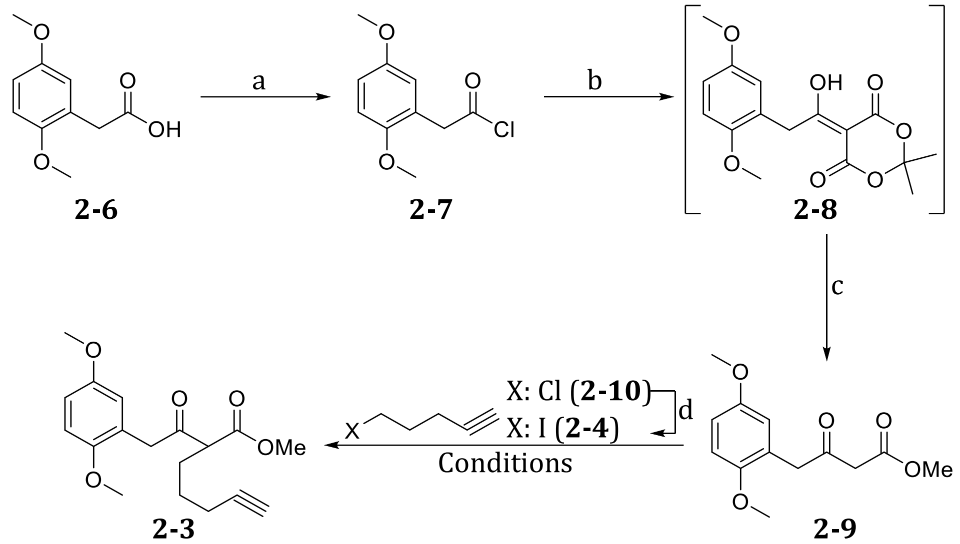
The retrosynthetic analysis of the Conia-ene route can be seen in *Scheme 10*



Scheme 10 *Retrosynthetic analysis of Conia-ene route*

The key ring forming reaction, namely the intramolecular Friedel-Crafts alkylation between C3 and C7´ is similar to Qin's[56] and Maier's[61], with its precursor **2-1** could be envisioned from **2-2** through allylic oxidation at C6'[64] and epoxidation of the exocyclic double bound at C7'. **2-2** could be in turn synthesized through a Conia-type reaction from**2-3**. The synthesis of **2-3** from simple starting materials is easily conceived. One should mention however an inherent problem of the route regarding the oxidation pattern of Lingzhiol. As can be seen in *Scheme 10*, at the end of the sequence the C2' carbon would bear the carbonyl group as opposed to the natural molecule that has it on its C1´ carbon and it is thus necessary that at one point during the total synthesis the carbonyl groups to be transposed.

It was decided that the synthesis (*Scheme 11*) would start from the commercially available 2,5-dimethoxyphenylacetic acid (**2-6**) and that the ketoester moity would be introduced through the utilization of Meldrum´s acid (**2-5**) that serves as a surrogate to dialkyl malonates. Accordingly, **2-6** was converted to its corresponding acyl chloride **2-7** by refluxing it in neat thionyl chloride. Acid chloride **2-7** was then reacted with the enolate formed from MELDRUM´s acid under mild conditions taking advantage of its anomalously high acidity.[65] The so formed acyl ketoester **2-8** was not isolated, but was immediately converted to methyl ketoester **2-9** by refluxing it in methanol, which, again due to the reactive nature of **2-8** effortlessly performed the decarboxylation.[66,67]



Scheme 11 *Synthesis of the precursor to the CONIA-ene reaction. Reagents:* ***a.)*** *SOCl$_2$, neat, reflux, 4 h, 87%;* ***b.)*** *Meldrum´s acid (**2-5**) (1.0 eq.), pyridine (2.5 eq.), DCM, 0 °C to RT, 2 h;* ***c.)*** *MeOH, reflux, 3 h, 68% (two steps);* ***d.)*** *NaI (6.0 eq.), acetone, RT, 24 h, 66%*

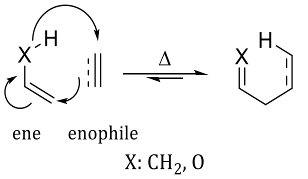
Then, the introduction of the alkyne side chain was investigated. Formally a simple analogue to the malonic ester synthesis it proved to be the difficult. As electrophile 5-iodo-1-pentyne (**2-4**) was an obvious choice, which was synthesized from the corresponding chloropentyne **2-10** through a FINKELSTEIN reaction, and one attempt was made whether it was possible to combine the two steps into a one-pot reaction.

Table 1 *Attempts to introduce alkyl side chain*

Entry	Reagents	Conditions	Result
1	1.0 eq. NaOMe 1.1 eq. 5-Iodo-1-pentyne	MeOH, Reflux, 8 h	No reaction
2	1.0 eq. K_2CO_3 1.0 eq. 5-Iodo-1-pentyne	DMF, RT, 3 d	No reaction
3	1.0 eq. LiHMDS 1.0 eq. 5-Iodo-1-pentyne	THF, -78°C to RT, 4 h	No reaction
4	1.0 eq. KHMDS 1.0 eq. 5-Iodo-1-pentyne	THF, -78°C to RT, 4 h	No reaction
5	1.2 eq. NaH 1.0 eq. 5-Iodo-1-pentyne	DMF, RT, 1 d	33 % **2-3**
6	1.2 eq. NaH 2.0 eq. 5-chloro-1-pentyne 0.5 eq. TBAI	DMF, 60 °C, 2.5 d	19 % **2-3**

As can be seen in *Table 1* among the various bases and conditions only sodium hydride in DMF provided any positive result (*Table 1*, Entry 5). Also, the effort to combine the FINKELSTEIN reaction and the alkylation into a single step, while worked, resulted in a lower yield (*Table 1*, Entry 6), and thus was not used in the synthesis. With **2-3** in hand we could start to investigate the cyclization reaction needed to form the five-membered ring with the exocyclic double bond.

Classical ”ene”-reactions belong to the group transfer reaction class of the pericyclic reactions[68] The reaction consists of an “ene” and an “enophile” component (*Scheme 12*)[68,69].

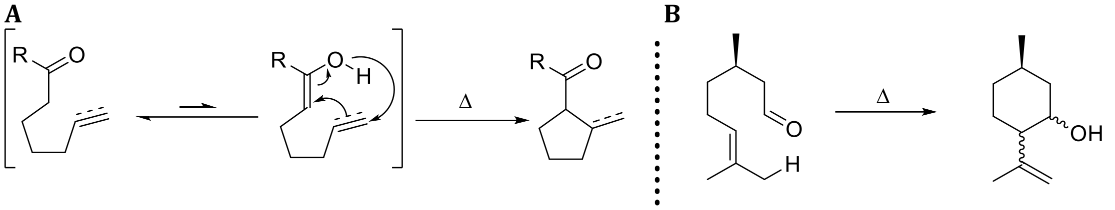


Scheme 12 *Ene-reaction*

Although the reaction is in principle reversible, it usually takes place from left to right (in which case a π-bond is replaced by a σ-bond).[68] The “ene”-component is a three-atom moity (it is not necessary for all three atoms to be carbon), that contains a double bond and at the allylic position the group which is to be transferred.[68,69] This group is in the vast majority of cases hydrogen, other than that it could be silicon, tin, or some other metals (Li, Mg, Pd)[68] The “enophile”-component can be quite varied: alkenes, alkynes, (thio)carbonyl groups, diazo compounds, singlet oxygen,[69] nitroso compounds[70] etc. In case of alkenes/alkynes, activation of the “enophile” through substitution with electron-withdrawing groups (EWG) accelerates the reaction.[68] The mechanism of the parent reaction (i.e.: reaction of an all-carbon “ene” with an alkene/alkyne) is a thermally allowed $[_{\sigma}2_{s}+_{\pi}2_{s}+_{\pi}2_{s}]$ pericyclic reaction, although in some cases evidence for a reaction through biradicals was forthcoming (usually the absence of trace amounts of cyclobutene product is a good indicator for a concerted mechanism).[68,69,71] Whilst somewhat resembling DIELS-ALDER reactions and sigmatropic rearrangements, one definitive difference is the much harsher conditions that are required for the reaction (for a thermally induced reaction that usually means 200-400 °C).[68,72]

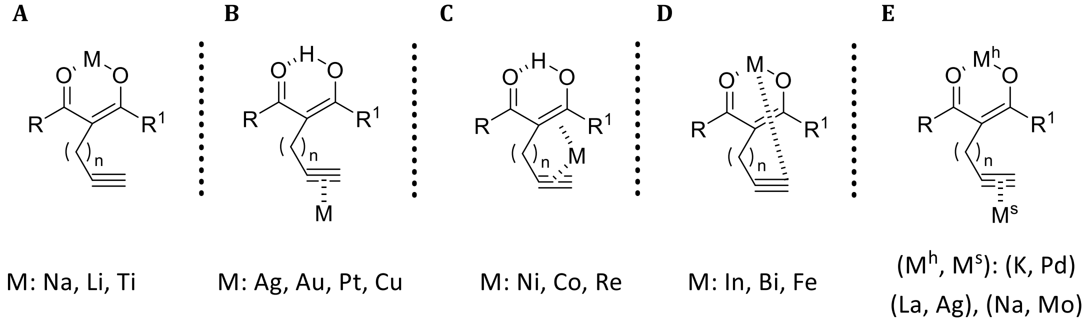
In 1975 CONIA and LE PERCHEC published an extensive research about the thermal intramolecular cyclization of unsaturated carbonyl compounds. It was noticed, that in most cases the carbonyl group participated in the reaction through its enol tautomer[73]

(*Scheme 13A*). This type of cyclization is therefore nowadays collectively known as the Conia-ene reaction.[72,74] It should be noted however, that even an enolizable carbonyl compound can undergo cyclization in which the carbonyl group acts as the enophile[72,73] (*Scheme 13B*)



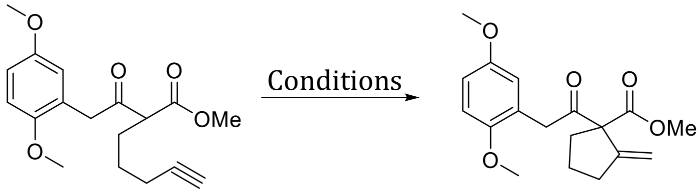
Scheme 13 *Intramolecular cyclizations of enolizable carbonyl compounds*[72,73]*:* ***A.*** *Reaction through the enol tautomer (Conia-ene reaction).* ***B.*** *Cyclization of (+)-citronellal*

In its simplest form the Conia-ene reaction is still plagued by the harsh conditions required to its initiation and progression (200-300 °C) rendering its scope of substrates rather limited.[74] Ketones and aldehydes exist mostly as carbonyl compounds and not as enols. It is thus necessary that readily enolizable carbonyl compounds should be used, the common substrates being β-ketoesters, β-diketones, β-ketoamides, malonates etc. In addition to that, in almost all the cases the system is further activated through either by facilitating the enolate formation (i.e.: deprotonation) and/or by coordination of a Lewis acid to the alkyne. The different activation modes are summarized in *Scheme 14*[74]



Scheme 14 *Different activation possibilities for Conia-ene reactions*[74]*:* ***A.*** *Enolate activation.* ***B.*** *Alkyne activation.* ***C.*** *Ene-yne activation.* ***D.*** *Double activation by single metal.* ***E.*** *Double activation by two metals (M^h: hard metal, M^s: soft metal)*

We thus started to investigate the applicability of some of the more straightforward methods existing in literature to find out whether it is possible to perform the cyclisation reaction with our substrate **2-3**.



2-3 **2-2**

Scheme 15 *Conia-ene reaction for the synthesis of* ***2-2***

First, we tried a gold(I) catalysed protocol developed by Toste *et al.*[75] Using chloro(triphenylphosphine)gold(I) as described by them (*Table 2*, Entry 1) delivered the product in 17 % yield. This could be improved to 56 % by employing a different ligand (JohnPhos, *Table 2* Entry 2). Although this yield was adequate enough to enable further investigation of the route, we also tried different methods to materialize the ring closing. Thus, we attempted the reaction by deprotonating with potassium tert-butoxide (*Table 2*, Entry 3) according to Trauner *et al.*[76] which however failed to deliver the product. Executing the reaction with double activation using copper(I) iodide[77] to activate the triple bond (*Table 2*, Entry 4) also did not lead to product formation, neither did the use of titanium enolate[78] instead of potassium (*Table 2*, Entry 5). We then turned to activation of the alkyne moity without the use of base. Conia himself published a simple method in which a Brønsted acid would serve as an assist to the enolization and mercury(II) chloride activates the triple bond[79] that however failed in our case (*Table 2*, Entry 6).

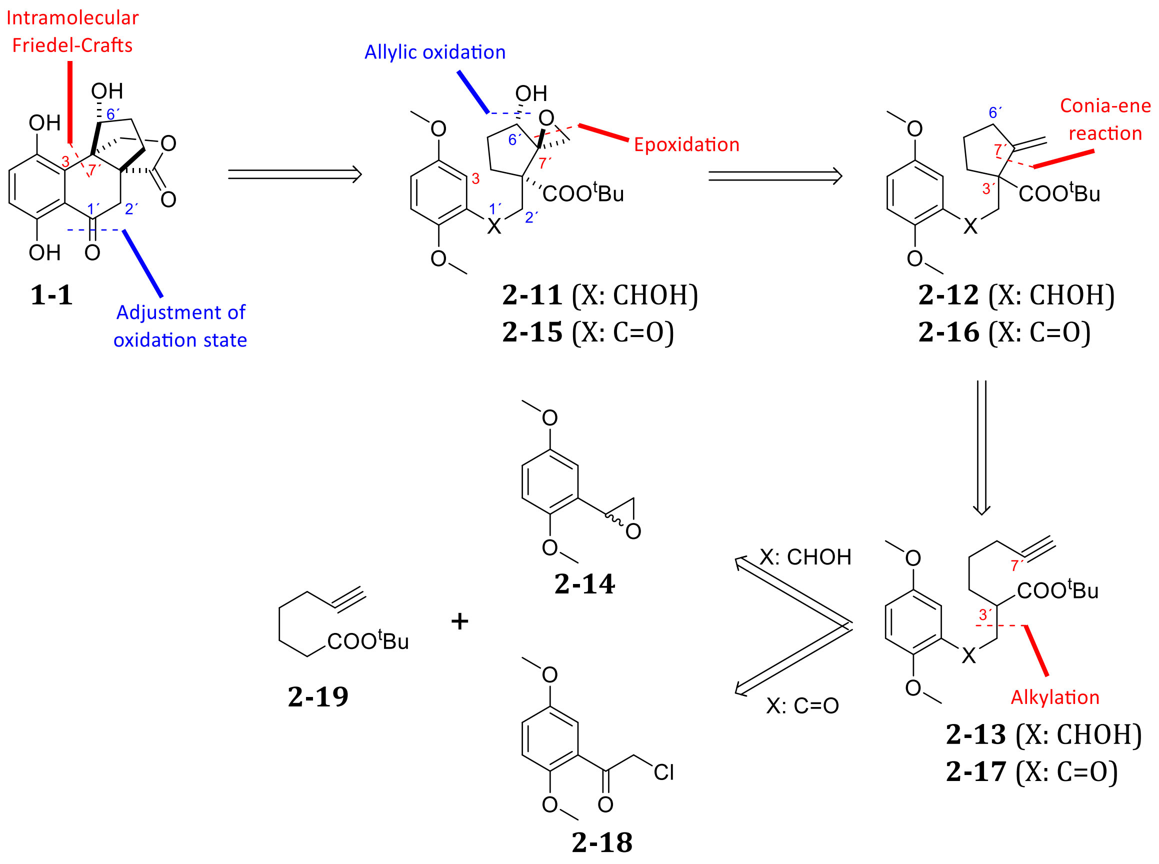
Table 2 *Attempts to Conia-ene reaction*

Entry	Reagents	Conditions	Result	Activation type (see *Scheme 14*)
1[75]	0.1 eq. $(PPh_3)AuCl$ 0.1 eq. AgOTf	DCM, RT, 1 h	17%	**B**
2[75]	0.1 eq. (JohnPhos)AuCl 0.1 eq. AgOTf	DCM, RT, 1 h	56%	**B**
3[76]	1.0 eq. KO^tBu	DMSO, RT, 3 h	No reaction	**A**
4[77]	1.0 eq. KO^tBu 1.0 eq. CuI	THF, RT, 12 h	No reaction	**E**
5[78]	0.4 eq. $Ti(O^iPr)_4$ 1.2 eq. CuI (1.2 eq.)	THF, -78 °C to RT, 1 d	No reaction	**E**
6[79]	0.1 eq. $HgCl_2$ 0.1 eq. HCl	DCM/EtOH, RT, 2 d	No reaction	**B** (or **E**)

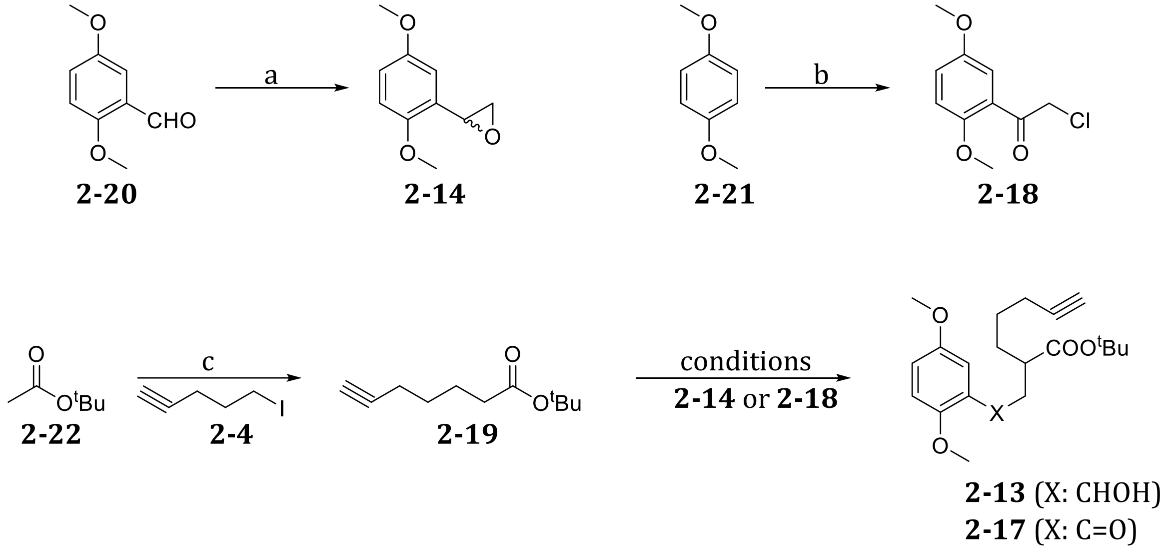
With **2-2** in hand we turned our attention to the oxidation of the allylic position. We intended to follow the procedure that was already used in our research group.[61] However upon performing the reaction with catalytic amounts of selenium dioxide and

TBHP we obtained a highly complex mixture with signs of decomposition. Since selenium dioxide is known to oxidize the α-position of carbonyl group[80,81] in addition to the allylic position of an alkene, we tried to achieve the allylic oxidation using singlet oxygen as a milder alternative, that is known to react with alkenes at the allylic position through an ene-reaction generating allylic peroxides that can be reduced by simple means to alcohols.[82–84] Singlet oxygen was generated through the irradiation of a methanolic solution of **2-2** by visible light under oxygen atmosphere using either tetraphenylporphyrin (TPP)[85–87] or rose bengal (RB)[87] as photosensitizer. Regrettably all our attempts proved to be in vain, as conversion of any kind was never observed.

In order to circumvent the problems associated with the presence of the carbonyl group at the 2’ position instead at 1’, a slightly modified strategy was devised, that nevertheless still utilised the CONIA-ene reaction as one of its key steps (*Scheme 16*). In this scenario the precursor to the CONIA-ene cyclisation would be acquired through the alkylation of the *tert*-butyl ester **2-19** either with epoxide **2-14** or with α-ketochloride **2-18**. Thus, the position of the oxygen would correspond to the natural product. One major disadvantage of this approach is the loss of the double activation of the “*ene*” component. Although transformations of this kind are known, they usually require the prior activation of the carbonyl group as silyl enol ethers or as analogous compounds.[88,89] Another problematic aspect is the alkylation of **2-19** with **2-14** or **2-18**, which is scarcely know in the literature. Epoxide **2-14** was synthesized (*Scheme 17*) from 2,5-dimethoxybenzaldehyde (**2-20**) following the protocol of COREY and CHAYKOVSKY,[90] while α-ketochloride **2-18** was acquired by treating 1,4-dimethoxybenzene (**2-21**) with chloroacetyl chloride in a FRIEDEL-CRAFTS acylation.[91] *Tert*-butyl hept-6-ynoate (**2-19**) was synthesized from *tert*-butyl acetate and iodide **2-4**.



Scheme 16 *Modified retrosynthetic analysis of the Conia-ene route*



Scheme 17 *Synthesis of precursors to the modified Conia-ene route. Reagents and conditions:* ***a.)*** *NaH (1.2 eq.), trimethylsulfonium iodide (1.2 eq.), THF, 55 °C, 2 h, 51%;* ***b.)*** *$AlCl_3$ (2.0 eq.), chloroacetyl chloride (2.0 eq.), DCM, RT, 8 h, 47%;* ***c.)*** *DIPA (1.2 eq.), ^{n}BuLi (1.2 eq.), DMPU (4.0 eq.), 5-iodopent-1-yne (**2-4**) (1.0 eq.), THF, -78 °C to RT, 24 h, 77%*

Having all precursors at hand, the alkylation of **2-19** was investigated. As mentioned before, these type of alkylations are seldom reported in literature[92–95], thus we opted to investigate a number of general methods. (*Table 3*)

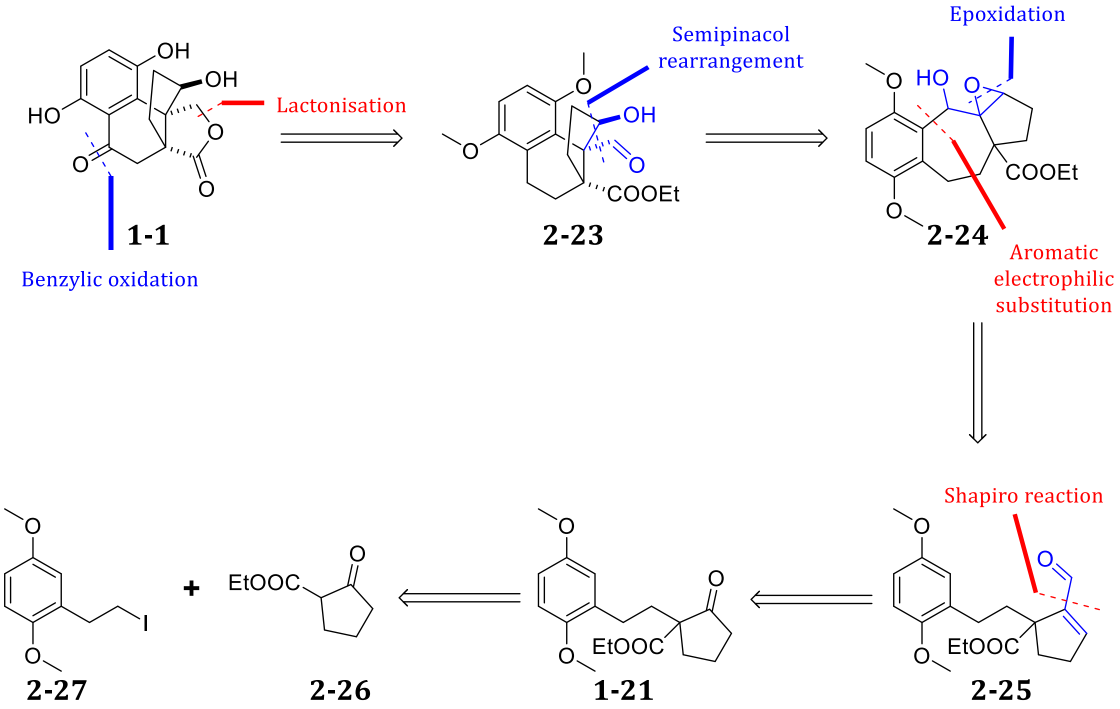
Table 3 *Attempts to alkylate alkyne* ***2-19***

Entry	Electrophile (Product)	Reagents and Conditions	Result
1	**2-14** (**2-13)**	1.2 eq. DIPA 1.2 eq. ^{n}BuLi 1.0 eq. **2-19** THF, -78 °C to RT, overnight	No conversion
2	**2-14** (**2-13)**	1.2 eq. DIPA 1.2 eq. ^{n}BuLi 4.0 eq. DMPU 1.0 eq. **2-19** THF, -78 °C to RT, overnight	No conversion
3	**2-14** (**2-13)**	1.2 eq. LiHMDS 1.0 eq. **2-19** THF; -78 °C to RT, overnight	No conversion
4	**2-18**(**2-17)**	1.2 eq. DIPA 1.2 eq. ^{n}BuLi 1.0 eq. **2-19** THF, -78 °C to RT, overnight	No conversion

As can be seen, no attempt was successful, and this negative outcome combined with the fact, that the CONIA-ene reaction itself was expected to be more difficult led us to abandon this route. With this we concluded our investigation of routes utilizing the CONIA-ene reaction and our attention was directed to other possibilities.

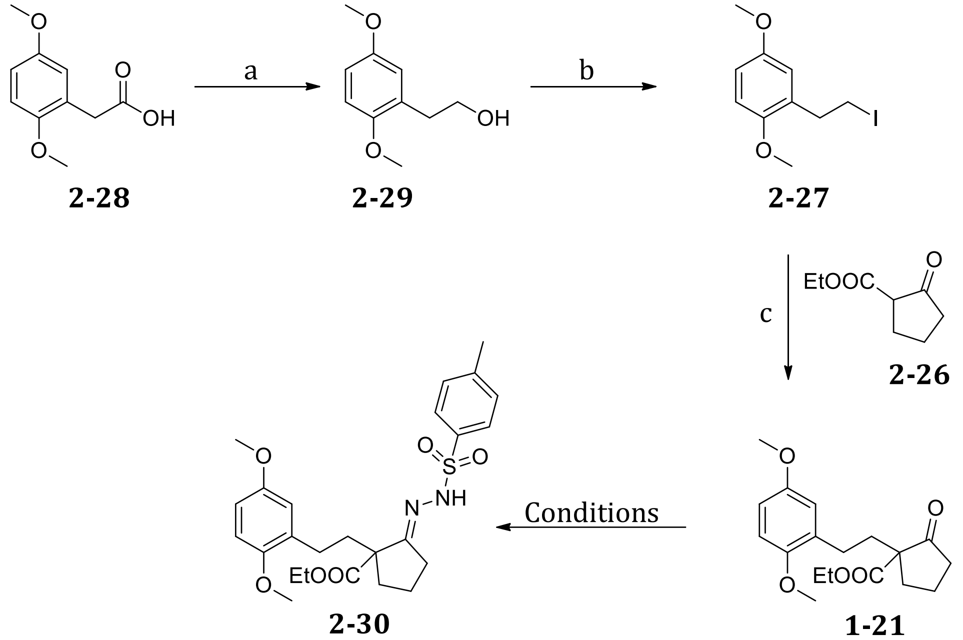
2.2. Semipinacol reaction as key step

As a short detour we investigated a strategy that relies on a Semipinacol rearrangement as key step, the retrosynthetic analysis thereof can be seen in *Scheme 18.*



Scheme 18 *Retrosynthetic analysis of the Semipinacol route*

We envisioned that epoxide **2-24** could be subjected to a Semipinacol rearrangement,[96] which would give advanced intermediate **2-23**, the conversion of which to Lingzhiol akin to literature should be straightforward. Since compound **1-21** is literature known, our efforts were focused on the exploration of the Shapiro reaction, which in turn requires a corresponding sulfonyl hydrazone. We synthesized ketoester **1-21** (*Scheme 19*) from 2-(2,5-dimethoxyphenyl)acetic acid (**2-6**) as reported by Rengarasu and Maier[61] by first reducing the acid to its corresponding alcohol **2-29** with lithium aluminium hydride, then converting the alcohol into iodide **2-27** by reacting it with iodine and triphenyl phosphine. Alkylation of **2-26** with this iodide furnished **1-21** with acceptable yields. We then turned our attention to the synthesis of the required sulfonyl hydrazone. We chose to use *p*-toluenesulfonyl hydrazide as substrate and tried to achieve the hydrazone formation at first by using methods known in literature. We thus first refluxed **1-21** with *p*-toluenesulfonyl hydrazide according to Hodgson *et al.*[97] (*Table 4*, *Entry 1*), and when this procedure provided no product we tried a slightly modified method using neutral alumina as catalyst to facilitate the conversion according to Szántay *et al.*[98], again, without success. (*Table 4*, *Entry 2*). Having met these failures, we opted to attempt a simple procedure using titanium tetrachloride as LEWIS acid to enable the hydrazone formation, which to our delight provided us the hydrazone **2-30** in reasonable yield. (*Table 4*, *Entry 3*).

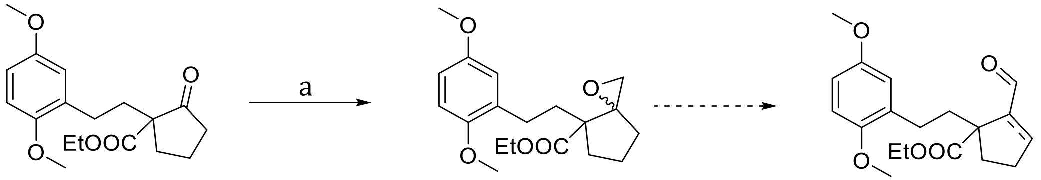


***Scheme 19** Synthesis of hydrazone **2-30** . Reagents and conditions: **a.)** $LiAlH_4$ (2.0 eq.), THF, 55 °C, overnight, 80%; **b.)** I_2 (1.1 eq.), PPh_3 (1.1 eq.), Imidazole (3.0 eq.), DCM, 0 °C to RT, overnight, 70%; **c.)** K_2CO_3 (3.0 eq.), **2-26** (1.0 eq.), DMF, 75 °C, overnight, 55%*

Table 4** Synthesis of hydrazone **2-30** from ketoester **1-21

Entry	Reagents and Conditions	Result
1[97]	1.0 eq. **1-21** 2.0 eq. *p*-Toluenesulfonyl hydrazide THF/EtOH: 1/1, Reflux, 8 h	No conversion
2[98]	1.0 eq. **1-21** 2.0 eq. *p*-Toluenesulfonyl hydrazide 10.0 eq. Al_2O_3 (Brockmann I, neutral) EtOH, Reflux, 8 h	No conversion
3	1.0 eq. **1-21** 1.0 eq. *p*-Toluenesulfonyl hydrazide 1.0 eq. $TiCl_4$ THF, 0 °C to RT, overnight	50%

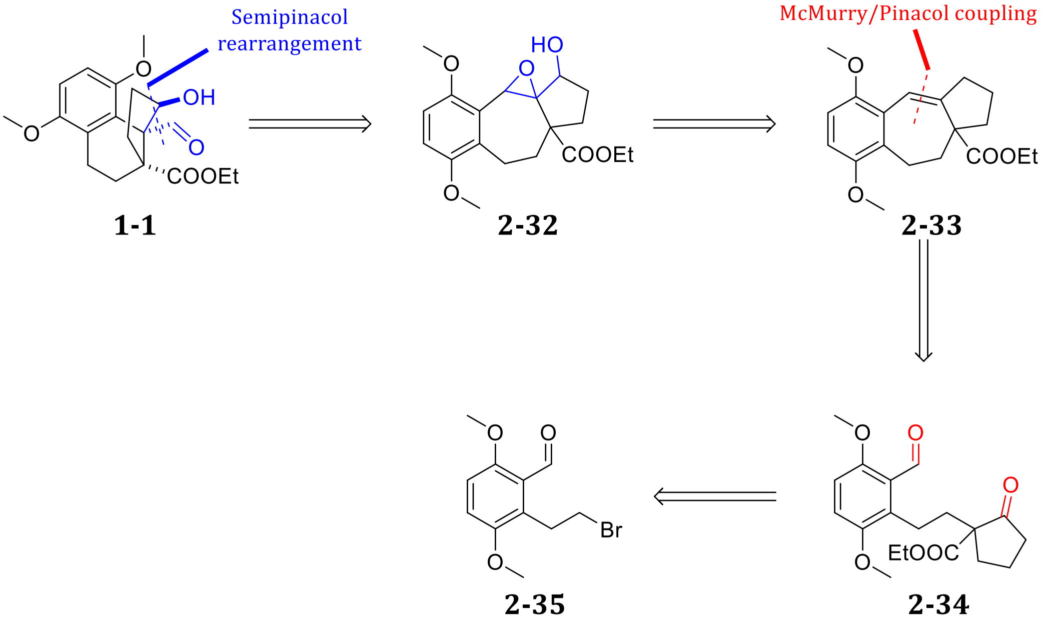
With **2-30** at hand, the SHAPIRO reaction[99] was investigated. However, reacting **2-30** with *n*-buthyllithium at -78 °C using tetramethylethylenediamine (TMEDA) as solvent, then quenching the mixture with dimethylformamide as described in the literature[100,101] provided no product. In order to circumvent this problem, we synthesized epoxide **2-31** from **1-21** (*Scheme 20*) using a procedure already reported in our group[54], and tried to perform an epoxide-aldehyde rearrangement either with sulfuryl chloride,[102] that would have directly given **2-25**, or with boron trifluoride[103,104] which would have provided the saturated analogue of **2-25**, neither of which proved to be successful.



1-21 **2-31** **2-25**

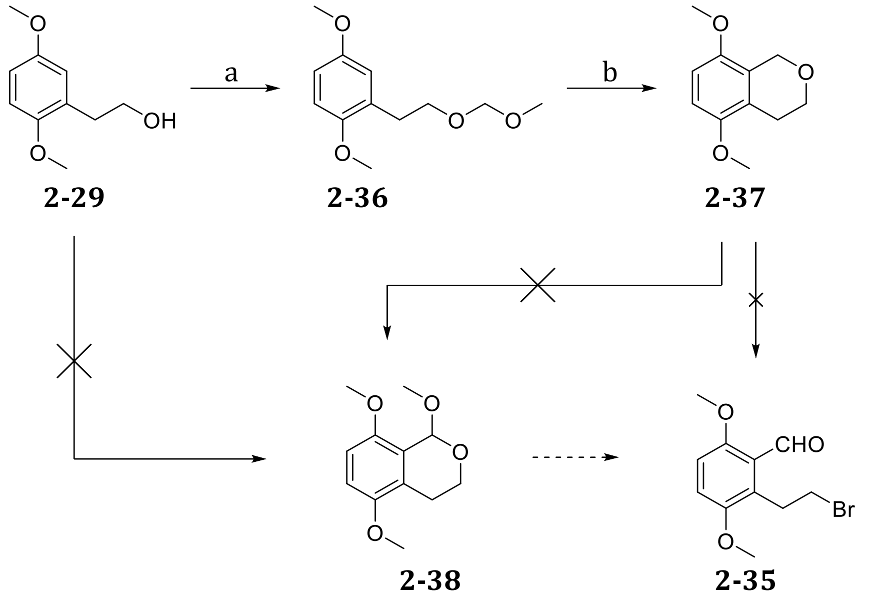
Scheme 20 *Synthesis of **2-31**. Reagents and conditions: **a**.) CH_2Br_2 (1.5 eq.), ^nBuLi (1.2 eq., 2.5 M in hexane), THF, -78 °C to RT, overnight, 54%*

We also tried to synthesize a precursor to an alternative Semipinacol rearrangement. (*Scheme 21*) Lingzhiol **1-1** could thus be formed from epoxide **2-32**, provided, that the tertiary cation emerges. Accordingly, **2-32** could be envisioned from alkene **2-33**, which in turn could be gained from **2-34** through a MCMURRY or Pinacol coupling.[105–107] We thus investigated the possibility to synthesize **2-34** from aldehyde **2-35**, which, after suitable carbonyl group protection could partake in an alkylation analogous to the synthesis of **1-21**. We planned the synthesis **2-35** according to literature examples.



Scheme 21 *Retrosynthetic analysis of the modified Semipinacol route*

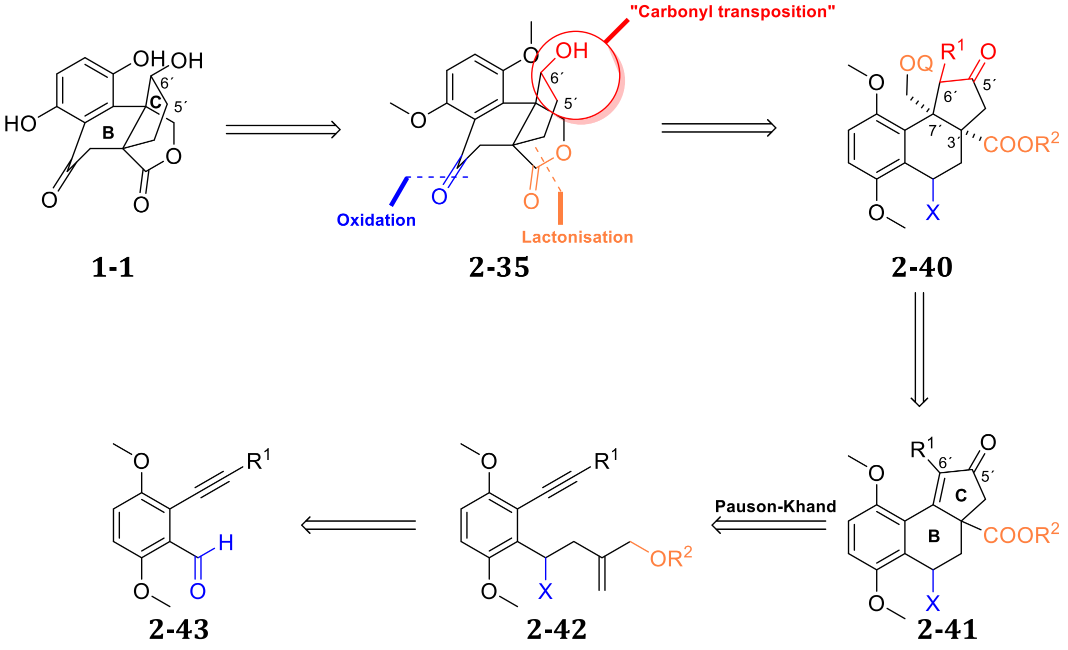
We conceived the synthesis of **2-35** starting from alcohol **2-29** which was converted to its MOM ether followed by the cyclisation to isochroman derivative **2-37** by treating **2-36** with trimethylsilyl trifluoromethanesulfonate.[108,109] (*Scheme 22*) Opening of isochromans directly to compounds analogous to **2-35** is literature know, thus we first tried reacting **2-37** with copper(II) bromide in refluxing acetonitrile[110,111] from which however no product could be isolated. We then tried to synthesize 1-methoxyisochroman **2-38** the conversion of which to **2-35** could have been achieved by treatment with trimethylsilyl bromide and tetrabutylammonium bromide.[108] We therefore attempted the oxidation of **2-37** with DDQ unfortunately without success.[108] We also tried to access **2-38** directly from alcohol **2-29** by refluxing it in triethyl orthoformate in the presence of catalytic amounts of *p*-toluenesulfonic acid,[112] however only starting material was isolable. Since with this result we deemed this route to be futile, we shifted our attention to other possibilities.



Scheme 22 *Synthetic studies towards* ***2-35****. Reagents and conditions:* ***a.)*** *MOMCl (1.5 eq.), DIPEA (1.5 eq.), DCM, 0 °C to RT, overnight, 87%;* ***b.)*** *TMSOTf, (0.25 eq.), MeCN, 0 °C to RT, 6 h, 24%*

2.3. PAUSON-KHAND reaction as key step

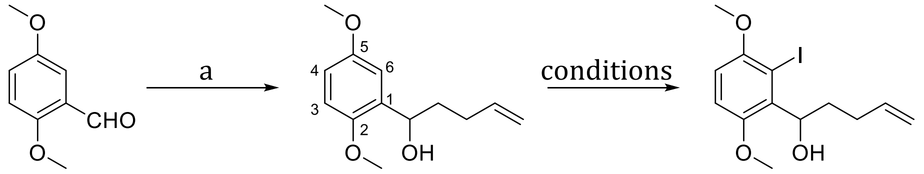
We envisioned a route using the PAUSON-KHAND reaction as one of the key reaction the form the **B** and **C** ring in a single step. The retrosynthetic analysis can be seen in *Scheme 23*.



***Scheme 23** Retrosynthetic analysis of the PAUSON-KHAND route*

Starting from an adequately substituted benzaldehyde derivative like **2-43**, the alkene containing moiety could be introduced using nucleophilic addition followed by the oxidation of the terminal allylic position and adequate protection or conversion of the hydroxyl group. Then the PAUSON-KHAND reaction[113,114] would be applied, that would afford **2-41**, which already contains three out of four rings found in the natural product. The introduction of the necessary hydroxymethyl portion could be materialized through umpolung chemistry[115] (the stereochemical outcome, i.e the relationship between the substituents on 3´ and 7´ is expected to be *syn* due to the geometry of **2-41**, after which however the transposition of the carbonyl group needs to be addressed. As can be seen in *Scheme 23* the newly formed **C** ring bears the oxygen atom on its 5´ position (Lingzhiol numbering), that does not correspond to the natural product. The transposition of the carbonyl group[116] must be therefore attempted, which nevertheless raises issues, namely the number of steps of such procedure and the regiochemistry in case if the intermediate after the addition of a formyl anion synthon to **2-41** cannot be trapped as an enolate anion. Both difficulties could be potentially tackled if the PAUSON-KHAND reaction would be performed with a silylalkynyl analogue (then $R^1 = SiR_3$ in *Scheme 23*) then after reducing the carbonyl group on C5´ to a methylene group, the silyl group on C6´could be converted to a hydroxyl group using FLEMING-TAMAO oxidation.[117] This approach should thus mitigate the problems associated with the carbonyl transposition, also should not pose any setback to the ring closing step, as reactions of alkynylsilanes under PAUSON-KHAND[118–121] or other conditions providing analogous products[122–125] are amply reported.

We thus started to consider our options to synthesize the precursor for the PAUSON-KHAND reaction. The use of the SONOGASHIRA coupling[126] to introduce the acetylenic side chain is evident. This in turn requires the appropriate substitution of the aromatic core, which however should be quite feasible using directed *ortho* metalation[127,128] to substitute the ortho position with iodine. We could also utilize the fact, that the *ortho* metalation of lithium benzylalcoholate salts were reported,[129,130] and therefore we conceived a route starting from the commercially available 2,5-dimethoxybenzaldehyde (**2-20**) (*Scheme 24*). We converted it through a GRIGNARD reaction to **2-44**, which served as a model compound to flesh out the feasibility of the directed *ortho* metalation.



2-20 **2-44** **2-45**

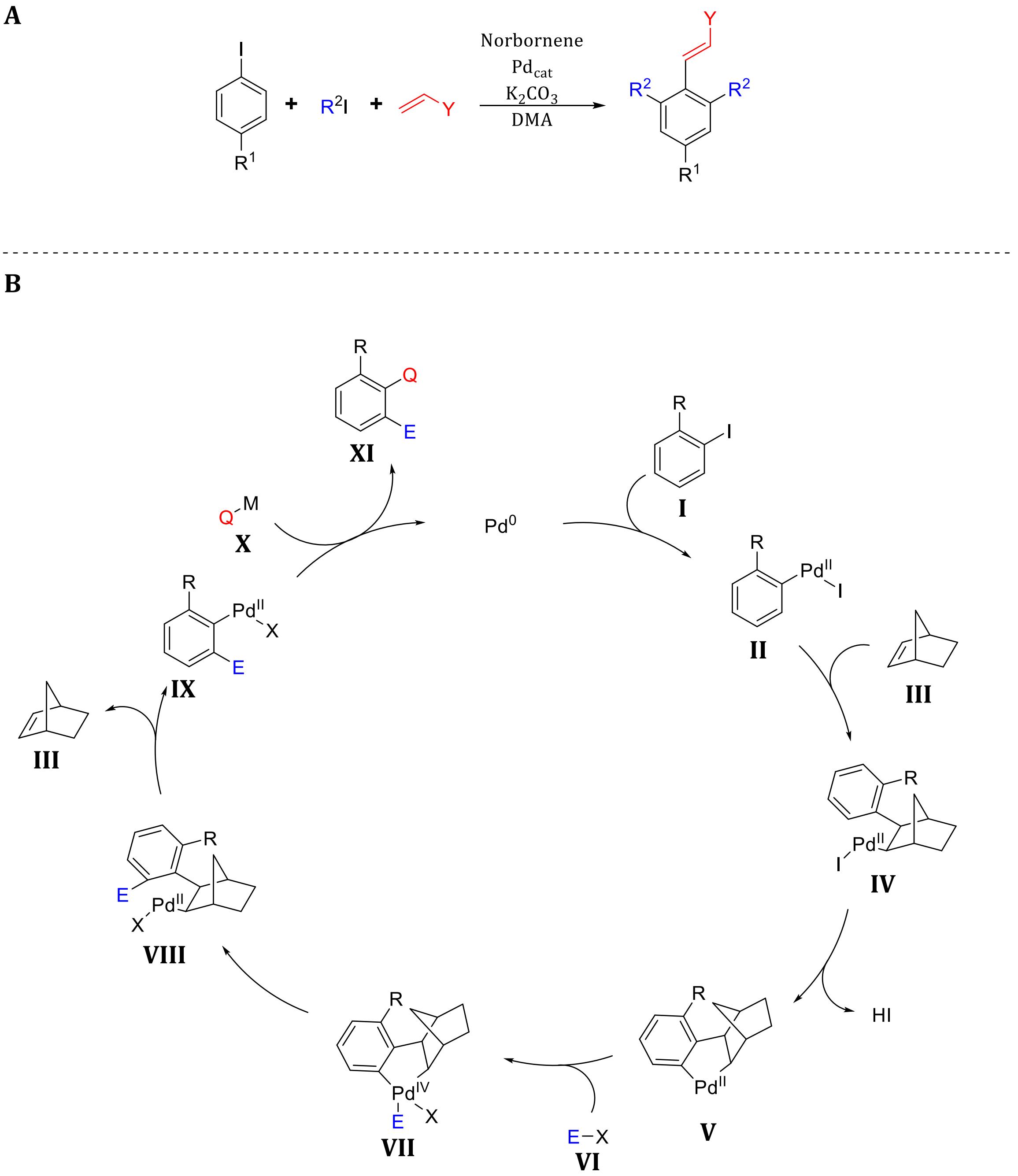
Scheme 24 *Synthetic studies towards SONOGASHIRA precursor. Reagents and conditions:* ***a.)*** *Mg (1.8 eq.), 4-bromo-1-butene (1.5 eq.), THF, Reflux to RT, overnight, 79%*

When we however applied literature reported conditions,[131,132] we found that either no reaction occurred, or the iodination took place at the regioisomeric 4 position (*Table 5*). Lowering the temperature resulted in no conversion, and switching the source of lithium generally has not changed the outcome neither did the use of benzene as a solvent, which may be ascribed to the low solubility of the resulting dianion.

Table 5 *Attempts to lithiate* ***2-44***

Entry	Reagents and Conditions	Result
1	2.2 eq. ^{n}BuLi 1.1 eq. Iodine Diethyl ether, 0 °C	No conversion
2	2.2 eq. ^{n}BuLi 1.1 eq. Iodine Diethyl ether, -78 °C	No conversion
3	2.2 eq. ^{t}BuLi 1.1 eq. Iodine Diethyl ether, 0 °C	Small amounts of regioisomer
4	2.2 eq. ^{t}BuLi 1.1 eq. Iodine Diethyl ether, -78 °C	No conversion
5	2.2 eq. ^{n}BuLi 1.1 eq. Iodine Benzene, 0 °C	No conversion
6	2.5 eq. ^{n}BuLi 3.0 eq. ^{n}BuMgBr 2.5 eq. TMEDA 1.5 eq. Iodine Diethyl ether, -15-(-10) °C	Small amounts of regioisomer

Considering these results, we turned to an alternative, that would have enabled us to doubly functionalise an aromatic iodide with control over regiochemistry in a single step. In the late 90s and early 2000s CATELLANI and her co-workers developed a palladium catalysed methodology, that made it possible to simultaneously functionalise the *ortho* and the *ipso* position of an aryl iodide. (*Scheme 25A*)[133–135] The catalytic cycle[136–141] starts with the oxidative addition of aryl iodide **I** to the Pd(0) affording aryl palladium iodide **II.** Subsequently, norbornene (**III**) insertion into complex **II** results in the formation of the stable *cis,exo*-aryl norbornyl palladium adduct **IV** followed by C-H metalation of the *meta* hydrogen of the aryl substituent to form aryl norbornyl palladacycle **V.**[142] The following step is the oxidative addition of an appropriate organic halogenide **VI** to afford complex **VII** on which rapid reductive elimination takes place producing complex **VIII.**



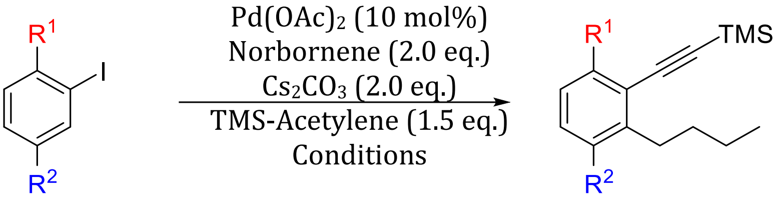
***Scheme 25** Catellani reaction. **A**: Original methodology by Catellani.[133] **B**: Catalytic cycle (ligands on palladium are omitted for clarity)*

The mechanism of the conversion of **V** to **VIII** was investigated by ECHAVARREN *et al.*, whose theoretical calculations suggested, that if an aryl iodide is used as the electrophilic species **VI**, then complex **V** is transmetallated directly to **VIII** by an aryl palladium halide (i.e.: E-Pd-X formed by the oxidative addition of E-X to Pd(0)).[143] This was nevertheless refuted by the computational studies of CATELLANI, which showed, that such transmetallation is energetically favoured only if the *ortho* position with respect to the iodide is not substituted (i.e.: R: H), and the formation of the Pd(IV) oxidative adducts are favoured in other cases.[144] Moreover, Pd(IV) complexes formed by the oxidative addition of various allylic and benzylic halides to aryl norbornyl palladacycles had already been characterised in the late 80s and early 90s,[145–147] thus the involvement of Pd(IV) species is nowadays rarely disputed.[148] *Retro*-carbopalladation of **VIII**, accelerated by steric crowdedness,[136,138,148] affords **IX**, which then participates in an another cross-coupling reaction (HECK, SUZUKI, SONOGASHIRA)[136,138–140,148] with an appropriate organometallic species **X** that terminates the reaction affording the *ortho*/*ipso* functionalised product **XI** and Pd(0), and thus regenerating the catalyst.

The role of norbornene in the reaction is pivotal. Carbopalladation of **II** is accelerated by the fact, that the strain in norbornene is relieved upon the addition.[136] Also, the β-hydride elimination, which usually makes alkyl palladium complexes rather unstable,[149] is severely inhibited by the *cis*/*exo* stereochemistry of complex **IV**,[150,151] since it would require a *syn*-coplanar conformation of the hydrogen and the palladium unit.[152] The bulkiness of norbornene is also beneficial in order to facilitate the *retro*-carbopalladation (**VIII** → **IX**) as mentioned before.

The issue of selectivity still needs to be addressed. Since the CATELLANI reaction is performed as a one-pot procedure, theoretically a plethora of products could arise, as two organic halogenides (**I** and **VI**), an organometallic compound (**X**) and different palladium species are present at the same time. General guidelines however can reduce the number of possibilities. For example, it has been shown that aryl halogenides tend to participate in an oxidative addition onto Pd(0) with higher reactivity then their aliphatic counterparts, due to the back-donation between the Pd(0) and the iodoarene's π^* orbital.[153] Also the oxidative addition of the aliphatic halide to the Pd(II) species **V** is expected to be easier than that of an aryl halide owing to the steric crowdedness of the aryl norbornene palladacycle.[138] Regardless, there are still other side reactions, that could take place (e.g.: aryl palladium **II** reacting with the terminating reagent **X**) which can be suppressed with the careful adjustment of the reaction conditions.[154]

We thus decided to investigate if the reaction could serve our needs. We oriented ourselves along the work of ZHOU *et al.*[155] who used different terminal alkynes in a copper free SONOGASHIRA reaction[156,157] to terminate the reaction sequence. We applied their methodology to three substrates (*Scheme 26*), two of which (2-iodotoluene (**2-46a**) and 2-iodoanisole (**2-46b**)) were reported by themselves and were included to validate their findings. Moreover, we used *n*-butyl bromide or iodide as an electrophilic species to introduce a butyl group to the *meta* position in order to reduce the complexity associated with the presence of an additional double bond as well as for the sake of comparison with literature results.



2-46a-c **2-47a-c**

Scheme 26 *Screening the applicability of the CATELLANI reaction*

During our screening process, we left the palladium source (Pd(OAc)$_2$), the norbornene, the base (Cs$_2$CO$_3$) and TMS-acetylene unchanged. (*Scheme 26*) The conditions reported by the literature[155] are using *n*-butyl bromide as electrophilic reagent, sodium iodide, presumably to further activate the butyl bromide, tri(2-furyl)phosphine as ligand, acetonitrile as solvent, and heating the mixture at 90 °C (*Table 6*, *Entry 1*). We further tried to replace the butyl bromide with butyl iodide and omit sodium iodide (*Table 6*, *Entry 2*), to use a different solvent (NMP instead of acetonitrile, *Table 6*, *Entry 3*) or to use tris(4-methoxyphenyl)phosphine as ligand (*Table 6*, *Entry 4*). The reactions were followed by GC-MS measurements to investigate the mixtures. Regardless of the employed conditions, the outcome for each case was less than satisfactory.

Table 6 *Screening of conditions of the* CATELLANI *reaction*

Entry	Starting Material	Reagents and Conditions	Result
1	**2-46a** (R^1: CH$_3$, R^2: H) **2-46b** (R^1: OCH$_3$, R^2: H) **2-46c** (R^1: OCH$_3$, R^2: OCH$_3$)	2.0 eq. NaI 4.0 eq. ^{n}BuBr 20 mol% P(2-furyl)$_3$ CH$_3$CN, 90 °C	**2-46a**: Complex mixture **2-46b**: Complex mixture **2-46c**: Mainly homo-coupled side product
2	**2-46a** (R^1: CH$_3$, R^2: H) **2-46b** (R^1: OCH$_3$, R^2: H) **2-46c** (R^1: OCH$_3$, R^2: OCH$_3$)	4.0 eq. ^{n}BuI (4.0 eq.) 20 mol% P(2-furyl)$_3$ CH$_3$CN, 90 °C	**2-46a**: Complex mixture **2-46b**: Complex mixture **2-46c**: Mainly homo-coupled side product
3	**2-46a** (R^1: CH$_3$, R^2: H) **2-46b** (R^1: OCH$_3$, R^2: H) **2-46c** (R^1: OCH$_3$, R^2: OCH$_3$)	2.0 eq. NaI 4.0 eq. ^{n}BuBr 20 mol% P(2-furyl)$_3$ NMP, 90 °C	**2-46a**: Complex mixture **2-46b**: Complex mixture **2-46c**: Mainly homo-coupled side product
4	**2-46a** (R^1: CH$_3$, R^2: H) **2-46b** (R^1: OCH$_3$, R^2: H) **2-46c** (R^1: OCH$_3$, R^2: OCH$_3$)	2.0 eq. NaI 4.0 eq. ^{n}BuBr 20 mol% P(4-MeO-Ph)$_3$ CH$_3$CN, 90 °C	**2-46a**: Complex mixture **2-46b**: Complex mixture **2-46c**: Mainly homo-coupled side product

When we used 2-iodotoluene (**2-46a**) or 2-iodoanisole (**2-46b**) as substrates, the reaction resulted in complex mixtures in which the respective products were indeed present, however usually only in small amounts, with the major constituents being undesired side products. To showcase such a mixture, the GC-MS spectrum of the reaction of 2-iododtoluene (**2-46a**) under the reported literature conditions (*Table 6*, *Entry 1*) is presented in *Figure 7.*

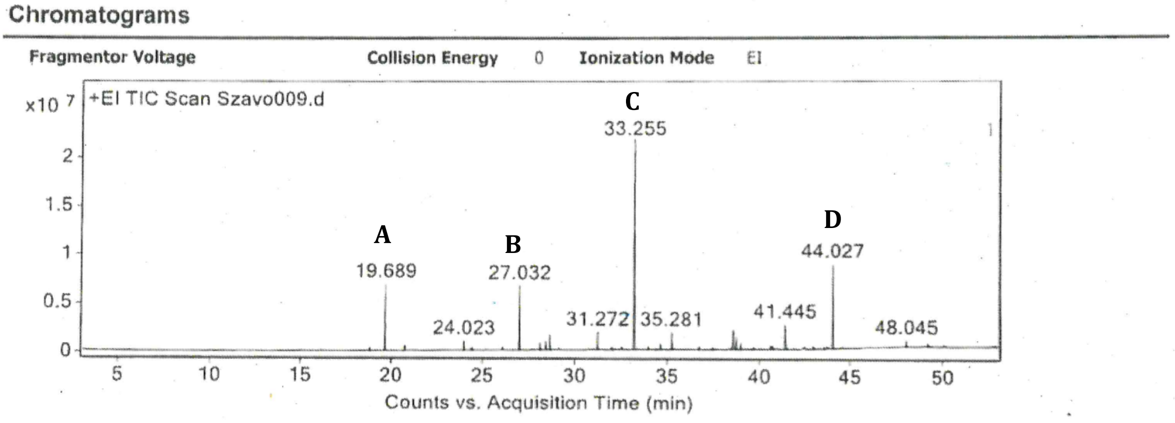
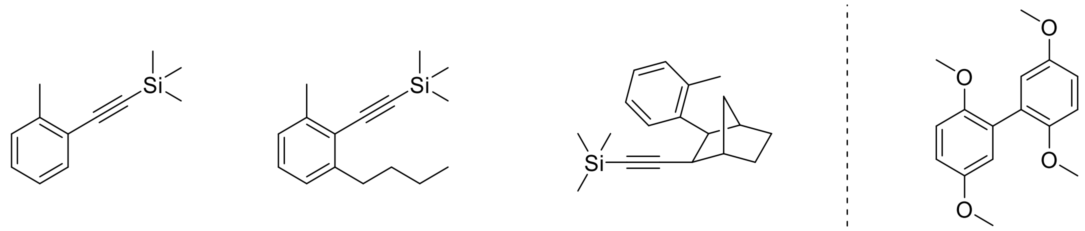


Figure 7 *GC-MS spectra of the* CATELLANI *reaction of 2-iodotoluene (**2-46**) under literature reported conditions.*

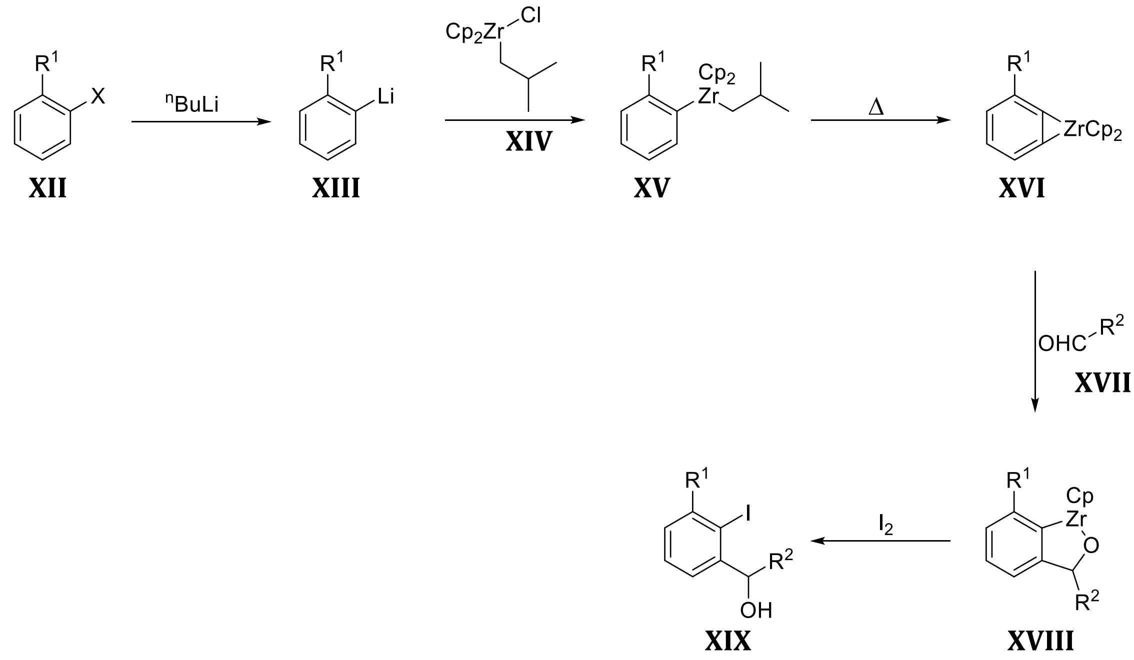
As can be seen, the mixture consists of four major components (*Figure 8*): **A** which is the SONOGASHIRA product between 2-iodotoluene **2-46a** and TMS-acetylene, **B** which is the expected CATELLANI product **2-47a** (R^1: CH$_3$, R^2: H), **C** that is the SONOGASHIRA product of the arylnorbornyl palladium species and TMS-acetylene and lastly **D** which could not be identified with certainty. Large number of other, smaller impurities were also present. The reaction of 2-iodo-1,4-dimethoxybenzene (**2-46c**) under these conditions was even more disappointing. GC-MS analysis showed no formation of product, with the major constituent of the reaction mixture being the presumed homo diaryl coupled product **2-48** (*Figure 8*).



A **B (= 2-47a)** **C** **2-48**

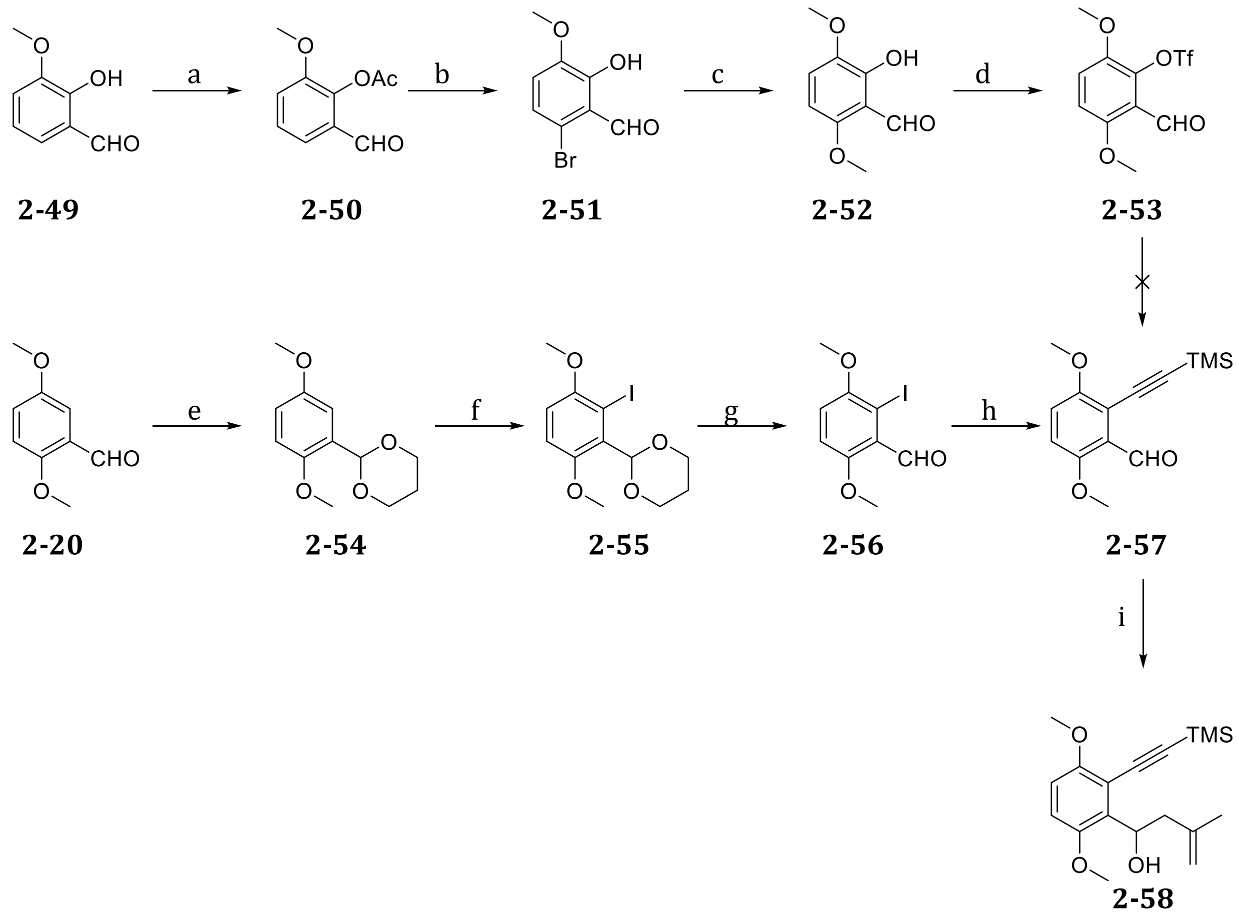
Figure 8 *Constituents of CATELLANI reaction mixtures (**A**-**C**: 2-iodotoluene (**2-46a**) as starting material; **2-48**: 2-iodo-1,4-dimethoxybenzene (**2-46c**) as starting material)*

During these investigations we also attempted to furnish the *ortho*/*ipso* substitution through zirconium chemistry, the basic principle of which[158–161] can be seen in *Scheme 27*. Aryl halide **XII** lithiated to give **XIII** which then participate in a transmetalation with **XIV** affording **XV** that is converted upon heating to zirconocene benzyne complex **XVI**. Reaction of this complex with an electrophile (carbonyl compounds, nitriles etc.) affords **XVIII** (the regiochemistry is determined by steric factors), which in turn can react with a second electrophile to give the *ortho*/*ipso* substituted compound **XIX**. Correspondingly, we attempted to convert 2-iodo-1,4-dimethoxybenzene (**2-46c**) according to this procedure, however the reaction mainly gave homo diaryl coupled product **2-48** again.



Scheme 27 *Ortho/ipso substitution of aryl halides through zirconium chemistry*

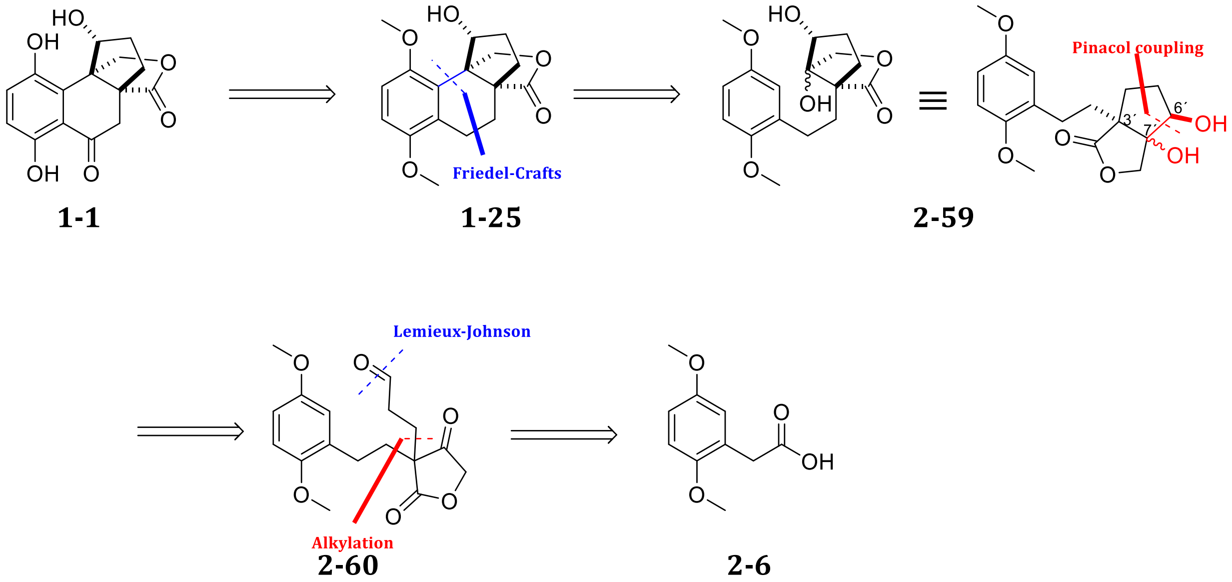
Since the ortho litihation of **2-44** could not be materialised, two alternative routes were attempted. At first, we aimed to synthesize triflate **2-53**, from which aldehyde **2-57** would be accessible. Following a literature procedure[162] we started from *ortho*-vanillin (**2-49**), which was acetylated and brominated affording **2-51**, that was subjected to an ULLMANN condensation[163] that resulted in the formation of **2-52** with poor yields. Conversion of **2-52** to its triflate followed standard procedures using *N*-phenyl-bis(trifluoromethanesulfonimide) as triflating agent. The SONOGASHIRA reaction of **2-53** however never afforded the desired **2-57**. We thus investigated our second alternative route reverting to aldehyde **2-20** as starting material. The aldehyde was protected as cyclic acetal,[164] which was followed by the ortho lithiation of **2-54**[165] which provided the correct regioisomer **2-55** albeit with rather poor yield. Interestingly, in a trial run we tried to replace the hexane/benzene solvent mixture with THF, upon which however the wrong regioisomer was again formed. Cleavage of the acetal group followed by SONOGASHIRA coupling to afford **2-57** were performed without difficulties. The addition of the GRIGNARD reagent prepared from 3-bromo-2-methylpropene however could be facilitated only with yields below 10%. Preliminary attempts to oxidize the allylic positions did not show any formation of product which, combined with the low yield and length just to synthesize **2-58**, led us to abandon this route.



Scheme 28 *Synthesis of* ***2-58****. Reagents and conditions:* ***a.)*** *Ac$_2$O (1.0 eq.), pyridine, RT, 24 h, 76%;* ***b.)*** *Br$_2$ (1.1 eq.), KBr (3.3 eq.), water, RT, 1 h, then HCl (6 M), RT, 24 h, 83%;* ***c.)*** *Na (7.4 eq.), CuI (10 mol%), MeOH/DMF, 85 °C, overnight, 39%;* ***d.)*** *N-phenyl-bis(trifluoromethanesulfonimide) (1.0 eq.), DMAP (10 mol%), DCM, RT, 1 d, 48%;* ***e.)*** *1,3-propanediol (4.0 eq.), trimethyl orthoformate (1.0 eq.), TBABr$_3$ (1 mol%), neat, RT, 1 h, 89%;* ***f.)*** *^{n}BuLi (11.0 M in hexane, 1.5 eq.), 1,2-diiodoethane (1.9 eq.), hexane/benzene, -25 °C, overnight, 29%;* ***g.)*** *cc. HCl, THF, RT, 30 min, 50%;* ***h.)*** *ethynyltrimethylsilane (3.0 eq.), CuI (12mol%), (PPh$_3$)$_2$PdCl$_2$ (4 mol%), TEA/THF, RT, overnight, 73%;****i.)*** *Mg (1.8 eq.), 3-bromo-2-methylpropene (1.5 eq.), THF, Reflux to RT, overnight, 8%*

2.4. Pinacol reaction as key step

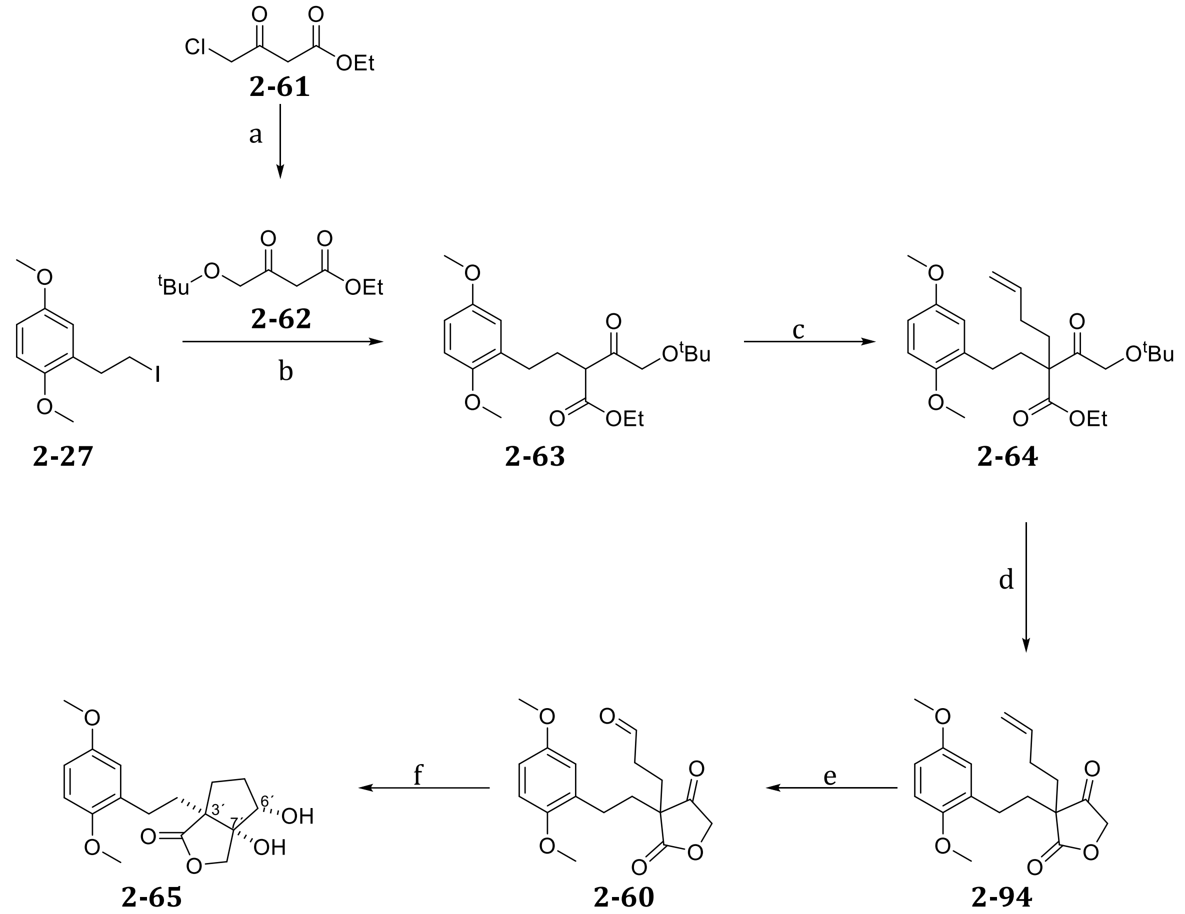
We devised a route that is conceptually similar to the Conia route in that that the B ring would here also be formed as last by a Friedel-Crafts type alkylation. The retrosynthetic analysis can be seen in *Scheme 29*.



Scheme 29 *Retrosynthetic analysis of the samarium route*

As discussed in the introduction, Lingzhiol (**1-1**) can be accessed from **1-25**. A corresponding precursor to the cation needed for the Friedel-Crafts alkylation could be vicinal diol **2-59**, which could be synthesized from **2-60** through an intramolecular Pinacol type reaction.[107] **2-60** in turn should be available from **2-6**.

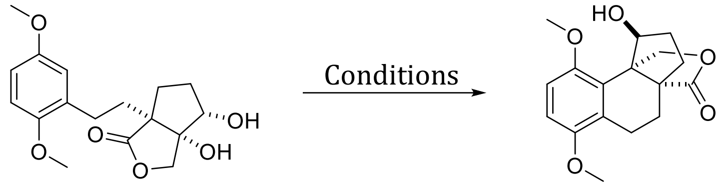
In order to obtain **2-60**,[166] we first synthesized ketoester **2-62** from commercially available ethyl 4-chloroacetoacetate (**2-61**),[167] which was alkylated with phenylethyliodide **2-27** prepared from 2-(2,5-dimethoxyphenyl)acetic acid (**2-6**) as described before. Alkylating **2-63** gave rise to **2-64** which was converted to tetronic acid derivative **2-94** by treating it with hydrogen chloride gas in acetic acid. LEMIEUX-JOHNSON oxidation[168,169] of the terminal double bond afforded aldehyde **2-60** which was subjected to samarium(II) iodide[170–172] mediated intramolecular Pinacol coupling to provide diol **2-65**.



***Scheme 30** Synthesis of precursor to the ring closing **2-65**. Reagents and conditions: **a.)** KO^{t}Bu (2.4 eq.), THF, RT, 1 d, 67%; **b.)** K_2CO_3 (2.0 eq.), **2-62** (1.1 eq.), DMF, RT, overnight, 75%; **c.)** K_2CO_3 (2.0 eq.), KI (1.5 eq.), 4-bromo-1-butene (1.5 eq.), DMF, RT, 20 h, 48%; **d.)** HCl (gas, large excess), AcOH, RT, 1 h, 74%; **e.)** OsO_4 (2 mol%), $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), water/1,4-dioxane, RT, overnight, 45%; **f.)** Sm (4.0 eq.), 1,2-diiodoethane (2.2 eq.), THF, RT, 6 h, 61%*

The stereochemical outcome (the determination of which will be discussed shortly below) of the Pinacol coupling needs to be addressed. If we examine the relative stereochemistry of **2-65**, it is immediately obvious that it does not correspond to the natural product. Although the configuration of the C7´ carbon is irrelevant, since according to our synthetic plan a cation will eventually form on it destroying the stereocenter in the process, but the relative relationship between the C3´ and C6´ is *cis* instead of the required *trans*.

Nevertheless, we pushed forward since the stereochemistry can be adjusted later. We, thus, investigated the FRIEDEL-CRAFTS cyclization of **2-65**. In accordance with literature examples[173] we screened a variety of BRØNSTED and LEWIS acids. The general trend is obvious. Methanesulfonic acid did not facilitate the reaction (*Table 7, Entry 1)*. Commonly employed LEWIS acids gave complex, decomposition mixtures when nitromethane was used as solvent, or no reaction at all if DCM was employed (*Table 7,* *Entries 2-5)*. Using scandium(III) triflate[174,175] as milder and more water resistant LEWIS acid also gave no conversion (*Table 7, Entry 6)*.



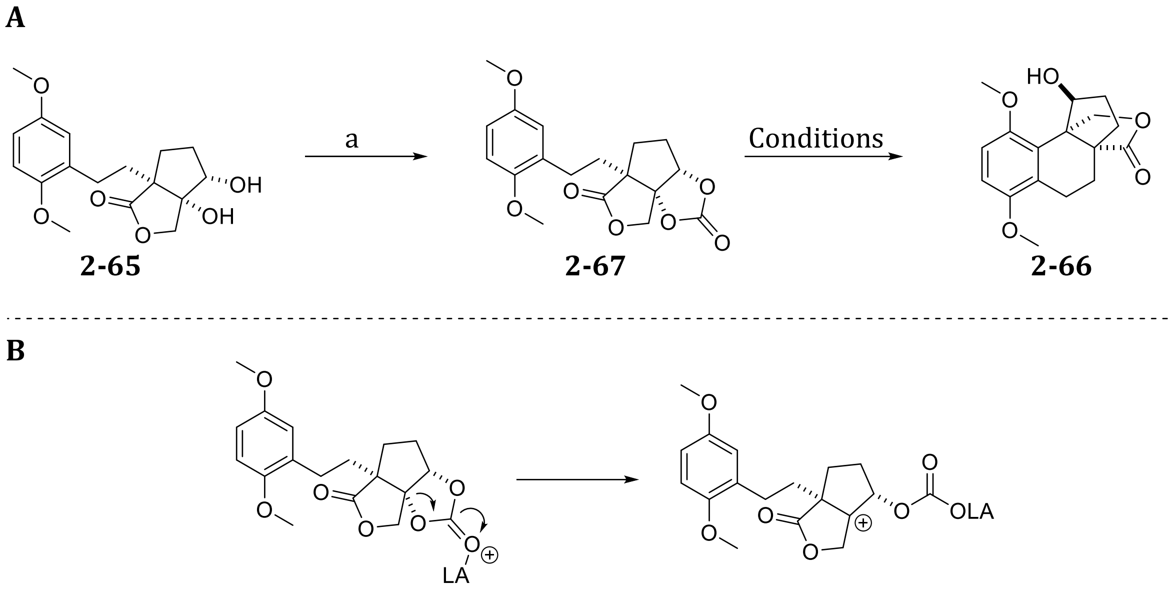
2-65 **2-66**

Scheme 31 *Cyclization of* ***2-65***

Table 7 *Attempts to cyclise* ***2-65*** *through intramolecular* FRIEDEL-CRAFTS *reaction*

Entry	Reagents and Conditions	Result
1	$MeSO_3H$ (neat), RT, 8 h	No conversion
2	5.0 eq. $ZrCl_4$ DCM or CH_3NO_2 RT, 8 h	DCM: No Conversion CH_3NO_2: Decomposition
3	5.0 eq. $TiCl_4$ DCM or CH_3NO_2 RT, 8 h	DCM: No Conversion CH_3NO_2: Decomposition
4	5.0 eq. $AlCl_3$ DCM or CH_3NO_2 RT, 8 h	DCM: No Conversion CH_3NO_2: Decomposition
5	5.0 eq. $SnCl_4$ DCM or CH_3NO_2 RT, 8 h	DCM: No Conversion CH_3NO_2: Decomposition
6	10 mol% $Sc(OTf)_3$ DCM or CH_3NO_2 RT, 2 d	DCM: No Conversion CH_3NO_2: No Conversion

We then converted diol **2-65** to its cyclic carbonate ester (*Scheme 32A*) with the idea, that if a LEWIS acid would coordinate to the carbonyl group of the carbonate, it could lead to the formation of a cation on the tertiary carbon (*Scheme 32B*).



***Scheme 32 A**: Synthesis of cyclic carbonate **2-67** and its cyclization to **2-66**. Reagents and conditions: **a.)** triphosgene (1.1 eq.), pyridine (2.1 eq.), DCM, RT, 2 h, 79%. **B**: Emergence of the tertiary cation upon treating **2-67** with LEWIS acid*

***Table 8** Attempts to cyclise **2-67** through intramolecular FRIEDEL-CRAFTS reaction*

Entry	Conditions	Result
1	2.0 eq. Me_3OBF_4 DCM, RT, 8 h	No conversion
2	3.0 eq. $ZrCl_4$ DCM or CH_3NO_2 RT, 8 h	DCM: No Conversion CH_3NO_2: Decomposition
3	3.0 eq. $TiCl_4$ DCM or CH_3NO_2 RT, 8 h	DCM: No Conversion CH_3NO_2: Decomposition
4	3.0 eq. $AlCl_3$ DCM or CH_3NO_2 RT, 8 h	DCM: No Conversion CH_3NO_2: Decomposition
5	3.0 eq. $SnCl_4$ DCM or CH_3NO_2 RT, 8 h	DCM: No Conversion CH_3NO_2: Decomposition
6	10 mol% $Sc(OTf)_3$ DCM or CH_3NO_2 RT, 2 d	DCM: Stating material + **2-65** CH_3NO_2: No Conversion

As can be seen in *Table 8* our efforts practically had the same outcome as with **2-65** as substrate. BRØNSTED acids was not selected in this screen, instead we made an attempt to use MEERWEIN salt to facilitate the conversion (*Table 8*, *Entry 1*) without success. LEWIS acids provided the same results as before (*Table 8*, *Entries 2-5*). Scandium triflate in DCM mostly gave the starting material, however small amounts of **2-65** were also observable. Changing the solvent to nitromethane only gave us complex mixtures with presumed decomposition.

One advantage of synthesizing **2-67** was however, that it was, as opposed to **2-65**, a solid, which enabled us to grow crystals of it suitable for X-ray diffraction (XRD) analysis, whereby the relative stereochemistry of the bicycle could be unambiguously determined, therefore the all-*cis* relative configuration of the substituents in **2-67** and consequently in **2-65** was proven.

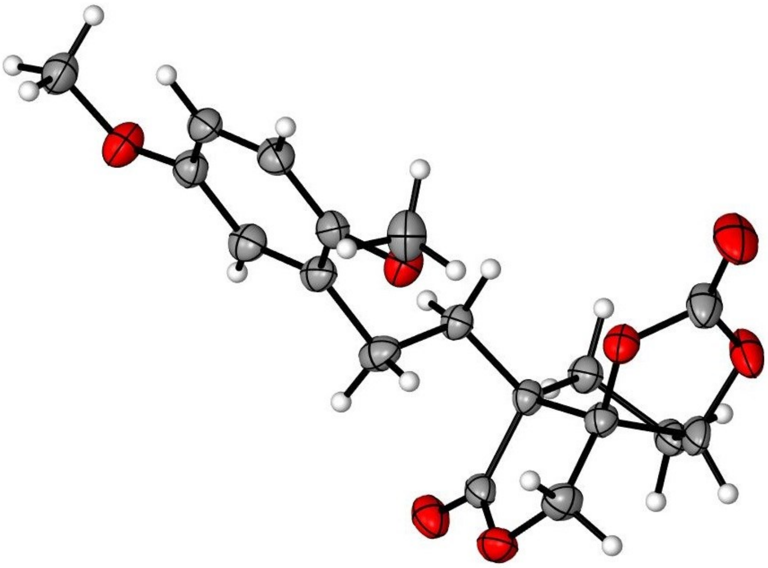
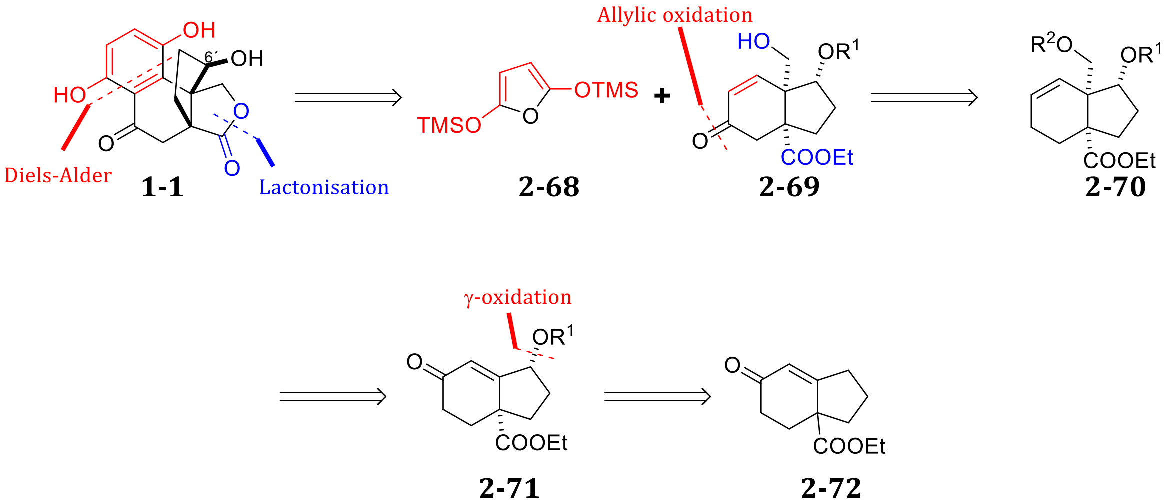


Figure 9 *X-ray crystallographic structure of* ***2-67***

2.5. DIELS-ALDER reaction as key step

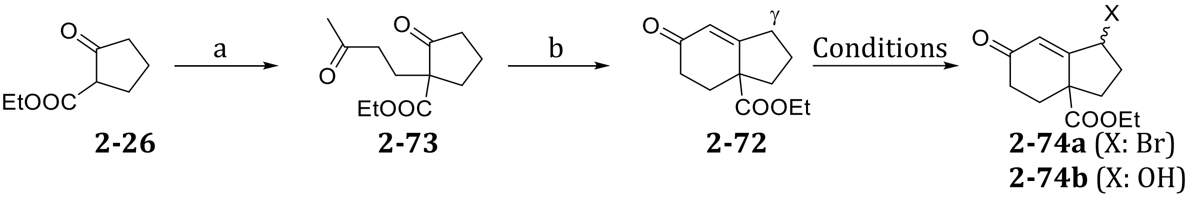
The last route, which we will consider differs from the previously mention insofar as it creates the aromatic **A** ring rather than incorporating it from the beginning (*Scheme 33*).



Scheme 33 *Retrosynthetic analysis of the DIELS-ALDER route*

Lingzhiol (**1-1**) is thus disconnected to bicyclic compound **2-69** and to furan derivative **2-68**, which is indeed used for the synthesis of hydroquinones through DIELS-ALDER reactions with various dienophiles.[176] **2-69** can be conveniently accessed from **2-70** which in turn could be acquired from **2-71**. The way how this transformation is practically implemented will be fleshed-out in this chapter. Note, that the relative configuration between the ethyl ester and the hydroxymethyl function must be *cis*, otherwise the lactone formation would be impossible. This necessitates the stereoselective introduction of the hydroxymethyl substituent to **2-71**.

First, we investigated the γ-functionalisation of **2-72**. Therefore, commercially available ethyl 2-oxocyclopentanecarboxylate (**2-26**) was converted to **2-72** through a two-step ROBINSON annulation procedure first reacting it with methyl vinyl ketone using iron(III) chloride as catalyst[177,178] followed by the ring closing upon treatment of **2-73** with acetic acid and pyrrolidine.[179] (*Scheme 34*)



Scheme 34 *Synthesis of **2-72** and the substitution of its γ-position (see Table 9). Reagents and conditions:* ***a.)*** *MVK (1.2 eq.), $FeCl_3.6H_2O$ (2 mol%), neat, RT, 1 d, 51%;* ***b.)*** *Acetic acid (1.0 eq.), pyrrolidine (1.0 eq.), EtOAc, RT, overnight, 63%*

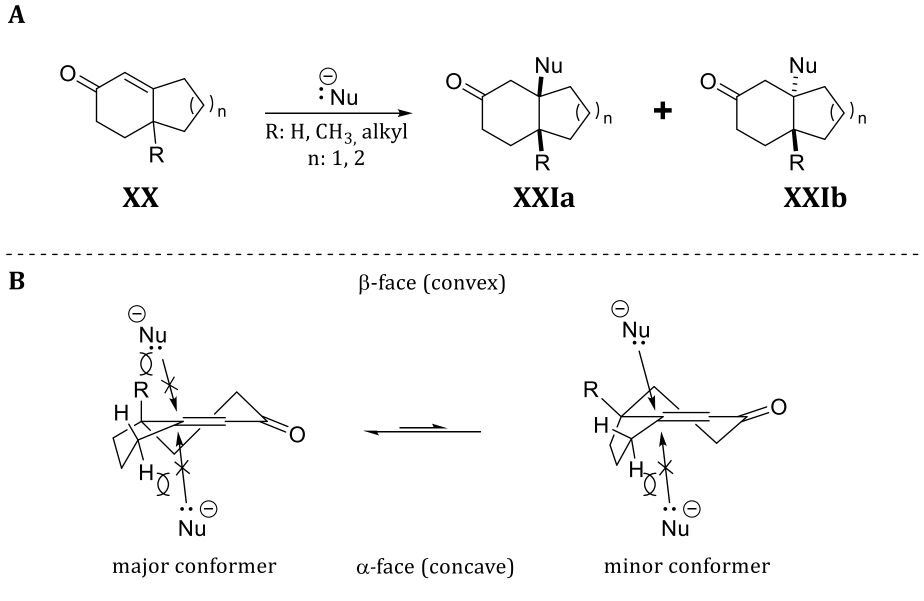
Having **2-72** at hand we investigated the substitution of the γ-position. γ-bromination of α,β-unsaturated ketones under WOHL-ZIEGLER conditions is literature reported,[180] and did indeed provide **2-74a**, albeit only with poor yield (*Table 9*, *Entry 1*). Introduction of a hydroxyl function to the γ-carbon is also well known. First we tried a simple procedure using air under basic conditions[181] to facilitate the oxidation, which however did not provide us any product (*Table 9*, *Entry 2*). Then, we opted to investigate an improved version of the oxidation, which employs a copper-aluminium mixed oxide as catalyst under basic conditions,[182] but it also failed (*Table 9*, *Entry 3*). We were able to hydroxylate the γ-position through a two-step procedure,[183] reacting **2-72** first with isopropenyl acetate in the presence of catalytic amounts of BRØNSTED acid, which afforded the extended enol acetate,[184,185] the reaction of which with dimethyl dioxirane, generated in situ from acetone and Oxone, under basic conditions provided **2-74b** with poor yield (*Table 9*, *Entry 4*). Although NMR-spectra of both **2-74a** and **2-74b** suggest, that they were formed as a single diastereomer, at this stage no further efforts were undertaken to determine whether they exist as the *cis* or *trans* isomer.

Table 9 *γ-substitution of **2-72***

Entry	Reagents and Conditions	Result
1[180]	1.5 eq. NBS 4 mol% AIBN DCE, Reflux, 6 h	**2-74a** (36%)
2[181]	10 w/w% KOH in MeOH (as solvent), Air RT, 2 d	No conversion
3[182]	1.3 eq. ^tBuOK Cu/Al-oxide (70 mg/mmol) Air EtOH, RT, 1 d	No conversion
4[183]	0.2 eq. *p*-TsOH Isopropenyl acetate (as solvent), Reflux, 1 d **then** 3.0 eq. Oxone Acetone/water/sat. $NaHCO_3$ sol. RT, 1 d	**2-74b** (33%)

At this point we decided to press forward with our investigation regarding the introduction of the hydroxymethyl function at the β-position. Due to the low yields of the substitution of the γ-positions as well as for the sake for simplicity it was decided, that we first limit our scope to **2-72**. Although a successful synthesis would thus result in 6'-deoxy-Lingzhiol as product, we considered **2-72** a suitable alternative the flesh out the proceeding reactions.

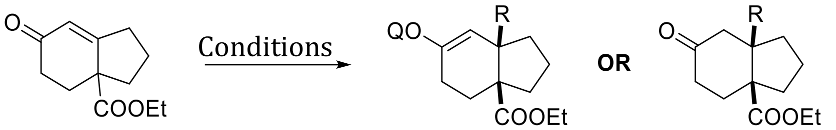
As mentioned before, the stereoselective introduction of the hydroxymethyl side chain is of great importance. Inspecting the structure of **2-72**, a 1,4-addition of an appropriate C1 nucleophile can be quickly conceived. Fortunately, the chemistry of structurally closely related compounds was extensively researched from the mid-20th century due to their importance in steroid chemistry, which provided insights into the conjugate addition of nucleophiles (mostly cuprates[186,187,196,188–195] but also carbanions[197] and cyanide ion[186,198,199]) to enones of type **XX** or to related steroidal compounds (*Scheme 35A*). Theoretically, two possible diastereomers could arise: one in which the substituents are *cis* to each other (**XXIa**), and one in which they are *trans* (**XXIb**). Experiments showed, that in the majority of cases *cis* products are formed, which would enable us to introduce the hydroxymethyl motif with the correct stereochemistry for later lactone formation.



***Scheme 35 A** Conjugate addition to bicyclic enones analogous to **2-72**. **B** Facial selectivity of conjugate addition to **2-72** (R: COOEt)*

To explain this selectivity, we consider the 3D structure of an arbitrary indenone (*Scheme 35B*, if R: COOEt, then we have **2-72**). The cyclohexene ring exists mostly in its two half-chair conformations as is expected[200–204] (with the major conformer being present at about 95%[201]) and the whole geometry of the molecule creates two diastereotopic faces (an "outer" convex termed β, and an "inner" concave termed α, borrowed from the steroid nomenclature[205,206]) along the C-C double bond. We supposed, that although no nucleophilic attack would be possible on the major conformer due to steric hindrance, the nucleophile could approach from the convex face of the minor conformer. Facial selectivity in bent molecules has been observed quite early and generally speaking an approach trajectory from the less hindered convex face is preferred.[188,207–212] However, we also acknowledge, that the above presented simple rationale does not apply for every case. Examples, which violate the rule, certainly exist, mostly with cyanide ion as nucleophile.[213] Also, when cuprates are used, specific interactions between the organometallic species and the substrate have to be taken into consideration. It was suggested quite early,[188] and was later proven[190,214,215] that during the addition of cuprates different copper complexes emerge, the stability of which is then paramount for the stereoselectivity. The steric effect of the substituent R in **XX** must also be considered. It was noted, that the more sterically demanding the R group is, the more sluggish the addition of a cuprate becomes. It is worthwhile to mention however, that only the yield changed but never the stereoselectivity, which remained to be *cis*.[188,194]

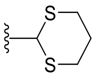
We thus started to investigate the conjugate addition of formyl anion equivalents (*Scheme 36*).[115] We screened a wide range of possible methodologies, however the best case scenario was hoped to be in which the intermediate enolate could be trapped to avoid later regioselectivity issues (**2-75a**).



Scheme 36 *Conjugate addition onto **2-72** (see Table 10)*

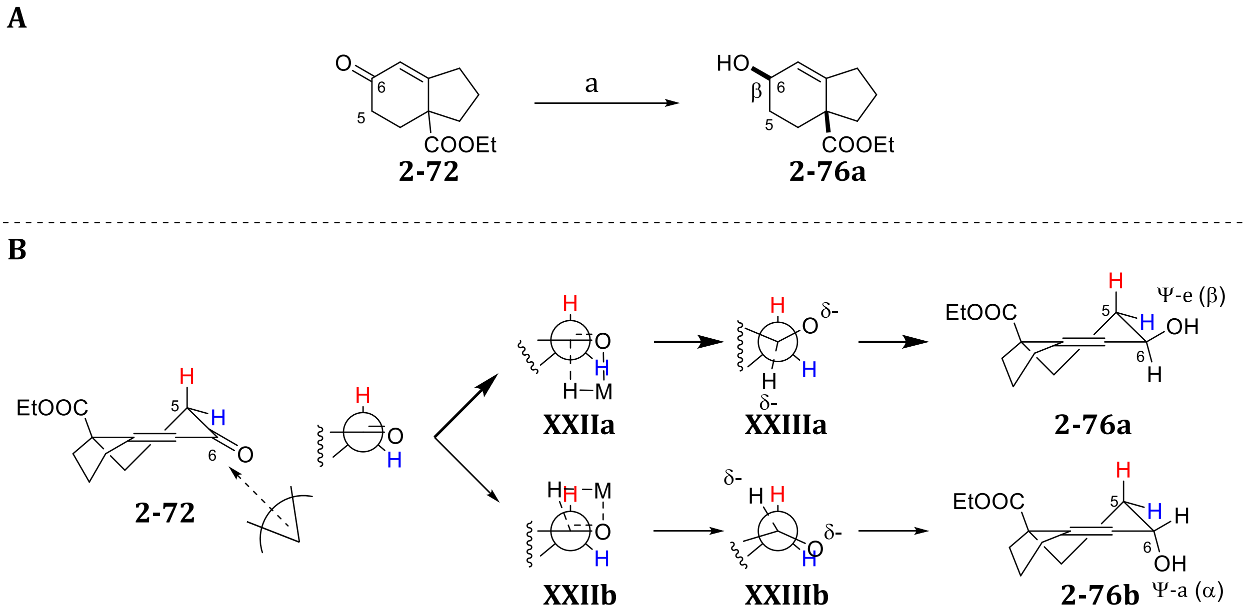
We first tried to introduce a *tert*-buthoxymethyl function using the addition of *tert*-butoxymethyl cuprate to the enone **2-72** (*Table 10*, *Entry 1*),[216] which however provided no product. We also attempted a modified version of the COREY-SEEBACH reaction[217,218] in which copper catalysis is utilised to ensure the 1,4-addition of the reagent[219] without success (*Table 10*, *Entry 2*). We also tried to facilitate the addition through a STETTER reaction[220] in which a thiazolium salt was used as catalyst with glucose serving as the source of the formaldehyde anion synthon,[221] unfortunately, however, we could isolate only the starting material (*Table 10*, *Entry 3*). Lastly, we attempted the addition of a hydroxymethyl radical, generated from methanol upon irradiation with UV-light in the presence of benzophenone as photosensitiser,[222–224] without success (*Table 10*, *Entry 4*).

Table 10** Conjugate addition to **2-72

Entry	Reagents and Conditions	Expected Product	Result
1[216]	3.0 eq. KO^{t}Bu 3.0 eq. ^{s}BuLi MTBE (as reactant and solvent), -78 °C, 1.5 h, *then* 1.1 eq. CuBr.Me$_2$S 10.0 eq. ^{i}Pr$_2$S -78 °C, 30 min, *then* 2.0 eq. TMSCl	**2-75a** R: CH$_2$O^{t}Bu Q: Me$_3$Si	Starting Material
2[219]	1.1 eq. ^{n}BuLi 1.1 eq. 1,3-Dithiane 1.0 eq. CuI 2.0 eq. TMSCl THF, -78 °C, overnight	**2-75a** R:  Q: Me$_3$Si	Starting Material
3[221]	2.0 eq. Glucose 0.2 eq. 3-Ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide 0.2 eq. K$_2$CO$_3$ Acetonitrile, 90 °C, 5 h	**2-75b** R: CHO	Starting Material
4[222–224]	0.8 eq. Benzophenone hν (Hg-Lamp) MeOH, RT, 6 h	**2-75b** R: CH$_2$OH	Starting Material

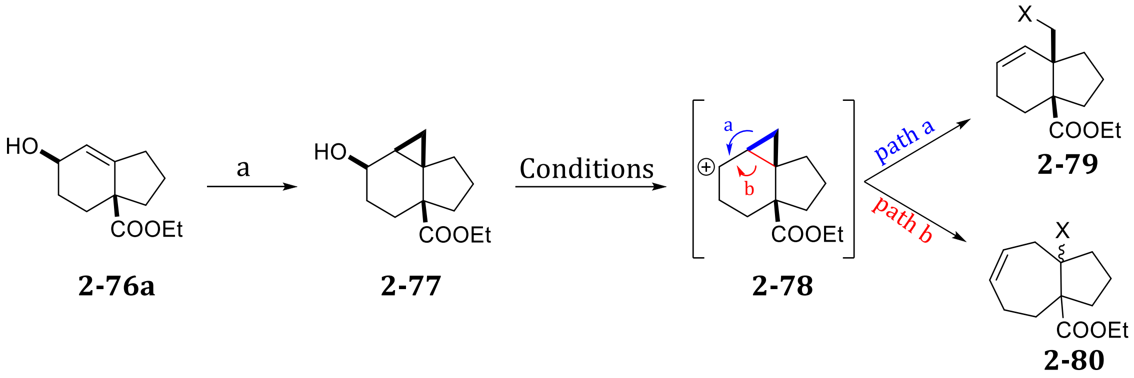
The failure of these reactions led us to believe, that the steric hindrance of the ethylester group is indeed significant, and thus the convex face of the double bond is for all intents and purposes blocked. The concave face of the molecule remains to be shielded by the shape of the molecule itself, therefore no reaction can occur.

In light of the failure to introduce the hydroxymethyl function through a conjugated addition, we opted for C1 synthons, which can be introduced to allylic alcohols. Optimal candidates include the utilisation of cyclopropanes and the [2,3]-WITTIG rearrangement. First, however, we had to facilitate the stereoselective reduction of the ketone **2-72** to *cis* alcohol. Luckily, reducing **2-72** under LUCHE conditions[225,226] (*Scheme 37A*) provided the required *cis* alcohol **2-76a** with good yields and stereoselectivity. To explain the observed stereochemistry, we shall consider the major conformer of **2-72** again, particularly the NEWMAN-projection of the carbonyl group along the C6-C5 bond. (*Scheme 37B*). The reduction of a carbonyl group with metal hydrides takes place through a cyclic transition structure[227–229] and thus the Bürgi-Dunitz angle of the approaching hydride is considerably smaller then it would be for a "free" nucleophile (~90° as opposed to 105-115°).[230] If the approaching reagent forms the cyclic transition structure on the α-face resulting in **XXIIa**, the reduction can proceed effortlessly through the almost perfectly staggered **XXIIIa** to give the required *cis* alcohol **2-76a** with the hydroxyl group occupying the *pseudo*-equatorial (Ψ-e) β-position. If, however, the reagent formed the transition structure on the β-face, **XXIIb** would arise, in which already a small steric repulsion is present due to the eclipsing nature of the hydride and the axial hydrogen on C5. Even worse, the reduction would need to proceed through **XXIIIb** with fully eclipsed substituents inducing tremendous torsional strain, making this reaction path hugely disfavoured.[203,230,231]



***Scheme 37 A**: Reduction of **2-72**. Reagents and conditions: **a.)** NaBH$_4$ (1.0 eq.), CeCl$_3$.7H$_2$O (1.0 eq.), MeOH, RT, 30 min, 75%. **B:** Rationalisation of stereochemical outcome of the reduction.*

We then tried to utilize a cyclopropane moity as a one-carbon synthon, the rearrangement of which could later serve as precursor to the hydroxymethyl group. For this purpose we wanted to utilise the cyclopropylcarbinyl rearrangement[232–236], that necessitated the cyclopropanation of **2-76a**, which we achieved through the Furukawa modification[237] of the Simmons-Smith reaction (*Scheme 38*).[238,239] Since the hydroxy group exerts immense directing effect in Simmons-Smith reactions,[240] the all-*cis* relative configuration of **2-77** and thus the correct relative stereochemistry at the bridgehead carbons was established. We then tried to flesh-out the applicability of the cyclopropylcarbinyl rearrangement. Upon treating **2-77** with Brønsted- or Lewis acid, formally a secondary cation **2-78** forms, followed by the opening of the cyclopropane ring to give either **2-79** or **2-80** where “X” depends on the conditions, but usually is OH or halogens.[232–236] Naturally, if we except products to form according to Markovnikov´s rule, one would presume **2-80** or rather its elimination product to be prevalent, however reversal of regioselectivity using Lewis acids has been reported.[233]



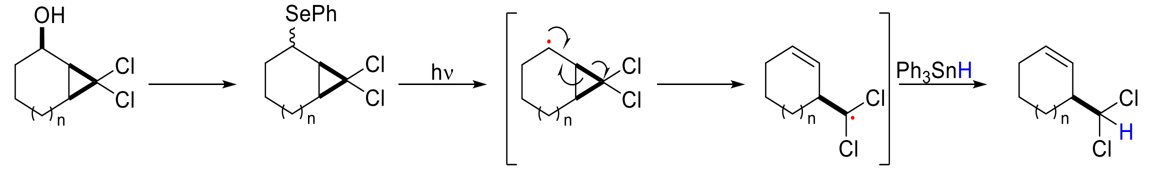
***Scheme 38** Synthesis of **2-77** and attempted cyclopropylcarbinyl rearrangement. Regents and conditions: Et_2Zn (4.0 eq., 1 M in hexane), CH_2I_2 (4.0 eq.), Et_2O, 0° C to RT, 3 d, 55%*

As can be seen in *Table 11* four different conditions were attempted. Treating **2-77** with aqueous hydrogen bromide led to a complex reaction mixture with no clear isolable product (*Table 11*, *Entry 1*). Using hydrogen bromide in acetic acid instead of water gave a less complex mixture from which however only **2-80** was detectable (*Table 11*, *Entry 2*). Using Lewis-acid or catalytic amount of Brønsted acid gave only the starting material (*Table 11*, *Entries 3 and 4*).

Table 11 *Attempts to facilitate the cyclopropylcarbinyl rearrangement of* ***2-77***

Entry	Reagents and Conditions	Result
1[232]	HBr (48% in H_2O, as reagent and solvent) RT, 6 h	Decomposition
2	HBr (33% in AcOH, as reagent and solvent) RT, 6 h	Small amounts of **2-80** (X: Br)
3[233]	1.4 eq. $ZnBr_2$ 1.0 eq. $MgBr_2$ Et_2O, RT, Overnight	Start. Mat.
4[236]	10 mol% $TsOH.H_2O$ CH_3CN/H_2O: 1/1 Reflux, 6 h	Start. Mat.

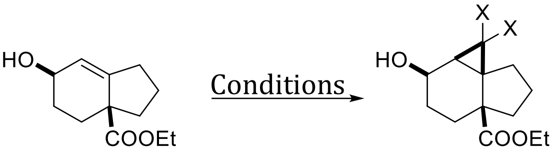
Since the acid induced rearrangement gave us no product, we also attempted a radical pathway to facilitate the conversion. The concept[241] can be seen in *Scheme 39* and starts with converting cyclopropylcarbinyl compound **XXIV** to its phenylselenyl analogue **XXV**, which under irradiation homolyses to radical **XXVI**, that is, after the opening of the cyclopropane ring, converted into radical **XXVII**, the reaction thereof with a hydrogen source then provides the product **XXVIII**.



XXIV **XXV** **XXVI** **XXVII** **XXVIII**

Scheme 39 *Radical opening of the cyclopropane ring*[241]

For this purpose, we examined the dihalocarbene addition to **2-76a** (*Scheme 40* and *Table 12*). The stereochemistry of the addition was expected to be *cis* according to literature.[241–243] From the known methods to form dichlorocyclopropanes we tried the classical method employing chloroform and alkaline biphasic system in the presence of phase transfer catalyst benzyltriethylammonium chloride (BTEAC)[241,242] (*Table 12*, *Entry 1*) and using chloroform in solution treated by strong base[244] (*Table 12*, *Entry 2*) however only decomposition was observable. We also tried to generate dichlorocarbene either from sodium trichloroacetate[245,246] or from ethyl trichloroacetate[247] (*Table 12*, *Entries 3 and 4*), however only decomposition was detected. We as well attempted to utilise procedures, which bypass the use of strongly alkaline media, namely forming dichlorocarbene either from tetrachloromethane upon treatment with magnesium[248] (*Table 12*, *Entry 5*) or from the thermal decomposition of phenyl(trichloromethyl)mercury[249] (*Table 12*, *Entry 6*), neither of which showed any conversion. We also tried to form the dibromocyclopropane by using bromoform and a strong base either in a biphasic[250] or in a single phase[251] reaction (*Table 12*, *Entries 7 and 8*), which however also showed only slow decomposition. This tendency of **2-76a** to decompose under basic conditions will continue to plague our reactions.



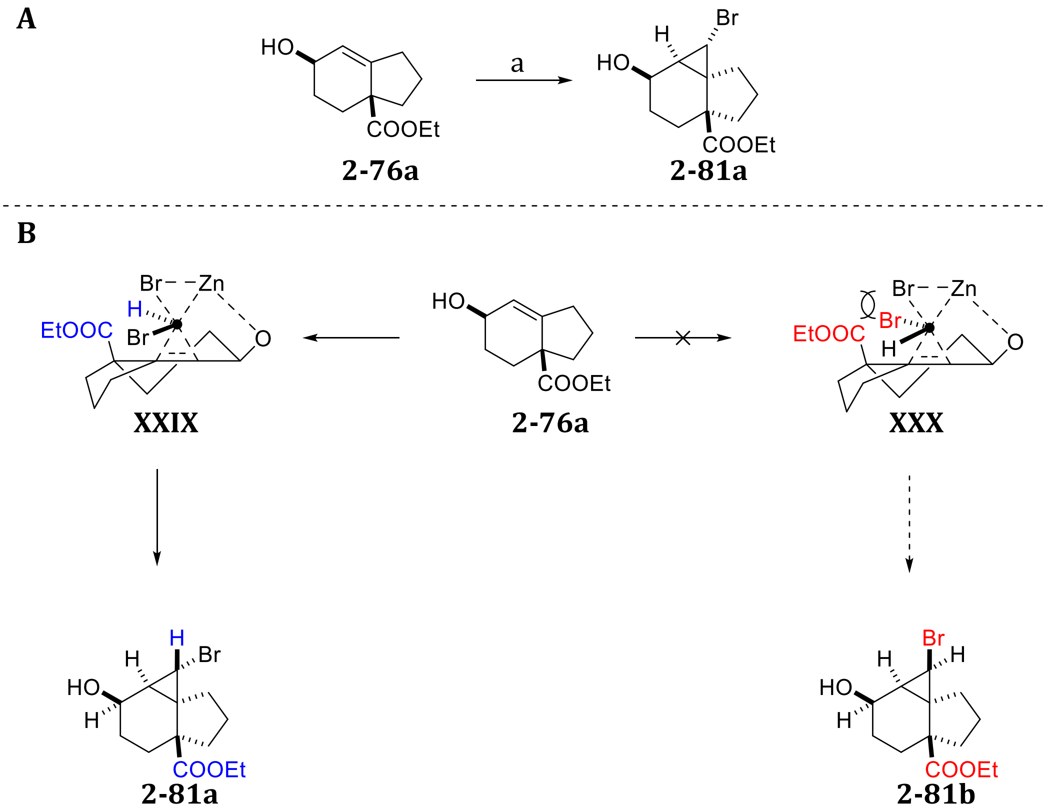
2-76a

Scheme 40 *Dihalocarbene addition onto* ***2-76a***

Table 12 *Attemtps to the dihalocarbene additions onto* ***2-76a*** *(see Scheme 40)*

Entry	Reagents and Conditions	Result
1[241,242] (X: Cl)	2 mol% BTEAC $CHCl_3$/NaOH (50% in H_2O) 0 °C (or 0 °C to RT), 2-12 h	Start. Mat. + Decomposition
2[244] (X: Cl)	1.3 eq. KO^tBu 1.0 eq. $CHCl_3$ Et_2O, -30 °C to RT, 6 h	Start. Mat. + Decomposition
3[245,246] (X: Cl)	6.0 eq. Cl_3COONa Diglyme/1,1,2,2-Tetrachloroethylene Reflux, 4 h	Start. Mat. + Decomposition
4[247] (X: Cl)	20.0 eq. Cl_3COOEt 0.7 eq. NaOEt Pentane, 0 °C to RT, overnight	Start. Mat. + Decomposition
5[248] (X: Cl)	1.0 eq. Mg 2.0 eq. CCl_4 Et_2O/THF: 4/1 Ultrasound, RT, 6 h	Start. Mat.
6[249] (X: Cl)	3.0 eq. $PhHgCCl_3$ Toluene, 80 °C, 2 h	Start. Mat
7[250] (X: Br)	1.5 eq. $CHBr_3$ 2 mol% BTEAC CH_2Cl_2/NaOH (50% in H_2O) 0 °C, 4 h	Start. Mat. + Decomposition
8[251] (X: Br)	1.0 eq. KO^tBu 1.0 eq. $CHBr_3$ Hexane, RT, 6 h	Start. Mat. + Decomposition

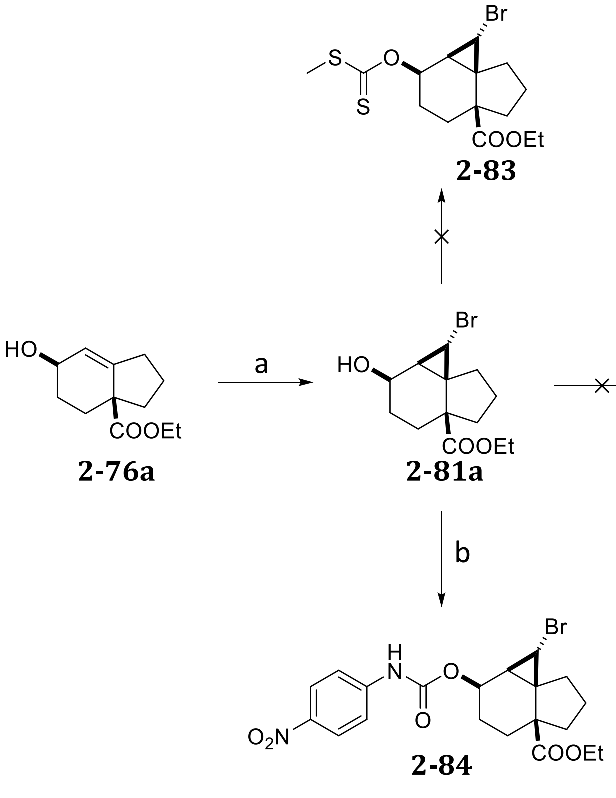
These failures led us to realise that only SIMMONS-SMITH conditions can convert **2-76a** into its cyclopropane derivative. Luckily, modifications exist which allow the introduction of substituted cyclopropanes under SIMMONS-SMITH conditions, we thus employed the methodology developed by CHARETTE *et al.*[252] that itself was based on earlier results.[253–255] Cyclopropane **2-81a** was isolated as a single diastereomer from the reaction mixture with medium yield (*Scheme 41A*). The observed diastereoselectivity warrants a closer look. That the cyclopropane forms on the same side with the hydroxyl group is not surprising, as mentioned before. However, the stereochemistry of the cyclopropyl carbon carrying the bromine is not determined by the hydroxyl group. A possible explanation, which was put forward by GADEMANN *et al.* after their use of this procedure on a structurally very similar compound, can be seen in *Scheme 41B*.[256] The coordinated bromocarbenoid can approach the double bond either with the bromine facing outwards and the hydrogen inwards to the ring or conversely the bromine facing inwards and the hydrogen outwards. The former leads to the formation of transition structure **XXIX** in which the steric interaction between the hydrogen and the ethylcarboxylate is negligible, and the reaction can proceed into **2-81a** without difficulty. In the latter case however the sterically demanding bromine and ethylcarboxylate come close to each other creating considerable repulsion in the process, destabilizing **XXX** and thus ultimately disfavouring the formation of the epimeric **2-81b**.



Scheme 41 A:** Bromocyclopropanation of **2-76a**. Reagents and conditions: **a.)** $CHBr_3$ (3.0 eq.), Et_2O (3.0 eq.), Et_2Zn (1 M in hexane, 3.0 eq.), DCM, 0 °C to RT, overnight, 59%, **B:** Transition structures leading to epimers **2-81a** and **b

This rationale could be also used to explain the apparent lack of reaction when we tried to facilitate the cyclopropanation using dichlorocarbene. Since the geometry of the transition states for the two reactions are similar[240,257–261] one could imagine a transition structure not too dissimilar to **XXIX** or to **XXX**. In this case however, since both substituents are chlorine, there is no possibility to alleviate the steric repulsion which in turn hinders the reaction.

With **2-81a** in hand, we tried to convert it to selenyl ether **2-82**,[262] the irradiation thereof would provide the radical necessary to the rearrangement, however no product was isolable. We also attempted the conversion of **2-81a** to its xanthate ester **2-83**,[263] since the generation of radicals from xanthate esters is quite straightforward,[264] however classic method to form methylxanthates from alcohols failed to give **2-83** presumably due to the basic nature of the reaction.



Scheme 42 *Cyclopropanation of* ***2-76a*** *and derivatization of* ***2-81****. Reagents and conditions:* ***a.)*** *$CHBr_3$ (3.0 eq.), Et_2O (3.0 eq.), Et_2Zn (1 M in hexane, 3.0 eq.), DCM, 0 °C to RT, overnight, 59%;* ***b.)*** *4-nitrophenyl isocyanate (1.2 eq.), TEA (1.6 eq.), DCM, RT, overnight, 68%*

Finally, we also intended to unambiguously assign the relative stereochemistry of **2-81a** (and thereby that of **2-76a**). For this purpose, we converted **2-81a** into its 4-nitrophenylcarbamate,[265] which afforded crystals suitable to XRD analysis. The X-Ray structure of **2-84** can be seen in *Figure 10* and it unambiguously shows the previously expected all-*cis* relative configuration of the indane core.

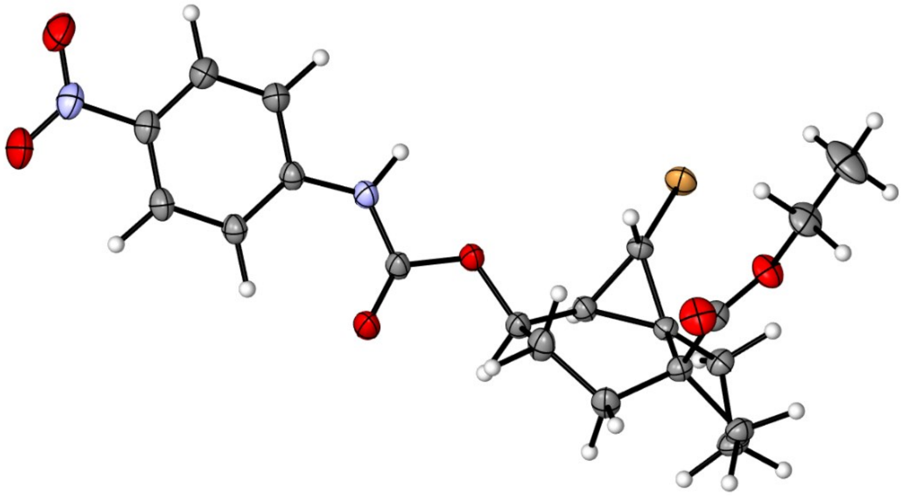
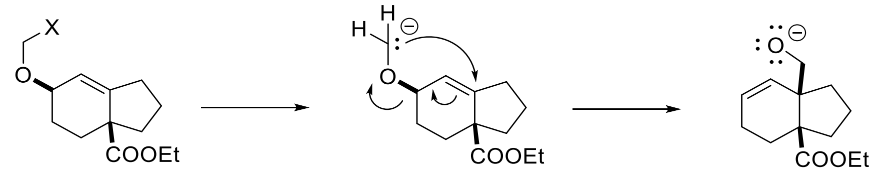


Figure 10 *X-ray crystallographic structure of carbamate* ***2-84***

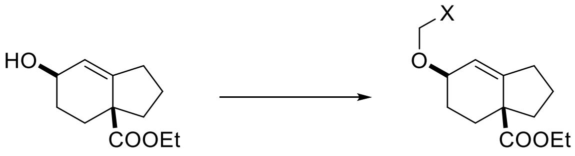
Since the cyclopropane moity failed to serve as a one-carbon synthon, we lastly investigated the [2,3]-WITTIG rearrangement,[266,267] the principle of which can be seen *Scheme 43*. Since the sigmatropic rearrangement of the anion **2-86** is suprafacial in nature (for both component), the stereochemistry of the alcohol is transferred to the bridgehead carbon, thus creating the necessary *cis* relationship between the hydroxymethyl and ethylcarboxylate substituents. Generating the anion **2-86** requires however, that **2-85** be adequately substituted, since the direct deprotonation of a methyl ether (X: H) is not possible due to its extremely low acidity.



2-85a-d **2-86** **2-87**

Scheme 43 *[2,3]-WITTIG rearrangement to introduce the hydroxymethyl side chain*

By far, the most common method to generate anion **2-86** is the transmetalation of stannylated ether **2-85a** (X: $^{n}Bu_3Sn$) with *n*-buthyllithium, which is known as WITTIG-STILL rearrangement (or STILL´s variant of the WITTIG rearrangement).[268,269] One can, however, use other substituents on **2-85** to generate **2-86**: notably by the treatment of chloromethyl ethers (**2-85b**, X: Cl)[270] or S,O-acetals (**2-85c**, X: PhS)[271,272] with lithium arene complexes or through the treatment of silylmethyl ethers (**2-85d**, X: R_3Si) with large excess of *n*-buthyllithium.[273] Naturally, we first had to investigate the conversion of **2-76a** into **2-85a-c** (silylmethyl ethers were not investigated).



2-76a **2-85a-c**

Scheme 44 *Derivatization of* ***2-76a*** *for the [2,3]-WITTIG rearrangement*

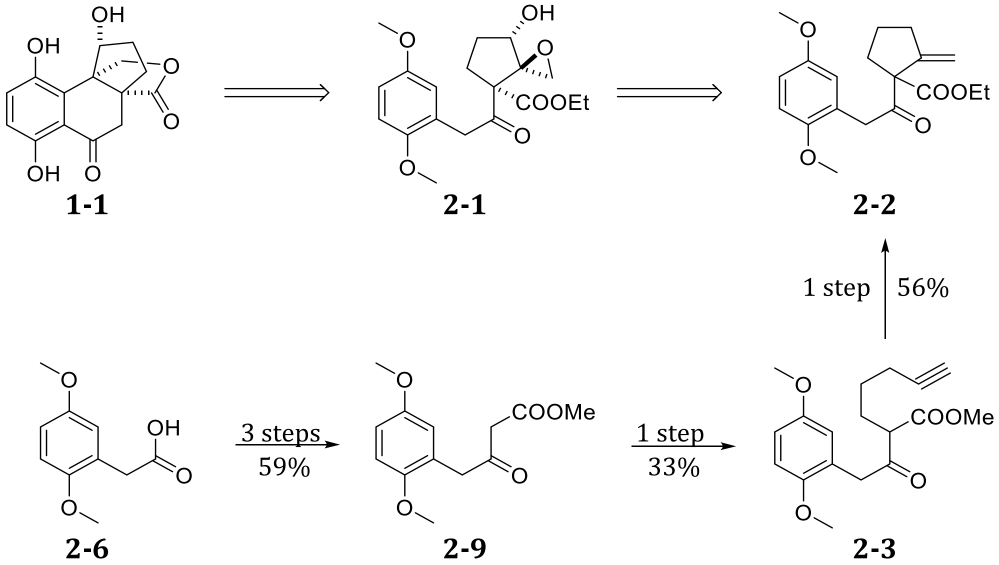
Table 13 *Attempts to derivatise* ***2-76a*** *for [2,3]-WITTIG rearrangement*

Entry	Reagents and Conditions	Result
1[274,275] (X: $^nBu_3Sn$)	2.0 eq. KH (30% in mineral oil) 1.2 eq. $^nBu_3SnCH_2I$ THF, RT, 6 h	Decomposition
2 (X: $^nBu_3Sn$)	1.2 eq. NaH (60% in mineral oil) 1.5 eq. $^nBu_3SnCH_2I$ DMF, RT, 6 h	Decomposition
3 (X: $^nBu_3Sn$)	1.0 eq. DBU or TEA 1.5 eq. $^nBu_3SnCH_2I$ DCM, RT, 6 h	No reaction
4[272] (X: PhS)	3.0 eq. DIPEA 2.7 eq. $PhSCH_2Cl$ Toluene, 130 °C, 4 h	Decomposition
5 (X: PhS)	1.2 eq. DIPEA or DBU 1.2 eq. $PhSCH_2Cl$ 1.2 eq. TBAI DCM or MeCN, RT, overnight	No reaction
6 (X: PhS)	1.2 eq. NaH (60% in mineral oil) 1.2 eq. $PhSCH_2Cl$ DMF, RT, 6 h	Decomposition
7[276] (X: PhS)	2.0 eq. NaH (60% in mineral oil) 1.2 eq. $PhSCH_2Cl$ 1.0 eq. NaI Monoglyme, RT, 6 h	Decomposition
8[277] (X: Cl)	1.0 eq. Paraformaldehyde or 1,3,5-Trioxane 1.1 eq. TMSCl neat, RT, 6 h	Decomposition
9 (X: Cl)	2.0 eq. Paraformaldehyde or 1,3,5-Trioxane ~6.0 eq. HCl (gas) Et_2O, 0 °C, overnight	Decomposition

As can be seen in *Table 13*, all our efforts to convert **2-76a** into a precursor to the Wittig rearrangement were met with failure. Methods employing strong bases (*Table 13, Entries 1, 2, 6 and 7*) led to the decomposition of **2-76a** in accordance what we experienced earlier. Introduction of the stannylmethyl group using milder bases (*Table 13*, *Entry 3*) gave no reaction whatsoever. Attempts to form S,O-mixed acetal using weaker bases afforded either no product (*Table 13*, *Entry 5*) or a complex mixture from which no product was isolable (*Table 13*, *Entry 4*). Experiments towards the formation of the chloromethyl ethers also gave complex mixtures (*Table 13*, *Entries 8 and 9*). Since we failed to synthesize an appropriate precursor to the [2,3]-WITTIG rearrangement, this route was also abandoned and with it the thesis came to its end.

3. Summary

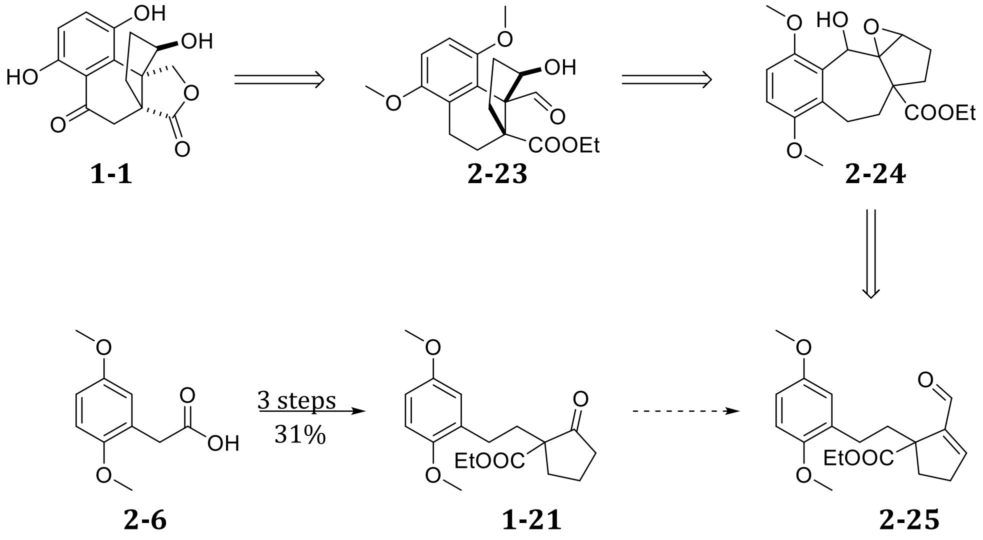
The aim of the present work was to investigate different synthetic routes towards the total synthesis of the fungal meroterpenoid Lingzhiol. During the thesis we investigated several routes that might afford the natural product.



Scheme 45 *The Conia-ene route*

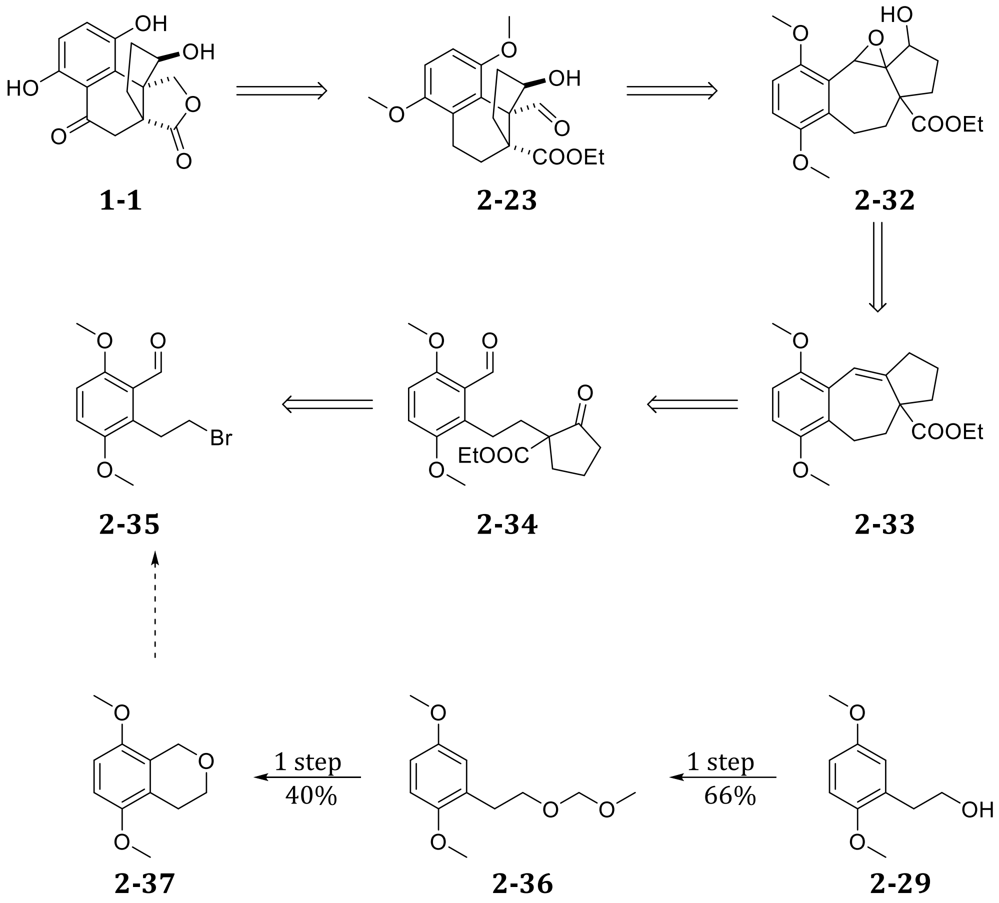
Firstly, we investigated the Conia-ene reaction as can be seen in *Scheme 45*. Synthesis of precursor **2-3** was fairly straightforward, and the following cyclisation could be facilitated with medium yields. Hydroxylation of the α-position of the exocyclic double bond was however not possible. Classical method like Riley oxidation but also photochemical oxidation using triplet oxygen generated by the irradiation of oxygen in presence of photosensitizer failed to facilitate the oxidation. Some other alternative routes utilising the Conia-ene reaction were also conceived but abandoned after the failure to synthesize of the necessary precursors.

We then turned our attention to routes the key reaction of which were the Pinacol rearrangement. As can be seen *Scheme 46* Lingzhiol (**1-1**) would be accessible from **2-23** which in turn should be synthesized by the Semipinacol rearrangement of **2-24**. Thus **1-21** was synthesised from phenylacetic acid **2-6** in an overall yield of 31%. Conversion of **1-21** into aldehyde **2-25** was planned to involve hydrazone formation followed by a Shapiro reaction. Although the tosylhydrazone of **1-21** could be synthesized, all attempts to facilitate the Shapiro reaction failed. Alternatively, the keto group in **1-21** was converted into an epoxide, the rearrangement of which under the action of either Lewis acid or thionyl chloride, that was hoped to provide **2-25**, was nevertheless met with failure.



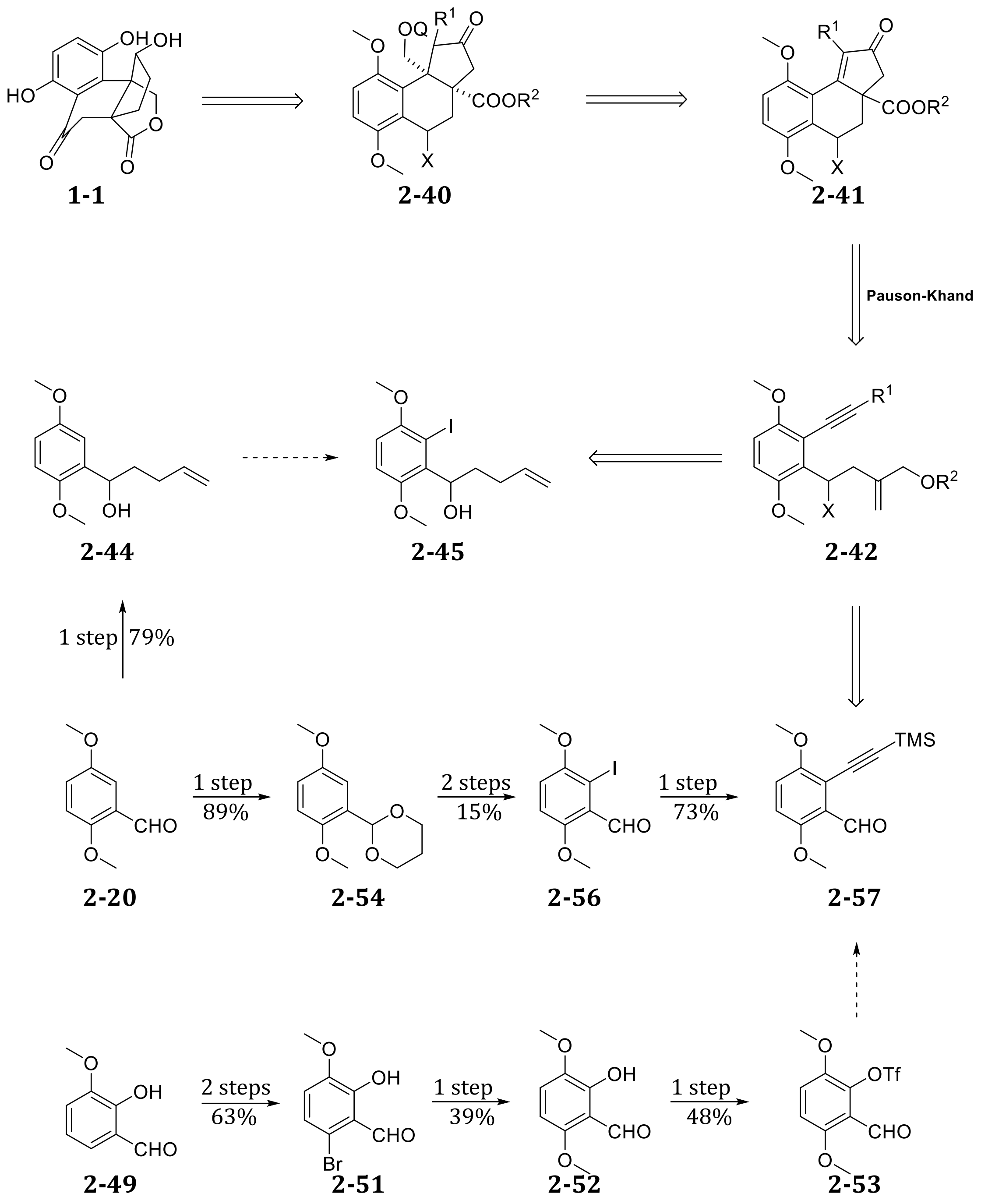
Scheme 46 *Summary of the Pinacol route*

An alternative approach to synthesize **2-23** was also investigated (*Scheme 47*), which started with phenylethanol **2-29** that was converted into isochromane **2-37** in two steps with an overall yield of 26%. Attempts to convert **2-37** into bromide **2-35** were unsuccessful.



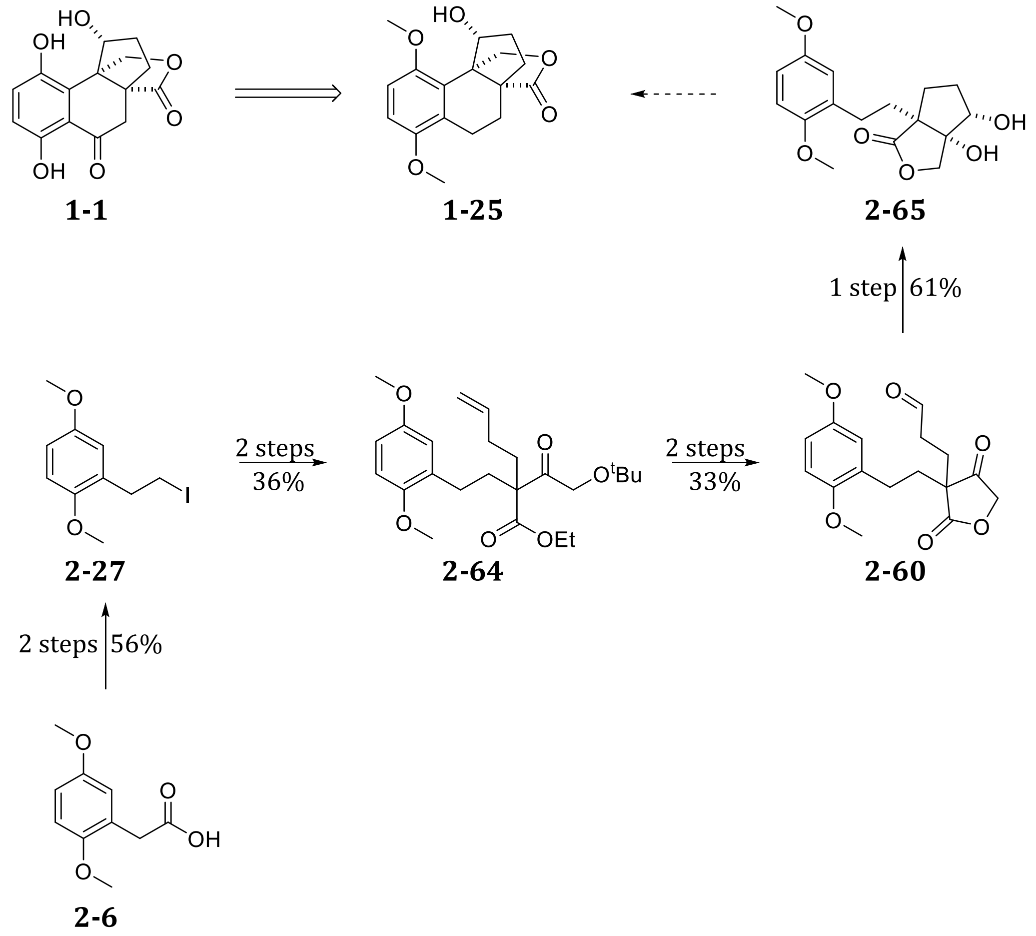
Scheme 47 *Alternative approach to* ***2-33***

Next, we investigated a strategy in which the core structure would have been established through a PAUSON-KHAND reaction (*Scheme 48*). Our attention was focused around the synthesis of **2-42**. First, we converted benzaldehyde **2-20** into **2-44** and attempted to iodinate the aromatic core, taking advantage of the directing effect of hydroxyl group in ortho lithiation reported in literature. It was however found that the sterically less crowded iodide would form, and thus the synthesis of **2-45** was unsuccessful. We then aimed to synthesize aldehyde **2-57**. Starting from *ortho*-vanillin (**2-49**) triflate **2-53** was accessible in four steps with an overall yield of 12%, the SONOGASHIRA coupling of which with TMS-acetylene was however unsuccessful. We could synthesize **2-57** starting from aldehyde **2-20** in four steps with 10% overall yield. Attempts to convert **2-57** into a precursor to the PAUSON-KHAND reaction was met with failure.



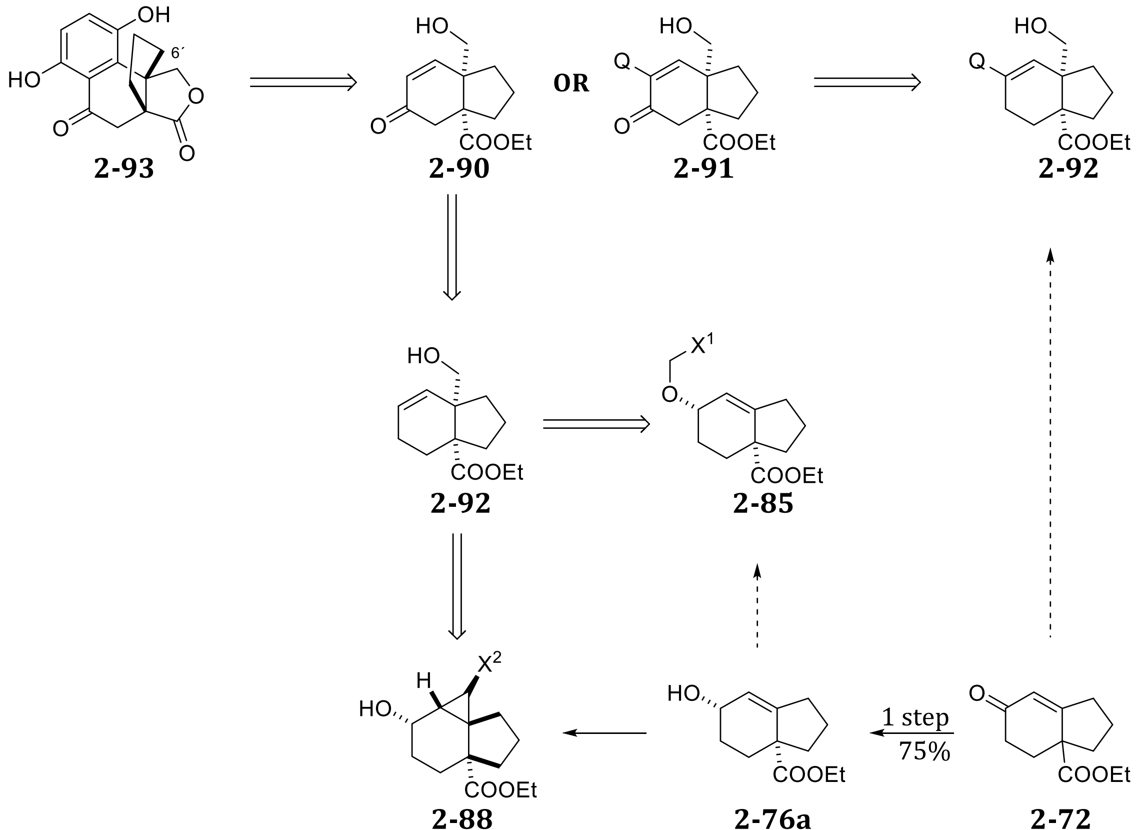
Scheme 48 *Summary of the* PAUSON-KHAND *route*

We also explored a route involving a Friedel-Crafts alkylation step to create the core structure of Lingzhiol. In our first approach we aimed to synthesize aldehyde **2-60** from **2-63** which we synthesized from phenylacetic acid **2-6** in two steps, however both alkylation and Michael addition were unsuccessful. We therefore synthesized an adequately substituted precursor and formed the lactone ring afterwards affording aldehyde **2-60** in six steps with 7% overall yield. Samarium diiodide initiated Pinacol coupling gave **2-65** which served as a precursor to the cationic ring closing. Experiments to the Friedel-Crafts ring closing of **2-65** were executed using Lewis- or Brønsted acids in either DCM or in nitromethane, mostly affording no conversion in the former and complex decomposition in the latter. Converting **2-65** into its cyclic carbonate ester and attempting the cyclisation with it gave almost identical results, it had however the advantage that, the carbonate ester being crystalline, the relative stereochemistry could be definitively established through XRD analysis.



Scheme 49 *Summary of the Friedel-Crafts route*

The last approach towards Lingzhiol rests on the late-stage introduction of the aromatic part through a DIELS-ALDER reaction (*Scheme 50*). For sake of simplicity we, investigated a strategy, that would result in 6′-deoxylingzhiol **2-93**. A possible disconnection of **2-93** could be either **2-90** or **2-91**. In order to synthesize these compounds, we started with indenone **2-72**, which is readily available from ethyl 2-oxocyclopentanecarboxylate in a ROBINSON annulation with methyl vinyl ketone. We then attempted to introduce the hydroxymethyl substituent through conjugated addition of different C1 synthons without success. We therefore diverted our attention to methods that indirectly introduce the required substitution pattern. We first reduced **2-72** stereoselectively to afford *cis* alcohol **2-76a**. We attempted to introduce various cyclopropane moieties, the ring opening or rearrangement of which serving as the source of the one carbon synthon. Accordingly, we explored the idea of a cyclopropylcarbinyl rearrangement (**2-88**, X^2: H) without success, we also tried to convert an adequately substituted cyclopropane derivative (**2-88**, X^2: Br) into a precursor to a radical rearrangement which was as well unsuccessful. We then investigated the suitability of [2,3]-WITTIG rearrangement, and thus attempted to convert **2-76a** into accordingly substituted methyl ether derivatives **2-85** (X^1: Cl, SPh, Sn^nBu_3) without success, which concluded this work.



X^1: Cl, $SnBu_3$, SPh
X^2: H, Cl, Br
Q: $OSiR_3$, OTf, Cl, Br

Scheme 50 *Summary of the* DIELS-ALDER *route*

4. Zusammenfassung

Der Zweck der vorliegenden Arbeit bestand darin, Studien zu der Totalsynthese des aus dem Fungus *Ganoderma lucidum* isolierten Meroterpenoids Lingzhiol vorzulegen. Untersuchungen zur biologischen Wirkung des Naturstoffes ergaben, dass er unter anderem die Produktion von reaktiven Sauerstoffspezies (ROS) hemmt, ohne zytotoxisch zu sein. Es wurde infolgedessen vorgeschlagen, dass Lingzhiol in der Behandlung der von Zuckerkrankheit hervorgerufenen diabetischen Nephropathie Verwendung finden könnte. Im Rahmen dieser Promotion wurden verschiedene Synthesestrategien verfolgt, die zu dem Naturstoff führen sollten.

Als erstes nahmen wir uns vor, eine Route mit der CONIA-En-Reaktion als Schlüsselschritt auszuprobieren. Wie in *Abbildung 1* zu sehen ist, könnte Lingzhiol (**1-1**) aus **2-1** durch eine kationische Zyklisierung entstehen. Epoxid **2-1** lässt sich auf Alken **2-2** zurückführen, welches durch eine CONIA-En-Reaktion aus Alkin **2-3** herzustellen ist. Die Synthese von **2-3** war unkompliziert, und die Zyklisierung zu **2-2** konnte auch mit akzeptabler Ausbeute durchgeführt werden. Die Hydroxylierung des α-Kohlenstoffes der exozyklischen Doppelbindung war jedoch nicht zu bewerkstelligen. Klassische Methoden, wie die RILEY-Oxidation, aber auch z.B. photochemische Oxidation mit Triplett-Sauerstoff, welcher durch Belichtung mithilfe eines Photosensibilisators entstand, sind gescheitert. Einige andere Wege, in denen die bereits erfolgreich angewendete CONIA-En-Reaktion weiterhin Verwendung fände, waren auch vorgeschlagen, sind jedoch aufgegeben worden, denn die zu der Zyklisierung benötigten Edukte konnten nicht hergestellt werden.

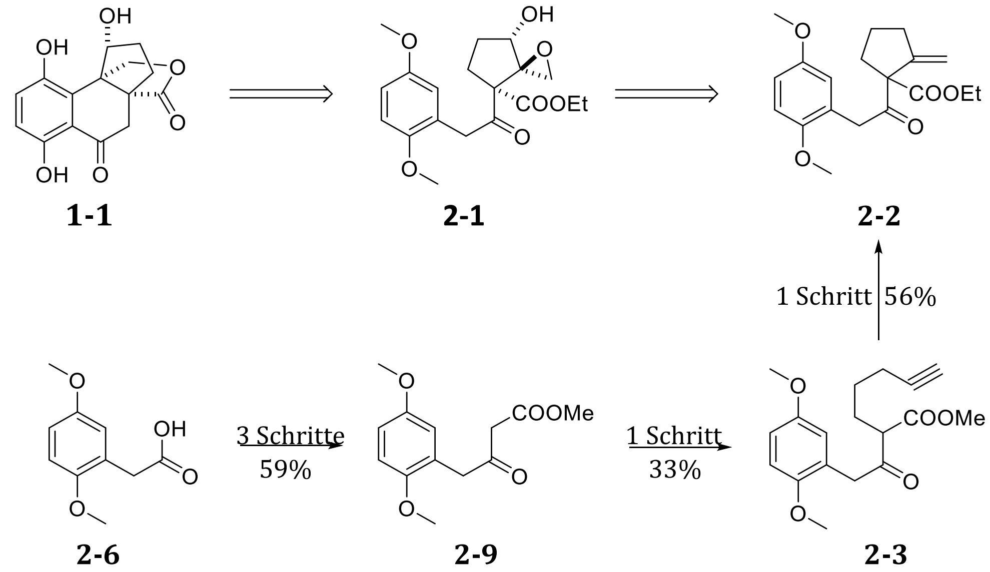


Abbildung 1 *Zusammenfassung der* CONIA-En-Route*

Demnach haben wir unsere Aufmerksamkeit auf einen anderen Weg (*Abbildung 2*) konzentriert, in dem sich Lingzhiol (**1-1**) aus Aldehyd **2-23** herstellen ließe, der in der Semipinakol-Umlagerung von **2-24** entstünde. Keton **1-21** wurde aus Phenylessigsäure **2-6** in drei Schritten mit Gesamtausbeute von 31% dargestellt. Zu der Umsetzung des Ketons **1-21** zum Aldehyd **2-25** erschien die SHAPIRO-Reaktion anwendbar zu sein. Wir haben deswegen Keton **1-21** zu seinem Tosylhydrazon umgesetzt, dessen Reaktion unter SHAPIRO-Bedingungen jedoch kein Produkt lieferte. Die Ketogruppe in **1-21** wurde deshalb in ein Epoxid umgewandelt, dessen Umlagerung zu **2-25** mithilfe einer LEWIS-Säure oder Thionylchlorid aber gescheitert ist. Ein alternativer Vorschlag zu der Synthese von **2-23** ist *Abbildung 3* zu sehen. Phenylethanol **2-29** wurde in zwei Schritten in Isochroman **2-37** mit Gesamtausbeute von 26% umgesetzt. Verschiedene Versuche, die **2-37** in Aldehyd **2-35** hätten umwandeln sollen, waren aber nicht erfolgreich.

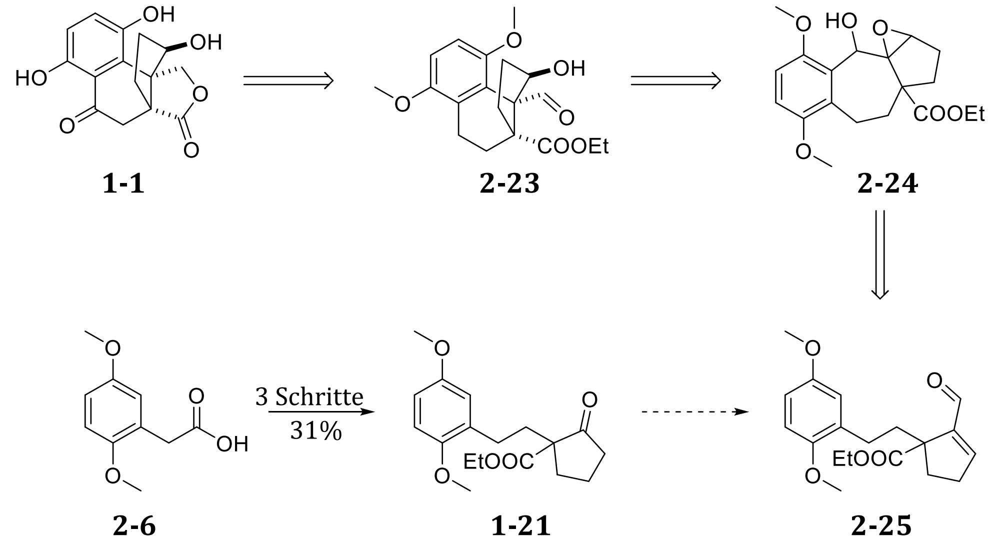


***Abbildung 2** Zusammenfassung der Pinakol-Route*

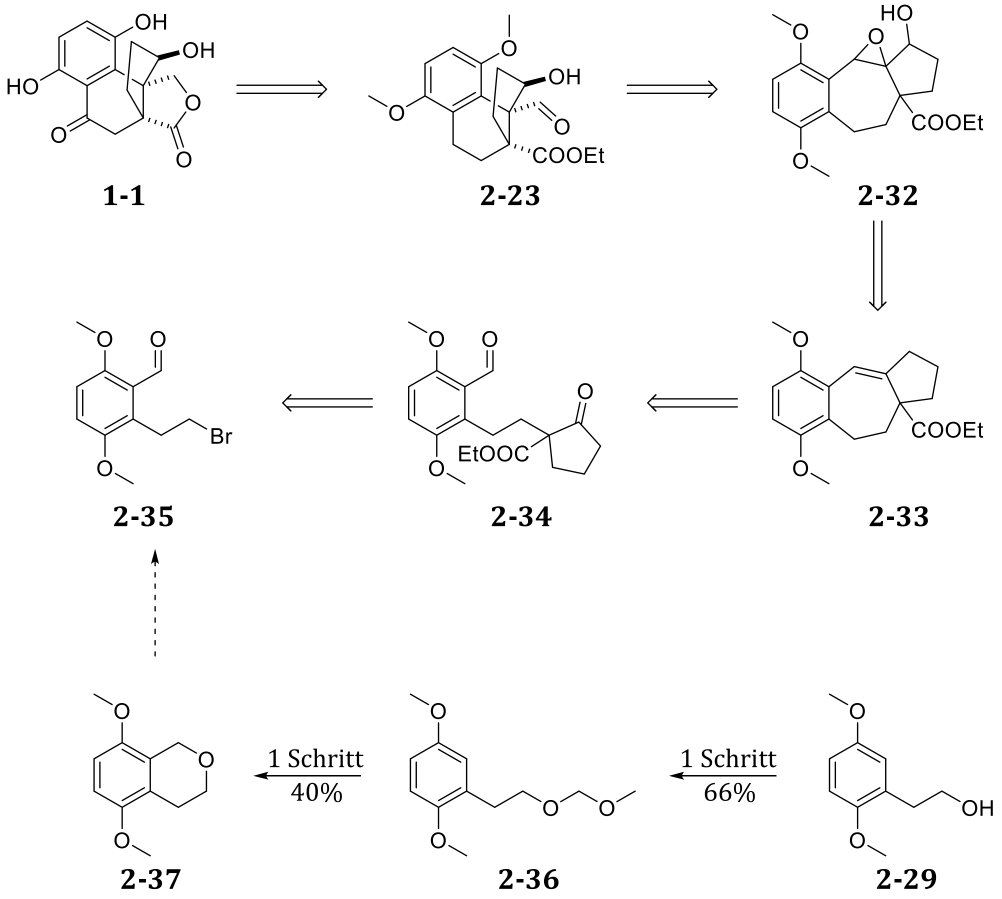


Abbildung 3** Alternativer Vorschlag zu der Synthese von **2-23

Als nächstes haben wir die Anwendbarkeit der PAUSON-KHAND-Reaktion zu der Synthese von Lingzhiol erforscht. Zu diesem Zweck musste erst die Herstellung des entsprechend substituierten Alkins **2-42** erarbeitet werden. Wir begannen die Forschung mit der Umsetzung des Aldehyds **2-20** in Alkohol **2-44** durch eine GRIGNARD-Reaktion mit guter Ausbeute. Wir hatten vor, eine regioselektive *ortho*-Metallierung gefolgt von einer Iodierung durchzuführen, die laut Literaturbeispielen dasjenige Regioisomer ergäbe, welches den einzuführenden Substituenten direkt neben dem benzylischen Alkohol enthält. Es ist in unserem Fall jedoch festgestellt worden, dass sich das sterisch weniger gehinderte Produkt gebildet hat. Demnach haben wir uns mit der Herstellung des Alkins **2-57** auseinandergesetzt. Triflat **2-53** war aus *ortho*-Vanillin (**2-49**) in vier Schritten mit einer Gesamtausbeute von 12% zugänglich, dessen SONOGASHIRA-Kupplung aber **2-57** nicht geliefert hat. Alkin **2-57** ließ sich schließlich aus Aldehyd **2-20** in vier Schritten mit 10% Gesamtausbeute herstellen. Versuche zur Umsetzung von **2-57** in das Edukt der PAUSON-KHAND-Reaktion sind allerdings gescheitert.

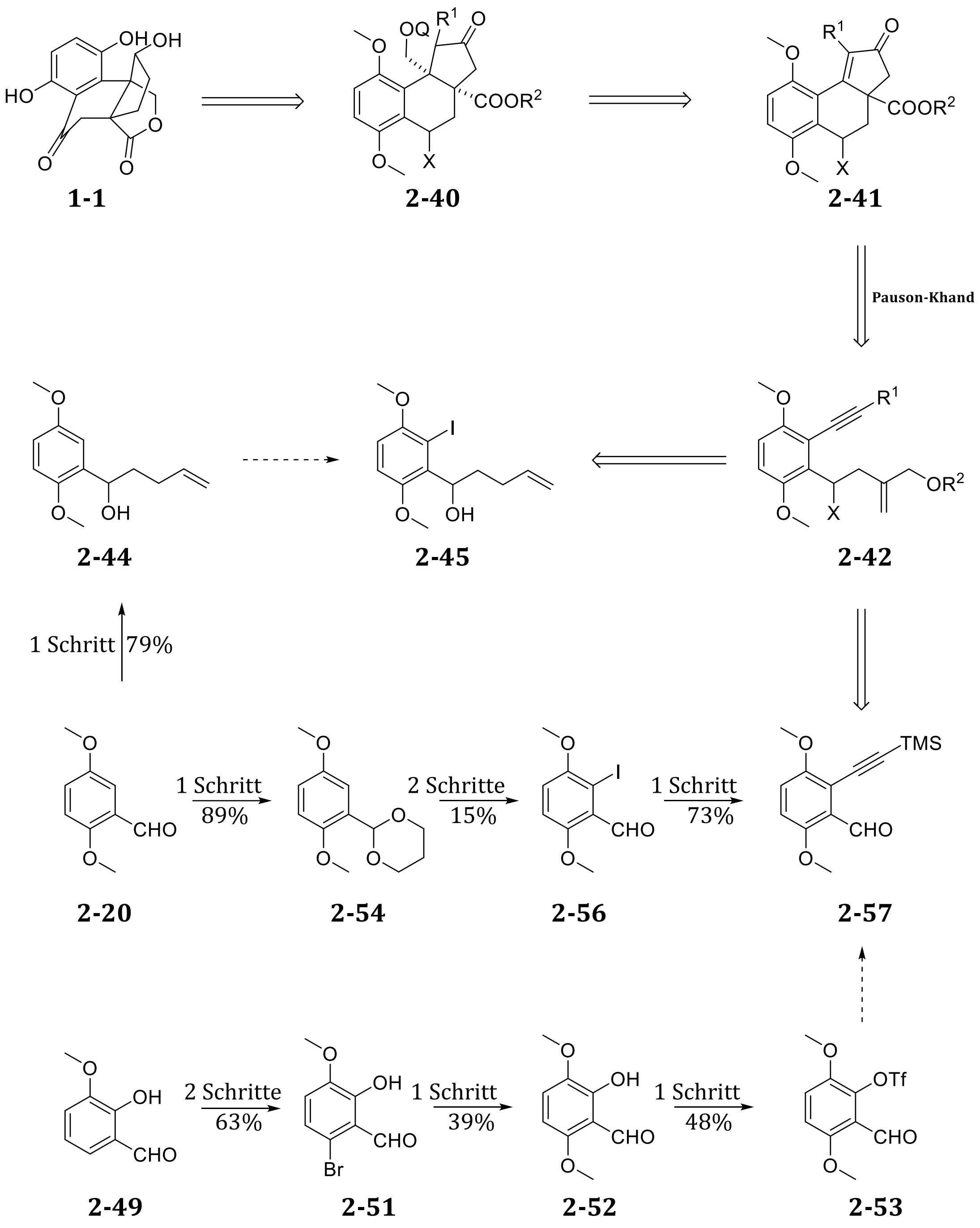


Abbildung 4 *Zusammenfassung der* PAUSON-KHAND*-Route*

Wir haben auch eine Route untersucht, in der sich die Kernstruktur von Lingzhiol in einer Friedel-Crafts-Alkylierung bilden würde. Erst haben wir Ketolacton **2-60** aus Phenylessigsäure **2-6** in zwei Schritten hergestellt, aber jeglicher Versuch sie in **2-60** umzusetzen war erfolglos. Wir haben deshalb **2-60** durch einen alternativen Weg in sechs Schritten mit 6% Gesamtausbeute synthetisiert. Pinakol-Kupplung mit Samariumdiiodid hat das Edukt der Friedel-Crafts-Reaktion **2-65** geliefert. Die Friedel-Crafts-Reaktion wurde mit Lewis- oder Brønsted-Säuren in DCM oder in Nitromethan versucht, es hat jedoch entweder keine Reaktion oder komplexe Zersetzungsmischungen ergeben. Die Friedel-Crafts-Reaktion des aus **2-65** hergestellten cyclischen Carbonatesters hat das gleiche Ergebnis geliefert. Allerdings hatte die Synthese des Carbonatesters den Vorteil, dass sich seine Struktur durch XRD aufklären ließ und somit die relative Stereochemie eindeutig zugeordnet werden konnte.

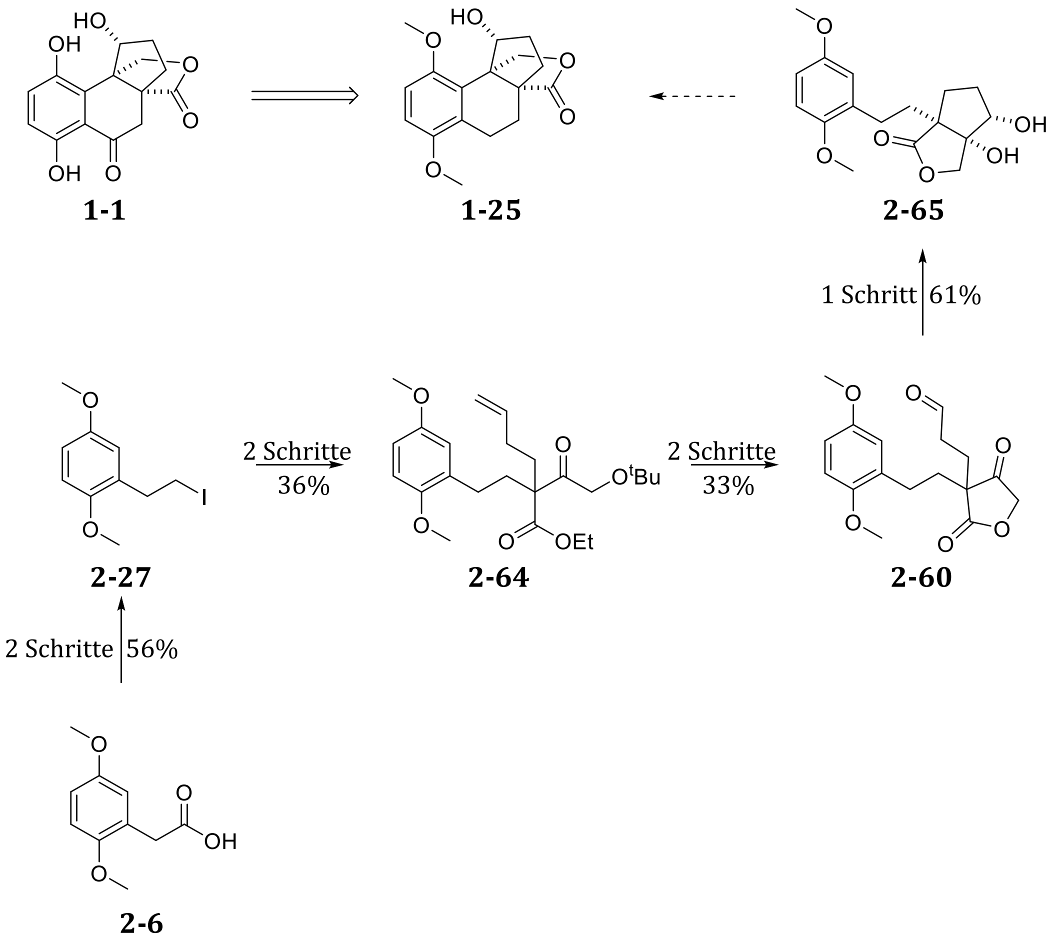
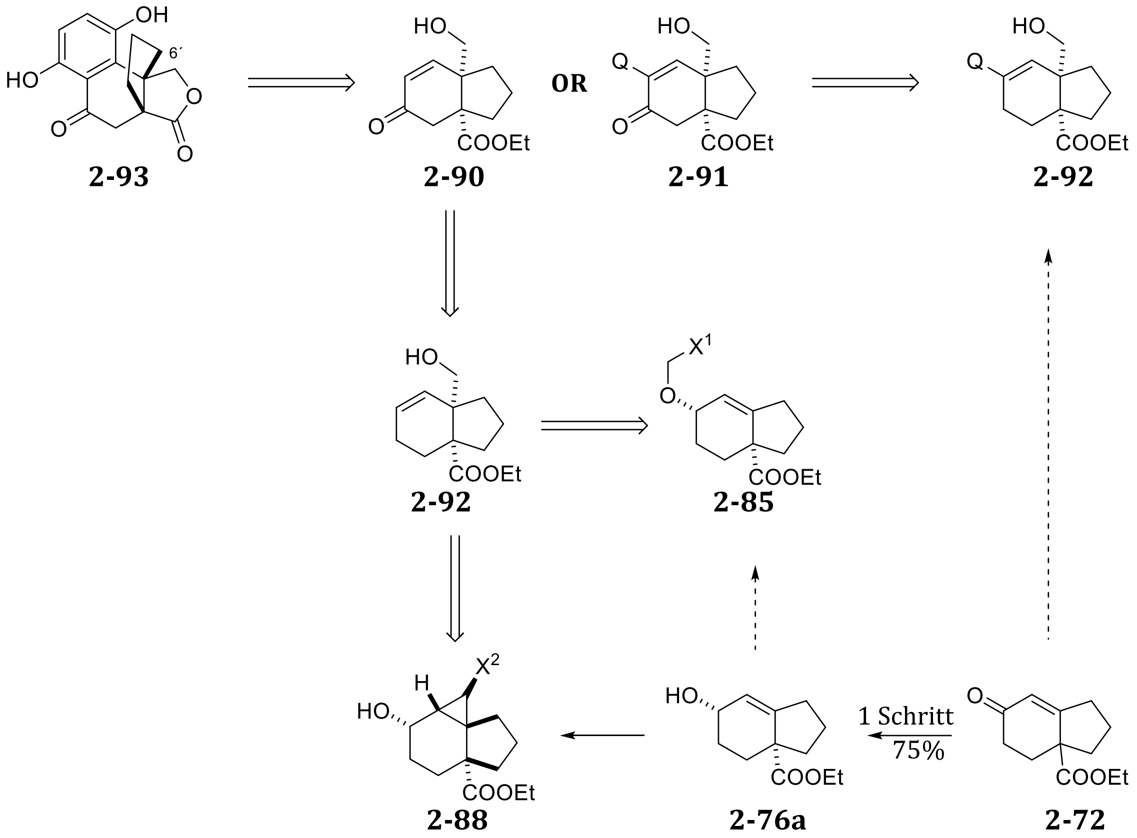


Abbildung 5 *Zusammenfassung der Friedel-Crafts-Route*

Die letzte Route, die wir zu der Totalsynthese des Lingzhiols vorgeschlagen haben, ist in *Abbildung 6* zu sehen. Der Einfachheit halber haben wir uns nach einer Strategie gerichtet, die schließlich 6´-Deoxylingzhiol **2-93** ergäbe. Als mögliches Synthon von **2-93** könnte entweder **2-90** oder **2-91** auftreten. Um sie herzustellen, haben wir die Synthese mit Indenon **2-72** angefangen, welches in einer ROBINSON-Anellierung leicht zugänglich ist. Wir haben versucht den Hydroxymethyl-Substituenten erst durch konjugierte nucleophile Addition einzuführen, die jedoch keinen Erfolg geliefert hat. Demnach haben wir einige indirekte Routen ausprobiert. Indenon **2-72** wurde unter LUCHE-Bedingungen stereoselektiv zu *cis*-Alkohol **2-76a** reduziert. Dann haben wir **2-76a** in verschiedene Cyclopropanderivate umgesetzt, deren Ringöffnung und Umlagerung als Quelle des Hydroxymethyl-Substituenten dienen würde. Wir haben deshalb erst die von LEWIS- oder BRØNSTED-Säuren getriebene Cyclopropylcarbinyl-Umlagerung (**2-88**, X^2: H) untersucht, danach versuchten wir **2-88** (X^2: Br) in ein Edukt einer radikalischen Umlagerung umzusetzen, beide Ansätze waren jedoch erfolglos. Als letzte Möglichkeit haben wir die Anwendbarkeit der [2,3]-WITTIG-Umlagerung geprüft. Wir haben deswegen versucht **2-76a** in entsprechend substituierte Methylether-Derivate **2-85** (X^1: Cl, SPh, Sn^nBu_3) umzuwandeln. Diese Versuche sind jedoch gescheitert und damit ist diese Arbeit zu ihrem Schluss gekommen.



X^1: Cl, $SnBu_3$, SPh

X^2: H, Cl, Br

Q: $OSiR_3$, OTf, Cl, Br

Abbildung 6 *Zusammenfassung der DIELS-ALDER-Route*

5. Experimental section

5.1. Techniques and Chemicals

All reactions were performed using standard laboratory equipment. Air- and/or moisture-sensitive reactions were performed using Schlenk technique (Schlenk line, rubber septa, Schlenk flasks etc.) under nitrogen or argon atmosphere. For this purpose, all reaction vessels were flame-dried under vacuum, followed by flushing with an inert gas, this process being repeated three times. Solutions, solvents, liquid reagents etc. were manipulated using syringes, needles, and cannulas.[278] Chemicals were purchased from commercial vendors (Merck, TCI, ABCR, ThermoFisher, Fluorochem etc.) and – unless otherwise noted – were used without further purification. Solvents were purified according to literature protocols.[279]

Preparative column chromatography was performed using silica gel (MACHEREY-NAGEL Gmbh & Co. KG, Silica 60 M, 0.04-0.063 mm, henceforth referred to as “silica”) or neutral aluminium(III) oxide (Merck, Aluminium oxide 90 active neutral, activity stage I, 0.063-0.200 mm, henceforth referred to as “neutral alumina”) as stationary phase.

5.2. Thin Layer Chromatography

The progression of reactions was followed by thin layer chromatography (TLC). For this purpose, silica coated (0.20 mm thick layer of silica gel 60 with fluorescent indicator) plastic sheets (MACHEREY-NAGEL GmbH & Co. KG, Pre-coated TLC sheets POLYGRAM® SIL G/UV$_{254}$) of adequate size were used. Development of the plates was performed using solvent mixtures. Visualisation of the TLC spots were done by exposing the plates to UV light (254 and/or 366 nm) and/or staining the plates with one of the following stains.

$KMnO_4$: The plates were dipped into an alkaline potassium permanganate solution (1.5 g $KMnO_4$, 10.0 g K_2CO_3 and 1.5 ml 10 w/w% NaOH (aq.) dissolved in 200 ml water) followed by gentle heating.

Vanillin: The plates were dipped into an ethanolic vanillin solution (15 g vanillin, 2.5 ml 96 w/w% H_2SO_4 dissolved in 250 ml ethanol) followed by gentle heating.

$FeCl_3$: The plates were dipped into a methanolic $FeCl_3$ solution (5 w/w% $FeCl_3.6H_2O$ in methanol) followed by gentle heating.

5.3. NMR-Spectroscopy

All NMR-spectra were obtained with a Bruker Avance III HD 400 spectrometer, which operated at 400.16 MHz for ^1H and at 100.62 MHz for ^{13}C nuclei. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual proton and carbon shifts of the solvents: $CDCl_3$: 7.26 ppm for ^1H and 77.16 ppm for ^{13}C, DMSO-d^6: 2.50 ppm for ^1H and 39.52 ppm for ^{13}C. The NMR-data are reported as follows: chemical shift(s) in ppm (multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened; coupling constant(s) reported in Hz; normalized integral; assignment). The shifts are listed from downfield to upfield, that is, the first entry corresponds to the highest chemical shift.

5.4. Mass Spectrometry

High resolution mass spectrometry (HRMS) was performed on a Bruker maXis 4G spectrometer with either electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI), with the ions separated and analysed by time of flight (TOF) analyser.

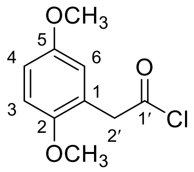
Gas chromatography-mass spectrometry (GC-MS) was performed on an Agilent 5977B MSD; 8890 GC System with electron ionisation (EI) and quadrupole analyser.

5.5. X-Ray Crystallography

X-ray diffraction (XRD) analysis was performed on a XtaLAB Synergy-S, Dualflex, HyPix diffractometer with the exact procedures described in detail in the corresponding experimental segment.

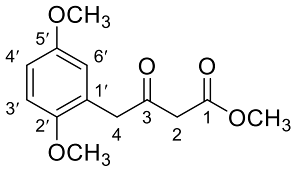
5.6. Experimental procedures

2-(2,5-Dimethoxyphenyl)acetyl chloride (2-7)



2-(2,5-Dimethoxyphenyl)acetic acid (10.0 g, 50.97 mmol, 1.0 eq.) was mixed in thionyl chloride (14 mL, 22.8 g, 191.93 mmol, 3.8 eq.) and was then heated at reflux (bath temperature: 80°C) for 2.5 hours. The excess thionyl chloride was then removed through distillation in vacuo (10 mbar) at RT, and then the temperature was gradually increased to 160 °C at which the acid chloride **2-7** (9.5 g, 44.3 mmol, 87%) was distilled as a yellow oil. This yellow oil was used immediately without further analysis and purification.

Methyl 4-(2,5-dimethoxyphenyl)-3-oxobutanoate (2-9)[66]



Meldrum's acid (6.4 g, 44.26 mmol, 1.0 eq.) was dissolved in DCM (16 mL) and was then cooled to 0°C, upon which the clear solution became slightly cloudy. Pyridine (8.9 mL, 8.8 g, 110.65 mmol, 2.5 eq.) was then added giving a clear solution, that was stirred at 0°C for 10 min. Then a solution of 2-(2,5-dimethoxyphenyl)acetyl chloride (**2-7**) (9.5 g, 44.26 mmol, 1.0 eq.) in DCM (16 mL) was added over 10 min. After ~10 mL of acid chloride solution was added, the originally clear mixture became cloudy, and gradually turned more viscous during the addition of the rest of the acyl chloride solution. After the addition was complete, the mixture was stirred at 0 °C for 1 h and at RT for another hour. The orange mixture was then diluted with DCM (50 mL) and poured into ice-cold hydrochloric acid (1 M, 200 mL), the phases were separated, the aqueous phase was extracted with DCM (1×100 mL), the combined organic phases were washed with hydrochloric acid (2 M, 150 mL) and sat. sodium chloride solution (1×150 mL) and were then dried over sodium sulphate. The drying agent was filtered, and the volatiles were evaporated in vacuo to afford an orange oil, that was dissolved in methanol (200 mL), and it was refluxed for 4 h, the methanol was then removed in vacuo to afford a deep orange oil, that was subjected to flash chromatography (petroleum ether/ethyl acetate: 3/1) to afford ketoester **2-9** (8.7 g, 34.52 mmol, 78%) as a light-yellow oil.

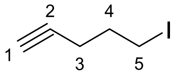
R_f: 0.23 (petroleum ether/ethyl acetate: 1/1, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]: 6.80 – 6.78 (m, 2H, 3'-H, 4'-H), 6.72 (dd, *J*=2.5, 1.0 Hz, 1H, 6'-H), 3.76 (s, 3H, Ar-OC$\underline{H}_3$), 3.75 (s, 3H, Ar-OC$\underline{H}_3$), 3.73 (s, 2H, 4-H), 3.70 (s, 3H, COOC$\underline{H}_3$), 3.46 (s, 2H, 2-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm]: 200.9 (C3), 167.9 (C1), 153.7 (C5'), 151.6 (C2'), 123.6 (C1'), 117.5 (C6'), 113.3 (C3' or C4'), 111.5 (C3' or C4'), 56.0 (Ar-O$\underline{C}H_3$), 55.8 (Ar-O$\underline{C}H_3$), 52.3 (COO$\underline{C}H_3$), 48.1 (C2), 45.1 (C4).

HRMS (ESI-TOF): m/z: calcd. for $[C_{13}H_{16}O_5+Na]^+$: 275.08899; found: 275.08942

5-iodopent-1-yne (2-4)[280]



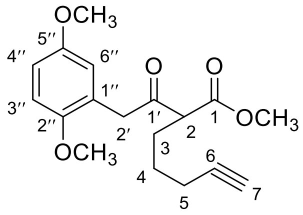
To a solution of sodium iodide (92.2 g, 615.36 mmol, 6.0 eq.) in acetone (600 mL) 5-chloro-1-pentyne (10.1 mL, 10.0 g, 97.50 mmol, 1.0 eq.) was added, and this solution was stirred at reflux for 24 h. The precipitated sodium chloride was then filtered, and the acetone was removed in vacuo, affording a slurry of product and excess sodium iodide. This slurry was taken up with DCM (1×150 mL), and water (1×200 mL) was added, the phases were separated after shaking, the aqueous phase was extracted with DCM (1×150 ml) and the combined organic phases were dried over sodium sulphate, filtered, then they were concentrated in vacuo to afford the product (12.5 g, 64.35 mmol, 66%) as a yellow liquid, that was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]: 3.31 (t, *J*=6.7 Hz, 2H), 2.34 (td, *J*=6.7, 2.7 Hz, 2H), 2.05 – 1.96 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm]: 82.39, 69.59, 31.95, 19.58, 5.19.

NMR data conform to literature.[280]

Methyl 2-(2-(2,5-dimethoxyphenyl)acetyl)hept-6-ynoate (2-3)



Sodium hydride (60% dispersion in mineral oil, 380 mg, 9.50 mmol, 1.2 eq.) was suspended in abs. DMF (10 mL) and methyl 4-(2,5-dimethoxyphenyl)-3-oxobutanoate (**2-9**) (2.0 g, 7.92 mmol, 1.0 eq.) was added dropwise while the mixture was kept at RT with a water bath. After the addition, the mixture was stirred for 15 min, then 5-iodopent-1-yne (**2-4**) (3.1 g, 15.84 mmol, 2.0 eq.) was added in a single portion, and the mixture was stirred at RT for 24 h. The mixture was poured into hydrochloric acid (1 M, 100 mL), and it was extracted with diethyl ether (3×50 mL). The combined organic phases were washed with saturated sodium chloride solution (1×150 mL) then the organic phases were dried over sodium sulphate, filtered, and the volatiles were removed in vacuo affording the crude product, that was subjected to flash chromatography (silica, petroleum ether/ethyl acetate: 3/1) to afford a pale oil, that was not adequately pure, and thus was purified by a second chromatographic step (silica, petroleum ether/ethyl acetate: 4/1) to afford ketoester **2-3** (840 mg, 2.63 mmol, 33%), as a pale yellow oil.

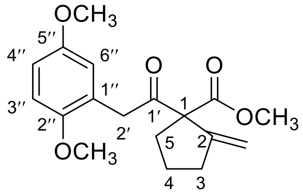
R_f : 0.20 (petroleum ether/ethyl acetate: 1/1, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]: 6.78 – 6.77 (m, 2H, 3''-H, 4''-H), 6.70 (t, *J*=1.6 Hz, 1H, 6''-H), 3.77 (s, 1H, 2'-H), 3.76 (s, 1H, 2'-H), 3.74 (s, 3H, Ar-OC$\underline{H}_3$), 3.74 (s, 3H, Ar-OC$\underline{H}_3$), 3.70 (s, 3H, COOC$\underline{H}_3$), 3.60 (t, *J*=7.2 Hz, 1H, 2-H), 2.15 (td, *J*=7.1, 2.7 Hz, 2H, 5-H), 2.00 – 1.91 (m, 3H, 3-H, 7-H), 1.51 – 1.42 (m, 2H, 4-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm]: 202.6 (C1'), 170.1 (C1), 153.6 (C2'' or C5''), 151.6 (C2'' or C5''), 123.6 (C1''), 117.6 (C6''), 113.1 (C3'' or C4''), 111.4 (C3'' or C4''), 83.7 (C6), 68.9 (C7), 57.1 (C2), 55.9 (Ar-O$\underline{C}H_3$), 55.8 (Ar-O$\underline{C}H_3$), 52.4 (COO$\underline{C}H_3$), 44.2 (C2'), 27.3 (C3), 26.2 (C4), 18.3 (C5).

HRMS (ESI-TOF): m/z: calcd. for $[C_{18}H_{22}O_5+Na]^+$: 341.13594; found: 341.13554

Methyl 1-(2-(2,5-dimethoxyphenyl)acetyl)-2-methylenecyclopentane-1-carboxylate (2-2)[75]



To a mixture of chloro[(1,1′-biphenyl-2-yl)di-tert-butylphosphine]gold(I) (32 mg, 0.06 mmol, 10 mol%) and silver trifluoromethanesulfonate (15 mg, 0.06 mmol, 10 mol%) in a Schlenk flask under nitrogen atmosphere, a solution of methyl 2-(2-(2,5-dimethoxyphenyl)acetyl)hept-6-ynoate (**2-3**) (200 mg, 0.63 mmol, 1.0 eq.) in DCM (1 mL) was added upon which a cloudy pink, later a blue mixture formed. This mixture was stirred overnight at RT. The mixture was then directly loaded onto a column (without work-up) and was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 4/1) to afford ketoester **2-2** (112 mg, 0.35 mmol, 56%) as a colourless oil.

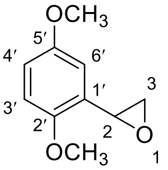
R_f : 0.55 (petroleum ether/ethyl acetate: 3/1, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]: 6.76 (m, 2H, 3”-H, 4”-H), 6.70 (s, 1H, 6”-H), 5.33 (t, *J*=2.2 Hz, 2H, 2-C$\underline{H}_2$), 3.85 (d, *J*=2.8 Hz, 2H, 2’-H), 3.76 (s, 3H, Ar-OC$\underline{H}_3$ or COOC$\underline{H}_3$), 3.75 (s, 3H, Ar-OC$\underline{H}_3$ or COOC$\underline{H}_3$), 3.72 (s, 3H, Ar-OC$\underline{H}_3$), 2.52 – 2.45 (m, 3H, Ring-H), 2.33 (dt, *J*=13.4, 6.9 Hz, 1H, Ring-H), 1.75 (pd, *J*=7.2, 2.0 Hz, 2H, Ring-H).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm]: 203.3 (C1’), 171.77 ($\underline{C}OOCH_3$), 153.5 (C2” or C5”), 151.7 (C2” or C5”), 149.0 (C2), 124.4 (C1”), 117.6 (C6”), 112.9 (C3” or C4”), 112.5 (C2-$\underline{C}H_2$), 111.5 (C3” or C4”), 70.6 (C1), 56.0 (Ar-O$\underline{C}H_3$ or COOO$\underline{C}H_3$), 55.8 (Ar-O$\underline{C}H_3$ or COOO$\underline{C}H_3$), 52.8 (Ar-O$\underline{C}H_3$ or COOO$\underline{C}H_3$), 40.4 (C2’), 35.3 (Ring-C), 34.2 (Ring-C), 24.3 (Ring-C).

HRMS (ESI-TOF): m/z: calcd. for $[C_{18}H_{22}O_5+Na]^+$: 341.13594; found: 341.13615

2-(2,5-Dimethoxyphenyl)oxirane (2-14)[90]



Sodium hydride (60% in mineral oil, 530mg, 14.45 mmol, 1.2 eq.) was suspended in THF (100 mL), and a solution of trimethylsulfonium iodide (2.9 g, 14.45 mmol, 1.2 eq.) in THF (20 mL) was added slowly, then the mixture was stirred at room temperature for 30 min. Then, a solution of 2,5-dimethoxybenzaldehyde (2.0 g, 12.04 mmol, 1.0 eq.) in THF (20 mL) was added over 30 min, the mixture was then heated to ~55 °C and was kept there for an additional hour. It was then allowed to cool to room temperature, and about 100 mL THF was distilled off in vacuo. To the remaining thick slurry water (150 mL) was added, and the aqueous mixture was extracted with ethyl acetate (3×100 mL), the combine organic phases were washed with saturated sodium chloride (1×200 mL) and dried over sodium sulphate. The mixture was filtered and then concentrated in vacuo, and the crude product was purified by flash chromatography (silica, petroleum ether/diethyl ether: 10/1 to 6/1 to 4/1) to afford epoxide **2-14** (1.1 g, 6.10 mmol, 51%) as a colourless liquid.

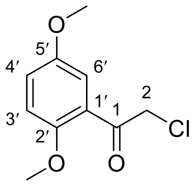
R_f : 0.53 (petroleum ether/ethyl acetate: 6/1, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]: 6.82 – 6.76 (m, 2H, 3’-H, 4’-H), 6.73 (dd, *J*=2.7, 0.7, 1H, 6’-H), 4.19 (dd, *J*=4.1, 2.6 Hz, 1H, 2-H), 3.82 (s, 3H, 2’-OC*H*$_3$), 3.75 (s, 3H, 5’-OC*H*$_3$), 3.13 (dd, *J*=5.8, 4.2 Hz, 1H, 3-H^a), 2.67 (dd, *J*=5.8, 2.6, 1H, 3-H^b).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm]: 154.1 (C5’), 152.4 (C2’), 127.3 (C1’), 113.7 (C4’), 111.6 (C3’), 110.6 (C6’), 56.2 (2’-O*C*H$_3$), 55.8 (5’-O*C*H$_3$), 50.9 (C3), 48.3 (C2).

NMR data conform to literature[281]

2-Chloro-1-(2,5-dimethoxyphenyl)ethan-1-one (2-18)[91]



Aluminium chloride (23.2 g, 174.0 mmol, 2.0 eq.) was added to a solution of 1,4-dimethoxybenzene (12.0 g, 86.9 mmol, 1.0 eq.) in DCM (100 mL) at room temperature. To this stirred mixture then chloroacetyl chloride (14 mL, 19.9 g, 176.2 mmol, 2.0 eq.) was added carefully, and the resulting mixture was stirred for 8 h at room temperature. The solution was then poured into a mixture of hydrochloric acid (36 w/w%, 40 mL) and ice (~200 g), the phases were separated, the aqueous phase was extracted with DCM (3×100 mL), the combined organic phases were washed with water (2×100 mL), aqueous sodium hydroxide solution (10 w/w%, 100 mL) and again with water (2×100 mL), then were dried over sodium sulphate. The mixture was then filtered, and the solvent was evaporated in vacuo to give a white solid as crude product, which was recrystallised from methanol to give 2-chloroketone **2-18** as a fine crystalline mass (8.8 g, 41.0 mmol, 47%).

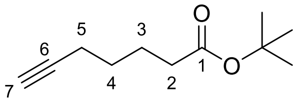
R_f : 0.31 (petroleum ether/ethyl acetate: 7/1, UV)

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]: 7.40 (d, *J*=3.2 Hz, 1H), 7.09 (dd, *J*=9.0, 3.3 Hz, 1H), 6.93 (d, *J*=9.0 Hz, 1H), 4.79 (s, 2H), 3.90 (s, 3H), 3.80 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm]: 192.0, 153.8, 153.6, 125.1, 122.0, 114.4, 113.2, 56.3, 56.0, 51.3

NMR data conform to literature[63]

***tert*-Butyl hept-6-ynoate (2-19)**[282]



^{n}BuLi (2.5 M in hexane, 36.0 mL, 90.0 mmol, 1.2 eq.) was added slowly into a solution of DIPA (12.5 mL, 9.0 g, 88.9 mmol, 1.2 eq.) in THF (300 mL) under nitrogen atmosphere at -78 °C. The mixture was stirred for 45 min at this temperature, then *tert*-butyl acetate (10.0 mL, 8.7 g, 74.9 mmol, 1.0 eq.) was added dropwise and the mixture was stirred for 1 h, then DMPU (36.0 mL, 38.2 g, 298.0 mmol, 4.0 eq.) was introduced, and the mixture was stirred for 10 min and 5-iodopent-1-yne (**2-4**) (14.5 g, 74.7 mmol, 1.0 eq.) was added then the mixture was allowed to warm to room temperature and was stirred for 24 h. The mixture was quenched with sat. ammonium chloride solution (150 mL) and diluted with petroleum ether (150 mL). The phases were separated, the organic layer was washed with hydrochloric acid (1 M, 2×150 mL) and water (1×150 mL) and was dried over sodium sulphate. The mixture was filtered, the filtrate was concentrated in vacuo and the crude product was subjected to flash chromatography (silica, petroleum ether) to afford ester **2-19** as a colourless, viscous liquid (10.5 g, 57.6 mmol, 77%).

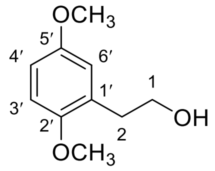
R_f : 0.30 (petroleum ether, $KMnO_4$)

^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm]: 2.24 – 2.16 (m, 4H), 1.93 (t, *J*=2.7 Hz, 1H), 1.73 – 1.64 (m, 2H), 1.59 – 1.49 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm]: 172.9, 84.2, 80.2, 68.6, 35.1, 28.2, 28.0, 24.3, 18.3

NMR data conform to literature[283]

2-(2,5-Dimethoxyphenyl)ethan-1-ol (2-29)[61]



A solution of 2-(2,5-dimethoxyphenyl)acetic acid (10.0 g, 51.0 mmol, 1.0 eq.) in THF (50 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (4.0 g, 102.0 mmol, 2.0 eq.) in THF (150 mL) at 0 °C. After the addition was complete, the mixture was heated to 50 °C and was stirred at that temperature overnight. The mixture was let to cool to room temperature, afterwards it was placed into an ice-water bath and was quenched by the addition of water (10 mL) followed by the addition of an aqueous sodium hydroxide solution (15 w/w%, 5 mL). The mixture was then filtered through a celite pad, and the precipitates were washed with hot ethyl acetate (2×100 mL), and the combined ethyl acetate solution was dried over sodium sulphate, filtered, then the solvents were evaporated in vacuo affording alcohol **2-29** (7.4 g, 40.6 mmol, 80%) as a yellow oil, which was used without further purification.

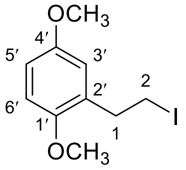
R_f : 0.24 (petroleum ether/ethyl acetate: 9/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.80 – 6.71 (m, 3H, Ar-H), 3.81 (t, *J*=6.5 Hz, 2H, 1-H), 3.77 (s, 3H, 2’-OC$\underline{H}_3$), 3.75 (s, 3H, 5’-OC$\underline{H}_3$), 2.87 (t, *J*=6.5 Hz, 2H, 2-H), 2.17 (s, 1H, O$\underline{H}$)

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 153.6 (C5’), 151.9 (C2’), 128.4 (C1’), 117.2 (C3’ or C4’ or C6’), 111.8 (C3’ or C4’ or C6’), 111.4 (C3’ or C4’ or C6’), 62.9 (C1), 56.0 (2’-O$\underline{C}H_3$), 55.7 (5’-O$\underline{C}H_3$), 34.3 (C2).

NMR data conform to literature[61]

2-(2-Iodoethyl)-1,4-dimethoxybenzene (2-27)[61]



Iodine (8.3 g, 32.6 mmol, 1.1 eq.) was added to a solution of imidazole (6.1 g, 88.8 mmol, 3.0 eq.) and triphenylphosphine (8.5 g, 32.6 mmol, 1.1 eq.) in DCM (40 mL) at 0 °C, and the mixture was stirred for 5 minutes followed by the addition of a solution of 2-(2,5-dimethoxyphenyl)ethan-1-ol (**2-29**) (5.4 g, 29.6 mmol, 1.0 eq.) in DCM (20 mL), then the flask was tightly wrapped in aluminium foil, and was left stirring overnight at RT. The mixture was then washed with saturated sodium thiosulfate solution (1×50 mL), the aqueous phase was extracted with DCM (2×100 mL), the combined organic phases were dried over sodium sulphate followed by the evaporation of volatiles in vacuo to afford a yellowish liquid which was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 10/1) to afford iodide **2-27** (5.2 g, 17.9 mmol, 60%) as a colourless oil.

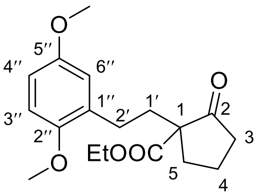
R_f : 0.45 (petroleum ether/ethyl acetate: 10/1, UV)

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm]: 6.78 – 6.77 (m, 2H), 6.73 – 6.72 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.36 (t, *J*=8.2 Hz, 2H), 3.16 (t, *J*=8.0 Hz, 2H)

^{13}C NMR (CDCl$_3$, 101 MHz): δ [ppm]: 153.4, 151.6, 130.0, 116.6, 112.2, 111.3, 55.8, 55.8, 35.8, 4.5

NMR data conform to literature.[61]

Ethyl 1-(2,5-dimethoxyphenethyl)-2-oxocyclopentane-1-carboxylate (1-21)[61]



To a solution of ethyl 2-oxocyclopentanecarboxylate (3.5 g, 3.3 ml, 22.2 mmol, 1.2 eq.) in DMF (30 mL), potassium carbonate (6.4 g, 46.3 mmol, 2.5 eq.) was added, and the mixture was stirred for 15 minutes at RT, followed by the addition of 2-(2-iodoethyl)-1,4-dimethoxybenzene (**2-27**) (5.4 g, 18.5 mmol, 1.0 eq.) in DMF (20 mL), then the mixture was stirred overnight at 75 °C . The mixture was diluted with water (100 mL) and was extracted with ethyl acetate (3×100 mL). The combined organic phases were washed with sat. sodium chloride solution (1×100 mL) and were dried over sodium sulphate followed by filtration and evaporation of the volatiles in vacuo to afford a yellow liquid as crude product, which was then subjected to flash chromatography (silica, petroleum ether/ethyl acetate: 30/1 to 10/1) to afford ketoester **1-21** (5.6 g, 17.5 mmol, 79%) as a colourless oil.

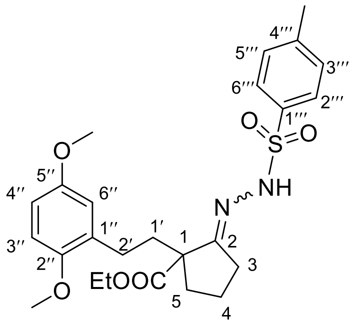
R_f : 0.43 (petroleum ether/ethyl acetate: 4/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.75 – 6.67 (m, 3H, 3”-H, 4”-H, 6”-H), 4.21 – 4.13 (m, 2H, $COOC\underline{\textit{H}}_2CH_3$), 3.76 (s, 3H, Ar-$OC\underline{\textit{H}}_3$), 3.74 (s, 3H, Ar-$OC\underline{\textit{H}}_3$), 2.65 – 2.49 (m, 3H, 2’-H, Ring-H), 2.46 – 2.38 (m, 1H, Ring-H), 2.32 – 2.17 (m, 2H, 1’-H^a, Ring-H), 2.06 – 1.94 (m, 3H, Ring-H), 1.78 (ddd, *J* = 13.6, 11.7, 5.0 Hz, 1H, 1’-H^b), 1.27 (t, *J* = 7.1 Hz, 3H, $COOCH_2C\underline{\textit{H}}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 214.9 (C2), 171.0 ($\underline{\textit{C}}OOCH_2CH_3$), 153.6 (C2” or C5”), 151.7 (C2” or C5”), 131.1 (C1”), 116.2 (C6”), 111.5 (C3” or C4”), 111.3 (C3” or C4”), 61.5 ($COO\underline{\textit{C}}H_2CH_3$), 60.7 (C1), 56.0 (Ar-$O\underline{\textit{C}}H_3$), 55.8 (Ar-$O\underline{\textit{C}}H_3$), 38.1 (Ring-$\underline{\textit{C}}H_2$), 34.2 (C1’), 32.8 (Ring-$\underline{\textit{C}}H_2$), 26.0 (C2’), 19.8 (Ring-$\underline{\textit{C}}H_2$), 14.3 ($COOCH_2\underline{\textit{C}}H_3$).

NMR data conform to literature.[61]

Ethyl 1-(2,5-dimethoxyphenethyl)-2-(2-tosylhydrazineylidene)cyclopentane-1-carboxylate (2-30)



To a solution of ethyl 1-(2,5-dimethoxyphenethyl)-2-oxocyclopentane-1-carboxylate (**1-21**) (500 mg, 1.56 mmol, 1.0 eq.) in THF (3 mL), *p*-toluenesulfonyl hydrazide (291 mg, 1.56 mmol, 1.0 eq.) then titanium(IV) chloride (175 µL, 296 mg, 1.56 mmol, 1.0 eq.) were added at RT and the resulting brown mixture was stirred overnight. The mixture was then diluted with ethyl acetate (50 mL) and water (50 mL), the phases were separated, the aqueous phase was extracted with ethyl acetate (2x50 mL), the combined organic layers were washed with sat. sodium chloride (1×50 mL) and were dried over sodium sulphate, filtered and the solvents were removed in vacuo to afford the crude product as a yellowish oil, which was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 7/1 to 4/1 to 2/1) to afford hydrazone **2-30** (414 mg, 0.85 mmol, 54%) as a colourless resin, which retained traces of ethyl acetate despite of extensive drying in vacuo.

R$_f$: 0.30 (petroleum ether/ethyl acetate: 2/1, UV)

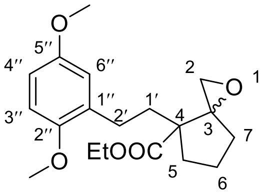
^{1}H NMR (400 MHz, DMSO-d$_6$): δ [ppm]: 10.15 (s, 1H, N$\underline{H}$), 7.70 (d, *J*=8.2 Hz, 2H, 2’’’-H, 6’’’-H), 7.30 (d, *J*=8.1 Hz, 2H, 3’’’-H, 5’’’-H), 6.84 (d, *J*=8.9 Hz, 1H, 3’’-H), 6.71 (dd, *J*=8.8 Hz, 3.1, 1H, 4’’-H), 6.58 (d, *J*=3.0 Hz, 1H, 6’’-H), 3.93 (qd, J=7.1, 1.6 Hz, 2H, COOC$\underline{H}_2$CH$_3$), 3.69 (s, 3H, OC$\underline{H}_3$), 3.69 (s, 3H, OC$\underline{H}_3$), 2.44 (dd, *J*=12.5, 4.6 Hz, 1H, 2’-H^a), 2.41 – 2.35 (m, 1H, 2’-H^b), 2.35 – 2.24 (m, 5H, 4’’’-C$\underline{H}_3$, 4-H^a, 2’-H^b), 2.21 – 2.14 (m, 1H, Ring-C$\underline{H}_2$), 1.92 (ddd, *J*=13.3, 11.9, 4.6 Hz, 1H, Ring-C$\underline{H}_2$), 1.81 – 1.70 (m, 3H, Ring-C$\underline{H}_2$), 1.63 (ddd, *J*=13.4, 12.0, 4.8 Hz, 1H, Ring-C$\underline{H}_2$), 1.03 (t, *J*=7.1 Hz, 3H, COOCH$_2$C$\underline{H}_3$).

^{13}C NMR (101 MHz, DMSO-d$_6$): δ [ppm]: 172.5 ($\underline{C}$OOCH$_2$CH$_3$), 165.5 (C2), 153.1 (C2’’ or C5’’), 151.1 (C2’’ or C5’’), 143.0 (C1’’’), 136.3 (C4’’’), 131.0 (C1’’), 129.2 (C2’’’/C6’’’), 127.3 (C3’’’/C5’’’), 115.7 (C6’’), 111.5 (C3’’ or C4’’), 110.9 (C3’’ or C4’’), 60.4 (COO$\underline{C}$H$_2$CH$_3$), 56.8

(C1), 55.8 (Ar-O*C*H3), 55.3 (Ar-O*C*H3), 35.5 (C1'), 34.1 (Ring-*C*H2), 28.6 (Ring-*C*H2), 25.2 (C2'), 21.5 (Ring-*C*H2), 20.9 (4'''-*C*H3), 13.7 (COOCH2*C*H3).

HRMS (ESI-TOF): m/z: calcd. for $[C_{25}H_{32}N_2O_6S+Na]^+$: 511.18733; found: 511.18761

Ethyl 4-(2,5-dimethoxyphenethyl)-1-oxaspiro[2.4]heptane-4-carboxylate (2-31)[54]



To a solution of ethyl 1-(2,5-dimethoxyphenethyl)-2-oxocyclopentane-1-carboxylate (**1-21**) (1.0 g, 3.12 mmol, 1.0 eq.) and dibromomethane (330 μL, 814 mg, 4.68 mmol, 1.5 eq.) at -78 °C, *n*-buthyllithium (2.5 M in hexane, 1.5 mL, 3.74 mmol, 1.2 eq.) was added, and the mixture was stirred at -78 °C for an hour, then it was allowed to warm to RT, and was stirred overnight. It was then directly concentrated in vacuo, and the deep orange crude product was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 5/1) to afford epoxide **2-31** (563 mg, 1.68 mmol, 54%) as a colourless oil.

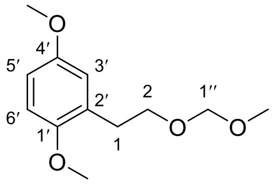
R_f : 0.27 (petroleum ether/ethyl acetate: 5/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.75 – 6.64 (m, 3H), 4.16 (ddt, *J*=10.6, 7.1, 3.5 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 2.94 (d, *J*=4.7 Hz, 1H), 2.82 (d, *J*=4.7 Hz, 1H), 2.61 – 2.48 (m, 2H), 2.42 (td, *J*=12.7, 4.9 Hz, 1H), 2.13 – 2.06 (m, 1H), 1.90 – 1.66 (m, 5H), 1.62 (ddd, *J*=13.4, 12.2, 4.7 Hz, 1H), 1.28 (t, *J*=7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 175.1, 153.5, 151.7, 131.9, 116.2, 111.2, 111.1, 68.1, 60.8, 56.0, 55.8, 54.6, 50.0, 34.3, 33.0, 32.9, 26.3, 21.7, 14.4.

NMR data conform to literature.[61]

1,4-Dimethoxy-2-(2-(methoxymethoxy)ethyl)benzene (2-36)[108,109]



To an ice-cool solution of 2-(2,5-dimethoxyphenyl)ethan-1-ol (**2-29**) (2.0 g, 11.0 mmol, 1.0 eq.) and DIPEA (2.9 mL, 2.1 g, 16.5 mmol, 1.5 eq.) in DCM (10 mL), MOMCl (1.2 mL, 1.3g, 16.5 mmol, 1.5 eq.) was added slowly, and the mixture was allowed to warm to room temperature and was then stirred overnight. The orange mixture was then diluted with DCM (20 mL) and was quenched with sat. sodium hydrogencarbonate solution (50 mL), the phases were separated, the aqueous phase was extracted with DCM (1×50 mL), the combined organic phases were dried over sodium sulphate, then filtered and the volatiles were removed in vacuo affording an orange oil as crude product that was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 10/1 + 1 v/v% TEA) to give MOM-ether **2-36** (2.2 g, 9.6 mmol, 87%) as a colourless oil.

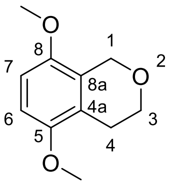
R_f : 0.37 (petroleum ether/ethyl acetate: 10/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.80 – 6.75 (m, 2H, 3’-H, 6’-H), 6.71 (dd, *J*=8.8, 3.0 Hz, 1H, 5’-H), 4.62 (s, 2H, 1’’-H), 3.78 (s, 3H, 4’-OC$\underline{H}_3$), 3.76 – 3.71 (m, 5H, 1’-OC$\underline{H}_3$, 2-H), 3.32 (s, 3H, 1’’-OC$\underline{H}_3$), 2.90 (t, *J*=7.2 Hz, 2H, 1-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 153.5 (C1’), 152.0 (C4’), 128.3 (C2’), 117.0 (C3’), 111.6 (C5’), 111.3 (C6’), 96.4 (C1’’), 67.2 (C2), 56.0 (Ar-O$\underline{C}H_3$), 55.7 (Ar-O$\underline{C}H_3$), 55.2 (1’’-O$\underline{C}H_3$), 31.1 (C1).

HRMS (ESI-TOF): m/z: calcd. for $[C_{12}H_{18}O_4+Na]^+$: 249.10973; found: 249.10986

5,8-Dimethoxyisochromane (2-37)[108,109]



To an ice-cool solution of 1,4-dimethoxy-2-(2-(methoxymethoxy)ethyl)benzene (**2-36**) (1.5 g, 6.63 mmol, 1.0 eq.) in acetonitrile (10 mL), TMSOTf (300 µL, 370 mg, 1.66 mmol, 0.25 eq.) was added dropwise and the red mixture was then allowed to warm to room temperature and was stirred for 6 h. The mixture was then diluted with DCM (50 mL) and washed with water (1×50 mL), the aqueous phase was washed with DCM (1×25 mL) the combined organic phases were washed with sat. sodium hydrogencarbonate solution (1×50 mL), and were dried over sodium sulphate, filtered, and the volatiles were removed in vacuo to afford an orange oil as crude product which was subjected to flash chromatography (silica, petroleum ether/ethyl acetate: 10/1) to afford isochromane **2-37** (310 mg, 1.60 mmol, 24 %) as a colourless, viscous oil.

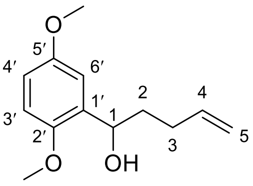
R_f : 0.41 (petroleum ether/ethyl acetate: 10/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.68 – 6.59 (m, 2H, 6-H, 7-H), 4.72 (s, 2H, 1-H), 3.92 (t, *J*=5.7 Hz, 2H, 3-H), 3.79 (s, 3H, $OC\underline{H}_3$), 3.76 (s, 3H, $OC\underline{H}_3$), 2.72 (t, *J*=5.7 Hz, 2H, 4-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 151.1 (C5 or C8), 149.6 (C5 or C8), 125.0 (C8a), 123.8 (C4a), 107.5 (C6 or C7), 106.9 (C6 or C7), 64.7 (C3), 64.4 (C1), 55.7 ($O\underline{C}H_3$), 55.5 ($O\underline{C}H_3$), 23.1 (C4).

HRMS (ESI-TOF): m/z: calcd. for $[C_{11}H_{14}O_3+Na]^+$:217.08352; found: 217.08332

1-(2,5-Dimethoxyphenyl)pent-4-en-1-ol (2-44)[284]



To a mixture of magnesium turnings (530 mg, 21.65 mmol, 1.8 eq.) in THF (10 mL) a solution of 4-bromo-1-butene (1.9 mL, 2.5 g, 18.05 mmol, 1.5 eq.) in THF (10 mL) was added according to the following procedure: about 5 mL of the above mentioned solution was given to the magnesium mixture, then the reaction was initiated by heating, and the rest of the solution was given in a pace that the magnesium mixture kept refluxing. After the addition was complete the blackish Grignard-solution was allowed to cool to RT, and a solution of 2,5-dimethoxybenzaldehyde (2.0 g, 12.03 mmol, 1.0 eq.) in THF (20 mL) was added, and the mixture was stirred at RT overnight. The mixture was then poured into hydrochloric acid (1 M, 100 mL), and was extracted with ethyl acetate (1×150 mL), the organic phase was then dried over sodium sulphate filtered and the volatiles were removed in vacuo, and the yellow crude product was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 5/1) to afford alkenol **2-44** (2.1 g, 9.51 mmol, 79%) as a colourless oil.

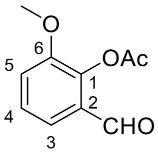
R_f : 0.35 (petroleum ether/ethyl acetate: 5/1, $KMnO_4$ or vanillin)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.90 (d, *J*=2.9 Hz, 1H, 6’-H), 6.81 – 6.73 (m, 2H, 3’-H, 4’-H), 5.86 (ddt, *J*=16.9, 10.2, 6.5 Hz, 1H, 4-H), 5.05 (dq, *J*=17.2, 1.7 Hz, 1H, 5-H^a), 4.97 (ddt, *J*=10.2, 2.2, 1.3 Hz, 1H, 5-H^b), 4.85 (dd, *J*=7.6, 5.5 Hz, 1H, 1-H), 3.80 (s, 3H, 2’-OC$\underline{H}_3$), 3.76 (s, 3H, 5’-OC$\underline{H}_3$), 2.62 (br, 1H, O$\underline{H}$), 2.27 – 2.07 (m, 2H, 3-H), 1.92 – 1.78 (m, 2H, 2-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 153.8 (C5’), 150.8 (C2’), 138.6 (C4), 133.7 (C1’), 114.7 (C5), 113.3 (C6’), 112.5 (C3’or C4’), 111.6 (C3’or C4’), 70.5 (C1), 55.9 (O$\underline{C}H_3$), 55.8 (O$\underline{C}H_3$), 36.5 (C2), 30.4 (C3).

HRMS (ESI-TOF): m/z: calcd. for $[C_{13}H_{18}O_3+Na]^+$: 245.11482; found: 245.11497

2-Formyl-6-methoxyphenyl acetate (2-50)[162]



ortho-Vanillin (50.0 g, 0.33 mol, 1.0 eq.) was dissolved in pyridine (50 mL) and to this solution acetic anhydride (32 mL, 34.6 g, 0.33 mol, 1.0 eq.) was added, and the yellow mixture was stirred for 24 h at RT. The mixture was then poured into hydrochloric acid (6 M, 300 mL), the precipitated crystals were collected by vacuum filtration, washed with hydrochloric acid (6 M, 3×200 mL) and water (3×200 mL), air-dried, and were recrystallized from methanol yielding aldehyde **2-50** (48.1 g, 0.25 mol, 76%) as colourless crystals.

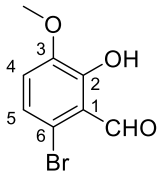
R_f : 0.25 (petroleum ether/ethyl acetate: 5/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 10.13 (s, 1H, C*H*O), 7.45 (dd, *J*=7.8, 1.5 Hz, 1H, 3-H or 5-H), 7.33 (t, *J*=8.0 Hz, 1H, 4-H), 7.21 (dd, *J*=8.2, 1.5 Hz, 1H, 3-H or 5-H), 3.87 (s, 3H, OC*H*$_3$), 2.40 (s, 3H, Ar-OCOC*H*$_3$)

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 188.8 (*C*HO), 168.8 (Ar-O*C*OCH$_3$), 151.8 (Ar-*C*^{q}), 141.6 (Ar-*C*^{q}), 129.3 (Ar-*C*^{q}), 126.9 (Ar-*C*^{t}), 121.4 (Ar-*C*^{t}), 117.9 (Ar-*C*^{t}), 56.4 (O*C*H$_3$), 20.6 (Ar-OCO*C*H$_3$).

NMR data conform to literature.[285]

6-Bromo-2-hydroxy-3-methoxybenzaldehyde (2-51)[162]



Bromine (10 mL, 31 g, 192.6 mmol, 1.1 eq.) was dissolved in a solution of potassium bromide (69 g, 577.8 mmol, 3.3 eq.) in water (680 mL), then 2-formyl-6-methoxyphenyl acetate (**2-50**) (34 g, 175.1 mmol, 1.0 eq.) was added in portions at RT, the mixture was stirred for an hour at this temperature, then it was filtered, the residue was washed with water, and was suspended in aqueous hydrochloric acid (6 M, 700 mL) and was stirred for 24 h at RT. The lemon-yellow solids were then filtered with suction, thoroughly washed with water (3×300 mL) and were then taken up with ethyl acetate (500 mL), the phases were separated, the organic phase was washed with sat. sodium hydrogencarbonate solution (1×200 mL), dried over sodium sulphate, filtered and the ethyl acetate was evaporated in vacuo affording aldehyde **2-51** as a lemon-yellow solid mass (37 g, 160.1 mmol, 83%) that was pure enough for all practical purposes and was thus used without further purification. An attempt to recrystallise one batch from methanol according to literature[162] resulted in the sole formation of the respective dimethylacetal.

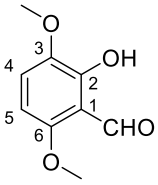
R_f : 0.40 (petroleum ether/ethyl acetate: 5/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 12.27 (s, 1H, O*H*), 10.29 (s, 1H, C*H*O), 7.09 (d, *J*=8.6 Hz, 1H, 4-H), 6.91 (d, *J*=8.5 Hz, 1H, 5-H), 3.89 (s, 3H, OC*H*$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 198.5 (*C*HO), 154.7 (C2), 148.6 (C3), 123.6 (C4), 118.3 (C5), 117.4 (C1), 116.6 (C6), 56.5 (O*C*H$_3$).

NMR data conform to literature.[286]

2-Hydroxy-3,6-dimethoxybenzaldehyde (2-52)[162]



Sodium metal (~11.0 g, 478.5 mmol, 7.4 eq.) was dissolved in methanol (150 mL) and a solution of 6-bromo-2-hydroxy-3-methoxybenzaldehyde (**2-51**) (15.0 g, 64.9 mmol, 1.0 eq.) in dimethyl formamide (60 mL) and then copper(I) iodide (1.2 g, 6.3 mmol, 10 mol%) were added, and the mixture was stirred at 85 °C overnight. The mixture was then allowed to cool to RT, and was filtered through a celite pad, washed with a small amount of methanol (30 mL) and was poured into a mixture of ice (~200 g) and hydrochloric acid (36 w/w%, 60 mL), upon which a solid mass precipitated, the mixture was then filtered by suction, the solids were washed with water, and were recrystallized from methanol affording aldehyde **2-52** (4.6 g, 25.3 mmol, 39%) as a yellow crystalline mass.

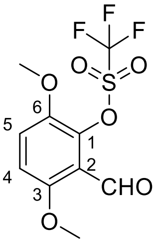
R_f : 0.50 (petroleum ether/ethyl acetate: 2/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 12.17 (s, 1H, O*H*), 10.31 (s, 1H, C*H*O), 7.01 (d, *J*=8.9 Hz, 1H, 4-H), 6.26 (d, *J*=8.9 Hz, 1H, 5-H), 3.83 (s, 6H, 2×OC*H*$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 195.0 (*C*HO), 156.0 (C3), 153.7 (C2), 142.2 (C6), 120.4 (C4), 111.19 (C1), 99.5 (C5), 57.0 (O*C*H$_3$), 55.9 (O*C*H$_3$).

NMR data conform to literature.[287]

2-Formyl-3,6-dimethoxyphenyl trifluoromethanesulfonate (2-53)



To a solution of 2-hydroxy-3,6-dimethoxybenzaldehyde (**2-52**) (500 mg, 2.74 mmol, 1.0 eq.) in DCM (6 mL) DMAP (33 mg, 0.27 mmol, 10 mol%), triethyl amine (760 µL, 555 mg, 5.48 mmol, 2.0 eq.) and *N*-phenyl-bis(trifluoromethanesulfonimide) (980 mg, 2.74 mmol, 1.0 eq.) were added, and the mixture was stirred at RT for a day, then it was diluted with DCM (20 mL) and was washed with hydrochloric acid (2 M, 2×50 mL), and was dried over sodium sulphate, filtered and evaporated to afford a dark oil as a crude product, that was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 4/1 to 2/1) to afford aldehyde **2-53** (410 mg, 1.30 mmol, 48%) as a brown solid.

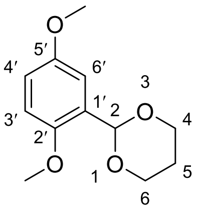
R_f : 0.17 (petroleum ether/ethyl acetate: 2/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 10.42 (s, 1H, C$\underline{H}$O), 7.23 (d, *J*=9.3 Hz, 1H, Ar-H), 6.99 (d, *J*=9.3 Hz, 1H, Ar-H), 3.91 (s, 3H, OC$\underline{H}_3$), 3.87 (s, 3H, OC$\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 187.4 ($\underline{C}$HO), 156.0 (Ar$\underline{C}^q$), 145.6 (Ar$\underline{C}^q$), 137.0(Ar$\underline{C}^q$), 119.2 (Ar$\underline{C}^t$), 118.8 ($\underline{C}F_3SO_2$-OAr), 111.9 (Ar$\underline{C}^t$), 56.9 (O$\underline{C}H_3$), 56.8 (O$\underline{C}H_3$).

HRMS (ESI-TOF): m/z: calcd. for $[C_{10}H_9F_3O_6S+Na]^+$: 336.99641; found: 336.99649

2-(2,5-Dimethoxyphenyl)-1,3-dioxane (2-54)[164]



To a mixture of 2,5-dimethoxybenzaldehyde (5.0 g, 1.0 eq., 30.1 mmol) in propane-1,3-diol (8.7 ml, 9.2 g, 120.4 mmol, 4.0 eq.) and trimethyl orthoformate (4.0 mL, 3.8 g, 36.1 mmol, 1.2 eq.), tetrabutylammonium tribromide (145 mg, 0.3 mmol, 1 mol%) was added, and the orange solution was stirred for one hour at RT, then it was diluted with ethyl acetate (100 mL) and was extracted with a mixture of sat. sodium hydrogencarbonate (50 mL) and water (50 mL), the aqueous phase was extracted with ethyl acetate (2×50 mL) the combined organic phases were extracted with sat. sodium hydrogencarbonate (1×50 mL) and sat. sodium chloride solution (1×100 ml), then they were dried over sodium sulphate, filtered, the volatiles were removed in vacuo affording a yellow liquid as crude product, which was then subjected to flash chromatography (silica, petroleum ether/ethyl acetate: 5/1 + 5 v/v% triethyl amine) to afford acetal **2-54** (6.0 g, 26.7 mmol, 89%) as a colourless liquid.

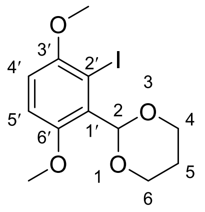
R_f : 0.41 (petroleum ether/ethyl acetate: 5/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 7.20 (d, *J*=2.9 Hz, 1H, 6’-H), 6.86 – 6.80 (m, 2H, 4’-H, 3’-H), 5.85 (s, 1H, 2-H), 4.27 – 4.23 (m, 2H, 4/6-H^a), 4.04 – 3.97 (m, 2H, 4/6-H^b), 3.80 (s, 3H, 5’-OC$\underline{H}_3$), 3.79 (s, 3H, 2’-OC$\underline{H}_3$), 2.30 – 2.18 (m, 1H, 5-H^a), 1.45 – 1.40 (m, 1H, 5-H^b).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 154.0 (C2’), 150.7 (C5’), 127.8 (C1’), 116.0 (C4’), 112.4 (C3’), 112.0 (C6’), 96.9 (C2), 67.7 (C4/C6), 56.5 (5’-O$\underline{C}H_3$), 55.9 (2’-O$\underline{C}H_3$), 26.0 (C5).

NMR data conform to literature.[164]

2-(2-Iodo-3,6-dimethoxyphenyl)-1,3-dioxane (2-55)[165]



2-(2,5-Dimethoxyphenyl)-1,3-dioxane (**2-54**) (5.0 g, 22.3 mmol, 1.0 eq.) was dissolved in a mechanically stirred mixture of abs. hexane (150 mL) and abs. benzene (50 mL). This solution was then cooled to -25 °C and *n*-buthyllithium (11.0 M in hexane, 3.0 mL, 33.5 mmol, 1.5 eq.) was added in portions, and the mixture was stirred at -25 °C overnight, after which it was quenched with a solution of 1,2-diiodoethane (12.0 g, 42.4 mmol, 1.9 eq.) in THF (50 mL), and the reddish mixture was stirred at RT for 24 h, then it was washed with sat. sodium thiosulphate solution (3×150 mL) and sat. sodium chloride solution (1×150 mL) and was dried over sodium sulphate, filtered, and the volatiles were evaporated to afford an orange oil that solidified upon standing as a crude product, which was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 7/3 to 1/1) to afford acetal **2-55** (2.3 g, 6.57 mmol, 29%) as a lemon-yellow solid.

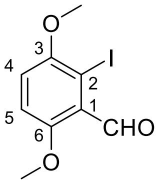
R$_f$: 0.38 (petroleum ether/ethyl acetate: 2/1, UV)

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm]: 6.89 (d, *J*=9.0 Hz, 1H, 5’-H), 6.79 (d, *J*=9.0 Hz, 1H, 4’-H), 6.18 (s, 1H, 2-H), 4.33 – 4.28 (m, 2H, 4/6-H^a), 4.03 – 3.96 (m, 2H, 4/6-H^b), 3.81 (s, 3H, OC$\underline{H}_3$), 3.81 (s, 3H, OC$\underline{H}_3$), 2.48 – 2.36 (m, 1H, 5-H^a), 1.40 – 1.36 (m, 1H, 5-H^b).

^{13}C NMR (CDCl$_3$, 101 MHz): δ [ppm]: 153.3 (C3’or C6’), 152.6 (C3’or C6’), 129.8 (C1’), 113.6 (C5’), 112.3 (C4’), 101.7 (C2), 90.8 (C2’), 67.9 (C4/C6), 57.6 (O$\underline{C}$H$_3$), 57.4 (O$\underline{C}$H$_3$), 25.7 (C5).

NMR data conform to literature.[165]

2-Iodo-3,6-dimethoxybenzaldehyde (2-56)[165]



To a solution of 2-(2-iodo-3,6-dimethoxyphenyl)-1,3-dioxane (**2-55**) (2.3 g, 6.57mmol, 1.0 eq.) in THF (35 mL) hydrochloric acid (36 w/w%, 30 mL) was poured, and the ochre mixture was stirred at RT for 30 min, then it was diluted with diethyl ether (250 ml), the phases were separated, and the organic phase was washed with sat. sodium chloride solution (3×100 mL) and was dried over sodium sulphate. The drying agent was then filtered off and the filtrate was evaporated in vacuo affording an olive-green solid mass as crude product, that was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 4/1) to afford aldehyde **2-56** (960 mg, 3.29 mmol, 50%) as a lemon-yellow solid mass.

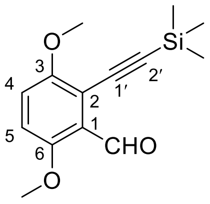
R_f : 0.20 (petroleum ether/ethyl acetate: 4/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 10.21 (s, 1H, C*H*O), 7.00 – 6.94 (m, 2H, Ar-H), 3.87 (s, 3H, $OC\underline{H}_3$), 3.87 (s, 3H, $OC\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 193.1 (*C*HO), 155.7 ($Ar\underline{C}^q$), 152.9 ($Ar\underline{C}^q$), 126.9 ($Ar\underline{C}^q$), 116.0 ($Ar\underline{C}^t$), 112.8 ($Ar\underline{C}^t$), 90.3 ($Ar\underline{C}^q$), 57.5 ($O\underline{C}H_3$), 56.8 ($O\underline{C}H_3$).

NMR data conform to literature.[165]

3,6-Dimethoxy-2-((trimethylsilyl)ethynyl)benzaldehyde (2-57)[288]



To a solution of 2-iodo-3,6-dimethoxybenzaldehyde (**2-56**) (960 mg, 3.29 mmol, 1.0 eq.) in THF (15 mL) copper(I) iodide (75 mg, 0.39 mmol, 12 mol%), bis(triphenylphosphine)palladium(II) dichloride (93 mg, 0.13 mmol, 4 mol%) and triethylamine (3.5 mL) were added, and the deep orange mixture was stirred at RT for 15 min. Then ethynyltrimethylsilane (1.4 mL, 970 mg, 9.87 mmol, 3.0 eq.) was added, and the resulting deep green solution was stirred overnight at RT. The mixture was then concentrated in vacuo and the black residue was directly subjected to flash chromatography (silica, petroleum ether/ethyl acetate: 4/1) to afford aldehyde **2-57** (630 mg, 2.40 mmol, 73%) as a colourless liquid.

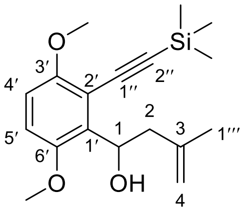
R_f : 0.25 (petroleum ether/ethyl acetate: 4/1, UV [366 nm])

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 10.57 (s, 1H, C$\underline{H}$O), 7.03 (d, *J*=9.2 Hz, 1H, 4-H), 6.90 (d, *J*=9.1 Hz, 1H, 5-), 3.85 (s, 3H, OC$\underline{H}_3$), 3.84 (s, 3H, OC$\underline{H}_3$), 0.26 (s, 9H, Si(C$\underline{H}_3$)$_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 191.0 ($\underline{C}$HO), 155.2 (C3), 154.3 (C6), 126.2 (C1), 117.4 (C4), 116.1 (C2), 113.1 (C5), 107.5 (C2´), 97.0 (C1´), 56.9 (O$\underline{C}$H$_3$), 56.5 (O$\underline{C}$H$_3$), 0.0 (Si($\underline{C}$H$_3$)$_3$).

HRMS (APCI-TOF): m/z: calcd. for $[C_{14}H_{18}O_3Si+H]^+$: 263.10980; found: 263.10967

1-(3,6-Dimethoxy-2-((trimethylsilyl)ethynyl)phenyl)-3-methylbut-3-en-1-ol (2-58)[284]



To a mixture of magnesium turnings (100 mg, 4.01 mmol, 1.8 eq.) in THF (4 mL) a solution of 3-bromo-2-methylpropene (340 µL, 452 mg, 3.55 mmol, 1.5 eq.) in THF (10 mL) was added and the reaction was initiated by heating. The blackish Grignard-solution was allowed to cool to RT, and a solution of 3,6-dimethoxy-2-((trimethylsilyl)ethynyl)benzaldehyde (**2-57**) (586 mg, 2.23 mmol, 1.0 eq.) in THF (4 mL) was added and the mixture was stirred at RT overnight. The mixture was then poured into sat. ammonium chloride solution (20 mL) and was extracted with diethyl ether (1×50 mL), the organic phase was then washed with sat. sodium hydrogencarbonate solution (1×50 mL) and was dried over sodium sulphate, the drying agent was filtered off, the volatiles were removed in vacuo, and the orange crude product was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 3/1) to afford the product (56 mg, 0.18 mmol, 8%) as a yellow oil.

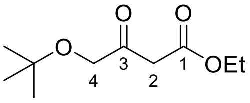
R_f : 0.40 (petroleum ether/ethyl acetate: 3/1, UV)

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm]: 6.81 (d, *J*=9.0 Hz, 1H, 4'-H), 6.69 (d, *J*=9.0 Hz, 1H, 5'-H), 5.45 – 5.38 (m, 1H, 1-H), 4.81 (s, 1H, 4-H^a), 4.74 (s, 1H, 4-H^b), 3.82 (s, 3H, OC$\underline{H}_3$), 3.81 (s, 3H, OC$\underline{H}_3$), 2.64 (dd, *J*=13.8, 9.3 Hz, 1H, 2-H^a), 2.44 (dd, *J*=13.8, 4.8 Hz, 1H, 2-H^b), 1.84 (s, 3H, 1'''-H), 0.25 (s, 9H, Si(C$\underline{H}_3$)$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ [ppm]: 155.2 (C3'), 151.2 (C6'), 142.9 (C3), 135.6 (C1'), 112.9 (C4), 112.3 (C4'), 111.7 (C2'), 109.7 (C5'), 104.5 (C2''), 98.7 (C1''), 70.7 (C1), 56.5 (3'-O$\underline{C}$H$_3$ or 6'-O$\underline{C}$H$_3$), 56.0 (3'-O$\underline{C}$H$_3$ or 6'-O$\underline{C}$H$_3$), 45.6 (C2), 22.5 (C1'''), 0.1 (Si($\underline{C}$H$_3$)$_3$).

HRMS (ESI-TOF): m/z: calcd for [$C_{18}H_{26}O_3Si$+Na]$^+$: 341.15434; found: 341.15477

Ethyl 4-(*tert*-butoxy)-3-oxobutanoate (2-62)[167]



To a mechanically stirred suspension of potassium *tert*-butoxide (80 g, 0.71 mol, 2.4 eq.) in THF (1500 mL) ethyl 4-chloroacetoacetate (41 mL, 50 g, 0.30 mol 1.0 eq.) was added slowly, and the resulting brown slurry was stirred for a day at room temperature. The reaction was then stopped by the slow addition of hydrochloric acid (4 M, 375 mL), the mixture was then extracted with ethyl acetate (3×400 mL), the combined organic phases were washed with sat. sodium hydrogencarbonate solution (2×200 mL) and dried over sodium sulphate. The mixture was then filtered, the filtrate was concentrated in vacuo and the brown crude product was distilled (95-100 °C, 10 mbar) to afford ketoester **2-62** (41.4 g, 205 mmol, 67%) as a colourless liquid.

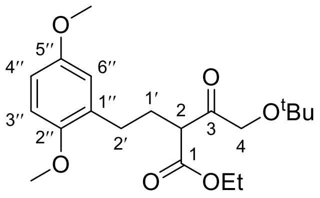
R_f : 0.61 (petroleum ether/ethyl acetate: 3/1, $FeCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 4.16 (q, *J*=7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 3.99 (s, 2H, 4-H), 3.52 (s, 2H, 2-H), 1.25 (t, *J*=7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.19 (s, 9H, $OC(C\underline{H}_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 203.6 (C3), 167.5 (C1), 74.4 ($O\underline{C}(CH_3)_3$), 68.1 (C4), 61.3 ($O\underline{C}H_2CH_3$), 46.3 (C2), 27.3 ($OC(\underline{C}H_3)_3$), 14.2 ($OCH_2\underline{C}H_3$).

NMR data conform to literature.[289]

Ethyl 4-(*tert*-butoxy)-2-(2,5-dimethoxyphenethyl)-3-oxobutanoate (2-63)[166]



Potassium carbonate (4.8 g, 35.0 mmol, 2.0 eq.) was added to a stirred solution of ethyl 4-(*tert*-butoxy)-3-oxobutanoate (**2-62**) (3.9 g, 19.3 mmol, 1.1 eq.) in DMF (40 mL). To this mixture a solution of 2-(2-iodoethyl)-1,4-dimethoxybenzene (**2-27**) (5.1 g, 17.5 mmol, 1.0 eq.) in DMF (20 mL) was added, and the mixture was stirred overnight at RT. The reaction was then quenched by adding water (120 mL), it was extracted with ethyl acetate (3×70 mL), the combined organic phases were washed with water (2×60 mL) and sat. sodium chloride solution (1×60 mL) and were dried over sodium sulphate. The drying agent was then filtered off and the filtrate was concentrated in vacuo affording a yellow oil as crude product which was then purified by flash chromatography (silica, petroleum ether/ethyl acetate: 30/1 to 4/1) to give ketoester **2-63** (4.8 g, 13.1 mmol, 75%) as a colourless oil.

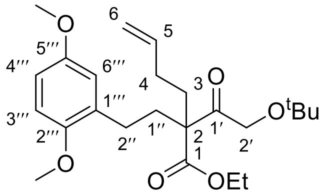
R_f : 0.33 (petroleum ether/ethyl acetate: 10/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.76 – 6.67 (m, 3H, 3×Ar-H), 4.15 (q, *J*=7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.01 (s, 2H, 4-H), 3.74 (s, 6H, 2×$OC\underline{H}_3$), 3.68 (t, *J*=7.1 Hz, 1H, 2-H), 2.69 – 2.55 (m, 2H, 2'-H), 2.20 – 2.04 (m, 2H, 1'-H), 1.25 (t, *J*=7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.17 (s, 9H, $OC(C\underline{H}_3)_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 205.1 (C3), 169.9 (C1), 153.5 (C5''), 151.8 (C2''), 130.7 (C1''), 116.4 (C6''), 111.6 (C3'' or C4''), 111.3 (C3'' or C4''), 74.3 ($O\underline{C}(CH_3)_3$), 67.7 (C4), 61.2 ($O\underline{C}H_2CH_3$), 55.9 ($O\underline{C}H_3$), 55.7 ($O\underline{C}H_3$), 54.5 (C2), 28.1 (C2'), 27.7 (C1'), 27.2 ($OC(\underline{C}H_3)_3$), 14.2 ($OCH_2\underline{C}H_3$).

NMR data conform to literature.[166]

Ethyl 2-(2-(*tert*-butoxy)acetyl)-2-(2,5-dimethoxyphenethyl)hex-5-enoate (2-64)[166]



To a solution of ethyl 4-(*tert*-butoxy)-2-(2,5-dimethoxyphenethyl)-3-oxobutanoate (**2-63**) (4.8 g, 13.1 mmol, 1.0 eq.) and 4-bromo-1-butene (2.7 g, 2.0 mL, 19.7 mmol, 1.5 eq.) in DMF (40 mL), potassium carbonate (3.6 g, 26.2 mmol, 2.0 eq.) and potassium iodide (3.3 g, 19.7 mmol, 1.5 eq.) were added, after which the mixture was stirred for 20 h at RT. The mixture was diluted with water (100 mL) and was extracted with ethyl acetate (3×100 mL) the combined organic phases were washed with sat. sodium chloride solution (1×100 mL) and were dried over sodium sulphate followed by filtration and evaporation of the volatiles in vacuo to afford a yellow liquid as crude product, which was then subjected to flash chromatography (silica, petroleum ether/ethyl acetate: 30/1 to 10/1) to afford ketoester **2-64** (1.60 g, 3.80 mmol, 29%) as a colourless oil.

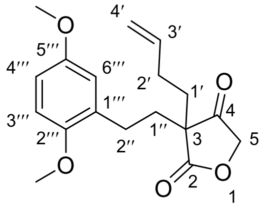
R$_f$: 0.49 (petroleum ether/ethyl acetate: 10/1, UV)

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm]: 6.76 – 6.65 (m, 3H, 3×Ar-H), 5.82 (ddt, *J*=16.7, 10.2, 6.4 Hz, 1H, 5-H), 5.07 – 5.02 (m, 1H, 6-H^a), 4.99 – 4.95 (m, 1H, 6-H^b), 4.16 (q, *J*=7.1 Hz, 2H, OC$\underline{H}_2$CH$_3$), 4.08 (s, 2H, 2’-H), 3.74 (s, 6H, 2×OC$\underline{H}_3$), 2.42 – 2.30 (m, 2H, 2’’-H$_2$), 2.25 – 2.15 (m, 1H, 1’’-H^a), 2.14 – 2.01 (m, 3H, 1’’-H^b, 3-H), 2.00 – 1.85 (m, 2H, 4-H), 1.26 (t, *J*=7.1 Hz, 3H, OCH$_2$C$\underline{H}_3$), 1.18 (s, 9H, OC(C$\underline{H}_3$)$_3$).

^{13}C NMR (CDCl$_3$, 101 MHz): δ [ppm]: 206.1 (C1’), 171.7 (C1), 153.5 (C5’’’), 151.6 (C2’’’), 138.0 (C5), 131.2 (C1’’’), 116.3 (C6’’’), 114.9 (C6), 111.2 (C3’’’ or C4’’’), 111.1 (C3’’’ or C4’’’), 74.1 (O$\underline{C}$(CH$_3$)$_3$), 67.1 (C2’), 60.9 (O$\underline{C}$H$_2$CH$_3$), 60.5 (C2), 55.7 (O$\underline{C}$H$_3$), 55.7 (O$\underline{C}$H$_3$), 31.0 (C1’’), 29.9 (C3), 27.9 (C4), 27.1 (OC($\underline{C}$H$_3$)$_3$), 25.0 (C2’’), 14.1 (OCH$_2\underline{C}$H$_3$).

NMR data conform to literature.[166]

3-(But-3-en-1-yl)-3-(2,5-dimethoxyphenethyl)furan-2,4(3*H*,5*H*)-dione (2-94)[167]



Ethyl 2-(2-(*tert*-butoxy)acetyl)-2-(2,5-dimethoxyphenethyl)hex-5-enoate (**2-64**) (1.6 g, 3.80 mmol, 1.0 eq.) was dissolved in glacial acetic acid (15 mL). In a separate flask sulphuric acid (96 w/w%, 200 ml, 368 g, 3.8 mol, 1000 eq.) was added dropwise to solid sodium chloride (75.0 g, 1.3 mol, 340 eq.), and the so generated hydrogen chloride gas was bubbled into the above-mentioned acetic acid solution. After all the sulphuric acid was added, the solution was stirred for 1 h at RT, it was then diluted with ethyl acetate (100 mL) and water (50 mL), the phases were separated, the aqueous phase was extracted with ethyl acetate (2×50 mL), the combined organic layers were washed with water (2×50 mL) and sat. sodium hydrogencarbonate solution (2×100 mL), then the organic layer was dried over sodium sulphate, filtered, and concentrated in vacuo to afford a lemon-yellow oil as crude product, which was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 7/1) to afford ketolactone **2-94** (900 mg, 2.83 mmol, 74%) as a colourless oil.

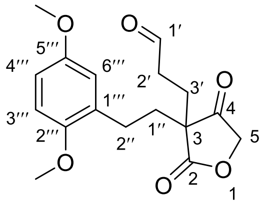
R_f : 0.18 (petroleum ether/ethyl acetate: 7/1, UV)

^{1}H NMR (CDCl$_3$, 400 MHz): δ [ppm]: 6.71 – 6.70 (m, 2H, 3‴-H, 4‴-H), 6.62 (dd, *J*=2.4, 1.1 Hz, 1H, 6‴-H), 5.64 (ddt, *J*=16.9, 10.1, 6.5 Hz, 1H, 3’-H), 5.03 – 4.96 (m, 2H, 4’-H), 4.47 (d, *J*=17.1 Hz, 1H, 5-H^a), 4.33 (d, *J*=17.1 Hz, 1H, 5-H^b), 3.75 (s, 3H, OC$\underline{H}_3$), 3.73 (s, 3H, OC$\underline{H}_3$), 2.60 (ddd, *J*=13.0, 10.9, 4.7 Hz, 1H, 2”-H^a), 2.48 (ddd, *J*=13.0, 10.9, 6.1 Hz, 1H, 2”-H^b), 2.18 – 2.06 (m, 2H, 1”-H^a, 2′-H^a), 2.04 – 1.97 (m, 2H, 1”-H^b, 2’-H^b), 1.96 – 1.89 (m, 2H, 1’-H).

^{13}C NMR (CDCl$_3$, 101 MHz): δ [ppm]: 210.5 (C4), 176.7 (C2), 153.4 (C5‴), 151.8 (C2‴), 136.5 (C3’), 129.0 (C1‴), 116.7 (C4’), 116.3 (C6‴), 112.3 (C3‴ or C4‴), 111.3 (C3‴ or C4‴), 73.3 (C5), 55.8 (O$\underline{C}$H$_3$), 55.8 (O$\underline{C}$H$_3$), 52.7 (C3), 35.8 (C1”), 34.4 (C1’), 29.2 (C2’), 26.0 (C2”).

NMR data conform to literature.[166]

3-(3-(2,5-Dimethoxyphenethyl)-2,4-dioxotetrahydrofuran-3-yl)propanal (2-60)[195]



3-(But-3-en-1-yl)-3-(2,5-dimethoxyphenethyl)furan-2,4(3*H*,5*H*)-dione (**2-94**) (860 mg, 2.70 mmol, 1.0 eq.) was dissolved in a mixture of 1,4-dioxane (27 mL) and water (9 mL) at RT, and to this mixture 2,6-lutidine (630 µL, 580 mg, 5.40 mmol, 2.0 eq.), sodium metaperiodate (2310 mg, 10.8 mmol, 4.0 eq.) and osmium(VIII) oxide (4 w/w% solution in water, 350 µL, 0.054 mmol, 2 mol%) were added, and the reaction mixture was stirred overnight. The reaction mixture was diluted with water (30 mL) and was extracted with dichloromethane (3×50 mL), the combined organic phases were dried over sodium sulphate, filtered, then the solvents were evaporated in vacuo affording a brownish oil as crude product that was subjected to flash chromatography (silica, petroleum ether/ethyl acetate: 1/1) to afford aldehyde **2-60** (390 mg, 1.22 mmol, 45%) as a yellowish oil.

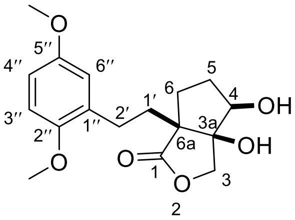
R_f : 0.44 (petroleum ether/ethyl acetate: 1/1; UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 9.70 (t, *J*=0.9 Hz, 1H, C$\underline{H}$O), 6.73 – 6.71 (m, 2H, 3’’’-H, 4’’’-H), 6.62 (dd, *J*=2.4, 1.1 Hz, 1H, 6’’’-H), 4.58 (d, *J*=17.1 Hz, 1H, 5-H^a), 4.37 (d, *J*=17.1 Hz, 1H, 5-H^b), 3.76 (s, 3H, OC$\underline{H}_3$), 3.74 (s, 3H, OC$\underline{H}_3$), 2.66 – 2.49 (m, 4H, alkyl-H), 2.17 – 2.00 (m, 4H, alkyl-H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 209.3 (C4), 200.0 ($\underline{C}$HO), 176.2 (C2), 153.5 (C5’’’), 151.9 (C2’’’), 128.8 (C1’’’), 116.5 (C6’’’), 112.4 (C3’’’ or C4’’’), 111.4 (C3’’’ or C4’’’), 73.0 (C5), 55.87 (2 x O$\underline{C}H_3$), 51.2 (C3), 38.3 (C^s), 34.9 (C^s), 26.5 (C^s), 26.1 (C^s).

HRMS (ESI-TOF): m/z: calcd for $[C_{17}H_{20}O_6+Na]^+$: 343.11521; found: 343.11508

(3a*R,4*R**,6a*R**)-6a-(2,5-Dimethoxyphenethyl)-3a,4-dihydroxyhexahydro-1*H*-cyclopenta[*c*]furan-1-one (2-65)**[290]



To a mixture of samarium powder (734 mg, 4.88 mmol, 4.0 eq.) and 1,2-diiododethane (756 mg, 2.68 mmol, 2.2 eq.) THF (10 mL) was added, and the mixture was vigorously stirred at RT for 1.5 h. Then a solution of 3-(3-(2,5-dimethoxyphenethyl)-2,4-dioxotetrahydrofuran-3-yl)propanal (**2-60**) (390 mg, 1.22 mmol, 1.0 eq.) in THF (7 mL) was added and the deep blue mixture was stirred for 4 h, then the reaction was quenched by the addition of saturated sodium hydrogencarbonate solution (50 mL) and the mixture was extracted diethyl ether (3×50 mL), the combined organic phases were washed with sat. sodium chloride solution (1×100 mL), and was dried over sodium sulphate, filtered, the volatiles were removed in vacuo, and the greyish residue was subjected to flash chromatography (silica, petroleum ether/ethyl acetate: 1/1) to afford diol **2-65** (240 mg, 0.75 mmol, 61%) as a pale, viscous oil, that solidified to an off-white waxy mass upon standing.

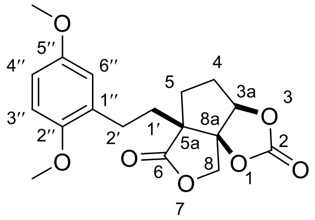
R_f : 0.21 (petroleum ether/ethyl acetate: 1/1; UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.76 – 6.67 (m, 3H, Ar-H), 4.24 (d, *J*=10.2 Hz, 1H, 3-H^a), 4.14 (d, *J*=10.2 Hz, 1H, 3-H^b), 4.01 (dd, *J*=4.6, 3.4 Hz, 1H, 4-H), 3.89 (s, 1H, O*H*), 3.77 (s, 3H, 2”-OC*H*$_3$), 3.73 (s, 3H, 5”-OC*H*$_3$), 3.30 (br, 1H, O*H*), 2.82 (td, *J*=12.6, 4.6 Hz, 1H, 2’-H^a), 2.57 (td, *J*=12.5, 5.2 Hz, 1H, 2’-H^b), 2.11 – 1.98 (m, 2H, 6-H), 1.96 – 1.90 (m, 1H, 1’-H^a), 1.88 – 1.80 (m, 2H, 1’-H^b, 5-H^a), 1.71 – 1.61 (m, 1H, 5-H^b).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 181.5 (C1), 153.6 (C5”), 151.4 (C2”), 131.3 (C1”), 116.2 (C6”), 111.5 (C3” or C4”), 111.5 (C3” or C4”), 84.0 (C3a), 78.6 (C4), 75.6 (C3), 56.2 (2”-O*C*H$_3$), 55.8 (5”-O*C*H$_3$), 54.6 (C6a), 33.8 (C6), 33.0 (C1’), 30.9 (C5), 26.1 (C2′).

HRMS (ESI-TOF): m/z: calcd. for $[C_{17}H_{22}O_6\text{-}H]^-$: 321.13436; found: 321.13477

(3a*R**,5a*R**,8a*R**)-5a-(2,5-Dimethoxyphenethyl)tetrahydro-6*H*,8*H*-furo[3',4':1,5] cyclopenta[1,2-*d*][1,3]dioxole-2,6-dione (2-67)[291]



Diol **2-65** (100 mg, 0.31 mmol, 1.0 eq.) was dissolved in DCM (1 mL) and pyridine (53 µL, 52 mg, 0.65 mmol, 2.1 eq.) was added. Then a solution of triphosgene (101 mg, 0.34 mmol, 1.1 eq.) in DCM (2 mL) was added and the reaction was stirred for 2 h at room temperature. The mixture was then diluted with diethyl ether (10 mL) and was washed with sat. copper(II) sulphate solution (1×20 mL), sat. sodium chloride solution (1×20 ml) and was dried over sodium sulphate. The mixture was filtered, the filtrate was concentrated in vacuo and the resulting brownish solids were purified by flash chromatography (silica, petroleum ether/ethyl acetate: 2/1) to afford the cyclic carbonate **2-67** (85 mg, 0.24 mmol, 79%) as a white powder.

R_f : 0.38 (petroleum ether/ethyl acetate: 2/1; Vanillin)

Mp.: 128-130 °C (petroleum ether/ethyl acetate)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.76 (d, *J*=9.7 Hz, 1H, Ar-H), 6.71 (dd, *J*=6.8, 2.9 Hz, 2H, Ar-H), 5.00 (d, *J*=4.7 Hz, 1H, 3a-H), 4.50 (d, *J*=2.0 Hz, 2H, 8-H), 3.78 (s, 3H, $OC\underline{H}_3$), 3.75 (s, 3H, $OC\underline{H}_3$), 2.82 (td, *J*=12.5, 5.0 Hz, 1H, 2'-H^a), 2.56 (td, *J*=12.5, 4.8 Hz, 1H, 2'-H^b), 2.46 (dd, *J*=13.4, 6.9 Hz, 1H, 5-H^a), 2.29 (dd, *J*=15.3, 6.4 Hz, 1H, 4-H^a), 2.06 – 1.90 (m, 3H, 1'-H, 5-H^b), 1.82 – 1.72 (m, 1H, 4-H^b).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 176.5 (C6), 153.6 (C5''), 152.5 (C2), 151.7 (C2''), 129.9 (C1''), 116.2 (C6''), 112.0 (C3'' or C4''), 111.4 (C3'' or C4''), 92.2 (C8a), 89.1 (C3a), 69.4 (C8), 56.7 (C5a), 55.9 ($O\underline{C}H_3$), 55.9 ($O\underline{C}H_3$), 32.8 (C5), 31.9 (C1') , 30.0 (C4), 26.0 (C2').

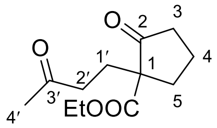
HRMS (ESI-TOF): m/z: calcd for $[C_{18}H_{20}O_7+Na]^+$: 371.11012; found: 371.11025

In order to obtain crystals suitable for XRD measurement the following procedure was performed: 20 mg of the product was measured into a 1.5 ml screw-necked vial (32.0 mm×Ø 11.6 mm; Macherey-Nagel, Product No.: 70213) and ethyl acetate (900 µL) was added, the mixture was then homogenised in an ultrasonic bath and the open 1.5 ml vial was placed into a bigger, 40 ml screw-necked vial (95.0 mm×Ø 27.5 mm; Fisher Scientific, Product No.: 10465982) and petroleum ether 40/60 (5 mL) was added, the 40 mL vial was closed and was carefully placed into a fridge (0-4 °C) so, that the inner, smaller vial would not slide to the side of the bigger vial. Suitable crystals presented themselves after 7 d.

The XRD measurement was performed as follows: a suitable crystal with dimensions $0.18 \times 0.14 \times 0.07$ mm^3 was selected and mounted on a XtaLAB Synergy-S, Dualflex, HyPix diffractometer. The crystal was kept at a steady T = 149.99(10) K during data collection. The structure was solved with the ShelXT 2018/2[292] solution program using dual methods and by using Olex2 1.5-ac5-024[293] as the graphical interface. The model was refined with ShelXL 2018/3[294] using full matrix least squares minimisation on $\boldsymbol{F}^2$.

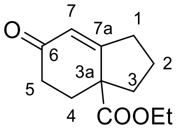
Crystal Data: $C_{18}H_{20}O_7$, M_r = 348.34, triclinic, P-1 (No. 2), a = 7.5303(4) Å, b = 10.1469(4) Å, c = 11.0137(4) Å, α = 80.071(3)°, β = 86.956(4)°, γ = 76.829(4)°, V = 807.05(6) Å^3, T = 149.99(10) K, Z = 2, Z' = 1, μ(Cu K_α) = 0.932, 29350 reflections measured, 3471 unique (R_{int} = 0.0275) which were used in all calculations. The final wR_2 was 0.1043 (all data) and R_1 was 0.0445 (I≥2 σ(I)).

Ethyl 2-oxo-1-(3-oxobutyl)cyclopentane-1-carboxylate (2-73)[177,178]



Iron(III) chloride hexahydrate (865 mg, 3.2 mmol, 2 mol%) was added to ethyl-2-oxocyclopentancarboxylate (25.0 g, 160 mmol, 1.0 eq.) and to this deep blue solution methyl vinyl ketone (16 ml, 13.5 g, 192 mmol, 1.2 eq.) was added dropwise over 1 h, while the reaction was being kept at room temperature with a water bath. After the addition was complete, the mixture was stirred for a day at RT, followed by the evaporation of volatiles in vacuo (70 °C, 15 mbar), then the crude product was distilled under high vacuum (110-115 °C, $1.5 \cdot 10^{-2}$ mbar) to afford ketoester **2-73** (18.4 g, 81.3 mmol, 51%) as a colourless liquid, that was used immediately in the next step without further purification or analysis.

Ethyl 6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (2-72)[179]



Ethyl 2-oxo-1-(3-oxobutyl)cyclopentane-1-carboxylate (**2-73**) (18.4 g, 81.3 mmol, 1.0 eq.) was dissolved in ethyl acetate (50 mL) and then acetic acid (4.7 mL, 4.9 g, 81.3 mmol, 1.0 eq.) and pyrrolidine (6.7 mL, 5.8 g, 81.3 mmol, 1.0 eq.) were added while the mixture was being kept in a water bath at RT. The resulting dark yellow solution was then stirred at RT overnight. Then it was concentrated in vacuo, and the dark greenish crude mixture was purified by flash chromatography (silica, petroleum ether/diethyl ether: 2/1) to afford indenon **2-72** (10.7 g, 51.4 mmol, 63%) as a colourless liquid.

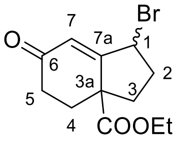
R_f : 0.31 (petroleum ether/diethyl ether: 2/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 5.88 (t, *J*=2.0 Hz, 1H, C7-H), 4.12 (p, *J*=7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 2.79 – 2.71 (m, 1H, 1-H^a), 2.59 – 2.45 (m, 2H, 1-H^b, 5-H^a), 2.35 – 2.30 (m, 3H, 3-H, 4-H^a), 1.83 – 1.74 (m, 3H, 5-H^b, 2-H), 1.61 – 1.53 (m, 1H, 4-H^b), 1.20 (t, *J*=7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 199.0 (C6), 173.4 ($\underline{C}OOCH_2CH_3$), 170.5 (C7a), 123.5 (C7), 61.5 ($COO\underline{C}H_2CH_3$), 54.4 (C3a), 38.4 (C4), 34.8 (C3), 33.4 (C5), 31.9 (C1), 22.1 (C2), 14.2 ($COOCH_2\underline{C}H_3$).

HRMS (ESI-TOF): m/z: calcd. for $[C_{12}H_{16}O_3+H]^+$: 209.11722; found: 209.11732

Ethyl 1-bromo-6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (2-74a)



Ethyl 6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (**2-72**) (500 mg, 2.40 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (10 mL) and NBS (512 mg, 2.88 mmol, 1.2 eq.) was added. The mixture was then heated to 75 °C and AIBN (8 mg, 0.048 mmol, 2 mol%) was added to initiate the reaction, and the mixture was stirred at this temperature for 3 h. Then an another portion of NBS (125 mg, 0.70 mmol, 0.3 eq.) and AIBN (8 mg, 0.048 mmol, 2 mol%) was added, and the heating was continued for another 3 h. Then the mixture was allowed to cool to room temperature, was partitioned between diethyl ether (50mL) and water (50 mL), separated, the aqueous phase was extracted with diethyl ether (1×50 mL), the combined organic layers were washed with water (1×50 mL) and dried over sodium sulphate. After the drying agent was removed by filtration and the volatiles were evaporated in vacuo, the deep orange crude product was subjected to flash chromatography (silica, petroleum ether/diethyl ether: 8/1 to 4/1 to 2/1 to 1/1) to afford indenon **2-74a** (248 mg, 0.86 mmol, 36%) as a yellow liquid.

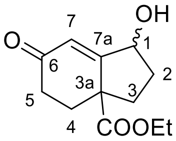
R_f : 0.48 (petroleum ether/diethyl ether: 1/1, $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.20 (s, 1H, 7-H), 5.13 – 5.10 (m, 1H, 1-H), 4.20 – 4.11 (m, 2H, $OC\underline{H}_2CH_3$), 2.66 (ddd, *J*=13.0, 4.9, 2.2 Hz, 1H, Ring-H), 2.49 – 2.40 (m, 2H, 1-H^a, Ring-H), 2.38 – 2.28 (m, 2H, 1-H^b, Ring-H), 2.21 – 2.14 (m, 1H, Ring-H), 2.01 – 1.91 (m, 2H, Ring-H), 1.23 (t, *J*=7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 198.6 (C6), 172.8 ($\underline{C}OOCH_2CH_3$), 167.6 (C7a), 127.4 (C7), 62.0 ($COO\underline{C}H_2CH_3$), 54.2 (C3a), 47.3 (C1), 35.3 (Ring-C), 35.3 (Ring-C), 34.7 (Ring-C), 33.7 (Ring-C), 14.2 ($COOCH_2\underline{C}H_3$).

HRMS (ESI-TOF): m/z: calcd. for $[C_{12}H_{15}BrO_3+H]^+$: 287.02773; found: 287.02801

Ethyl 1-hydroxy-6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (2-74b)[183]



Ethyl 6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (**2-72**) (500 mg, 2.40 mmol, 1.0 eq.) and *p*-toluenesulfonic acid monohydrate (90 mg, 0.48 mmol, 0.2 eq.) were dissolved in isopropenyl acetate (4 mL) and the solution was kept in gentle reflux for 24 h. Then the mixture was allowed to cool to RT and was diluted with diethyl ether (25 mL), the ethereal solution was washed with sat. sodium hydrogencarbonate solution (1×25 mL) and sat. sodium chloride solution (1×25 mL) and was dried over sodium sulphate, filtered, and the volatiles were evaporated in vacuo. The deep orange oil was immediately dissolved in acetone (35 mL) then water (7.5 mL) and sat. sodium hydrogencarbonate solution (7.5 mL) were added, followed by the addition of Oxone® (2220 mg, 7.2 mmol, 3.0 eq.), and the milky mixture was stirred for 24 h at RT. The mixture was then poured into water (50 mL) and was extracted with ethyl acetate (2×50 mL), the combined organic phases were dried over sodium sulphate, filtered and the volatiles were removed in vacuo affording a deep orange oil as crude product, that was subjected to flash chromatography (silica, petroleum ether/ethyl acetate: 1/1) to acquire indenon **2-74b** (176 mg, 0.78 mmol, 33%) as a light yellow oil.

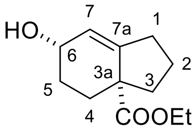
R_f : 0.23 (petroleum ether/ethyl acetate: 1/1, UV)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 6.03 (d, *J*=2.0 Hz, 1H, 7-H), 4.86 (ddd, *J*=8.8, 7.6, 2.2 Hz, 1H, 1-H), 4.13 (qd, *J*=7.1, 6.3 Hz, 2H, $OC\underline{H}_2CH_3$), 3.28 (s, 1H, $O\underline{H}$), 2.61 – 2.56 (m, 1H, 4-H^a), 2.38 – 2.34 (m, 2H, 5-H), 2.24 – 2.15 (m, 2-H^a, 3-H^a), 1.90 – 1.78 (m, 2H, 3-H^b, 4-H^b), 1.67 – 1.59 (m, 1H, 3-H^b), 1.21 (t, *J*=7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 199.5 (C6), 173.5 ($\underline{C}OCH_2CH_3$), 171.4 (C7a), 121.4 (C7), 73.4 (C1), 61.7 ($O\underline{C}H_2CH_3$), 51.1 (C3a), 35.1 (C5), 34.3 (C4), 33.7 (C3), 31.5 (C2), 14.1 ($OCH_2\underline{C}H_3$).

HRMS (ESI-TOF): m/z: calcd. for $[C_{12}H_{16}O_4+Na]^+$: 247.09408; found: 247.09421

Ethyl (3a*R**,6*S**)-6-hydroxy-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (2-76a)[225]



Ethyl 6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (**2-72**) (4.0 g, 19.2 mmol, 1.0 eq.) was dissolved in methanol (50 mL) and cerium(III) chloride heptahydrate (7.2 g, 19.2 mmol, 1.0 eq.) was added followed by the portionwise addition of sodium borohydride (730 mg, 19.2 mmol, 1.0 eq.) and the mixture was stirred for 30 min at room temperature. Then the mixture was diluted with water (100 mL) and diethyl ether (100 mL) was added, the phases were separated, the aqueous phase was extracted with diethyl ether (2×100 mL) and the combined organic phases were dried over magnesium sulphate. The drying agent was filtered of, and the filtrate was concentrated in vacuo to afford a yellow oil as crude product which was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 2/1) to give allylic alcohol **2-76a** (3.0 g, 14.3 mmol, 75%) as a faint yellow oil.

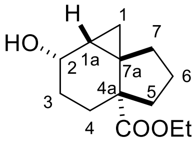
R_f : 0.26 (petroleum ether/ethyl acetate: 2/1, $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 5.55 (s, 1H, 7-H), 4.25 (br, 1H, 6-H), 4.13 (qq, *J*=10.8, 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 2.59 – 2.50 (m, 1H, 1-H^a), 2.39 – 2.36 (m, 1H, 3-H^a), 2.30 – 2.17 (m, 2H, 1-H^b, 4-H^a), 2.10 – 2.03 (m, 1H, 5-H^a), 1.78 (br, 1H, O$\underline{H}$), 1.70 – 1.59 (m, 2H, 2-H), 1.44 – 1.35 (m, 3H, 3-H^b, 4-H^b, 5-H^b), 1.24 (t, *J*=7.1 Hz, 3H, $OCH_2C\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 176.0 ($\underline{C}OCH_2CH_3$), 146.5 (C7a), 123.7 (C7), 68.3 (C6), 60.9 ($O\underline{C}H_2CH_3$), 53.5 (C3a), 38.5 (C4), 33.0 (C3), 31.1 (C5), 30.3 (C1), 21.5 (C2), 14.3 ($OCH_2\underline{C}H_3$).

HRMS (ESI-TOF): m/z: calcd. for $[C_{12}H_{18}O_3+Na]^+$: 233.11536; found: 233.11501

Ethyl (1a*R**,2*S**,4a*R**,7a*S**)-2-hydroxyhexahydro-1*H*-cyclopropa[*d*]indene-4a(5*H*)-carboxylate (2-77)[295]



To a solution of ethyl (3a*R**,6*S**)-6-hydroxy-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (**2-76a**) (500 mg, 2.38 mmol, 1.0 eq.) in diethyl ether (25 mL), diethyl zinc (1 M in hexane, 4.8 mL, 4.76 mmol, 2.0 eq.) and a solution of diiodomethane (390 µL, 1275 mg, 4.76 mmol, 2.0 eq.) in diethyl ether (5 mL) were added dropwise at 0 °C. The mixture was then allowed to warm to RT and was stirred for 24 h after which another portion of diethyl zinc (1 M in hexane, 2.4 mL, 2.38 mmol, 1.0 eq.) and diiodomethane (200 µL, 660 mg, 2.46 mmol, 1.0 eq.) were added at RT, and the reaction was stirred at RT overnight, after which a third portion of diethyl zinc (1 M in hexane, 2.4 mL, 2.38 mmol, 1.0 eq.) and diiodomethane (200 µL, 660 mg, 2.46 mmol, 1.0 eq.) were added at RT, and the reaction was stirred again at RT overnight, then it was cooled to 0 °C, and quenched with sat. ammonium chloride solution until the zinc salts dissolved, diethyl ether (100 mL) was added, the phases were separated, and the aqueous layer was extracted with diethyl ether (2×50 mL). The combined organic layers were washed with sat. sodium hydrogencarbonate solution (1×100 mL), dried over sodium sulphate, filtered, and concentrated in vacuo to afford a colourless oil as crude product which was then purified by flash chromatography (silica, petroleum ether/ethyl acetate: 3/1 to 2/1) to afford cyclopropane **2-77** (294 mg, 1.31 mmol, 55%) as a colourless oil.

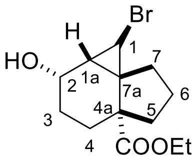
R_f : 0.20 (petroleum ether/ethyl acetate: 2/1, $KMnO_4$)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 4.19 – 4.05 (m, 3H, $\mathrm{OC\underline{H}_2CH_3}$, 2-H), 2.23 – 2.13 (m, 2H, 4-H^a, 7-H^a), 2.10 – 2.02 (m, 1H, 6-H^a), 1.85 – 1.77 (m, 1H, 5-H^a), 1.69 – 1.57 (m, 4H, $\mathrm{O\underline{H}}$, 3-H^a, 4-H^b, 5-H^b), 1.34 – 1.29 (m, 6-H^b), 1.24 (t, *J*=7.1 Hz, 3H, $\mathrm{OCH_2C\underline{H}_3}$), 1.18 – 1.12 (m, 1H, 1a-H), 1.03 – 0.89 (m, 2H, 3-H^b, 7-H^b), 0.67 (dd, *J*=8.7, 5.6 Hz, 1H, 1-H^a), 0.52 (t, *J*=5.7 Hz, 1H, 1-H^b).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 177.6 ($\mathrm{\underline{C}OCH_2CH_3}$), 68.2 (C2), 60.4 ($\mathrm{O\underline{C}H_2CH_3}$), 49.3 (C4a), 41.1 (C4), 39.6 (C6), 35.0 (C7a), 32.1 (C7), 27.9 (C1a), 26.8 (C3), 25.4 (C5), 14.4 ($\mathrm{OCH_2\underline{C}H_3}$), 10.6 (C1).

HRMS (ESI-TOF): m/z: calcd. for $[C_{17}H_{20}O_6+Na]^+$: 247.13047; found: 247.13064

Ethyl (1*R**,1a*R**,2*S**,4a*R**,7a*S**)-1-bromo-2-hydroxyhexahydro-1*H*-cyclopropa[*d*]indene-4a(5*H*)-carboxylate (2-81)[252]



To a cooled (0 °C) solution of ethyl (3a*R**,6*S**)-6-hydroxy-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (**2-76a**) (200 mg, 0.95 mmol, 1.0 eq.) in DCM (3 mL), bromoform (250 µL, 720 mg, 2.85 mmol, 3.0 eq.) and diethyl ether (300 µL, 211 mg, 2.85 mmol, 3.0 eq.) were given. This was followed by the dropwise addition of the diethylzinc solution (1 M in hexane, 2.85 mL, 2.85 mmol, 3.0 eq.). The mixture was allowed to warm to RT and was stirred overnight, then was diluted with DCM (20 mL), and was washed with water (2×20 mL), dried over sodium sulphate, filtered and concentrated in vacuo affording an orange oil as crude product, that was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 3/1) to afford a faint yellow oil (169 mg, 0.56 mmol, 59%) as product.

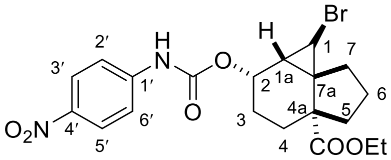
R_f: 0.48 (petroleum ether/ethyl acetate: 2/1, $KMnO_4$)

^1H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 4.27 – 4.19 (m, 1H, $OC\underline{H}_2{}^aCH_3$), 4.12 – 4.06 (m, 2H, $OC\underline{H}_2{}^bCH_3$, 2-H), 3.00 (d, *J*=4.4 Hz, 1H, 1-H), 2.28 – 2.15 (m, 3H, 4-H^a, Ring-$C\underline{H}_2$), 2.00 – 1.92 (br, 1H, O*H*), 1.93 – 1.87 (m, 1H, Ring-$C\underline{H}_2$), 1.78 – 1.65 (m, 3H, 3-H^a, Ring-$C\underline{H}_2$), 1.64 – 1.58 (m, 1H, Ring-$C\underline{H}_2$), 1.50 (t, *J*=5.2 Hz, 1H, 1a-H), 1.29 (t, *J*=7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 0.96 – 0.88 (m, 2H, 3-H^b, 4-H^b).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 176.5 ($\underline{C}OCH_2CH_3$), 67.0 (C2), 60.9 ($CO\underline{C}H_2CH_3$), 50.1 (C4a), 41.2 (Ring-$\underline{C}H_2$), 39.9 (C7a), 38.7 (Ring-$\underline{C}H_2$), 36.2 (C1a), 31.1 (C4), 27.0 (C3), 26.8 (C1), 25.0 (Ring-$\underline{C}H_2$), 14.4 ($COCH_2\underline{C}H_3$).

HRMS (ESI-TOF): m/z: calcd. for $[C_{13}H_{19}BrO_3+Na]^+$: 325.04098; found: 325.04107

Ethyl (1*R**,1a*R**,2*S**,4a*R**,7a*S**)-1-bromo-2-(((4-nitrophenyl)carbamoyl)oxy) hexahydro-1*H*-cyclopropa[*d*]indene-4a(5*H*)-carboxylate (2-84)[265]



To a solution of ethyl (1*R**,1a*R**,2*S**,4a*R**,7a*S**)-1-bromo-2-hydroxyhexahydro-1*H*-cyclopropa[*d*]indene-4a(5*H*)-carboxylate (**2-81**) (200 mg, 0.66 mmol, 1.0 eq.) in DCM (2 mL) 4-nitrophenyl isocyanate (130 mg, 0.78 mmol, 1.2 eq.) and TEA (150 µL, 107 mg, 1.06 mmol, 1.6 eq.) were added, and the mixture was stirred at RT overnight, then it was poured into aqueous hydrochloric acid (1 M, 10 mL), the phases were separated, the aqueous phase was extracted with DCM (2×10 mL) the combined organic layers were dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (silica, petroleum ether/ethyl acetate: 5/1) to afford carbamate **2-84** as an off-white solid (211 mg, 0.45 mmol, 68%).

R_f: 0.55 (petroleum ether/ethyl acetate: 5/1, UV)

Mp.: 87-89 °C (ethanol)

^{1}H NMR ($CDCl_3$, 400 MHz): δ [ppm]: 8.30 – 8.27 (m, 2H, 3’-H, 5-H), 8.21 – 8.18 (m, 2H, 2’-H, 6’-H), 5.42 (dt, *J*=11.1, 6.3 Hz, 1H, 2-H), 4.27 (dq, *J*=10.7, 7.1 Hz, 1H, $COOC\underline{H}_2^aCH_3$), 4.12 (dq, *J*=10.7, 7.1 Hz, 1H, $COOC\underline{H}_2^bCH_3$), 3.12 (d, *J*=4.3 Hz, 1H, 1-H), 2.32 – 2.23 (m, 3H,3-H^a, Ring-H), 2.01 – 1.92 (m, 1H, Ring-H), 1.91 – 1.71 (m, 4H, 4-H^a, 1a-H, Ring-H), 1.69 – 1.64 (m, 1H, Ring-H), 1.32 (t, *J*=7.1 Hz, 3H, $COOCH_2C\underline{H}_3$), 1.23 (tdd, *J*=13.3, 11.1, 2.0 Hz, 1H, 4-H^b), 1.08 (td, J=13.7, 2.1 Hz, 1H, 3-H^b).

^{13}C NMR ($CDCl_3$, 101 MHz): δ [ppm]: 176.1 ($\underline{C}OOCH_2CH_3$), 164.6 (Ar-NH-$\underline{C}$O-O-C2), 150.7 (C4’), 135.8 (C1’), 130.9 (C2’/C6’), 123.7 (C3’/C5’), 71.9 (C2), 61.0 ($COO\underline{C}H_2CH_3$), 50.1 (C4a), 41.1 (Ring-$\underline{C}H_2$), 40.3 (C7a), 38.5 (Ring-$\underline{C}H_2$), 32.6 (C1a), 30.7 (C3), 26.9 (C1), 25.0 (Ring-$\underline{C}H_2$), 23.5 (C4), 14.5 ($COOCH_2\underline{C}H_3$).

HRMS (ESI-TOF): m/z: calcd. for $[C_{20}H_{23}BrN_2O_6+Na]^+$: 489.06317; found: 489.06389

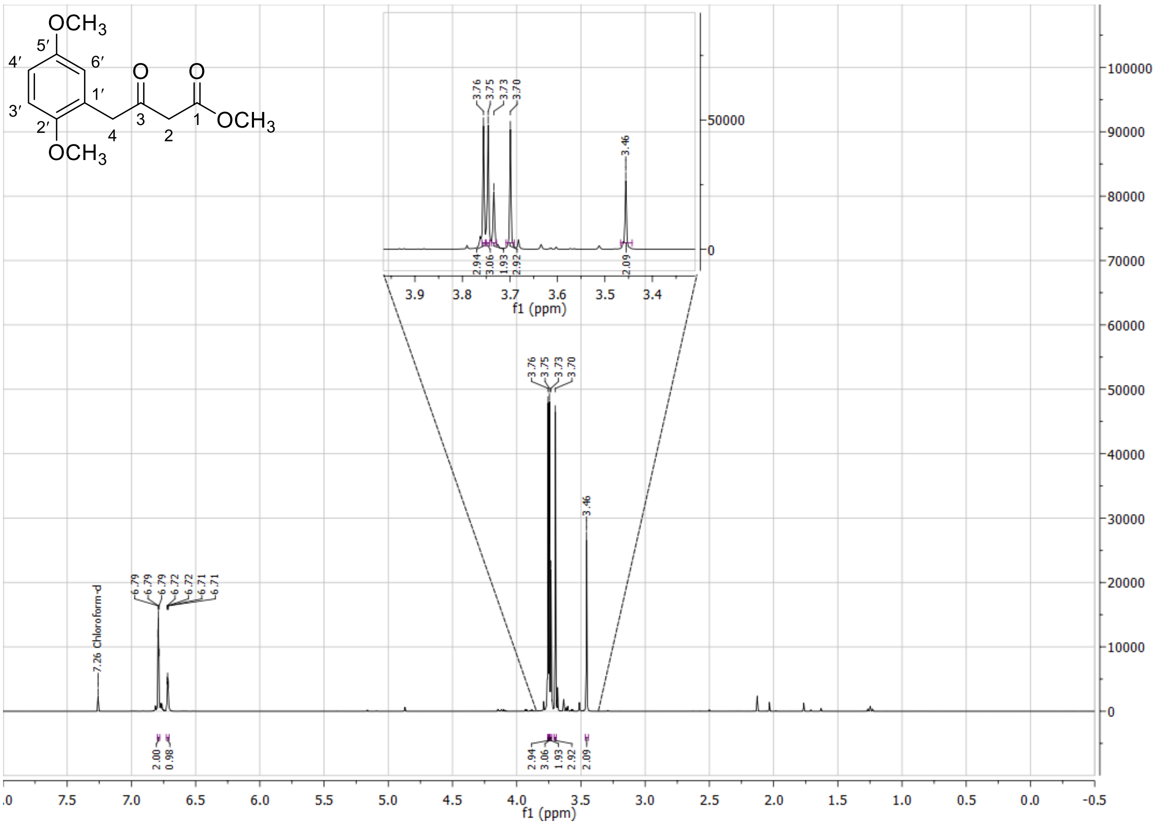
In order to obtain crystals suitable for XRD measurement the following procedure was performed: 100 mg of the product was measured into a 1.5 ml screw-necked vial (32.0 mm×Ø 11.6 mm; Macherey-Nagel, Product No.: 70213) and ethanol (~100 µL) was added, the vial was heated and ethanol was dropped to the mixture until all solids were dissolved hot, followed by additional ethanol (~100 µL). The vial was closed with the appropriate cap, which was punctured three times with a needle (Ø 1.1 mm) that allowed the slow evaporation of the solvent. The vial was then placed into a polystyrene box and was left undisturbed at RT. Suitable crystals presented themselves after 7 d.

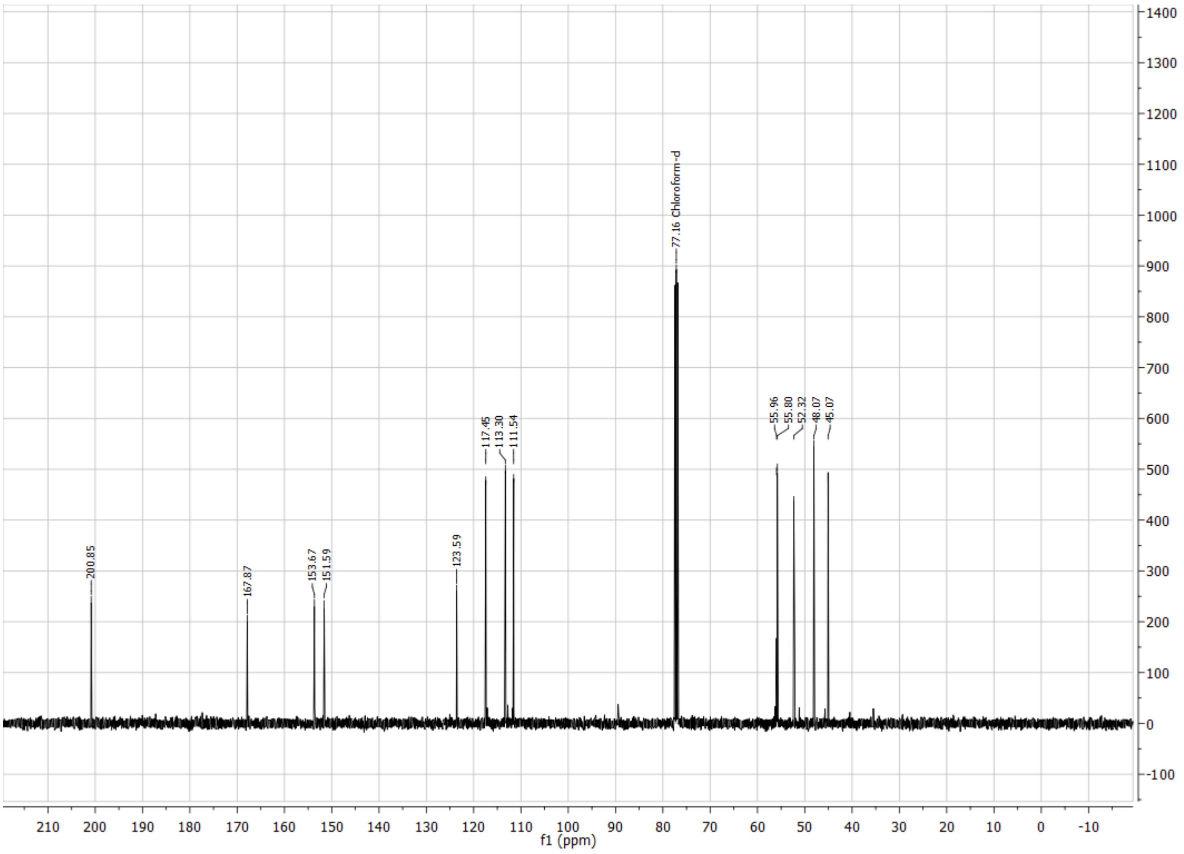
The XRD measurement was performed as follows: A suitable crystal with dimensions 0.22 × 0.09 × 0.04 mm^3 was selected and mounted on a XtaLAB Synergy-S, Dualflex, HyPix diffractometer. The crystal was kept at a steady T = 149.99(10) K during data collection. The structure was solved with the ShelXT 2018/2[292] solution program using dual methods and by using Olex2 1.5[293] as the graphical interface. The model was refined with olex2.refine 1.5[296] using full matrix least squares minimisation on $\boldsymbol{F^2}$.

Crystal Data: $C_{20}H_{23}BrN_2O_6$, M_r = 467.319, triclinic, P-1 (No. 2), a = 8.9606(1) Å, b = 14.9434(2) Å, c = 16.4576(2) Å, α = 81.249(1)°, β = 76.856(1)°, γ = 73.416(1)°, V = 2047.70(5) Å^3, T = 149.99(10) K, Z = 4, Z' = 2, μ(Cu K_α) = 3.083, 88242 reflections measured, 8821 unique (R_{int} = 0.0236) which were used in all calculations. The final wR_2 was 0.0358 (all data) and R_1 was 0.0159

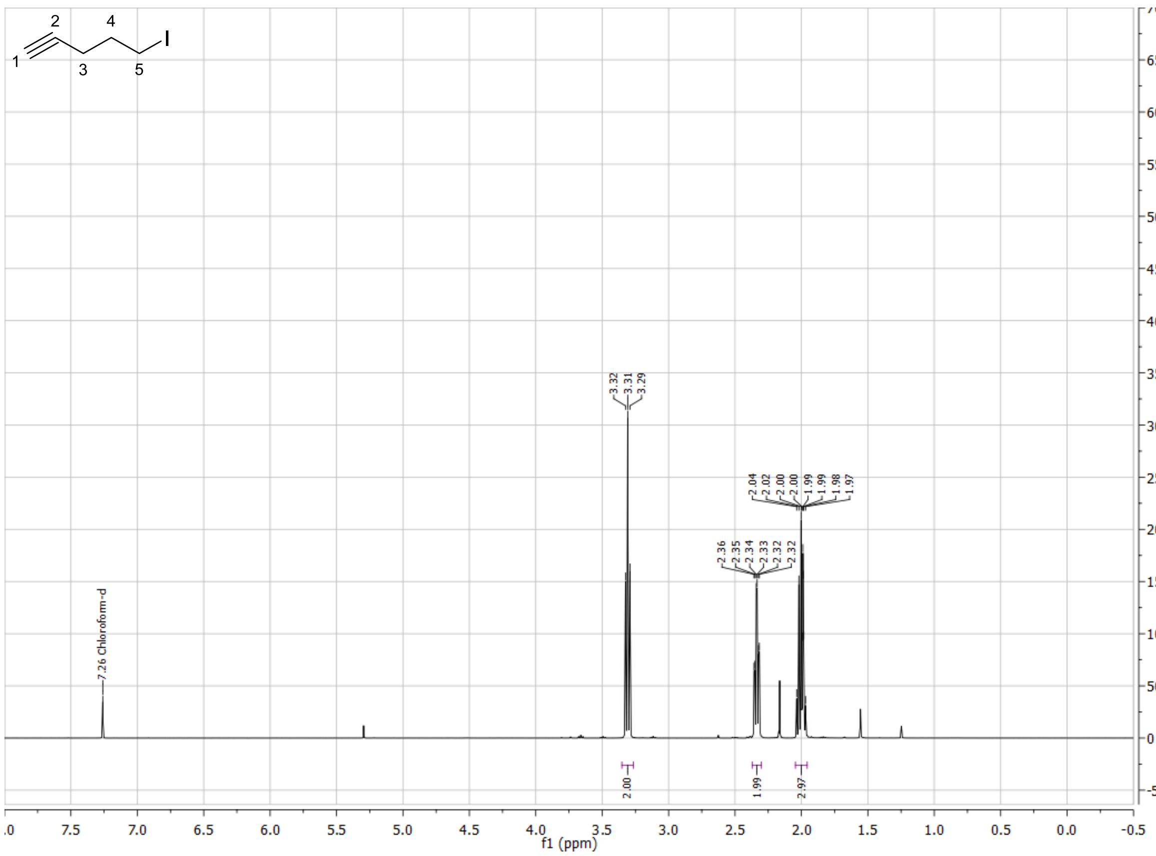
6. NMR Spectra

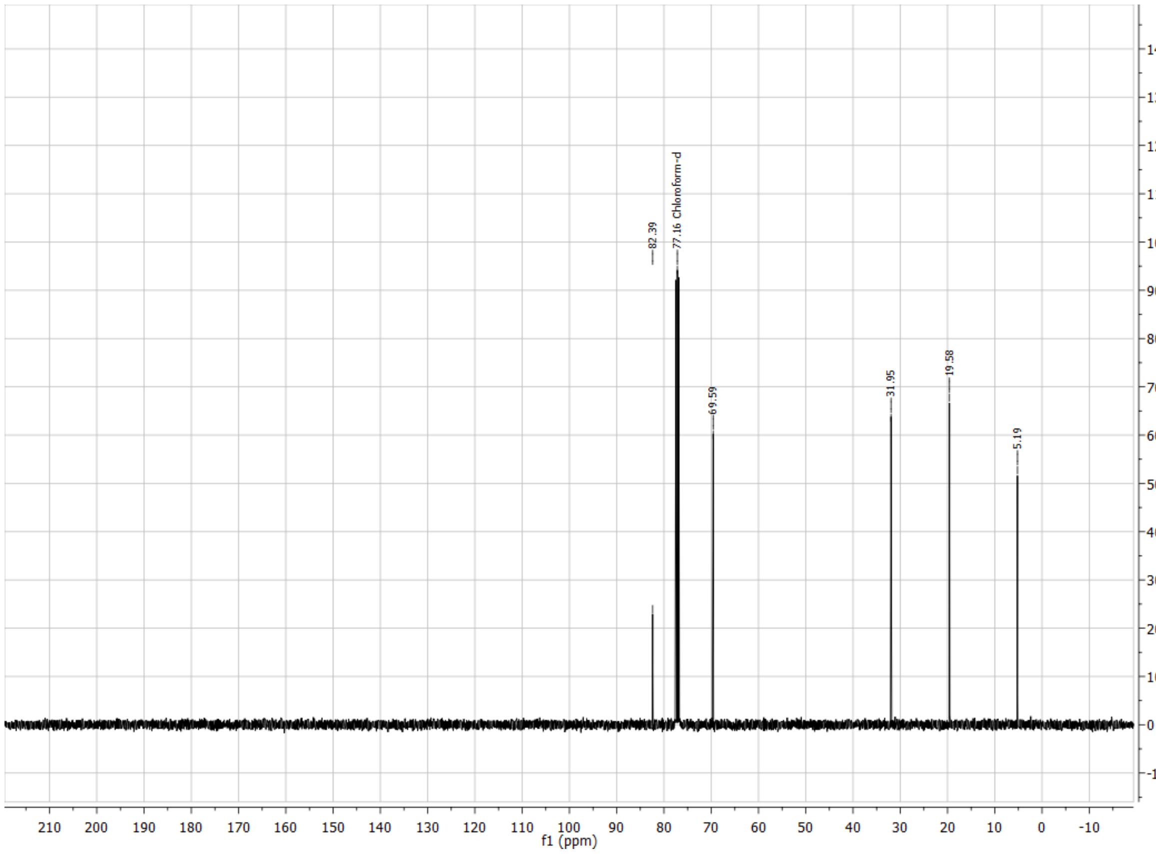
Methyl 4-(2,5-dimethoxyphenyl)-3-oxobutanoate (**2-9**)



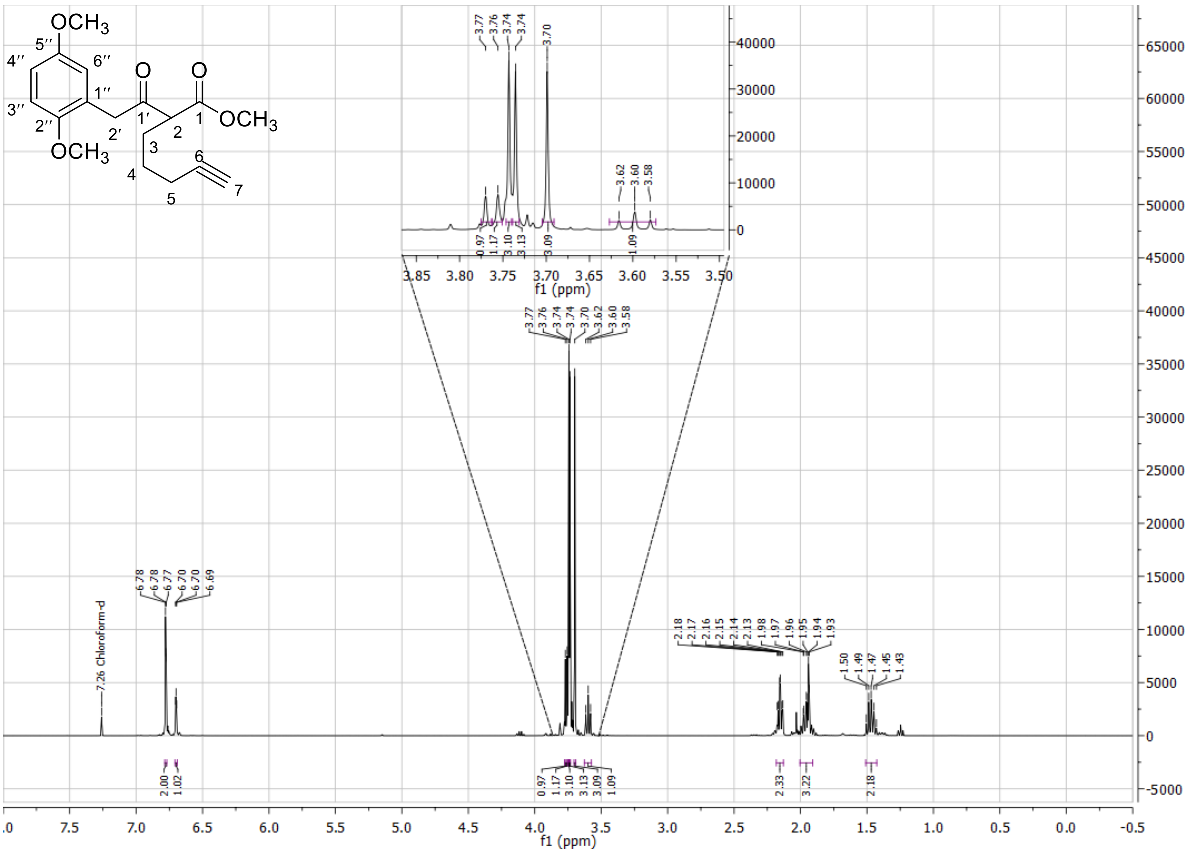


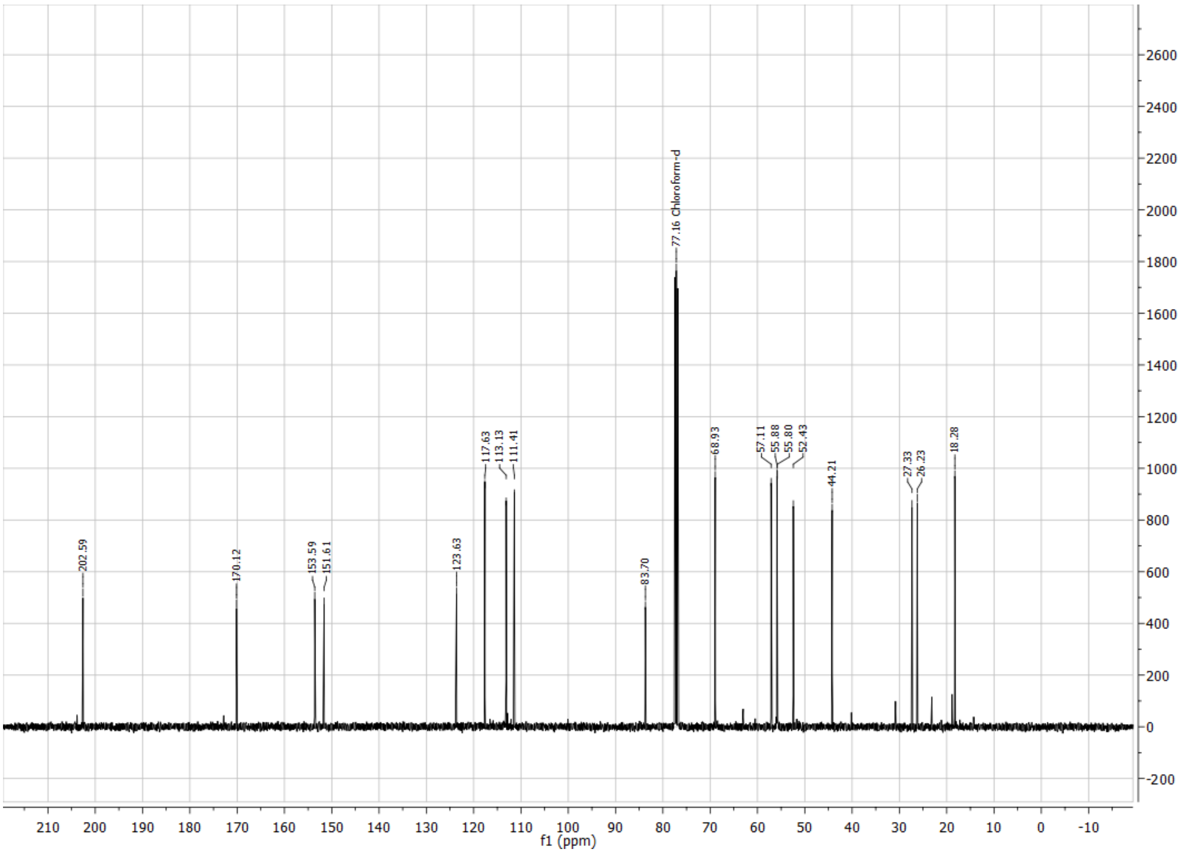
5-Iodopent-1-yne (**2-4**)



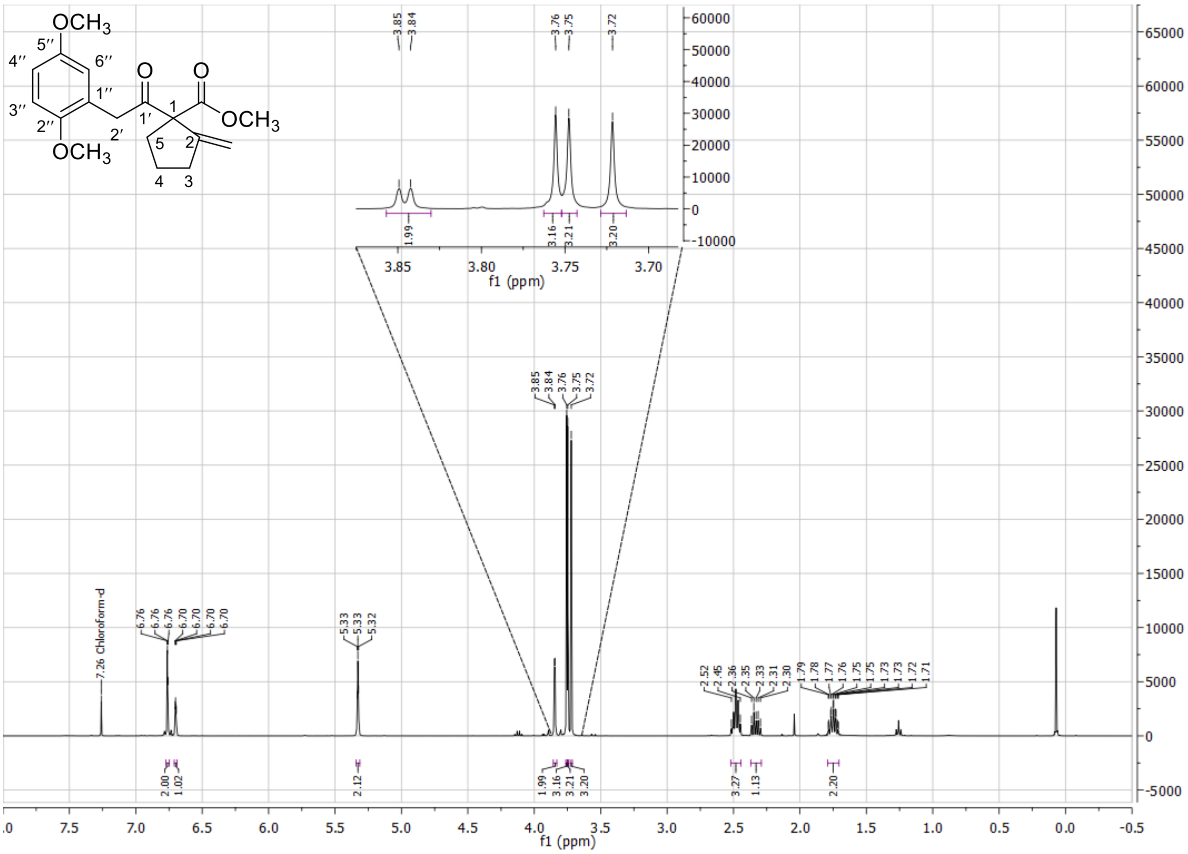


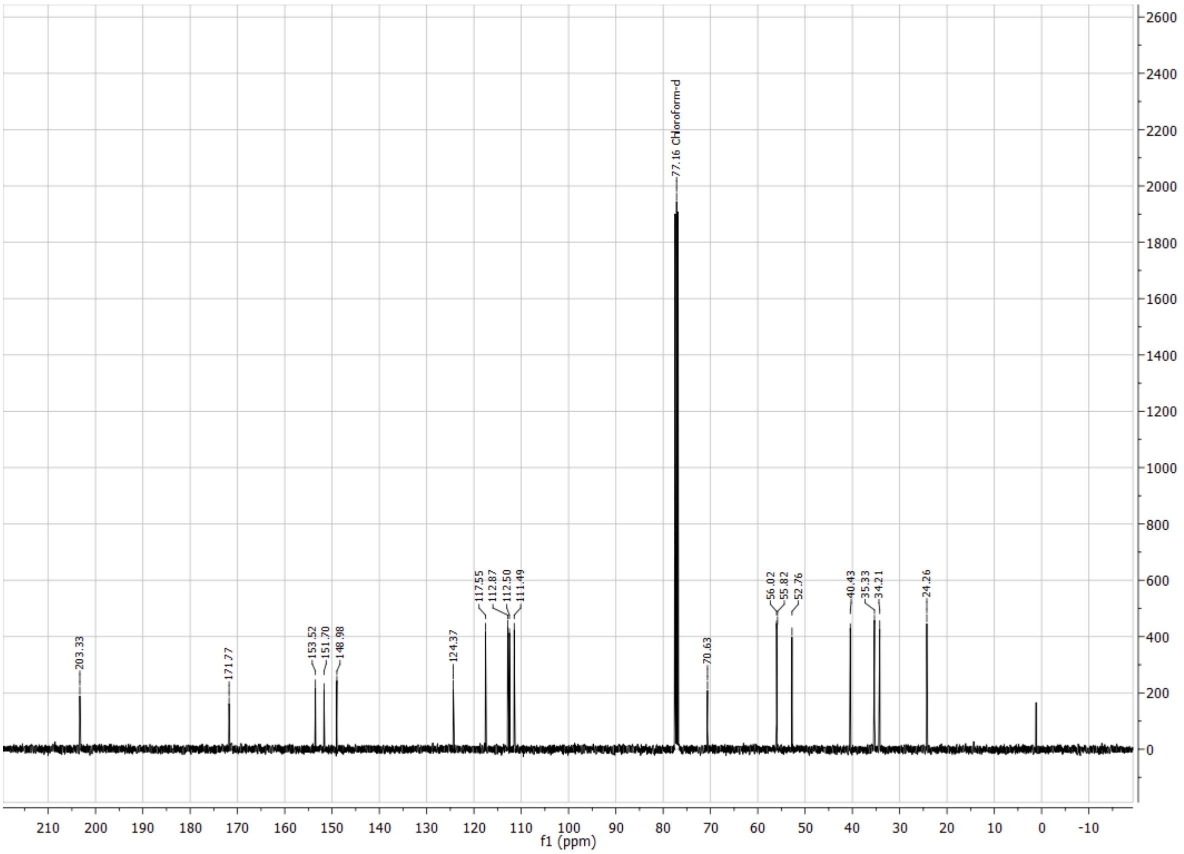
Methyl 2-(2-(2,5-dimethoxyphenyl)acetyl)hept-6-ynoate (**2-3**)



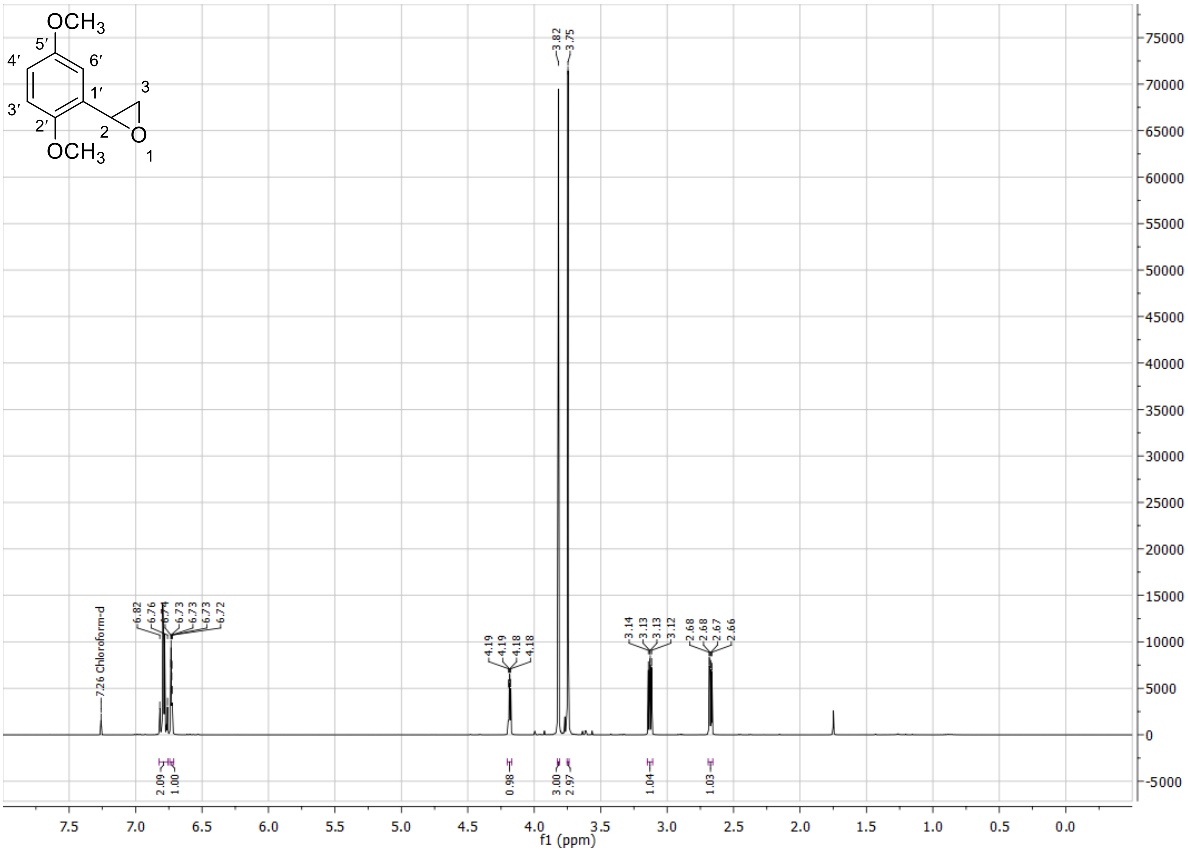


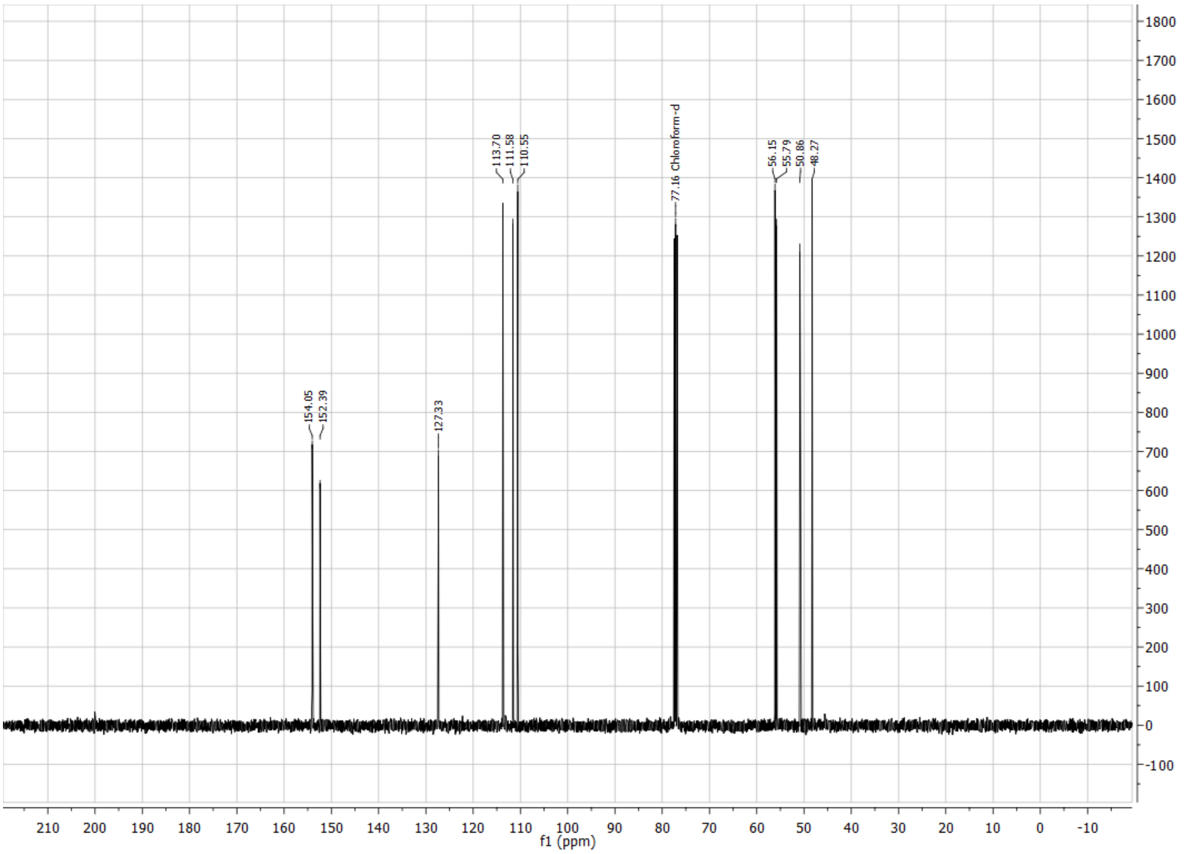
Methyl 1-(2-(2,5-dimethoxyphenyl)acetyl)-2-methylenecyclopentane-1-carboxylate (**2-2**)



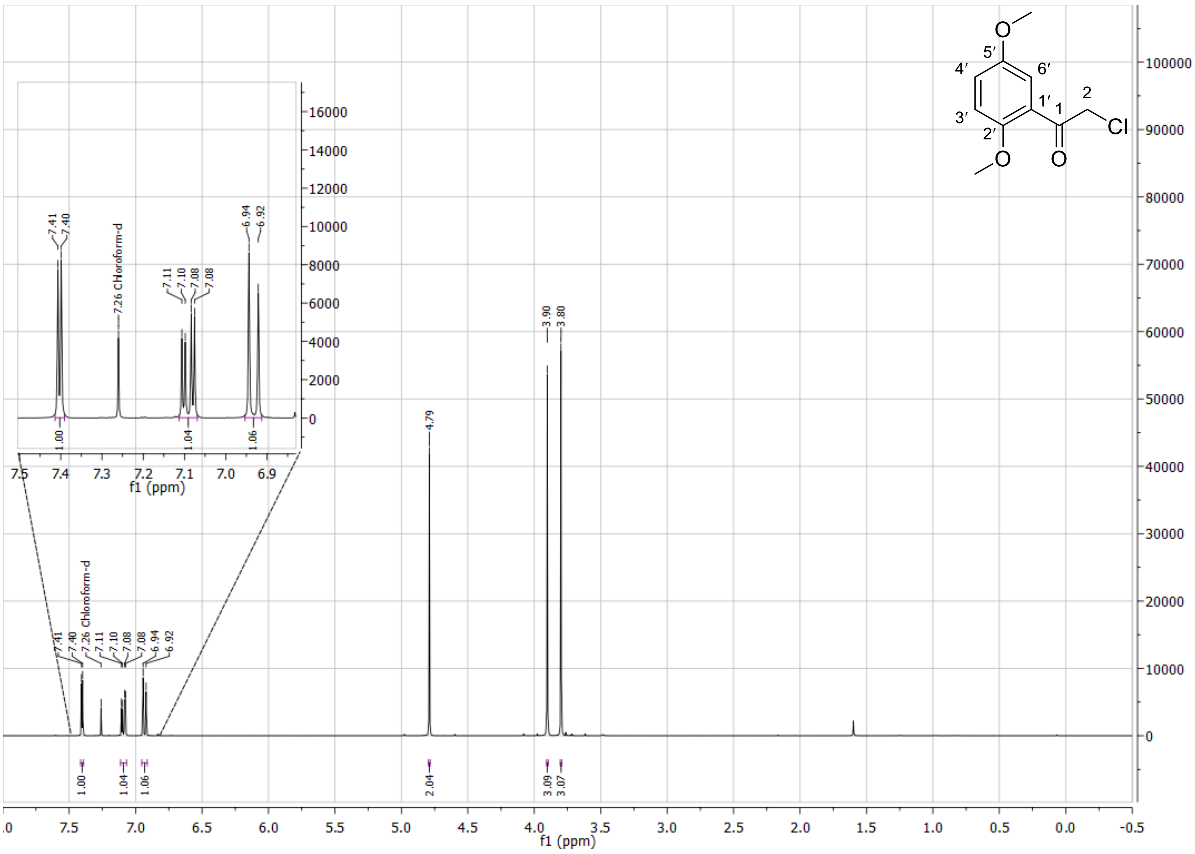


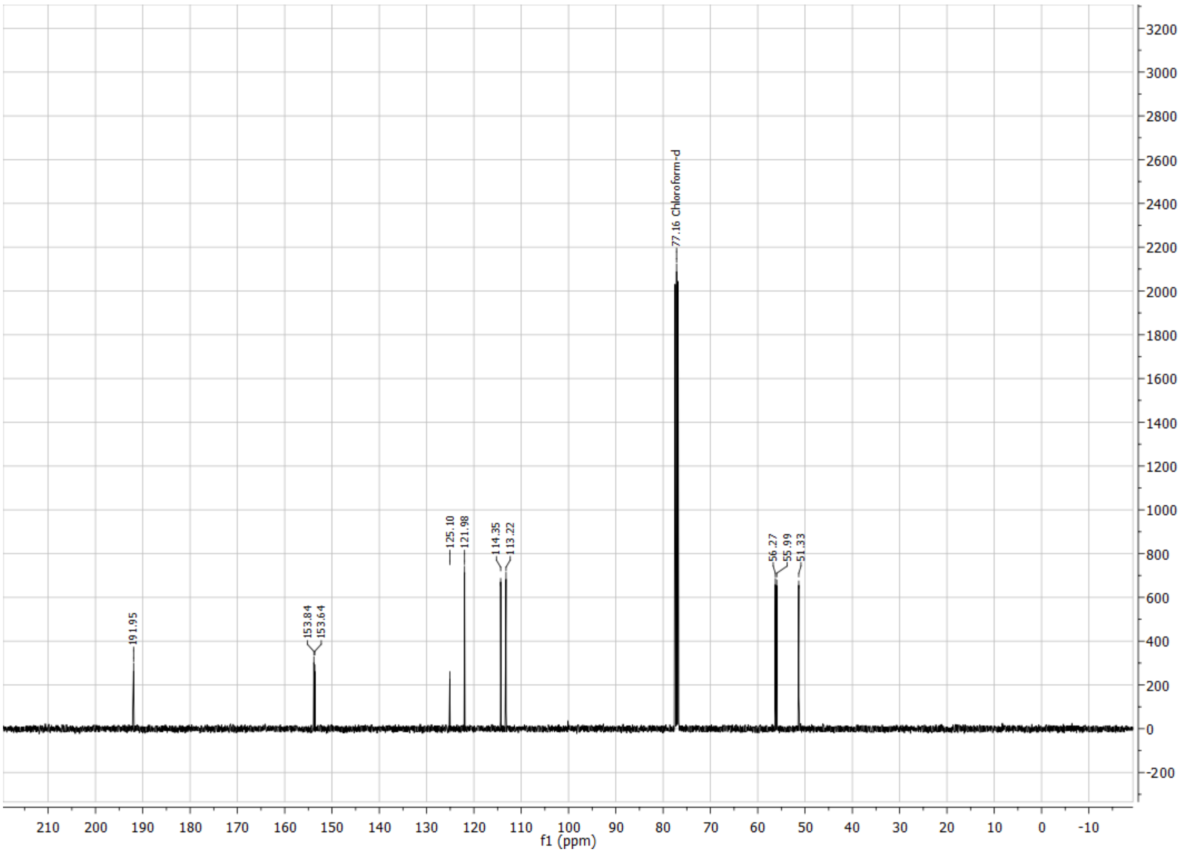
2-(2,5-Dimethoxyphenyl)oxirane **(2-14)**



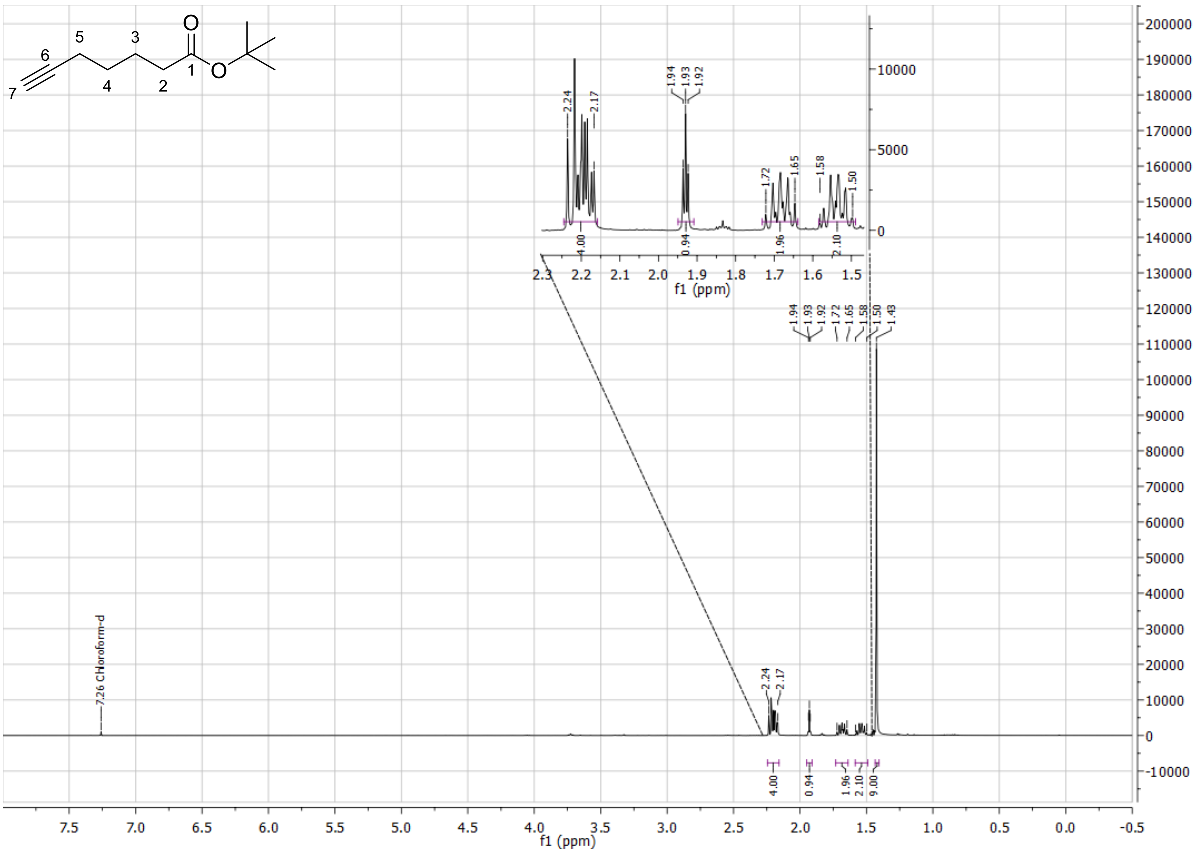


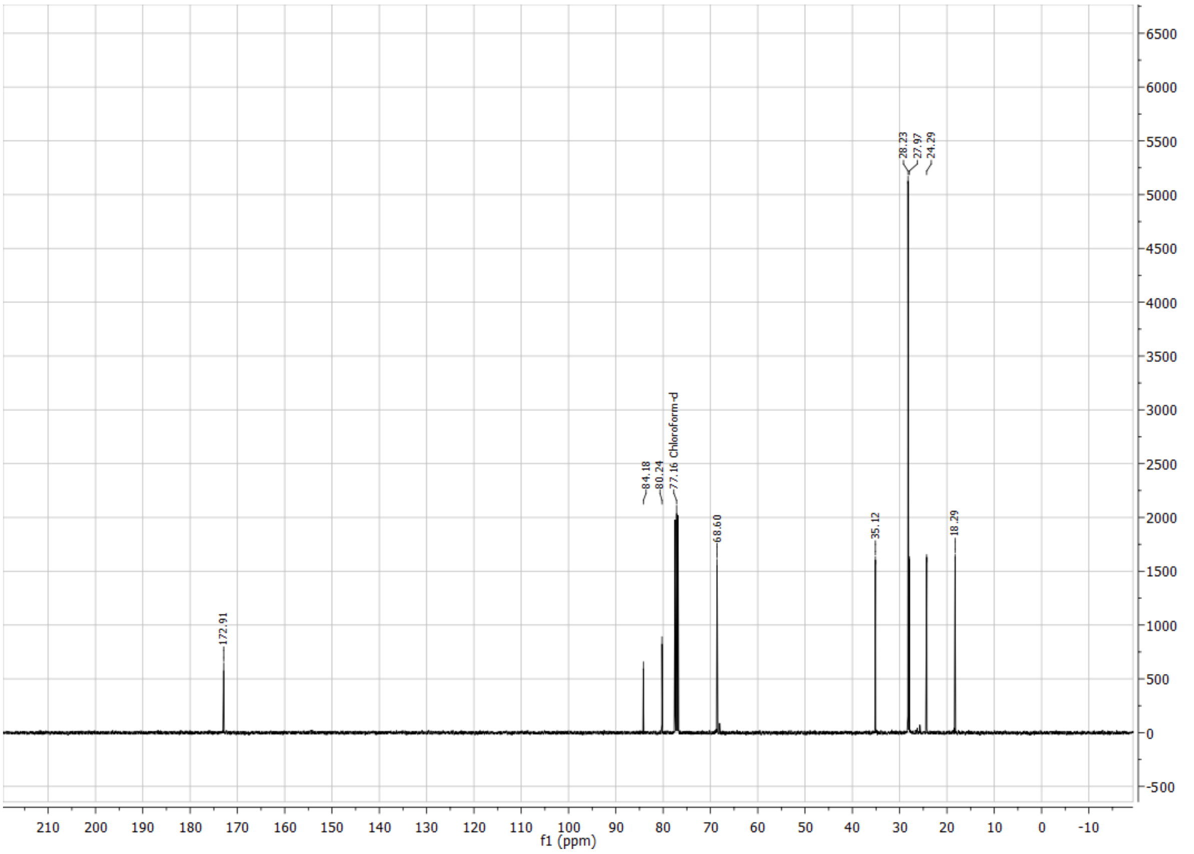
2-Chloro-1-(2,5-dimethoxyphenyl)ethan-1-one (**2-18**)



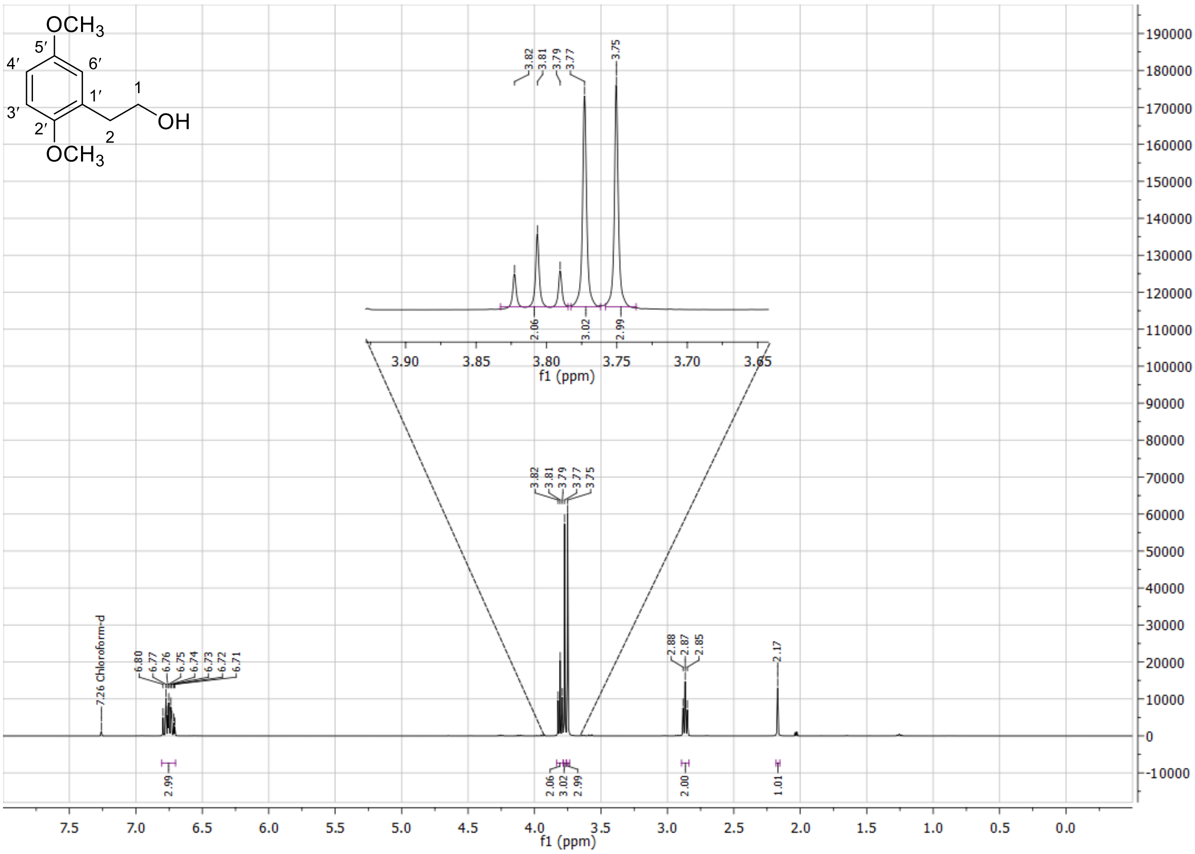


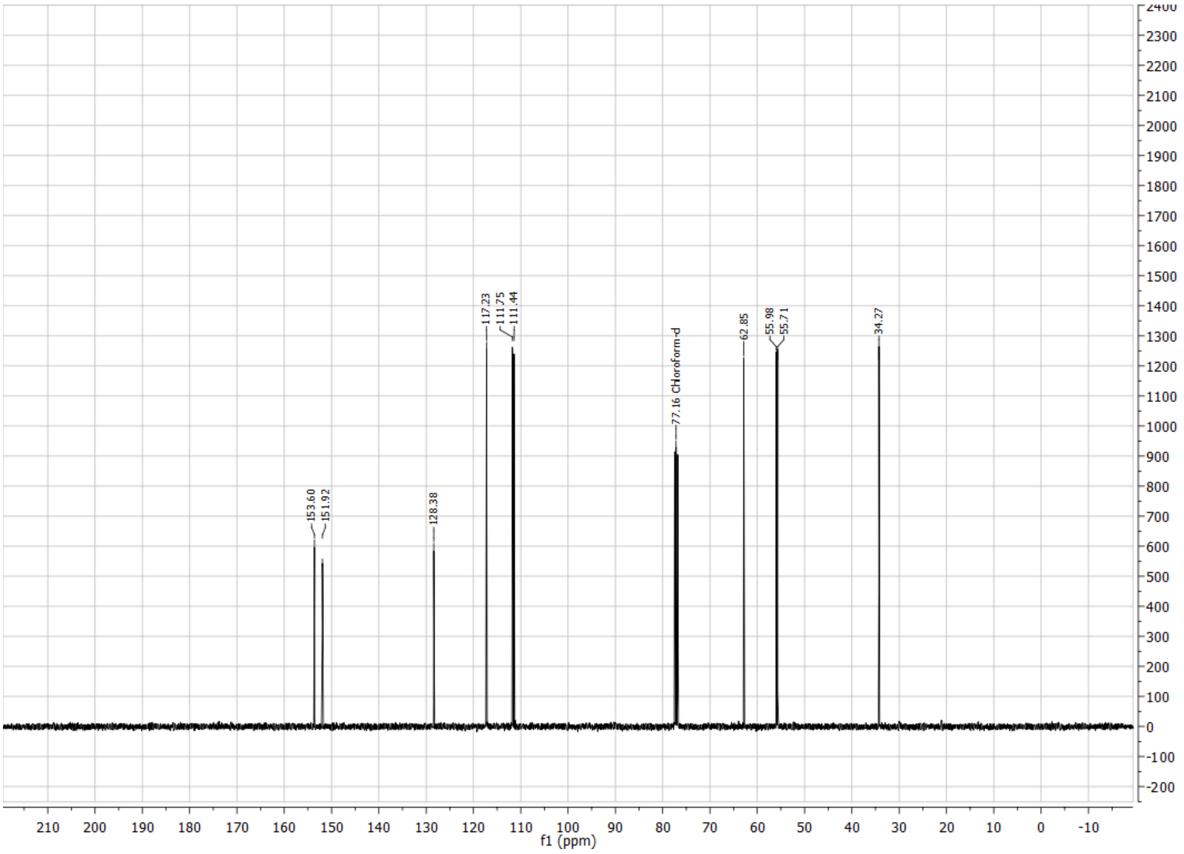
tert-Butyl hept-6-ynoate **(2-19)**



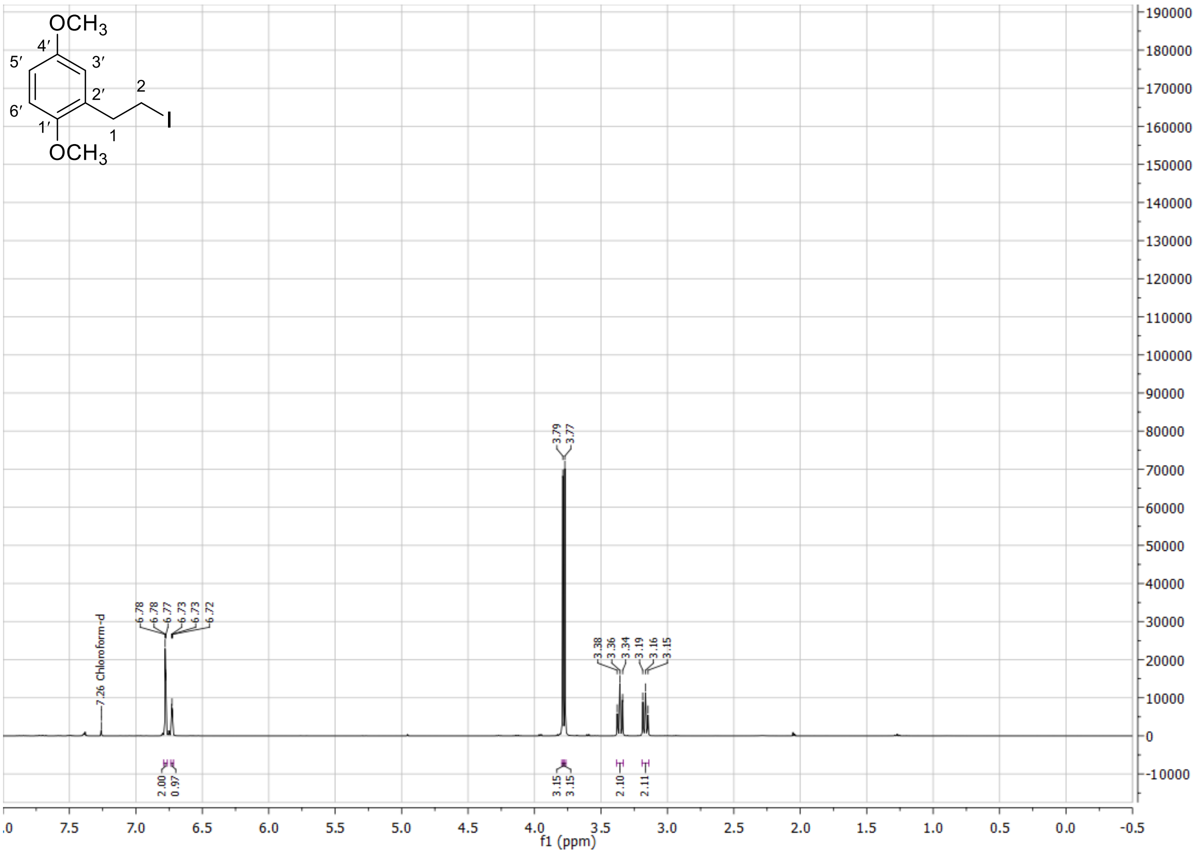


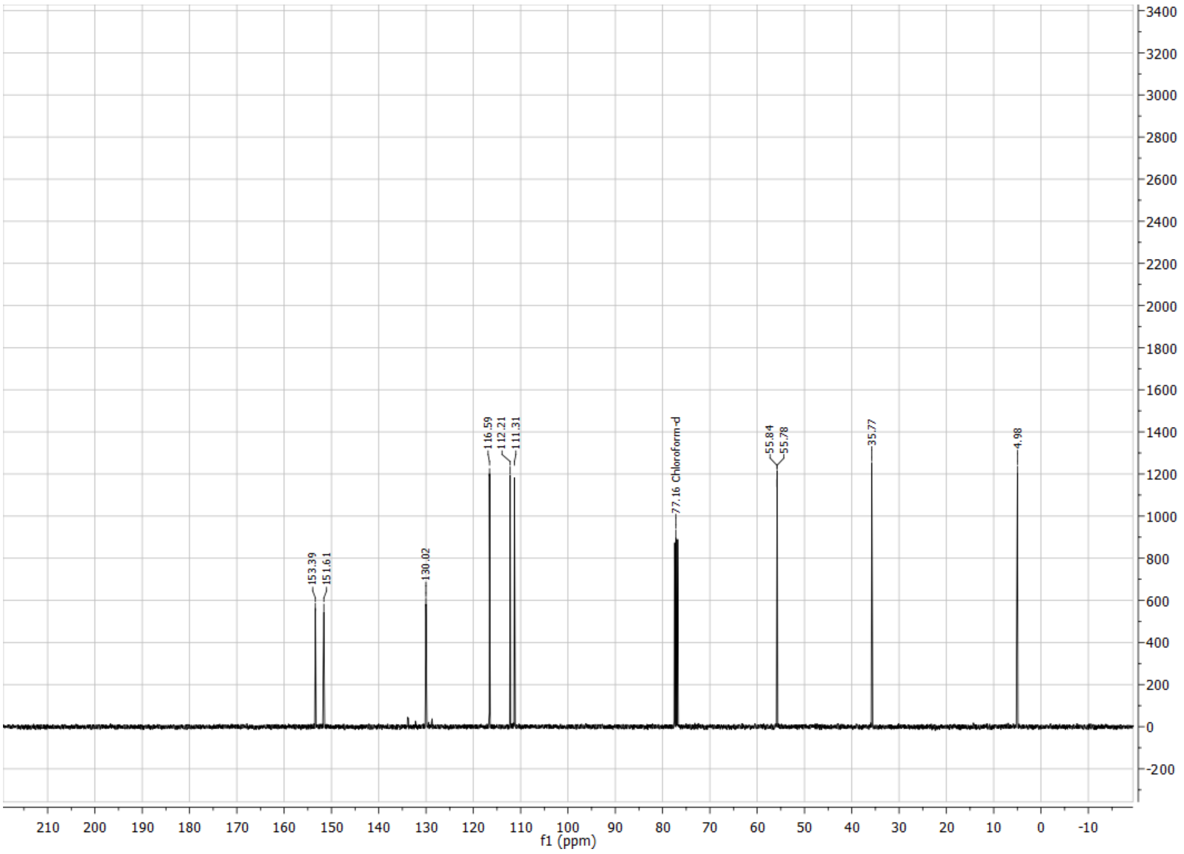
2-(2,5-Dimethoxyphenyl)ethan-1-ol **(2-29)**



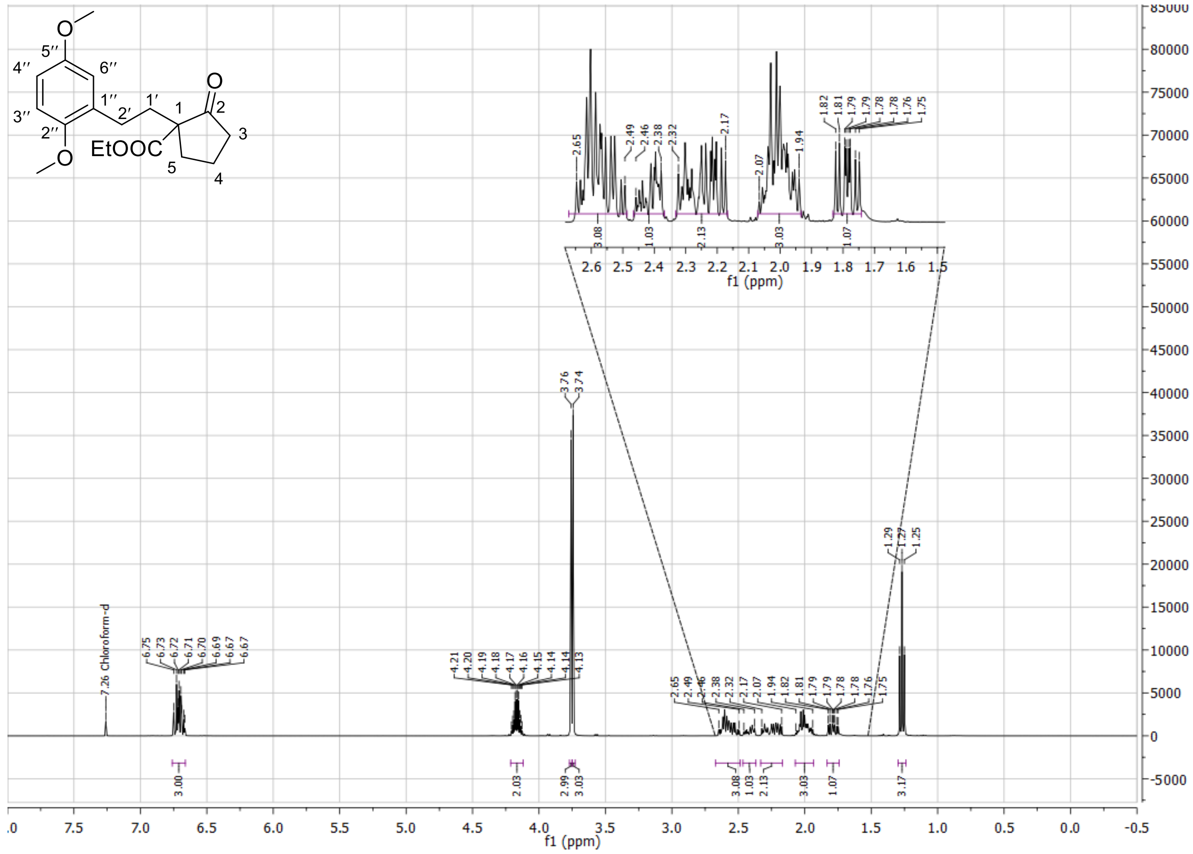


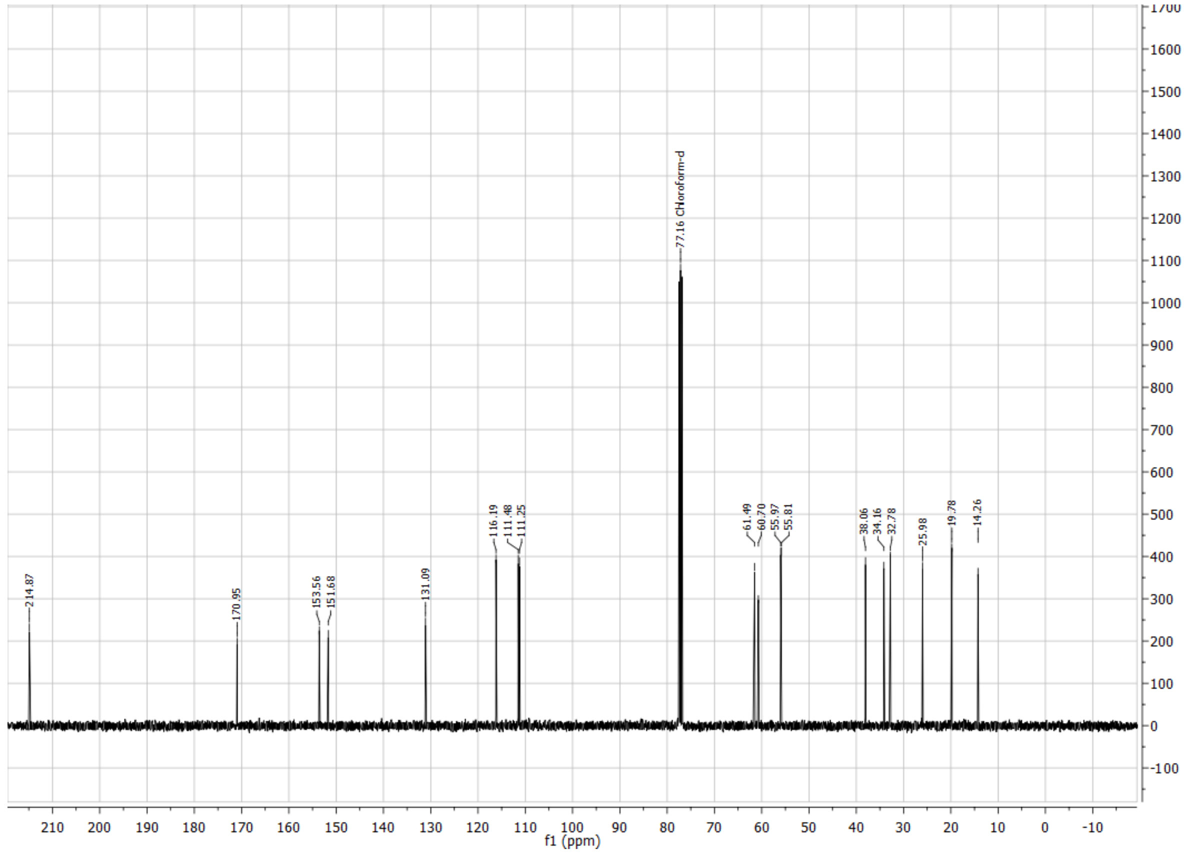
2-(2-Iodoethyl)-1,4-dimethoxybenzene **(2-27)**



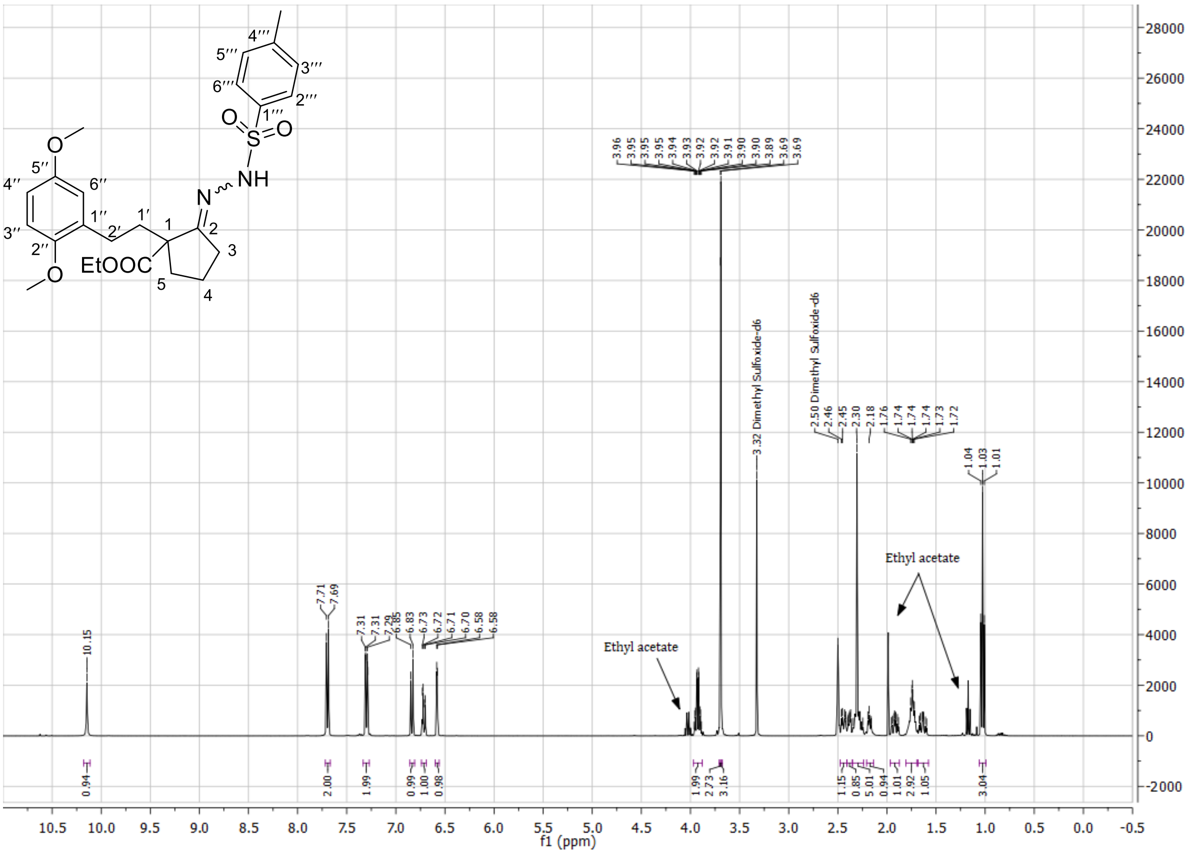


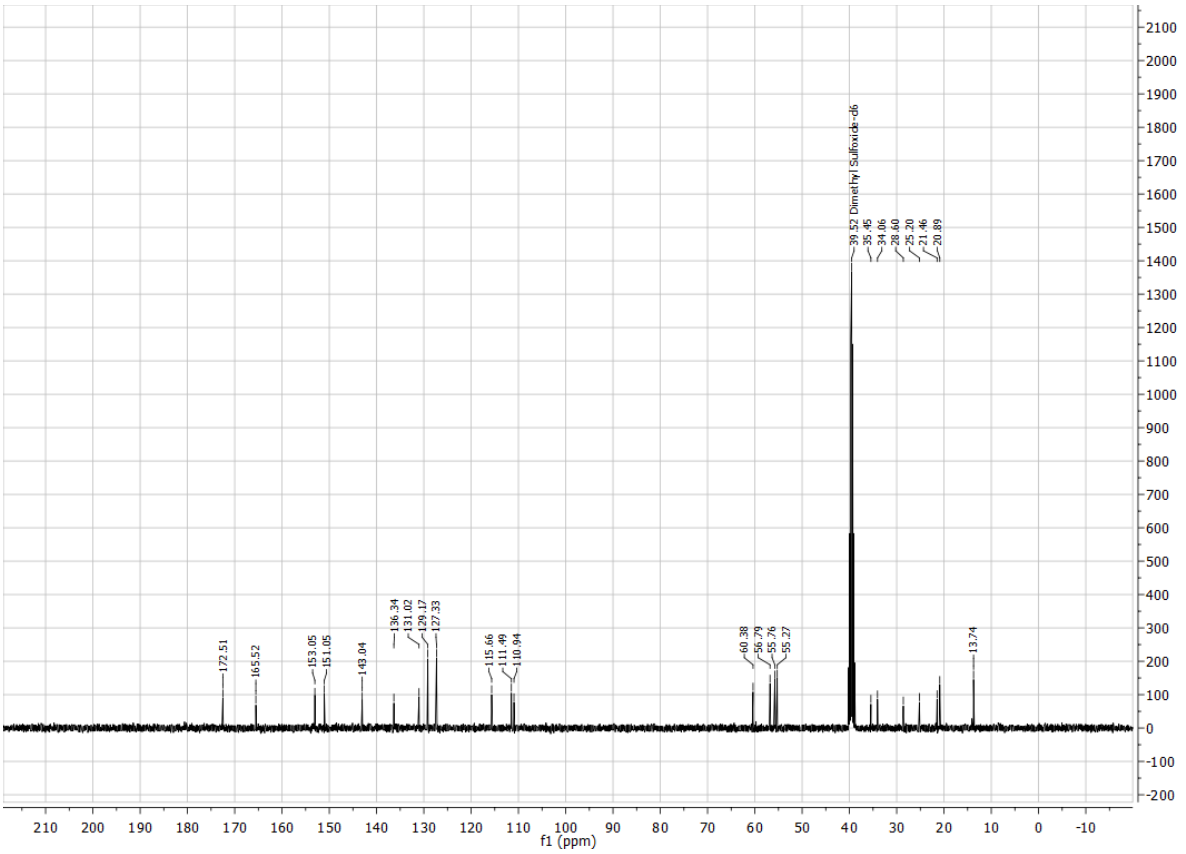
Ethyl 1-(2,5-dimethoxyphenethyl)-2-oxocyclopentane-1-carboxylate **(1-21)**



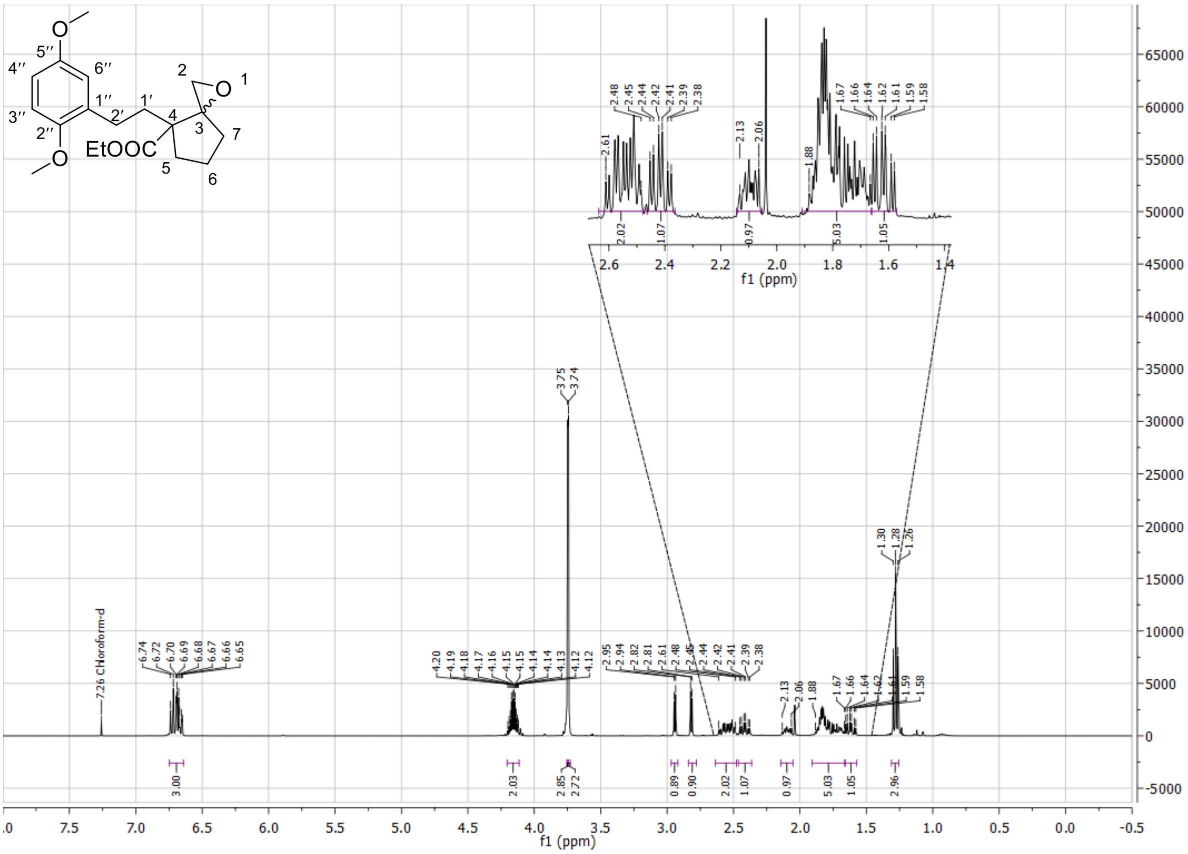


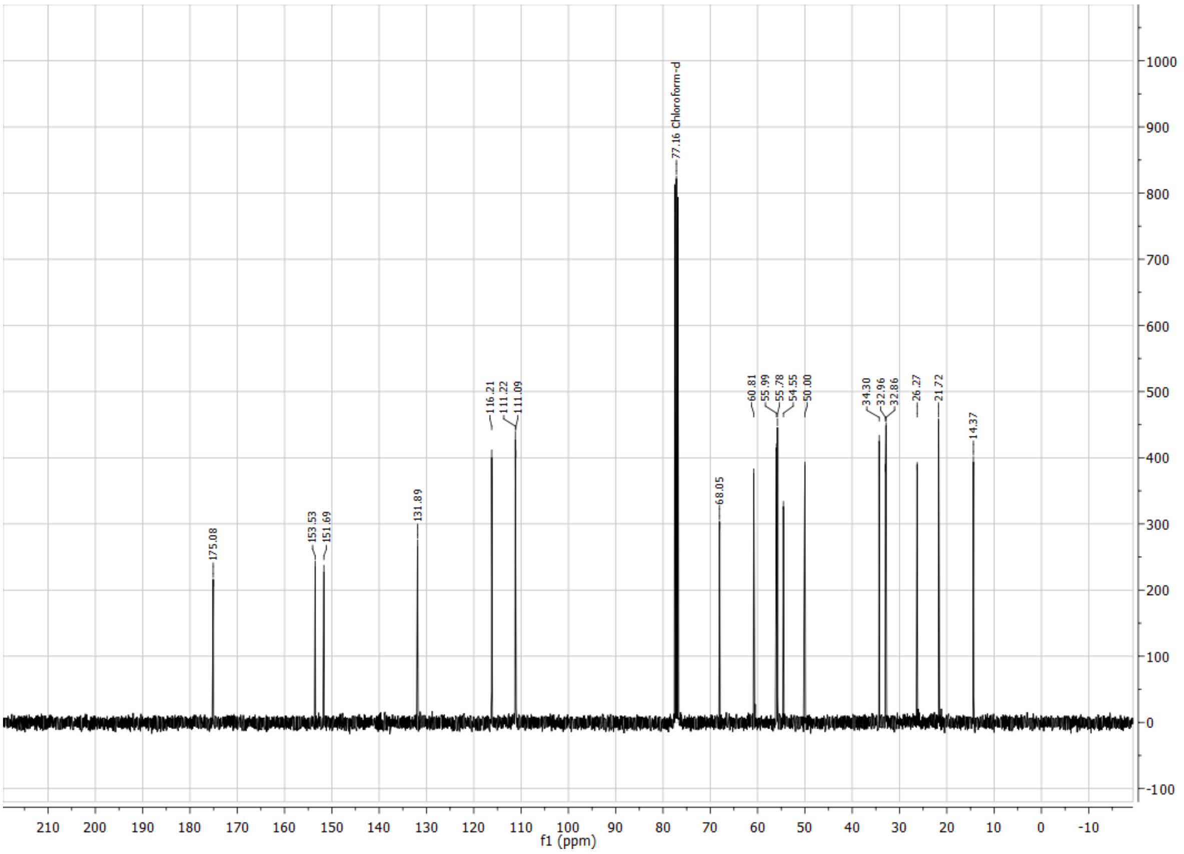
Ethyl 1-(2,5-dimethoxyphenethyl)-2-(2-tosylhydrazineylidene)cyclopentane-1-carboxylate **(2-30)**



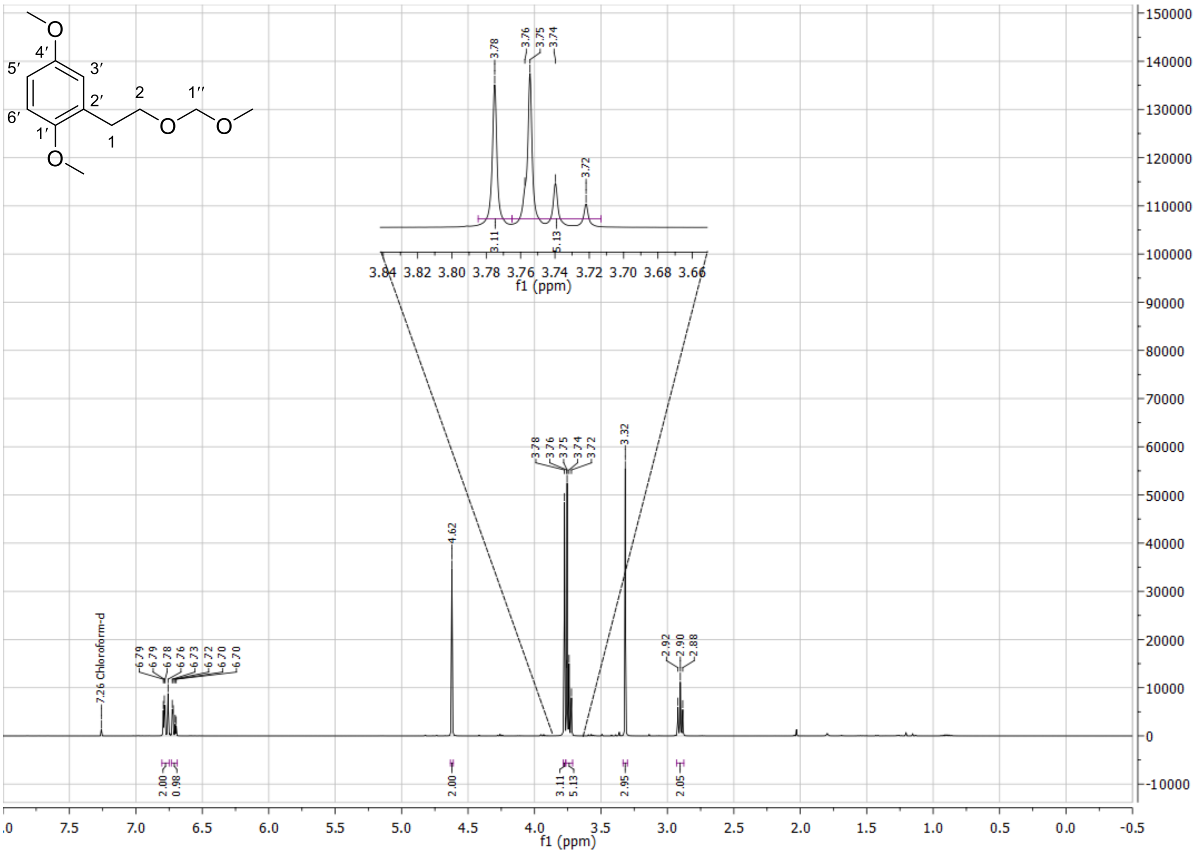


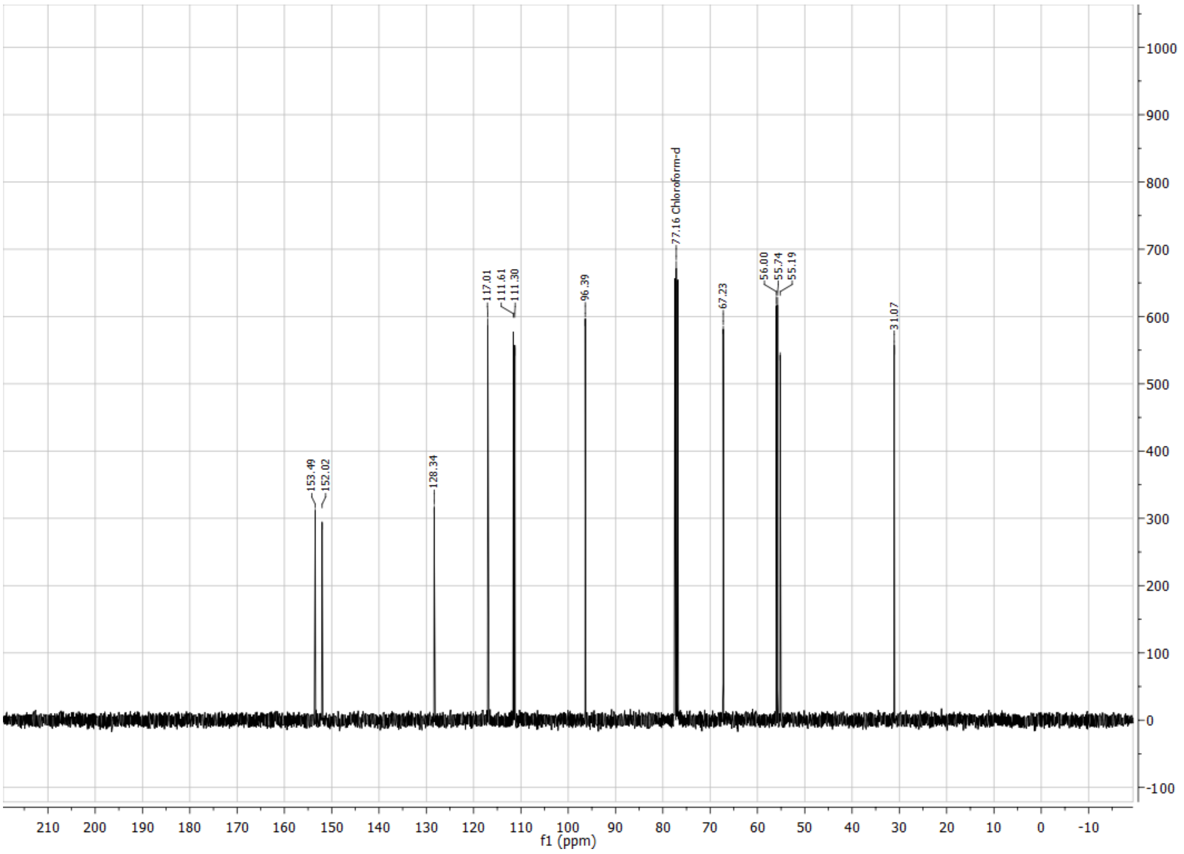
Ethyl 4-(2,5-dimethoxyphenethyl)-1-oxaspiro[2.4]heptane-4-carboxylate **(2-31)**



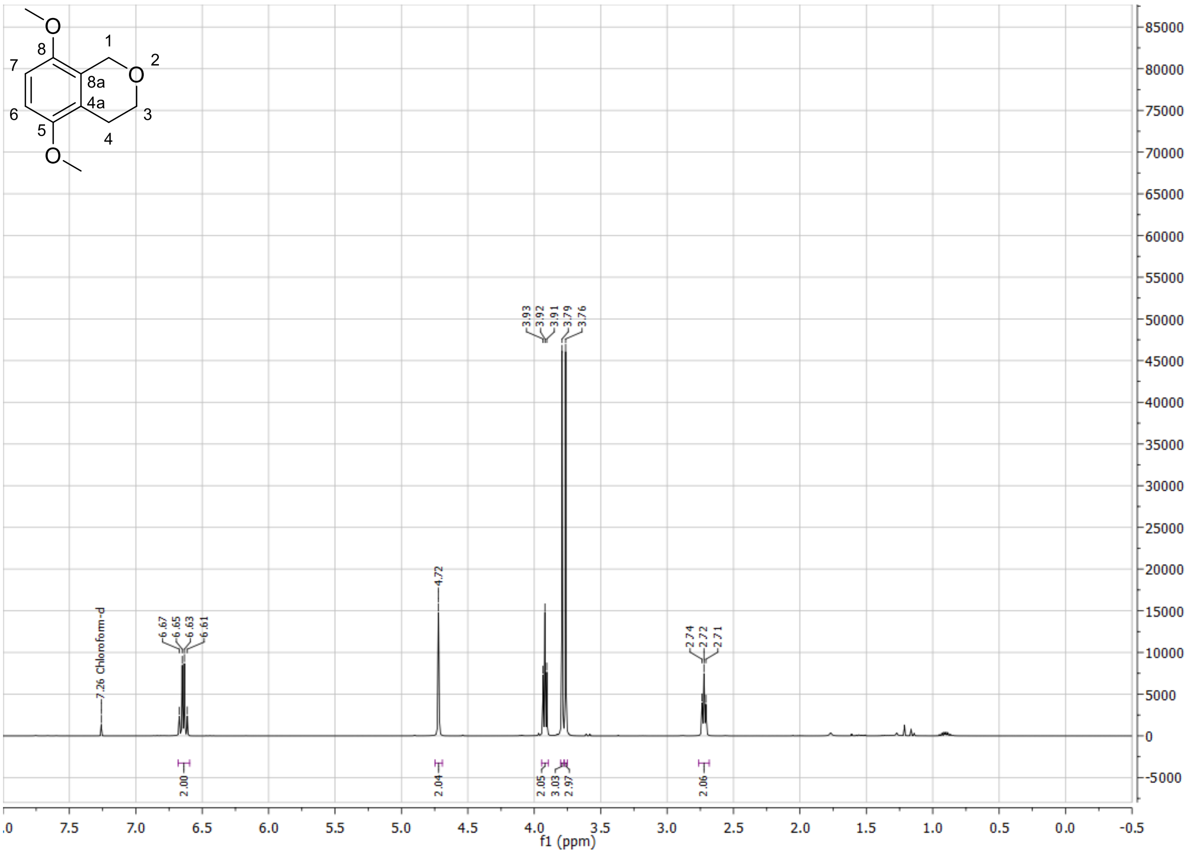


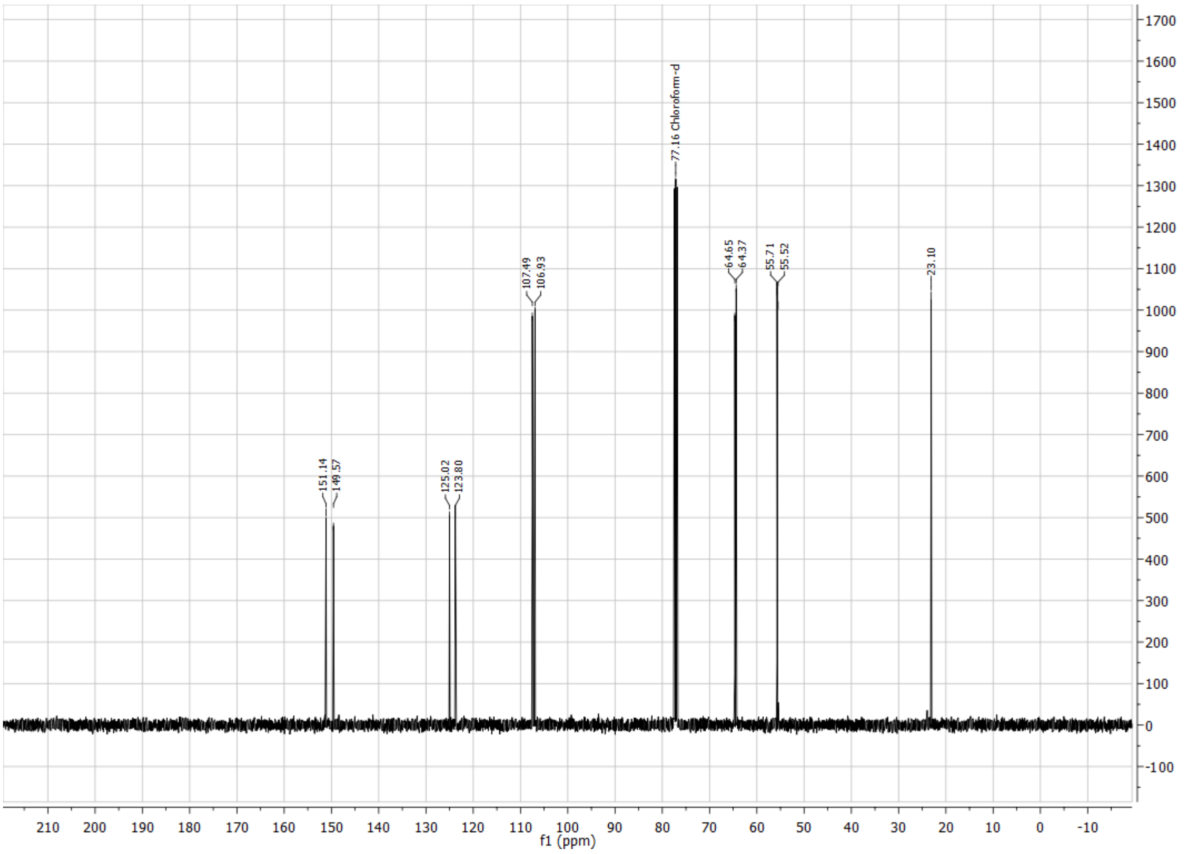
1,4-Dimethoxy-2-(2-(methoxymethoxy)ethyl)benzene **(2-36)**



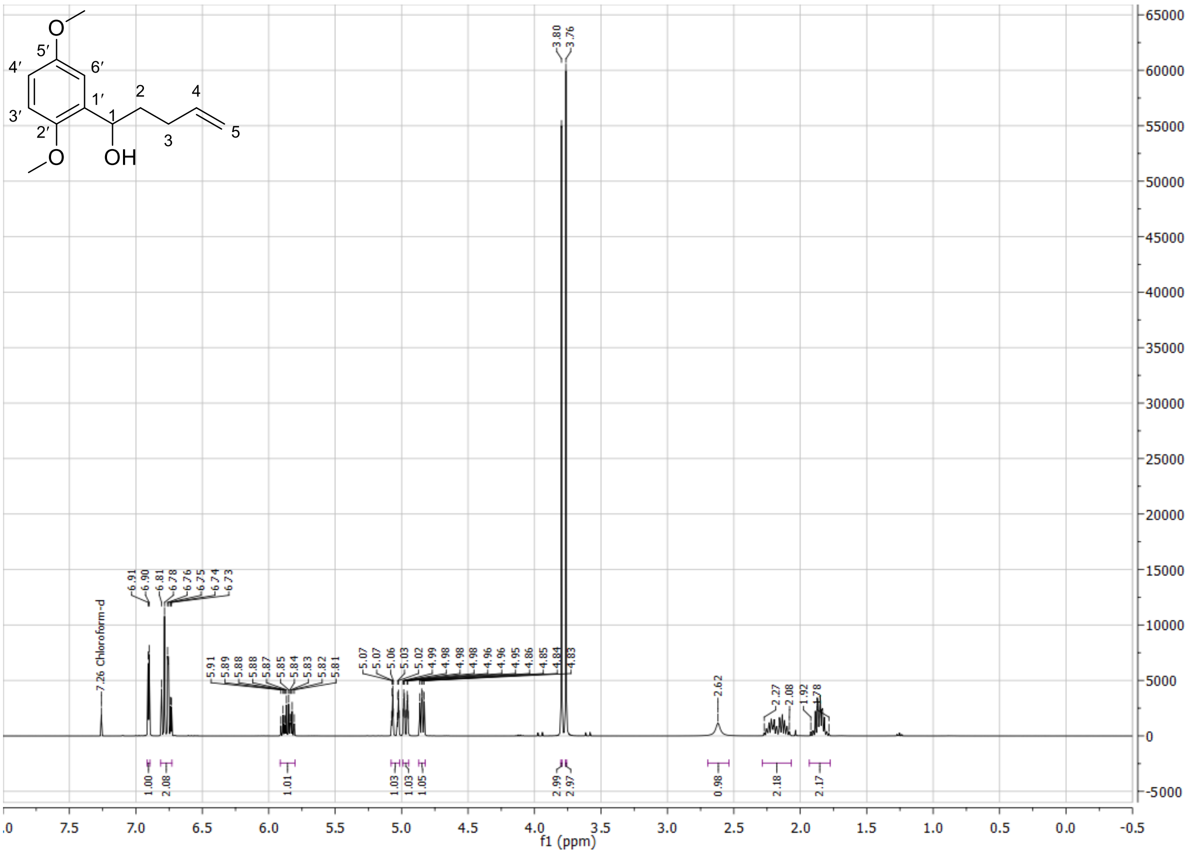


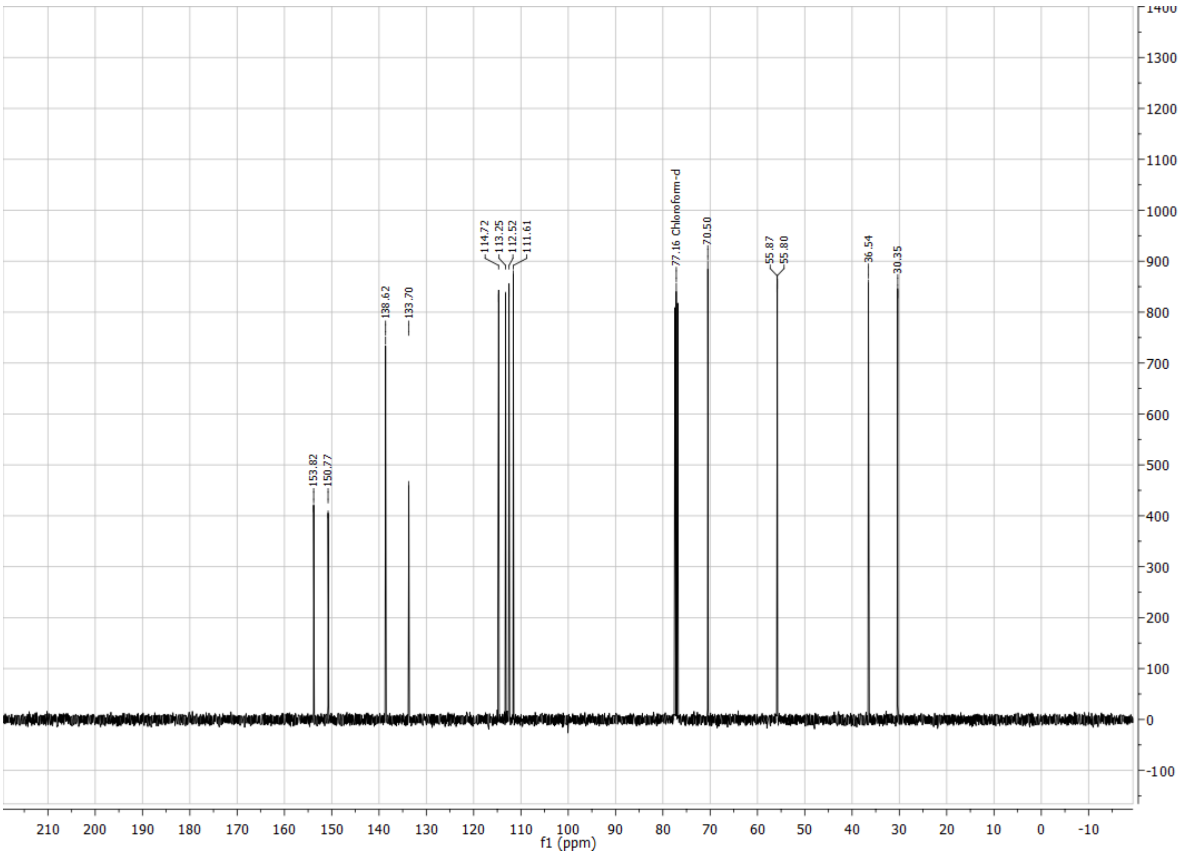
5,8-Dimethoxyisochromane **(2-37)**



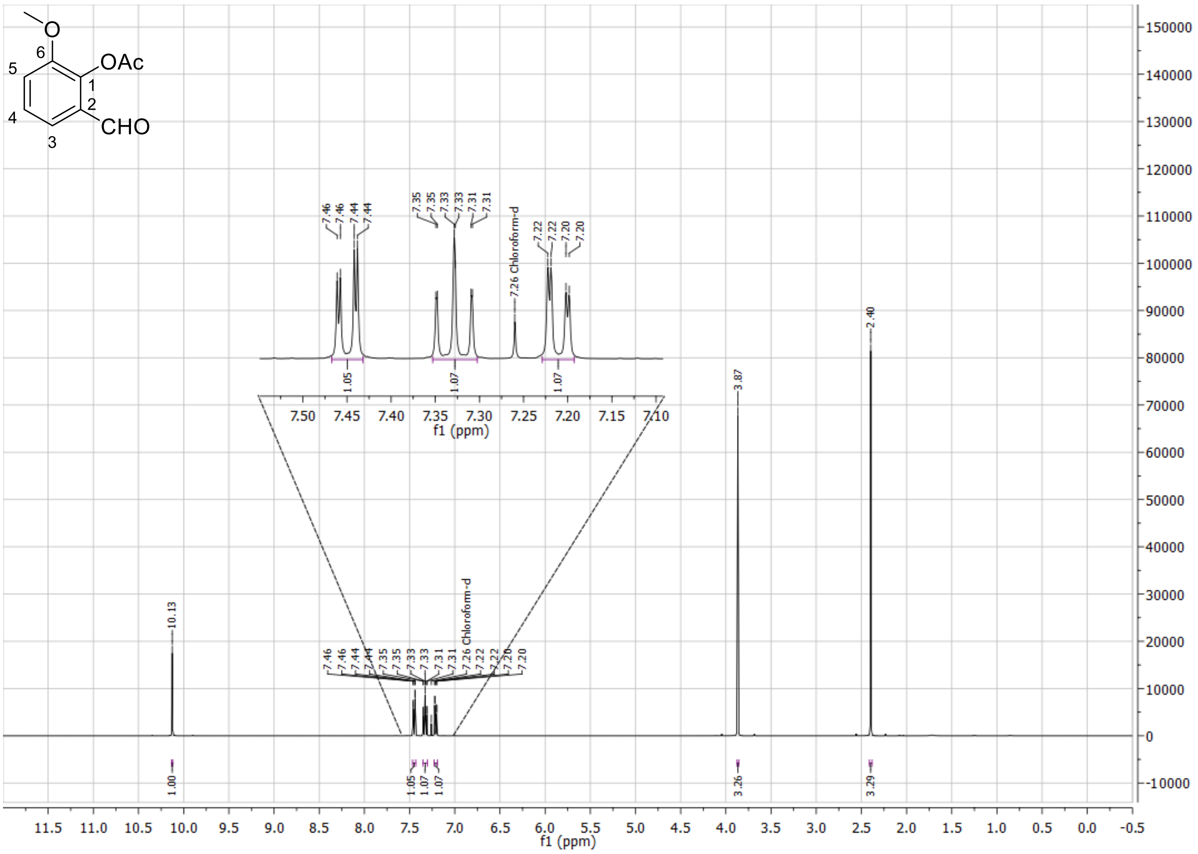


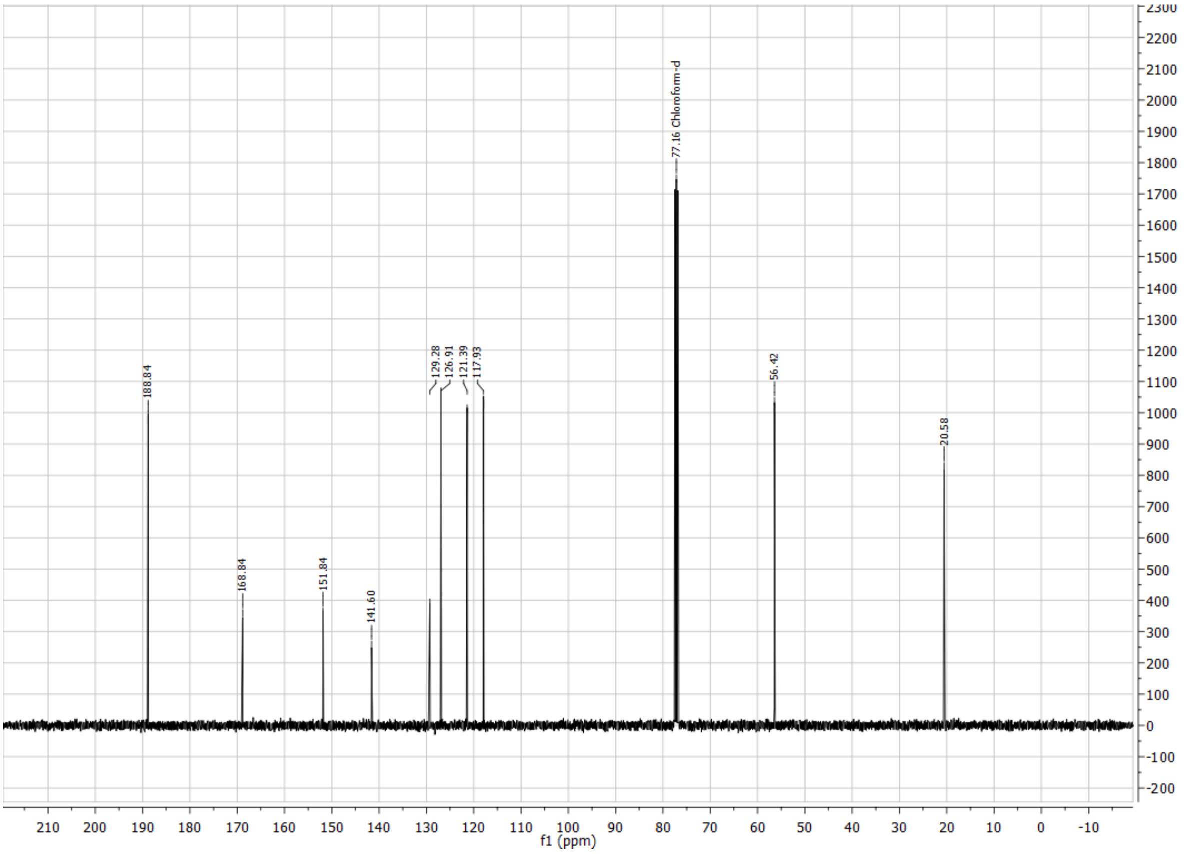
1-(2,5-Dimethoxyphenyl)pent-4-en-1-ol **(2-44)**



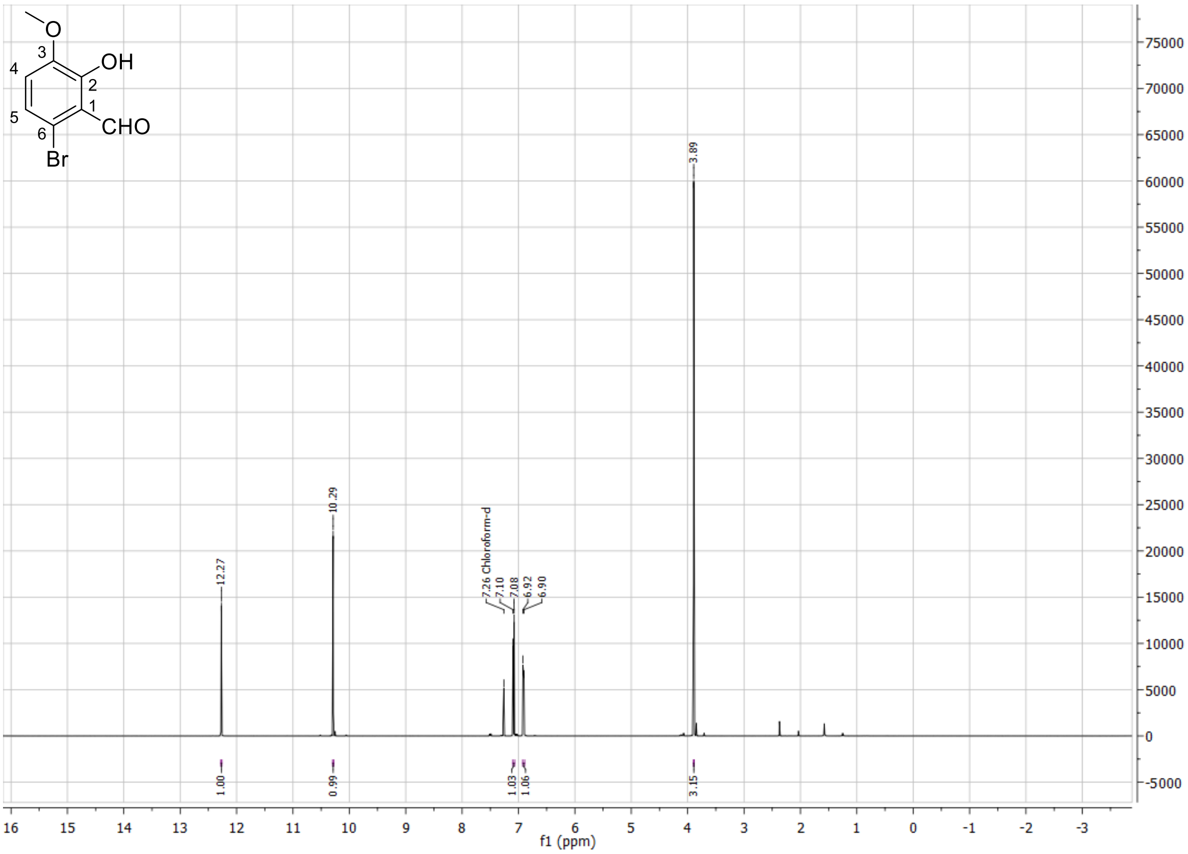


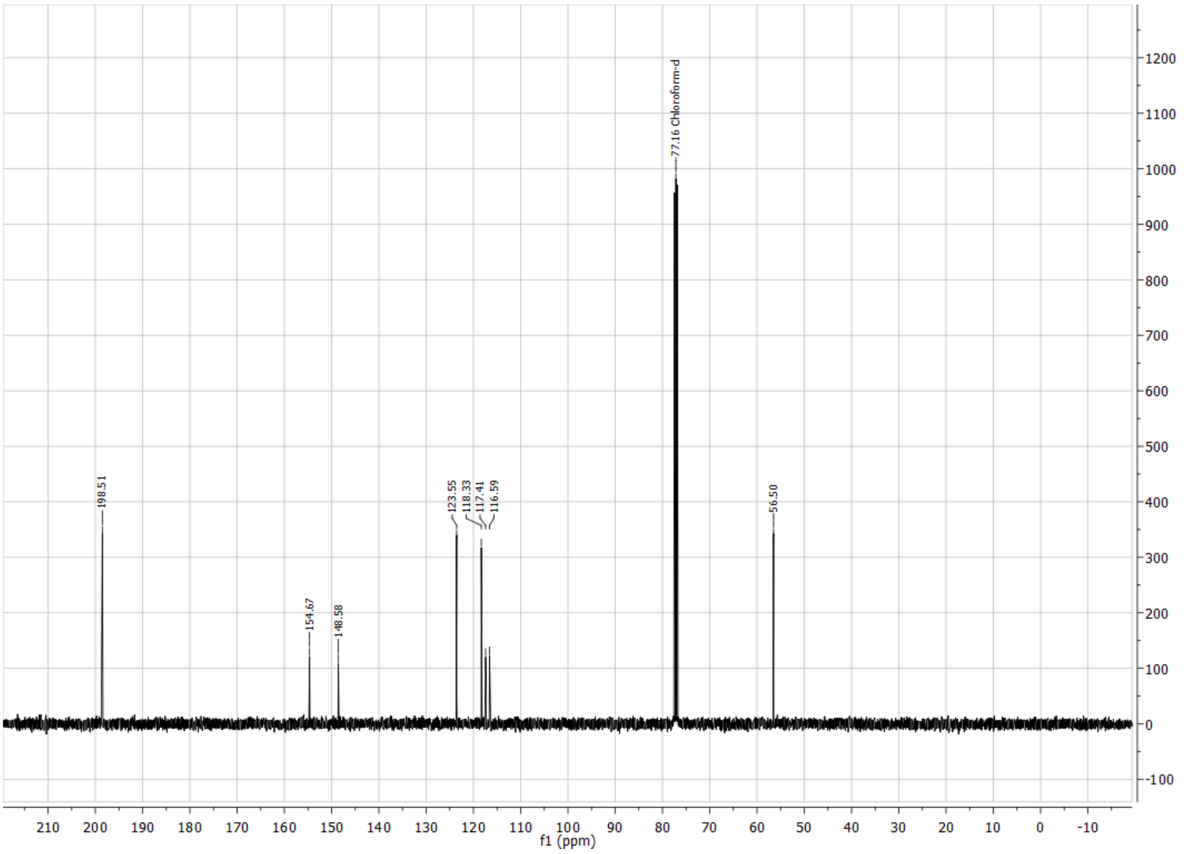
2-Formyl-6-methoxyphenyl acetate **(2-50)**



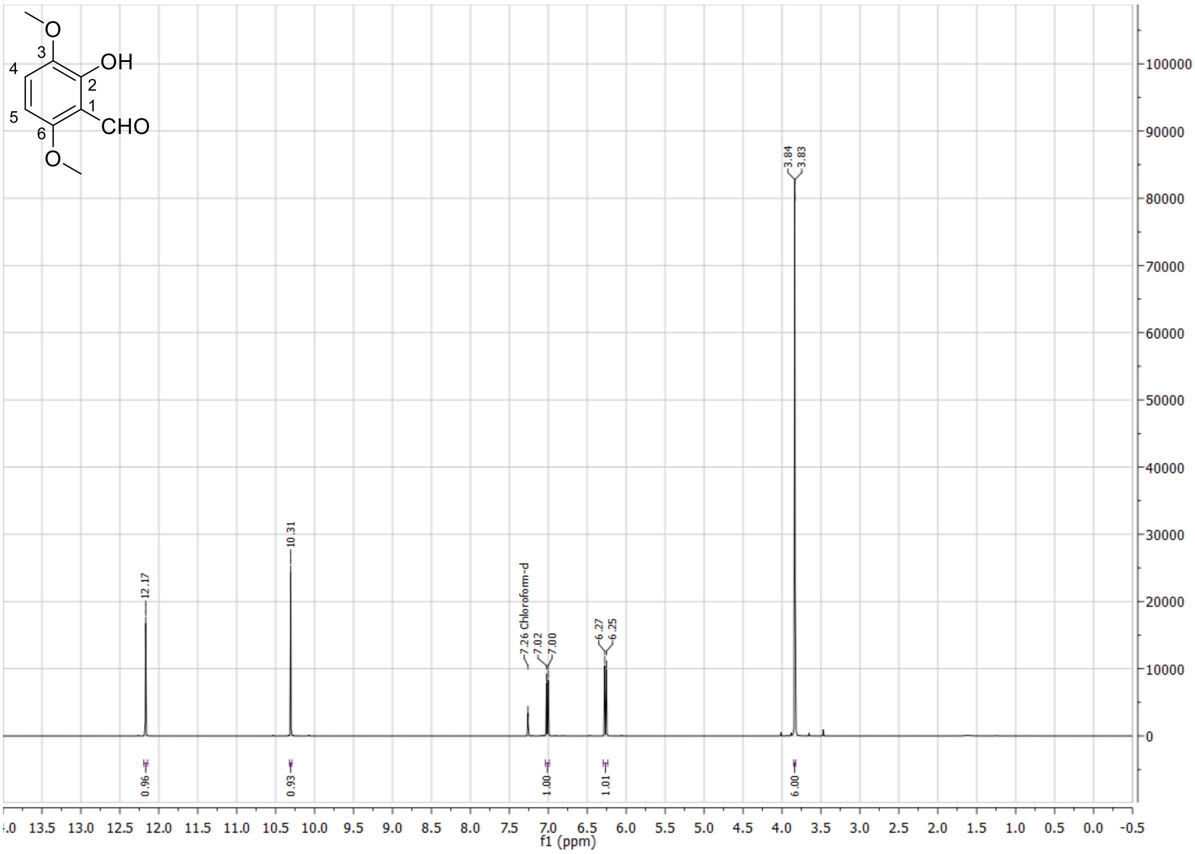


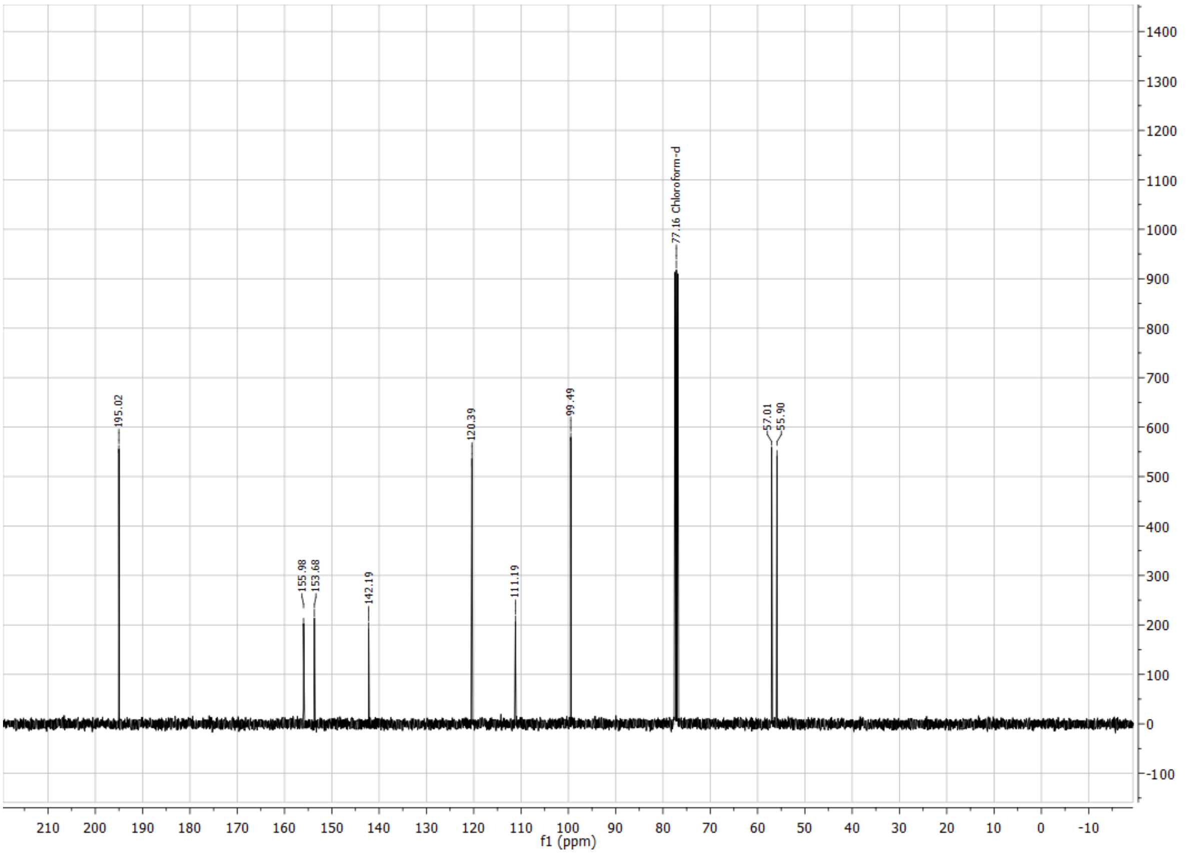
6-Bromo-2-hydroxy-3-methoxybenzaldehyde **(2-51)**



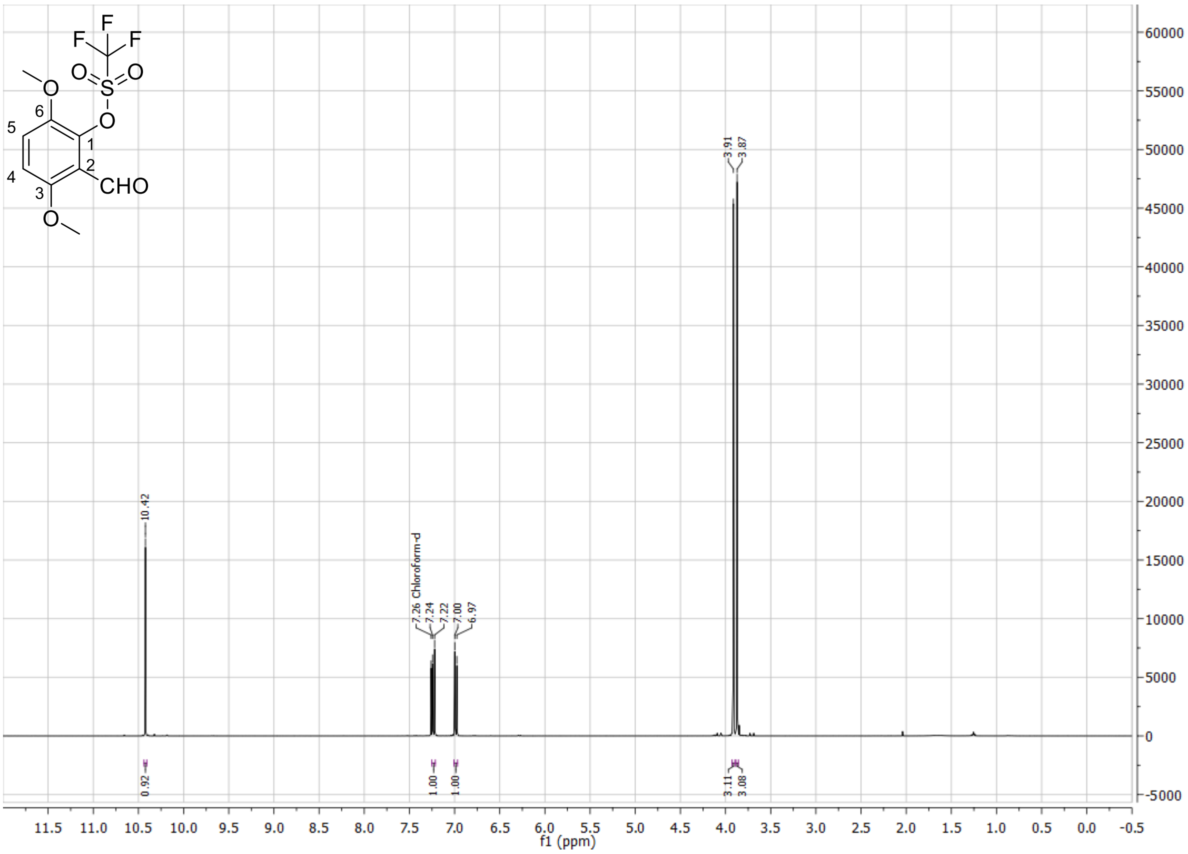


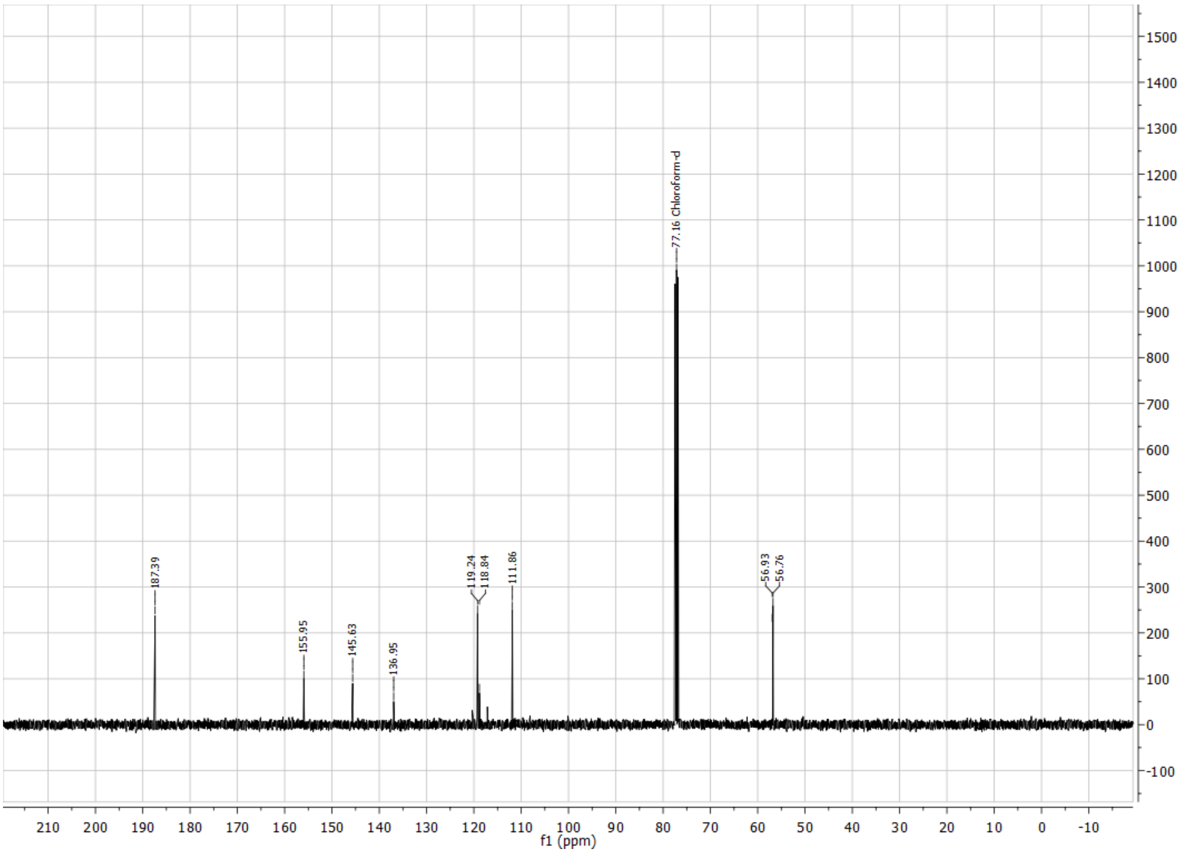
2-Hydroxy-3,6-dimethoxybenzaldehyde **(2-52)**



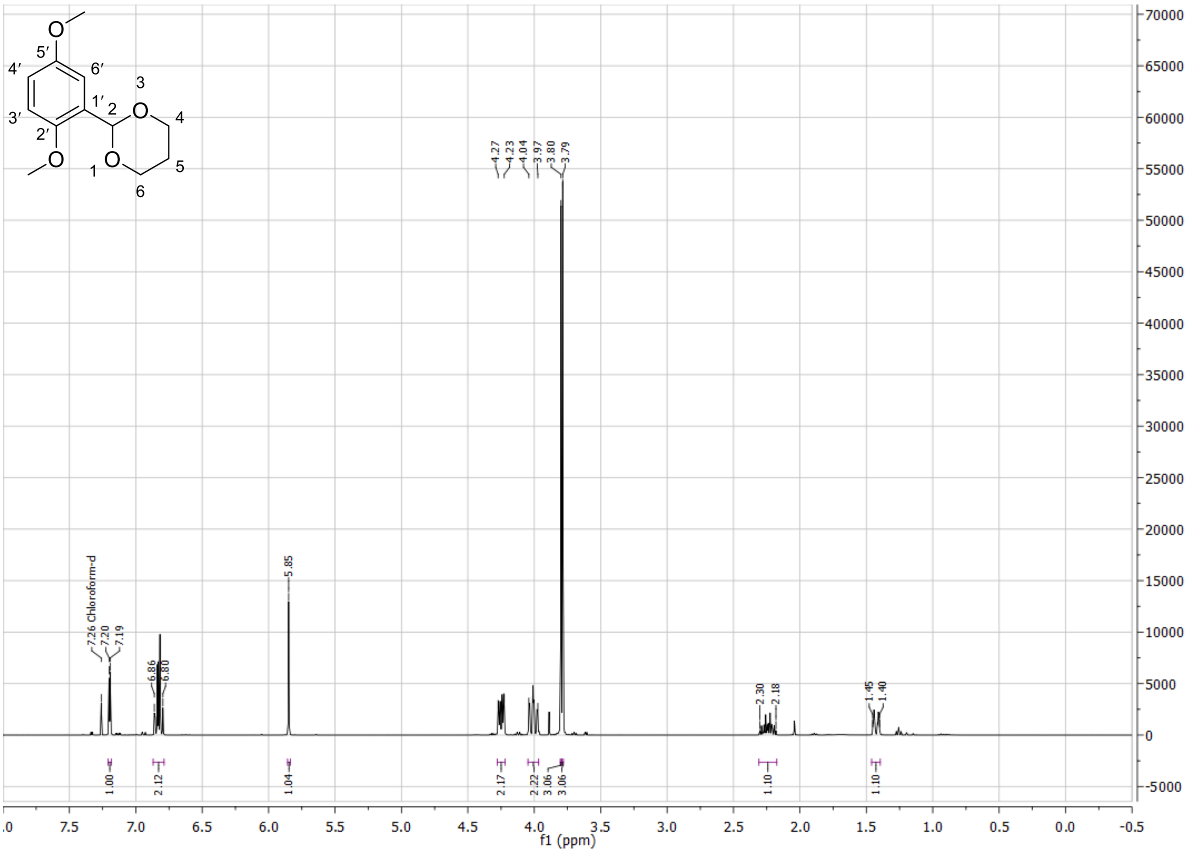


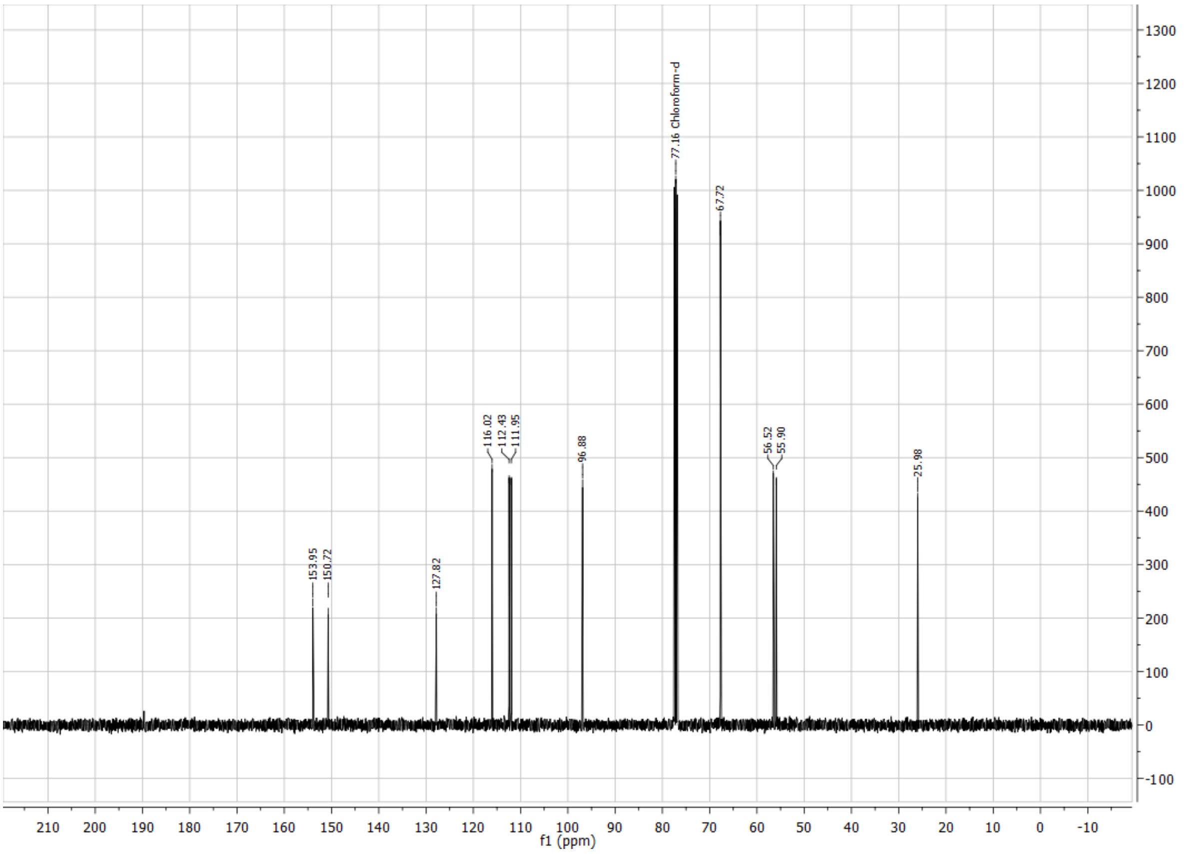
2-Formyl-3,6-dimethoxyphenyl trifluoromethanesulfonate **(2-53)**



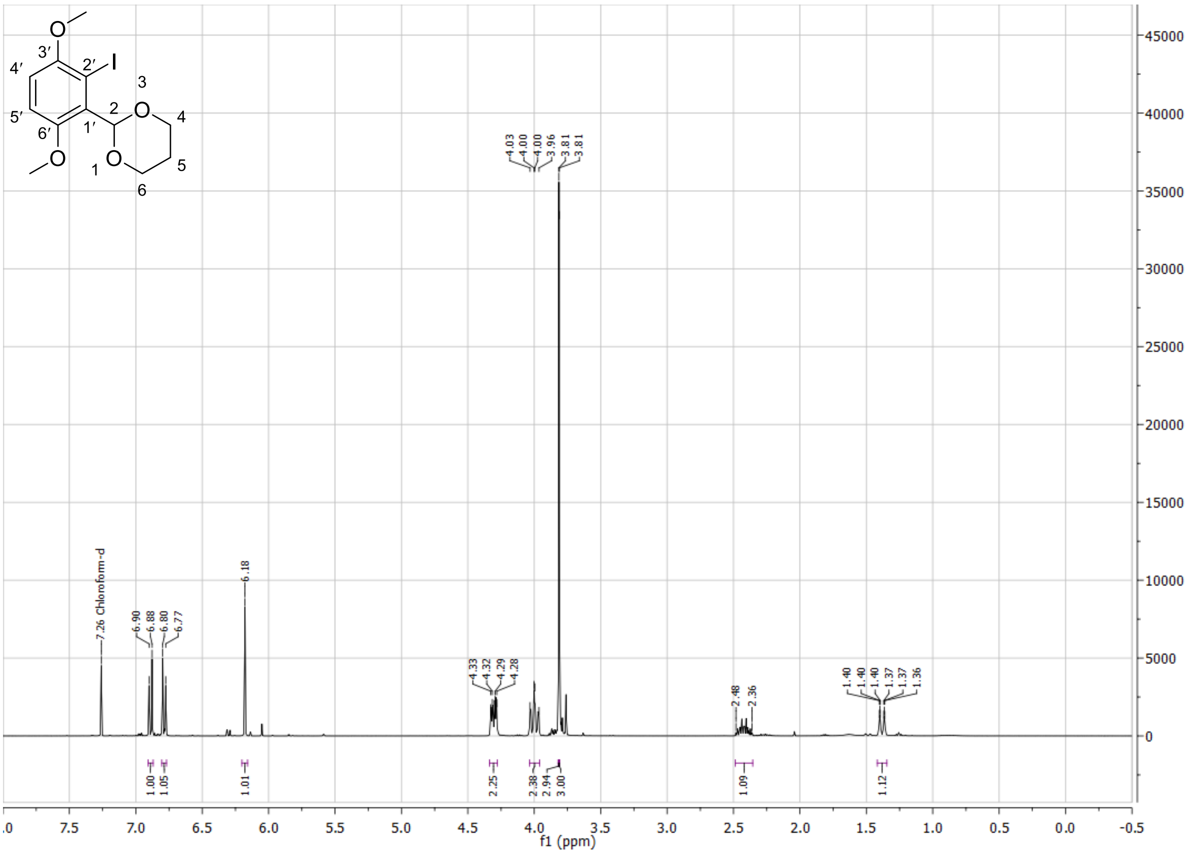


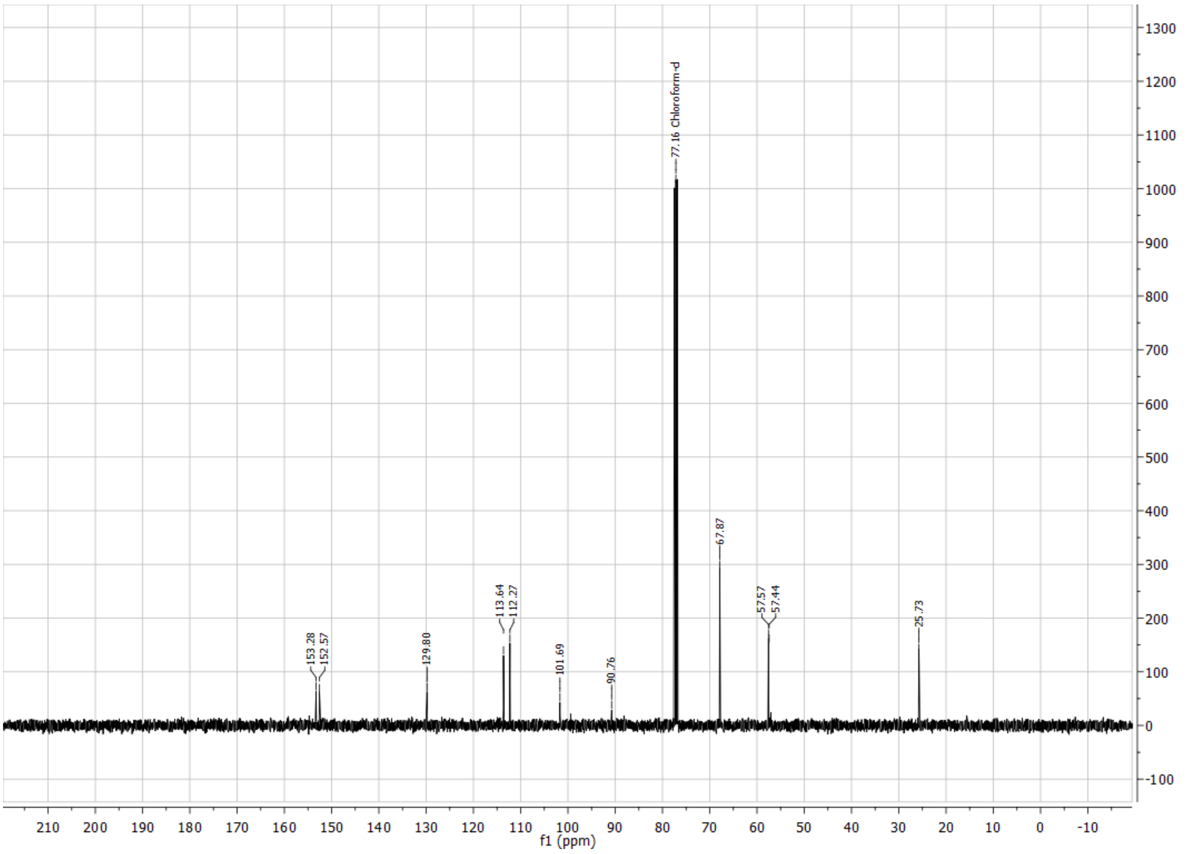
2-(2,5-Dimethoxyphenyl)-1,3-dioxane **(2-54)**



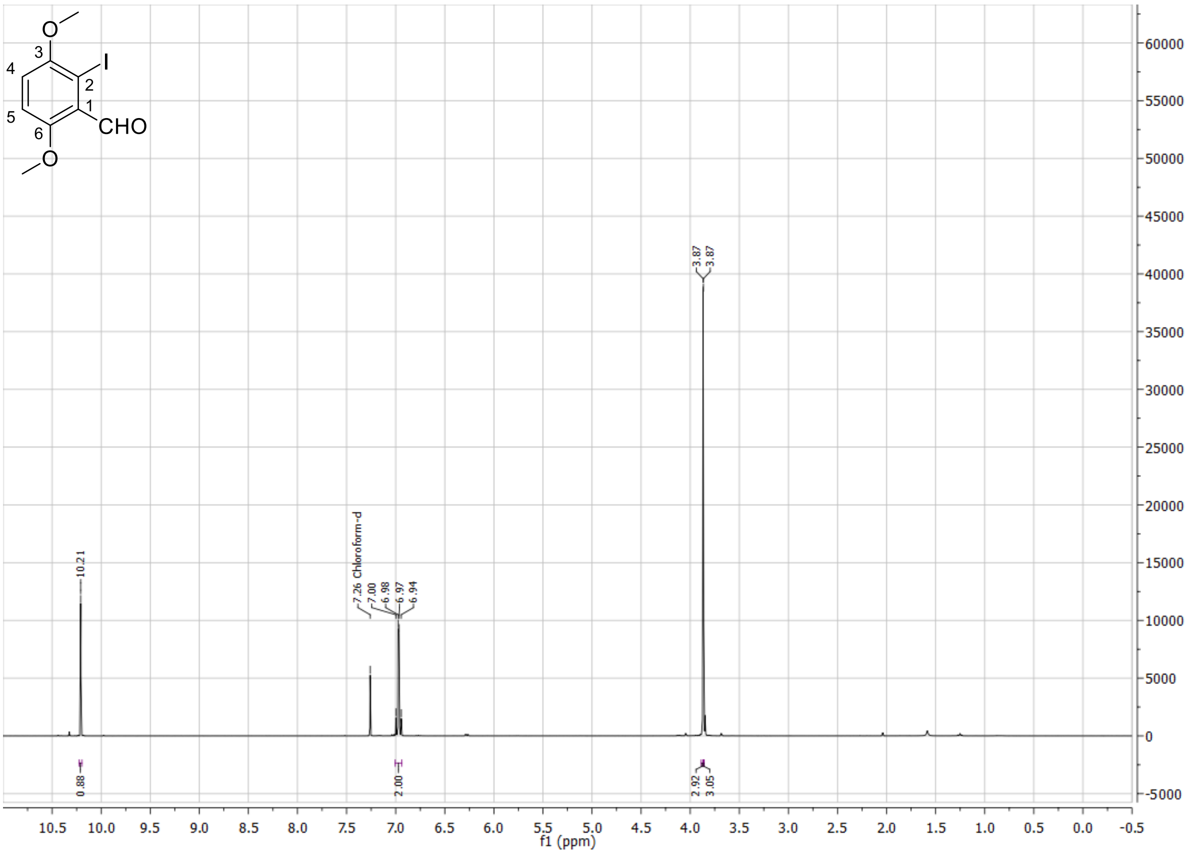


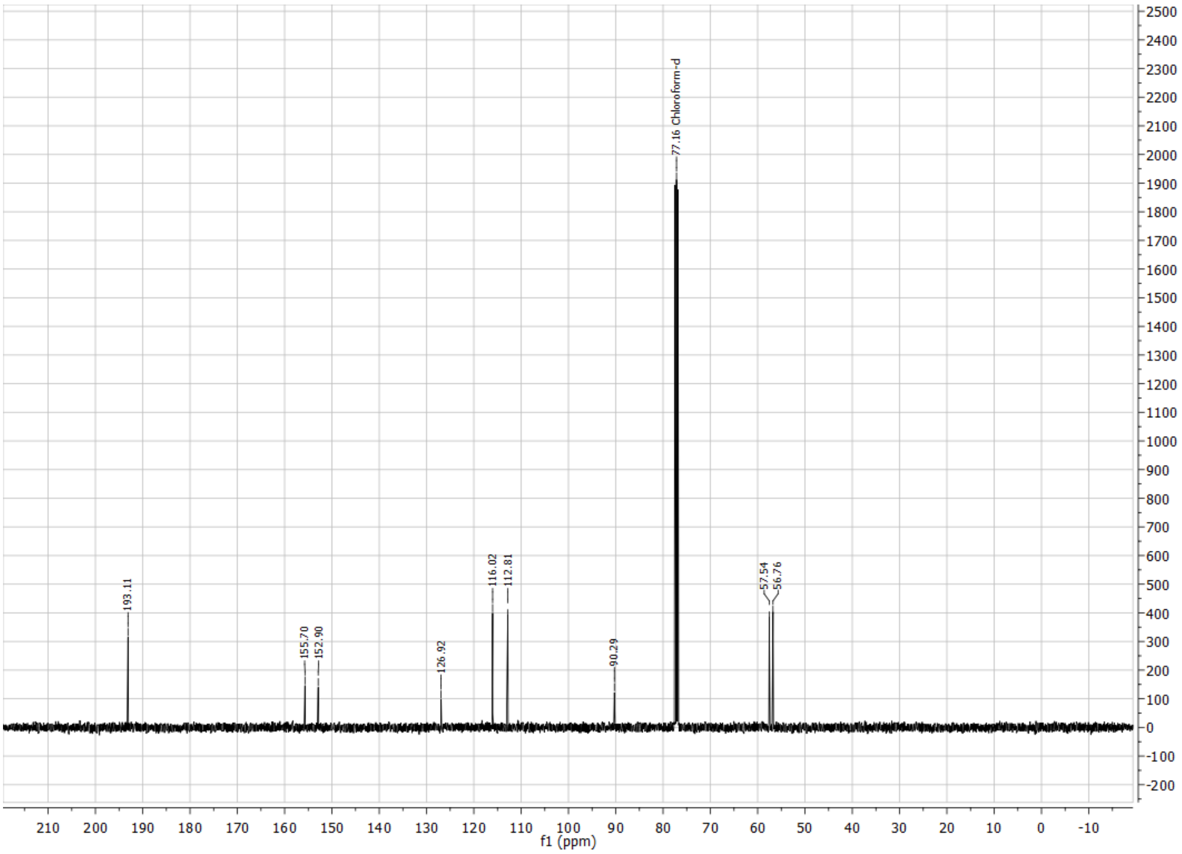
2-(2-Iodo-3,6-dimethoxyphenyl)-1,3-dioxane **(2-55)**



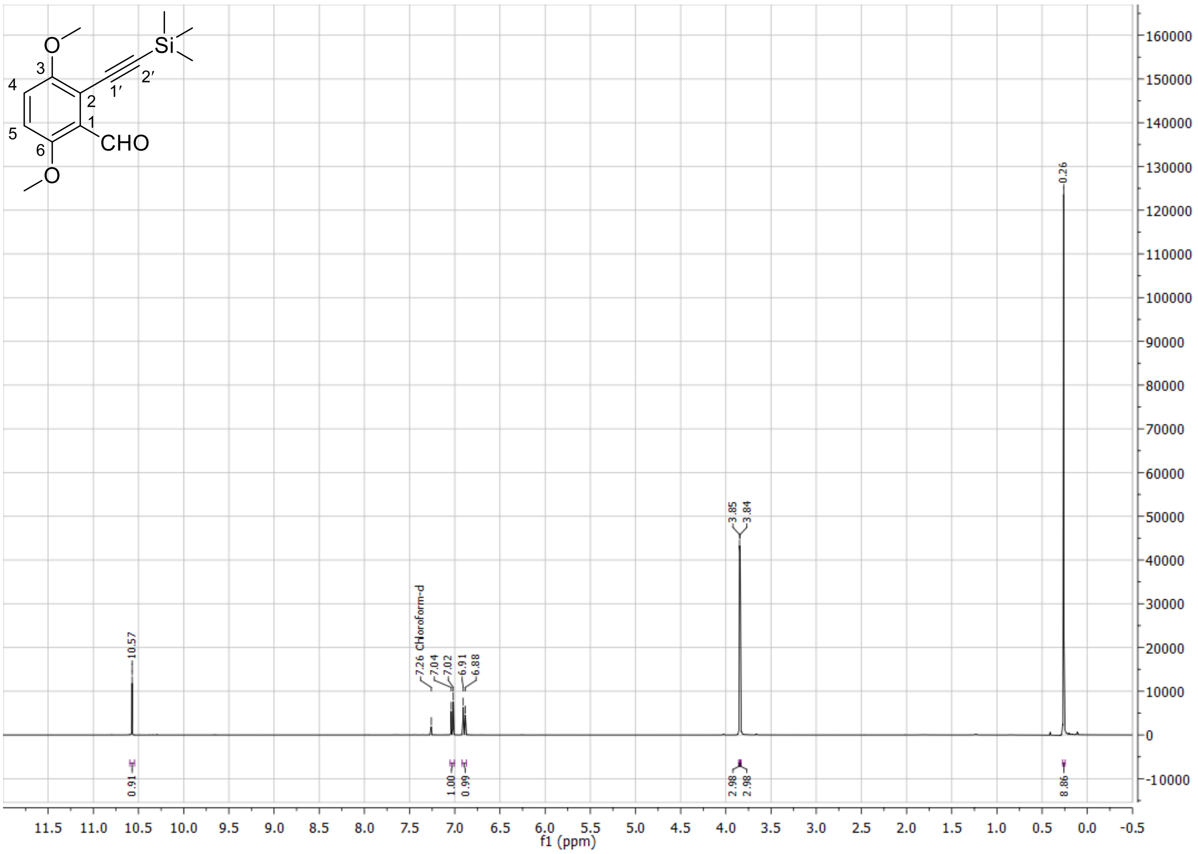


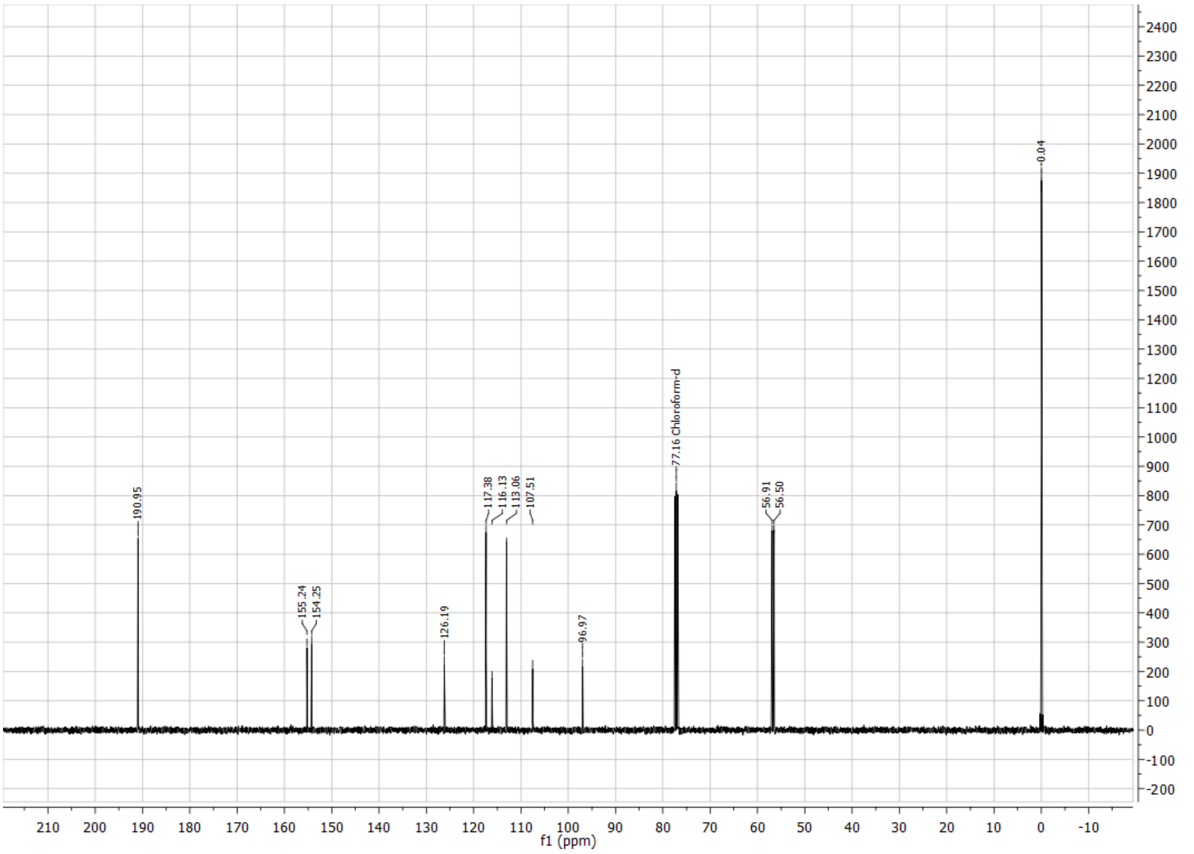
2-Iodo-3,6-dimethoxybenzaldehyde **(2-56)**



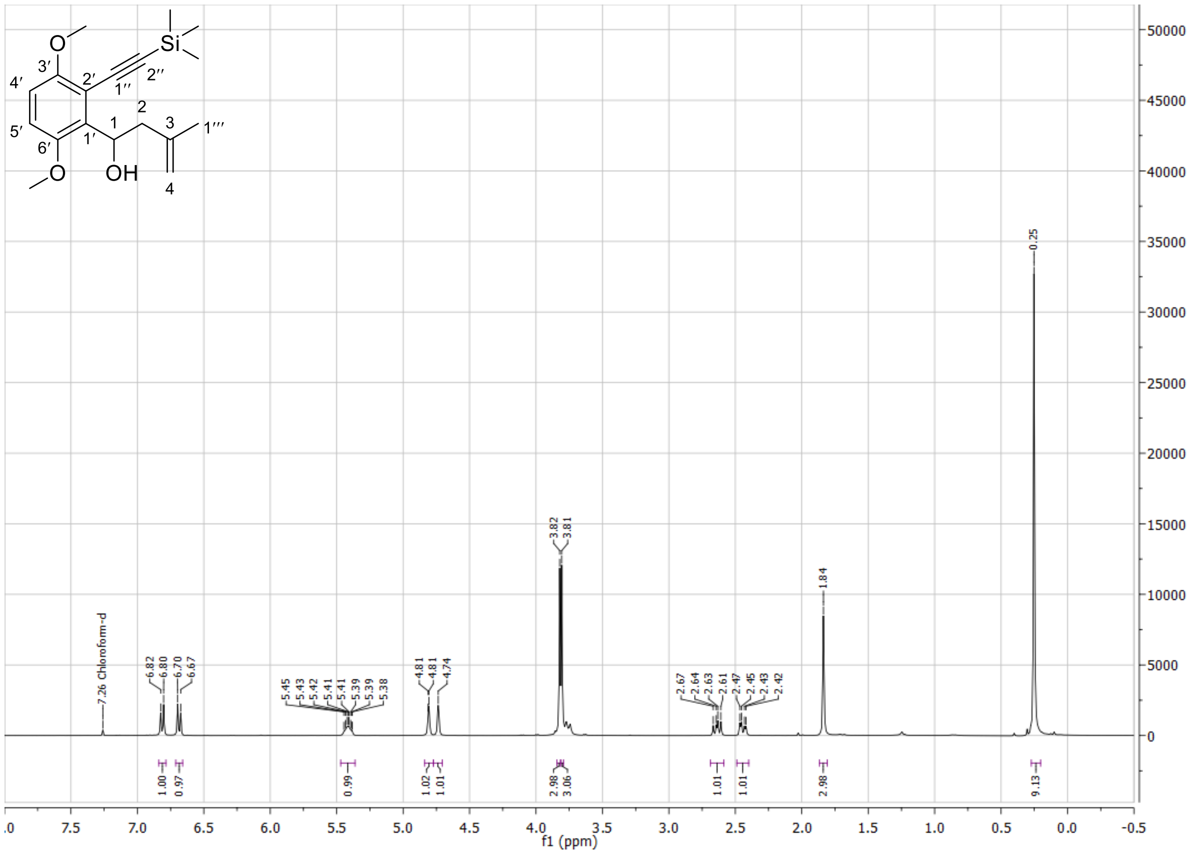


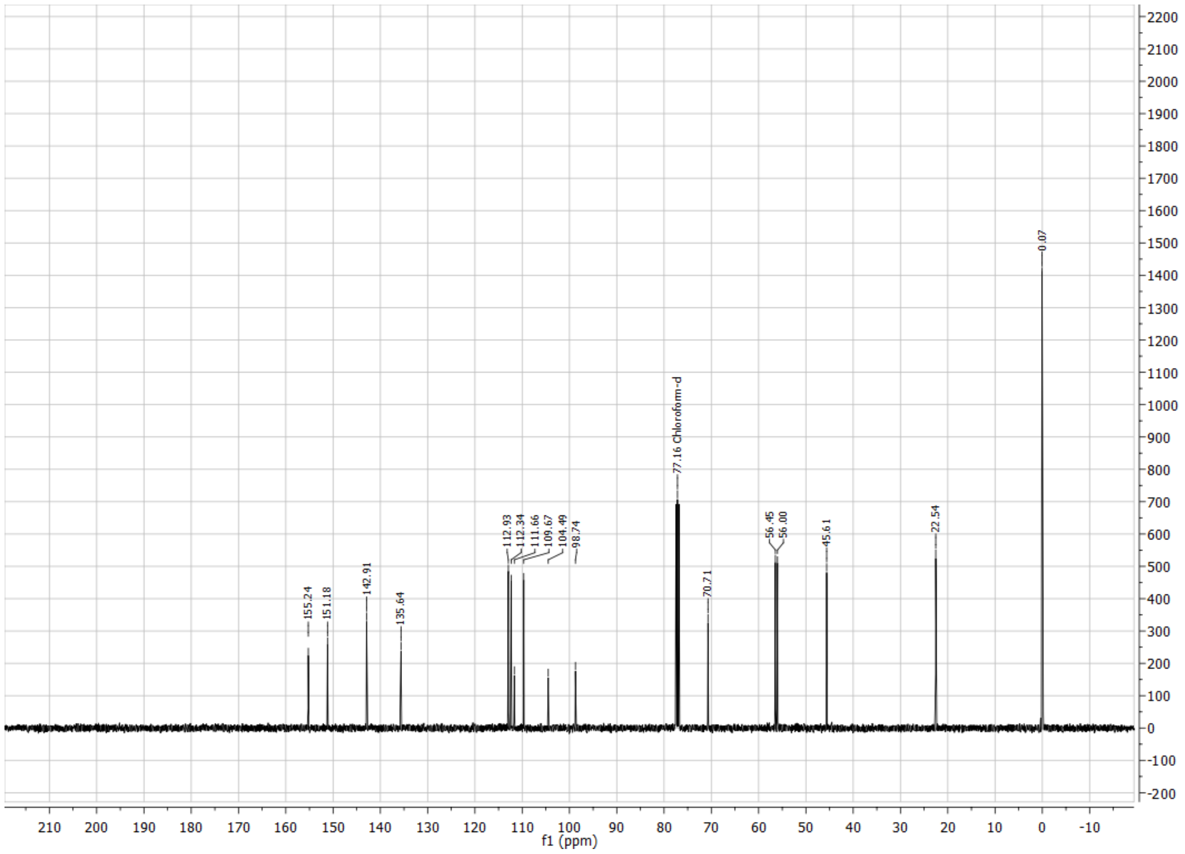
3,6-Dimethoxy-2-((trimethylsilyl)ethynyl)benzaldehyde **(2-57)**



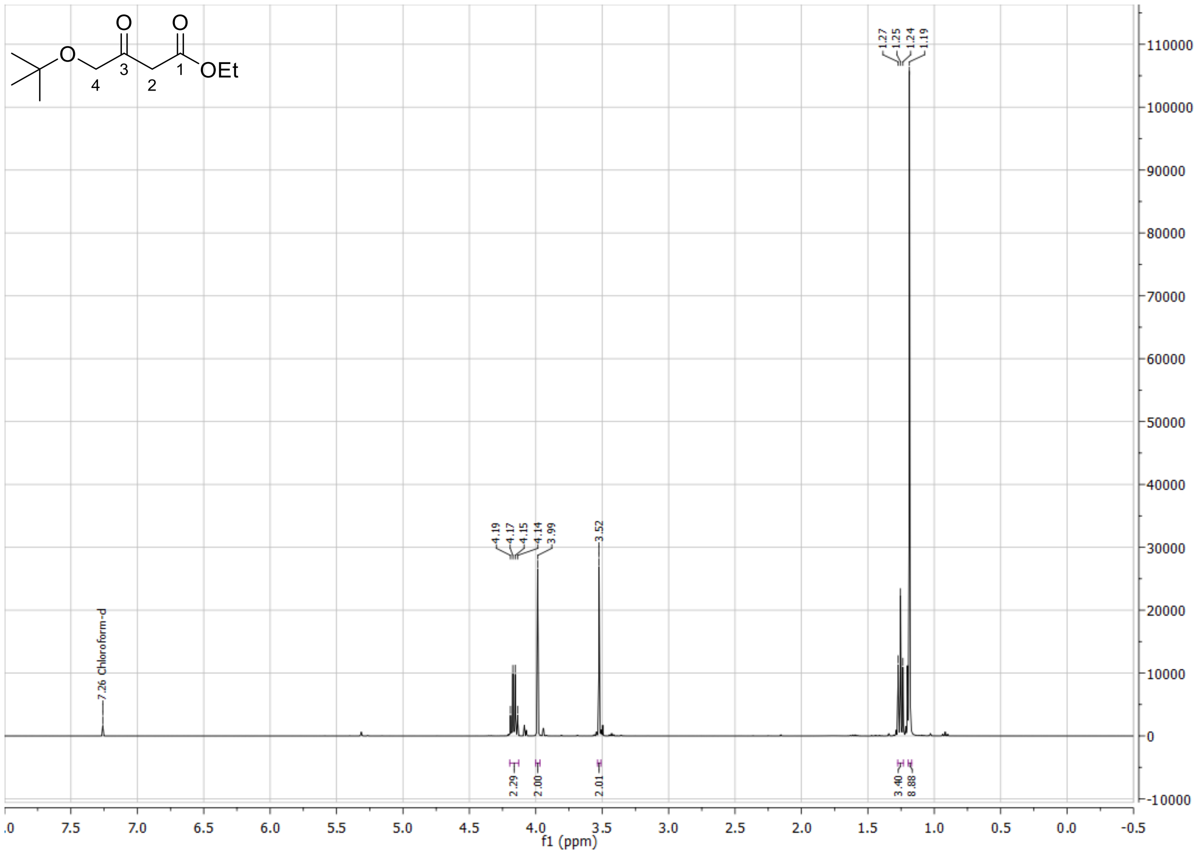


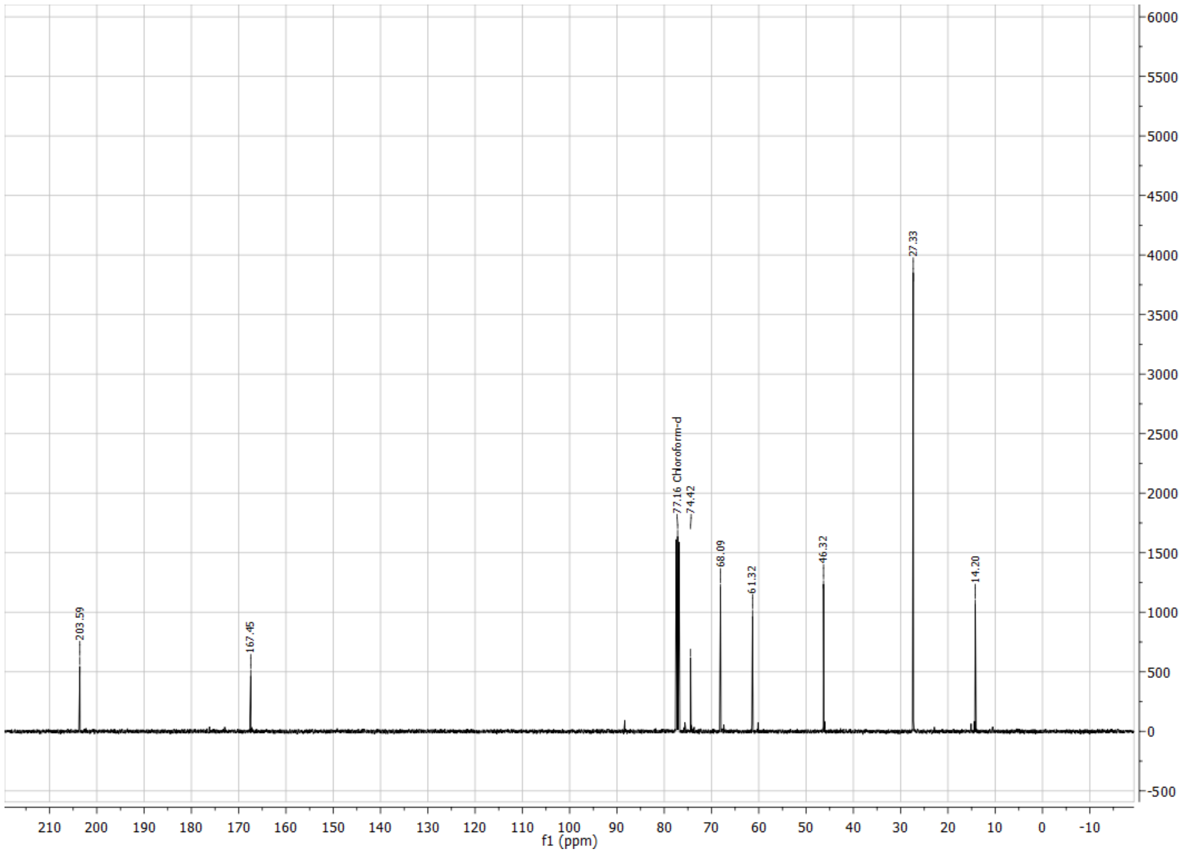
1-(3,6-Dimethoxy-2-((trimethylsilyl)ethynyl)phenyl)-3-methylbut-3-en-1-ol **(2-58)**



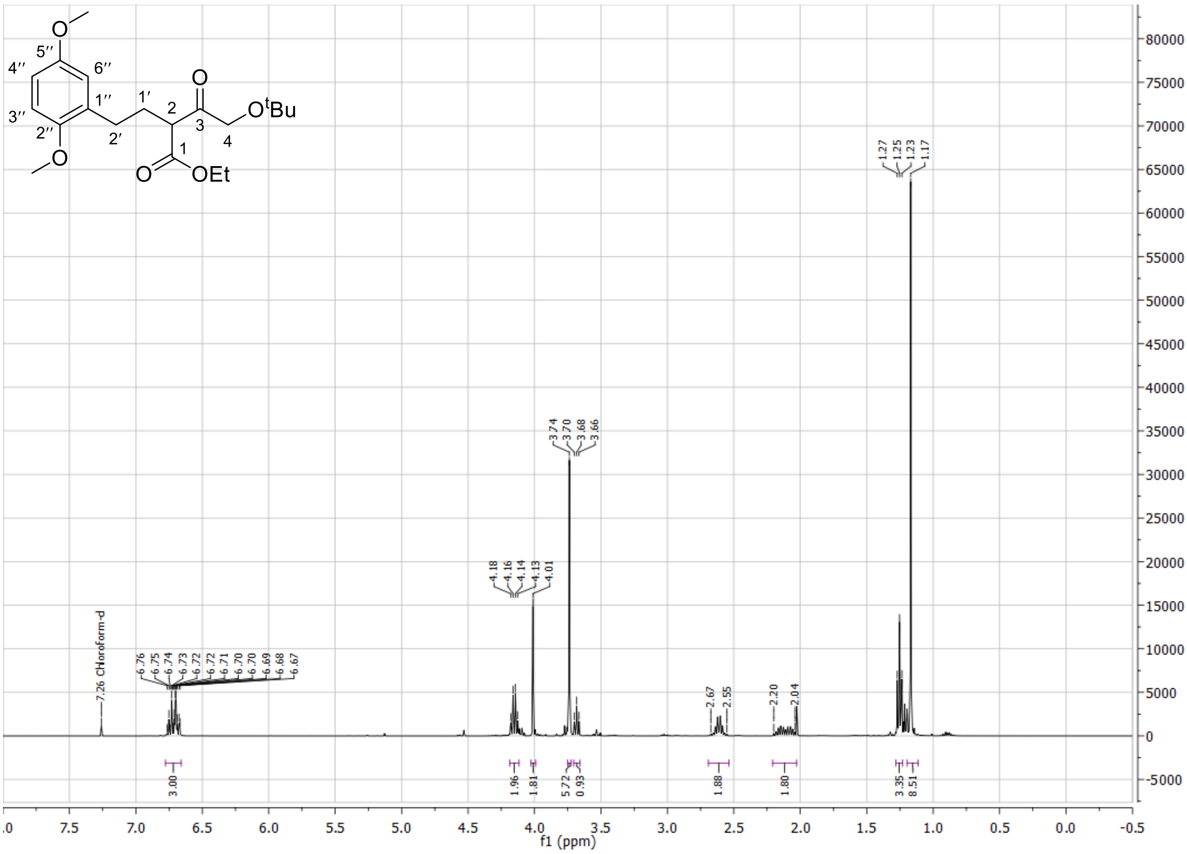


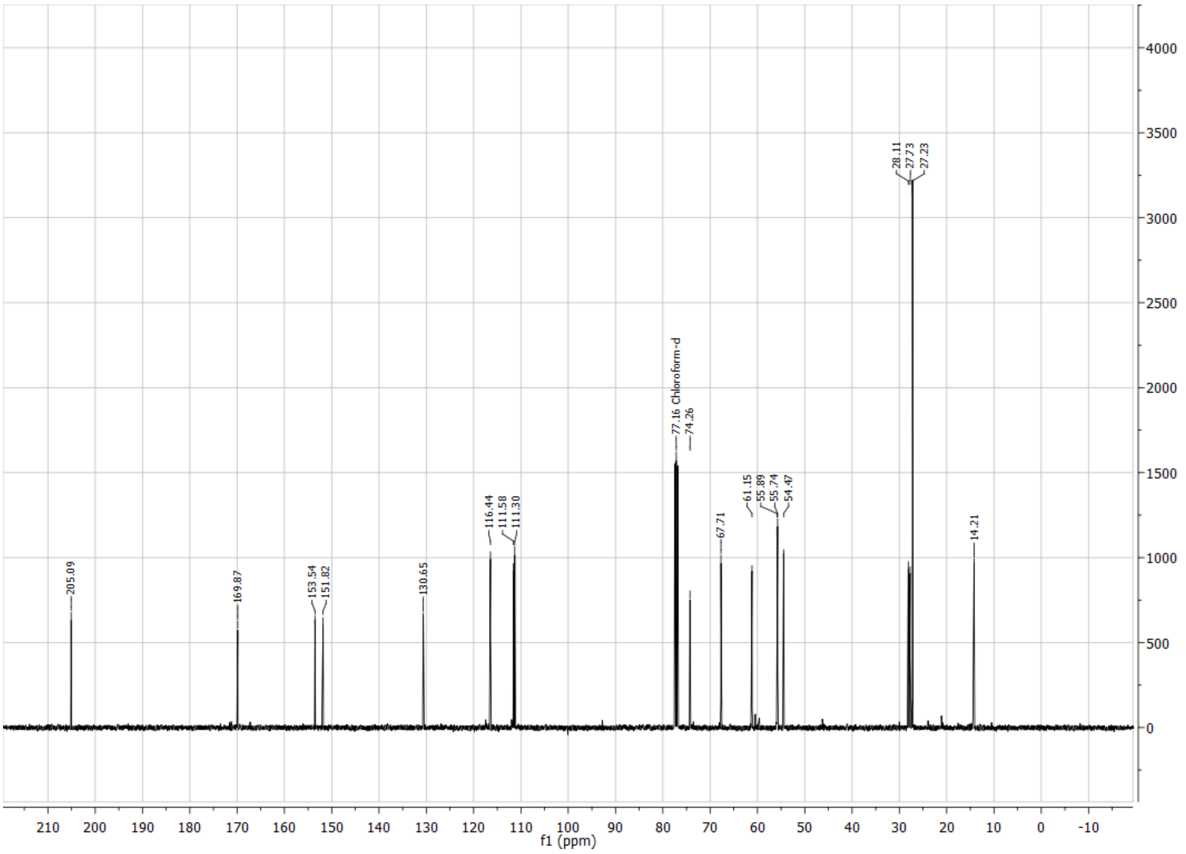
Ethyl 4-(*tert*-butoxy)-3-oxobutanoate **(2-62)**



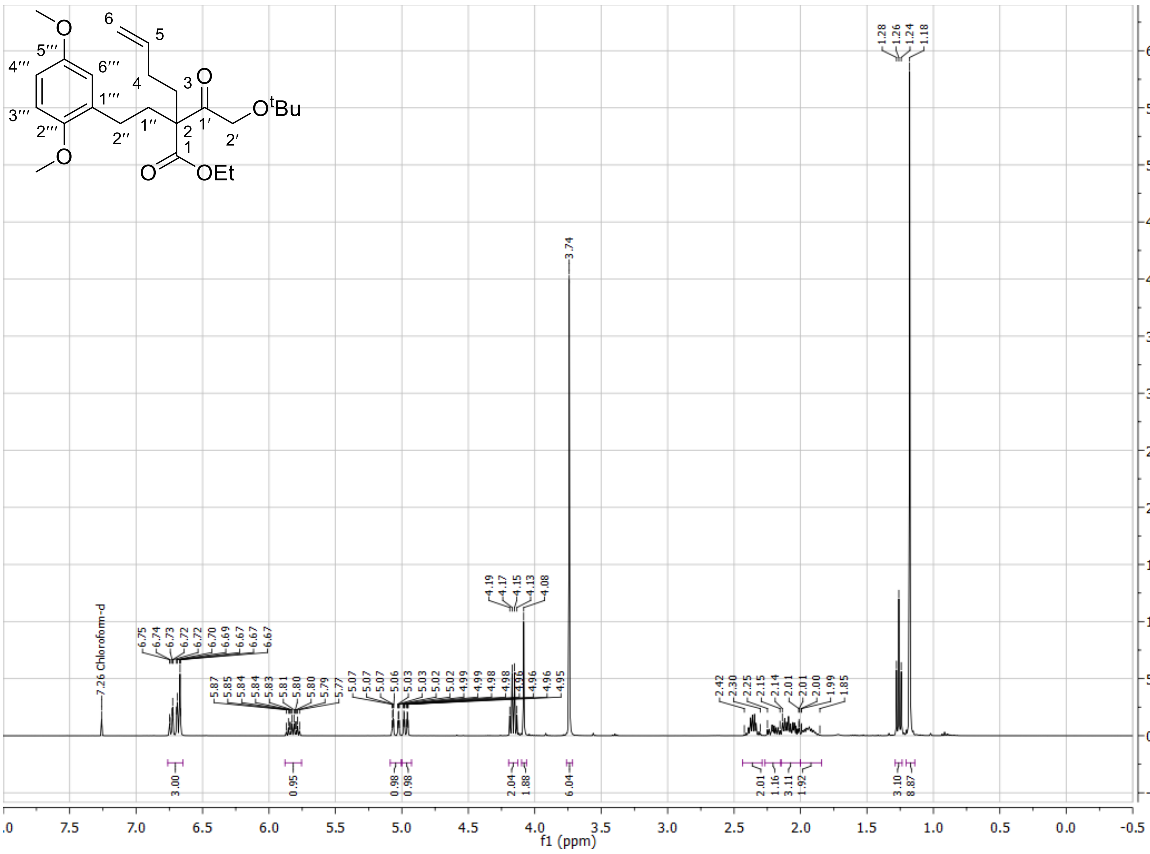


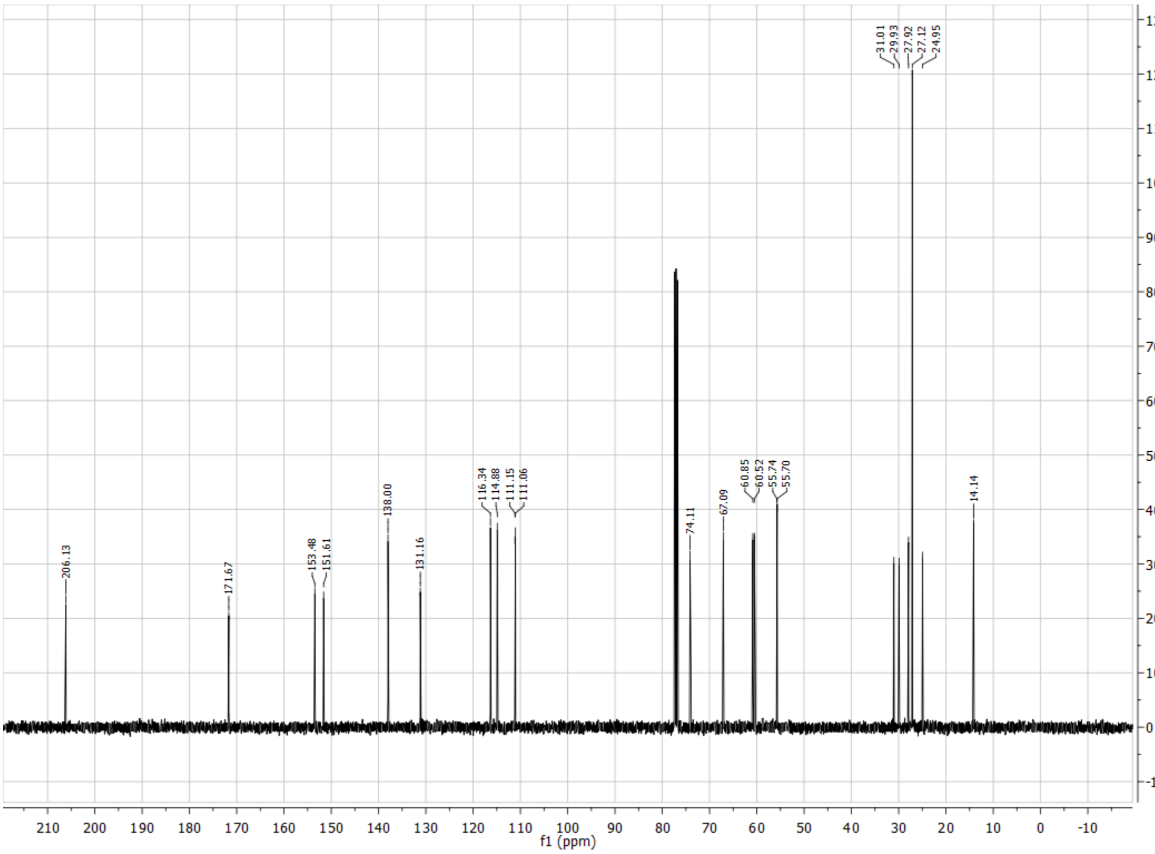
Ethyl 4-(*tert*-butoxy)-2-(2,5-dimethoxyphenethyl)-3-oxobutanoate **(2-63)**



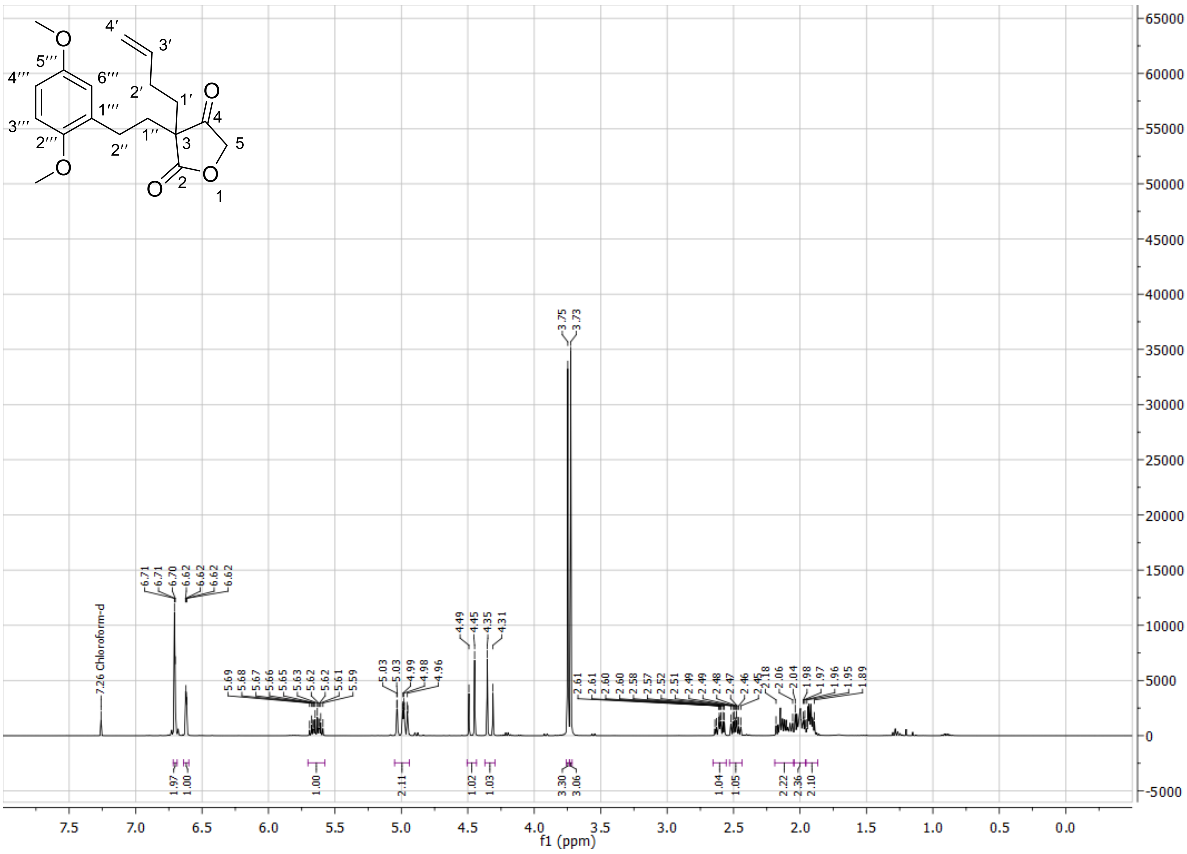


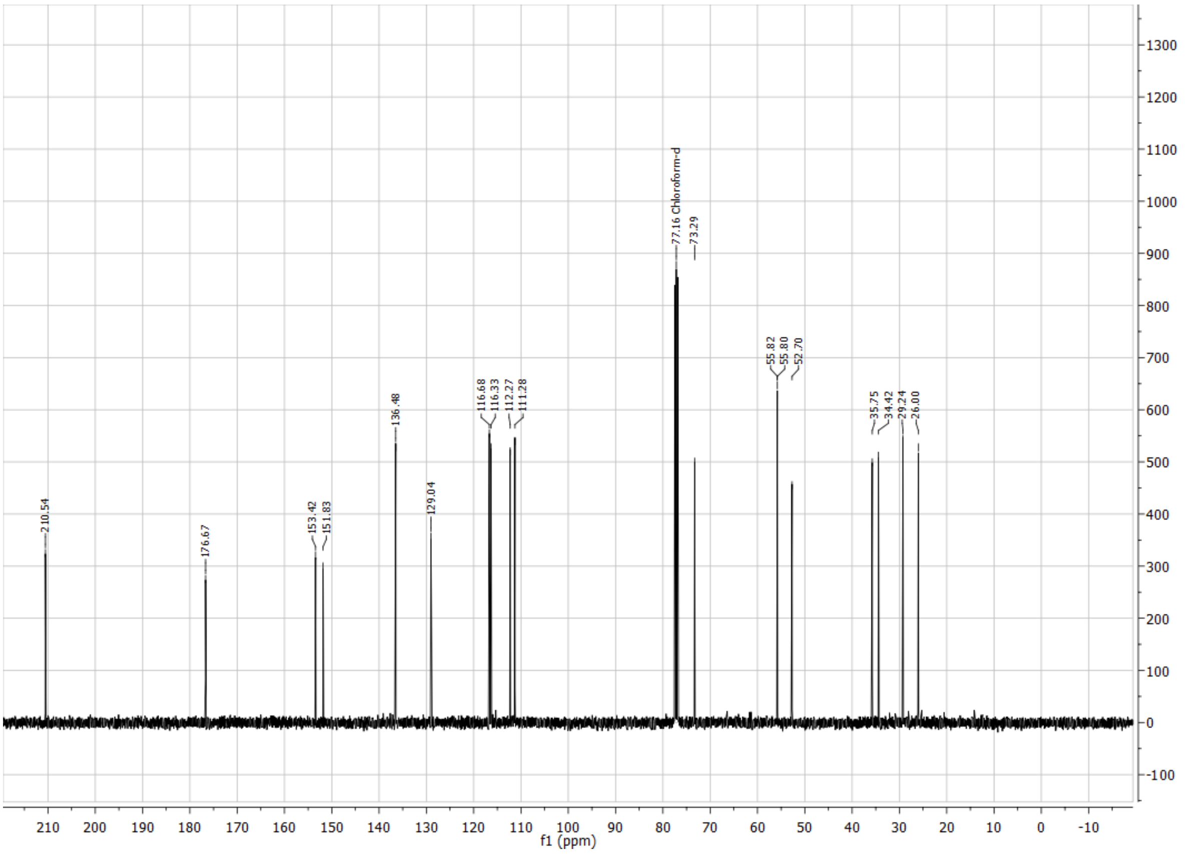
Ethyl 2-(2-(*tert*-butoxy)acetyl)-2-(2,5-dimethoxyphenethyl)hex-5-enoate **(2-64)**



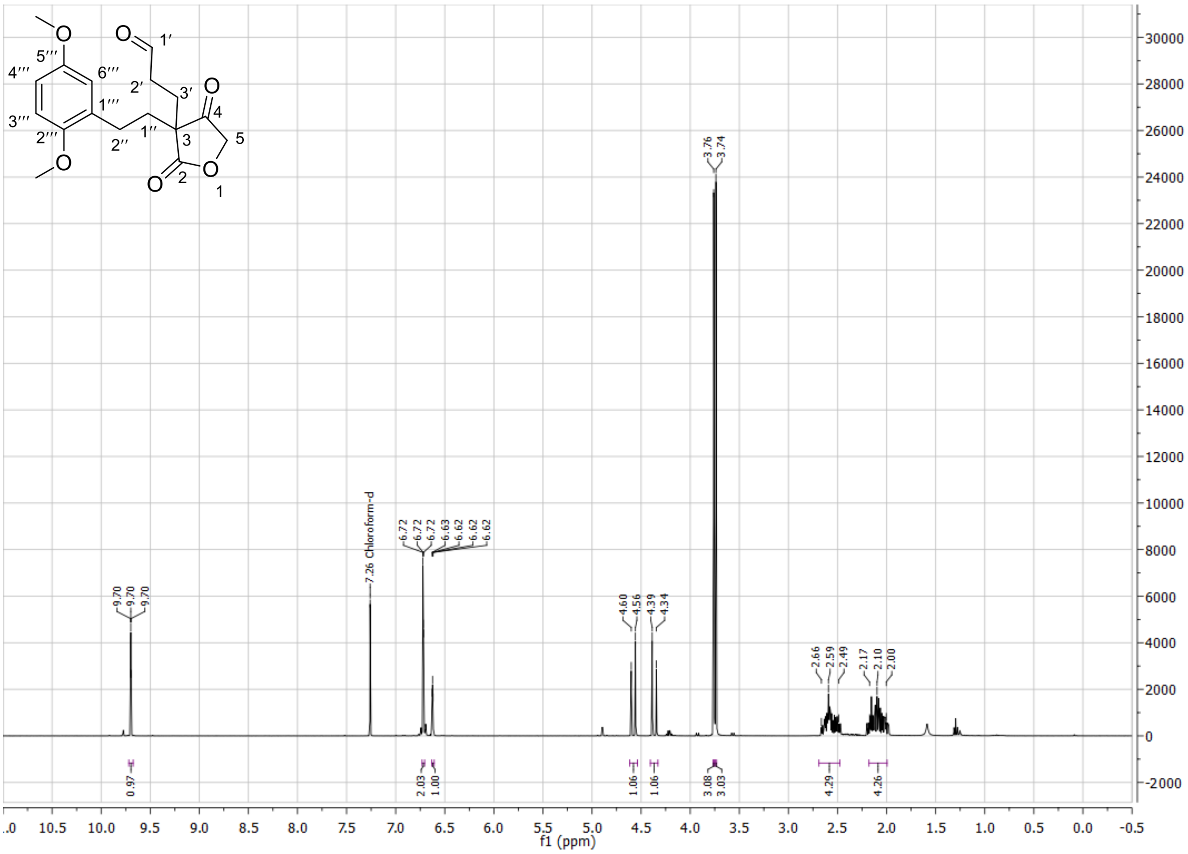


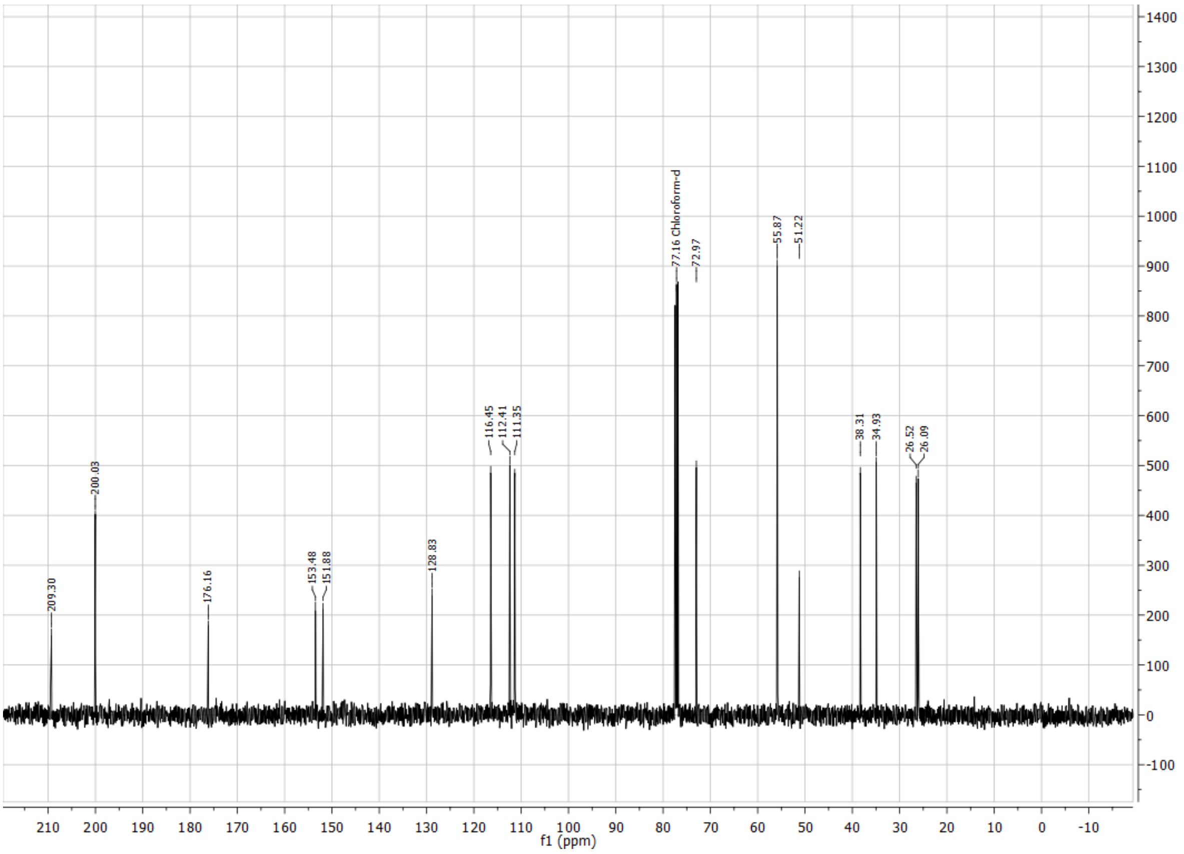
3-(But-3-en-1-yl)-3-(2,5-dimethoxyphenethyl)furan-2,4(3*H*,5*H*)-dione **(2-94)**



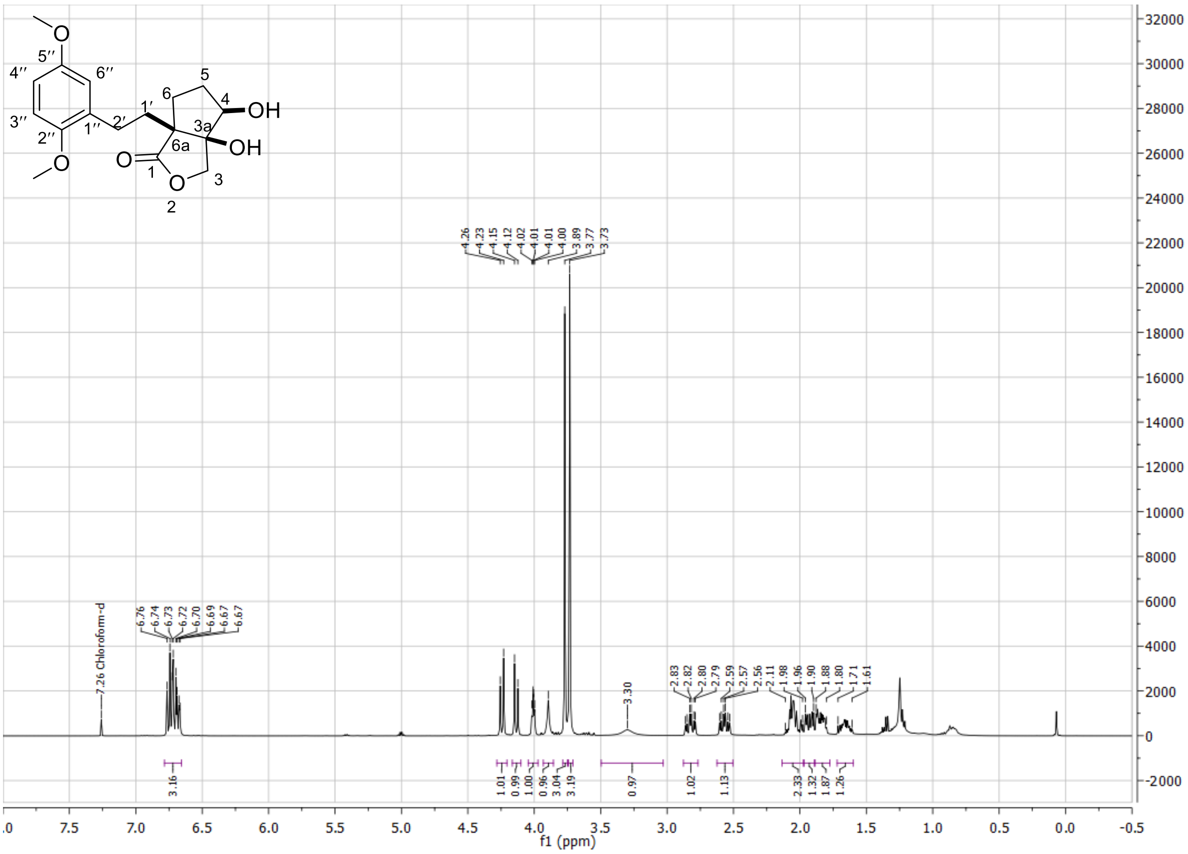


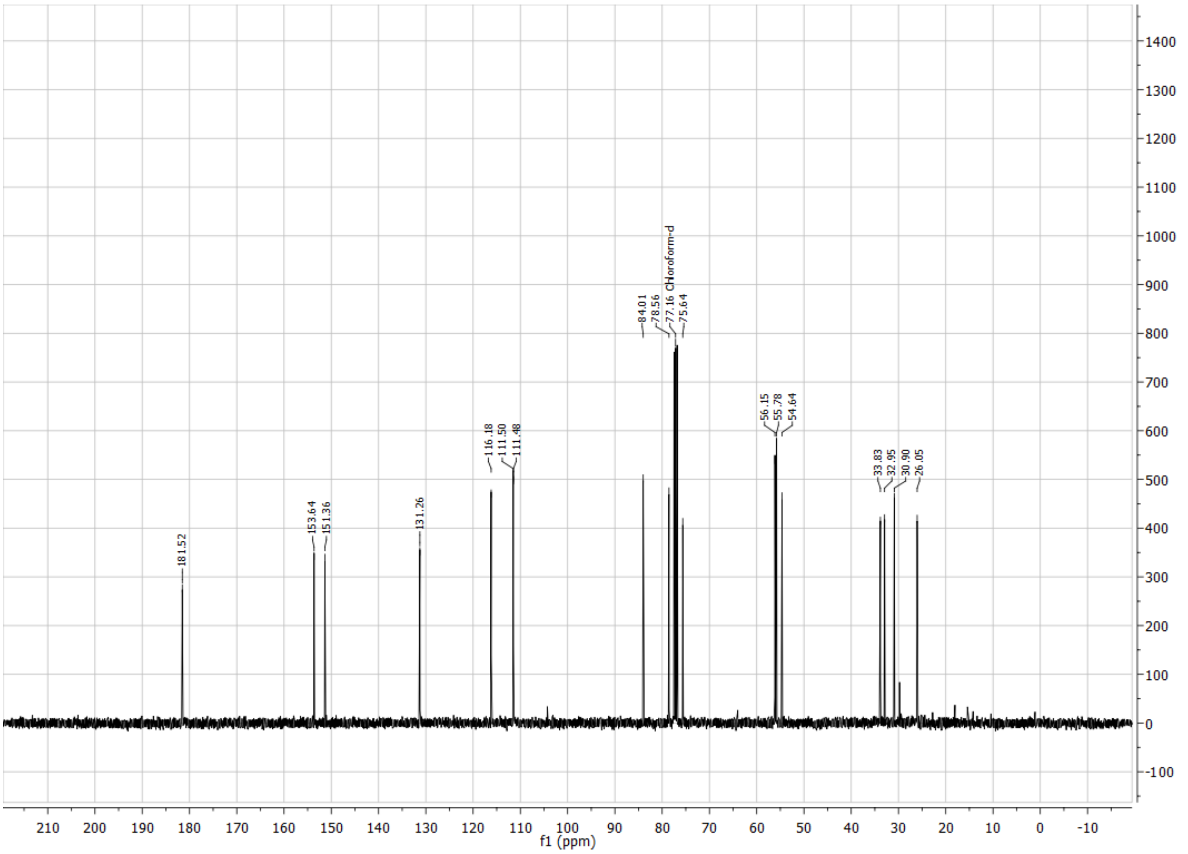
3-(3-(2,5-Dimethoxyphenethyl)-2,4-dioxotetrahydrofuran-3-yl)propanal **(2-60)**



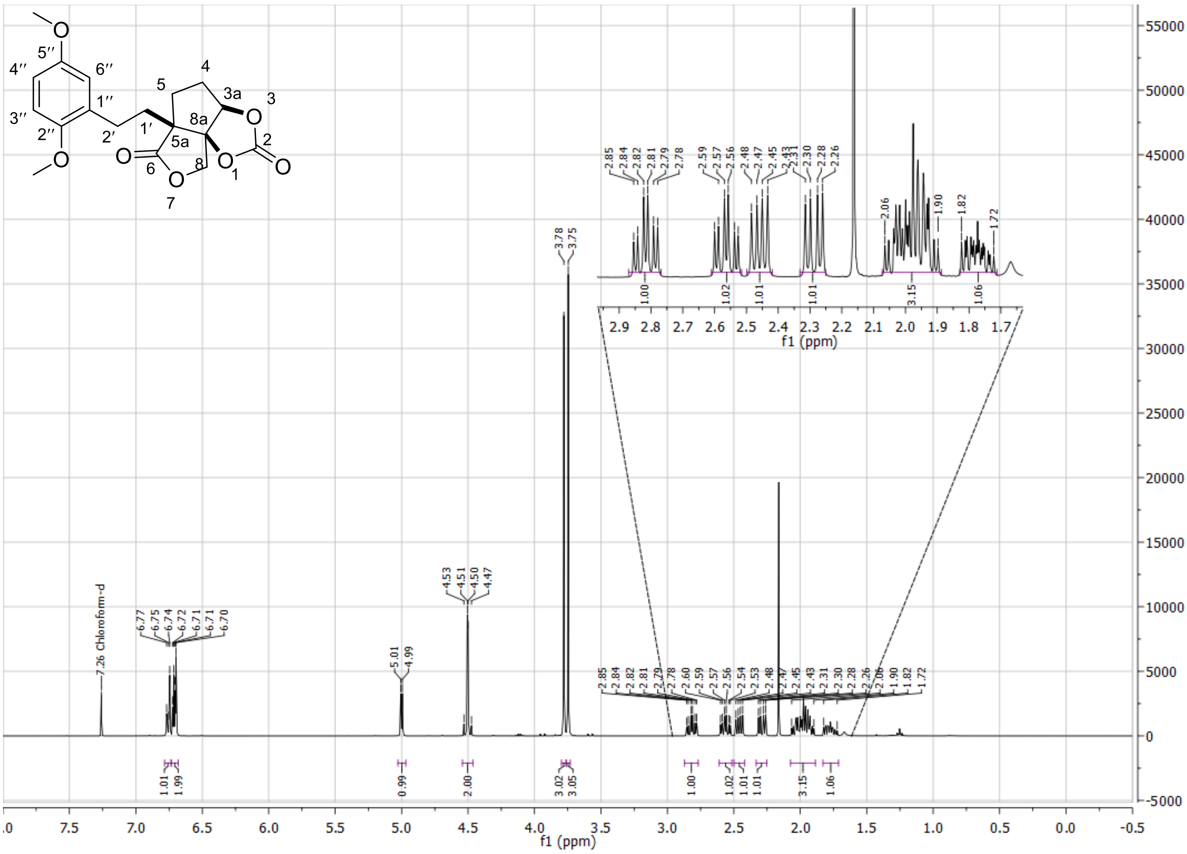


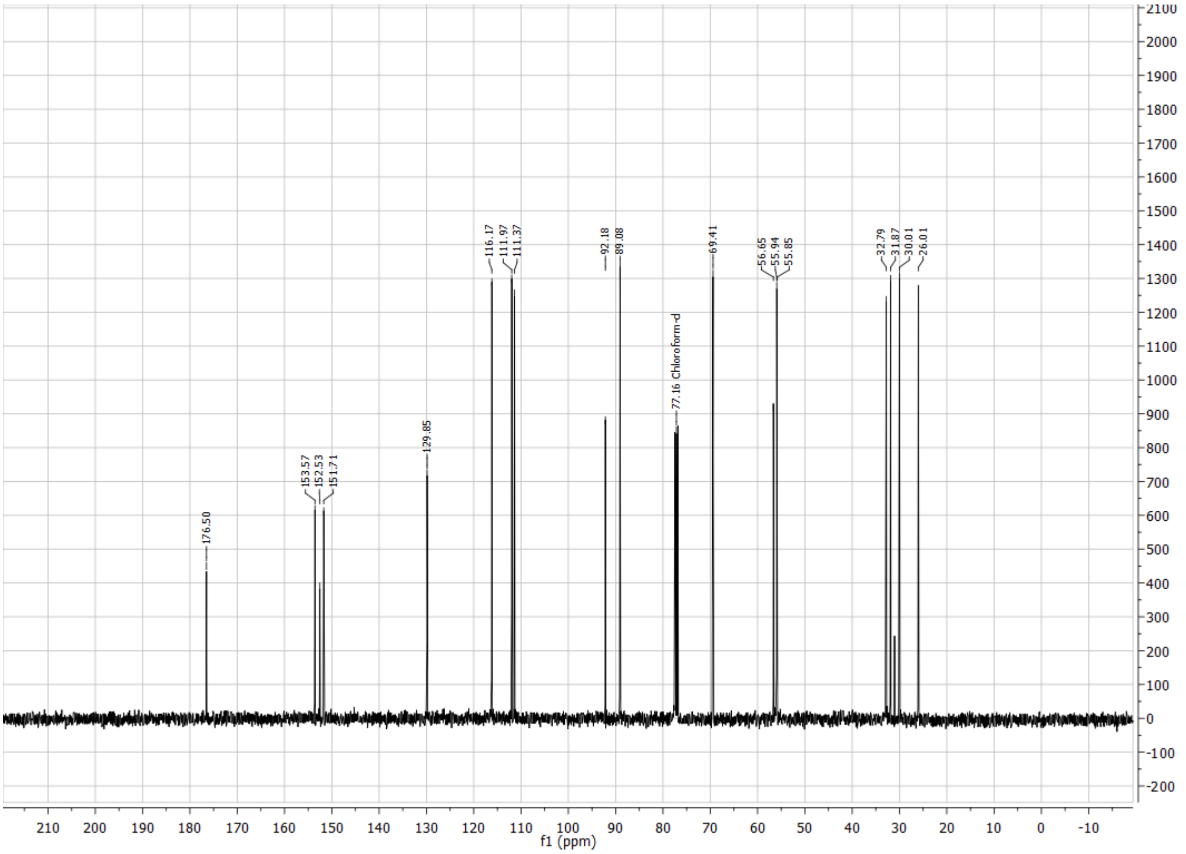
(3a*R**,4*R**,6a*R**)-6a-(2,5-Dimethoxyphenethyl)-3a,4-dihydroxyhexahydro-1*H*-cyclopenta[*c*]furan-1-one **(2-65)**



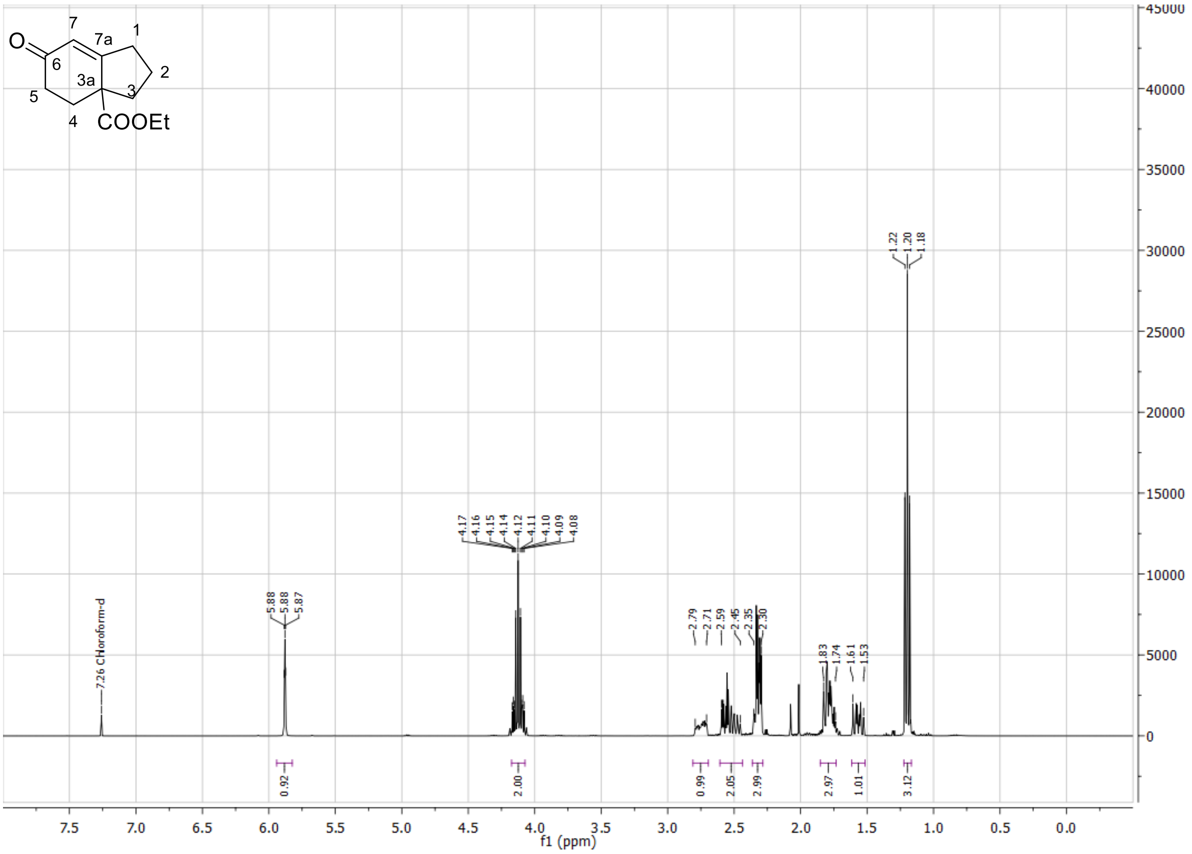


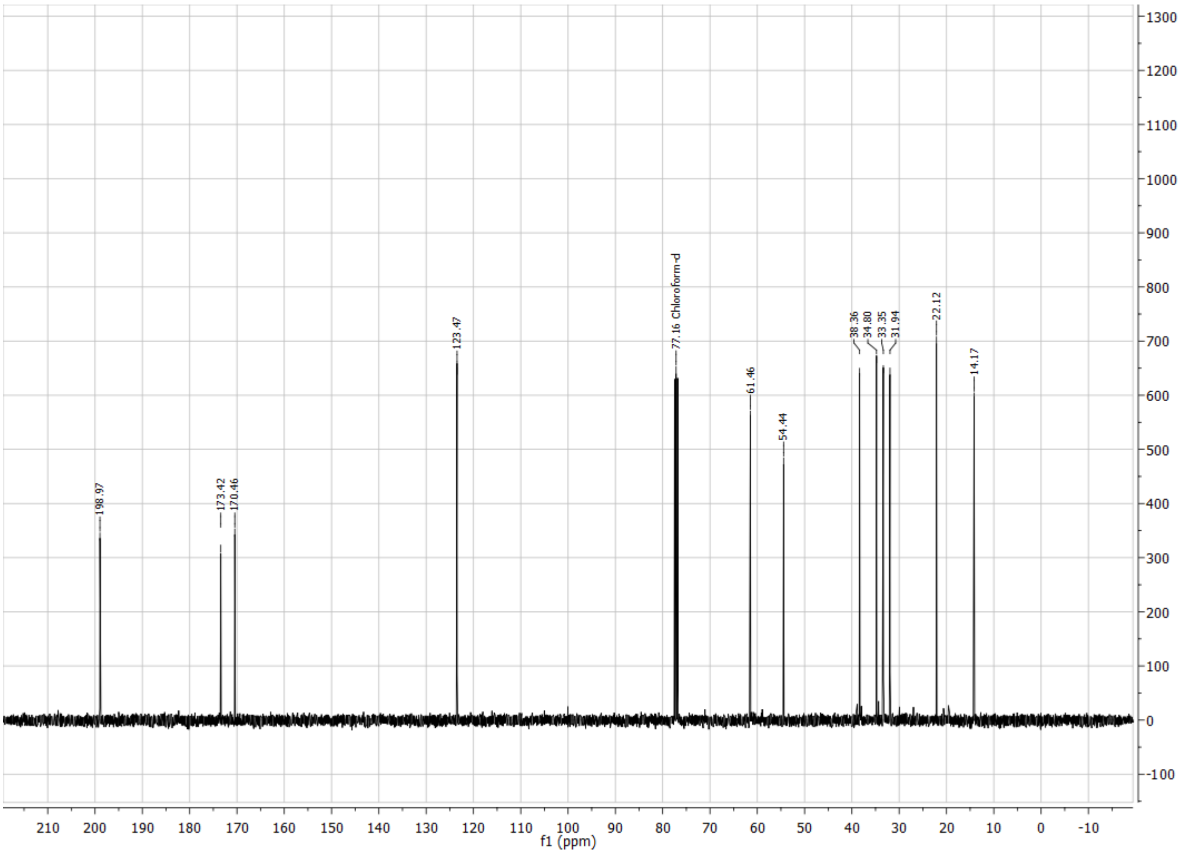
(3a*R**,5a*R**,8a*R**)-5a-(2,5-Dimethoxyphenethyl)tetrahydro-6*H*,8*H*-furo[3',4':1,5]cyclopenta[1,2-*d*][1,3]dioxole-2,6-dione **(2-67)**



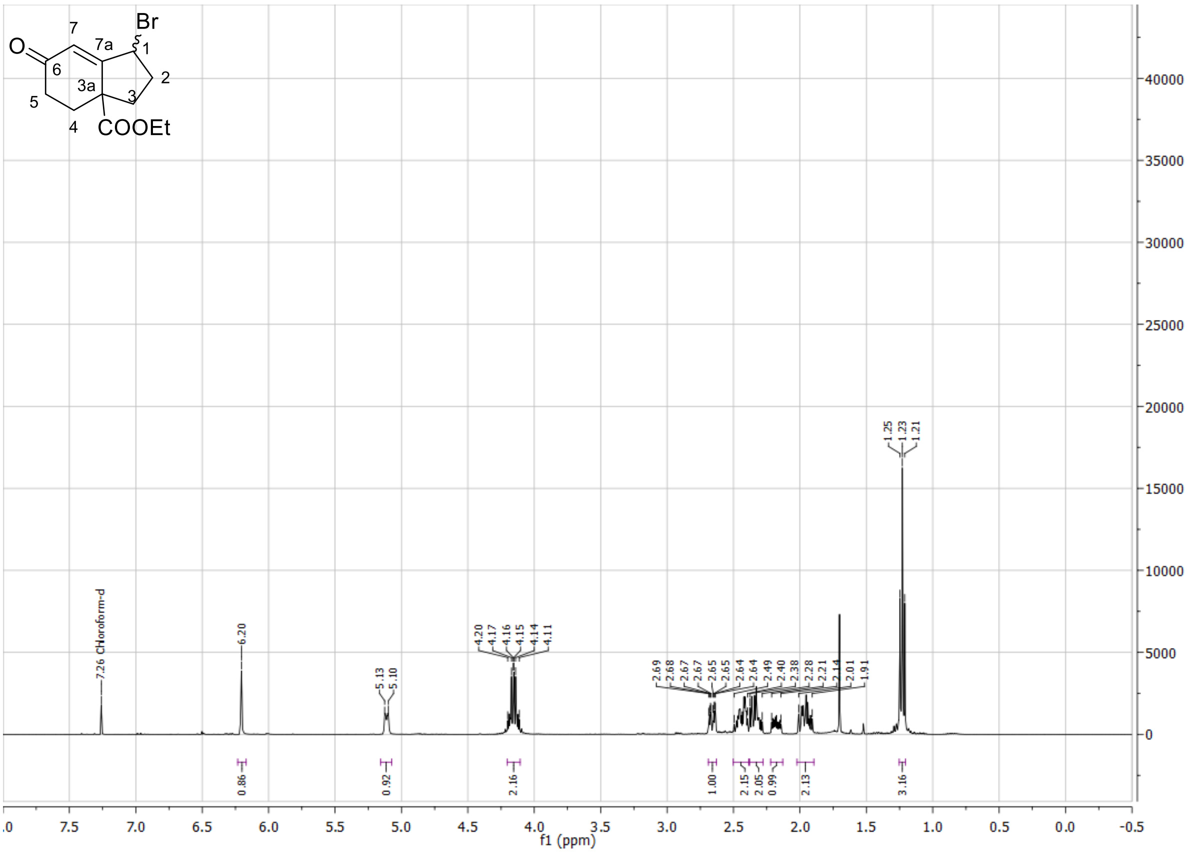


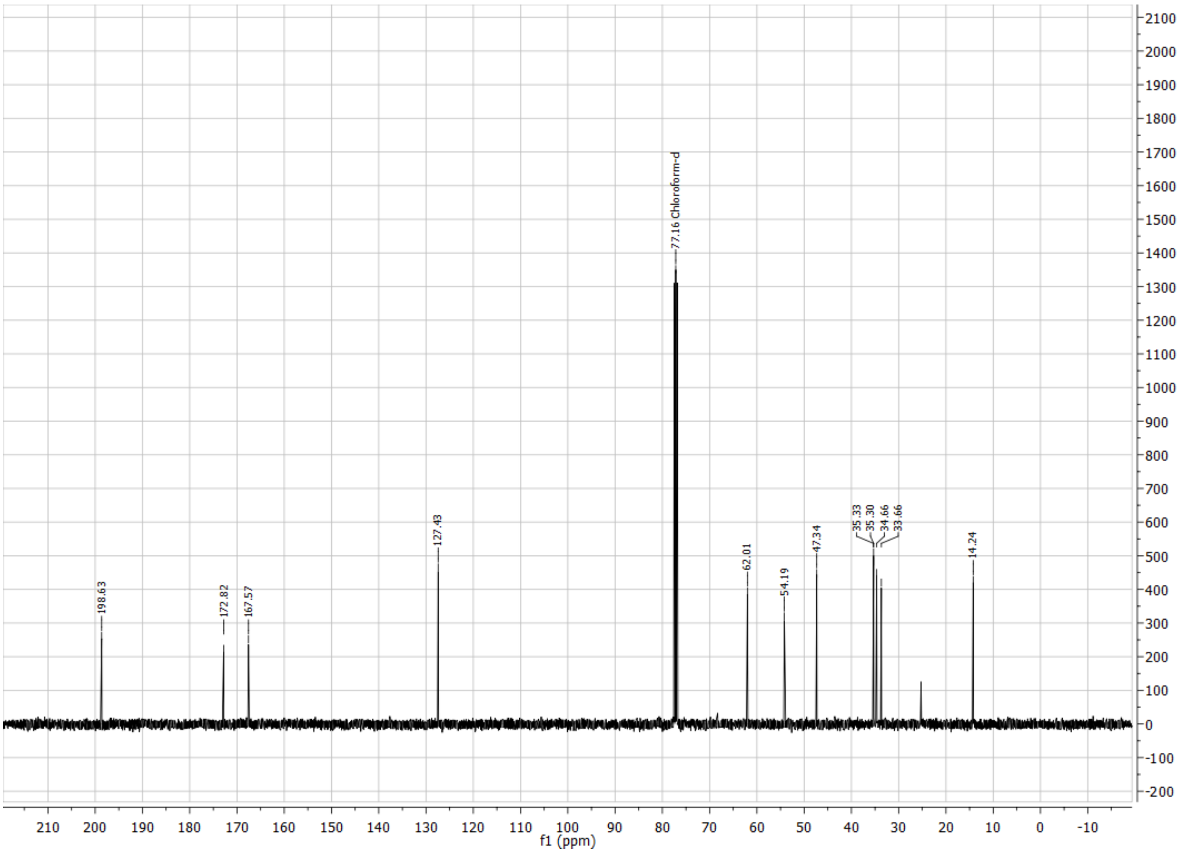
Ethyl 6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate **(2-72)**



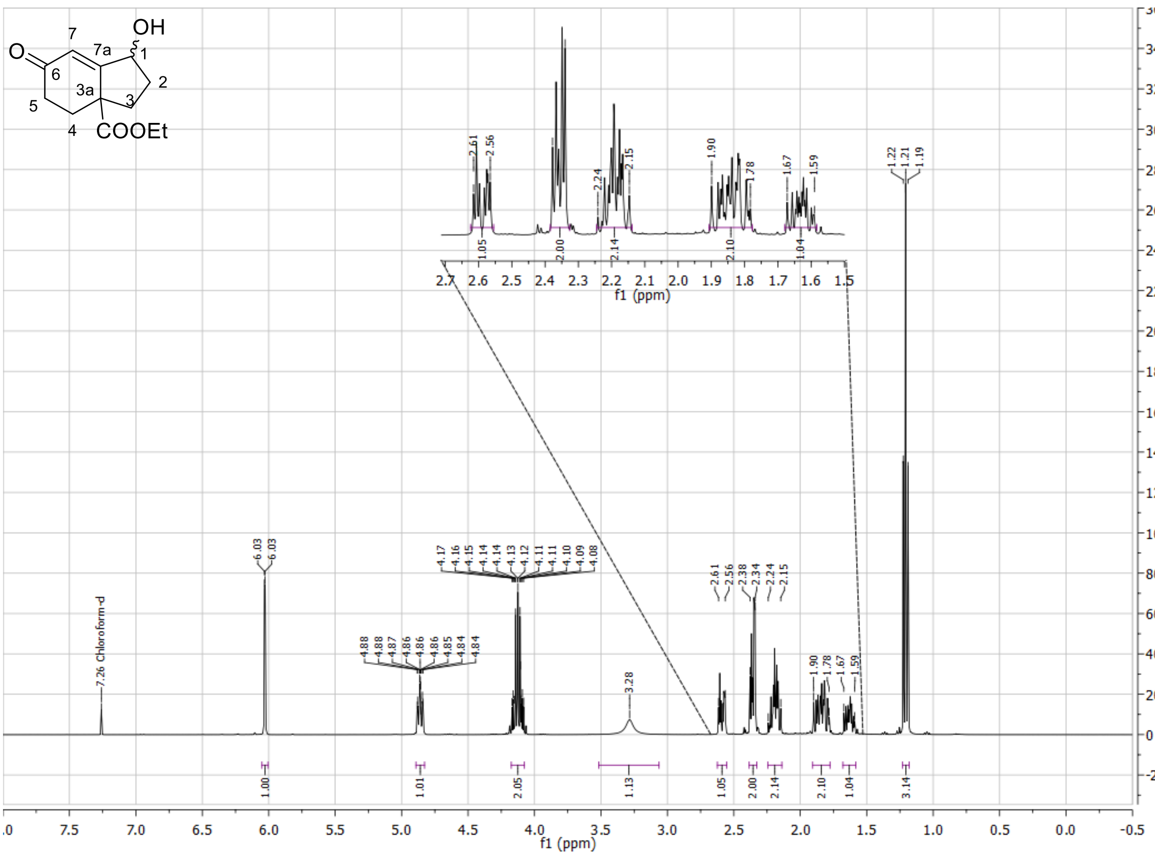


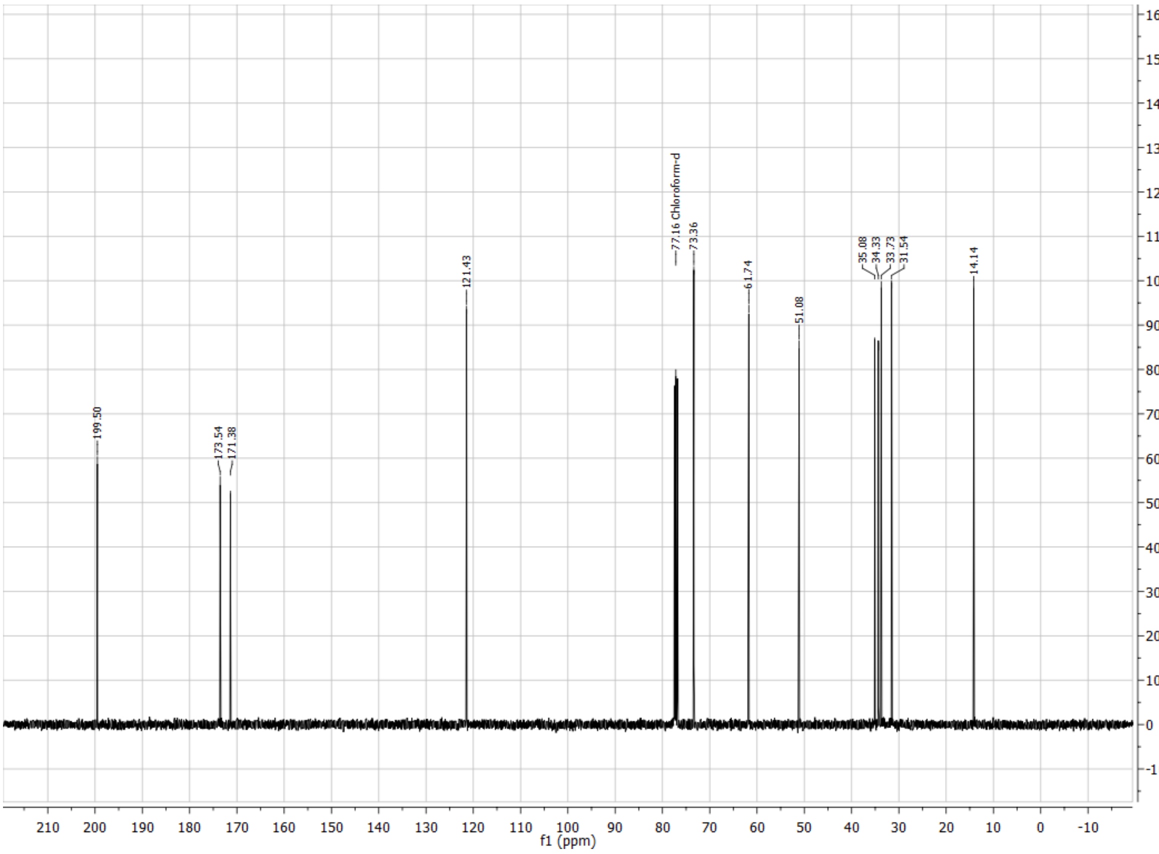
Ethyl 1-bromo-6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate **(2-74a)**



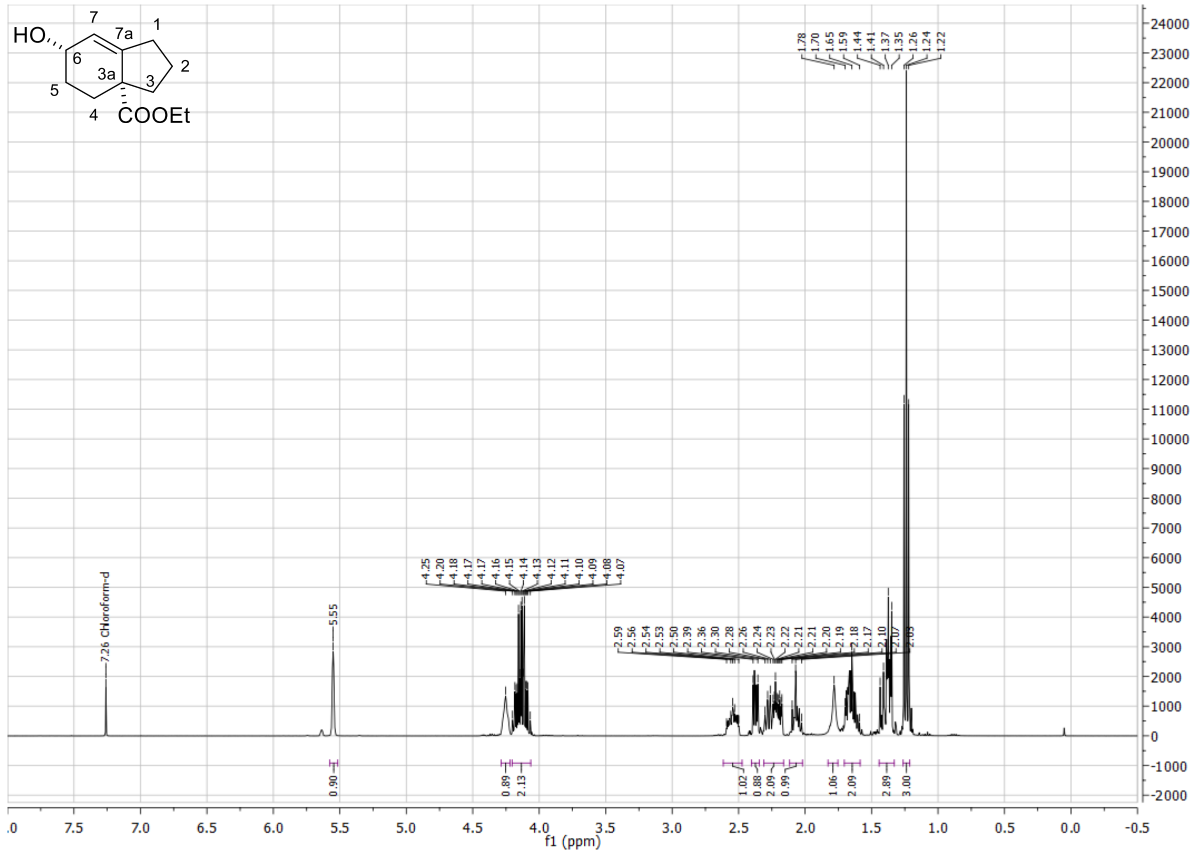


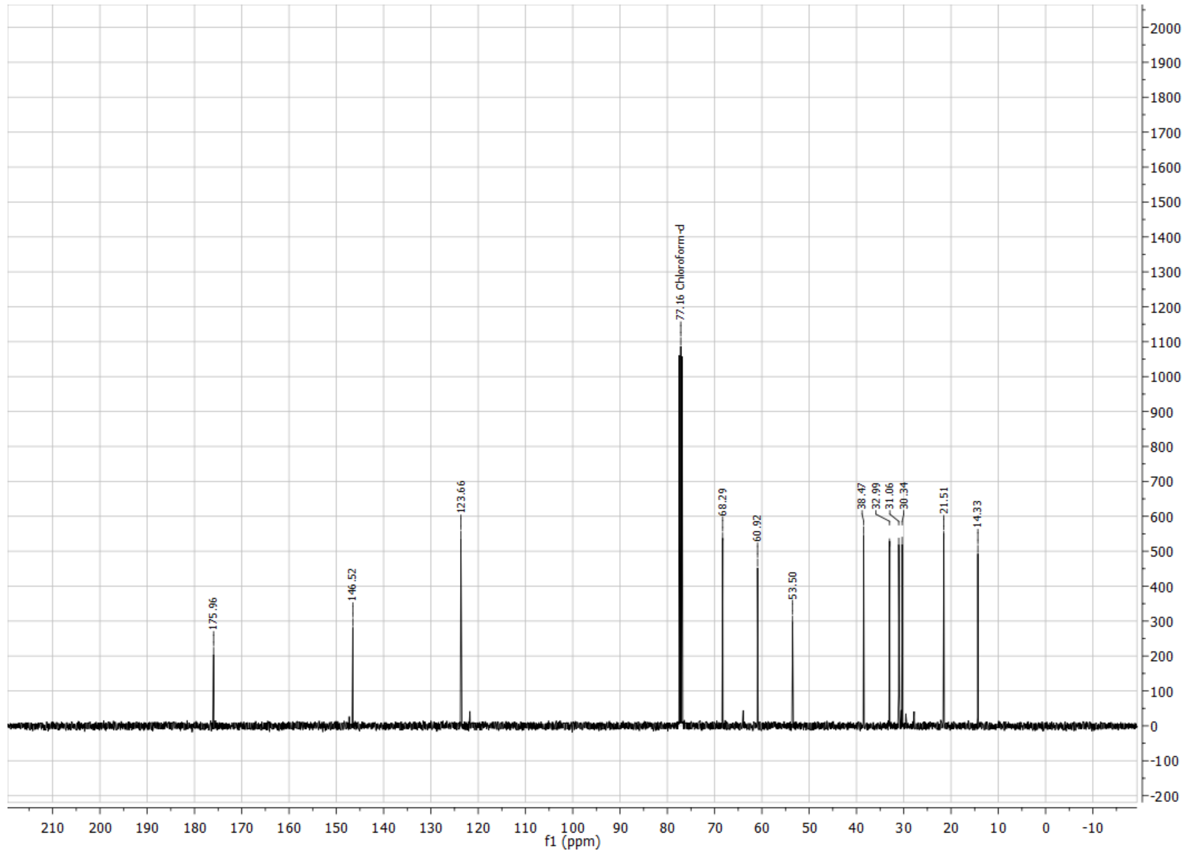
Ethyl 1-hydroxy-6-oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate **(2-74b)**



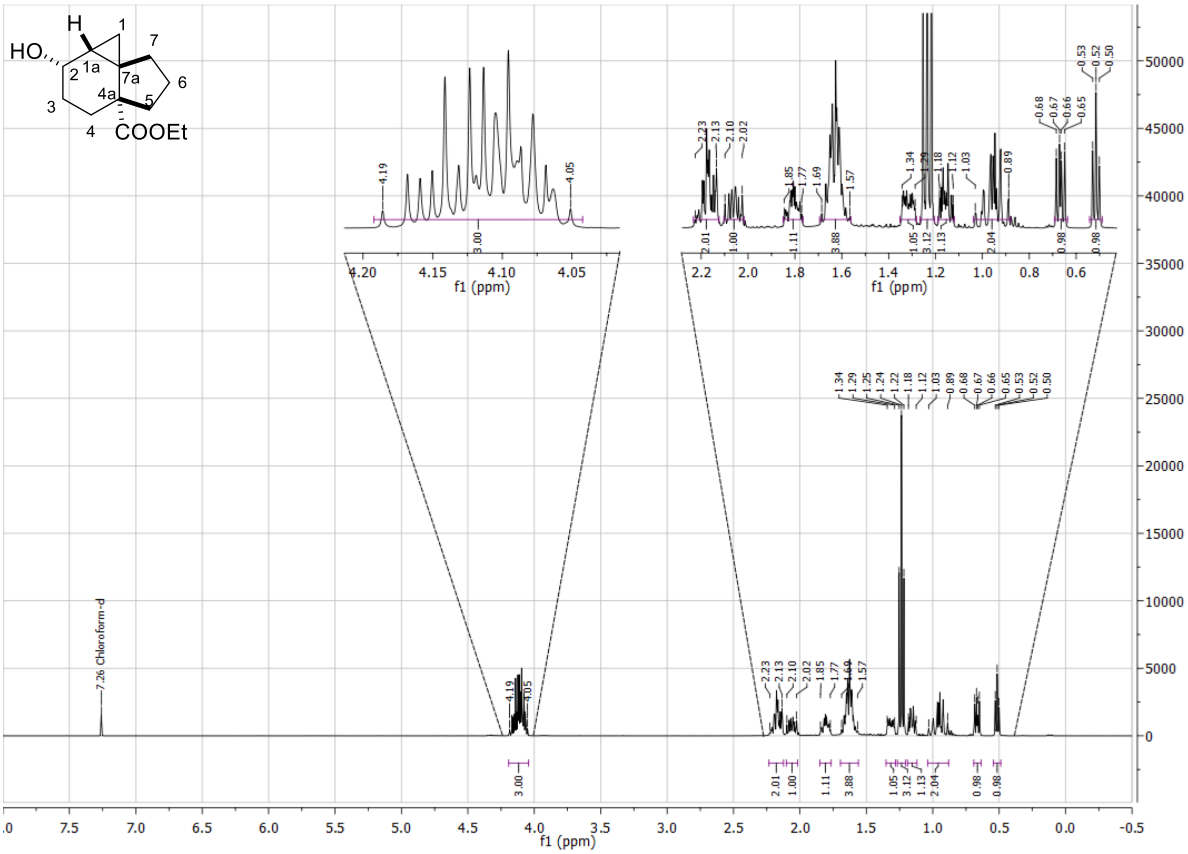


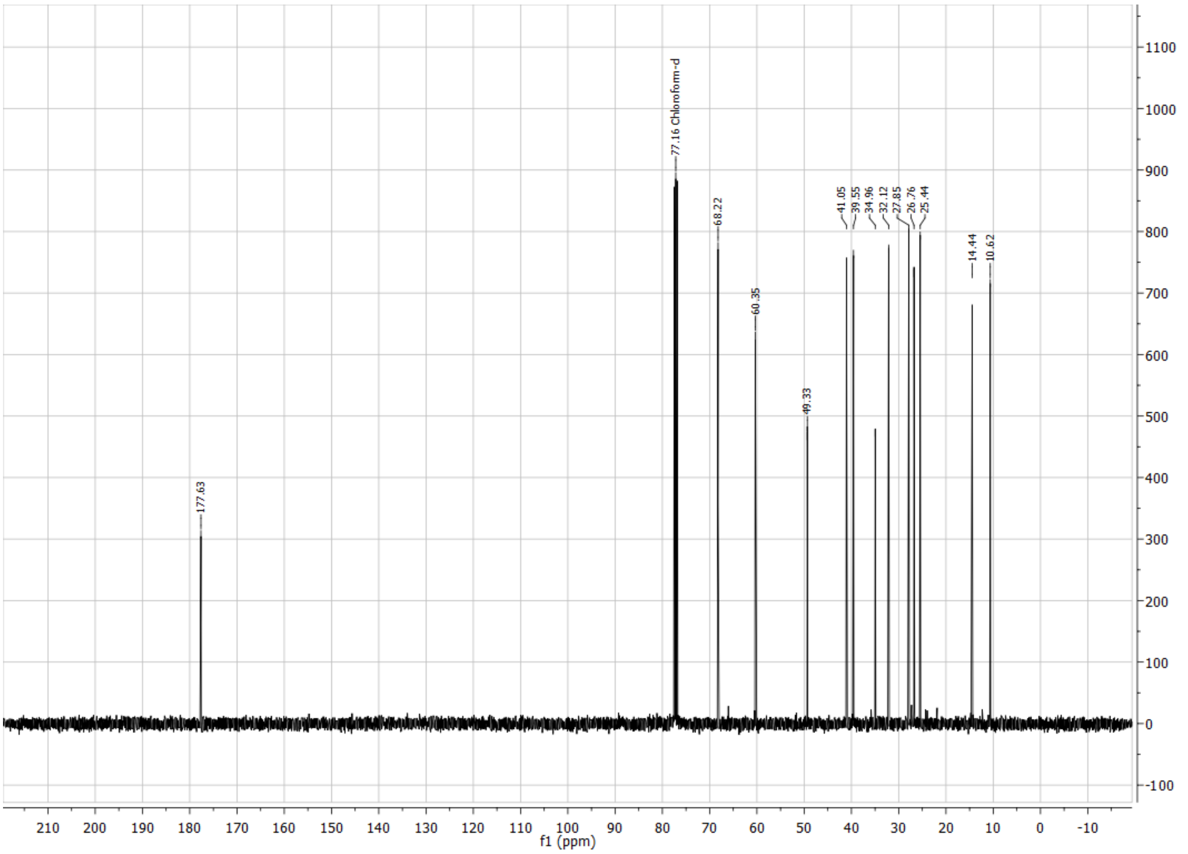
Ethyl (3a*R**,6*S**)-6-hydroxy-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate **(2-76a)**



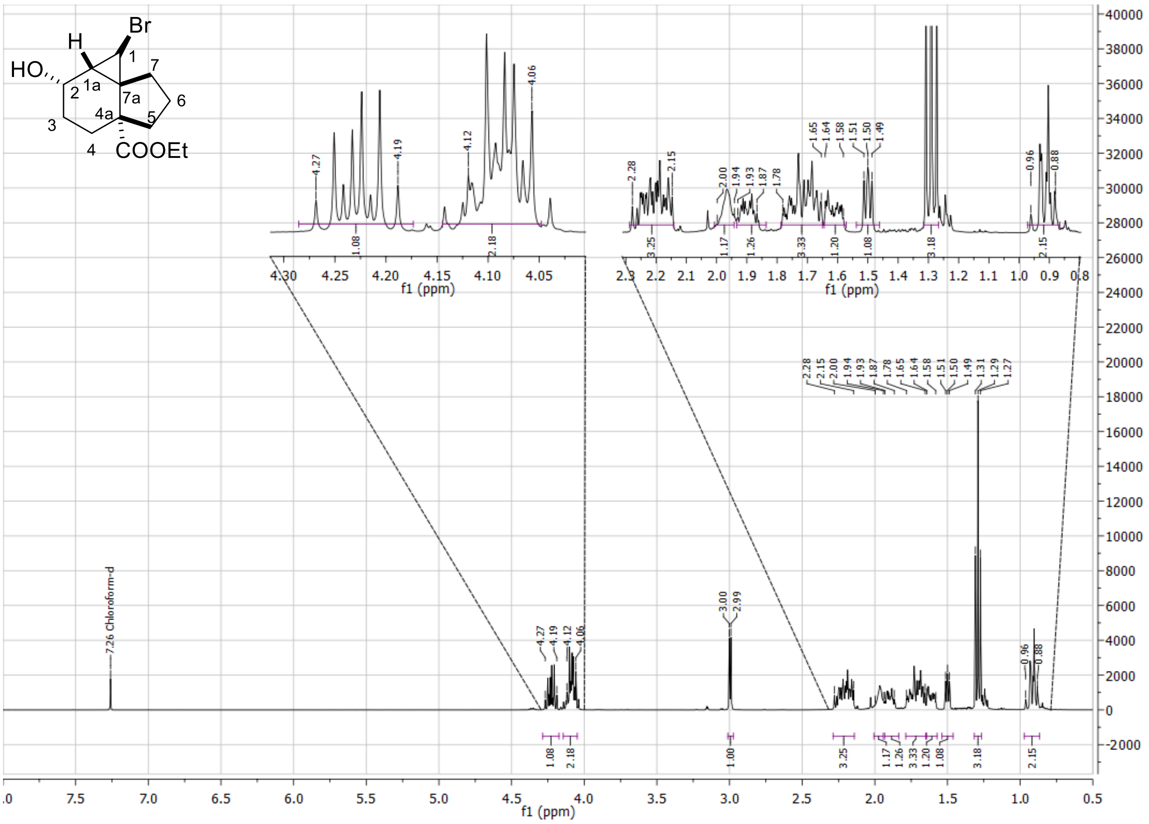


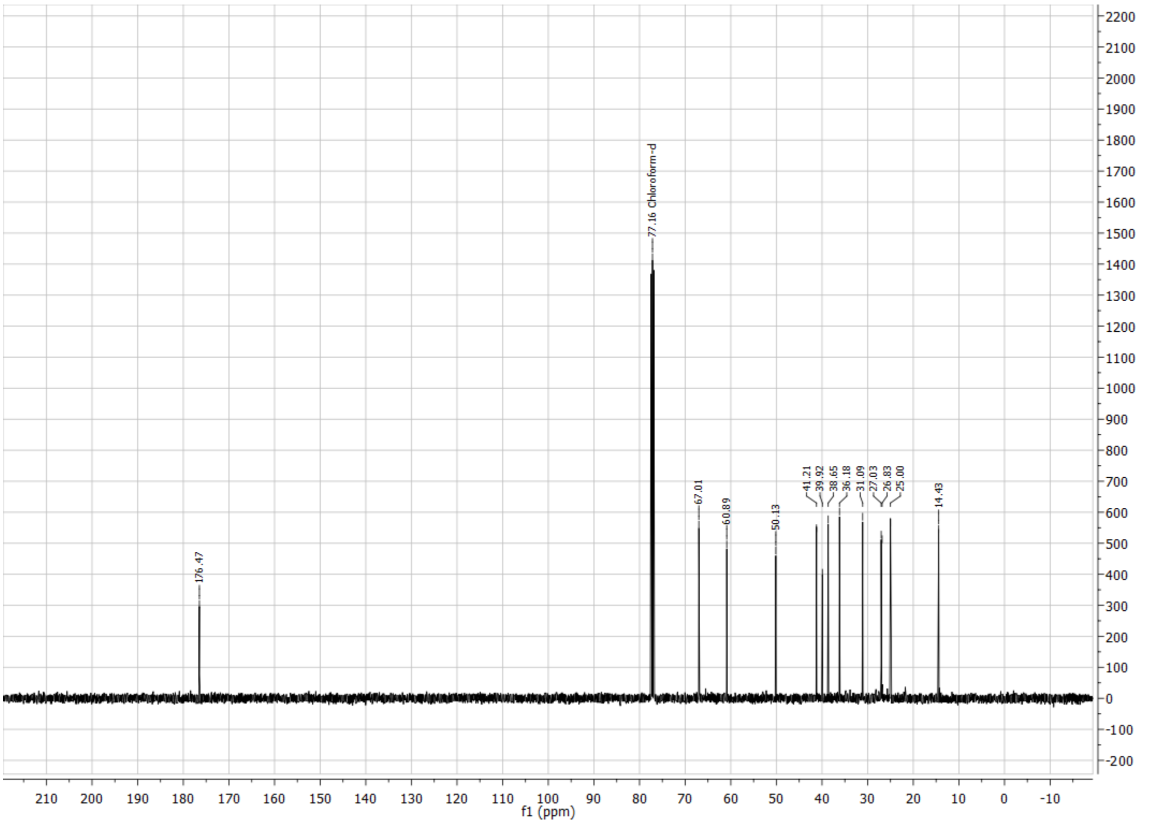
Ethyl (1a*R**,2*S**,4a*R**,7a*S**)-2-hydroxyhexahydro-1*H*-cyclopropa[*d*]indene-4a(5*H*)-carboxylate **(2-77)**



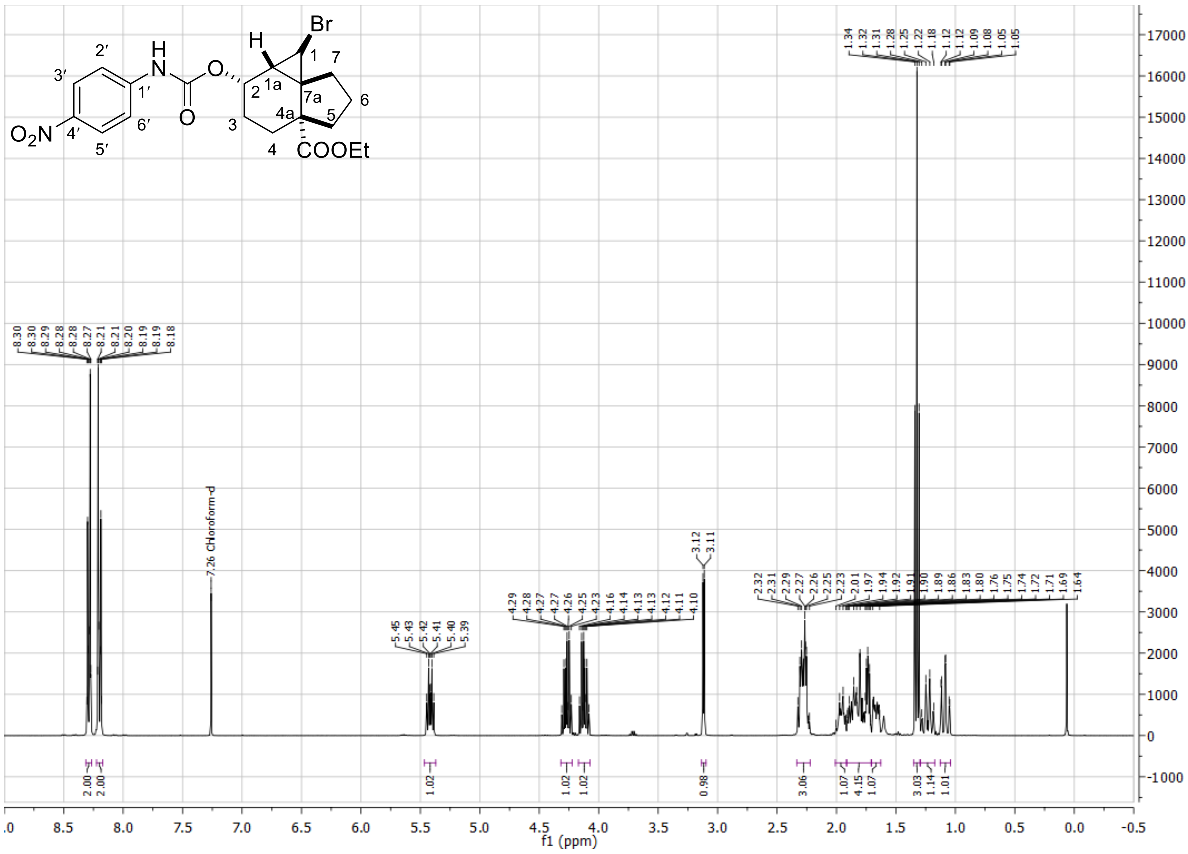


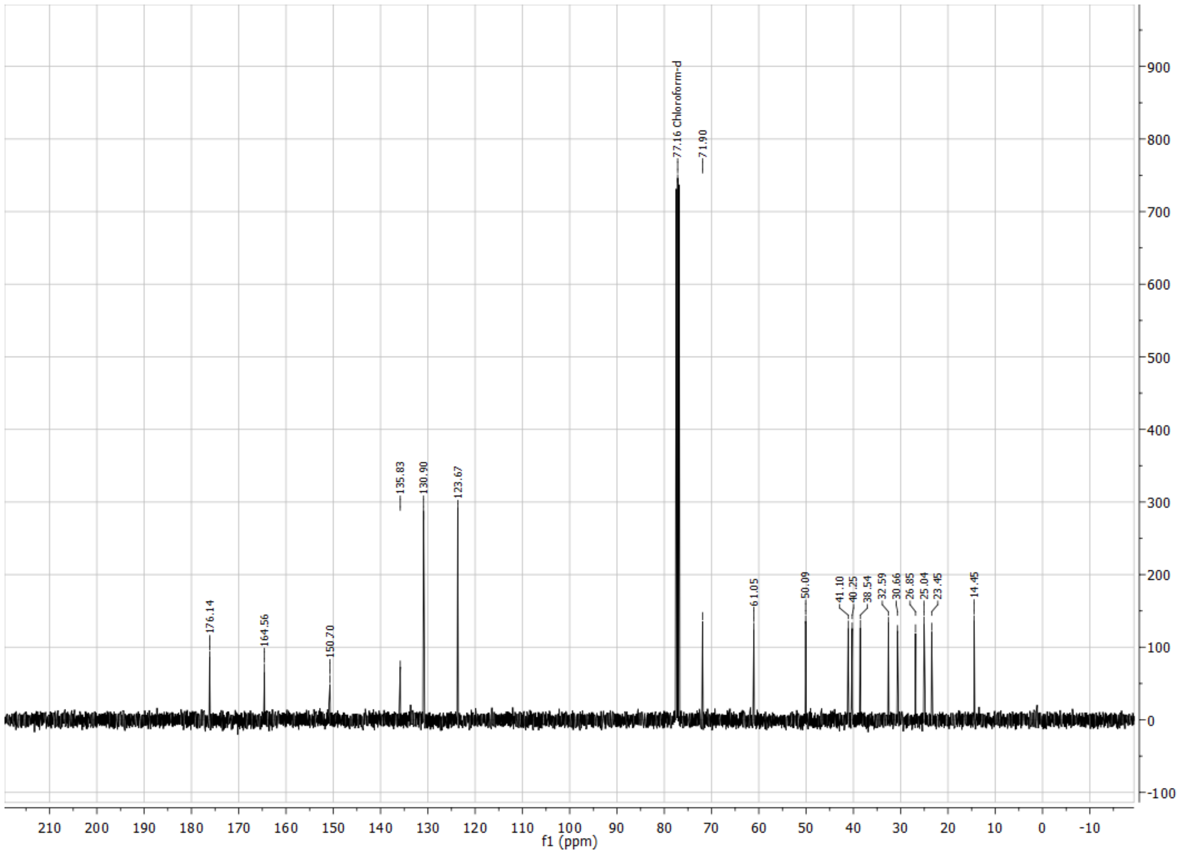
Ethyl (1*R**,1a*R**,2*S**,4a*R**,7a*S**)-1-bromo-2-hydroxyhexahydro-1*H*-cyclopropa[*d*]indene-4a(5*H*)-carboxylate **(2-81)**





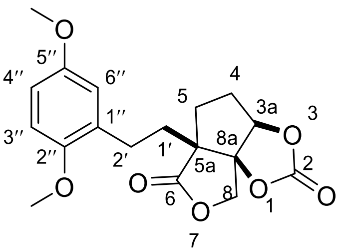
Ethyl (1*R**,1a*R**,2*S**,4a*R**,7a*S**)-1-bromo-2-(((4-nitrophenyl)carbamoyl)oxy) hexahydro-1*H*-cyclopropa[*d*]indene-4a(5*H*)-carboxylate **(2-84)**





7. X-ray structures

(3a*R**,5a*R**,8a*R**)-5a-(2,5-Dimethoxyphenethyl)tetrahydro-6*H*,8*H*-furo[3',4':1,5]cyclopenta[1,2-*d*][1,3]dioxole-2,6-dione **(2-67)**



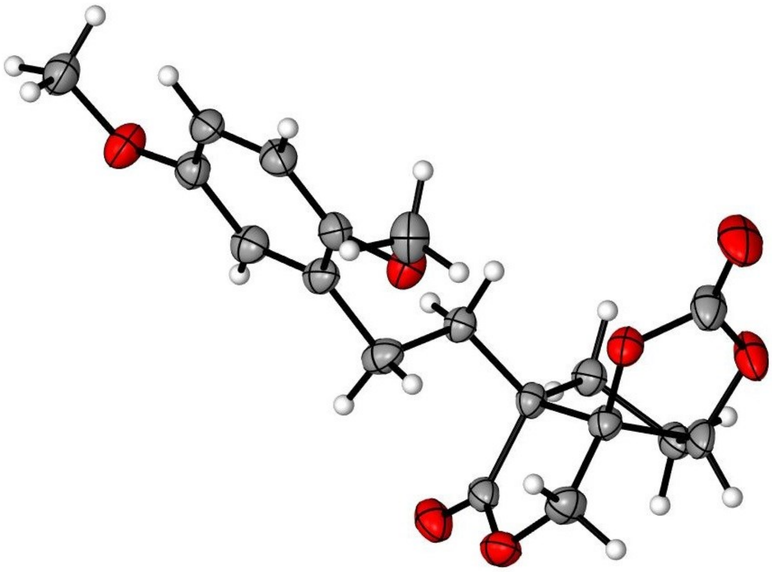
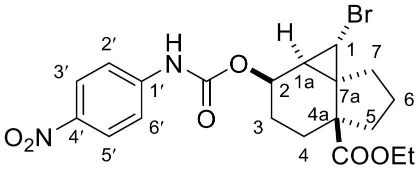


__Figure 11__ X-ray structure of cyclic carbonate __2-67__

Table 14 *Crystallographic data for cyclic carbonate* ***2-67***

Formula	$C_{18}H_{20}O_7$
CCDC	2210466
$D_{calc.}$/ g cm^{-3}	1.433
μ/mm^{-1}	0.932
Formula Weight	348.34
Colour	clear colourless
Shape	block-shaped
Size/mm^3	0.18×0.14×0.07
T/K	149.99(10)
Crystal System	triclinic
Space Group	P-1
a/Å	7.5303(4)
b/Å	10.1469(4)
c/Å	11.0137(4)
$\alpha/^\circ$	80.071(3)
$\beta/^\circ$	86.956(4)
$\gamma/^\circ$	76.829(4)
V/Å^3	807.05(6)
Z	2
Z'	1
Wavelength/Å	1.54184
Radiation type	Cu K_α
$\Theta_{min}/^\circ$	4.075
$\Theta_{max}/^\circ$	80.122
Measured Refl's.	29350
Indep't Refl's	3471
Refl's I≥2 σ(I)	3340
R_{int}	0.0275
Parameters	356
Restraints	6
Largest Peak	0.222
Deepest Hole	-0.195
GooF	1.180
wR_2 (all data)	0.1043
wR_2	0.1037
R_1 (all data)	0.0460
R_1	0.0445

Ethyl (1*R**,1a*R**,2*S**,4a*R**,7a*S**)-1-bromo-2-(((4-nitrophenyl)carbamoyl)oxy) hexahydro-1*H*-cyclopropa[*d*]indene-4a(5*H*)-carboxylate **(2-84)**



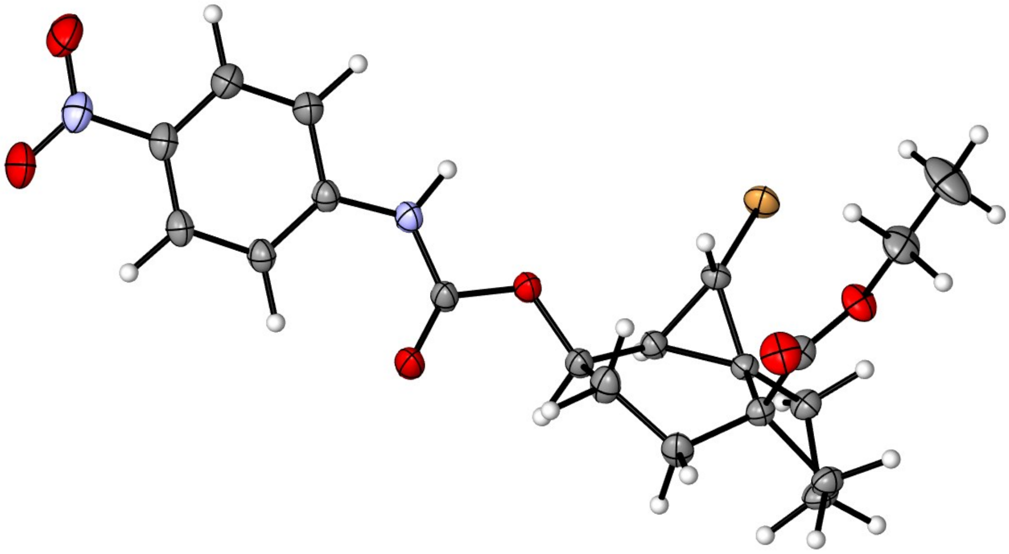


Figure 12 *X-ray structure of carbamate* ***2-84***

Table 15 *Crystallographic data for carbamate* ***2-84***

Formula	$C_{20}H_{23}BrN_2O_6$
CCDC	2244971
$D_{calc.}$/ g cm^{-3}	1.516
μ/mm^{-1}	3.083
Formula Weight	467.319
Colour	clear colourless
Shape	block-shaped
Size/mm^3	0.22×0.09×0.04
T/K	149.99(10)
Crystal System	triclinic
Space Group	P-1
a/Å	8.9606(1)
b/Å	14.9434(2)
c/Å	16.4576(2)
α/°	81.249(1)
β/°	76.856(1)
γ/°	73.416(1)
V/Å^3	2047.70(5)
Z	4
Z'	2
Wavelength/Å	1.54184
Radiation type	Cu K$_\alpha$
Θ_{min}/°	2.77
Θ_{max}/°	80.03
Measured Refl's.	88242
Indep't Refl's	8821
Refl's I≥2 σ(I)	8561
R_{int}	0.0236
Parameters	937
Restraints	0
Largest Peak	0.5098
Deepest Hole	-0.6949
GooF	1.0911
wR_2 (all data)	0.0358
wR_2	0.0356
R_1 (all data)	0.0165
R_1	0.0159

8. Bibliography

[1] L. C. Cross, W. Klyne, *Pure Appl. Chem.* **1976**, *45*, 11–30.

[2] G. P. Moss, *Pure Appl. Chem.* **1996**, *68*, 2193–2222.

[3] J. Brecher, *Pure Appl. Chem.* **2006**, *78*, 1897–1970.

[4] H. Maehr, *J. Chem. Educ.* **1985**, *62*, 114–120.

[5] H. Maehr, *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 894–902.

[6] E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley & Sons Ltd, New York, **1994**.

[7] M. A. Brook, *J. Chem. Educ.* **1987**, *64*, 218–220.

[8] H. A. Favre, W. H. Powell, *Nomenclature of Organic Chemistry*, The Royal Society Of Chemistry, Cambridge, **2013**.

[9] D. J. Newman, G. M. Cragg, K. M. Snader, *Nat. Prod. Rep.* **2000**, *17*, 215–234.

[10] M. J. Brownstein, *Proc. Natl. Acad. Sci.* **1993**, *90*, 5391–5393.

[11] L. C. Tapsell, I. Hemphill, L. Cobiac, D. R. Sullivan, M. Fenech, C. S. Patch, S. Roodenrys, J. B. Keogh, P. M. Clifton, P. G. Williams, V. A. Fazio, K. E. Inge, *Med. J. Aust.* **2006**, *185*, S1–S24.

[12] K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem. Int. Ed.* **2000**, *39*, 44–122.

[13] K. C. Nicolaou, S. Rigol, R. Yu, *CCS Chem.* **2019**, *1*, 3–37.

[14] K. C. Nicolaou, S. A. Snyder, *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044.

[15] R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2013**, *52*, 123–130.

[16] P. S. Baran, *J. Am. Chem. Soc.* **2018**, *140*, 4751–4755.

[17] J. Mulzer, *Nat. Prod. Rep.* **2014**, *31*, 595–603.

[18] J. D. Keasling, A. Mendoza, P. S. Baran, *Nature* **2012**, *492*, 188–189.

[19] T. Hudlicky, J. W. Reed, *The Way of Synthesis*, Wiley-VCH, Weinheim, **2007**.

[20] J. D. Keasling, *Science* **2010**, *330*, 1355–1358.

[21] A. W. Sun, S. Lackner, B. M. Stoltz, *Trends Chem.* **2019**, *1*, 630–643.

[22] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.

[23] F. Lovering, *Med. Chem. Commun.* **2013**, *4*, 515–519.

[24] C. F. Stratton, D. J. Newman, D. S. Tan, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4802–4807.

[25] N. E. Thomford, D. A. Senthebane, A. Rowe, D. Munro, P. Seele, A. Maroyi, K. Dzobo, *Int. J. Mol. Sci.* **2018**, *19*, 1578.

[26] H. Lachance, S. Wetzel, K. Kumar, H. Waldmann, *J. Med. Chem.* **2012**, *55*, 5989–

6001.

[27] B. J. Huffman, R. A. Shenvi, *J. Am. Chem. Soc.* **2019**, *141*, 3332–3346.

[28] Z. Lin, Ganoderma (Lingzhi) in Traditional Chinese Medicine and Chinese Culture, in *Ganoderma and Health: Biology, Chemistry and Industry (Advances in Experimental Medicine and Biology Volume 1181)* (Eds.: Z. Lin, B. Yang), Springer Nature Singapore Pte Ltd, Singapore, **2019**, pp. 1–14.

[29] X. Peng, M. Qiu, *Nat. Products Bioprospect.* **2018**, *8*, 137–149.

[30] A. L. Loyd, B. S. Richter, M. A. Jusino, C. Truong, M. E. Smith, R. A. Blanchette, J. A. Smith, *Front. Microbiol.* **2018**, *9*, 1557.

[31] B. Sanodiya, G. Thakur, R. Baghel, G. Prasad, P. Bisen, *Curr. Pharm. Biotechnol.* **2009**, *10*, 717–742.

[32] S. Jong, J. M. Birmingham, Medicinal Benefits of the Mushroom Ganoderma, in *Advances in Applied Microbiology Volume 37* (Eds.: S. L. Neidleman, A. I. Laskin), Academic Press Inc., San Diego, **1992**, pp. 101–134.

[33] M. S. Shiao, *Chem. Rec.* **2003**, *3*, 172–180.

[34] M.-S. Shiao, K. R. Lee, L.-J. Lin, C.-T. Wang, Natural Products and Biological Activities of the Chinese Medicinal Fungus Ganoderma lucidum, in *Food Phytochemicals for Cancer Prevention II* (Eds.: C.-T. Ho, T. Osawa, M.-T. Huang, R. T. Rosen), American Chemical Society, Washington, DC, **1994**, pp. 342–354.

[35] S. Wu, S. Zhang, B. Peng, D. Tan, M. Wu, J. Wei, Y. Wang, H. Luo, *Food Sci. Hum. Wellness* **2024**, *13*, 568–596.

[36] E. Ekiz, E. Oz, A. Abd El-Aty, C. Proestos, C. Brennan, M. Zeng, I. Tomasevic, T. Elobeid, K. Çadırcı, M. Bayrak, F. Oz, *Foods* **2023**, *12*, 1512.

[37] D. Cör Andrejč, Ž. Knez, M. Knez Marevci, *Front. Pharmacol.* **2022**, *13*, 934982.

[38] I. Ismail Iid, S. Kumar, S. Shukla, V. Kumar, R. Sharma, *Trends Food Sci. Technol.* **2020**, *97*, 317–340.

[39] R. Ahmad, M. Riaz, A. Khan, A. Aljamea, M. Algheryafi, D. Sewaket, A. Alqathama, *Phyther. Res.* **2021**, *35*, 6030–6062.

[40] A. F. El Sheikha, *Foods* **2022**, *11*, 1030.

[41] I. Leskosek-Cukalovic, S. Despotovic, N. Lakic, M. Niksic, V. Nedovic, V. Tesevic, *Food Res. Int.* **2010**, *43*, 2262–2269.

[42] F. Azi, Z. Wang, W. Chen, D. Lin, P. Xu, *Trends Biotechnol.* **2024**, *42*, 197–211.

[43] D. Danninger, R. Pruckner, L. Holzinger, R. Koeppe, M. Kaltenbrunner, *Sci. Adv.* **2022**, *8*, eadd7118.

[44] Y. M. Yan, J. Ai, L. L. Zhou, A. C. K. Chung, R. Li, J. Nie, P. Fang, X. L. Wang, J. Luo, Q. Hu, F. F. Hou, Y. X. Cheng, *Org. Lett.* **2013**, *15*, 5488–5491.

[45] H. Ha, I. A. Hwang, J. H. Park, H. B. Lee, *Diabetes Res. Clin. Pract.* **2008**, *82*, S42–S45.

[46] H. B. Lee, M. R. Yu, Y. Yang, Z. Jiang, H. Ha, *J. Am. Soc. Nephrol.* **2003**, *14*, S241–S245.

[47] S. Gao, P. Zhang, C. Zhang, F. Bao, H. Li, L. Chen, *Fitoterapia* **2018**, *131*, 73–79.

[48] X. Peng, J. Liu, C. Wang, Z. Han, Y. Shu, X. Li, L. Zhou, M. Qiu, *Food Chem.* **2015**, *171*, 251–257.

[49] M. Jiang, Z. Wu, L. Liu, S. Chen, *Org. Biomol. Chem.* **2021**, *19*, 1644–1704.

[50] D. Liu, J. Gong, W. Dai, X. Kang, Z. Huang, H.-M. Zhang, W. Liu, L. Liu, J. Ma, Z. Xia, Y. Chen, Y. Chen, D. Wang, P. Ni, A.-Y. Guo, X. Xiong, *PLoS One* **2012**, *7*, e36146.

[51] P. M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, John Wiley & Sons Ltd, Chichester, **2009**.

[52] H. Inouye, S. Ueda, K. Inoue, H. Matsumura, *Phytochemistry* **1979**, *18*, 1301–1308.

[53] V. P. Papageorgiou, A. N. Assimopoulou, E. A. Couladouros, D. Hepworth, K. C. Nicolaou, *Angew. Chem. Int. Ed.* **1999**, *38*, 270–300.

[54] L. M. Mehl, M. E. Maier, *J. Org. Chem.* **2017**, *82*, 9844–9850.

[55] R. Long, J. Huang, W. Shao, S. Liu, Y. Lan, J. Gong, Z. Yang, *Nat. Commun.* **2014**, *5*, 5707.

[56] D. Chen, H. M. Liu, M. M. Li, Y. M. Yan, W. D. Xu, X. N. Li, Y. X. Cheng, H. B. Qin, *Chem. Commun.* **2015**, *51*, 14594–14596.

[57] K. Sharmah Gautam, V. B. Birman, *Org. Lett.* **2016**, *18*, 1499–1501.

[58] X. Li, X. Liu, X. Jiao, H. Yang, Y. Yao, P. Xie, *Org. Lett.* **2016**, *18*, 1944–1946.

[59] P. S. Riehl, A. D. Richardson, T. Sakamoto, C. S. Schindler, *Org. Lett.* **2020**, *22*, 290–294.

[60] D. Chen, W. D. Xu, H. M. Liu, M. M. Li, Y. M. Yan, X. N. Li, Y. Li, Y. X. Cheng, H. B. Qin, *Chem. Commun.* **2016**, *52*, 8561–8564.

[61] R. Rengarasu, M. E. Maier, *Asian J. Org. Chem.* **2017**, *6*, 108–117.

[62] A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.

[63] D. W. Zhang, H. L. Fan, W. Zhang, C. J. Li, S. Luo, H. B. Qin, *Chem. Commun.* **2020**, *56*, 10066–10069.

[64] A. Nakamura, M. Nakada, *Synthesis* **2013**, *45*, 1421–1451.

[65] S. Nakamura, H. Hirao, T. Ohwada, *J. Org. Chem.* **2004**, *69*, 4309–4316.

[66] Y. Oikawa, T. Yoshioka, K. Sugano, O. Yonemitsu, *Org. Synth.* **1985**, *63*, 198.

[67] Y. Oikawa, K. Sugano, O. Yonemitsu, *J. Org. Chem.* **1978**, *43*, 2087–2088.

[68] I. Fleming, *Molecular Orbitals and Organic Chemical Reactions (Reference Edition)*, John Wiley & Sons Ltd, Hoboken, NJ, USA, **2010**.

[69] H. M. R. Hoffmann, *Angew. Chem. Int. Ed.* **1969**, *8*, 556–577.

[70] W. Adam, O. Krebs, *Chem. Rev.* **2003**, *103*, 4131–4146.

[71] I. Fernández, F. M. Bickelhaupt, *J. Comput. Chem.* **2012**, *33*, 509–516.

[72] M. L. Clarke, M. B. France, *Tetrahedron* **2008**, *64*, 9003–9031.

[73] J. M. Conia, P. Le Perchec, *Synthesis* **1975**, *1975*, 1–19.

[74] D. Hack, M. Blümel, P. Chauhan, A. R. Philipps, D. Enders, *Chem. Soc. Rev.* **2015**, *44*, 6059–6093.

[75] J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527.

[76] F. W. W. Hartrampf, T. Furukawa, D. Trauner, *Angew. Chem. Int. Ed.* **2017**, *56*, 893–896.

[77] D. Bouyssi, N. Monteiro, G. Balme, *Tetrahedron Lett.* **1999**, *40*, 1297–1300.

[78] T. Inoue, O. Kitagawa, Y. Oda, T. Taguchi, *J. Org. Chem.* **1996**, *61*, 8256–8263.

[79] M. A. Boaventura, J. Drouin, J. M. Conia, *Synthesis* **1983**, *1983*, 801–804.

[80] H. L. Riley, J. F. Morley, N. A. C. Friend, *J. Chem. Soc.* **1932**, 1875–1883.

[81] N. Rabjohn, *Org. React.* **1976**, *24*, 261–416.

[82] G. O. Schenck, K.-H. Schulte-Elte, *Justus Liebigs Ann. Chem.* **1958**, *618*, 185–193.

[83] H. S. Dang, A. G. Davies, I. G. E. Davison, C. H. Schiesser, *J. Org. Chem.* **1990**, *55*, 1432–1438.

[84] M. A. Ponce, R. Erra-Balsells, A. C. Bruttomesso, E. G. Gros, *Helv. Chim. Acta* **2004**, *87*, 2987–3003.

[85] H. G. Jeong, M. S. Choi, *Isr. J. Chem.* **2016**, *56*, 110–118.

[86] R. Costa e Silva, L. O. da Silva, A. de Andrade Bartolomeu, T. J. Brocksom, K. T. de Oliveira, *Beilstein J. Org. Chem.* **2020**, *16*, 917–955.

[87] A. A. Ghogare, A. Greer, *Chem. Rev.* **2016**, *116*, 9994–10034.

[88] Z. Lu, Y. Li, J. Deng, A. Li, *Nat. Chem.* **2013**, *5*, 679–684.

[89] B. M. Trost, G. Zhang, H. Gholami, D. Zell, *J. Am. Chem. Soc.* **2021**, *143*, 12286–12293.

[90] E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.

[91] A. K. Ray, H. Patel, M. R. Patel, *Synthesis of Midodrine HCL from a Novel Intermediate 1-(2',5'-Dimethoxyphenyl)-2-Azidoethanone, US 6201153 B1*, **2001**.

[92] P. Hullot, T. Cuvigny, M. Larchevêque, H. Normant, *Can. J. Chem.* **1977**, *55*, 266–273.

[93] J. Vader, H. Sengers, A. de Groot, *Tetrahedron* **1989**, *45*, 2131–2142.

[94] I. S. Ponticello, *J. Polym. Sci. Polym. Chem. Ed.* **1979**, *17*, 3509–3518.

[95] J. D. Little, S. Ghosh, S. Harrison, A. E. Elder, C. C. Renou, K. G. Carson, *Pgd2 Receptor Antagonists for the Treatment of Inflammatory Diseases, WO2006091674A1*, **2006**.

[96] Z.-L. Song, C.-A. Fan, Y.-Q. Tu, *Chem. Rev.* **2011**, *111*, 7523–7556.

[97] Y. Fegheh-Hassanpour, F. Ebrahim, T. Arif, H. O. Sintim, T. D. W. Claridge, N. T. Amin, D. M. Hodgson, *Org. Biomol. Chem.* **2018**, *16*, 2876–2884.

[98] P. Vinczer, L. Novak, C. Szantay, *Synth. Commun.* **1984**, *14*, 281–288.

[99] R. M. Adlington, A. G. M. Barrett, *Acc. Chem. Res.* **1983**, *16*, 55–59.

[100] J. E. Stemke, F. T. Bond, *Tetrahedron Lett.* **1975**, *16*, 1815–1818.

[101] P. C. Traas, H. Boelens, H. J. Takken, *Tetrahedron Lett.* **1976**, *17*, 2287–2288.

[102] C. L. Willis, *Tetrahedron Lett.* **1987**, *28*, 2175–2178.

[103] I. Hueso-Falcón, N. Girón, P. Velasco, J. M. Amaro-Luis, A. G. Ravelo, B. de las Heras, S. Hortelano, A. Estevez-Braun, *Bioorganic Med. Chem.* **2010**, *18*, 1724–1735.

[104] A. V. Gaidai, D. M. Volochnyuk, O. V. Shishkin, A. A. Fokin, I. A. Levandovskiy, T. E. Shubina, *Synthesis* **2012**, *44*, 810–816.

[105] A. Fürstner, B. Bogdanović, *Angew. Chem. Int. Ed.* **1996**, *35*, 2442–2469.

[106] M. Ephritikhine, *Chem. Commun.* **1998**, 2549–2554.

[107] A. Chatterjee, N. N. Joshi, *Tetrahedron* **2006**, *62*, 12137–12158.

[108] D. Zhang, J. Liu, Z. Kang, H. Qiu, W. Hu, *Org. Biomol. Chem.* **2019**, *17*, 9844–9848.

[109] T. Yang, Y. Sun, H. Wang, Z. Lin, J. Wen, X. Zhang, *Angew. Chem. Int. Ed.* **2020**, *59*, 6108–6114.

[110] M. Y. Zhou, S. S. Kong, L. Q. Zhang, M. Zhao, J. A. Duan, Z. Ou-Yang, M. Wang, *Tetrahedron Lett.* **2013**, *54*, 3962–3964.

[111] D. S. Sharada, A. H. Shinde, S. M. Patel, S. Vidyacharan, *J. Org. Chem.* **2016**, *81*, 6463–6471.

[112] J. Deguchi, T. Sasaki, Y. Hirasawa, T. Kaneda, I. Kusumawati, O. Shirota, H. Morita, *Tetrahedron Lett.* **2014**, *55*, 1362–1365.

[113] I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Foreman, *J. Chem. Soc. Perkin Trans. 1* **1973**, 977–981.

[114] Y. K. Chung, *Coord. Chem. Rev.* **1999**, *188*, 297–341.

[115] A. Kirschning, C. Kujat, S. Luiken, E. Schaumann, *European J. Org. Chem.* **2007**, 2387–2400.

[116] D. G. Morris, *Chem. Soc. Rev.* **1982**, *11*, 397–434.

[117] G. R. Jones, Y. Landais, *Tetrahedron* **1996**, *52*, 7599–7662.

[118] C. Mukai, J. S. Kim, H. Sonobe, M. Hanaoka, *J. Org. Chem.* **1999**, *64*, 6822–6832.

[119] A. De Meijere, H. Becker, A. Stolle, S. I. Kozhushkov, M. Teresa Bes, J. Salaüin, M. Noltemeyer, *Chem. - A Eur. J.* **2005**, *11*, 2471–2482.

[120] K. M. Brummond, H. Wan, J. L. Kent, *J. Org. Chem.* **1998**, *63*, 6535–6545.

[121] M. C. P. Yeh, W. C. Tsao, J. S. Ho, C. C. Tai, D. Y. Chiou, L. H. Tu, *Organometallics* **2004**, *23*, 792–799.

[122] E. Negishi, S. J. Holmes, J. M. Tour, J. A. Miller, *J. Am. Chem. Soc.* **1985**, *107*, 2568–2569.

[123] E. ichi Negishi, S. J. Holmes, J. M. Tour, J. A. Miller, F. E. Cederbaum, D. R. Swanson, T. Takahashi, *J. Am. Chem. Soc.* **1989**, *111*, 3336–3346.

[124] H. Urabe, K. Suzuki, F. Sato, *J. Am. Chem. Soc.* **1997**, *119*, 10014–10027.

[125] E. I. Negishi, J. L. Montchamp, L. Anastasia, A. Elizarov, D. Choueiry, *Tetrahedron Lett.* **1998**, *39*, 2503–2506.

[126] R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922.

[127] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.

[128] G. A. El-Hiti, K. Smith, A. S. Hegazy, M. B. Alshammari, A. M. Masmali, *Arkivoc* **2015**, 19–47.

[129] N. Meyer, D. Seebach, *Angew. Chem. Int. Ed.* **1978**, *17*, 521–522.

[130] N. Meyer, D. Seebach, *Chem. Ber.* **1980**, *113*, 1304–1319.

[131] S. Neufeind, N. Hülsken, J. M. Neudörfl, N. Schlörer, H. G. Schmalz, *Chem. - A Eur. J.* **2011**, *17*, 2633–2641.

[132] Y. Tanoue, A. Terada, I. Seto, Y. Umezu, O. Tsuge, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1221–1224.

[133] M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem. Int. Ed.* **1997**, *36*, 119–122.

[134] M. Catellani, E. Motti, *New J. Chem.* **1998**, *22*, 759–761.

[135] M. Catellani, E. Motti, S. Baratta, *Org. Lett.* **2001**, *3*, 3611–3614.

[136] M. Catellani, *Top. Organomet. Chem.* **2005**, *14*, 21–53.

[137] D. I. Chai, P. Thansandote, M. Lautens, *Chem. - A Eur. J.* **2011**, *17*, 8175–8188.

[138] J. Wang, G. Dong, *Chem. Rev.* **2019**, *119*, 7478–7528.

[139] A. Martins, B. Mariampillai, M. Lautens, *Top. Curr. Chem.* **2010**, *292*, 1–33.

[140] N. Della Ca', M. Fontana, E. Motti, M. Catellani, *Acc. Chem. Res.* **2016**, *49*, 1389–1400.

[141] H. Cheng, S. Chen, R. Chen, Q. Zhou, *Angew. Chem. Int. Ed.* **2019**, *58*, 5832–5844.

[142] M. Catellani, M. C. Fagnola, *Angew. Chem. Int. Ed.* **1995**, *33*, 2421–2422.

[143] D. J. Cárdenas, B. Martín-Matute, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 5033–5040.

[144] G. Maestri, E. Motti, N. Della Ca', M. Malacria, E. Derat, M. Catellani, *J. Am. Chem. Soc.* **2011**, *133*, 8574–8585.

[145] M. Catellani, G. P. Chiusoli, *J. Organomet. Chem.* **1988**, *346*, C27–C30.

[146] M. Catellani, B. E. Mann, *J. Organomet. Chem.* **1990**, *390*, 251–255.

[147] G. Bocelli, M. Catellani, S. Ghelli, *J. Organomet. Chem.* **1993**, *458*, C12–C15.

[148] J. Ye, M. Lautens, *Nat. Chem.* **2015**, *7*, 863–870.

[149] R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526.

[150] H. Horino, M. Arai, N. Inoue, *Tetrahedron Lett.* **1974**, *15*, 647–650.

[151] M. Catellani, G. P. Chiusoli, *J. Organomet. Chem.* **1983**, *250*, 509–515.

[152] R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, John Wiley & Sons Inc., Hoboken, NJ, USA, **2014**.

[153] A. Ariafard, Z. Lin, *Organometallics* **2006**, *25*, 4030–4033.

[154] M. Catellani, *Synlett* **2003**, 0298–0313.

[155] C. Lei, X. Jin, J. Zhou, *ACS Catal.* **2016**, *6*, 1635–1639.

[156] F. Mohajer, M. M. Heravi, V. Zadsirjan, N. Poormohammad, *RSC Adv.* **2021**, *11*, 6885–6925.

[157] M. Gazvoda, M. Virant, B. Pinter, J. Košmrlj, *Nat. Commun.* **2018**, *9*, 4814.

[158] S. L. Buchwald, B. T. Watson, J. C. Huffman, *J. Am. Chem. Soc.* **1986**, *108*, 7411–7413.

[159] S. L. Buchwald, B. T. Watson, R. T. Lum, W. A. Nugent, *J. Am. Chem. Soc.* **1987**, *109*, 7137–7141.

[160] S. L. Buchwald, A. Sayers, B. T. Watson, J. C. Dewan, *Tetrahedron Lett.* **1987**, *28*, 3245–3248.

[161] K. J. Barr, B. T. Watson, S. L. Buchwald, *Tetrahedron Lett.* **1991**, *32*, 5465–5468.

[162] U. Wriede, M. Fernandez, K. F. West, D. Harcour, H. W. Moore, *J. Org. Chem.* **1987**, *52*, 4485–4489.

[163] F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971.

[164] C. D. Donner, *Synthesis* **2010**, 415–420.

[165] A. Saxena, F. Perez, M. J. Krische, *Angew. Chem. Int. Ed.* **2016**, *55*, 1493–1497.

[166] D.-W. Zhang, W.-D. Xu, H.-L. Fan, H.-M. Liu, D. Chen, D.-D. Liu, H.-B. Qin, *Org. Lett.* **2019**, *21*, 6761–6764.

[167] K. Fujita, M. Ohno, *Process for the Preparation of Tetronic Acid, EP2163549A1*, **2006**.

[168] R. Pappo, D. Allen, Jr., R. Lemieux, W. Johnson, *J. Org. Chem.* **1956**, *21*, 478–479.

[169] W. Yu, Y. Mei, Y. Kang, Z. Hua, Z. Jin, *Org. Lett.* **2004**, *6*, 3217–3219.

[170] J. Souppe, L. Danon, J. L. Namy, H. B. Kagan, *J. Organomet. Chem.* **1983**, *250*, 227–236.

[171] G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307–338.

[172] J. L. Namy, J. Souppe, H. B. Kagan, *Tetrahedron Lett.* **1983**, *24*, 765–766.

[173] F. F. Fleming, G. Wei, O. W. Steward, *J. Org. Chem.* **2008**, *73*, 3674–3679.

[174] T. Tsuchimoto, K. Tobita, T. Hiyama, S. Fukuzawa, *Synlett* **1996**, 557–559.

[175] A. Kawada, S. Mitamura, J. Matsuo, T. Tsuchiya, S. Kobayashi, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2325–2333.

[176] P. Brownbridge, T.-H. Chan, *Tetrahedron Lett.* **1980**, *21*, 3423–3426.

[177] J. Christoffers, *Chem. Commun.* **1997**, 943–944.

[178] J. Christoffers, *Org. Synth.* **2002**, *78*, 249.

[179] C. L. Diedrich, W. Frey, J. Christoffers, *European J. Org. Chem.* **2007**, 4731–4737.

[180] K. Yamamoto, M. F. Hentemann, J. G. Allen, S. J. Danishefsky, *Chem. - A Eur. J.* **2003**, *9*, 3242–3252.

[181] F. J. Aladro, F. M. Guerra, F. J. Moreno-Dorado, J. M. Bustamante, Z. D. Jorge, G. M. Massanet, *Tetrahedron* **2001**, *57*, 2171–2178.

[182] A. L. García-Cabeza, R. Marín-Barrios, R. Azarken, F. J. Moreno-Dorado, M. J. Ortega, H. Vidal, J. M. Gatica, G. M. Massanet, F. M. Guerra, *European J. Org. Chem.* **2013**, 8307–8314.

[183] R. Iyengar, K. Schildknegt, M. Morton, J. Aubé, *J. Org. Chem.* **2005**, *70*, 10645–10652.

[184] A. J. Liston, M. Howarth, *J. Org. Chem.* **1967**, *32*, 1034–1041.

[185] W. Fukuda, H. Sato, H. Kakiuchi, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 751–756.

[186] M. Torigoe, J. Fishman, *Tetrahedron Lett.* **1963**, *4*, 1251–1256.

[187] J. A. Settepani, M. Torigoe, J. Fishman, *Tetrahedron* **1965**, *21*, 3661–3668.

[188] J. A. Marshall, W. I. Fanta, H. Roebke, *J. Org. Chem.* **1966**, *31*, 1016–1020.

[189] J. A. Marshall, H. Roebke, *J. Org. Chem.* **1968**, *33*, 840–843.

[190] S. H. Bertz, R. A. J. Smith, *J. Am. Chem. Soc.* **1989**, *111*, 8276–8277.

[191] B. H. Lipshutz, E. L. Ellsworth, *J. Am. Chem. Soc.* **1990**, *112*, 7440–7441.

[192] M. Pfau, I. Jabin, G. Revial, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1935–1936.

[193] Y. Murata, D. Yamashita, K. Kitahara, Y. Minasako, A. Nakazaki, S. Kobayashi, *Angew. Chem. Int. Ed.* **2009**, *48*, 1400–1403.

[194] G. H. Posner, Conjugate Addition Reactions of Organocopper Reagents, in *Organic Reactions*, John Wiley & Sons Inc., Hoboken, NJ, USA, **2011**, pp. 1–114.

[195] L. M. Schneider, V. M. Schmiedel, T. Pecchioli, D. Lentz, C. Merten, M. Christmann, *Org. Lett.* **2017**, *19*, 2310–2313.

[196] T. Pecchioli, M. Christmann, *Org. Lett.* **2018**, *20*, 5256–5259.

[197] M.-C. Roux-Schmitt, J. Seyden-Penne, G. V. Baddeley, E. Wenkert, *Tetrahedron Lett.* **1981**, *22*, 2171–2174.

[198] E. V. Dehmlow, C. Sauerbier, *Liebigs Ann. der Chemie* **1989**, 181–185.

[199] H.-J. Quan, J. Koyanagi, K. Hagiwara, X.-R. Cui, Y. Isshiki, S. Kondo, F. Komada, S. Saito, *Chem. Pharm. Bull.* **2006**, *54*, 72–79.

[200] J. A. Marshall, A. E. Greene, *J. Org. Chem.* **1971**, *36*, 2035–2042.

[201] A. Aamouche, F. J. Devlin, P. J. Stephens, *J. Am. Chem. Soc.* **2000**, *122*, 7358–7367.

[202] J. W. Huffman, W. E. Swain, J. Jacobus, A. T. McPhail, *J. Org. Chem.* **1980**, *45*, 3088–3096.

[203] E. Toromanoff, *Top. Stereochem.* **1967**, *2*, 157–198.

[204] S. V. Shishkina, O. V. Shishkin, S. M. Desenko, J. Leszczynski, *J. Phys. Chem. A* **2008**, *112*, 7080–7089.

[205] D. H. R. Barton, *Experientia* **1950**, *6*, 316–320.

[206] G. P. Moss, *Pure Appl. Chem.* **1989**, *61*, 1783–1822.

[207] R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *Tetrahedron* **1958**, *2*, 1–57.

[208] W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood, E. T. Jones, *J. Am. Chem. Soc.* **1958**, *80*, 661–679.

[209] W. S. Johnson, D. S. Allen, R. R. Hindersinn, G. N. Sausen, R. Pappo, *J. Am. Chem. Soc.* **1962**, *84*, 2181–2196.

[210] J. A. Marshall, G. L. Bundy, W. I. Fanta, *J. Org. Chem.* **1968**, *33*, 3913–3922.

[211] J. Wu, Y. Kadonaga, B. Hong, J. Wang, X. Lei, *Angew. Chem. Int. Ed.* **2019**, *58*, 10879–10883.

[212] B. C. Ranu, M. K. Basu, *Tetrahedron Lett.* **1991**, *32*, 4177–4178.

[213] W. Nagata, M. Yoshioka, T. Terasawa, *J. Am. Chem. Soc.* **1972**, *94*, 4672–4683.

[214] E. J. Corey, F. J. Hannon, *Tetrahedron Lett.* **1990**, *31*, 1393–1396.

[215] C. L. Kingsbury, R. A. J. Smith, *J. Org. Chem.* **1997**, *62*, 4629–4634.

[216] E. J. Corey, T. M. Eckrich, *Tetrahedron Lett.* **1983**, *24*, 3165–3168.

[217] E. J. Corey, D. Seebach, *Angew. Chem. Int. Ed.* **1965**, *4*, 1077–1078.

[218] D. Seebach, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 231–237.

[219] T. Mukaiyama, K. Narasaka, M. Furusato, *J. Am. Chem. Soc.* **1972**, *94*, 8641–8642.

[220] H. Stetter, *Angew. Chem. Int. Ed.* **1976**, *15*, 639–647.

[221] J. Zhang, C. Xing, B. Tiwari, Y. R. Chi, *J. Am. Chem. Soc.* **2013**, *135*, 8113–8116.

[222] B. Fraser-Reid, N. L. Holder, D. R. Hicks, D. L. Walker, *Can. J. Chem.* **1977**, *55*, 3978–3985.

[223] Z. Benko, B. Fraser-Reid, P. S. Mariano, A. L. J. Beckwith, *J. Org. Chem.* **1988**, *53*, 2066–2072.

[224] A. Vázquez-Romero, J. Rodríguez, A. Lledó, X. Verdaguer, A. Riera, *Org. Lett.* **2008**, *10*, 4509–4512.

[225] J. L. Luche, L. Rodriguez-Hahn, P. Crabbé, *J. Chem. Soc. Chem. Commun.* **1978**, 601–602.

[226] J. Luche, A. L. Gemal, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

[227] E. Kaufmann, P. v. R. Schleyer, K. N. Houk, Y. D. Wu, *J. Am. Chem. Soc.* **1985**, *107*,

5560–5562.

[228] Y. Suzuki, D. Kaneno, S. Tomoda, *J. Phys. Chem. A* **2009**, *113*, 2578–2583.

[229] D. Rodrigues Silva, L. A. Zeoly, P. Vermeeren, R. A. Cormanich, T. A. Hamlin, C. Fonseca Guerra, M. P. Freitas, *J. Phys. Org. Chem.* **2023**, e4556.

[230] K. N. Houk, M. N. Paddon-Row, N. G. Rondan, Y.-D. Wu, F. K. Brown, D. C. Spellmeyer, J. T. Metz, Y. Li, R. J. Loncharich, *Science* **1986**, *231*, 1108–1117.

[231] H. Wang, K. N. Houk, *Chem. Sci.* **2014**, *5*, 462–470.

[232] S. F. Brady, M. A. Ilton, W. S. Johnson, *J. Am. Chem. Soc.* **1968**, *90*, 2882–2889.

[233] J. P. McCormick, D. L. Barton, *J. Org. Chem.* **1980**, *45*, 2566–2570.

[234] P. H. Di Chenna, V. Dansey, A. A. Ghini, G. Burton, *Arkivoc* **2005**, *12*, 154–162.

[235] P.-F. Li, C.-B. Yi, J. Qu, *Org. Biomol. Chem.* **2015**, *13*, 5012–5021.

[236] P.-F. Li, C.-B. Yi, S.-J. Ren, J. Qu, *Adv. Synth. Catal.* **2016**, *358*, 2088–2092.

[237] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* **1968**, *24*, 53–58.

[238] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324.

[239] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1959**, *81*, 4256–4264.

[240] M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2003**, *125*, 2341–2350.

[241] D. L. J. Clive, S. Daigneault, *J. Chem. Soc. Chem. Commun.* **1989**, 332–335.

[242] F. Mohamadi, W. C. Still, *Tetrahedron Lett.* **1986**, *27*, 893–896.

[243] E. E. Jacobsen, M. F. El-Behairy, L. Skattebøl, T. Anthonsen, *J. Biotechnol.* **2013**, *168*, 284–288.

[244] E. Vogel, W. Klug, A. Breuer, *Org. Synth.* **1974**, *54*, 11.

[245] L. F. Fieser, D. H. Sachs, *J. Org. Chem.* **1964**, *29*, 1113–1115.

[246] M. G. Banwell, K. A. Herbert, J. R. Buckleton, G. R. Clark, C. E. F. Rickard, C. M. Lin, E. Hamel, *J. Org. Chem.* **1988**, *53*, 4945–4952.

[247] M. G. Banwell, J. N. Lambert, M. Corbett, R. J. Greenwood, J. M. Gulbis, M. F. Mackay, *J. Chem. Soc. Perkin Trans. 1* **1992**, 1415–1426.

[248] H. Lin, M. Yang, P. Huang, W. Cao, *Molecules* **2003**, *8*, 608–613.

[249] D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Yick-Pui Mui, H. D. Simmons, A. J. H. Treiber, S. R. Dowd, *J. Am. Chem. Soc.* **1965**, *87*, 4259–4270.

[250] M. S. Baird, V. M. Boitsov, A. V. Stepakov, A. P. Molchanov, J. Kopf, M. Rajaratnam, R. R. Kostikov, *Tetrahedron* **2007**, *63*, 7717–7726.

[251] R. Huwyler, A. Al-Dulayymi, M. Neuenschwander, *Helv. Chim. Acta* **1999**, *82*, 2336–2347.

[252] S. Taillemaud, N. Diercxsens, A. Gagnon, A. B. Charette, *Angew. Chem. Int. Ed.* **2015**, *54*, 14108–14112.

[253] S. Miyano, Y. Matsumoto, H. Hashimoto, *J. Chem. Soc. Chem. Commun.* **1975**, 364–365.

[254] S. Miyano, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3665–3668.

[255] H. Y. Kim, L. Salvi, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 954–962.

[256] G. A. Chesnokov, K. Gademann, *J. Am. Chem. Soc.* **2021**, *143*, 14083–14088.

[257] K. N. Sedenkova, E. B. Averina, Y. K. Grishin, J. V. Kolodyazhnaya, V. B. Rybakov, T. S. Kuznetsova, A. Hughes, G. D. P. Gomes, I. V. Alabugin, N. S. Zefirov, *Org. Biomol. Chem.* **2017**, *15*, 9433–9441.

[258] L. Xu, C. E. Doubleday, K. N. Houk, *J. Am. Chem. Soc.* **2011**, *133*, 17848–17854.

[259] A. E. Keating, S. R. Merrigan, D. A. Singleton, K. N. Houk, *J. Am. Chem. Soc.* **1999**, *121*, 3933–3938.

[260] J. F. Blake, S. G. Wierschke, W. L. Jorgensen, *J. Am. Chem. Soc.* **1989**, *111*, 1919–1920.

[261] F. Bernardi, A. Bottoni, G. Pietro Miscione, *J. Am. Chem. Soc.* **1997**, *119*, 12300–12305.

[262] P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485–1486.

[263] T. A. Reekie, M. G. Banwell, A. C. Willis, *J. Org. Chem.* **2013**, *78*, 7100–7111.

[264] D. Crich, L. Quintero, *Chem. Rev.* **1989**, *89*, 1413–1432.

[265] S. Ruccolo, Y. Qin, C. Schnedermann, D. G. Nocera, *J. Am. Chem. Soc.* **2018**, *140*, 14926–14937.

[266] G. Wittig, H. Döser, I. Lorenz, *Justus Liebigs Ann. Chem.* **1949**, *562*, 192–205.

[267] T. Nakai, K. Mikami, *Chem. Rev.* **1986**, *86*, 885–902.

[268] W. C. Still, A. Mitra, *J. Am. Chem. Soc.* **1978**, *100*, 1927–1928.

[269] L. Rycek, T. Hudlicky, *Angew. Chem. Int. Ed.* **2017**, *56*, 6022–6066.

[270] B. Maciá, C. Gómez, M. Yus, *Tetrahedron Lett.* **2005**, *46*, 6101–6104.

[271] C. A. Broka, T. Shen, *J. Am. Chem. Soc.* **1989**, *111*, 2981–2984.

[272] B. Kruse, R. Brückner, *Chem. Ber.* **1989**, *122*, 2023–2025.

[273] J. Mulzer, B. List, *Tetrahedron Lett.* **1996**, *37*, 2403–2404.

[274] L. A. Paquette, T. Sugimura, *J. Am. Chem. Soc.* **1986**, *108*, 3841–3842.

[275] T. Sugimura, L. A. Paquette, *J. Am. Chem. Soc.* **1987**, *109*, 3017–3024.

[276] A. Pelter, R. S. Ward, G. M. Little, *J. Chem. Soc. Perkin Trans. 1* **1990**, 2775–2790.

[277] M. B. Smith, B. T. Dembofsky, Y. C. Son, *J. Org. Chem.* **1994**, *59*, 1719–1725.

[278] A. M. Borys, *Organometallics* **2023**, *42*, 182–196.

[279] W. L. F. Armarego, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, **2017**.

[280] D. Gasperini, L. Maggi, S. Dupuy, R. M. P. Veenboer, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Adv. Synth. Catal.* **2016**, *358*, 3857–3862.

[281] A. Guy, J. Doussot, C. Ferroud, R. Garreau, A. Godefroy-Falguieres, *Synthesis* **1992**, 821–822.

[282] S. Riedel, *Gold-Katalysierte Cycloisomerisierung von Eninolen Zu Substituierten Furanen Und Deren Anwendung in Der Totalsynthese Des Naturstoffs Auxofuran (PhD Thesis)*, Tübingen, **2020**.

[283] N. Zhang, J. Jiang, M. Liu, M. Taniguchi, A. K. Mandal, R. B. Evans-Storms, J. B. Pitner, D. F. Bocian, D. Holten, J. S. Lindsey, *New J. Chem.* **2016**, *40*, 7750–7767.

[284] T. Hamaguchi, Y. Takahashi, H. Tsuji, M. Kawatsura, *Org. Lett.* **2020**, *22*, 1124–1129.

[285] M. Moreno, W. Elgaher, J. Herrmann, N. Schläger, M. Hamed, S. Baumann, R. Müller, R. Hartmann, A. Kirschning, *Synlett* **2015**, *26*, 1175–1178.

[286] K. Xu, H. Liu, D. Liu, C. Sheng, J. Shen, W. Zhang, *Tetrahedron* **2018**, *74*, 5996–6002.

[287] T. Capecchi, C. B. de Koning, J. P. Michael, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2681–2688.

[288] N. Nicolaus, S. Strauss, J.-M. Neudörfl, A. Prokop, H.-G. Schmalz, *Org. Lett.* **2009**, *11*, 341–344.

[289] V. T. H. Nguyen, B. D. Cam, Z. Ahmed, P. Langer, *Zeitschrift für Naturforsch. B* **2013**, *68*, 836–840.

[290] P. Schröder, J. O. Bauer, C. Strohmann, K. Kumar, H. Waldmann, *J. Org. Chem.* **2016**, *81*, 10242–10255.

[291] Y. Kawato, N. Takahashi, N. Kumagai, M. Shibasaki, *Org. Lett.* **2010**, *12*, 1484–1487.

[292] G. M. Sheldrick, *Acta Crystallogr. Sect. A Found. Adv.* **2015**, *71*, 3–8.

[293] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, H. Puschmann, *J. Appl. Crystallogr.* **2009**, *42*, 339–341.

[294] G. M. Sheldrick, *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71*, 3–8.

[295] N. T. Tzvetkov, B. Neumann, H. G. Stammler, J. Mattay, *European J. Org. Chem.* **2006**, 351–370.

[296] L. J. Bourhis, O. V. Dolomanov, R. J. Gildea, J. A. K. Howard, H. Puschmann, *Acta Crystallogr. Sect. A Found. Adv.* **2015**, *71*, 59–75.